DESIGN AND CHARACTERIZATION OF DRUG DELIVERY SYSTEM USING HOT-MELT COATING TECHNIQUE

हॉट–मेल्ट कोटिंग तकनीक का उपयोग करके दवा वितरण प्रणाली का डिजाइन और लक्षण वर्णन

A

Thesis

Submitted for the Award of the Ph.D. degree of

PACIFIC ACADEMY OF HIGHER EDUCATION AND RESEARCH UNIVERSITY

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2024

DECLARATION

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CERTIFICATE

It gives me immense pleasure in certifying that the thesis **"DESIGN AND CHARACTERIZATION OF DRUG DELIVERY SYSTEM USING HOT-MELT COATING TECHNIQUE"** and submitted by **LAKDE SATISHKUMAR KACHARAPPA** is based on the research work carried out under my guidance. He / She has completed the following requirements as per Ph.D. regulations of the University;

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DATE: - **LAKDE SATISHKUMAR KACHARAPPA**

DEDICATED TO MY
BELOVED BROTHER
LATE. SANTOSH LAKDE

PREFACE

Better patient compliance, reduced adverse effects and more efficient delivery of active ingredients are primary goals of product researchers and formulators, who have at their disposal an array of new drug delivery technologies to assist them with their work. The ways in which medicinal agents are administered have gained increasing attention in the past three decades. Major attention has been focused on methods for giving these biologically active agents, continuously for prolonged time periods and in a controlled fashion. The oral route of drug administration can be considered the simplest and safest because of its excellent patient compliance.

Waxes obtained from the natural origin are the mostly the ingredients of food can be served as release retardant to achieve modified release of drugs. Some of these waxes were useful alone whereas some of them were useful in combination. Very little research has been carried out by using waxes as a hot melt coating agent.

Looking at incredible merits of hot melt coating technology and recommendations of the regularity authorities, in future the water based and solvent based coating technologies will be replaced by hot melt coating technology. The future hot melt coating agents can expect many more waxes for the preparation of dosage form. Such approaches seem, likely to provide considerable scope for creative approaches, and formulation scientists are interestingly enjoy fulfilling the requirements of newer drug delivery.

The present work was under taken to confirm taste masking potential natural film formers using hot melt coating technique and enhancing stability of water sensitive drug from environment. The suitability of drug delivery systems to increase the patient compliance and providing the quality and stable medication will be focused. These systems provide more safety and quality dosage form to obtain higher therapeutic efficacy.

ABBREVIATIONS

ABBREVIATIONS	ABBREVIATIONS TERMINOLOGY
TDF	Tenofovir Disoproxil Fumarate
SPM	Sitagliptin Phosphate Monohydrate
g or gm	Gram
FDA	Food and Drug Administration
API	Active Pharmaceutical Ingredients
BA	Bioavailability
BE	Bioequivalence
BCS	Biopharmaceutics Classification System
EPA	Environmental Protection Agency
°C	Degree Celsius
M	Molar
DT	Disintegration Time
N	Normal
DSC	Differential Scanning Calorimetry
(f2)	Similarity Factor
FTIR	Fourier Transform Infrared Spectroscopy
GIT	Gastrointestinal Tract
HCl	Hydrochloric Acid
HLB	Hydrophilic-lipophilic Balance
HMC	Hot Melt Coating
ICH	International Conference on Harmonization
IR	Infrared Spectroscopy
Log P = Ko/w	Distribution/Partition Coefficient
LOD	Loss on Drying
MP	Melting Point
NLT	Not Less Than
NMT	Not More Than
OSHA	Occupational Safety and Health Administration
EPA	Environment Protection Agency

% w/w	Percent Weight by Weight
% w/v	Percent Weight by Volume
% v/v	Percent Volume by Volume
PEG	Polyethylene Glycol
pH	Negative Logarithm of Hydrogen Ion Concentration.
pKa	Negative log of Dissociation Constant
PVP	Polyvinyl pyrrolidone
Q.S.	Quantity Sufficient
RH	Relative Humidity
rpm	Revolutions Per Minute
S.D.	Standard Deviation
SSG	Sodium Starch Glycolate
λmax	Absorption Maxima
USA	United States of America
USP	United State Pharmacopoeia
UV	Ultraviolet
Vs	Verses
WHO	World Health Organization
XRD	X-ray diffraction

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INTRODUCTION

PART A

1 Introduction

1.1 Hot Melt Coating:

The process of coating is a crucial step in the production of certain solid dosage forms. It is used to alter drug release patterns, enhance visual appeal, or safeguard the chemical and physical properties of the drug. Pharmaceutical coating therefore dates as far back as the late nineteenth or early the twentieth century, when it was in effect a confectionery item. Because of small production volumes the art of sugar coating was taken to pharmacies where this paraphernalia was not available.[1] The modern era of pharmaceutical coating began in the 1950s with the introduction of advanced film coating technology, which brought about significant innovations in coating equipment and polymer chemistry.[1]

Today, the industry is confronted with various challenges in the development of oral dosage forms due to the diverse properties of new molecules. To address these challenges, pharmaceutical scientists are required to utilize new technologies such as-

Table 1.1 : Molecules Properties and Technologies Employed

Properties of molecule	Examples of conventional technology employed
Poor solubility	Solid dispersion, Lyophilization, Spray drying
Taste and Odor	Sugar coating, Film coating with flavors
Bioavailability	Solid dispersion, Lyophilization, Spray drying
Acid-degradation	Delayed-release coating, Extended-release coating
Stability	Protective coating

The table above shows that coating is the most commonly used conventional technology for various purposes. As more and more drugs require the coating technologists are being forced to find ways of improving the yield, quality and reduce the time spent in the process. Two significant steps in this field were the introduction of the perforated pan and the application of the fluid bed coater that enabled satisfactory coating of many forms of dosages and of practically every size of production batches[1,2].

The coating materials are usually dispersed or made soluble in a suitable solvent before spraying, but the use of solvents is now restricted due to toxicity and

environmental concerns. Aqueous-based coating technology has largely eliminated these drawbacks. However, it requires slower drying and high energy input[3]. Polymeric coatings allow the use of large quantities of organic solvents, which are not environmentally friendly. Regulatory agencies[1] like US FDA, Environmental Protection Agencies (EPA)[4], and Occupational Safety and Health Administration (OSHA) to strongly restrict the use of such solvents[5].

Method was used to coat large materials (paper, foil, textiles, etc.) and not discrete particles or dosage forms.[6] During the 1980s, the pharmaceutical industry was looking for affordable, effective, simple, and novel coating technology, and hot melt coating was found the answer for the same.[7] In the hot melt coating technique, the coating molten mass is allowed to spray or spread on the substrate and cured. No solvent is required for the hot melt coating of the substrate. Hot melt coating (HMC) with carbowaxes, resins, waxes, or mixtures thereof began in the 1940s in the textile and paper industries.[8]

The hot melt coating has following merits and demerits over other coating techniques because the coating material is used in a molten state.[1] The system is solvent-free. Nevertheless, the advantages that go with this technology are outweighing the disadvantages that could be accorded to it.

1.2 Merits

- There is no need for expensive organic solvents, which eliminates the steps of solvent disposal, treatment, or recovery associated with organic solvents[9].
- The process is cost-effective due to the absence of costly organic solvents, low energy required for drying, and the use of low-cost lipids as coating excipients.
- The process is fast because coating agents are used in molten form.
- It is recommended by regulatory directions as the usage of organic solvents is fully excluded, making the HMC process environmentally friendly [4,5].
- There is no risk of microbial contamination or hydrolysis of drugs since no water is used in the method [10].
- Modified drug release patterns, masking of unwanted organoleptic properties of drugs, improvement of substrate flow properties, and protection of dosage forms from the environment are possible with such coating [10].

- The conventional method coating equipment, such as pan-coaters or fluid bed coaters (FBD), may be conveniently modified to serve the necessitate of this approach.
- The majority of lipids are food components, hence there are fewer chances of hypersensitivity reactions or toxicity.

1.3 Demerits

- Hot melt coating, performed at 40-200°C, is not suitable for drugs that are sensitive to heat.
- There is a limit to the amount of coating agent that can be deposited on the substrate's surface.
- The process is limited when applying multi-layer coatings, as it can increase the coating weight. In multi-layer coating, the internal coating agents must have a significantly higher melting point than the outer polymer [11].
- It's important to investigate the thermal behavior of individual drugs, excipients, drug-excipient interactions at high temperature, and the stability of the dosage form [12].
- Variability within batches of dosage forms may occur due to the polymorphic behavior of the coating material. Polymorphic forms have different physical properties, such as density, transition temperature, melting point, and solubility, which can have impression on intrinsic dissolution profile and other solid- state-properties of constituents. Hence, a thorough investigation of excipient polymorphs is necessary[1, 13].
- Sorption of moisture by the coating mass may affect drug stability[14].
- Operators should follow safety measures during operation since process is conducted at higher temperature[1].
- It is mandatory to know the toxicology of the coating agents as well as the minutiae of in-vivo investigations because the coating agents are ingested along with the dosage forms.
- High-temperature equipment and the associated high energy costs are required for the heating process.
- For the coating excipients, few of the recommended properties include melt viscosity should be less than 300 centipoises and melting point should be below

80°C in order to ensure good flow and good spreading ability of the coat materials [8,15].

1.4 Applications

Hot melt coating offers a wide range of applications. The technique has shown promising results in acid resistance, bioavailability enhancement, flow property improvement, prolonged release, and taste masking, depending on the type of coating material used[3].

- Hot melt coating can improve and mask the taste of drugs such as Aspirin, Paracetamol, Bromhexine hydrochloride, and Salbutamol[16-20].
- It reduces the acidity of vitamins[21].
- It protects the drug from environmental factors such as light and/or humidity[14,22,23].
- When spread on a solid substrate, hot melt coating material provides lubrication to the material and enhances compressibility[24].
- It is useful in the design of modified-release dosage forms for a variety of drugs including Ambroxol, Chlorpheniramine maleate, and Chloroquine[25-28].

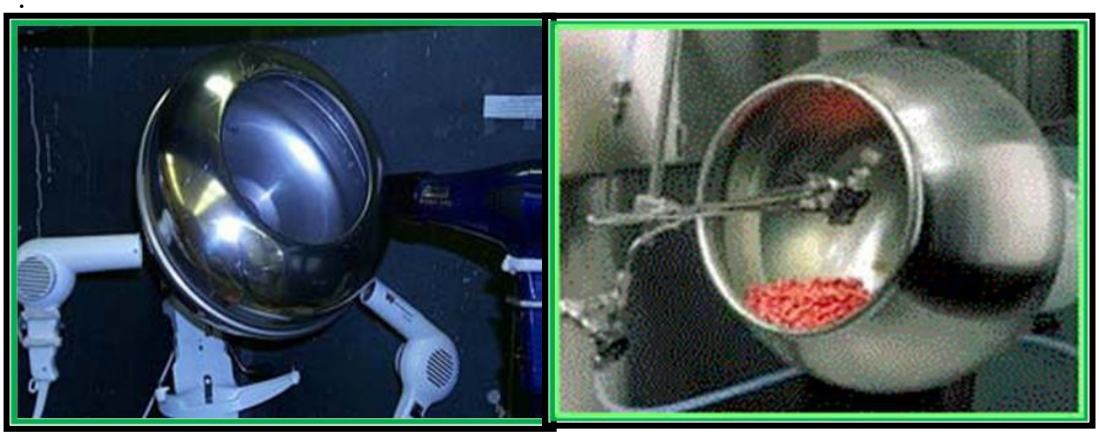
1.5 Hot Melt Coating Equipment

The process variables and equipment utilized in hot melt coating of pharmaceuticals have been published by Jones and Percel[29]. The equipment used for the hot melt coating process includes modified conventional pan coaters and fluid bed coaters. The fluid bed coater is equipped for top spray, bottom spray, tangential spray, and turbojet[30].

1.5.1 Pan Coater

Hot melt coating can be executed with minimal modifications to a basic pan coater, such as the pan pour or pan spray procedures depicted in figure 1.1. The pan spray coating approach has proven successful for maintaining release due to in line film creation, nevertheless the pan pour technique produces slight variation in drug release from the same batch, most likely due to non-uniform coating and low coating efficiency.[1] Hot melt coating may be used to coat granules, pellets, spherules, and tablets with minor modifications[31,32].

The substrates to be coated with molten mix coating agents are put into a coating pan that has radially organised baffles and a heating system. This process starts with melting the coating agent, which is then heated slightly beyond its melting point while stirring at the same temperature. The substrates are then rolled in the heated coating pan until the bed temperature reaches 60°C, which is accomplished through convection heating with room heaters. The molten coating mass is then carefully poured onto the warmed rolling substrates or sprayed at a monitored pace with an insulated spray nozzle. After the application of the coating mass, the substrates are allowed to roll for a few minutes, during which the bed temperature gradually comes down. The substrates are then removed and cured in a dryer for a few hours to days [8, 33].



(A) **(B)**

Fig. 1.1 : Hot Melt Coating by (A) Pan pour and (B) Pan Spray Method

1.5.2 Spouted Bed

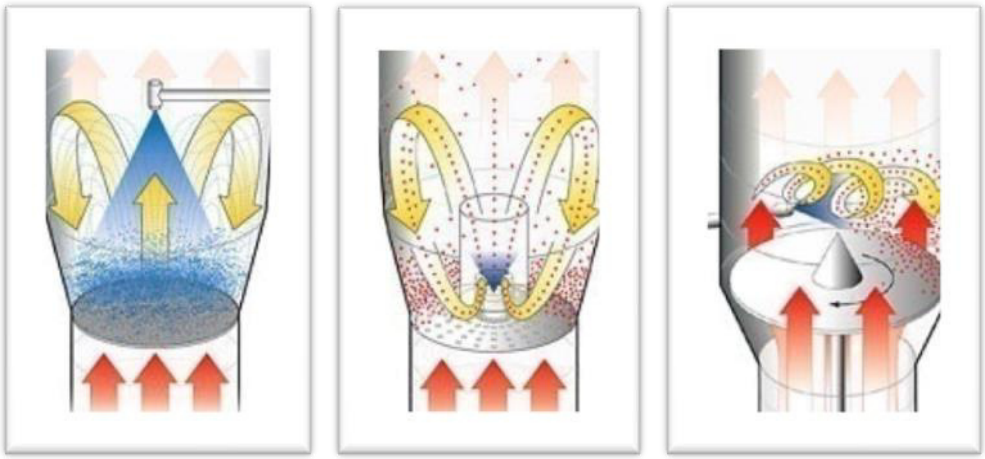
The basic fluid dynamic properties for tablet spouting were obtained using a prismatic spouted bed setup. The equipment was made of clear acrylic glass with two horizontal and adjustable gas inlets. The coating was applied at the maximum spouted bed height, with an air flow rate 40% higher than the lowest spouting velocity. The tablets were weighed and introduced into the column, following which the desired air flow rate had been adjusted and the temperature was preset. Once the bed temperature had stabilised, wax beads were added into the apparatus by dropping them from the column top all at once. The solid suspension was spouted for 5 minutes prior to the heating was switched off. Temperature decline was observed until it reached room temperature, after which it was left to spout for an additional 5 minutes. Coated pills were collected and weighed. Process efficiencies were determined utilising the

beginning and end substrate weight and coating material load according to the definition in equation (1.1)[34].

$$\text{Coating Efficiency} = \frac{\text{Initial substrate weight} - \text{Final substrate weight}}{\text{Coating material loaded}} \times 100 \quad (1.1)$$

1.5.3 Fluidized Bed Coater

Any fluidized bed coating equipment can be adapted for the HMC process. In the pharmaceutical industry, there are five commonly used hot melt coating techniques: top spray, bottom spray, tangential spray, turbo jet, and solid dispersion [2,8,35].



(A) **(B)** **(C)**

Fig. 1.2 : Hot Melt Coating in Fluidized Bed Coater Showing Spray Pattern

The unusual nozzle featured a triaxial shape with a melt-filled centre tube surrounded by a tiny air gap that allowed for the introduction of high-pressure, low-volume air to operate the nozzle's valve. When the pump runs, the valve opens. Both of these tubes were enclosed by a larger air gap through which hot atomisation air was delivered (refer to Figure 1.3). The nozzle should be located near to the substrate bed to reduce the distance that molten droplets must travel before reaching the substrate surface[1,35].

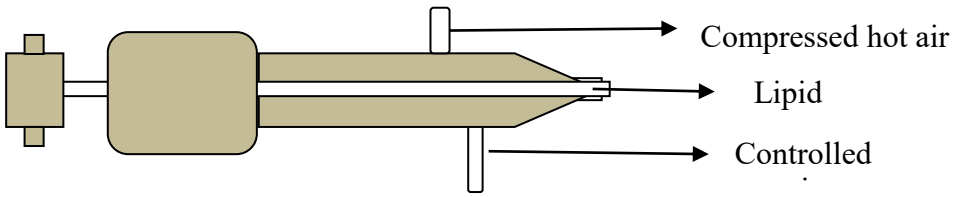


Fig. 1.3: Nozzle for Hot Melt Coating

Top Spray Fluid Bed Coater: The top spray fluidised bed coating technique is the most usual for hot melt application. This technique includes covering core-like grains, particles, or small pellets. The top spray mode sprays molten wax downward onto an upward-moving substrate, making it the more beneficial approach for hot melt coating. In contrast with the other two spray types, the temperature of the substrate should be roughly the same as the temperature at which the wax congeals. The wax must be melted before being sprayed into the fluidised bed.[8]

The top spray method has restricted due to product fluidisation and flow, but it is the best option for hot melt coating since it operates at product temperatures near to the congealing temperatures of the molten excipient. Top spray coating allows for a minimum product temperature above the melting point. The procedure is divided into three steps: (i) melting the hot melt coating materials; (ii) spraying the molten material onto the substrate surface and allowing it to spread; and (iii) congealing the coated substrates. The liquid coating agent is normally held at 40 to 60°C above the melting point, while the substrates are kept at 10 to 20°C below the coating agents' melting points[1].

Bottom Spray Fluid Bed Coater: Bottom spray is an alternative to top spray fluid bed that works well with tiny substrates such as beads, granules, bigger particles, pellets, and spherules. It produces an orderly flow and is suitable for modest coating levels. Large coating levels can be achieved at the expense of the PT/MP ratio.[1,26]

Bottom spray is distinguished by an air distribution plate at the tank's base and a Wurster insert. The distribution plate aids in the dispersion of fluidizing particles inside the expanding zone. The centre of the distribution plate is punctured with holes that are bigger and thicker than the peripheral portions, and the majority of air flows through these holes, dragging particles from the periphery to the centre of the coating zone. The substrate enters the coating zone via the Wurster, a cylindrical tube with a diameter equal to half of the expansion chamber (partition area). When the substrate exits the Wurster, it expands and falls into the tank's outer zone. Distribution plates used for hot melt coating include more holes with larger widths, allowing for more efficient airflow than in typical coating procedures. As a result, particles agglomerate

less.[1] Furthermore, the Wurster position is elevated twice as much to allow for intense substrate fluidisation at first, which decreases as coating thickness increases.[22]

The spray nozzle, which should be insulated without interfering with particle fluidisation, is situated at the bottom of the tank in the centre of the partition area and disperses the lipid with the particle flow (rather than top spray). Substrates with poor fluidisation properties, such as bigger and/or denser particles, are difficult to coat using the top spray mode, hence the bottom spray mode should be used.[1] Additional critical parameters for this type of equipment include the height of the partition area (determined by the size, density and the desired substrate speed), and the type of the distribution plate, which is chosen according to the substrate nature (particles of 50 μm, pellets or tablets).[35]

Tangential Spray Fluid Bed Coater: It is a novel fluid bed system in which the energy from the disk aids in spreading and smoothing the coat is a modification of the equipment used for the fluid bed method. Large coating levels are possible at the expense of the PT/MP ratio. It is mainly used to produce pellets by powder layering (alone, in suspension or solution). The rotor system features the spray nozzle, which is located laterally to the substrate, and the rotating disk (rotor) based at the bottom of the tank. Three mechanical forces cause particle movement, mixing, and granulation. The centrifugal force developed by the rotating disk projects the substrate to the periphery where the fluidization air suspends, and particles gravimetrically fall back on the disk. Relative to the other two fluid bed techniques, particles are exposed to higher mechanical stress therefore substrates that are highly resistant to these forces are well suited for this process. Similarly, to the top or bottom fluid bed systems, the spray nozzle is heated through compressed air and insulated to prevent re-melting of the lipid coat.[1] However, as particle adhesion to the tank is likely the product temperature is kept lower compared to the top spray system. Demerit of this device is its limited capacity.[37]

Solid Dispersion Coating Technique: The solid dispersion coating technique does not require the spraying process. The Wurster columns in the fluid bed coater are devoid of the nozzle spray system in this technique. Hence this technique is the least complicated. The substrate is combined with a coating agent in the fluid bed chamber

due to the temperature inside the chamber by following four simple steps: (i) chamber warming up, (ii) preheating, (iii) melting of coating excipient, and (iv) spreading and cooling-congealing.[8]

The cores and coated excipients are placed in a chamber at high temperatures, which is not very practicable. The method's repeatability was impacted by the porosity and density of the substrates. Nonpareil-sugar beads tend to agglomerate if the particle size is less than 40 mesh for coating agents such as polyethylene glycol (PEG) 1450 to 8000 and methyl PEG 2000–5000. The coating agent's viscosity should be less than 300 centipoises for uniform spreading. Furthermore, this process enables for a low proportion of hot melt coating (2.5 to 5%). In reality, in most circumstances, a larger proportion of coating is necessary for deposition.[1]

This enhanced method was used by Kennedy and co-researchers to prepare chlorpheniramine maleate-coated beads. The tests were conducted on their in-vitro dissolution characteristics. According to reports, a minimum of 15°C should separate the melting temperatures of the two coating agents when applying them via the hot melt fluid bed technique for dual coating.[27,38]

The inherent benefits of fluidised bed coaters, including high particle material flowability, temperature homogeneity, more uniform coating from excellent solids mixing, and shorter process times from rapid heat transfer, make them the preferable choice for coating. Macroscopic and microscopic assessments of the fluidised bed coating processes' quality are possible. Based on the coater's performance, energy, materials, manufacturing time, and yield are taken into account at the previous level.[17]

At the latter stage, the quality of the coating is determined by two factors: the uniformity of the coating mass and the shape of the coating. It is also assessed based on the standard attained and the repeatability of its properties or specifications, such as an active ingredient assay, appearance, dissolution characteristics, particle size distribution, and shelf life. The mass of the final product that satisfies the standards divided by the total mass of materials added to the process is known as the product yield. The differential is an indication of the product losses that happen while coating. Product losses in the fluidised bed coating process are mostly caused by raw materials that exit the system before coating and agglomerated particles whose particle size and

specifications fall outside of the allowable particle size range. These losses typically result from the process's imprecise design.[17]

The quality of the coating is also impacted by improper coating process design. As a result, it is crucial to precisely regulate the process parameters through proper design. This is not a simple undertaking, either, since the fluidised bed coating process is a multifaceted one with a lot of interconnected process factors. The fluidised bed coating involves around twenty different product and process factors, according to Jones.[1] These variables fall into one of three categories: process, equipment, or product variables. The equipment employed determines apparatus factors including the distribution grid, filter mechanism, unit geometry, spray nozzle characteristics, etc. The formula that is applied determines the product's variables.[1,29]

The most significant and readily changing factors are those related to the process, as Scherzinger and Schmidt have shown. Determining these parameters is crucial to creating a successful and controlled process. In spite of the fact that the fluidised bed coating process has been studied and applied for many years in other sectors, the pharmaceutical industry still prefers to employ experience and trial and error to determine the ideal values of these parameters. The literature on how process factors affect the functionality of various fluidised bed systems is scarce.[39]

Turbo Jet Coating: It is designed to coat solid particles by suspending them in an air spiral that ascends, distributing each particle uniformly. Scattered from the tank's bottom and perpendicular to the particle movement is the molten lipid. Here, a microenvironment around the nozzle outlet inhibits lipid crystallisation within the nozzle expansion. Using this method, extremely small suspended particles in the rising air stream may be coated.[1,35]

1.5.4 Direct Blending

HMC direct blending is the most straightforward way for coating particles. The method works with a variety of substrate sizes and many coated layers, and while it doesn't require sophisticated equipment, the results are surprisingly excellent. It involves the five phases listed below: (i) The coating agent melting; (ii) Drug dissolution or dispersion in the molten coating material; (iii) Thoroughly mixing the

molten coating agent with the substrate; (iv) Cooling while stirring the mixture continuously; and (v) Congealing the coated particles. [1]

Granules can be used to deposit the active substance in the core, and a coating layer can subsequently be applied to the exterior. Another option is to combine the medication with the coating agent and coat the exterior of the coating core. Commercially, sugar beads in a range of sizes are premade. fragments. Wax formulations for coating drug-loaded sugar beads have been investigated by Bhagwatwar and Bodmeier. These sugar beads are homogenous in size and shape and easily adhere to waxes. Customers can select an appropriate size of sugar beads for a reasonable price. The smaller the size of the substrate, the larger will be the surface area available for the coating agent to deposit onto. In this technique very small modification is done that is molten coating material contains less than 10% solvent.[40]

Gaining weight while coating might be rather significant. The variability of the coated beads is increased by the likelihood of agglomeration of minuscule particles, therefore proper control over coating and mixing is necessary to prevent variability. The procedure is most straightforward to achieve substantial weight increases using ready-made substrates if the core is large enough in surface area but not too tiny in size (to prevent agglomeration). Stated otherwise, it is ideal for the coated beads to have a high medication content while minimising variability. It has been discovered that the size range of sugar beads—30 to 60 mesh—works well for laboratory-scale research initiatives.

Although nifedipine is light-sensitive, its behaviour at high temperatures has not yet been documented. Therefore, it is important to thoroughly examine the active substance's thermal stability. Furthermore, sucrose, the ingredient in sugar beads, burns readily at high temperatures. Thus, 100°C is the limiting temperature. Applying a molten coating substance to beads or capsules in a heated tablet coating pan is known as hot melt direct mixing coating. Cetyl alcohol and Gelucire® (Gelucire) 50/13 were employed as coating agents in the hot melt pan coating.[1,41]

1.6 Hot Melt Coating Agents

Hot melt coating materials come from synthetic, semi-synthetic, and natural sources. Pharmaceutical firms may now generate a variety of fatty compounds with several

aliphatic carbon molecules attached to both the main chain and its branches thanks to advancements in technology. It is possible to introduce several kinds of substitution into the molecular structure.[8] The physicochemical criteria of flexibility, hydrophobicity, melting point, molecular weight, rheological behaviour, and stiffness might offer valuable insights into the correlation between the capacity of excipients to prolong drug release.[42]

Table 1.2 : Hot Melt Coating Agents[8,35]

Excipients	Chemical composition	Characteristics	Applications	Examples
Animal fats	Clarified butter	MP ≈ 80°C	Modified release	Cow ghee.
Fatty acids	Long chain fatty acids	MP = 60-90°C	Modified release	Behenic acid, Palmitic acid, Stearic acid.
Fatty alcohol	Long chain fatty alcohol	MP = 50-55°C	Modified release, Taste-masking	Cetyl alcohol, Wool alcohol.
Partial glycerides	Mixtures of mono-, di-and triglycerides	MP = 54-74°C	Modified release, Taste-masking, Lubrication.	Compritol® 888 ATO, Myvaplex™ 600, Precirol ATO 5.
Polyoxyl-glycerides	Mixture of glycerides and esters of fatty acid and PEG	MP ≈ 50°C, partially digestible.	Immediate release, Modified release.	Gelucire® 50/02, Gelucire® 50/13.
Vegetables oils	Mixture of triglycerides, Free fatty acids, and phospholipids.	MP = 60-71°C, often digestible.	Taste-masking, Modified release.	Hydrogenated cottonseed oil, Hydrogenated palm oil, Hydrogenated soybean oil.

Excipients	Chemical composition	Characteristics	Applications	Examples
Waxes	Esters of fatty acids and long chain alcohols.	MP = 62-86°C, hydrophobic.	Modified release.	Beeswax, Carnauba wax, Candelilla wax, Rice bran wax, Hydrogenated jojoba oil.

Where, MP is melting point in °C.

1.6.1 Challenges in Use of Lipids as HMC Agent

Lipids, namely fatty acids and unsaturated triglycerides, are susceptible to oxidation. It occurs during manufacture or storage and reduces the quality of the finished product. When exposed to light, air, or temperature, lipids can self-oxidize. This might result in a change in texture, colour, rancid flavour, or quality loss, as well as the production of toxic substances that endanger the patient's health. Lipoxygenase is an enzyme that catalyses other degradation processes. Iron, copper, and cobalt traces, for example, can considerably promote oxidation. Auto-oxidation appears to be a significant and complex lipid oxidation mechanism. It typically creates volatile compounds and hydroperoxides in three steps (initiation, propagation, and termination).

Nitrogen flushing can help to prevent oxidation in closed systems such as capsules. Chelating compounds, such as citric acid or EDTA, can be used in place of metal-based catalysts. Karabulut and other scientists have published and explored several strategies for using antioxidants to inhibit oxidation processes. One of the key antioxidants, α tocopherol, breaks up free-radical chain reactions by giving them electrons or hydrogen, converting them into more stable forms. Antioxidants inhibit oxidation by methods such as ascorbic acid deactivating singlet oxygen, ascorbyl palmitate scavenging free radicals, and β-carotene chain-breaking.

Antioxidant blends can be used to combine their effects. Several analytical approaches may be used to analyse the effects of antioxidants on oxidative stability, including peroxide value for primary oxidation and p-anisidine value for secondary

oxidation products, scanning calorimetry, and thermogravimetric analysis. Cyclic voltammetry is a quick approach for finding excipients that make the medicine more susceptible to oxidation, as well as screening antioxidants.

1.6.2 Regulatory Issues in Use of Lipids as HMC Agent

From a regulatory standpoint, the key challenges in releasing a lipid-based dosage form on the market will be quality and safety problems connected to preclinical and clinical research, as well as the proof of therapeutic efficacy. The overall medication stability and the lack of immunological responses to oils or lipids must be established. To persuade regulatory authorities of their acceptance, sufficient information on the use of lipids, the varieties of dosage forms, the drug release mechanism, and their manufacture should be supplied.

A Consortium of academics and industrial scientists has been formed to rationalise the design of HMC lipid formulations and better understand the destiny of a medicine following oral delivery in an HMC lipid formulation (www.lfcsconsortium.org). The Consortium funds and conducts research to develop in-vitro methodologies for evaluating the effectiveness of lipid-based drug delivery systems during dispersion and digestion, which are essential criteria.

The major goal is to provide guidelines that rationalise and expedite the development of drug candidates by identifying important performance criteria, validating and eventually publishing universal standard tests and operational processes. In order to produce acceptable criteria, relevant communication with pharmaceutical regulatory agencies (FDA, EMEA) is also planned.

1.7 Evaluation of Hot Melt Coating Agents

Harvesting vegetable or insect waxes is frequently done from non-cultivated natural sources with complicated compositions. As a result, it is critical to standardise waxes utilising their chemical and physical characteristics. Natural materials' composition varies greatly depending on location, weather, harvest season, and age. Quality monitoring of raw materials is critical for producing high-quality pharmaceutical products. Waxes are characterised using physical measures such as melting temperature, refractive index, polymorphism, specific gravity, and viscosity.

Chemical approaches for characterising waxes include determining the acid, iodine, and saponification values, among others. [43-57]

1.7.1 Physical Characterization

Color: The colour of the wax will influence the colour of the final result. A Lovibond tintometer is commonly used for colour measurements, comparing the colour of the raw material to a series of coloured standard glasses under a standard light source. The colour of the solidified wax in the same sample might vary based on the quantity of occluded air, the velocity of cooling, and the surface quality. As a result, many waxes' colours are best assessed when they are still molten. Two ASTM colour standards are used to measure the colour range of dark brown to off-white and off-white to pure white.

Dilatometry: Wax expansion or contraction is also crucial during wax melt processing, such as microparticle production via spray congealing, hot-melt coating, or hot-melt filling of hard gelatin capsules. A dilatometer can quantify wax dilatation or heat expansion during the solid-liquid transition.[4]

Goniometry: Goniometry is the measurement of the contact angle between the lipid coated surface and a droplet of water. It is commonly used to determine the hydrophobicity of a coating agent. This simple approach allows for a rough estimate of the coating's influence on drug release: drug release rate reduces as the hydrophobicity of the lipid coating increases.[1]

Hardness: The hardness of a wax is determined by a penetration test, which measures the extent of passage of a needle under an appropriate weight, ideally at different temperatures.[1]

Melting Point and Polymorphism: Various tests to determine the melting point of waxes often produce varied results. Because waxes are non-homogeneous in chemical composition, a melting range rather than a specific melting point is most commonly seen. The melting point of glycerides rises with increasing hydroxyl number, decreasing unsaturation, and rising fatty acid molecular weight. Capillary tubes are useful for determining the melting point of several waxes. It is critical to understand the thermal behaviour of a lipid excipient when used for coating since the procedure

involves melting and, in some circumstances, exposure to temperatures approaching 150°C.[1]

Therefore, ideally, the lipid should possess the following thermal properties: (i) physicochemical stability at temperatures up to 150°C; (ii) melting points no higher than 85°C since the product is maintained 40-60°C above during the coating process; (iii) a narrow melting range to prevent sticking, a consequence of low melting point fractions agglomerating the coating substrates; (iv) a stable fusion/crystallization profile, i.e. not affected by the storage conditions and thermal history. It is well known that lipids are chemically complicated, with a wide melting range. The melting point typically rises with the hydroxyl value and/or molar mass and falls with the degree of unsaturation.[1]

Differential scanning calorimetry (DSC) is an important technique for determining the thermal behaviour of lipid excipients, such as their melting and solidification temperatures, phase transition temperature, and solid/liquid ratio. DSC can be used with X-ray diffraction (XRD) to acquire a better understanding of the polymorphic behaviour of lipid excipients. This combination allows for the understanding of morphological and structural changes during these heat episodes. The thermal history of a glyceride affects its composition in terms of crystal structures comprising (i) hexagonal (α), (ii) orthorhombic (β'), and/or (iii) triclinic (β), with various polymorphic transition temperatures and melting points. [1]

Glyceride polymorphism may often be regulated by tempering the lipid about its melting point for a set period of time or by managing the pace of crystallisation. Crystallisation towards the thermodynamically most stable state can be done by seeding hydrogenated vegetable oils with triclinic crystals (0.1-30.0 wt%).[1] It should be noted that polyethylene glycols utilised as coating agents, whether alone or in conjunction with lipids (e.g., polyoxyl glycerides), display polymorphism. Again, this may be managed with the proper heat treatment.[4]

Slip Point Test: The slip point is the temperature at which a column of testing material begins to rise in an open-ended capillary tube dipped in water, filled in a beaker, and heated under specified circumstances. [4]

Drop Point Test: The drop-point test can be employed; however, it is not accurate for thicker waxes. The congealing point of a wax is the temperature at which the molten wax ceases to flow after cooling. Thermal techniques such as differential scanning calorimetry (DSC) are commonly used to characterise the heating and cooling patterns of waxes in both qualitative and quantitative terms. Running multiple temperature profiles allows you to model potential polymorphic transitions and recrystallisation during the operation.[4]

Smoke Point: The smoke point is the temperature at which a sample begins to smoke when evaluated under specific conditions. The temperature at which a thin, continuous stream of bluish smoke initially appears. [4]

Flash Point: The flash point is the temperature at which a flash emerges anywhere on the sample's surface as a result of the ignition of volatile gaseous products. The fire point is the temperature at which the development of volatiles caused by the thermal breakdown of lipids is sufficiently rapid that continuous combustion occurs. The Wiley melting point is the temperature at which a disc transforms shape into a spherical. [1]

Cloud Point: Cloud point refers to the temperature at which crystallisation begins in liquid oil. It is frequently practical to have oil that does not crystallise when kept at 0°C for an extended length of time. A simple test to measure lipids' capacity to survive low temperatures without crystallisation. [4]

Refractive Index: The sample (10 g) was melted in a water bath (60°C continuous temperature) until a clear solution was formed. The refractive index was obtained using an Abbe's refractometer. A drop of molten Sample was put on the surface of Prism A. The liquid forms a film when the two prisms A and B are clamped together. The light reflected by mirror M is subsequently directed towards the prism system. When light strikes the ground surface of A, it scatters into the liquid film.

This light is separated into bright and dark areas. When the edge of the brilliant area corresponds with the refractometer's cross wire, write the refractive index on the scale. A sodium vapour lamp or a mercury vapour lamp is used as a light source. The refractometer should be calibrated using distilled water, which has a refractive index of 1.3325 at 25°C.[4]

Viscosity: The viscosity of the molten wax is an essential characteristic, particularly in operations that include wax melts, such as hot melt coating or spray congealing. An ASTM monograph (D 88) measures the time necessary for a specific amount of melted wax to flow through a specified aperture. The viscosity of the lipid as a function of temperature must be determined in order to guarantee that the molten lipid has a low enough viscosity to flow continuously through the peristaltic pump and nozzle during substrate coating. The molten lipid excipient typically has a viscosity of less than 300 cPs at 80°C. [1]

Water Sorption: Water sorption/desorption isotherms determined by Dynamic Vapour Sorption (DVS) demonstrate the behaviour of lipid excipients under regulated relative humidity. This information is relevant when considering using a lipid coating to protect a water-sensitive chemical from the effects of relative humidity. For example, lipophilic films made of Compritol® 888 ATO produce a particularly efficient barrier against water vapour, protecting substrates from relative humidity and deterioration.

1.7.2 Chemical Characterization

Standardization of coating agents is necessary as they were obtained from natural sources. The samples were evaluated for various analytical tests like acid value, Reichert-Meissl value, Polenske value, iodine value, peroxide value, saponification value, refractive index etc .[45-47]

Acid value: The number of milligrams of potassium hydroxide required to neutralize 1 gram of the fat called as acid value. The excipient is dissolved in a mixture of ethanol and diethyl ether and titrated with a dilute alkali solution.[16]

Reagents

1. Ethanolic potassium hydroxide solution (0.1N)
2. Mixture of equal volumes of ethanol (96% v/v) or of ethanol denatured with methanol and diethyl ether
3. Neutral solution of phenolphthalein 1% w/v in ethanol (96% v/v), or in ethanol denatured with methanol. All the reagents should be of analytical grade.

Procedure: Accurately weighed 5 to 10 g of the material was accurately weighed and placed in a 250 mL conical flask. The flask was filled with approximately 50-100 ml of the ethanol-ether combination, which was properly mixed before adding 0.1 ml of phenolphthalein solution. The aforementioned mixture was gently heated in a water bath (if required) until completely melted, then titrated with 0.1N potassium hydroxide while shaking continuously until a faint pink colour lasted for 15 seconds.[4] The acid value was calculated by using equation.

$$\text{Acid value} = V \times 0.0561 \times 1000 / W \quad (1.2)$$

Where, V = volume in ml of 0.1N KOH solution consumed during the titration

W = weight of sample taken for analysis

Soluble volatile fatty acid value (Reichert Meissl value): This is a reference method for the determination of water-soluble fatty acid value. The soluble volatile fatty acid value is the number of millilitres of aqueous 0.1N alkali solution needed to neutralise the water-soluble volatile fatty acids extracted from 5 gms of fat under the method's specified conditions. After saponifying the fat using a solution of sodium hydroxide in glycerin the soap solution was diluted with water and acidified with sulphuric acid. The volatile fatty acids were distilled, while the insoluble fatty acids were separated from the soluble acids using filtering. The aqueous solution of soluble acids and the ethanolic solution of insoluble acids were then titrated independently with a standardised alkali solution. The procedure was empirical, as it only determined a subset of these acid[4]. Specifications for procedure and apparatus must be followed rigorously to obtain accurate and reproducible results.

Reagents

Glycerin (density = 1.26 g/ml or 98 % w/w)

Sodium hydroxide solution in distilled water (44% w/w), stored in a bottle protected from carbon dioxide (use clear portion free from carbonate deposit).

Distilled water made free from carbon dioxide by boiling for 15 min

Sulphuric acid solution (1N)

Sodium or potassium hydroxide solution in distilled water (0.1N) accurately standardized.

Phenolphthalein indicator solution (1% in 96% ethanol)

Ethanol (96% v/v) neutral to phenolphthalein.[16]

Procedure: Accurately weighed 5.00 ± 0.01 g of the sample was transferred into a 250 ml conical flask. 20 g (16 ml) of glycerol and 2 ml of the sodium hydroxide solution (44% w/w) were added to a sample containing a conical flask. The conical flask was heated over a naked flame, overheating was avoided and shaken continuously until the liquid no longer foams and becomes clear. The flask was allowed to cool to about 90°C, 90 ml of freshly boiled distilled water was added at about the same temperature and mixed. The liquid remained clear. Pumice about 0.6 to 0.7 g and 50 ml Sulphuric acid solution (1N) was added to the flask. The flask was quickly connected to the distillation apparatus. The flask was warmed gently until the free fatty acids formed a clear surface layer.[4]

Heating was initiated, and the flame was adjusted such that 110 ml of distillate was collected in the measuring cylinder in 19 to 21 min, with the first drop in the condenser marking the start of the distillation period. The condenser's water flow was adjusted to maintain a temperature of 20 ± 1°C for 1 hour. When exactly 110 ml of distillate was obtained, the burner was turned off immediately and the measuring flask was replaced with a tiny beaker. The contents of the measuring flask were gently shaken. The flask was submerged in a water bath at 20 ± 1°C for 10-15 minutes.[4,16]

The 110 ml mark on the flask is 1 cm below the level of the water in the water bath, and the flask is rotated periodically. The flask was sealed and mixed by inverting it four or five times without shaking. The 110 ml of distillate was filtered using a dry medium-speed filter paper that fits tightly into the funnel. The filtrate was clear (Note: The filter should be large enough to fill entirely with 15 ml). About 100 ml of the filtrate was transferred to a 300-ml conical flask, and 0.5 ml of phenolphthalein indicator solution was added to the filtrate. It was titrated with the standardized aqueous alkali solution (0.1N) to a pink color persistent for 0.5 to 1 min.[4,16]

A blank test with no sample was also performed, and instead of saponifying the sample over a naked flame, it was cooked in a boiling water bath for 15 minutes. (Note: The titration should not take more than 0.5 ml of the standardised alkali solution. Otherwise, new reagent solutions need to be produced.[4] The soluble volatile fatty acid value (RM value) was computed using an equation.

$$RM\ value = 11 \times N \times (V1 - B) \quad (1.3)$$

Where, V1 = number of ml standardized alkali solution (0.1N) required for the sample

B = number of ml of standardized alkali solution (0.1N) required for the blank test

N = exact normality of the standardized alkali solution (0.1N)[7]

Insoluble Volatile Fatty Acid Value (Polenske Value): The insoluble volatile fatty acid value (Polenske value) is the number of milliliters of aqueous 0.1N alkali solution required to neutralize the water-insoluble volatile fatty acids obtained from 5 gram of fat under the specific conditions of method.[4]

Procedure: The filter was washed with three 15 ml volumes of distilled water at 20 ± 1°C. The funnel and filter were inserted in the neck of a dry clean 200 mL conical flask. The insoluble fatty acids were dissolved by repeating the washing operation with 15 ml portions of 96% ethanol. The combined ethanolic washings were titrated with a standardised aqueous alkali solution (0.1N) and 0.5 mL of phenolphthalein indicator solution to produce a pink hue that lasted for 0.5 to 1 minute.[7]

Calculations: Insoluble volatile fatty acid value i.e., Polenske value was calculated using equation.

$$Polenske\ value = 10 \times N \times V_2 \quad (1.4)$$

Where, V_2 = ml of standardized alkali solution (0.1 N) required for the sample

N = exact normality of the standardized alkali solution (0.1N)

The difference between results of triplicate determinations (results obtained simultaneously or in rapid succession by the same analyst) should not exceed 0.5 for the Reichert Meissl value and 0.3 for the Polenske value.[7]

Iodine Value: It measures the unsaturation of lipids and hence their oxidative potential. The sample interacts with iodine, resulting in the addition of iodine to the C=C double bond. Iodine trichloride interacts with the unsaturated bonds to form a dihalogenated single bond, with one carbon linked to an iodine atom. The iodine value is the number of milligrams of iodine absorbed per 100 grammes of sample. In this procedure, the sample is treated with an excessive quantity of iodine. Back titration with sodium thiosulphate solution is used to measure free iodine, with starch solution serving as an indicator.[7]

Iodine Value Using Wijs Method[16]

Reagents

1. Wijs reagent
2. Carbon tetrachloride inert to Wijs solution
3. 10% potassium iodide solution free from iodine and iodates
4. 0.1N sodium thiosulphate solution and starch solution

Preparation Of Wijs Reagent: Approximately 9 g of iodine- trichloride was dissolved in 1000 ml of a solution containing 700 ml of concentrated acetic acid (99 to 100%) and 300 ml of carbon tetrachloride, both devoid of oxidisable materials. The halogen content can be calculated in the following manner: A burette was used to accurately measure 5 ml of the solution, which was then added to the flask. In addition, 5 mL of 10% potassium iodide solution and 30 mL of water were added to the flask. Titration was carried out with 0.1N sodium thiosulphate solution and starch solution as an indicator. The starch solution was introduced just before the conclusion of the titration.[16]

After determining the halogen concentration of the iodine trichloride solution, 10 g of iodine powder was added and spun until enough iodine had dissolved to boost the halogen content to more than 1.5 times the initial value. The content was filtered or decanted to produce a clear solution, which was then diluted with a combination of acetic acid and carbon tetrachloride until 5 ml of the solution equalled 10 ml of the 0.1N sodium thiosulphate solution. The solution was kept in a dark, carefully sealed amber-coloured stoppered glass container. [16]

Preparation Of Starch Solution: Weighed 5 g of soluble starch and 10 mg of mercuric iodide were mixed in 30 ml distilled water. It was then transferred to 1000 ml of boiling water and boiled further for 3 min.[4]

Preparation Of Sample: For the determination of the iodine value molten, clear, filtered and well-mixed sample was used.[4]

Procedure: About 0.4 to 0.45 g of the material was accurately weighed and placed in a clean, dry Erlenmeyer flask. The sample was dissolved in 15 ml of carbon tetrachloride, and 25 ml of Wijs reagent was added to the mixture using a burette. The flask was capped with a stopper, gently mixed, and let to stand in the dark for 1 hour.

About 20 ml of potassium iodide solution was combined with 150 ml of purified water and stirred. Titration was performed with 0.1N sodium thiosulphate solution (using 2 ml of starch solution as an indicator) while stirring the liquid continually. The starch solution was added shortly before the end of the titration. A blank test was carried out, using the same quantities of the reagents without a sample.[7] The iodine value was calculated by means of the equation.

$$\text{Iodine value} = 1.269\ (b - a) / w \qquad (1.5)$$

Where, a = number of ml of 0.1 N sodium thiosulphate used in the blank test,

b = number of ml of 0.1 N sodium thiosulphate solution used in the titration with the sample present and

w = weight of sample taken for the analysis

The results of triplicate determinations should not differ by more than 0.4.

Peroxide Value: The peroxide value is the amount of milligram of oxygen per kilogram of anhydrous fat. When performed in conjunction with other tests during shelf-life research, the peroxide value (PV) test can help predict shelf-life. However, it is not always effective in quality control, particularly in the absence of sensory evaluation and other testing. There are various recognised processes and routes for lipid degradation and the associated formation of rancid odours. Although an analytical chemist can employ a variety of procedures to detect chemical indications of rancidity, a single test is not always convincing.[7]

Procedure: About 5.0 g sample was accurately weighed and transferred to a 250 mL stoppered conical flask. Approximately 30 ml of a combination of 3 volumes glacial acetic acid and 2 volumes chloroform was spun until the sample was completely dissolved. A standard saturated potassium iodide solution (0.5 mL) was added to the flask contents. The mixture was let to stand for exactly one minute while shaking. To the aforementioned combination, 30 ml of water was added and progressively titrated with 0.01M sodium thiosulphate while shaking continuously and vigorously until the yellow colour faded. About 0.5 mL of starch solution was added, and the titration was aggressively maintained until the blue colour had completely faded.[24] The procedure was repeated for blank titration without a sample (b mL). The volume of 0.01M

sodium thiosulphate in the blank determination must be NMT 0.1 mL. The peroxide value is calculated using equation.

$$\text{Peroxide value} = 10\ (a - b) / w \qquad (1.6)$$

Where, w = weight of sample used for analysis

Saponification Value: It is the number of milligrams of potassium hydroxide necessary to neutralise the fatty acids produced by the full hydrolysis of one gramme of fat. It provides information on the fatty acid composition of the fats; the longer the carbon chain, the less acid is freed per gramme of fat hydrolysed. It is also regarded as a measure of the average molecular weight (or chain length) of all fatty acids present. Long-chain fatty acids present in fats have a low saponification value because they contain fewer carboxylic functional groups per unit amount of fat and so have a high molecular weight.[7]

Method: About 2 g of sample was accurately weighed and transferred to a 250 mL borosilicate glass flask with a reflux condenser. The flask contained approximately 25 ml of 0.5M ethanolic potassium hydroxide and a little amount of pumice powder. The mixture was heated under reflux on a water bath for 30 minutes, then 1 ml of phenolphthalein solution was added and promptly titrated with 0.5N hydrochloric acid solution. The technique was repeated for blank titration without a sample (b mL).[4,15] The saponification value was calculated using equation.

$$\text{Saponification value} = 28.05\ (b - a) / w \qquad (1.7)$$

Where, w = weight of sample in g used for analysis

Determination of Refractive Index: The 10 g sample was melted in a water bath (90°C constant temperature) till a clear solution was obtained. The refractive index was determined on Abbe's refractometer by the following method.

Method: A drop of molten sample was placed upon the surface of the prism A. On clamping the two prisms A and B, the liquid spreads as a film. Light reflected by a mirror M was then directed towards the prism system. On reaching the ground surface of prism A, the light scatters into the liquid film. This light is divided into bright and dark portions. When the edge of the bright portion coincides with the cross wire of the refractometer, the refractive index is noted on the scale. A sodium vapor lamp was

used as a light source. The refractometer should be calibrated against distilled water, which has a refractive index of 1.3325 at 25°C.[4]

1.8 Oral Solid Dosage Forms

Oral solid dosage forms can be classified into 4 groups:

- Single units.
- Multi-particulates (pellets or granules).
- Multi-particulates in tablets and
- Multi-particulates in hard capsules.

A concept of multiple-unit dosage forms was first put forward in the early 1950s. They play a vital part in the development of solid dosage form processes due to their unique characteristics and manufacturing flexibility. These forms can be characterised as oral dosage forms made up of a number of small discrete units, each with certain desirable properties. These characteristic units work together to give the correct adjusted dosage release. These numerous units are also known as pellets, spherical granules, or spheroids.[5] In recent years, there has been an increasing interest in the topic of pelletisation, which produces spherical pellets that may be converted into various dosage forms such as tablets and capsules or delivered directly.[12] Pelletization involves a size enlargement process and if the final agglomerates are spherical in the size range of 0.3 to 1.5 mm, they are called pellets. [63]

1.8.1 Merits of Multi-Unit Drug Delivery Systems[64-70]

- Greater flexibility of dosage form design and development
- Ease of coating
- Ease of capsule filling or tableting
- Improved elegance, product identification, and patient compliance
- Ease of design of modified-release formulations containing more than one drug
- Ease of drug dissolution and analysis
- Greater stability of chemically incompatible drugs
- Ease of dose divisibility
- Greater safety and efficacy of drugs
- Lowered tendency for dose dumping

- Reproducibility of plasma profile and therapeutic effect
- Market edge

1.8.2 Merits of Single Unit Dosage Forms

- Greater stability
- Uniform dosing
- Ease in administration
- Accuracy in dose
- Better therapeutic efficacy
- Compact and hence have higher bioavailability.
- Greater stability of chemically incompatible drugs
- Can be available in variety of release profile.
- Suitability for administration by oral, vaginal, and rectal route

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CHAPTER – II

REVIEW OF LITERATURE

2 Review of Literature

2.1 Hot Melt Coating

Patel N, et al., (2021) developed lipid based oral controlled release formulation system for anti-epileptic drug Oxcarbazepine using HMC. The active ingredient in core pellets was prepared using extrusion Spheronization and coated with hot-melt coating technology. The formulation and process parameters were optimized to achieve a targeted drug release profile and product profile, with a focus on HMCP. Quality by design (QbD) with DOE approach was used for formulation development, involving risk assessment, screening, and optimization studies. The study found that the drug release rate in a formulation is influenced by the level of low melting coating component and hydrophilic component, and can be optimized by adjusting these components. Other factors like coating temperature, atomization air, pressure, spray rate, coating efficiency, and particle size also impact the release rate. The dissolution data model fitting to the Higuchi model suggests drug release is predominantly by diffusion.[1]

Bannow J, et al., (2020) performed hot melt coating of amorphous carvedilol. Amorphous drug delivery systems can improve bioavailability of low molecular weight drugs with poor aqueous solubility. However, these drugs often suffer from recrystallization during storage and lumping upon dissolution. This study used hot melt coating (HMC) to coat amorphous carvedilol particles with tripalmitin containing 10% and 20% of polysorbate 65 (PS65) in a fluid bed coater. The lipid coated particles were evaluated for their stability during storage and drug release during dynamic in vitro lipolysis. The release of CRV during lipolysis is primarily dependent on the concentration of PS65 in the coating layer. A 20% concentration results in an immediate release profile. However, the lipid coating negatively affects the physical stability of the amorphous CRV core, leading to recrystallization at the interface between the crystalline lipid layer and the drug core. The study suggests lipid spray coating as a viable strategy for modifying drug release from amorphous systems.[2]

Diogo G L, et al., (2017) reviewed hot-melt coating as a solvent-free technology grants faster and more economic coating processes with reduced risk of dissolving the drug during the process. The HMC process, which can be modified to enable

traditional coating equipment, has advantages and is still limited in the pharmaceutical industry due to the need for alternative materials. The review focuses on HMC formulations and their properties, particularly their crystallization and solid-state behavior, which impact the performance of coated drug products, particularly on the stable drug release profile. The need for alternative materials is a major obstacle to widespread application. The development of stable formulations for pharmaceutical products requires extensive work, requiring a mechanistic understanding of macroscopic properties and stable solid-state behavior. This is crucial for the successful implementation of HMC as an advanced coating technology.[3]

Jannin V, et al., (2013) reviewed on hot melt coating with lipid excipients highlights their use in drug protection, taste masking, coloration, and modified drug release. These coatings require dilution or dispersion in solvents and gliding agents to prevent particle sticking. Lipid excipients offer an attractive alternative to standard polymer coatings as they only require melting before application directly onto the substrate.[4]

Tiwari R, et al., (2013) developed and optimized oral controlled-release formulations for highly water-soluble model drug Venlafaxine hydrochloride using a combination of hot melt sub-coatings-based coating polymer and aqueous polymer coating. The hot melt sub-coating was achieved using a centrifugal granulator, while Acrylate-based polymer coatings (Eudragit RS 30D and Eudragit NE 30D) were used. The study found that using hot melt sub-coating reduced the polymer coating level of pellets by half, resulting in a sustained release profile. The study found that the optimal release profile for pellets was achieved at a 4% level of hot melt sub coating and 15% level of Eudragit® NE30D polymer coating combination. This technique successfully prepared sustained-release pellets containing venlafaxine hydrochloride, satisfying the first order plot with a R2 = 0.9434, indicating the release of water-soluble drug from porous matrices.[5]

Patil A, et al., (2012) demonstrated utility of hot melt coating technique for enteric coating. Pellets made from extrusion-spheronization were chosen as the core for diclofenac sodium due to their advantages over single-unit formulations. Stearic acid and palmitic acid were evaluated as enteric hot melt coating materials. The coating

was carried out in a modified pan, achieving a 5-15% w/w coating level. The results showed excellent enteric coating ability of both SA and PA.[6]

Homar M, et al., (2011) prepared immediate release clarithromycin microparticles using a hot melt fluid bed technique. Key process parameters were identified and optimized during course of study. Their influence on process yields and microparticles characteristics was determined. % yield was around 70% and 60% in the case of PEG and poloxamer 188 respectively. The dissolution rate and equilibrium concentration of clarithromycin released from prepared microparticles was improved compared to similar particles prepared by wet granulation.[7]

Guan T, et al., (2011) The study compared the stability of venlafaxine hydrochloride sustained-release pellets, which were prepared using double-polymer coatings, hot melt sub-coating, and Eudragit® NE30D outer coating, ensuring drug dissolution met standard requirements and acceptable storage stability.[8]

Chandrikapure PL, et al., (2011) utilized cetyl alcohol and beeswax as hot melt coating agents in preparation of multi-particulate sustained release formulations for water soluble drug like diclofenac sodium. Targeted release profile cannot achieve by the use of either cetyl alcohol or beeswax. Therefore, ethyl cellulose was used as rate controlling polymer in combination with cetyl alcohol or beeswax. [9]

Patil A, et al., (2011) demonstrates the use of hot melt coating to mask bitter or unpleasant tastes in bromhexine hydrochloride and salbutamol sulphate pellets. Beeswax and cetyl alcohol were evaluated as hot melt coating materials. The panel method determined the threshold bitterness concentrations and taste evaluation of the coated pellets. Beeswax and cetyl alcohol were found to be better taste masking agents at 5% coating level.[10]

Chen H, et al., (2010) used extrusion-spheronization and hot melt coating technologies to enhance moisture-proofing of Guizhi Fuling (GF) compound herbal extracts. The pellets were coated with a 96:4 mixture of stearic acid and polyethylene glycol 6000, resulting in better moisture-proofing than Opadry AMB due to different moisture sorption mechanisms. The Higuchi model was the best fit for the hot melt coating, while Opadry AMB fitted the Nuttanan model.[11]

Patel JU, et al., (2010) prepared Ranolazine sustained release tablets using hot melt coating technique. The pH-dependent binders Eudragit L100® 55 inhibit rapid release of drugs from a tablet during residence time in stomach. Ranolazine tablets were coated with hydroxypropyl methyl cellulose phthalate, hydrogenated castor oil using hot melt coating technique. In vitro drug dissolution study proved that amount of drug release was depends upon concentration of rate controlling polymer Eudragit L100® 55 present in the formulation. The drug release in stomach was negligible in 2 hrs. The drug release from sustained release occurred by diffusion of drug from tablet, reflects Higuchi model.[12]

Sakarkar DM, et al., (2009) studied has developed sustained release pellets of diclofenac using cow ghee as a hot melt coating agent. The study found that the release from the pellets depends on the drug's physicochemical properties, specifically its aqueous solubility. The study successfully prepared these pellets by using cow ghee and ethyl cellulose as a coating agent.[13]

Knezevic Z, et al., (2009) utilized hot melt coating process for designing a lipid based controlled release drug delivery system of paracetamol. The study analyzed the effects of varying lipid levels on the release pattern of paracetamol granules, which were then compressed into tablets. The results showed that the granule composition can affect the drug release rate, and the lactose-based formulation with 9% lipid coating was found to be suitable for controlled delivery over 12 hours, making it suitable for highly water-soluble drug candidates like paracetamol with a twice daily dose regimen. Moreover, the dissolution data adequately fitted into Higuchi model suggesting that the drug release occurred predominantly by diffusion.[14]

Pham LT, et al., (2009) prepared controlled release of acetaminophen (APAP) beads using hot melt coating by direct blending method. The single and dual coated beads were coated by hot melt coating using oleaginous waxes to achieve near zero-order release pattern. The beads were prepared by coating sugar spheres (420-500 μm) with thirteen different waxes containing APAP by direct blending. The efficiency of drug loading was 75-85% depending on the wax used. The drug release rate profiles from the beads followed pattern that was consistent with the hardness of the waxes. The drug release was observed to be faster in case of softer waxes and slower in case of

harder waxes. Initial burst of drug release was observed in single coated beads while a lag time in drug release was observed in dual coated beads. The convolution predicted therapeutic plasma APAP concentrations lasting 16 hr for dual coated beads. The hot melt dual coating by direct blending released APAP in a consistent near zero-order release pattern for 16-24 hr.[15]

Yang ZY, et al., (2008) Pseudoephedrine hydrochloride sustained release pellets were prepared using a combination of hot melt sub-coating and polymer coating. The pellets met USP-29 dissolution requirements for extended-release capsules. The polymer coating level was reduced by half due to the hot melt sub-coating. This technology successfully prepared sustained release pellets containing pseudoephedrine hydrochloride, meeting the dissolution requirement.[16]

Padsalgi A, et al., (2008) prepared sustained release tablets of theophylline by using hot melt wax coating technology. The effect of different coating technique i.e., pan spray method and pan pour method and the effect of different pore former like sodium lauryl sulfate (SLS) and hydroxypropyl methyl cellulose (HPMC) on release pattern of theophylline for SR tablets were studied. The pan spray technique was reported as the best technique than pan pour method, and faster release was seen when SLS was used as a pore former in lower concentration than HPMC.[17]

Homar M, et al., (2008) fabricated immediate release and prolonged release microparticles using hot melt fluid bed technique. Hot melt methods use molten or softened materials like polymers, waxes, and lipids as binders in solid dosage forms like tablets, microparticles, pellets, and granules. Fluid bed technology is used to prepare agglomerates using meltable binders like polyethylene glycol, poloxamer 188, Gelucire 50/13, or glyceryl monostearate. The study examines the mechanism of agglomerate growth, binder droplet size, viscosity, starting material size, and binder type. Microparticles are characterized by their dissolution rate of clarithromycin.[18]

Chansanroj K, et al., (2007) designed multi-unit floating drug delivery system using hot melt coating technique. A study on metoprolol tartrate and hydrogenated soybean oil (HSO) was conducted to develop multi-unit floating drug delivery systems. The drug was coated on inert nonpareils in a fluid bed chamber, and the drug release varied due to brittle fractures. The coated pellets showed good floating properties in

vitro, suggesting the use of a drug-lipid dispersion coating for drug delivery systems. The study also highlighted the influence of process parameters and the potential optimizations or limitations of the binders used.[19]

Le H et al., (2007) A hot melt coating method was used to create a sustained release nifedipine dosage form. Sugar beads were coated with various waxes, including Gelucire 50/13, stearic acid, Syncrowax HGLC, natural beeswax, polawax regular, and carnauba wax. Single and dual layer coated beads were fabricated, and a 24-hour drug release study was conducted. The convolution process in Kinetica 2000 software was used to predict plasma concentrations for commercial products Adalat® CC and Procardia® XL 30 mg. In vitro dissolution test results showed dual coating was more effective.

Two-process hot melt coating technique can be used to prepare dual coated beads with high and low melting point waxes. The method yielded capsules with similar dissolution profiles and plasma concentrations to Procardia XL, demonstrating the feasibility of producing zero-order kinetics for drug dissolution. Multiple coating can improve the coating and ensure acceptable sustained release of nifedipine.[20]

Sinchaipanid N, et al., (2006) examined the impact of catalyst amount, hydrogen pressure, and temperature on hydrogen consumption, hydrogenation time, reaction rate, and final product quality. The study found that increasing catalyst and temperature significantly improved reaction rate and acid values. The product showed thermal tolerance to high temperatures, with unchanged exothermic peaks. Hydrogenated soybean oil can be used for modified release formulations through hot melt coating.[21]

Wen-Ting K, et al., (2006) analyzed the physicochemical characterizations of ambroxol SR matrix tablets, which contained hot melt coated granules of ambroxol with Compritol® 888. The dissolution study was conducted over 24 hours, and the pharmacokinetic study on 16 healthy male human subjects showed that Amsolvon tablets provided a slow and less variable release of ambroxol. The study concluded that Amsolvon SR tablets offer optimal therapeutic efficacy and improve patient compliance.[22]

Nguyen C (2005) developed sustained release capsules by tamper-resistant coatings using hot melt coating. The capsules were filled with verapamil, chlorpheniramine, or diltiazem and coated with Gelucire 50/13, cetyl alcohol, and polyethylene glycol 300. The weight gain led to slower drug release, lasting up to 12 hours. The capsules also had a pulse release pattern with a lag time of 4 to 6 hours between the two releases.[23]

Jannin V, et al., (2005) ibuprofen capsules were fabricated using hot melt coating with mixtures of Compritol™ 888 ATO and non-ionic surfactants. Non-ionic surfactants in Compritol™ modify the release of ibuprofen after hot melt coating. Surfactants should be miscible with Compritol™, water-soluble and liquid. Labrasol™ was the promising surfactant as it allows obtaining the greatest dissolution efficiency after compaction and release profiles equivalent whatever the dosage form.[24]

Freitas Luis AP., et al., (2004) prepared paracetamol tablets in spouted bed using hot melt coating. The paracetamol tablets and beeswax beads were loaded in the column and a cycle of heating/cooling while spouting caused the beeswax melting, substrate coating and wax solidification. The data revealed that only the effects of tablets load and the squared air temperature were significant at 5% and 10% level, respectively. The results revealed that it was a promising method for particles coating in spouted bed.[25]

Sinchaipanid N, et al., (2004) demonstrated the application of hot melt coating in design of controlled release of propranolol hydrochloride pellets. The study investigated the use of Gelucire 50/02 and Precirol ATO5 as drug release regulators. Results showed that the dissolution of coated pellet decreased with increased Precirol ATO5 proportion and coating thickness. The linear relationship between log% drug release and reciprocal of time was found, suggesting that drug release can be adjusted by adjusting these factors.[26]

Mittal B, et al., (2003) demonstrated taste masking of aspirin using hot melt coating. The coated aspirin were analyzed for changes in particle size distribution and specific surface area. The coated aspirin was compressed into fast orally dissolving tablets. Taste testing of coated API was conducted amongst 4 volunteers. Reduced dissolution in the mouth during the first minute leads to better taste masking. The present

research was a follow up study that will continue to examine the effect of these variables on the coating process using Precirol ATO®5.[10]

Jannin V, et al., (2003) conducted a study comparing the lubricant performance of Compritol 888 ATO using blending and hot melt coating found that hot melt coating induces homogenous repartition on the lactose surface, making it an efficient method for large surface area particulate systems producing high friction, unlike classical blending procedures.[28]

Achanta AS, et al., (2001) studied the water sorption behavior of excipient films encapsulated by hot melt coating was studied. The study investigates the interaction of water with moisture-protective coatings using lipidic and polymeric coating excipients. It found that temperature and film thickness significantly influence the nature of moisture interaction and distribution in the excipient films, allowing for the encapsulation of water-labile, drug-loaded substrates. [29]

Faham A, et al., (2000) prepared hot melt coated granules of chloroquine by using Compritol 888 ATO as coating agent using fluidized bed coater. The study suggests that controlling granule size can adjust chloroquine release rate, with dissolution profiles characterized by a rapid release phase followed by a slow-release phase. The study indicated that the active substance diffused across the Compritol matrix generated during compression. Determination of the dissolution kinetics using the Higuchi model demonstrated the diffusion release mechanism.[7]

Faham A, et al., (2000) studied the effect of Compritol® 888 ATO and granule size on theophylline release using hot melt coating performed in a fluidized bed apparatus. The dissolution profiles of prepared granules differed from those coated with classical agents and varied among sieve fractions. Drug release was characterized by rapid and slow phases. Results indicate that Higuchi model was the best model to describe the release kinetics of the drug from tablets.[30]

Barthelemy P, et al., (1999) coated drug-loaded sugar beads and lactose granules with Compritol® 888 using hot melt coating. Theophylline was layered on the granules of lactose and beads of sugar. Several competing mechanisms were involved in the drug release, including a diffusion-controlled process and a dissolution mechanism. Dissolution profiles appear to be consistent from one batch to another.[31]

Griffin EN, et al., (1999) designed hot melt coated multi-particulate controlled release dosage forms using lipophilic materials. The release kinetics were determined using a dual equation that combined first-order and square-root-of-time kinetics. The study found the dual equation to be a superior model for the chosen controlled release system and applicable to other literature.[32]

Kennady JP, et al., (1998) demonstrated extended-release applications for solid dispersion hot melt fluid bed coatings using hydrophobic coating agents. Chlorpheniramine maleate (CPM) was chosen as a model drug. The CPM-loaded nonpareils and hydrophobic coating agents was charged in the solid state in fluid bed chamber. Dual coatings demonstrated a cumulative extension of release superior to than a single coat. The method was proved as a viable alternative to the hot melt spray coating method. Multiple coatings that have a cumulative effect on release retardation are feasible.33

Kennady JP, et al., (1996) optimized solid dispersion using Hot Melt fluid bed coating using polyethylene glycol as a model coating agent. They have charged substrate and polyethylene glycol into the fluid bed chamber in the solid state for the set objectives. The technique was proved to be a viable alternative to hot melt spray-coating processes. Organic solvents, spraying equipment, steam jackets, and/or heating tape are eliminated from the process.[34]

Bodimeier R, et al., (1992) have studied the effect of process variables and formulation variables in the preparation of wax microparticles by melt dispersion. Ibuprofen-wax (bees wax, Caurnauba wax, paraffin wax, and glyceryl esters like Gelucire 64/02 and Precirol ATO5) microparticles were prepared using solvent free coating. The study proposed that the drug release was controlled by the hydrophobicity of the wax. The wax microparticles could be formulated into an aqueous sustained-release oral suspension.[35]

Jozwiakowski MJ, et al., (1990) characterized the fine granules of a hydrophobic drug and sucrose coated by hot melt fluid bed coating using partially hydrogenated cottonseed oil. The physical properties of wax-coated granules fabricated using combinations of process variables were examined. The response surface analysis was used to determine the optimum process settings in terms of dissolution, particle size

and density of the coated product. The study revealed that uniformly coated granules were obtained at the optimized conditions.[36]

2.2 Tenofovir

Ulu A, et al., (2024) prepared a controlled drug release of Tenofovir Alafenamide-loaded chitosan nanoparticles and evaluated cell viability study. The researcher developed chitosan nanoparticles (CHS NPs) loaded with TAF, which showed a spherical and homogeneous shape. The NPs had a hydrodynamic diameter, zeta potential, and PDI of around 340 nm, 48.9 mV, and 0.65, respectively. The encapsulation efficiency was around 50%, and TAF was released around 93% after 80 hours at pH 7.4. TAF-loaded CHS NPs had 1.24 times less viable cells than the control, suggesting they could be an effective formulation for treating chronic HBV infection.[37]

Mahajan N, et al., (2024) developed a self-emulsifying drug delivery system to enhance oral delivery of tenofovir. Tenofovir (TNF) is known for its poor membrane permeability and low oral bioavailability. To improve oral availability and membrane permeation, a self-emulsifying drug delivery system (SEDDS) was developed. The system was formulated using eucalyptus oil as an oil phase, Kolliphor EL and Kollisolv MCT 70 as surfactants and cosurfactants, and glycerol as a cosolvent. The optimized SEDDS formulation, F6, produced oil droplets with a size of 98.82 nm and a zeta potential of -13.03 mV, indicating good stability. F6 is a fast-release drug with higher drug permeability than basic TNF and TNF-marketed tablets. Its pharmacokinetic research in rats showed greater Cmax and AUC0-t than commercial tablets and pure drug suspension. SEDDS formulation showed significantly increased bioavailability by 21.53-fold compared to marketed tablets and 66.27-fold compared to pure medicines. This suggests that SEDDS containing eucalyptus oil, glycerol, Kolliphor EL, and Kollisolv MCT 70 could improve TNF absorption and oral bioavailability of weakly water-soluble medicines.[38]

Rao H, et al., (2022) studied tenofovir disoproxil fumarate in patients anguish from chronic hepatitis B and advanced fibrosis or compensated cirrhosis. A study assessing the efficacy and safety of TDF in patients with chronic hepatitis B and advanced fibrosis in China found that it was effective in preventing newly diagnosed

hepatocellular carcinoma (HCC) and disease progression. The study enrolled 197 patients and found that the prevalence of HCC was 2.1%, and disease progression was observed in 3.6%. The mean change in liver stiffness was 5.1 kPa. 67.7% of patients experienced one adverse event, 13.8% experienced TDF-related adverse events, and 16.4% experienced serious adverse events. The study found that at week 144 of TDF treatment, low frequency of HCC and disease development were reported, with virological suppression in 94.1% patients, related to fibrosis regression, and no new safety events were identified.[39]

Del Amo J, et al., (2022) studied effectiveness of TDF /emtricitabine (FTC) and severity of coronavirus disease 2019 in people with HIV infection. Coronavirus disease 2019 (COVID-19) requires antivirals that are effective, safe, and inexpensive. Tenofovir may be effective against COVID-19, but no large-scale human studies have been conducted. A 2020 study in Spain investigated HIV-positive individuals on antiretroviral medication (ART) at 69 clinics. The study collected data on sociodemographics, ART, CD4+ cell count, HIV-RNA viral load, comorbidities, and outcomes. It compared 48-week hazards for different regimens, adjusted for clinical and sociodemographic factors using inverse probability weighting. A study of 51,558 eligible persons found that 39.6% were on TAF/FTC, 11.9% on TDF/FTC, 26.6% on ABC/3TC, and 21.8% on other regimes. There were 2402 confirmed SARSCoV-2 infections, with 425 hospitalizations, 45 ICU admissions, and 37 fatalities. TDF/FTC had higher risk ratios of hospitalization, ICU admission, and death compared to ABC/3TC. TDF/FTC had comparable RRs of hospitalization in individuals over 50 years old and younger people.[40]

Paredes AJ, et al., (2022) developed tenofovir alafenamide dissolved implanted microneedle patches to deliver drug systemically. About 37.7 million people already infected and 1.5 million new cases reported each year. The current oral administration of antiretroviral medications leads to pill tiredness and poor treatment adherence. To address this, innovative formulations for administering ARV medications via alternate routes are being developed. Microneedle array patches (MAPs) offer a user-centric platform for painlessly applying medications to the skin. This study focuses on creating dissolving and implantable MAPs loaded with tenofovir alafenamide (TAF) for systemic drug delivery. The study found that both MAPs were effective in

penetrating newborn pig skin and creating drug stores. In-vitro release studies showed quick drug delivery in all conditions. Franz cells experiment showed dissolving and implantable MAPs deposited 47.87 ± 16.33 μg and 1208.04 ± 417.9 μg of TAF in skin after 24 hours. In rats, TAF metabolized quickly into tenofovir, and was quickly eliminated from plasma. [41]

Garcia CR, et al., (2022) studied the effect of drug-to-lipid ratio on nanodisc-based tenofovir drug delivery to the brain for HIV-1 infection. The study explores the use of nanotechnology-based drug carriers, such as nanodiscoidal bicelles, to treat HIV-1 in the brain. The researchers used tenofovir-loaded nanodiscs for both in vitro and in vivo treatment, capturing the medicine in their hydrophobic core and releasing it in a regulated manner. The study also compared nanodisc formulations in both models, identifying potential applications for nanodiscs in HIV-1 treatment development. This approach could help address the persistence of HIV-1 in the brain.[42]

Stalter RM, et al., (2021) Tenofovir levels in urine were evaluated using a new immunoassay to predict human immunodeficiency virus protection. Novel tools are needed to improve pre-exposure prophylaxis (PrEP) obedience for HIV anticipation, especially those that provide real-time response. In a large, recently finished PrEP experiment, appropriate urine tenofovir levels evaluated with a new immunoassay predicted HIV protection and demonstrated good sensitivity and specificity for detectable plasma tenofovir.[43]

Plum PE, et al., (2021) studied impact of switch from tenofovir disoproxil fumarate-based regimens to tenofovir alafenamide-based regimens on lipid profile, weight gain and cardiovascular risk score in people living with HIV. The study analyzed the impact of switching from tenofovir disoproxil fumarate (TDF)-based regimens to tenofovir alafenamide (TAF) regimens on the lipid profile, weight gain, and cardiovascular risk change in HIV-infected patients with suppressed viral load. The patients were divided into two groups: those who had been treated continuously with TDF-based regimens, and those who had been treated with TDF regimens for at least 6 months before switching to TAF regimens.

The study examined various factors such as age, gender, ethnicity, and lipid profile in patients with ARV. It found that switching from TDF to TAF-based therapy led to a

significant increase in triglyceride levels, total cholesterol, and HDL cholesterol. However, LDL cholesterol and total cholesterol/HDL ratios did not significantly change. The calculated cardiovascular risk increased after switching from TDF to TAF-based therapy. The study suggests that considering the unfavourable influence of TAF on lipid profile is crucial when proposing personalized ARV treatment.[44]

Bagus SB, et al., (2021) described a Tenofovir disoproxil fumarate prenatal as a complementary treatment to prevent vertical transmission of hepatitis B virus. Vertical transmission is the most common mode of hepatitis B transmission in endemic countries, with 1% to 4% of newborns at risk of immunoprophylactic failure. Tenofovir disoproxil fumarate (TDF) is preferred over lamivudine and telbivudine due to its potency and reduced resistance. A systematic review of 3,765 participants found that six studies reduced viral load HBV DNA levels in the treated group, and five investigations showed a higher vertical transmission rate than in the control group. The systematic review of studies found that prenatal TDF administration and prophylactic procedure can lower vertical transmission rates and the risk of immunoprophylactic failure in infants aged 6-12 months old. No significant safety differences were found between the intervention and control groups. The public health sector and clinicians should explore TDF prenatal as a supplemental treatment for preventing vertical transmission.[45]

Safari JB, et al., (2021) developed pH-sensitive chitosan-g-poly (acrylamide-co-acrylic acid) hydrogel for controlled drug delivery of tenofovir disoproxil fumarate. Free radical polymerization was used to create thermally stable chitosan-g-poly hydrogels with well-defined holes on a fibrous surface. These hydrogels were pH and ionic strength sensitive, with swelling reduced under acidic and strong ionic strength conditions but increased in neutral and basic solutions. Cytotoxicity experiments on HeLa cell lines demonstrated the material's cytocompatibility and preparedness for physiological applications. TDF encapsulation in hydrogels was optimized, resulting in 96% efficiency and 10% drug loading percentage. More intriguingly, in vitro release tests revealed a pH-dependent release of TDF from hydrogels. The drug release at pH 7.4 was five times greater than at pH 1.2 within 96 h. The novel formulated hydrogel-loaded TDF proposed as a smart delivery system for oral administration of anti-hepatitis B drugs.[46]

Sarma A, et al., (2020) designed nanostructured lipid carriers (NLCs)-based intranasal drug delivery system of tenofovir disoproxil fumarate (TDF) for brain targeting. Brain is one of the main reservoirs of HIV. The Blood Brain Barrier (BBB) presents a substantial hurdle in the distribution of TDF to the CNS following systemic injection, rendering it therapeutically ineffective. The intranasal route provides direct access to the brain, bypassing the BBB. As a result, these novel TDF-loaded biodegradable NLCs administered intranasally have the potential to deliver TDF to the brain at a therapeutic level. TDF is modestly soluble in water (13.4 mg/ml) and is pumped out by the BBB's endothelial layers. The current study focused on developing TDF-loaded NLCs made from Compritol 888 ATO and oleic acid. The drug content and entrapment efficiency were determined by UV analysis. The stability investigation demonstrates that NLCs are highly stable in refrigerated conditions and are safe. Three cell line and a histopathology analysis on pig nasal mucosa. TDF NCLs was showing sustained release profile from in CSF. In-vivo pharmacokinetics studies on rat plasma and brain indicated that NLCs are rapidly available in the brain, resulting in increased MRT, Cmax, and AUC. CLSM images of brain cryosections labelled with caumarin-6 NLCs reveal that NLCs localize and accumulate in the brain, delivering TDF over time. The findings indicate that the produced NLCs have the ability to administer TDF in the brain for an extended period of time in the treatment of NeuroAIDS.[47]

Tao X, et al., (2020) studied efficacy and safety of the regimens containing Tenofovir alafenamide versus tenofovir disoproxil fumarate in fixed-dose single-tablet regimens for initial treatment of HIV-1 infection using a meta-analysis of randomized controlled trials. A study comparing the non-inferiority of a TAF-containing combination regimen to a TDF-containing fixed-dose single-tablet regimen in HIV-1-infected individuals compared data from seven eligible randomised controlled trials (RCTs). The study found that TDF can cause renal and bone damage when combined with high plasma tenofovir concentrations in HIV-1 patients receiving antiretroviral therapy. The study used a meta-analysis model built with Stata/SE, combining data from seven RCTs, totalling 6269 individuals. The meta-analysis found that TAF-containing regimens were effective, safe, and tolerable for HIV-1 treatment,

outperforming fixed-dose single-tablet regimens in terms of renal function, bone metrics, and lipid profile in naive patients. [48]

Wassner C, et al., (2020) reviewed about the clinical understanding of TDF against Tenofovir alafenamide. HIV is a chronic medical condition with no cure, and lifetime therapy with a mix of medicines is essential to limit viral replication and prevent consequences. Tenofovir, a newer, more tolerable nucleotide reverse transcriptase inhibitor, is a mainstay in many antiretroviral therapy combinations and is available in two formulations: Tenofovir disoproxil fumarate (TDF) and Tenofovir Alafenamide (TAF). However, their pharmacokinetics significantly influence their efficacy and safety, as they have vastly different pharmacokinetics. Manuscript discusses the history of TDF and TAF development, their distinct pharmacokinetics and pharmacology, clinically significant adverse effects, monitoring, interactions, resistance, a review of clinical studies, guideline recommendations, and clinical applications for tenofovir's various indications.[49]

Puri A, et al., (2019) developed a transdermal delivery system for Tenofovir Alafenamide, a prodrug of tenofovir with potent antiviral activity against HIV and HBV. This study aimed to create a transdermal patch containing TAF for HIV prevention, as oral TAF regimens require daily ingestion, reducing adherence and increasing viral resistance risk. Two types of TAF patches were produced: transparent with acrylate adhesive and suspended with silicone and polyisobutylene adhesives. Vertical Franz diffusion cells were used for seven days to conduct in vitro permeation investigations. An optimized silicone-based patch was evaluated for adhesive qualities and skin discomfort.

The study shows that silicone-based transdermal patches can deliver a therapeutically meaningful dosage of TAF for HIV and HBV control, with acrylate-based patches achieving a maximum flow of 0.60 ± 0.09 μg/cm^2/h and silicone-based patches achieving maximum penetration of 7.24 ± 0.47 μg/cm^2/h. [50]

Venter WD, et al., (2018) describe tenofovir therapy in renal disease for HIV. Antiretroviral therapy (ART) is often linked to TDF-induced nephrotoxicity, with patients on ART at higher risk of developing renal illness due to ART and comorbidities. Clinicians need to control renal illness in TDF patients. TDF is not

commonly associated with acute kidney injury (AKI) or chronic kidney disease (CKD), so doctors should rule out other possibilities. In cases of TDF-associated AKI, TDF should be stopped or ART discontinued entirely. TDF poisoning can manifest as acute kidney injury or chronic kidney disease. TDF significantly impacts kidney function, causing a 10% drop-in glomerular filtration rate (GFR) due to altered tubular function in individuals exposed to TDF for treatment or pre-exposure prophylaxis. Renal function should be evaluated using creatinine-based estimated GFR at the beginning of TDF, after 1-3 months if ART is modified, and every 6-12 months if stable. Specific tubular function tests are not recommended, but spot protein or albumin: creatinine ratios are preferred. Patients with established CKD or risk factors may require more regular monitoring.

Common risk factors for kidney disease include comorbid hypertension, diabetes, HIV-associated kidney disease, co-infection with hepatitis B or C, and TDF combined with ritonavir. Prioritizing these conditions is crucial. If eGFR is below 50 mL/min/1.73 m2, abacavir and dose-adjusted TDF are preferred. If kidney function declines or proteinuria worsens, clinicians should review ART, potentially nephrotoxic medications, comorbidities, and conduct additional testing. If kidney function doesn't improve after treating reversible causes of renal failure, a nephrologist is recommended. In severe CKD cases, prompt referral for renal replacement therapy is advised. Tenofovir alafenamide, a less harmful prodrug, may eventually replace TDF.[51]

Spinks CB, et al., (2017) characterized novel tenofovir liposomal formulations for enhanced oral drug delivery: in vitro pharmaceutics and Caco-2 permeability investigations. Tenofovir disoproxil fumarate, a drug used against HIV/AIDS, has low oral bioavailability. This study aimed to increase its bioavailability by developing and characterizing model liposomal formulations. The entrapment procedure was carried out using the film hydration method, and formulations were evaluated for efficiency and Caco-2 permeability. An effective reverse-phase high-performance liquid chromatography method for tenofovir quantification was devised and confirmed in both in vitro liposomal formulations and Caco-2 permeability samples. Separation was performed isocratically on a Waters Symmetry C8 column.

A method was validated using a flow rate of 1 mL/min and a 12 minutes elution period. The injection volume was 10 µL, and UV detection was done at 270 nm. The positive charge-imparting agent determined the amount of tenofovir encapsulated in the liposomes. The calibration curves were linear, with r2 > 0.9995, and the accuracy and precision varied from 95% to 101% and 0.3% to 2.6%, respectively. The vectors potentiated tenofovir permeability by ten times compared to oral solution. In conclusion, novel and validated method was successfully applied to characterize both in vitro encapsulation efficiency and Caco-2 permeability transport for the pharmaceutical assessment of novel tenofovir formulations.[52]

Ray AS, et al., (2016) published a clinical review of Tenofovir Alafenamide used to treat HIV. Antiretroviral regimens to suppress HIV infection and improve long-term, chronic therapy safety are needed. TAF has superior qualities compared to TDF, which is powerful and well-tolerated but has been linked to renal function changes, decreased bone mineral density, and rare renal adverse effects. TAF is more effective in improving HIV therapy and addressing lifetime therapy in an older, comorbid HIV population, and is more effective in addressing the needs of an increasingly comorbid HIV population. TAF enhances the production of TFV diphosphate, the active metabolite, in HIV-target cells with lower oral dosages. This enhances stability in biological matrices and quick cell activation. All TFV produced in the body is eventually removed renally, reducing off-target kidney exposure. Effective therapy achieves 90% reduced systemic TFV exposure, leading to significant improvements in safety metrics like bone mineral density and kidney function markers.[39]

Agarwal K, et al., (2015) conducted twenty-eight-day safety, antiviral activity, and pharmacokinetics of tenofovir alafenamide for treatment of chronic hepatitis B infection. Tenofovir alafenamide, a phosphonate prodrug of tenofovir, efficiently delivers active drug to hepatocytes while reducing systemic exposure. A study randomized 51 non-cirrhotic, treatment-naïve subjects with chronic hepatitis B to receive either alafenamide or disoproxil fumarate for 28 days. Safety, antiviral response, and pharmacokinetics were assessed, followed by a 4-week off-treatment period. All patients completed the research treatment, with no major or severe adverse events reported.

Tenofovir alafenamide showed similar mean changes in serum HBV DNA at week 4 compared to the control group. The pharmacokinetics of viral decrease were linear and proportional to dose. Doses ⩽25 mg resulted in a 92% reduction in mean tenofovir area under the curve compared to tenofovir disoproxil fumarate 300 mg. Tenofovir alafenamide was safe and well tolerated, with HBV DNA decreases comparable to tenofovir disoproxil fumarate at all dosages tested. [54]

Duwal S, et al., (2012) pharmacokinetics and pharmacodynamics of the reverse transcriptase inhibitor tenofovir and prophylactic efficacy against HIV-1 infection. This study aims to estimate the efficacy of preventive regimens using Tenofovir-disoproxil-fumarate (TDF) and analyze its sensitivity to time, manner of administration, adherence, and the number of transmitted viruses. A pharmacokinetic model for TDF and its active anabolite, tenofovir-diphosphate (TFV-DP), was created and validated using data from four trials with different dosage regimens. The model was applied to an HIV model, and viral decay during TDF monotherapy was predicted based on current data.

A study used a stochastic technique to estimate the percentage of infections avoided by daily TDF-based PrEP, one-week TDF, and a single dose oral TDF. Analytical solutions were developed to determine the relationship between intracellular TFV-DP levels and preventive efficacy. TDF's expected efficacy was limited by slow accumulation of active compound and variable half-life. Daily TDF-based PrEP provided 80% protection when at least 40% of pills were consumed. Sd-PrEP, with 300 mg or 600 mg TDF, can prevent up to 50% of infections when administered before virus exposure. However, its effectiveness decreases to around 10% when taken 1 hour before exposure. Dosage and administration time cannot boost efficacy. Post-exposure prophylaxis doesn't significantly reduce infection rates. The use of faster-accumulating medicines or local tenofovir gel may eliminate the need for drug administration before viral exposure.[55]

Mesquita PM, et al., (2012) developed intravaginal ring delivery of tenofovir disoproxil fumarate for the prevention of HIV and herpes simplex virus infection. A safe and effective topical preventative strategy will most likely include the continuous supply of powerful antiviral medicines, as well as a delivery technology that exploits

drug distribution while also overcoming adherence-related behavioral difficulties. The epidemiological relationship between HIV and herpes simplex virus (HSV), antiviral activity would be helpful. Authors hypothesize that tenofovir disoproxil fumarate (tenofovir DF), a tenofovir prodrug, is more powerful and more suited for sustained intravaginal ring (IVR) distribution. [56]

Patil AT, et al., (2012) employed hot melt coating technique for enteric coating has demonstrated in the present investigation. Pellets made from extrusion-spheronization were chosen as the core for diclofenac sodium due to their advantages. Stearic acid and palmitic acid were evaluated as enteric HMC materials. HMC was performed on preheated pellets in a modified coating pan, achieving a 5-15% w/w coating level. Both SA and PA showed excellent enteric coating ability.[57]

Yu D, et al., (2011) written an article on Tenofovir in the treatment of chronic hepatitis B. Chronic hepatitis B (CHB) is prevalent worldwide. It can cause major consequences, including cirrhosis, and is the most prevalent risk factor for hepatocellular cancer. Treatment for CHB could last a lifetime, and pharmacological interventions must be both effective and safe. The US FDA authorized TDF in 2008 as a therapy for CHB in adults. The clinical trials of TDF have shown exceptional efficacy with powerful antiviral activities, a high barrier to resistance, and a favorable safety profile. This review will include the outcomes of clinical trials that have investigated TDF's efficacy and safety in the treatment of CHB, as well as a discussion of TDF's comparative effectiveness with other licensed CHB medications.[58]

Le H, et al., (2007) A sustained release dosage form of nifedipine by hot melt coating method was designed. Sugar beads, mesh size 30-35 were coated with different waxes: Gelucire 50/13, stearic acid, Syncrowax HGLC, natural beeswax, polawax regular and carnauba wax. Dual coated beads with high melting point waxes in the inner layer and lower melting point waxes as the outmost layers can be prepared by two process hot melt coating technique. Capsules with dual coated beads, carnauba wax and stearic acid, showed similar dissolution profiles and plasma concentration predictions to Procardia XL. Multiple coating can improve the coating and render acceptable sustained release of nifedipine.[59]

Peterson L, et al., (2007) Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial. The study aimed to evaluate the safety and efficacy of a daily dose of 300 mg of tenofovir disoproxil fumarate (TDF) versus a placebo in preventing HIV in women. The phase II, double-blind, placebo-controlled experiment was conducted in Tema, Ghana, Douala, Cameroon, and Ibadan, Nigeria, involving 936 HIV-negative women at high risk of HIV infection. The study focused on safety outcomes of a drug for HIV-1 or HIV-2 infection, including serum creatinine elevations, hepatic function elevations, and phosphorus abnormalities. Participants provided 428 person-years of laboratory testing for the principal safety analysis, with no significant differences between treatment groups. The primary efficacy analysis involved 476 person-years of testing, with eight seroconversions occurring during the study.

A study found that two HIV-negative women were diagnosed with TDF and six with a placebo, resulting in a rate ratio of 0.35. However, the study's effectiveness was not conclusive due to the early closure of the Cameroon and Nigeria study sites, and the daily oral use of TDF was not linked to increased clinical or laboratory adverse effects. The small number of HIV infections identified during the trial also hindered further evaluation. [60]

Kuo A, et al., (2004) proposed TDF for the treatment of lamivudine-resistant hepatitis B. Lamivudine resistance in chronic hepatitis B patients is increasing at rates of 16%-32% after 1 year and 49% after 3 years. Adefovir dipivoxil, a nucleotide analogue licensed by the FDA, is effective against HBV but has been linked to kidney damage. TDF, another nucleotide analogue, has shown antiviral effectiveness against both wild-type and lamivudine-resistant HBV. Tenofovir, at the approved dose, has not been linked to renal impairment. A series of 9 patients with lamivudine-resistant hepatitis B was studied.

Tenofovir treatment significantly reduced HBV DNA levels in patients with lamivudine-resistant hepatitis B after 12 months of treatment. It resulted in a median drop of 4.5 log10 copies/mL, HBeAg seroconversion in two patients, and normalization of four of seven individuals with high ALT levels. Tenofovir treatment

was well-tolerated and resulted in significant virological, serological, and biochemical improvements comparable to high-dose adefovir without renal toxicity risk.[61]

2.3 Sitagliptin

Ng II, et al., (2024) identified sitagliptin as an antitumor drug targeting dendritic cells network based screening approach. The priming and activation of tumor-specific T lymphocytes is dependent on dendritic cell (DC)-mediated antigen presentation. However, few medicines that directly target DC activities. The discovery of medicines that target DC has enormous potential for cancer immunotherapy. Researchers discovered that after antigen presentation, type 1 conventional DCs (cDC1s) launched a unique transcriptional programme. Researchers employed a network-based strategy to find cDC1-targeting medicines. The potential drug's anticancer activity and underlying mechanisms were studied both in-vitro and in-vivo. Sitagliptin is used to treat type 2 diabetes, has been discovered as a medication that targets DCs. In animal models, sitagliptin decreased tumour development via improving cDC1-mediated antigen presentation, which led to increased T-cell activation.

Sitagliptin inhibited dipeptidyl peptidase 4 (DPP4), preventing the truncation and degradation of chemokines/cytokines required for DC activation. Sitagliptin improved cancer immunotherapy by allowing DCs to prime antigen-specific T cells more efficiently. In humans, using sitagliptin was associated with a decreased incidence of tumour recurrence in colorectal cancer patients having curative surgery. The results showed that sitagliptin-mediated DPP4 inhibition improves antitumor immunity by improving cDC1 activities. These findings indicate that sitagliptin can be repurposed as an anticancer medication targeting DC, offering a possible method for cancer immunotherapy.[62]

Iswariya VT, et al., (2024) developed gastro-retentive floating tablets containing sitagliptin. The tablets contain Pectin and HPMC K as matrix former and lactose monohydrate serving as a diluent. The effervescent agent, utilizing citric acid was the basis for causing the tablet to float. Magnesium stearate and talc are used in this tablet to increase the flow properties of the powder thus it helps in punching of the tablet. The direct compression method facilitated the production of six distinct formulations.

Evaluation of these formulations focused on pre compression studies and post compression studies of the tablet. Consistency was observed across all formulations, indicated by minimal weight variation and good in-vitro dissolution profiles. Among these formulations, M5 distinguished itself as the most promising. It was composed of 3 mg of Pectin and 7 mg of HPMC K, achieving an extended floating duration of 12 hours coupled with an efficient drug release profile over 8 hrs. The performance of M5 suggests its potential as an effective gastroretentive delivery system for Sitagliptin, offering a controlled release that could enhance patient compliance and therapeutic efficacy.[63]

Kumar SD, et al., (2024) validated bioanalytical method for forced degradation, and pharmacokinetic application of sitagliptin in human plasma spiking tests using the UV-HPLC technique. The Shimadzu LC 20AD liquid chromatographic system, which uses manual injection, developed a simple and accurate approach. The optimised chromatogram was produced using acetonitrile in the isocratic mobile phase technique at a flow rate of 1.0 mL/min. The stationary phase was a thermal C-8 column (4.6 × 250 mm, 5 μm), and the detection wavelength was 265.0 nm, using a UV-Vis detector. The proposed approach was validated using ICH recommendations. The approach was linear from 10 to 50μg/mL, with a correlation value of R2 = 0.9746. Recovery studies predicted percentage RSDs of 19.14, 3, and 9.95, respectively. The injection repeatability values were determined to be % RSD 17 and 10.63 for intraday and interday, respectively. The stress degradation experiments found that sitagliptin degrades faster when exposed to 0.1 NaOH. Human plasma spiking investigations found 3.02 ng/mL at 3.02+/-60 minutes of C and T max, respectively.[64]

Nagao M, (2023) conducted study to determine the effectiveness and safety of sitagliptin therapy in elderly Japanese individuals with T2D. The STREAM study involved 176 T2D outpatients aged 65-80 years with moderately controlled glycaemic levels. They were divided into two groups: those who received sitagliptin as an initial or additional anti-diabetic treatment, and those who did not. The treatment aimed to achieve a HbA1c level of less than 7.4%. The study examined the effectiveness and safety of the treatment over a 12-month period. The mean age of the participants was 70.6 years. A study found that sitagliptin significantly improved the glycaemic profile of elderly T2D patients without major side effects. The sitagliptin group experienced

average changes in fasting plasma glucose, HbA1c, and glycated albumin, while the control group experienced changes of 0.50 mg/dL, -0.29%, and -0.93%. The study concluded that sitagliptin medication significantly improved the glycaemic profile of elderly T2D patients without major side effects. [65]

Ardestani, N. S., et al., (2023) proposed new association experimental model to estimate solubility of sitagliptin phosphate, in supercritical carbon dioxide. The solubility of sitagliptin in supercritical carbon dioxide was determined using analytical and dynamic techniques at various temperatures and pressures. The measured solubilities ranged from 3.02 × 10–5 to 5.17 × 10–5, 2.71 × 10–5 to 5.83 × 10–5, 2.39 × 10–5 to 6.51 × 10–5, and 2.07 × 10–5 to 6.98 × 10−5 in mole fraction. The data was correlated with existing density models and a new association model. [66]

Hossain MS, et al., (2023) developed combination of empagliflozin and sitagliptin dosage form to treat type-2 diabetes might be more economical and patient compliance with an additive improvement in glycemic control due to complementary modes of action. The study aimed to create an instant tablet dosage form of empagliflozin and sitagliptin using a statistically valid research design. The formulation was created using Design Expert Software version v.13, focusing on the effects of crospovidone and croscarmellose sodium amounts on disintegration time and drug release. High-performance liquid chromatography (HPLC) testing techniques were used to analyze the formulations. Mice were used to test the efficacy of the anti-diabetic therapy after a high-fat diet and streptozotocin injections.

F3 was found to have the best in-vitro performance out of nine formulations, with an optimal formulation of 100.99% empagliflozin and 100.19% sitagliptin. The disintegration time was 5.32 minutes, and the percentage release of empagliflozin was 89.05% in 30 minutes, while sitagliptin was 93.76%. F3 administration significantly reduced FBG, total cholesterol, triglycerides, HDL, and LDL levels compared to the diabetic control, similar to metformin treatment. A novel combination tablet with empagliflozin and sitagliptin was created using direct compression technique. [66]

Rao A, et al., (2023) formulated floating microspheres of sitagliptin for the treatment of type 2 diabetes mellitus. Because gastro-retentive dosage forms have a lower bulk density than gastric fluids, they can be used as controlled-release drug delivery

systems. The surface morphology of microspheres was examined using SEM. The microspheres were found to be spherical and porous. The Fourier transform infrared (FTIR) technology was used to conduct compatibility. The manufactured microspheres had a 12-hour medication release and were buoyant for longer than that. In-vitro release kinetics were investigated using various release kinetics models, including zero order, first order, Higuchi, and Korsmeyer- Peppas models, and the best match model was determined to be the Higuchi plot with a release exponent n value smaller than 0.89. It was determined that the produced floating microspheres of Sitagliptin provide a good and feasible technique for long-term drug release, improving oral bioavailability, efficacy, and patient compliance.[67]

Gurjar PN, et al., (2023) studied the impact of selective polymer on optimization of sustained release matrix pellets of sitagliptin. Sitagliptin is used in the treatment of non-insulin-dependent diabetes mellitus. The goal of study was to design a flexible dosage form that controlled release and provided therapeutic effects while minimizing negative effects. Various batches of pellets were created using the extrusion-spheronization technique to determine which batch resulted in a sustained release pattern for Sitagliptin. The pellets demonstrated outstanding flow qualities due to their sphericity, which influenced the dosage production rate, as well as the tiny particle size, which allowed for easy dispersion and helped to reduce dose dumping. The pellets released 89.10% in 12 hours. The study shows that the development of sustained-release pellets using selected excipients results in enhanced medication release while minimizing difficulties.[70]

Shi P, et al., (2022) conducted the pharmacokinetics and bioequivalence of test and reference (JANUMET®) formulations of sitagliptin phosphate/metformin hydrochloride tablets at a single dose of 50 mg/850 mg. The study involved 24 volunteers who received a single oral dose of sitagliptin phosphate/metformin hydrochloride tablets 50 mg/850 mg. Liquid chromatography tandem mass spectrometry was used to measure the amounts of sitagliptin and metformin in their plasma. Pharmacokinetic parameters were generated using WinNonlin 7.0, and bioequivalence was assessed using SAS 9.4.

The study found that sitagliptin and metformin had similar geometric mean ratios under fasting and fed conditions. Under fasting conditions, the Cmax, AUC0-t, and AUC0-∞ values were 101.70-120.62%, 99.81-105.61%, and 100.27-106.12%, respectively. Under fed conditions, the Cmax, AUC0-t, and AUC0-∞ values were 90.39-111.48%, 94.76-109.12%, and 95.76-110.38%, respectively. Both formulations were generally well-accepted and bioequivalent in healthy Chinese participants.[71]

Charoo NA, et al., (2022) assessed methods based on the Biopharmaceutics Classification System (BCS) could be used to assess the bioequivalence of solid immediate-release (IR) oral dosage forms containing sitagliptin phosphate monohydrate, as an alternative to a pharmacokinetic study in human volunteers. The BCS was used to evaluate sitagliptin's solubility, permeability, dissolution, therapeutic index, applications, pharmacokinetics, pharmacodynamics, bioequivalence/ bioavailability problems, and drug-excipient interactions. The findings support sitagliptin's classification as a BCS Class 1 medication. The clinical risks associated with moderately supra-optimal and moderately suboptimal dosages are considered insignificant due to its broad therapeutic index and lack of serious side effects. The BCS-based biowaiver can be used for solid IR oral drug products containing sitagliptin phosphate monohydrate, provided the test product is formulated with excipients commonly found in approved solid IR oral drug products and used in the appropriate amounts, and data supporting the BCS-based biowaiver is obtained using the method.[72]

El-Megharbel SM, et al., (2022) synthesized and characterized sitagliptin with divalent transition metals manganese and cobalt metals and their complexes. Mn (II) and Co (II) complexes were examined and characterized using physical methods such as FTIR, DG/TG, XRD, ESM, and TEM. The study found that STG, a bidentate ligand, functions as a bidentate ligand with a square planner shape. The experiment involved 40 male albino rats divided into four groups: control, STG, STG/Mn, and Co/STG. Biomarkers for hepatic enzymes and antioxidants were found in the blood. STG combined with Mn and Co treatment provided significant protection against hepatic biochemical changes, suppression of oxidative stress, and structural changes. These complexes reduced stress and enhanced hepatic enzymatic levels more than STG alone.

The STG/Mn complex effectively combats Bacillus subtilis and Streptococcus pneumonia, while STG/Co is highly effective against Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus. This synergistic effect on oxidative stress enhances liver tissue structure, and STG metal complexes containing Mn and Co show the most potential for antioxidant and hepatoprotective actions.[73]

Shakir R, et al., (2022) developed a mucoadhesive buccal delivery system for the sustained delivery of metformin (MET) and sitagliptin (SIT) against diabetes mellitus (DM) to improve bioavailability. A polymeric blend of Carbopol® 940, agarose, or polyvinylpyrrolidone K30 was used as mucoadhesive agents in formulations R1-15. The tablets were characterized for solid state, physicochemical, and in-vivo mucoadhesion studies in healthy volunteers. Results showed no unusual peak or interaction between drugs and polymers. The mucoadhesive blend of CP and PVP was superior, with complete drug release for 6 hours and ex-vivo mucoadhesive strength and time of 26.99 g and 8.1 hrs, respectively. The optimized formulation was stable for up to 6 months. The formulation R4 demonstrated Korsmeyer-Peppas model and first-order release for SIT and MET, demonstrating hemocompatibility, biocompatibility, and stability. The CP blend with PVP was found suitable for achieving desired release and optimizing mucoadhesive properties of buccal tablets, ensuring pharmaceutical stability. [74]

Patel YD, et al., (2022) quantitatively computed and stability of phase III composition comprising sitagliptin and dapagliflozin propanediol monohydrate by RP-HPLC. The stability performance of a formulation, such as sitagliptin and dapagliflozin propanediol monohydrate, is crucial before it enters the commercial market or clinical trials. A reverse phase high performance liquid chromatography was used to quantify both components in the presence of degradation products from stress testing. The chromatogram was performed on an Inertsil ODS C18 column using Methyl Nitrile and 0.02 M KH2 PO4 buffer, with a flow rate of 1 ml/minute and monitored at 210 nm. All system suitability criteria indicate good separation.The home formulation showed oxidative instability, indicating predictive results of induced stress. The optimized analytical technique was validated and found highly reproducible with higher specificity, making it suitable for routine quantification of

sitagliptin and dapagliflozin propanediol monohydrate from the proposed formulation, as per ICH Q1 guidelines.[75]

Kazi M, et al., (2021) developed & optimized sitagliptin and dapagliflozin loaded oral self-nanoemulsifying formulation against type 2 diabetes mellitus. This study focuses on developing an oral combination dosage form for two anti-diabetic medicines, sitagliptin and dapagliflozin, using self-nanoemulsifying drug delivery systems (SNEDDS). The SNEDDS were created using bioactive triglyceride oil, mixed glycerides, and non-ionic surfactants. Droplet size and antioxidant activity were tested. In-vitro digestion, bioavailability, and anti-diabetic activities were compared with the marketed medication Dapazin®. The SNEDDS with black seed oil demonstrated good self-emulsification performance.

SNEDDS nanodroplets, sized 50-66.57 nm, have a high drug loading capacity and strong antioxidant activity. They significantly increased the Cmax, AUC, and oral absorption of dapagliflozin compared to the commercial product in a rat model. Anti-diabetic research showed that SNEDDS combination dose significantly inhibited glucose levels in treated diabetic mice compared to solo medication therapy. This suggests SNEDDS could be a potential oral pharmaceutical product for the enhanced treatment of type 2 diabetes mellitus. [76]

Sahu E, et al., (2020) developed bilayer tablet containing Metformin Hydrochloride and Sitagliptin Phosphate as a fixed dosage combination for treating type II diabetes. The study was aimed to lower the dosage, frequency, and adverse effects of Metformin Hydrochloride while also promoting medication synergy. Pre-formulation investigations, including drug excipient compatibility, were done for both medications. Metformin Hydrochloride was examined in several formulations with sustained release employing natural hydrophilic polymers, such as Tamarind seed mucilage. They examined Sitagliptin Phosphate quick release formulations made with synthetic super-disintegrants and microcrystalline cellulose. In-vitro dissolving data identified MF3 and SG8 as the most effective formulations for Metformin Hydrochloride and Sitagliptin Phosphate, respectively. Bilayer tablets were created by compressing Metformin Hydrochloride (MF3) and adding Sitagliptin Phosphate (SG8) to achieve a final hardness of 5.0. They were then tested. The bilayer tablet had

a cumulative medication release of 98.6% Sitagliptin Phosphate in 30 minutes and 97.9% Metformin Hydrochloride in 12 hours. The study demonstrated that tamarind seed mucilage had strong polymeric activity and can maintain release for 12 hrs.[77]

Zhao R, et al., (2020) Diabetes mellitus has been described as a chronic endocrine and metabolic disease, which is characterized by hyperglycemia and the coexistence of multiple complications. Currently, diabetes mellitus is treated with insulin, insulin analogues, non-insulin oral hypoglycemic drugs, and genetic drugs. However, there is no complete therapy strategy due to drug deficiencies and administration routes. Adverse reactions from long-term subcutaneous injections and oral challenges like enzymatic degradation, chemical instability, and poor gastrointestinal absorption are challenges. Therefore, developing appropriate delivery systems and exploring complete therapy strategies based on drug characteristics and diabetes mellitus is crucial.

Delivery systems have shown potential benefits in diabetes treatment, improving drug stability, overcoming biological barriers, and acting as intelligent automatized systems to mimic endogenous insulin delivery. This review provides an overview of research advances, drug therapy trends, and their application in diabetes treatment, offering reference for various drugs in the field. It also highlights the potential of delivery systems in reducing hypoglycemia risk.[78]

Bossi AC, et al., (2020) Long-term clinical data from the single-arm persistent sitagliptin treatment & outcomes project were analyzed, which collected information on 440 patients with TD2 (275 men, 165 women; mean age 64.1 years; illness median duration: 12 years) treated with sitagliptin as 'add-on'. Researchers used the UK Prospective Diabetes Study (UKPDS) Risk Engine (RE) to assess the 10-year cardiovascular (CV) risk for each individual patient. Kaplan-Meier survival curves were used to assess drug survival, while repeated measures mixed effects models were employed to examine the development of glycated hemoglobin (HbA1c) and CV risk following sitagliptin administration. At baseline, the majority of patients were overweight or obese (median BMI (kg/m2) 30.2); median HbA1c was 8.4%; median fasting plasma glucose was 172 mg/dL; and median UKPDS RE score was 24.8%, with males (median 30.2%) scoring higher than women (median 17.0%), as predicted.

The median follow-up period after initiating sitagliptin medication was 5.6 years. The study found that sitagliptin medication significantly improved HbA1c levels, with a quick reduction after 4-6 months. Patients who maintained sitagliptin treatment had a significant difference in HbA1c evolution compared to those who switched to another antihyperglycemic medicine. Sitagliptin therapy also improved UKPDS RE score and BMI at 10 years. Adverse outcomes were infrequent, and patients with T2D treated with sitagliptin had better metabolic control and lower CV risk, with no significant side effects. [79]

SreeHarsha N, et al., (2019) designed novel mucoadhesive prolonged release nanocarrier of Sitagliptin for the treatment of diabetics. Patients typically take sitagliptin 50mg twice daily, but only 38% of the medication is reversibly attached to plasma proteins, while 79% is eliminated in urine. The drug content in formulations is 72.5% ± 5%, with a practical yield of 84.9% ± 3%. Sitagliptin nanoparticles with diameters ranging from 210 to 618 nm contribute to long-term drug release, consistent with the Peppas model. FTIR spectroscopy and DSC studies show no significant interactions between sitagliptin and chitosan.

Mucoadhesive nanoparticles with sitagliptin were found to be effective in the gastrointestinal tract for 12 hours, providing superior oral benefits compared to traditional administration methods. This marks the first time a drug-delivery approach using nanoparticles' mucoadhesive qualities has been shown to prolong sitagliptin's release time.[80]

Shukla KV, et al., (2019) formulated transdermal drug delivery of sitagliptin. Sitagliptin was used for treating diabetes, but its oral administration caused such severe side effects. Transdermal patches containing Sitagliptin phosphate were created using solvent casting evaporation techniques. The physicochemical properties of the patches were assessed, including flexibility, thickness, smoothness, weight variation, moisture content, hardness, folding endurance, and tensile strength. The formulation showed flexibility, homogeneous thickness and weight, smoothness, high drug concentration, and low moisture content. In-vitro diffusion studies showed that the formulation with ethyl cellulose: HPMC polymers had a faster release rate than Eudragit: HPMC. The stability studies showed that all patches maintained their

physicochemical properties and medication content even after storage. The compatibility study found no contact between medication and polymers, enabling sustained release of sitagliptin through transdermal patches.[81]

Nair AB, et al., (2019) designed mucoadhesive nanoparticles to represent a potential drug delivery strategy to enhance the therapeutic efficacy in oral therapy. In this study, HPMC and PLGA-based sitagliptin nanoparticles using a nano spray drier were prepared. They were tested for their efficacy in an animal model. Particle size was optimized using response surface methods by investigating the effect of spray-drying process factors (inlet temperature, feed flow, and polymer concentration) on particle size. Ex-vivo and in-vivo investigations in rats were used to characterize the produced nanoparticles for several physicochemical aspects (practical yield, drug content, shape, particle size, temperature, and crystallographic properties), as well as to assess drug release, stability, and mucoadhesive activity. The experiment design advised that a linear model was used to best suit the given design and values. A study found that mucoadhesive nanoparticles, with a drug content of 90.5 ± 3.5%, could be a useful alternative delivery mechanism for sitagliptin oral treatment. The nanoparticles had a yield of 77.4% and a drug content of 90.5 ± 3.5%. They released drugs in two phases: quickly (24.9 ± 2.7% at 30 min) and gradually (98.9 ± 1.8% over 12 hours). The nanoparticles also increased sitagliptin retention in the gastrointestinal tract (GIT) compared to controls, suggesting their potential as an effective oral medication delivery mechanism. [82]

Begum A, et al., (2019) developed floating tablets of Sitagliptin using hydroxypropyl methyl cellulose (HPMC), Xanthum gum, and Guar gum polymers. Floating pills were created utilizing an effervescent technique using sodium bicarbonate as a gas former. The tablets were prepared using the direct compression method. The polymers were tested based on their swelling characteristics and floating time. The in-vitro drug release profile shows that increasing polymer concentration leads to more sustained release. The formulation with 40% Guar gum was optimized for medication release lasting up to 12 hrs. Optimized formulation with 35 mg of floating agent per tablet achieved the required floating lag time. [83]

Ghumman SA, et al., (2018) formulated a floating controlled release drug delivery system of Sitagliptin phosphate to increase drug bioavailability. Tablets were made by wet granulation with psyllium husk and tragacanth gum as release retarding polymers and sodium bicarbonate as a gas generator. Nine batches of floating tablets were tested for physical properties, with all formulations having a floating lag time of less than 1 minute and floating continuously for 12 hours. In-vitro drug release studies were conducted for 8 hours, and the release mechanism was further analyzed using linear regression analysis. F9, which contained 30% psyllium husk, 10% tragacanth gum, and 18% sodium bicarbonate, maintained drug release for longer duration. All formulations followed first-order Higuchi drug release kinetics, with diffusion being the major mechanism of drug release. The produced floating tablets of STP (F9) may be a viable drug delivery technology with prolonged release action and increased bioavailability.[84]

Revathi S, et al., (2018) studied the effects of different variables on the release profile of sitagliptin microspheres. The study prepared sitagliptin microspheres using emulsion-solvent diffusion and ionotropic gelation methods, using cellulose and sodium alginate as polymers. The formulations were optimized using a 2^3 factorial design, considering drug-polymer ratio, stirring speed, and production mode. FTIR and DSC analysis revealed no incompatibility between the polymers. The microspheres were tested for shape, morphology, particle size, swelling, encapsulation efficiency, and drug release kinetics. The drug release was sustained, and the diffusion path followed the cube root law of Hixson-Crowell kinetics. The batch F3 was found to be desirable and was further characterized by scanning electron microscope for morphology.[85]

Haq Asif A, et al., (2018) optimized mucoadhesive nanoparticles of sitagliptin. Due to sitagliptin's short half-life, patients must take 50 mg twice daily, and the protein binding of sitagliptin is about 38%. Roughly about 79% of sitagliptin is excreted intact in urine and eliminated without metabolism. Hence, a better delivery system is required to maximize the benefits of sitagliptin for patients. The optimized sitagliptin nanoparticle sizes ranged from 350 to 950 nm, and their surfaces were smooth and virtually spherical. The drug content and percentage yield were 73 ± 2% and 92 ± 2%, respectively. The optimised sitagliptin nanoparticles showed high bioadhesion time

about 6.1 ± 0.5 h. The swelling of the nanoparticles is 168 ± 15%. The release pattern of sitagliptin from mucoadhesive nanoparticles is consistent with the Korsmeyer-Peppas model. The extended sitagliptin retention time of up to 12 hrs in GIT suggests that the optimised mucoadhesive nanoparticle formulation is more efficient and has a higher potential for oral delivery than traditional sitagliptin administration in the drug solution. The optimized mucoadhesive nanoparticles to improve sitagliptin efficacy.[86]

Jahangir MA, et al., (2018) formulated and statistically optimized sitagliptin-loaded Eudragit nanoparticles (SIT-NPs) and evaluated the in-vitro pharmaceutical quality and in-vivo anti-diabetic assessment. SIT-NPs were created using solvent evaporation and nano-precipitation methods. Factors like eudragit RL100 concentration, tween 80 concentration, and sonication duration impacted particle size, drug loading, and in-vitro drug release. The optimized formulation was tested for surface morphology, CLSM, ex-vivo permeability, and in-vivo anti-diabetic efficacy and stability. The SIT-NPs had a particle size range of 135.86-193.45 nm, 6.36-8.76% drug loading, and extended drug release over 24 hours. The study reveals that SIT-NPopt, a new formulation of SIT, has higher release and permeation rates than SIT-Fs, has been shown to lower blood sugar levels over an extended period, and is stable at both temperatures and has a shelf life of 488 days, indicating its potential for future development in diabetes management. [87]

Mishra RV, et al., (2017) examines pre-clinical and clinical studies on DPP4 inhibitors as prospective treatments for metabolic syndrome. They summaries study findings on DPP4 inhibitors' effectiveness in managing obesity, hyperlipidemia, hypertension, atherosclerosis, and cardiometabolic risk. They discussed formulation techniques for DPP4 inhibitors as a dosage form. Common formulation options for DPP4 inhibitors include instant release, sustained release, and combination treatment.[88]

Griffin JD, et al., (2017) formulated sitagliptin as gel reservoir on a transdermal patch, optimized using mathematical modelling, and verified in-vitro diffusion with Franz diffusion cell. The mathematical model was established the ideal design parameters, which comprised 1% w/w cellulose as a drug reservoir, transdermal patch rate control membranes, 1.25 mM beginning drug concentration, 2 mL initial volume,

and a patch size of 4.52 cm^2. To confirm the modelling, this optimized reservoir composition was produced in the transdermal patch system and tested using Franz Cell. The testing results from the constructed transdermal patch system demonstrated that Sitagliptin may be formulated in a patch to attain the desired effective plasma drug concentration in less than one hour and is capable of maintaining glycaemic control for more than 24 hours.[89]

Hayes J, et al., (2016) published an evidence-based review about Sitagliptin/metformin fixed-dose combination in type 2 diabetes mellitus. Type 2 diabetes is a progressive illness with high morbidity and death. The strict glycaemic management lowers the occurrence and progression of problems. To meet glycaemic objectives, patients frequently require a combination of oral medication and/or insulin, as well as lifestyle changes. Unfortunately, many standard medications for type 2 diabetes are linked with weight gain and hypoglycemia, resulting in low compliance and decreasing glycemic control. The sitagliptin is used in type 2 diabetes treatment offered in a fixed-dose combination with metformin. Phase III clinical studies have shown that this combination improves glucose control while having few side effects. They describe pharmacological action, effectiveness and safety along with role of combinations used in practice currently.[90]

Shakya S. (2016) designed and evaluated 50 mg Sitagliptin Phosphate immediate release (IR) tablet using response surface methodology (RSM) using Minitab 16 for optimization study. Minitab 16 was used to create 13 immediate release formulations using a two-factor, two-level Central Composite Design (CCD). The quantities of Sodium Starch Glycollate (SSG) and Croscarmellose Sodium (CCS) in the IR layer were employed as independent variables, while the percent drug release at 15 min was chosen as the dependent variable for optimization. All formulations were developed and tested with appropriate analytical technology. Based on the in-vitro dissolution data (dependent variable/response), the formulation composition with the best drug release for immediate release was determined and used to create optimized tablets, which were then evaluated. The physicochemical properties of all the tablets were satisfactory. The optimized sitagliptin phosphate IR tablet dissolved in 14 sec and demonstrated an initial Sitagliptin release of 99.072% within 15 min.[91]

Ahmed MG, et al., (2016) formulated gastro retentive floating drug delivery systems (GFDDS) of sitagliptin to increase the therapeutic efficacy & gastric residence time and to reduce frequency of administration. As a result, a controlled release drug was preferred in order to create a longer therapeutic effect while also reducing peak and valley effects in plasma concentrations. They developed gastro-retentive dosage forms that remain in the stomach for an extended period of time, allowing the drug to release near the absorption zone. The tablets were made using the direct compression method with polymers such as HPMCK100, polyvinylpyrrolidone, and polyacrylic acid in varying quantities. The prepared granules were evaluated for angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio, with satisfactory results. The compressed formulations were then evaluated for thickness, friability, hardness, swelling index, and in-vitro dissolution studies. All of the formulations produced satisfactory results that were consistent with pharmacopeial norms. In-vitro dissolution tests were performed in pH 1.2 buffers. In-vitro dissolution experiments revealed that the cumulative % drug release of all formulations ranged between 92.96% and 99.28% after 12 hours. The in-vitro drug release data was fitted to a variety of mathematical models.[92]

Kumari S, et al., (2016) developed gastro retentive matrix sitagliptin tablets are intended to prolonged stomach residence duration, boost drug bioavailability, and sustained drug release. The tablets were made using polymers like HPMC, xanthan gum, and a polymer-sodium bicarbonate combination. They were produced through a wet granulation process and tested for pre-compression parameters, physical properties, in-vitro release, buoyancy time, lag-time, and swelling index. Kinetic release studies revealed drug release was primarily diffusion combined with polymeric relaxation. The F13 formulation, which remained buoyant and released 98% of the drug after 12 hours, remained unchanged in physical appearance, content, and floating lag time after three months of storage.[93]

Sakura H, et al., (2016) studied effect of sitagliptin on blood glucose management in people with type 2 diabetes mellitus who had previously been untreated or who responded poorly to existing antidiabetic medicines. A study added sitagliptin to pre-existing type 2 diabetes treatment and compared changes in glycated hemoglobin (HbA1c) levels after three months. Results showed a significant reduction in HbA1c

levels after one month, with a mean reduction of -0.73%. Patients receiving medium dosages of glimepiride showed the least improvement. However, the percentage of patients with a HbA1c level below 7.0% increased dramatically after one month, reaching 53.1% after three months.

Sitagliptin therapy significantly increased the percentage of patients with a fasting blood glucose level below 130 mg/dL, reaching 50.9% after three months. It improved HbA1c levels and goal control levels in type 2 diabetes patients who were untreated or poorly responsive to conventional medications. However, adding sitagliptin to medium-dose glimepiride only minimally improved blood glucose management when adjusted for baseline HbA1c levels.[94]

Brahmandam KK, et al., (2014) developed a novel gastro-retentive floating tablets of Sitagliptin Phosphate employing a direct compression approach with lactose as a diluent. FTIR measurements were used to determine the drug-excipient interaction. Nine formulations of Sitagliptin Phosphate tablets were created using HPMC K100 and HPMC K4M as release retarding agents. All formulations showed minimal weight fluctuation, quick dispersion time, and rapid in-vitro drug release. The best formulation, with 15% HPMC K100, demonstrated an excellent release profile, with full drug release within 24 hours. This suggests that floating tablets of Sitagliptin Phosphate can be prepared effectively with release retarding polymers.[95]

Surinder K, et al., (2013) disguise the highly unpleasant taste of Sitagliptin Phosphate Monohydrate and develop a rapid disintegrating tablet (RDT) of the taste-masked medication. Sitagliptin Phosphate Monohydrate was complexed with Indion 414 in various ratios to disguise its taste. Drug-Resin complexes were evaluated for drug content, in-vitro taste in simulated salivary fluid (SSF), and molecular properties. Complexes that did not release medication in SSF were taste-masked and selected for formulation RDTs. The complex with drug-Resin ratios of 1:1 and 1:2 was chosen. Tablet attributes like tensile strength, wetting time, water absorption ratio, in-vitro disintegration time, and oral cavity disintegration were studied. The study found that batch F2 tablets containing microcrystalline cellulose for Crospovidone disintegrated faster in 25 seconds, with a strong association between disintegration behavior in-vitro and oral cavity. Sitagliptin Phosphate Monohydrate was scored higher, and batch

F2 tablets demonstrated fast drug release in SGF, indicating that the tablets effectively conceal flavor and disintegrate quickly.[96]

Johnson KM, et al., (2011) described Sitagliptin as a DPP-4 inhibitor for the treatment of type 2 diabetes mellitus. Type 2 diabetes mellitus (T2DM) is an epidemic with global forecasts predicting over 336 million people will have the condition by 2030. T2DM is defined as abnormally high blood glucose levels due to lack of insulin secretion or action. Less than half of patients with T2DM maintain good glycemic control. Sitagliptin, a new diabetes treatment authorized in the US and Europe, reduces the action of DPP-4, a peptidase that degrades GLP-1.[97]

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CHAPTER – III

PLAN OF WORK

3.1 Rational of The Study

The drugs are available in in the market majorly in two forms namely Solids or Liquids. The solid dosage forms include Beads, Capsules, Pellets, Spherules, Tablets, etc. The solid dosage forms are popular because they require less storage and transportation space and are cost-effective. They are also more stable than liquid dosage forms.[1]

They are often coated for various reasons, including masking of unwanted sensory properties, protecting against environmental factors and bodily fluids, increasing mechanical strength, improving appearance, enhancing flow, and achieving customized drug release.[2]

The coating agents are usually dissolved or dispersed in a suitable solvent and then sprayed over a substrate. The mixture is dried until a smooth layer is formed. Fluidized bed coaters are generally used for particulate systems, while perforated pan coaters are used for single-unit systems. Solid dosage forms are currently coated using either aqueous or non-aqueous coatings. An aqueous coating can achieve a smooth and lustrous surface. However, the aqueous coating may cause hydrolysis of some drugs and increase microbial burden, leading to decreased drug stability. Aqueous coating also requires more time for drying and consumes more energy.[3,4]

For non-aqueous coating of dosage forms using organic solvents, there are concerns about environmental pollution, solvent recycling costs, and operator safety issues. Organic solvents are expensive. In 1970, the U.S. Environmental Protection Agency (EPA) enforced the Clean Air Act to reduce atmospheric solvent emissions.[5] In 1976, the Occupational Safety and Health Administration (OSHA) restricted the use of organic solvents to prevent exposure of industrial workers.[6,7]

In order to avoid the issues that come with using solvents, an alternative technique called Hot Melt Coating (HMC) was attempted. HMC is a solvent-free method where the molten material is poured or sprayed onto the surface of the substrate. The Beads, Capsules, Microcapsules, Minitablets, Pellets, and Tablets can be coated using the Pan Coating or Fluidized Bed Coating methods. Generally, natural waxes are used as materials for the HMC technique, as they are more cost-effective compared to the polymers used in solvent-based coating. Waxes offer great flexibility in terms of

solubility and safety. The literature survey shows that HMC has a wide range of applications in Drug Delivery Systems.[8]

PART A: TENOFOVIR DISPROXIL FUMARATE

Tenofovir is an acyclic phosphonate nucleotide analog and the base form of the prodrug Tenofovir Disoproxil Fumarate (TDF). It is used in combination with other Antiretroviral drugs for treating adult patients infected with Human Immunodeficiency Virus (HIV) and Hepatitis. The recommended dosage regimen for TDF is once daily due to its long biological half-life. The bitter taste of TDF reduces patient compliance among all age groups including pediatric and adult patients.[9, 10]

The objective of the present investigation was to assess the taste-masking ability of the hot melt coating technique using Tenofovir Disoproxil Fumarate (TDF) as a model drug.

PART B: SITAGLIPTIN PHOSPHATE MONOHYDRATE

Sitagliptin is a novel antidiabetic agent used to treat type 2 diabetes. It works by inhibiting Dipeptidyl Peptidase-4 (DPP-4), which leads to increased levels of Glucagon-like Peptide-1 (GLP-1) and Glucose-dependent Insulinotropic Polypeptide (GIP).[11-14]

It is a white or off-white crystalline hygroscopic solid with a specific odor.[12,14] The formation of hydrates is crucial in the pharmaceutical industry due to the prevalence of water vapor, as hydrates tend to be more stable.[15] Consequently, the presence of solvates and hydrates significantly impacts the physicochemical properties of the crystals.[16]

Sitagliptin Phosphate Monohydrate (SPM) is commonly used in the pharmaceutical industry. However, little is known about other crystalline forms, such as the anhydrous and base form. This includes the effect of the dehydration process and the production of the base form on the physical and chemical stability of this pharmaceutical hydrate.[15,16]

It is primarily absorbed through the intestine with 89% oral bioavailability. It has a plasma half-life of 11-12 hours and 38% protein binding after oral administration.[17-19] The peak plasma concentration is achieved within 2 hours. Sitagliptin Phosphate is

rapidly absorbed from the gastrointestinal tract. It is administered in doses of 25mg, 50mg, or 100mg once a day, as it is extensively excreted through urine.[16]

Based on the literature review, Sitagliptin is sensitive to water and moisture. It is usually advised to store it in a cool, dry place, away from moisture and light, to maintain its potency and stability. Exposure to water or high humidity can lead to degradation of the drug, which may impact its effectiveness and shelf life. Therefore, some specific storage conditions are recommended for Sitagliptin:

1. Store in a tightly closed container, protected from moisture.
2. Store at room temperature (20°C - 25°C or 68°F - 77°F).
3. Keep away from light and moisture.
4. Do not store in a humid environment.

It is important to note that Sitagliptin is a hygroscopic drug, meaning it tends to absorb moisture from the air. Therefore, it is important to handle the drug carefully and store it in a way that minimizes exposure to moisture. It is important to follow proper handling and storage procedures to maintain the drug's potency and stability. This may include using a desiccant or other moisture-control measures to maintain a dry environment.[20,21]

Numerous solutions have been reported to enhance the stability of drugs in dosage forms like Coating, Microencapsulation, Complexation, etc. The aqueous and solvent-based coatings have multiple demerits and therefore an attempt has been made to improve the stability of Sitagliptin using Hot Melt Coating (HMC). HMC is an easy, economical, flexible, and rapid method to achieve the objective.

3.2 Plan of The Research Work

Part A:

1. Literature Survey
2. Selection of Hot Melt Coating (HMC) agents
3. Analysis of Drug properties
4. Design of Experiments
    a. Preparation of Hot Melt Coated Tenofovir Disoproxil Fumarate (TDF) Pellets and suitability of use of simple equipment such as coating pan.
    b. Preparation of Tablets using Hot Melt Coated TDF Pellets

5. In-vitro Dissolution Study
6. Evaluation of Taste masking using in-vitro method and taste panel method
7. Stability Studies

Part B:

1. Literature survey
2. Selection of Hot Melt Coating (HMC) agents
3. Analysis of Drug properties
4. Design of Experiments (Compression and Coating)
5. Evaluation of Core and Hot Melt Coated Tablets
6. In-vitro Dissolution- testing of Hot Melt Coated Tablets.
7. Comparison with marketed formulation
8. Stability Studies

CHAPTER – IV

AIM AND OBJECTIVE

4.1 AIM

The present research is aimed at **"Design and Characterization of Drug Delivery System using Hot Melt Coating Technique."** This involves the application of Hot Melt Coating (HMC) for

A. Taste Masking of Tenofovir Disoproxil Fumarate (TDF)
B. Improvement in Stability of Sitagliptin Phosphate Monohydrate (SPM)

4.2 Objectives

The important objectives of the proposed research work were,

1. Characterization of Tenofovir Disoproxil Fumarate (TDF) and Sitagliptin Phosphate Monohydrate (SPM) API.
2. Designing the manufacturing process for a pre-determined aim.
3. Selection of raw materials.
4. Optimization and evaluation of Manufacturing Process Parameters.
5. Evaluation of the final product of Tenofovir Disoproxil Fumarate (TDF) for Taste Masking and Stability Improvement for Sitagliptin Phosphate Monohydrate (SPM).
6. Comparative Dissolution Assessment.
7. Stability Evaluation of Optimized Dosage Forms.

4.3 Quality Target Product Profile (QTPP)

Part A:

The QTPP for Tenofovir Disoproxil Fumarate Pellets and Tablets is outlined in the table below. The Quality Attributes identified as Critical Quality Attributes (CQAs) are also provided. The goal is to develop solid oral dosage form pellets and tablets. The objective is to investigate the potential of the Hot Melt Coating technique for Taste-masking when formulating either Pellets or Tablets. Taste masking for the pellets is particularly important for pediatric and elderly patients who have difficulty swallowing large tablets.[22, 23]

Table 4.1 : Quality Target Product Profile (QTPP) for TDF Pellets and Tablets

QTPP Elements	Target (Pellets)	Target (Tablets)
Dosage form	Pellets (in Sachets)	Tablets (in Bottles)
Dosage design	Immediate Release	Immediate Release
Route of administration	Oral	Oral
Dosage Strength	300 mg	300 mg
Stability	At least 24 months at room temperature	At least 24 months at room temperature
Drug product Quality attributes	Physical attributes	Physical attributes
	Taste-masking (Bitterness)	Taste-masking (Bitterness)
	Assay	Assay
	Dissolution	Dissolution
Container closure system	Suitable for product stability	Suitable for product stability

Part B:

The QTPP for Sitagliptin Phosphate Tablets 50mg (SPM)is defined in the following table. The quality attributes that were identified as drug product Critical Quality Attributes (CQAs) are also given below. The target is to formulate a Hot Melt Coated Tablets. The aim is to explore the potential of the hot melt coating technique for stability enhancement.[22,23]

Table 4.2 : Quality Target Product Profile (QTPP) for SPM Tablets

QTPP Elements	Target
Dosage form	Hot Melt Coated Tablets
Dosage design	Immediate Release
Route of administration	Oral
Dosage Strength	50 mg
Stability	At least 24 months at Room Temperature
Drug product Quality attributes	Physical attributes
	Moisture uptake

QTPP Elements	Target
	Assay
	Dissolution
Container closure system	Suitable for product stability

4.4 Critical quality attributes

The Drug Product Critical Quality attributes of the drug products were identified[24] as below-

Part A:

Table 4.3 : Critical Quality Attributes of TDF Pellets

Drug Product Quality Attributes		Target	Is this CQA?	Justification
Physical Attributes	Appearance	White to off-white coated pellets	No	For better patient acceptance and compliance with treatment regimens, the target for pellet size is set. Formulation and process variables do not impact appearance. The size of pellets is controlled by fixing the screen sizes. Hence, it is not critical.
	Size	Easily swallowable	No	
	Taste	No Bitter taste	Yes	Affects patient acceptability, hence it is Critical.
Assay		95-105%	Yes	Assay variability will affect safety and efficacy and is influenced by process variables.
Dissolution		NLT 80% (Q) in 30 minutes	Yes	Failure to meet the dissolution specification may impact on therapeutic efficacy. Both formulation and process variables may affect dissolution.

Table 4.4 : Critical Quality Attributes of TDF Tablets

Drug Product Quality Attributes		**Target**	**Is this CQA?**	**Justification**
Physical Attributes	Appearance	White to off white tablets	No	Similar to marketed products. Formulation and process variables do not impact appearance and size. Hence, it is not critical.
	Size	Similar to marketed	No	
	Taste	No Bitter taste	Yes	Affects patient acceptability, hence CQA.
Assay		95-105%	Yes	Assay variability will affect safety and efficacy and is influenced by process variables.
Dissolution		NLT 80%(Q) in 30 minutes	Yes	Failure to meet the dissolution specification may impact on therapeutic efficacy. Both formulation and process variables may affect dissolution.

Part B:

Table 4.5 : Critical Quality Attributes of Sitagliptin Phosphate Monohydrate Tablets

Drug Product Quality Attributes		**Target**	**Is this CQA?**	**Justification**
Physical Attributes	Appearance	White to off-white tablets	No	Similar to marketed products. Formulation and process variables do not impact appearance and size. Hence,
	Size	Similar to	No	

Drug Product Quality Attributes	Target	Is this CQA?	Justification
	marketed		it is not critical.
Assay	90-110%	Yes	Assay variability will affect safety and efficacy and is influenced by process variables.
Moisture uptake	NMT 2%	Yes	Moisture uptake by the drug will result in degradation and loss of assay.
Dissolution	NLT 80% (Q) in 30 minutes	Yes	Failure to meet the dissolution specification may impact on therapeutic efficacy. Both formulation and process variables affect dissolution.

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CHAPTER – V

MATERIALS AND METHODS

PART A:

5.1 Drug Profile: Tenofovir Disoproxil Fumarate (TDF)

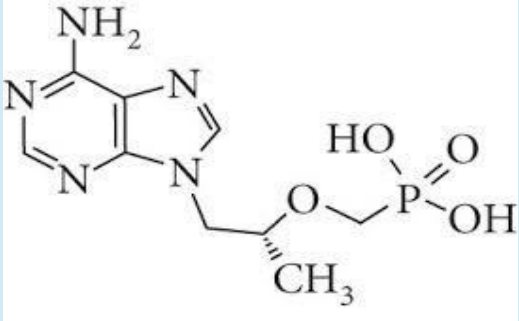
Tenofovir Disoproxil Fumarate is a tenofovir prodrug that is the fumaric acid salt of tenofovir's bis-isopropoxycarbonyloxymethyl ester derivative. In vivo, TDF is transformed into tenofovir, an acyclic nucleoside phosphonate (nucleotide) analogue of adenosine 5'-monophosphate. Tenofovir has action against HIV-1 reverse transcriptase. It is used in conjunction with other antiretroviral medications to treat human immunodeficiency virus type 1 infection in adults and paediatric patients aged two years and up who weigh at least ten kilogrammes. It is used to treat chronic hepatitis B virus (HBV) in adults and children aged two and above who weigh at least ten kilogrammes.[1]

Category: Nucleoside Reverse Transcriptase Inhibitor (NRTIs) namely HIV-1 reverse transcriptase inhibitor and an HBV reverse transcriptase inhibitor (HBV RTI)

Mechanism of Action: It is an acyclic nucleoside phosphonate diester, similar to adenosine monophosphate. It requires diester hydrolysis to become tenofovir, which is subsequently phosphorylated by cellular enzymes to become tenofovir diphosphate (TFV-DP), an essential chain terminator. Tenofovir diphosphate inhibits HIV-1 and HBV reverse transcriptase (RT) activity by competing with the natural substrate deoxyadenosine 5'-triphosphate and, if incorporated into DNA, ending the chain. Tenofovir diphosphate is a mild inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.[2]

Table 5.1 : Characteristics of Tenofovir Disoproxil Fumarate

Parameter	Tenofovir Disoproxil Fumarate
CAS No.	202138-50-9
Chemical Name	Tenofovir disoproxil fumarate is 9-[(R)-2[bis[[(isopropoxycarbonyl)oxy]-methoxy] phosphinyl] methoxy] propyl] adenine fumarate (1:1}
Empirical Formula	$C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$
Molecular Weight	635.52
Description	White to off-white bitter crystalline powder with

Parameter	Tenofovir Disoproxil Fumarate
	characteristic odor
Melting point	114-118°C
Structure	
Solubility	About 13.4 mg/mL in distilled water at 25 °C. In ethanol and DMSO solubility is about 100 mg/ml. Solubility in 0.1N hydrochloric acid is about 78.2 mg/ml and in methanol is about 96.3 mg/ml.
(log P)	1.25 at 25 °C
Peak plasma time (T_{max}):	1-1.4 hours
Metabolism	Metabolized by CYP enzymes.
Excretion	About 70-80% tenofovir is recovered in urine unchanged in 72 hours
Half-life	Approximately 17 hours
Dosage forms & Strengths	Tablets, Oral Powder 300 mg
Storage	Store tenofovir tablets or tenofovir powder dosage form at 20 to 25°C. The bulk powder of tenofovir should be below 4°C. Store in tightly closed container. Keep away the tenofovir tablets or tenofovir powder dosage form from the reach of children.

5.1.1 Determination of Organoleptic Properties (TDF)

The organoleptic properties of Tenofovir disoproxil fumarate were determined by sensory evaluation like color, odor, and taste.

Table 5.2 : Organoleptic Properties of Tenofovir Disoproxil Fumarate

Parameter	Observed
Color	White to off-white
Odor	Characteristic
Taste	Bitter

Inference: The taste of Tenofovir Disoproxil Fumarate was found to have bitter characteristics.

5.1.2 Particle Size Distribution (TDF):

The particle size distribution of Drug substance referred from Vendor COA. The method of testing is Malvern Master sizer.[3]

Inference: The Particle size distribution of Tenofovir disoproxil fumarate API: d (0.9) – 190 µm.

5.1.3 Density and Flow Properties (TDF):

Bulk density is the ratio of bulk weight to bulk volume. Fifty g of API was precisely weighed and carefully poured via a glass funnel into a 100 ml calibrated measuring cylinder. The surface was carefully levelled with no pressure.[4] The volume occupied by pellets was utilised to calculate the bulk density (g/ml) using the equation,

Bulk density = Weight of powder ÷ $Bulk\ volume\ of\ pellets$…….(5.1)

Tapped density is ratio of bulk weight and tapped volume. Tapped density was estimated in a similar way to that of bulk density. However, final volume was measured after tapping the cylinder from 3 inches until constant volume was obtained using Electrolab tapped density apparatus.[4] The volume occupied by pellets after tapping was noted and tapped density (g/ml) was calculated using the equation,

Tapped density = Weight of powder ÷ Tapped $volume\ of\ pellets$…….(5.2)

Carrs's Index is calculated using bulk density and tapped density data.[5]

$Carr's\ Index = (Tapped\ density - Bulk\ density) \div Tapped\ density \times 100$ …….(5.3)

Density and flow properties of Tenofovir disoproxil fumarate API was evaluated and the results are given in the following table,

Table 5.3 : Density and Flow Properties of TDF

Bulk density (g/mL)	Tapped density (g/mL)	Carr's Index (%)
0.35	0.51	30.85

Inference: Tenofovir disoproxil fumarate API showed poor to very poor flow characteristic.

5.1.4 Solubility of Tenofovir Disoproxil Fumarate

The aqueous solubility of the drug is significant in drug absorption. When the drug is administered orally, the composition of GI fluid changes with the position of the dosage form. Therefore, to simulate the conditions, the solubility of the drug in 0.1N HCl, distilled water, and phosphate buffer pH 6.8 was determined. Also, the solubility was determined in ethanol, methanol, and DMSO.[6]

Technique: Equilibrium solubility method was used.

Procedure: It is determined by placing 1 g of TDS in 100 ml of distilled water on a rotatory shaker for 24 hr at 37°C.After 24 hours the solution was filtered using 0.45 µ member filter. The amount dissolved in the filtrate was determined using UV- Visible spectrophotometer at 260 nm.[6,7]

Table 5.4 : Solubility of TDF

Solvent	Solubility (mg/ml)
0.1 N HCl	77.86 ± 2.06
Distilled water	13.27 ± 0.45
pH 6.8 phosphate buffer	68.33 ± 1.96
Ethanol	97.42 ± 3.57
Methanol	80.09 ± 2.81
DMSO	101.55 ± 3.32

Inference: The highest solubility among aqueous media is in 0.1 N acid and the lowest in distilled water. Among the organic solvents, highest solubility is found in DMSO.

5.1.5 Melting point of TDF:

The melting point of Tenofovir disoproxil fumarate API was evaluated using two different methods, Capillary technique using mineral oil and Differential Scanning Calorimetry (DSC)[8]

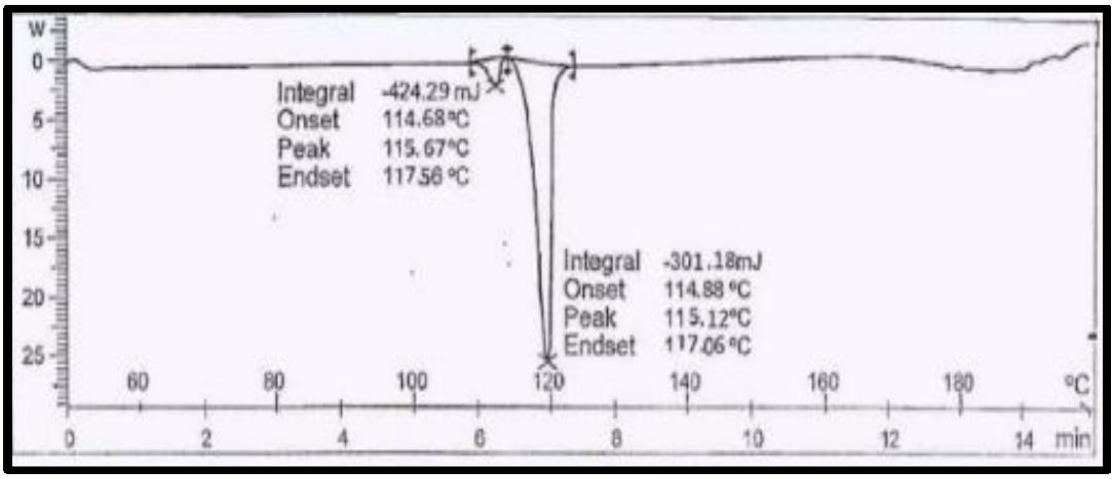


Fig. 5.1 : DSC Thermogram of Tenofovir Disoproxil Fumarate

Inference: Melting point of Tenofovir disoproxil fumarate API found to be between 115-118°C (by Capillary technique) and 115.67°C (by DSC).

5.1.6 Loss on Drying of TDF

The Loss on drying is determined using Hot air oven technique. The 1 g of TDF at 105±2°C was kept in hot air oven till constant weight was observed.

Inference: The % Loss on Drying for TDF sample was found to be 1.23%.

5.2 Risk Assessment for Drug Substance Attributes of TDF

A risk evaluation of the drug substance attributes was conducted to determine the potential influence of each attribute on the drug product Critical Quality Attributes. The assessment results and related reasoning are summarised here. The relative risk of each trait was rated as high, medium, or low. The high-risk features deserved additional research, but the low-risk attributes did not. According to current

understanding, a medium risk is tolerable. Further examination of medium risk may be required to lessen the danger.[9]

Table 5.5 : Overview of Relative Risk Ranking System

Low	Broadly acceptable risk. No further investigation is needed.
Medium	Risk is accepted. Investigation may be needed in order to reduce the risk.
High	Risk is unacceptable. Investigation is needed to reduce the risk.

The risk assessment of drug substance qualities that affect drug product CQAs is provided below based on the drug substance's physicochemical parameters.

Table 5.6 : Risk Assessment of the Drug Substance Attributes for TDF

Drug product CQA	Tenofovir drug substance attributes					
	Organoleptic properties	**Particle size**	**Solubility**	**Melting point**	**Loss on drying**	**Flow properties**
Taste	High	Low	Low	Low	Low	Low
Content uniformity	Low	Low	Low	Low	Low	Low
Assay	Low	Low	Low	Low	Low	Low
Dissolution	Low	Medium	Medium	Low	Low	Low

Table 5.7

Drug Substance Attributes	Drug Product CQAs	Justification
Organoleptic Properties (Color, Odor, Taste & nature)	Taste	High risk as the taste of API is bitter, so it impacts patients' acceptance. It may induce nausea.
	Content Uniformity	Low risk as organoleptic characteristics has no direct impact on Content uniformity, assay and dissolution.
	Assay	
	Dissolution	

Particle size	Taste	Low risk as Particle size has no direct impact on taste
	Content Uniformity	Particle size may have impact on flow properties and hence, assay and content uniformity. However, API is being granulated. Hence risk is low.
	Assay	
	Dissolution	Particle size may have impact on dissolution hence risk is medium.
Melting Point	Taste	Low risk as Melting Point has no direct impact on taste, Content uniformity, assay, and dissolution
	Content Uniformity	
	Assay	
	Dissolution	
Solubility	Taste	Low risk as Solubility has no direct impact on taste, content uniformity, assay and dissolution
	Content Uniformity	
	Assay	
	Dissolution	The solubility of drug substance in dissolution medium has impact on dissolution. The risk is medium.
Loss on Drying	Taste	Low risk as Loss on drying has no direct impact on taste, content uniformity, assay, and dissolution.
	Content Uniformity	
	Assay	
	Dissolution	
Flow Properties	Taste	Low risk as Flow properties has no direct impact on taste.
	Content Uniformity	Tenofovir disoproxil fumarate has very

	Assay	poor flow property. However, the drug substance would be subjected to dry granulation process to facilitate blend flow. Hence, impact of flow of Tenofovir disoproxil fumarate on content uniformity and assay is low.
	Dissolution	Flow of Tenofovir disoproxil fumarate is unlikely to impact dissolution. The risk is low.

5.3 Excipients for TDF:

The excipients were selected based on literature search, the requirement of immediate-release tablets and pre-formulation studies. Excipients were selected based on their functionality. For development of tablet dosage form, the grades suitable for wet granulation process and hot melt coating were selected.

5.3.1 Gelucire 43/01

A glyceride with intermediate melting point used as a matrix agent for sensitive APIs and a viscosity-increasing agent in oral and topical formulations. It is composed of mono-, di- and triglyceride esters of fatty acids (C_8 to C_{18}), the triester fraction being predominant. It is available in pellet form. It is a blend of saturated triglycerides of different fatty acids, viz., C8 - 3%, C10 - 2%, C12 - 29%, C14 - 2%, C16 - 17%, and C18 - 36%. Gelucire® 43/01 is ideal for API protection and capsule filling. Matrix-former for protection of APIs sensitive to oxidation, humidity, or light. It is composed of PEG-esters, a small glyceride fraction and free PEG. It is a solid at ambient temperature making it suitable for capsule filling, melt granulation and extrusion. It is available in pellet form.[10]

Synonyms (USP/NF/JPE/EP): Hard fats

Preferred FDA Name: Fat, Hard

CAS Number: 157710-38-8

Melting point: 42-46°C

Category: Protective, Lubricant, 3D printing drug carrier, emulsifier, viscosity modifier, solubilizes.

HLB: 1-2

Drop point: 53-57°C

Mean particle size: 50 μ

Formulations & Processes: Melt processes: granulation and capsule molding. Topical lotions, emulsion and ointment.

Pharmacopoeial compliance: Yes

Solubility: It is hydrophobic grades and insoluble in water.

Applications: Diltiazem hydrochloride (melt granulation) as matrix carrier in multi-unit floating drug delivery system, Metoprolol succinate (melt granulation) in sustained release floating drug delivery system, Cefuroxime axetile (melt granulation filled in capsule) in enhancement of bioavailability, Famotidine in floating tablet, Metformin hydrochloride (melt granulation) in enhancement of bioavailability, Tramadol HCL mouth dissolving tablets for taste masking, and increase drug release on aging from matrices using Gelucire® 43/01. It is used as a lipid binder in melt techniques so that the physicochemical properties and plasticity of the lipid agglomerate offers high resistance to fracture, useful for flash melt and chewable tablets.[10]

Safety: Safety of use is supported by toxicological data and food additive status.

Storage: Store in cool and dry place in moisture resistant plastic containers.

5.3.2 Precirol ATO 5

A glyceride with an intermediate melting point that is utilised as a lubricant and flow aid in powder mixes for capsule filling, as well as a coating agent for flavour masking. It is an organic molecule classified as long-chain fatty acid. These are fatty acids having an aliphatic tail that comprises 13 to 21 carbon atoms. Stearic acid is also commonly used as a solid lipid in the manufacture of NLCs. Aadhunik Industries is India's leading manufacturer of Glyceryl Palmitostearate or Glycerol Palmitostearate, Speciality Chemicals, Pharmaceutical Excipients, Food Fragrance and Flavour chemicals. It is made via direct esterification of stearic and palmitic acids with glycerine in the absence of a catalyst. FDA recommended as excipient in non-parenteral formulations.[11,12]

Synonym: Glycerin Palmitostearate; Glycerol Palmitostearate; 2-[(1-oxo-hexadecyl)-oxyl]-pxy]-1,3-Propanediyl Dicotadecanoate and 1,2,3-Propane Triol; Glyceryl Distearate; Glyceryl Distearate (Type I); Precirol® ATO 5

CAS Number: 8067-32-1

CAS name: Precirol ATO 5

Pharmacopoeial Compliance: USP-NF; Ph.Eur

IUPAC Name: Hexadecanoic acid; octadecanoic acid; propane-1,2,3-triol

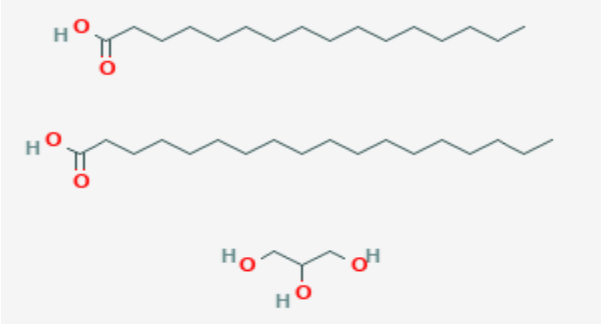


Fig. 5.2: Structure of Precirol ATO 5

Appearance: Fine white waxy powder.

Solubility: Freely soluble in chloroform and dichloromethane but practically insoluble in water, mineral oil and alcohol.

Category: Lubricant and flowing aid for capsules, coating for protection and taste masking, lipid matrix for sustained release and SLN/NLC, viscosity modification. It works as stabilizer, non-ionic emulsifier, emollient, gelling agent and as plasticizer in pharmaceutical formulations.

Molecular formula: $C_{37}H_{76}O_7$

Molecular weight: 633.0 g/mol

Melting point: 50-60 °C

Boiling point: 200°C

Drop point: 53-57°C

Flash point: 162 °C

Heavy metal: 10 ppm maximum.

Dosage forms: Oral and topical formulation

Particle size: About 50-60 µ

Hydrogen bond donor: 5

Hydrogen bond acceptor: 7

Covalently bonded unit: 3

Acid value: < 6

Iodine value: < 3

Peroxide value: < 3

Hydroxy value: 60-115

Saponification value: 175-195

Water content: < 1%

Free glycerine content: < 3%

1- Monoglyceride content: < 8-11%

Unsaponified matter: < 1%

Sulphated ash: < 0.1%

HLB: 1-2

Median lethal dose, LD_{50} (Rat oral dose): > 6 g/kg

GHS Hazards: Not classified. Food and Drug Administration (FDA) added to food substances (Document 184.1329)

Applications: In solid dosage forms as lubricant, matrix former in sustained release dosage forms using melt granulation or hot melt coating technique. It is used in immediate release formulation. It is used as polymer in microcapsules preparations and converting into tablet or capsule unit dosage form. It is used as biodegradable injectable gel.

Storage: It should be stored at temperature not exceeding 35 °C.

Containers: Air tight container, protected from light and moisture.

Incompatibilities: Ketoprofen and naproxen

5.3.3 Microcrystalline Cellulose (Avicel PH 101)

Synonyms: Avicel PH; Cellets; Celex; cellulose gel; hellulosum microcristallinum; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur.

Molecular Formula: $(C_6H_{10}O_5)_n$, $n \approx 200$

Molecular weight: 36000g/mol

CAS Number: 9004-34-6

Structural Formula:

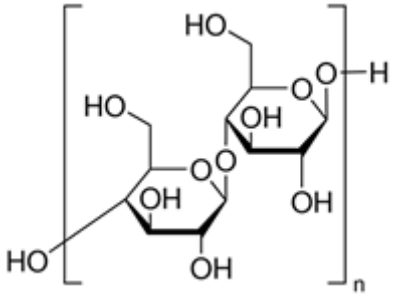


Fig. 5.3 : Structure of Microcrystalline Cellulose

Functional Category: Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrates.

Description: It is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

Solubility: Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

pH: pH 5.0-7.5

Melting point: Chars at 260–270°C.

Angle of repose: 33-49°

Bulk density: 0.337 g/ml

Tapped density: 0.478 g/ml

True density: 1.512- 1.668 g/ml

Moisture content: < 5%

Particle size: 20-200µ

Specific surface area: 0.78- 1.30 m^2/g

Incompatibilities: Microcrystalline cellulose is incompatible with strong oxidizing agents.

Stability & Storage condition: Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Applications: Microcrystalline cellulose is widely utilised in medicines, particularly as a binder/diluent in oral tablet and capsule formulations using both wet-granulation and direct-compression processes. In addition to its function as a binder/diluent, microcrystalline cellulose possesses lubricating and disintegrating qualities that make

it valuable in tableting. Microcrystalline cellulose is also utilised in cosmetics and culinary goods.[13]

Incompatibilities: It is incompatible with strong oxidizing agents.

Handling precaution: It may be irritant to the eyes. Use of gloves, eye protection aid, and dust mask is recommended.

Stability: Stable although it is hygroscopic material.

Storage: Store in well closed container in cool and dry place.

5.3.4 Spray Dried Lactose (DCL 11)[14]

Synonyms: Lactopress Spray-Dried, FlowLac 100, NF Lactose–316 Fast Flo, Pharmatose DCL 11, Pharmatose DCL 14, Super-Tab Spray-Dried, NF Lactose–315, Flowlac, Granulac, Microfine, Pharmatose, Prismalac, milk sugar, HMS, Sorbolac, Super-Tab, Tabletosse, Wyndale, Zeparox, Lactochem, Inhalac, Capsulac, Fastflo.

Chemical name: It is a mixture of α-and-β-lactose, and O-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate. O-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose anhydrous

CAS registry number: 63-42-3 and 64044-51-5.

Molecular formula: $C_{12}H_{22}O_{11}$ and $C_{12}H_{22}O_{11}.H_2O$

Molecular weight: 342.30 (anhydrous) and 360.31 (monohydrate)

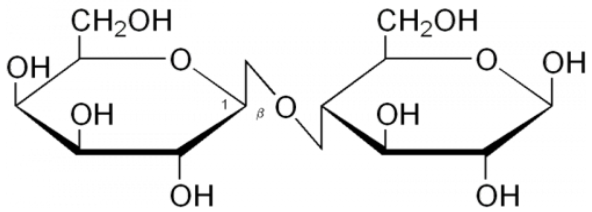


Fig. 5.4: Structure of Lactose

Category: Diluent or filler directly compressible tablet and capsule, binder. Diluent in dry powder inhaler.

Description: It is white or off-white crystalline odorless powder with sweet in taste. It is directly compressible and normally composed of 80–90% of α-lactose monohydrate and 10–20% of amorphous lactose. The α- lactose is about 15% sweet in comparison with sucrose. The β- lactose is sweeter than α- lactose.

Solubility: It is water-soluble, insoluble in ether and chloroform and having slight solubility in ethanol.

pH (10% solution): 4.5 to 7.5

Optical rotation: + 55.4 °

Melting point: 202–205 °C

Flash point: 358–360 °C

Bulk density: 0.57 – 0.62 g/ml

Tapped density: 0.67 – 0.78 g/ml

Moisture content: Maximum 6

Loss on drying: 0.3 – 0.6%

Osmolarity: 9.75% is osmolar with serum

Pharmaceutical applications: As a binder, filler-binder, spray-dried lactose is majorly preferred in direct compression of tablets.

Storage: Containers must be firmly sealed stored in a well-closed container in a cool, dry place.

Incompatibilities: Spray dried lactose is incompatible with agents with primary amino group, with amino acids, aminophylline, amphetamines, and also with lisinopril. Maillard reaction may occurs between lactose and these compounds to produce brown or yellow brown-coloured products.

Safety: Spray dried lactose is employed as diluents in oral solid medicaments. It is also preferred in parenteral. Lactose shows adverse reactions due to its intolerance, majorly in persons with deficient of enzyme lactase.

Handling precautions: Normal precautions as per the conditions and extent of material being handled need to be observed. During handling extreme creation of dust and inhalation of dust must be avoided.

5.3.5 Polyvinyl Pyrrolidone K-30[15]

Povidones are a family of water-soluble polymers based on N-vinylpyrrolidone that combine a unique set of properties for application in a wide variety of dosage forms. These are prepared by synthetic reaction. They contain linear chain of 1-vinyl 2-pyrrolidone with varying degree of polymerization. Based on polymerization molecular weight of polymer changes. The viscosity of these polymers is based on K-value, which is range from 10-120 corresponding to molecular weight range from 2,500 to 30,00,000. It manufactured by spray drying spherical form. They are commonly used as binders for the development of tablet formulations, whether

manufactured by wet granulation, dry granulation, or direct compression. The special grade pyrogen free povidone grades are available for parenteral preparation. These polymers are used in solid dispersion formulations to enhance the solubility of active pharmaceutical ingredients and increase bioavailability. Their various grades are also used to inhibit recrystallization in liquid soft gels. It was firstly used as plasma expander in 1940, now it was replaced by dextran. It is not absorbed by GIT and mucous membrane. It does not cause irritation to skin and mucous membrane and hence included in GRAS list.

Synonyms: Kollidone; Povidone; Plasdone; Poly[1-(2-oxo-1-pyrrolidinyl) ethylene];

Non-proprietary Names: BP, JP, USP: Povidone, and PhEur: Povidonum

Chemical Name: 1-Ethenyl-2-pyrrolidinone homopolymer

CAS Registry Number: 9003-39-8

Molecular formula: $(C_6H_9NO)_n$

Molecular weight: 50, 000

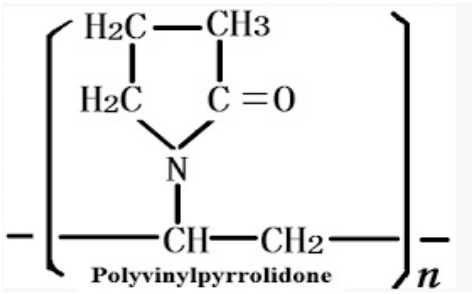


Fig. 5.5 : Structure of Polyvinyl Pyrrolidone

Description: Colourless to almost colourless, fine, white to creamy amorphous hygroscopic powder. It is pH stable and form transparent film.

Odour: Odourless

Melting point: 150° C

Residue on ignition: ≤ 0.05 %

Water content: ≤ 5.00 %

Sulphated ash: ≤ 0.10 %

pH of solution (5% at 25° C in water): 3.0-5.0

Viscosity of solution (5% at 25° C in water): 2.4 cP

K-value: 27-32.4

Residual monomer content: 0.8%

Peroxide content: ≤ 400 ppm

Hydrazine content: ≤ 1 ppm

Lead content (USP): ≤ 10 ppm

Nitrogen content: 11.5-12.8%

Bulk density: 0.29-0.39 g/ml

Tapped density: 0.39-0.54 g/ml

True density: 1.180 g/ml

Solubility: Freely soluble in acids, chloroform, ethanol Practically insoluble in ether. Soluble in water (0.5g/ 10 ml).

Functional category: Disintegrant; dissolution enhancer; emulsion stabilizer in creams & lotions, dispersant, suspending agent; tablet binder, viscosity modifier & coating agent.

Storage and Precautions: It darkens on heating at 150°C and reduce aqueous solubility. It is stable heat exposure around 110– 130°C for short cycle.

Incompatibilities: It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds. Handling precautions: Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

Regulatory status: Accepted as a food additive in Europe. Listed in the FDA Inactive Ingredients Database (IM and IV injections; ophthalmic preparations; oral capsules, drops, granules, suspension tablets; sublingual tablets; topical and vaginal preparations).

Applications: Used in adhesives, inks, glue stick, synthetic fiber and porous membrane manufacture. Dispersant in ceramics.

Storage: Store in tightly closed in a dry, cool and well-ventilated place. The containers should be resealed immediately after use and kept upright to prevent leakage.

Incompatibilities: The efficacy of preservatives like thiomersal was affected adversely by complexation when used with povidone.

Precautions: Avoid skin, and eye contact. Avoid inhalation of vapour or mist. Normal measures to be taken for preventive fire protection. Use protective aids.

Consult a physician in any case of following-

1. If inhaled or breathed in, move person into fresh air.
2. If not breathing, give artificial respiration.
3. In case of skin contact, wash off with soap and plenty of water.
4. In case of eye contact, rinse thoroughly with plenty of water for at least 15 minutes
5. If swallowed, never give anything by mouth to an unconscious person. Rinse mouth with water.

5.3.6 Alpha- Tocopherol[16]

Alpha-Tocopherol is a naturally occurring fat-soluble fatty molecule with varied levels of powerful antioxidant action, often known as vitamin E. It is an amphipathic chemical present in plant tissues, although it may also be produced synthetically. RRR-alpha-tocopherol acetate is a relatively stable version of vitamin E that is frequently employed as a food ingredient when necessary. It has the capacity to neutralise endogenous free radicals. Vitamin E naturally occurs in eight fat-soluble isoforms: α-, β-, γ-, and δ-tocopherol, as well as α-, β-, γ-, and δ-tocotrienol. Supplementing with α-tocopherol is the only way to correct symptoms of vitamin E insufficiency, as the body preferentially utilises it. Tocopherol additionally protects the skin from the sun's damaging UV radiation. It is used in a broad range of goods, including sunscreens and moisturisers, cosmetics, hair styling products, and more. It also acts as a preservative, keeping the items fresh. It is used as a moisturising and conditioning agent. It has anti-inflammatory qualities that moisturise and heal damaged, brittle hair. Tocopherol's antioxidant capabilities encourage healthy hair.

Synonym and trade name: Tocopherol; α-Tocopherol; Vitamin E; alpha-Tocopherol; Copherol Fl300; Vitamin E; all-rac- α-Tocopherol; DL-α-Tocopherol; α-Tocopherolum; E307; RRR-α-Tocopherol; Synthetic alpha Tocopherol; all-rac-α-Tocopherol;

Molecular formula: $C_{29}H_{50}O_2$

Molecular weight: 430.71

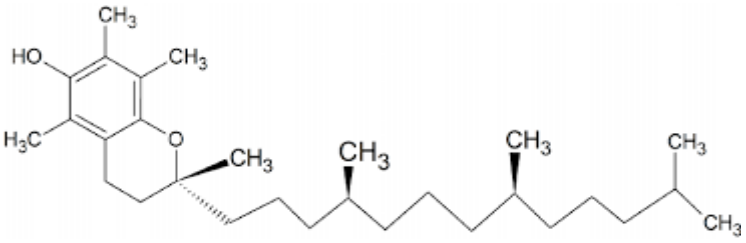


Fig. 5.6 : Structure of Alpha-tocopherol

IUPAC Name: 2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-6-chromanol, (±)-3,4-Dihydro-2,5,7,8-Tetramethyl-2-(4,8,12-Trimethyltridecyl)-2H-1 Benzopyran-6-ol; 5,7,8-trimethyltocol

CAS Number: 59-02-9

Category: Antioxidant; Fatting Agent; and Therapeutic Agent

Description: Alpha Tocopherol is supplied as a clear, colourless or yellowish-brown, viscous oily liquid.

Solubility: Soluble in DMSO (100 mg/ mL) and ethanol (100 mg/ mL) require ultrasonication. Practically insoluble in water. Freely soluble in ethanol, ether, acetone, and vegetable oils.

Melting point: 2.5-3.5°C

Boiling point: 200-220°C

Acid value: ≤ 2

Optical rotation: -0.01- + 0.01°

Heavy metals: < 20 ppm

Refractive index: 1.503-1.507

Specific gravity: 0.947-0.955

Density: 0.947-0.955 g/ml

Flash point: 240°C

Indications: Vitamin E, known for its antioxidant effects, has been demonstrated to protect against cardiovascular disease and some forms of cancer while also boosting the immune system. It may be of some use to persons with asthma or rheumatoid arthritis. It may help with a variety of neurological diseases, including Alzheimer's, ocular issues including cataracts, diabetes, and premenstrual syndrome. It may also help protect skin from UV rays, however claims that it reverses skin ageing, increases male fertility, and enhances exercise performance are unfounded. It may help relieve

muscle cramps. Because of vitamin E's biologic action, there is ongoing interest and study into whether its antioxidant characteristics may be used to help prevent or treat a range of conditions, including cardiovascular disease, eye issues, diabetes, cancer, and others. However, there is presently insufficient official data and evidence to suggest any novel uses for vitamin E.

Interactions: Orlistat may limit the absorption of D-alpha-Tocopherol acetate, resulting in a lower serum concentration and perhaps a reduction in effectiveness. A variety of cholesterol-lowering medicines (such as cholestyramine and colestipol), as well as orlistat, sucralfate, mineral oil, and the fat replacement olestra, which inhibit fat absorption, may theoretically reduce the absorption of fat-soluble vitamins, including vitamin E.

Storage: Below 4°C, protect from light, stored under inert environment

Shelf life: Below -20°C as powder for 3 years, below 4°C as powder, 2 years, in solvent below -80°C for 6 months, in solvent below -20°C for 1 month. Avoid freeze-thaw cycle.

Incompatibilities: Incompatible with metal ion and peroxides. It is absorbed by plastics.

5.3.7 Magnesium Stearate[17]

Molecular Formula: $[CH_3 (CH_2)_{16}COO]$ 2Mgs

Synonyms: Dibasic magnesium stearate; Magnesium Distearate

Structural formula:

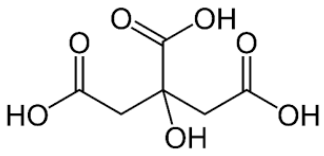


Fig. 5.7 : Structure of Magnesium Stearate

Synonyms: Dibasic magnesium stearate; Magnesium distearate; Magnesiistearas; Magnesium octadecanoate; Octadecanoic acid, magnesium salt; Stearic acid; Magnesium salt; Synpro90.

Empirical formula: $C_{36}H_{70}MgO_4$

Molecular weight: 591.24 g/mol

Description: It is a very fine, light white, precipitated or milled powder with a low bulk density, a mild stearic acid odour, and a distinct flavour. The powder feels oily to the touch and easily sticks to the skin.

Functional categories: Tablet and capsule lubricant.

Solubility: Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Melting point: 117–150˚C

Density: 1.092 g/cm^3

Loss on drying: 46.0%

Stability and storage conditions: Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

Incompatibilities: Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials.

Applications: It is primarily used as a lubricant in capsule and tablet manufacture.

5.3.8 Talc[18]

Non-proprietary names:

BP: Purified talc

JP and USP: Talc

Synonyms: Magsilosmanthus; Magsil Star; Powdered talc; Purified French chalk; Purtalc.

Empirical formula: $Mg_6 (Si_2O_5)_4(OH)_4$

Molecular Formula: $Mg_6 (Si_2O_5)_4(OH)_4$

Structure:

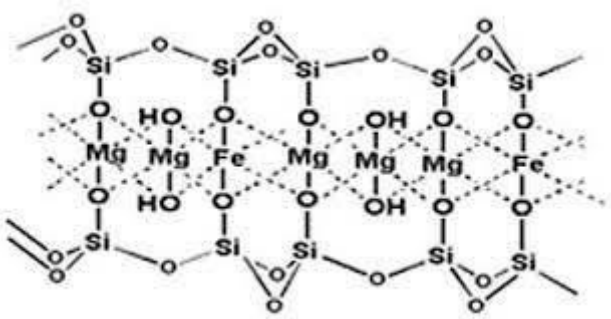


Fig. 5.8 : Structure of Talc

Description: Talc is a very fine; white to greyish-white, odourless, impalpable, unctuous, Crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Functional categories: Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Solubility: Practically insoluble in dilute acids and alkalis, organic solvents, and water.

Melting point: 150˚C

Handling Precautions: Talc is irritant if inhaled and prolonged excessive exposure may cause Pneumoconiosis. Eye protection, gloves and respirator is recommended.

Stability and storage conditions: Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities: Incompatible with quaternary ammonium compounds.

Applications:

1. It is used as a diluent, lubricant in tablet formulations.
2. In a novel powder coating for extended-release pellets and as an adsorbent.
3. In topical preparations, it is used as a dusting powder, used to clarify liquids.
4. It is also used in cosmetics and food products.

5.3.9 Crospovidone (CP)[19]

Non-proprietary Names

BP: Crospovidone

Ph Eur: Crospovidonum

USP/NF: Crospovidone

Synonyms: Crosslinked povidone; Kollidon CL; E1202; Kollidon CL-M; 1-vinyl-2-pyrrolidinone homopolymer; Polyplasdone XL.

Chemical Name: 1-Ethenyl-2-pyrrolidinone homopolymer

Empirical Formula: $(C_6H_9NO)_n$

Molecular weight: >1 000 000

Structural Formula

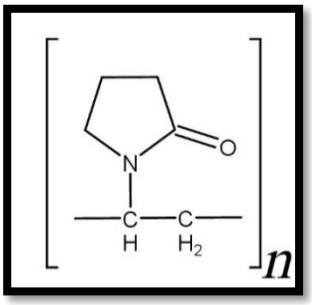


Fig. 5.9 : Structure of Crospovidone

Functional Category: Tablet disintegrant.

Description: Crospovidone is a hygroscopic powder that is white to creamy-white, free-flowing, almost tasteless, odorless or nearly odorless.

Typical properties

Acidity/alkalinity: pH 5.0–8.0 (aqueous slurry of 1% w/v)

Density: 1.22 g/cm^3

Solubility: In water and most typical organic solvents are almost insoluble.

Applications in pharmaceutical preparation or technology

Crospovidone is a water-insoluble tablet disintegrant and dissolving agent that is used at a rate of 2-5 percent in tablets manufactured by direct compression or wet and dry granulation. It has a strong capillary action and a high hydration capacity, with a low tendency to create gels. According to study, the crystal structure of crospovidone influences the breakdown of analgesic tablets. Larger molecules dissolve more quickly than smaller ones. Crospovidone can be used as a solubility enhancer. Crospovidone can be used in the co-evaporation method to increase the solubility of weakly water-soluble medications. In the presence of enough solvent, the medication is deposited on crospovidone, which is subsequently vaporised. This approach produces a faster rate of disintegration.

Storage Conditions and Stabilization: Crospovidone should be kept in a tightly sealed container in a cold, dry location since it is hygroscopic.

Incompatibilities: Most organic and inorganic medicinal compounds are compatible with crospovidone. When subjected to a specific water level, crospovidone may form molecular intermediates with some compounds.

Safety: Crospovidone is a safe and non-irritant substance that is utilised in oral medicinal formulations. Short-term animal toxicology tests have revealed no negative impacts associated with crospovidone.

Handling Precautions: Follow standard safety procedures that are suitable for the conditions and amount of material being handled. Eye protection, gloves, and a dust mask are recommended.

5.3.10 Silicified Microcrystalline Cellulose (PROSOLV)[20]

Non-proprietary Names

Synonyms: Silicified Microcrystalline Cellulose; SMCC; Microcrystalline Cellulose, Silicified; Comprecel® SMCC; PROSOLV® SMCC; Avicel® SMCC

Empirical Formula: (C6H10O5)n

Molecular weight: Approx. 36 000

Structural Formula

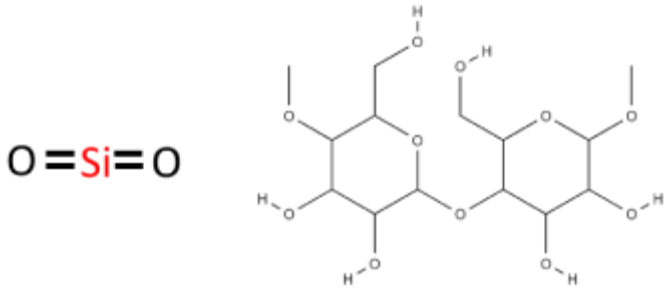


Fig. 5.10 : Structure of Silicified Microcrystalline Cellulose

Functional Category: Filler, Cushioning agent.

Description: It is a co-processed pharmaceutical excipient made up of two functional excipients: microcrystalline cellulose and colloidal silicon dioxide. The two component materials are not covalently bonded but quite stable.

Typical properties

Appearance: White fibrous powder with high flowability

pH value: 5.0-7.5 (10% w/v aqueous suspension)

Density: 1.58 g/cm

Applications in pharmaceutical preparation or technology

Silicified MCC has superior flowability and lower cohesion than non-silicified Microcrystalline cellulose grades. In pharmaceutical goods, silicified microcrystalline

cellulose is used as a filler-diluent in direct compression or capsule filling procedures. It can also be added to wet granulated powder mixtures (extra-granularly) to improve formulation compaction qualities, especially in cases when normal Microcrystalline cellulose is ineffective.

Storage Conditions and Stabilization: Should be kept in a tightly sealed container in a cold, dry location since it is hygroscopic.

Incompatibilities: Most organic and inorganic medicinal compounds are compatible

Safety: It is a safe and non-irritant substance that is utilised in oral medicinal formulations. Short-term animal toxicology tests have revealed no negative impacts associated with silicified MCC.

Handling Precautions: Follow standard safety procedures that are suitable for the conditions and amount of material being handled. Eye protection, gloves, and a dust mask are recommended.

5.3.11 Mannitol [21]

Non-proprietary Names

Synonyms: D-mannitol

Chemical Name: (2R,3R,4R,5R)-hexane-1,2,3,4,5,6-hexol

Empirical Formula: C6H14O6

Molecular weight: 182.17 g/mol

Structural Formula

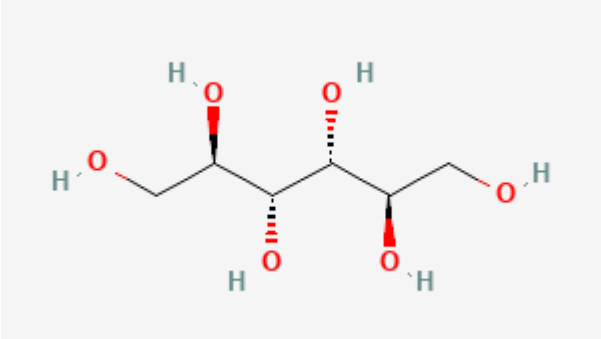


Fig. 5.11 : Structure of Mannitol

Functional Category: Filler

Description: white odourless crystalline solid having a sweet taste

Typical properties

Appearance: White powder

Flowability: Highly flowable

Density: 1.52 g/cm

Applications in pharmaceutical preparation or technology

Mannitol is generally used in pharmaceutical formulations and offers several benefits. It is known to contribute to the overall efficiency and safety of medications. Here are some key benefits of Mannitol in pharmaceutical formulations:

Enhanced Stability and Shelf Life: Mannitol is highly stable, making it an appropriate excipient for medicinal formulations. Its capacity to resist crystallisation contributes to the stability of medicinal formulations and guarantees that the product's quality remains consistent throughout time. This improved stability also helps to lengthen shelf life. As a result, it decreases the possibility of deterioration and guarantees that the drug stays effective for the prescribed storage term.

Osmotic Properties for Drug Delivery: Mannitol's osmotic qualities make it useful in medication delivery systems. It is often utilised in osmotic-controlled release formulations, which allow for regulated medication release over time. Mannitol's osmotic pressure may be modified to provide various release patterns, resulting in regulated and sustained distribution of the active pharmaceutical ingredient (API).

Compatibility with Active Ingredients: Mannitol is well-known for being compatible with a wide range of active medicinal substances. Its inert properties and lack of reactivity with diverse medicinal components make it an appealing choice as a filler or diluent in pharmaceutical formulation. This compatibility means that Mannitol does not interfere with the chemical stability or efficacy of the active components, hence contributing to the medication's overall trustworthiness.

Patient Safety and Tolerability: Mannitol is typically well tolerated by patients, with very few adverse events reported. Its safety profile makes it appropriate for use in formulations designed for a variety of patient groups. Mannitol is often used in oral dose forms including pills and capsules. Here, its sweetness improves the medication's palatability. Mannitol's low caloric content and non-cariogenic characteristics make it an ideal ingredient for sugar-free recipes. As a result, it caters to the demands of diabetics and those on a tight diet.

PART B

5.4 Drug Profile: Sitagliptin Phosphate Monohydrate[1-5]

Sitagliptin phosphate is used type II diabetes in which body cannot produce sufficient insulin or insulin produced cannot work appropriately. It is prescribed to patient who doing regular exercise and intake-controlled diet regularly. It increases the production of insulin and decrease glucagon preparation in patient body. It is available in market in tablet form alone or in combination with metformin or ertugliflozin. It is an oral dipeptidyl peptidase-4 (DPP-4) inhibitor used for the management of type 2 diabetes mellitus. It is FDA approved drug (16th October 2006).

Insulin is a molecule generated by the human body that helps remove sugar from the bloodstream and transport it to cells, where it may be utilised for energy. Incretins are hormones in the body that control insulin synthesis and release. Sitagliptin works by keeping incretin hormones from breaking down too rapidly. This improves insulin sensitivity and decreases blood sugar. Controlling high blood sugar levels helps avoid kidney disease, blindness, nerve difficulties, limb loss, and sexual dysfunction.

Category: Antidiabetic Agents

Mechanism of Action: Sitagliptin inhibits DPP-4, which delays the inactivation of incretins such as GLP-1 and GIP. Incretins are produced throughout the day and increased in response to meals to maintain glucose homeostasis. Reduced inhibition of incretins boosts insulin production and decreases glucagon release in a glucose concentration-dependent way. These effects result in improved blood glucose management, as seen by lower glycosylated haemoglobin (HbA1c).

Groups: Approved, Investigational

BCS Class: BSC Class III (low solubility and high permeability)

Mode of action: Inhibits DPP-4, increasing levels of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)

Molecular weight: 407.11

Molecular formula: $C_{16}H_{15}F_6N_5O$

CAS Number: 486460-32-6

IUPAC Name: (3R)-3-amino-1-[3-(trifluoromethyl)-6,8-dihydro-5H-[1,2,4] triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one

IUPAC Name: (3R)-3-amino-1-[3-(trifluoromethyl)-6,8-dihydro-5H-[1,2,4] triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one

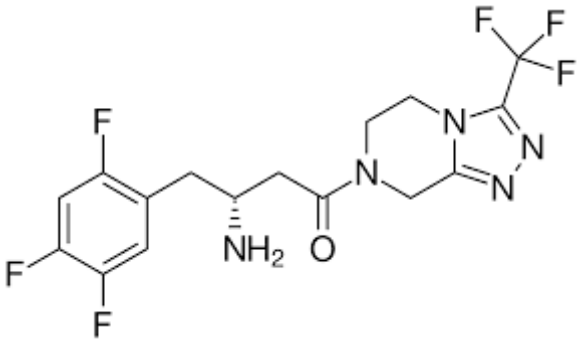


Fig. 5.12: Structure of Sitagliptin

Description: White to off-white crystalline non-hygroscopic solid with distinct odour and bitter taste

Solubility: Soluble in water and DMSO, slightly soluble in methanol and very slightly soluble in acetone, acetonitrile and ethanol. Insoluble in isopropanol and isopropyl acetate.

Water content: NMT 0.5%

Melting point: Melting point of Sitagliptin base, Sitagliptin phosphate monohydrate and Sitagliptin phosphate anhydrous are 120.29°C, 206.37°C and 214.92°C respectively.

Dissociation constant (pKa): 8.78

Nature: It is basic compound can accept H+ ion and became positively charged. Due to presence tertiary amine, it is categories under weak acid.

Partition coefficient: 1.8 for octanol/ water system

Peak time: 2 hr

Half-life: 11-12 hr

Drug absorption: Drug absorbed throughout intestine

Oral bioavailability: Before or after meal 87%

Volume of distribution: 198 L

Protein binding: 38%

Excretion: Approximately 79% of the dosage was eliminated unaltered via urine. Minor metabolites produced by CYP P450, CYP 3A4, and, to a lesser extent, CYP 2C8. Sitagliptin is a substrate for the human organic anion transporter-3 (hOAT-3),

which may play a role in its renal clearance. The clinical significance of hOAT-3 in sitagliptin transport has not been determined. Sitagliptin is also a p-glycoprotein substrate, which may play a role in sitagliptin's renal clearance. Cyclosporine, a p-glycoprotein inhibitor, did not alter sitagliptin's renal clearance.

Elimination: 87% of administered dose excreted through urine and remaining through faces.

Clearance: 350 ml/ min

Safety and efficacy: Safe to use throughout pregnancy and breastfeeding. There is no safety and efficacy data for paediatrics. There was no difference in reported safety or efficacy data when comparing to the elderly. Patient reaction did not vary significantly by gender, age, race, ethnicity, or BMI. When prescribing to a patient with renal impairment, use caution.

Side effects: Stomach upset and pain, diarrhoea, vomiting, upper respiratory infection, runny nose, sore throat, headache, lower sugar, skin rashes, swelling, hiving, etc.

Indication: Indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus. It is not used to treat type 1 diabetes or patients with a history of pancreatitis.

Warning: It increases the risk of pancreatitis and joint pain. If patient with gall stone, alcoholism, kidney issues, pancreatitis, smoking and high triglyceride levels should inform the patient before starting treatment.

Dose and Dosage form: Tablets of 25, 50 and 100 mg. Typical dose 100 mg once daily.

Storage: Store at temperature between 20-25°C. Protect from light and moisture. Stable if stored as directed under conditions directed. Avoid storage with oxidizing agents.

Stability: Sitagliptin phosphate monohydrate and Sitagliptin phosphate anhydrous are stable than Sitagliptin base.

5.5 Risk Assessment for Drug Substance Attributes (SPM)

A risk assessment of the drug substance attributes was performed to evaluate the impact that each attribute could have on the drug product Critical Quality Attributes. The outcome of the assessment and the accompanying justification is provided as a summary below. The relative risk that each attribute presents was ranked as high, medium or low. The high-risk attributes warranted further investigation whereas the low-risk attributes required no further investigation. The medium risk is considered acceptable based on current knowledge. Further investigation for medium risk may be needed in order to reduce the risk.[6]

Based upon the physicochemical properties of the drug substance, the risk assessment of drug substance attributes that impact the drug product CQAs is given below.[7]

Table 5.8 : Risk Assessment of the Drug Substance Attributes for SPM

Drug product CQA	Sitagliptin drug substance attributes				
	Particle size	Solubility	Melting point	Water content	Flow properties
Moisture uptake	Low	Low	Low	Medium	Low
Drug Content	Low	Low	Low	Medium	Low
Dissolution	Low	Low	Low	Low	Low

Table 5.9: Justification of Risk Assessment of Drug Substance Attributes of SPM

Drug Substance Attributes	Drug Product CQAs	Justification
Particle size	Moisture uptake	Low risk as Particle size has no direct impact on Moisture uptake. The API has good flow characteristics, thus does not have any impact on drug content of final product. This is BCS class III drug thus particle size has no impact on dissolution.
	Drug Content	
	Dissolution	
Solubility	Moisture uptake	Low risk as solubility has no direct impact on

Drug Substance Attributes	Drug Product CQAs	Justification
	Drug Content	Moisture uptake and drug content. This is BCS class I drug thus particle size has no impact on dissolution.
	Dissolution	
Melting point	Moisture uptake	Low risk as Melting point has no direct impact on Moisture uptake, drug content and dissolution
	Drug Content	
	Dissolution	
Water content	Moisture uptake	Medium Risk as Sitagliptin is affected by moisture and leads to degradation at higher rate. API has controlled water content about NMT 0.5%.
	Drug Content	
	Dissolution	Low risk as Water content has no direct impact on dissolution
Flow Properties	Moisture uptake	Low risk as Melting point has no direct impact on Moisture uptake, drug content and dissolution
	Drug Content	
	Dissolution	

5.6 Coating Agent Profile:

5.6.1 Palmitic Acid[8]

The majority of animal and vegetable fats include palmitic acid (35 to 45% of palm oil). It is the most abundant fatty acid found in animals, plants, and microbes. It is the primary component of palm tree oil (palm oil, palm kernel oil, and coconut oil), although it may also be found in meat, cheese, butter, and dairy products. It is composed of sixteen carbon atoms and contains long-chain saturated fatty acids. It is biochemically safe for use in food labelling and dietary advice. Excess carbs in the body are turned into palmitic acid. It is the first fatty acid created during fatty acid synthesis and serves as a precursor for longer fatty acids. Palmitate has a negative

feedback loop with acetyl CoA carboxylase (ACC), which converts acetyl-CoA to malonyl-CoA, which is then added to the expanding acyl chain, limiting further palmitate production.

Palmitoylation is a process that involves adding a palmitoyl group to some proteins. Palmitoylation plays a key role in the membrane localisation of several proteins. Palmitic acid is produced by processing fats and oils with water at high pressure and temperature (over 200°C), resulting in the hydrolysis of triglycerides. The combined mixture is then distilled.

Synonym: n-Hexadecanoic acid, 1-Pentadecanecarboxylic acid, Cetylic acid, Hexadecylic acid, palmitate, Palmitinic acid, palmitinsaeure, cetyl acid, n-hexadecoate, pentadecane carboxylate, 1-hexyldecocanoate, n-hexadecoate, palmic acid, Acid, palmitic

Occurrence: Animals, plants and microorganisms

Dietary sources: Meat, dairy products, palm oil, coconut oil, and breast milk

Chemical name: Palmitic acid

Molecular formula: CH3 (CH2)14COOH

Molecular weight: 256.42

Description: White or off-white, odourless or slight characteristic odour and oily taste large crystalline powder

Melting point: 59 to 63°C

Boiling point: 351.5°C

Acid value: 217 to 220

Iodine value: NMT 1.5

Saponification value: 208 to 222

Refractive index (nD80) = 1.4 to 1.6

Log P: 6.4

CD ratio: 16

Specific gravity: 0.849 to 0.851

Density: 0.8527 g/ml

Specific surface area: 0.51 to 0.53 m2/g

Polar surface area: 37.3 $A^{\circ 2}$

Viscosity: 7.80 mPa.sec (cP) at 62°C

pH: 2.7

Solubility: It is insoluble in water, freely soluble in chloroform, ether, isopropyl alcohol, hot ethanol (95%). It is soluble in amyl acetate, carbon tetrachloride, ethanol, acetone, and benzene. Miscible with diethyl ether.

Distribution coefficient: log (oil/water) = 8.6

Applications: Palmitic acid is commonly utilised as a lubricant and addition in industrial processes. It is used to produce metallic stearates, medicines, soaps, cosmetics, and food packaging. It functions as a softener, accelerator, activator, and dispersion agent in rubbers. It functions as a coating agent in modified release formulations. It is utilised as an emollient and emulsifier.

Physiological role: Crucial for membrane physical properties, protein palmitoylation, and surfactant activity

Stability: Palmitic acid is stable under ordinary conditions. Anti-oxidant may be added in the container.

Storage: Store in a tightly closed container in a cool, dry and well-ventilated area.

Keep away from sources of ignition and incompatible substances.

5.6.2 Stearic Acid[8,9]

Stearic acid is an eighteen-carbon, long-chain saturated fatty acid. It is biochemically safe for use in food labelling and dietary guidelines. However, studies from over 30 years ago shows that, in terms of diet and heart disease concerns involving saturated fatty acids, stearic acid may act differently than other saturated fatty acids found in considerable quantities in the diet. The predominant long-chain saturated fatty acids in the diet include lauric (C12), myristic (C14), palmitic (C16), and stearic (C18).

Stearic acid is found in a variety of foods, including meat and fat-containing dairy products. Stearic acid, as a proportion of total fat calories, is relatively consistent in beef, hog, lamb, and veal at 9 to 12%, whereas poultry has a lower percentage at 6 to 7%. Common cooking oils contain just 2-4% stearic acid, while hydrogenation of vegetable oils for shortening and margarine can raise the percentage. Of all

commercially available fats, cocoa butter has the highest amount of stearic acid. Stearic acid accounts for around 3 to 4% of total calories in the United States diet.

Occurrence: Found in many animal and vegetable fats

Dietary sources: Meat, poultry, fish, eggs, dairy products, fats, beef tallow, lard, butterfat, cocoa butter, and shea butter

Benefits: Moisturizing and anti-inflammatory properties

Synonym: Octadecanoic acid, 1-Heptadecane carboxylic acid, Stearophanic acid, n-Octadecanoic acid

Chemical name: Stearic acid

Molecular formula: $C_{18}H_{36}O_2$

Molecular weight: 284.48

Description: White to faintly yellowish glossy crystalline solid or white to yellowish white powder with slight tallow-like taste.

Melting point: 68 to 70°C

Acid value: 200 to 212

Iodine value: Less than 4

Saponification value: 200 to 220

Refractive index (n_D^{80}) = 1.4299

Specific gravity: 0.940 to 0.941 (Water = 1)

Specific surface area: 0.51 to 0.53 m^2/g

Density: 0.847 g/cm^3 (20°C)

Boiling point: 232°C (450°F; 505 K) at 15 mmHg

Solubility: It is easily soluble in benzene, diethyl ether, acetone, chloroform, carbon disulfide, carbon tetrachloride, amyl acetate, hexane, propylene glycol and toluene. It is insoluble in cold water, hot water, and slightly soluble in ethanol.

Distribution coefficient: The product is more soluble in oil and log (oil/water) = 8.2.

Applications: Its applications include food, medicines, and cosmetics. It is widely utilised as a lubricant, binder, and coating agent. It serves as a medication carrier with prolonged release. Stearic acid is commonly employed as an emulsifying and solubilising agent. It also serves as a hardening agent in glycerin suppositories.

Precautions: Do not ingest or breathe dust

Incompatibilities: It is not compatible with most metal hydroxides or oxidising agents. Many metals react to generate insoluble stearates; when combined with calcium and zinc salts, ointment base becomes lumpy. The compatibility of stearic acid with medicines was examined using Differential Scanning Calorimetry (DSC). Stearic acid induces pitting in aqueous tablet film coating, which is determined by its melting point.

Stability: Stearic acid is stable under ordinary conditions. Anti-oxidant may be added in the container.

Storage: Store in tightly closed container in a cool, dry and well-ventilated area. Keep away from sources of ignition.

5.7 Excipient Profile:

5.7.1 Dicalcium Phosphate[10, 11,12]

Dicalcium phosphate dibasic (DP) is an inorganic, insoluble diluent used in tablet and capsule production. In pharmaceutical development, two hydration forms of dicalcium phosphate are used: anhydrous (DPA) and dihydrate. The anhydrous form is a triclinic crystal, whereas the dihydrate generates a monoclinic structure. Dicalcium phosphate dihydrate has excellent flow characteristics and minimal hygroscopicity. However, depending on temperature (40-50 °C) and humidity (32-75% relative humidity), it tends to lose water of hydration, which may induce chemical instability of APIs in dosage forms. The anhydrous version offers an option without sacrificing medication stability.

The two forms have distinct porosities due to their hydration. Because there is no water in the crystal structure, the anhydrous form has a larger porosity, allowing for better compressibility and quicker disintegration. It is chemically made up of calcium ions (Ca^{2+}) and phosphate anions in a 1:1 molar ratio. Dibasic calcium phosphate is one of a family of eleven mineral compounds known as calcium phosphate. They have considerable uses in the medical, geological, construction, and dentistry industries. The materials created vary in function, composition, structure, physical qualities, and applications depending on the manufacturing processes used.

In the pharmaceutical industry, the three most significant minerals from this family are dibasic calcium phosphate anhydrous, dibasic calcium phosphate dihydrate, and

tricalcium phosphate, which are employed as diluents and fillers in solid dosage formulation. Dibasic calcium phosphate dihydrate has the empirical formula $CaHPO_4.2H_2O$ and so occurs as a dihydrate. The "di" prefix in the popular name comes from the fact that the HPO_4^{2-} anion is formed by removing two protons from phosphoric acid (H_3PO_4).

Synonyms: Dibasic calcium phosphate, calcium monohydrogen phosphate, monohydrogen calcium phosphate, phosphoric acid calcium salt, calcium phosphate, calcium phosphate dibasic Dibasic Calcium Phosphate Hydrate; Calcium Hydrogen Phosphate; Calcium Hydrogen Phosphate Dihydrate; Calcium Hydrogen Orthophosphate dihydrate; Calcium Monohydrogen Phosphate Dihydrate; Di-Cafos; Dicalcium Orthophosphate; DI-TAB; E341; Emcompress.

Pharmacopoeial Compliance: USP-NF; Ph. Eur; IP; J.P; FCC

Molecular Formula: $CaHPO_4$

Molecular weight: 172.09 g/mol (dihydrate), 136.057 g/mol (anhydrous)

CAS Number: 7757-93-9 (Calcium hydrogen phosphate) and 7789-77-7 (dicalcium phosphate)

EC Number: 231-826-1

UNII Code: O7TSZ97GEP

Structural Formula:

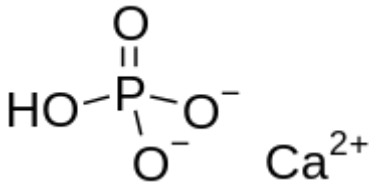


Fig. 5.13: Structure of Dicalcium Phosphate

IUPAC Name: Calcium hydrogen phosphate

Functional Category: Tablet and capsule diluent. Aid in tooth paste as polishing agent.

Description: White triclinic crystalline odourless taste less powder.

Solubility: Insoluble below pH 4.8 (dihydrate and anhydrous forms).

In water 0.02 g/100 mL (anhydrous) and 0.02 g/100 mL (dihydrate)

Practically insoluble in ethanol, ether, and water; soluble in dilute acids.

Structure: Insoluble below pH 4.8 (dihydrate and anhydrous forms)

Angle of repose: 28.3°

pH: pH 12.3-12.5

Melting point: 128°C.

Angle of repose: 33-49°

Bulk density: 0.915 g/ml

Tapped density: 1.17 g/ml

True density: 2.929 g/cm^3 (anhydrous); 2.31 g/cm^3 (dihydrate)

Flash point: Standard state at 25°C, 77°F, and 100 kPa (Non- inflammable)

Specific surface area: 0.44 – 0.46 m^2/g

Moisture content: < 5%

Loss on ignition: 24.5 -26.5%

Assay: 98.0 -105.0% (≥ 98.0%)

Regulatory Status: Dibasic calcium phosphate dihydrate is a permitted pharmaceutical excipient and food ingredient in Europe. It is currently registered with the USP-NF, Ph.Eur, and JP. It is also GRAS-listed and appears in the FDA Inactive Ingredients Database (for oral capsules and tablets). Dibasic calcium phosphate dihydrate is widely used in oral pharmaceuticals, food items, and toothpastes because to its acceptance as a reasonably harmless and non-irritant substance.

Stability & Storage condition: Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Applications: Dibasic calcium phosphate dehydrate is used in medicinal formulations because to its superior compactability and flow characteristics. Brittle fracture is the primary deformation mechanism of coarse grades, which considerably lowers strain-rate sensitivity and the potential for tablets to laminate. This is extremely useful during formulation scale-up in new product development, which is less difficult. The sole disadvantage is that dibasic calcium phosphate dihydrate is abrasive, significantly reducing tooling life. As a result, significant quantities of lubricants are necessary in formulations (often greater than 1% w/w for magnesium stearate or sodium stearyl fumarate).

Commercial grades of Dibasic calcium phosphate dihydrate include a milled grade that is commonly used in wet-granulation or roller-compaction, as well as a coarse grade designed for direct-compression applications. Dibasic calcium phosphate dihydrate does not absorb moisture from the environment and remains stable under normal settings. However, if the material is exposed to certain circumstances (high temperature and humidity), it may lose its water of crystallisation. This phenomena has the potential to affect high-temperature operations (such as packing and aqueous film coating) as well as the majority of moisture-sensitive actives.

Incompatibilities: It is incompatible with chelating agents

Handling precaution: Workers should take the necessary measures when working with Dibasic calcium phosphate dihydrate, taking into account the conditions and quantity of material involved. Because the milling grades might produce dust, a respirator or dust mask is required. It may cause irritation to the eyes. Gloves, eye protection, and a dust mask are suggested.

Stability and Storage: Dibasic calcium phosphate dihydrate is a non-hygroscopic, reasonably stable compound. However, if kept or treated wrongly, it might lose its water of crystallisation, affecting the excipient's stability and future dosage form processing. As a result, the bulk material should be properly kept (in a well sealed container in a cold, dry location away from direct heat or moisture).

5.7.2 Colloidal Silicon Dioxide (Aerosil)[13]

Aerosil(R) 200, also known as fumed silica, is used as an anticaking agent in powders and a thickening agent in solutions. Ungraded products supplied in a grade suitable for general industrial use or research purposes and typically are not suitable for human consumption or therapeutic use.

CAS Number: 7631-86-9

EC Number: 231-545-4

Molecular weight: 60.08

Molecular formula: SiO_2

Structural formula:

O = Si = O

Description: White odorless and tasteless crystalline as well as amorphous solid

Solubility: Almost insoluble in water, common acid, can be dissolved in hydrofluoric acid to generate silicon fluoride gas, slowly with the heat of concentrated phosphoric acid.

Melting point: 1,700 °C

Solubility in Water: > 1 mg/l

Density: Approximate 2.2 g/cm^3 (20 °C)

Specific surface area: 450m^2/g

Loss on drying: Less than 1.5% when sample dried at 105 °C

Weight loss on ignition: Not more than 8.5%

SiO2 content based on ignition: >99.8%

Stability: Stable under recommended storage conditions. The physical and chemical properties are stable, easy to form, inert, the melt is layered, and the expansion coefficient is small when heated.

Applications: Pharmaceutical excipients, glidants and suspending agents.

Precaution: Avoid contact with skin and eyes.

Shelf life: 5 years

5.7.3 Polyethylene Glycol 4000[14]

Polyethylene glycol, or PEG, is a hydrophilic polymer. It is easily synthesised from ethylene oxide via anionic ring opening polymerisation into a wide range of molecular weights and end groups. When PEG is crosslinked into networks, it can have a high water content and produce "hydrogels". PEG is an ideal substance for biological applications since it does not elicit an immune response.

Synonyms: Carbowaxes.

IUPAC Name: Polyethylene glycol

CAS Number: 25322-68-3

Chemical Formula: $C_{2n}H_{4n+2}O_{n+1}$, n = 91 units

Chemical Name: Alpha-Hydro-omega-hydroxypoly(oxy-1,2-ethanediyl)

Molecular weight: 4000 (3100-4010)

Structural Formula

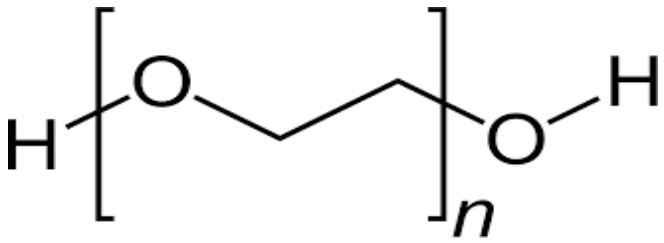


Fig 5.14: Structure of Polyethylene Glycol 4000

Description: White, odourless and slightly sweet flakes or powdered solid

Molar Mass: average molecular weight is about 4,000

Density: 1. 2 g/cm^3

Solubility: Soluble in water, acetone, alcohols, benzene, glycerin, glycols and aromatic hydrocarbons and slightly soluble in aliphatic hydrocarbons.

Melting Point: 53-58°C

pH: 5 – 7

Moisture content: NMT 1%

Flash Point: 138.6°C

Viscosity: 90.0 cSt at 25 °C, 7.3 cSt at 99 °C

Specific gravity: 1.11

Chemical Properties:

1. It is strongly hydrophilic.
2. The partition coefficient of PEG 400 between Hexane and Water is 0.00015.

Uses:

1. Pharmaceuticals: As a solvent, excipient, and coating agent in tablets, capsules, and ointments.
2. Cosmetics: As a humectant, emollient, and thickener in skincare products, hair care products, and makeup.
3. Food: As a food additive, texture modifier, and moisture-retaining agent in beverages, baked goods, and confectionery.
4. Biotechnology: As a precipitant, stabilizer, and protectant in biological samples and biopharmaceuticals.

5. Industrial: As a lubricant, binder, and dispersant in various industrial applications.
6. Polyethylene glycol can be used in medication formulations to increase dissolution rate and oral bioavailability. PEG may be utilised to effectively isolate edible nanoparticles (ENPs), which have powerful anti-cancer and anti-inflammatory properties. PEG acts as a crowding agent, forming a net-like mesh that traps and precipitates nanovesicles. For example, ginger-derived ENPs are separated utilising a cost-effective PEG-based approach rather than ultracentrifugation. PEG can be utilised as a precursor to create degradable hydrogels for the controlled release of hydrophilic and high-molecular-weight medicines.

Benefits: High structural flexibility, low viscosity, solubility in water and many solvents, biocompatible, amphiphilic, high hydration capacity, devoid of steric hinderance, ability to hold moisture avoid drying out, compatibility with many materials and stable.

1. Surfactant
2. The polymer functions as a lubricating coating surface.
3. It is employed as a stationary phase in chromatography.
4. It is employed as a solvent, humectant, lubricant and solubilizer.
5. It is added as a precipitant in Plasmid DNA isolation & Protein crystallization.
6. It is also utilizing microbiology for concentrating viruses by PEG precipitation.
7. It is employed in Gene therapy.
8. In blood bank it is applied as a potentiator for determination of antigen and antibodies.
9. It is employed in toothpaste as a dispersing agent, in food and drinks employed as a foaming agent.
10. It is a part of many lubricants.

Safety:

PEG is regarded as safe and non-hazardous by the FDA. Sometime sensitization and intolerance reactions have been reported in humans exposed to PEG 400 in topically. It was of very low acute oral toxicity in a range of animal species, causing impairment to the digestive tract and diarrhoea in high doses.

Storage: Stored in well closed plastic container in cool well-ventilated place at 25-40 °C

Stability: Stable for more than 2 years when stored at 25 °C in moisture resistant conditions

Precaution: Precaution during handling (protect eyes, avoid inhalation and skin contact).

CHAPTER – VI

EXPERIMENTAL WORK

6. Materials and Methods for Tenofovir Disoproxil Fumarate (TDF)

6.1 Materials and Equipment for TDF

Table 6.1: List of Material and Suppliers for TDF

Sr. No.	Name of material	Supplier
1.	Tenofovir Disoproxil Fumarate	Mylan Laboratories Ltd., Aurangabad (MS), India
2.	Mannitol	S. D. Fine Chemicals, Mumbai, India
3.	Polyvinyl pyrrolidone (K-30)	S.D. Fine Chemicals, Mumbai, India
4.	Hydroxypropyl Cellulose (HPC-L)	S.D. Fine Chemicals, Mumbai, India
5.	Microcrystalline Cellulose (Avicel PH 101)	S.D. Fine Chemicals, Mumbai, India
6.	Silicified Microcrystalline Cellulose (Prosolve)	S.D. Fine Chemicals, Mumbai, India
7.	Spray dried lactose (DCL-11)	S.D. Fine Chemicals, Mumbai, India
8.	α- Tocopherol	S.D. Fine Chemicals, Mumbai, India
9.	Magnesium stearate	S.D. Fine Chemicals, Mumbai, India
10.	Talc	S.D. Fine Chemicals, Mumbai, India
11.	Hydrochloric acid	S.D. Fine Chemicals, Mumbai, India
12.	Methanol	S.D. Fine Chemicals, Mumbai, India
13.	Ethanol	S.D. Fine Chemicals, Mumbai, India
14.	Sulphuric acid	S.D. Fine Chemicals, Mumbai, India
15.	Potassium Dihydrogen Phosphate	S.D. Fine Chemicals, Mumbai, India
16.	Dimethyl Sulfoxide (DMSO)	S.D. Fine Chemicals, Mumbai, India
17.	p-Dimethylamino cinnamaldehyde	S.D. Fine Chemicals, Mumbai, India
18.	Gelucire®43/01	Gattefose SAS, 69804 Saint-Prist Cedex, France

Sr. No.	Name of material	Supplier
19.	Precirol® ATO 5	Gattefose SAS, 69804 Saint-Prist Cedex, France

All other chemicals were of laboratory grade and used as received.

Table 6.2: List of Equipment and Make Used for TDF

Sr. No.	Name of Equipment	Make
1.	Double cone blender	Dolphin India Pvt. Ltd., India
2.	Extruder- Spheronizer	Umang Pharmatek, India
3.	Pan coater	Adinath International, India
4.	Sieve shaker	Dolphin India Pvt. Ltd., India
5.	Tray dryer	Remi Laboratory Instrument, India
6.	Pizer tester	Veego Instruments Corporation, India
7.	Bulk Density apparatus	Electrolab India Pvt Ltd., India
8.	Friability test apparatus	Veego Instruments Corporation, India
9.	Disintegration test apparatus	Electrolab India Pvt Ltd., India
10.	Dissolution test apparatus	Electrolab India Pvt Ltd., India
11.	Ultrasonicator	ISP Technologies, India
12.	UV spectrophotometer	UV1800, Shimadzu, Japan
13.	Stability chamber	Remi Laboratory Instrument, India
14.	Tablet punching machine	Riddhi Pvt. Ltd., India
15.	pH Meter	Global electronics, India
16.	Potentiometer	ISP Technologies, India
17.	Differential Scanning Calorimeter (DSC 2500)	Water TA Instruments, New Castle, DE
18.	Analytical balance	Denver instrument, Germany

All the chemicals used were of laboratory and analytical grade. They were used as received.

6.2 Methods for TDF

6.2.1 Preformulation Studies for TDF

6.2.1.1 Organoleptic Properties of TDF

The organoleptic properties of TDF like colour, odour and taste were recorded.

6.2.1.2 Density and Flow Properties

Bulk density is ratio of bulk weight and bulk volume. Accurately weighed 50 g of API was poured gently through glass funnel into 100 ml calibrated measuring cylinder. The surface was cautiously levelled with null pressure.[4] The volume occupied by pellets was used for calculation of bulk density (g/ml) using the equation,

Bulk density = Weight of powder ÷ $Bulk\ volume\ of\ pellets$ ……. (6.1)

Tapped density is ratio of bulk weight and tapped volume. Tapped density was estimated in a similar way to that of bulk density. However, final volume was measured after tapping the cylinder from 3 inches until constant volume was obtained using Electrolab tapped density apparatus.[4] The volume occupied by pellets after tapping was noted and tapped density (g/ml) was calculated using the equation,

Tapped density = Weight of powder ÷ Tapped $volume\ of\ pellets$……. (6.2)

Carrs's Index is calculated using bulk density and tapped density data.

$Carr$'s $Index$= $(Tapped\ density - Bulk\ density) \div Tapped\ density \times 100$ …….(6.3)

6.2.1.3 Solubility

The equilibrium solubility of TDF was determined by placing 1 g of TDF in 100 ml of distilled water on a rotatory shaker for 24 hr at 37°C. After 24 hours, the TDF solution was filtered using 0.45 µ member filter and the amount dissolved in filtrate was determined using UV- Visible spectrophotometer at 260 nm. Similarly, the solubility was determined in 0.1N hydrochloric acid and phosphate buffer pH 6.8. The values of TDF solubility in various solvent were reported.[6]

6.2.1.4 Melting Point

The determination of melting point of TDF is preliminary test for the determination of purity of the drug. The lowering or widening of melting point range indicates

presence of impurity in the pure drug. The melting point of TDF was determined using capillary technique and compared with the reference value.

The more accurate, precise reproducible and reliable method for estimation of melting point is differential scanning calorimetry. Using DSC technique, the sample was previous dried in desiccator and sieved from 80 number sieve to assure uniform size fine particles. Accurately weighed about 2 mg of sample was placed in pan such a way that it covered bottom of the aluminum pan. The pan was crimped without applying excessive pressure.

The DSC thermogram of TDF sample was taken and melting point was recorded using nitrogen as purged gas at 50 ml/ min purge rate for maintaining inert atmosphere using Differential Scanning Calorimeter (DSC 2500, Water TA Instruments, New Castle, DE) in a temperature range 25-600°C. DSC cell was calibrated with indium (m.p. 156.6 °C; ΔHm = 28.54 J/g). An empty pan was covered cap used as reference. The baseline was taken for 2-3 min. The care was taken to avoid decomposition of sample in DSC cell. The sample was heated at 2°C/min for good resolution, as faster heating rate may decrease the resolution.[8]

6.2.1.5 UV-Visible Spectrophotometric Method Development

Instrument: Instrument used UV-Visible double beam spectrophotometer, Shimadzu Corporation (Japan), Model UV-1800 with a bandwidth of 0.5nm and a pair of 1cm matched quartz cells. Analytical balance (Denver instrument, Germany) and sonicator (Electro quip Ultra sonicator, Texas), pH meter (Global electronics, India) was used in the study. Calibrated glass wares used throughout the work.

Chemicals:

The drug (Tenofovir Disoproxil Fumarate) supplied by Mylan was used. The chemicals used were Methanol, Hydrochloric acid, p-Dimethylamino cinnamaldehyde, Sulphuric acid (AR Grade, S.D. Fine Chemicals, Mumbai, India) and distilled water.

Method:

Standard graphs of TDF

Accurately weighed 10 mg of TDF was taken in 100 ml volumetric flask and dissolved in 5 ml of methanol. The volume was made up to 100 ml with 0.1N

hydrochloric acid, which constitute stock solution of 100 µg/ml concentration. The stock solution was suitably diluted with 0.1N hydrochloric acid to prepare the working solutions of 5, 10, 15, 20, 25, 30, 35 and 40 µg/ml. Suitability diluted sample was scanned between 200-400 nm to determine the absorption maxima of TDF. The working solutions were analyzed for their absorbance using UV-Visible spectrophotometer, at λmax about 260 and a standard graph was plotted. The procedure repeated to construct the standard graph of TDF in deionized water and phosphate buffer pH 6.8 (USP).[22]

Standard stock solution was prepared by dissolving 10 mg of Tenofovir in distilled water. The volume was made up to 10 ml with distilled water to get a concentration of 1000 mcg/ml. This was further diluted to get the working standard solution of 20 µg/ml.

Aliquots of standard drug solution of Tenofovir 0.5 – 3.5 ml. About 20 µg/ml TDF solution was taken and transferred into series of 10 ml graduated test tubes. To each test tube 2 ml of methanolic p-Dimethylamino cinnamaldehyde (3% w/v) (PDAC) and 0.5 ml of 0.1N sulphuric acid solution were added. After thorough shaking, the test tubes were set aside for 10 mins, for the reaction to complete. The volumes in each test tube were adjusted to 10 ml with methanol. The absorbances of the solutions were measured at 530 nm against reagent blank, and the calibration curve was plotted. Similarly, the absorbance of the sample solution was measured, and the amount of Tenofovir was determined by referring to the calibration curve.[23,24]

6.2.1.5 Loss on Drying

The percent loss on drying was estimated by keeping the 1 g of TDF at 105±2°C in hot air oven till constant weight was observed. The acceptance criteria as per Indian Pharmacopoeia is not more than 3.5%.[25]

6.2.1.7 Excipient Compatibility Studies for TDF

To evaluate the compatibility of selected excipients with Tenofovir disoproxil fumarate API, binary mixture of API and excipients were prepared with 1:1 ratio and exposed at 50 ± 2°C in glass vials closed with rubber stopper with aluminum cap sealing for 7 days. The samples were evaluated for physical characteristics (physical appearance).[26]

Table 6.3 : Excipient Compatibility Studies- Binary Mixture of TDF

Binary mixture
Tenofovir Disoproxil Fumarate (API)
Tenofovir Disoproxil Fumarate + Microcrystalline cellulose (Avicel PH101)
Tenofovir Disoproxil Fumarate + Spray-dried Lactose (DCL-11)
Tenofovir Disoproxil Fumarate + Mannitol
Tenofovir Disoproxil Fumarate + Polyvinyl Pyrrolidone (K-30)
Tenofovir Disoproxil Fumarate + Hydroxypropyl cellulose (HPC-L)
Tenofovir Disoproxil Fumarate + Magnesium stearate
Tenofovir Disoproxil Fumarate + Talc
Tenofovir Disoproxil Fumarate + Gelucire
Tenofovir Disoproxil Fumarate + Precirol ATO 5
Tenofovir Disoproxil Fumarate + Silicified Microcrystalline Cellulose (PROSOLV)
Tenofovir Disoproxil Fumarate + Cross-povidone
Tenofovir Disoproxil Fumarate + Alpha-tocopherol
Mixture of Tenofovir Disoproxil Fumarate + All above excipients

6.3 Formulation Development for TDF

Process Selection

Tenofovir disoproxil fumarate API has very poor flow characteristics, hence direct compression method was not chosen. Due to poor flow characteristics, wet mass followed by an extrusion-Spheronization process has been selected.

Initial Risk Assessment of the Process Variables

The initial risk assessment of the formulation variables and justification for the risk assessment are presented in table below.

Table 6.4 : Initial Risk Assessment of the Process Variables for TDF

Drug Product CQAs	Process Variables								
	Blending	Granulation (Wet mass)	Screening to form Extrudes	Spheronization	Drying (Oven)	Screening	HMC and Drying	Blending	Compression
Taste	Low	Low	Medium	Medium	Medium	Medium	High	Low	Medium
Content uniformity	Low	Low	Low	Low	Low	Low	Low	Low	Low
Assay	Low	Low	Low	Low	Low	Low	Low	Low	Low
Dissolution	Low	Low	Medium	Medium	Medium	Medium	High	Low	Low

Table 6.5 : Justification for the Initial Risk Assessment of the Process Variables for TDF

Process Variables	Drug Products CQAs	Justification
Blending	Taste	The blending stage has no direct impact on Taste of final product. Moreover, there is low risk for assay, content uniformity, and dissolution due to high drug content (More than 80% w/w)
	Content uniformity	
	Assay	
	Dissolution	
Granulation (Wet mass)	Taste	The granulation process has no control for taste masking, it will be controlled through hot melt coating, hence Low risk applicable. Risk of granulation for assay, content uniformity, and dissolution is Low due to high drug content (More than 80% w/w)
	Content uniformity	
	Assay	
	Dissolution	
Screening to	Taste	Medium risk as the attribute of Pellets strength

Process Variables	**Drug Products CQAs**	**Justification**
form Extrudes, Spheronization and Drying of Pellets	Dissolution	can be affected, which may impact on dissolution. Moreover, the strength of Pellets is critical for the further process of taste masking (Hot melt coating). Thus, this step is considered as Medium risk.
	Content uniformity	Low risk for assay due to high drug content (More than 80% w/w)
	Assay	
Screening	Taste	Screening of Pellets is critical for further process of taste masking (Hot melt coating, Lower or higher size of pellets may affect hot melt coating uniformity as well as dissolution consistency. Thus, Medium risk.
	Dissolution	
	Content uniformity	Low risk for assay due to high drug content (More than 80% w/w)
	Assay	
Hot melt coating and Drying	Taste	High risk for physical attribute –Taste, as it impacts on patient acceptability, and may side effect like nausea due to sever bitterness. Dissolution attribute may be impacted due to hot melt coating, as coating materials are waxy in nature i.e. hydrophobic. Thus, hot melt coating process considered as High-risk process variable.
	Dissolution	
	Content uniformity	Low risk for assay due to high drug content (More than 80% w/w)
	Assay	
Blending	Taste	Low risk as intragranular proportion is about 82% and drug is also more than 80%, hence impact of final blending of pellets with
	Dissolution	
	Content uniformity	

Process Variables	Drug Products CQAs	Justification
	Assay	extragranular material is minimal. As pellets are already coated, there is no direct impact of blending process over taste and dissolution
Compression	Taste	Medium risk as due to compression there may be rupturing of taste masking layer of hot melt coating of pellets, which leads to bitterness on oral administration.
	Dissolution	Low risk for assay due to high drug content (More than 80% w/w)
	Content uniformity	
	Assay	

6.3.1 Preparation of Drug Pellets for TDF

TDF and excipients were blended in a double-cone blender for 5 min. The polyvinyl pyrrolidone solution (2% w/v) was poured slowly over the powder blend.[26]

6.3.1.1 Selection of Filler

Three different fillers were evaluated for suitability. Granulation was performed using Microcrystalline Cellulose, Spray Dried Lactose, and Mannitol as filler. Polyvinyl Pyrrolidone solution of 2% concentration was used as a granulating agent.

Table 6.6 : Formulation of TDF Batches- Selection of Filler

Ingredients	Formulation code		
	F1	F5	F9
Tenofovir disoproxil fumarate	300	300	300
Microcrystalline Cellulose (Avicel PH 101)	25	--	--
Spray-dried Lactose (DCL-11)	--	25	--
Mannitol	--	--	25
Polyvinyl Pyrrolidone (K-30) (2% w/v)	q. s.	q. s.	q. s.

Note: Formulation code F2, F3, F4, F6, F7, and F8 are reproducibility batches of F1, and F5. Hence not captured in the table. The trial F9 was not satisfactory hence, not further considered.

Brief Manufacturing Process:

1. Tenofovir disoproxil fumarate and filler (Microcrystalline Cellulose (Avicel PH 101) or Spray dried lactose (DCL-11) or Mannitol) were sifted together through # 20 mesh.
2. Polyvinyl Pyrrolidone (K-30) was dissolved in purified water under stirring to form (2%w/w) solution.
3. Step 2. Binder solution was sprinkled over the sifted material of step 1 in the bowl with simultaneous manual mixing, till the wet mass (dough) formed.
4. The wet mass (dough) was squeezed through #16 mesh to form extrudes.
5. The wet extrudates charged into the extruder- spheronizer (Umang Pharmatek, India) and the spheronizer with cross-hatch plate of 1.2 mm was operated for 5 min at 850 rpm to produce TDF pellets.
6. The pellets were dried at 60°C for 3 h.
7. The dried pellets were sifted to collect 16-20 mesh fractions. The suitability is determined based on the % yield of good pellets fraction.

6.3.1.2 Selection of Binder

Two different binding agents were evaluated for suitability. Optimization was done using formulations of Microcrystalline Cellulose and Spray Dried Lactose. A 2% binder solution was prepared using Polyvinyl Pyrrolidone (K30) and Hydroxypropyl Cellulose (HPC-L). Granulation was performed at a fluid uptake of 8%.

Table 6.7 : Formulation of TDF Batches- Selection of Binder

Ingredients	Formulation code			
	F1A	F1B	F5A	F5B
Tenofovir disoproxil fumarate	300	300	300	300
Microcrystalline Cellulose (Avicel PH 101)	25	25	--	--
Spray-dried Lactose (DCL-11)	--		25	25
Polyvinyl Pyrrolidone (K 30) (2% w/v)	q. s.	--	q. s.	--
Hydroxypropyl Cellulose (HPC-L) (2% w/v)	--	q.s.	--	q.s.

Brief Manufacturing Process:

1. Tenofovir disoproxil fumarate and filler (Microcrystalline Cellulose (Avicel PH 101) or Spray dried lactose (DCL-11)) were sifted together through # 20 mesh.
2. Polyvinyl Pyrrolidone (K-30) was dissolved in purified water under stirring to form (2%w/w) solution.
3. Hydroxypropyl Cellulose (HPC-L) was dissolved in purified water under stirring to form (2%w/w) solution.
4. Step 3 or 4 Binder solution was sprinkled over the sifted material of step 1 in bowl with simultaneous manual mixing, till the wet mass (dough) formed.
5. The wet mass (dough) was squeezed through #16 mesh to form extrudes.
6. The wet extrudates charged into the extruder- spheronizer (Umang Pharmatek, India) and the Spheronizer with a cross-hatch plate of 1.2 mm was operated for 5 min at 850 rpm to produce TDF pellets.
7. The pellets were dried at 60°C for 3 h.
8. The dried pellets were sifted to collect 16-20 mesh fractions. The suitability is determined based on the % yield of good pellets fraction.

6.3.1.3 Optimization of Fluid uptake

Two different fluid uptake levels were evaluated using Polyvinyl Pyrrolidone (K30) solution (2% w/v). Optimization was done using formulations of Microcrystalline Cellulose (Avicel PH 101) and Spray Dried Lactose (DCL-11).

Table 6.8 : Formulation of TDF Batches- Optimization of Fluid Uptake

Ingredients / Parameter	Formulation code			
	F1C	F1D	F5C	F5D
Tenofovir Disoproxil Fumarate	300	300	300	300
Microcrystalline Cellulose (Avicel PH 101)	25	25	--	--
Spray-dried Lactose (DCL-11)	--	--	25	25
Polyvinyl Pyrrolidone (K-30) (2% w/v)	q. s.	q. s.	q. s.	q. s.
Fluid uptake level (%)	8	12	8	12

Brief Manufacturing Process:

1. Tenofovir disoproxil fumarate and filler (Microcrystalline Cellulose (Avicel PH 101) or Spray dried lactose (DCL-11)) were sifted together through # 20 mesh.
2. Polyvinyl Pyrrolidone (K-30) was dissolved in purified water under stirring to form (2%w/w) solution.
3. Step 2 Binder solution was sprinkled over the sifted material of step 1 in bowl with simultaneous manual mixing. The binder was added at the level of 8% and 12% fluid uptake.
4. The wet mass (dough) was squeezed through #16 mesh to form extrudes.
5. The wet extrudates were charged into the extruder- spheronizer (Umang Pharmatek, India) and the spheronizer with cross-hatch plate of 1.2 mm was operated for 5 min at 850 rpm to produce TDF pellets.
6. The pellets were dried at 60°C for 3 h.
7. The dried pellets were sifted to collect 16-20 mesh fractions. The suitability is determined based on the % yield of good pellets fraction.

6.3.1.4 Optimization of Screen Size for Preparation of Extrudes

Formulation of TDF batches

Two different sieve sizes were selected for optimization. The type of binder and Fluid uptake levels were kept constant. Optimization was done using formulations of Microcrystalline Cellulose (Avicel PH 101) and Spray Dried Lactose (DCL-11).

Table 6.9 : Formulation of TDF Batches- Optimization of Screen Size for Preparation of Extrudes

Ingredients/Parameters	Formulation code			
	F1E	F1F	F5E	F5F
Tenofovir disoproxil fumarate	300	300	300	300
Microcrystalline Cellulose (Avicel PH 101)	25	25	--	--
Spray-dried Lactose (DCL-11)	--	--	25	25
Polyvinyl Pyrrolidone (K-30) (2% w/v)	q. s.	q. s.	q. s.	q. s.
Screen used for extrusion	#16	#20	#16	#20

Brief Manufacturing Process:

1. Tenofovir disoproxil fumarate and filler (Microcrystalline Cellulose (Avicel PH 101) / Spray dried Lactose (DCL-11)) were sifted together through # 20 mesh.
2. Polyvinyl Pyrrolidone (K-30) was dissolved in purified water under stirring to form (2%w/w) solution.
3. Step 2 Binder solution was sprinkled over the sifted material of step 1 in bowl with simultaneous manual mixing.
4. The wet mass (dough) was squeezed through #16 mesh / #20 mesh to form extrudes.
5. The wet extrudates were charged into the extruder- spheronizer (Umang Pharmatek, India) and the spheronizer with cross-hatch plate of 1.2 mm was operated for 5 min at 850 rpm to produce TDF pellets.
6. The pellets were dried at 60°C for 3 h.
7. The dried pellets were sifted to collect 16-20 mesh fractions. The suitability is determined based on the % yield of good pellets fraction.

6.3.1.5 Optimization of Spheronization Process

Formulation of TDF batches

Three different spheronizer cross-hatch plates of 1.0, 1.2, and 1.5 mm sizes were selected for optimization. The type of binder, Fluid uptake levels and extrusion screen were kept constant. Optimization was done using formulations of Microcrystalline Cellulose (Avicel PH 101) and Spray Dried Lactose (DCL-11).

Table 6.10 : Formulation of TDF Batches- Optimization of Spheronization Process

Ingredients/Parameters	Formulation code					
	F1G	F1H	F1I	F5E	F5F	F5I
Tenofovir disoproxil fumarate	300	300	300	300	300	300
Microcrystalline Cellulose (Avicel PH 101)	25	25	25	--	--	--
Spray dried lactose (DCL-11)	--	--	--	25	25	25
Polyvinyl Pyrrolidone (K-30) (2% w/v)	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
Cross-hatch plate size (mm)	1.0	1.2	1.5	1.0	1.2	1.5

Brief Manufacturing Process:

1. Tenofovir disoproxil fumarate and filler (Microcrystalline Cellulose (Avicel PH 101) or Spray dried lactose (DCL-11)) were sifted together through # 20 mesh.
2. Polyvinyl Pyrrolidone (K-30) was dissolved in purified water under stirring to form (2%w/w) solution.
3. Step 2 Binder solution was sprinkled over the sifted material of step 1 in bowl with simultaneous manual mixing.
4. The wet mass (dough) was squeezed through #16 mesh to form extrudes.
5. The wet extrudates were charged into the extruder- spheronizer (Umang Pharmatek, India) and the spheronizer with cross-hatch plate of 1.0, or 1.2, or 1.5 mm was operated for 5 min at 850 rpm to produce TDF pellets.
6. The pellets were dried at 60°C for 3 h.
7. The dried pellets were sifted to collect 16-20 mesh fractions. The suitability is determined based on the % yield of good pellets fraction.

6.3.1.6 Optimization of Drying Process for Pellets

Formulation of TDF batches

Two different drying times were selected for optimization. The type of binder, Fluid uptake levels, extrusion screen, and cross-hatch plate size were kept constant. Optimization was done using formulations of Microcrystalline Cellulose (Avicel PH 101) and Spray Dried Lactose (DCL-11).

Table 6.11 : Formulation of TDF Batches- Optimization of Drying Process for Pellets

Ingredients/Parameters	Formulation code			
	F1J	F1K	F5J	F5K
Tenofovir disoproxil fumarate	300	300	300	300
Microcrystalline Cellulose (Avicel PH 101)	25	25	--	--
Spray dried lactose (DCL-11)	--	--	25	25
Polyvinyl Pyrrolidone (K-30) (2% w/v)	q. s.	q. s.	q. s.	q. s.
Drying time (hours)	1	3	1	3

Brief Manufacturing Process:

1. Tenofovir disoproxil fumarate and filler (Microcrystalline Cellulose (Avicel PH 101) or Spray dried Lactose (DCL-11)) were sifted together through # 20 mesh.
2. Polyvinyl Pyrrolidone (K-30) was dissolved in purified water under stirring to form (2%w/w) solution.
3. Step 2 Binder solution was sprinkled over the sifted material of step 1 in bowl with simultaneous manual mixing.
4. The wet mass (dough) was squeezed through #16 mesh to form extrudes.
5. The wet extrudates were charged into the extruder- spheronizer (Umang Pharmatek, India) and the Spheronizer with cross-hatch plate of 1.2 mm was operated for 5 min at 850 rpm to produce TDF pellets.
6. The pellets were dried at 60°C for 1 hour or 3 hours.
7. The dried pellets were sifted to collect 16-20 mesh fractions. The suitability is determined based on the % yield of good pellets fraction and Loss on Drying of pellets.

6.3.1.7 Optimization of Pellet Size/Screen Size

The marketed products (Vitamin D3 Sachet- Calcirol, Ibuprofen Effervescent Granules) were evaluated for their particle size by size analysis. Based on the observations, the 16 and 20 mesh fractions were found suitable.

6.3.2 Hot Melt Coating of Pellets:

Based on optimization studies, the optimized formula and process parameters of pellets manufacturing are as below,[27, 28]

Table 6.12 : Details Optimized Hot Melt Coating of TDF Pellets

Ingredients/Parameters	Formula/Parameter	
Tenofovir disoproxil fumarate	300	300
Microcrystalline Cellulose (Avicel PH 101)	25	--
Spray dried Lactose (DCl-11)	--	25
Mannitol	--	--
Polyvinyl Pyrrolidone (K-30) (2% w/v)	q. s.	q. s.
Fluid uptake (%)	8	8

Ingredients/Parameters	Formula/Parameter	
Screen size (#)	#16	#16
Spheronizer cross-hatch plate (mm)	1.2	1.2
Drying time (hrs)	3	3
Pellets fractions (#)	16/20	16/20

The 20 mesh undersized and 16 mesh oversized pellets were rejected. TDF pellets were loaded into 10 inches diameter perforated coating pan equipped with 4 radially organized baffles and temperature regulation system.

The design of experiments was planned for optimization and identification of suitable hot melt coating ingredients and process parameters.

Table 6.13 : Hot Melt Coating Weight Build-up Parameters for TDF Pellets

Variables	Levels	
Hot melt coating agent	Gelucire® 43/01	Precirol® ATO 5
Coating build-up (%)	3,4,5	3,4,5
Pan Speed (rpm)	15,20	15,20
Coating temperature(ºC)	50,60	50,60

6.3.2.1 Optimization Hot Melt Coating Agent and Level of Coating:

The TDF pellets based on Microcrystalline Cellulose (Avicel PH 101) and Spray-dried lactose (DCL-11) were utilized for coating optimization. Two hot melt coating agents, Gelucire® 43/01 and Precirol® ATO 5 were used for coating evaluation, along with α- Tocopherol as an antioxidant for the coating agent. The experiments were performed with the below composition,

Table 6.14 : Optimization Hot Melt Coating Agent and Level of Coating for TDF

Ingredients	Formulation code											
	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20	F21
Tenofovir disoproxil fumarate	300	300	300	300	300	300	300	300	300	300	300	300
Microcrystalline	25	25	25	25	25	25	--	--	--	--	--	--

Ingredients		Formulation code											
		F10	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20	F21
Cellulose (Avicel PH 101)													
Spray dried lactose (DCL-11)		--	--	--	--	--	--	25	25	25	25	25	25
Polyvinyl Pyrrolidone(K-30) (2% w/v)		q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
Hot melt coating (%)	Gelucire® 43/01 (%)	2	3	4	--	--	--	2	3	4	--	--	--
	Precirol® ATO 5 (%)	--	--	--	2	3	4	--	--	--	2	3	4
	α-Tocopherol (%)	1	1	1	1	1	1	1	1	1	1	1	1

Brief Manufacturing Process:

1. The TDF pellets of Microcrystalline Cellulose (Avicel PH 101) and Spray dried Lactose (DCL-11) were formulated as per optimized procedure.
2. The drug pellets were loaded into the coating pan and rolled until pellet bed temperature of 60°C was attained.
3. The α- Tocopherol was added into the molten Gelucire® 43/01 or Precirol® ATO 5 under continuous stirring.
4. The molten coating mass was sprayed onto the rolling drug pellets in slow stream.
5. After the complete application of coating mass, the pellets were allowed to roll further for 10 min during which time the bed temperature was allowed to gradually come down. The pellets were then removed and cured in a dryer for 48 h. The parameters employed for HMC of Tenofovir pellets in the coating pan are given below,

Table 6.15: Process Parameters for Hot Melt Coating for Level of Coating for TDF

Parameter	Setting
Pellet weight	500 g
Pan speed	15 rpm
Coating level	3, 4 and 5% w/w
Pellet bed temperature	60°C
Relative humidity	40% RH
Coating time	30 min
Curing time	30°C for 48 h

6.3.2.2 Optimization of Coating Process Parameters: Pan Speed

The TDF pellets based on Microcrystalline Cellulose (Avicel PH 101) and Spray-dried Lactose (DCL-11) were utilized for coating optimization. Two hot melt coating agents, Gelucire® 43/01 and Precirol® ATO 5 were used for coating evaluation, along with α- Tocopherol. The experiments were conducted with two different pan speeds keeping coating weight build up constant.

Table 6.16: Optimization of Coating Process Parameters: Pan Speed

Ingredients/Parameters		Formulation code							
		F22	F23	F24	F25	F26	F27	F28	F29
Tenofovir disoproxil fumarate		300	300	300	300	300	300	300	300
Microcrystalline Cellulose (Avicel PH 101)		25	25	25	25	--	--	--	--
Spray-dried Lactose (DCL-11)		--	--	--	--	25	25	25	25
Polyvinyl Pyrrolidone (K-30) (2% w/v)		q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
Hot melt coating (%)	Gelucire® 43/01 (%)	3	3	--	--	3	3	--	--
	Precirol® ATO 5 (%)	--	--	3	3	--	--	3	3

Ingredients/Parameters		Formulation code							
		F22	F23	F24	F25	F26	F27	F28	F29
	α- Tocopherol (%)	1	1	1	1	1	1	1	1
Pan Speed (RPM)		15	20	15	20	15	20	15	20

Brief Manufacturing Process:

1. The TDF pellets of Microcrystalline Cellulose (Avicel PH 101) and Spray-dried Lactose (DCL-11) were formulated as per optimized procedure.
2. The drug pellets were loaded into the coating pan and rolled until pellet bed temperature of 60°C was attained.
3. The α- Tocopherol was added into the molten Gelucire® 43/01 or Precirol® ATO 5 under continuous stirring.
4. The molten coating mass was sprayed onto the rolling drug pellets at pan speed 15 rpm or 20 rpm in slow stream.
5. After the complete application of coating mass, the pellets were allowed to roll further for 10 min during which time the bed temperature was allowed to gradually come down. The pellets were then removed and cured in a dryer for 48 h. The parameters employed for HMC of tenofovir pellets in coating pan are given below,

Table 6.17: Process Parameters for Hot Melt Coating for Optimization of Pan Speed

Parameter	Setting
Pellet weight	500 g
Pan speed	15 and 20 rpm
Coating level	4 % w/w
Pellet bed temperature	60°C
Relative humidity	40% RH
Coating time	30 min
Curing time	30°C for 48 h

6.3.2.3 Optimization of Coating Process Parameters: Temperature

The TDF pellets based on Microcrystalline Cellulose (Avicel PH 101) and Spray-dried Lactose (DCL11) were utilized for coating optimization. Two hot melt coating agents, Gelucire® 43/01 and Precirol® ATO 5 were used for coating evaluation, along with α- Tocopherol. The experiments were conducted with two different bed temperatures keeping pan rpm and coating weight build up constant.

Table 6.18: Optimization of Coating Process Parameters: Temperature

Ingredients/Parameters		Formulation code							
		F30	**F31**	**F32**	**F33**	**F34**	**F35**	**F36**	**F37**
Tenofovir disoproxil fumarate		300	300	300	300	300	300	300	300
Microcrystalline Cellulose (Avicel PH 101)		25	25	25	25	--	--	--	--
Spray-dried Lactose (DCL-11)		--	--	--	--	25	25	25	25
Polyvinyl Pyrrolidone (K-30) (2% w/v)		q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
Hot melt coating (%)	Gelucire® 43/01 (%)	3	3	--	--	3	3	--	--
	Precirol® ATO 5 (%)	--	--	3	3	--	--	3	3
	α- Tocopherol (%)	1	1	1	1	1	1	1	1
Bed Temperature (ºC)		40	60	40	60	40	60	40	60

Brief Manufacturing Process:

1. The TDF pellets of Microcrystalline Cellulose (Avicel PH 101) and Spray-dried Lactose (DCL-11) were formulated as per optimized procedure.
2. The drug pellets were loaded into the coating pan and rolled until pellet bed temperature of 40°C or 60°C was attained.

3. The α- Tocopherol was added into the molten Gelucire® 43/01 or Precirol® ATO 5 under continuous stirring.
4. The molten coating mass was sprayed onto the rolling drug pellets at pan speed 20 rpm in slow stream.
5. After the complete application of coating mass, the pellets were allowed to roll further for 10 min during which time the bed temperature was allowed to gradually come down. The pellets were then removed and cured in a dryer for 48 h. The parameters employed for HMC of Tenofovir pellets in coating pan are given below,.

Table 6.19: Process Parameters for Hot Melt Coating for Optimization of Temperature

Parameter	Setting
Pellet weight	500 g
Pan speed	15 rpm
Coating level	4 % w/w
Pellet bed temperature	40°C and 60°C
Relative humidity	40% RH
Coating time	30 min
Curing time	30°C for 48 h

6.4 Evaluation of the Pellets

6.4.1 Pellet appearance

The coated and uncoated were snapped using digital microscope connected with personal computer.[29]

6.4.2 Mean Pellet Size (d_{mean})

The average size of pellets was carried out using sieving analysis technique. A sieve shaker and set of four active ASTM standard test sieves (#14, #16, #18 and #20) were used for the analysis. Accurately weighed 100 g of drug pellets were placed in sieve arranged over decreasing order of aperture size from top to bottom. The sieve shaker was operated for 5 min. The size distribution of pellets expresses the efficiency of the process of manufacture of the uniform size pellets.[29] The mean pellet size was calculated using equation.

$d_{mean} = \sum$ (% retained x Average aperture size)/100……. (6.4)

6.4.3 Bulk Density (ρ_b)

Bulk density is ratio of bulk weight and bulk volume. Accurately weighed 50 g of Tenofovir coated pellet fraction of 16/20 mesh were poured gently through glass funnel into 100 ml calibrated measuring cylinder. The surface was cautiously levelled with null pressure. The volume occupied by pellets was used for calculation of bulk density (g/ml) using equation[4]

$$\text{Bulk density} = \frac{\text{Weight of pellets}}{\text{Bulk volume of pellets}}$$

…… (6.5)

6.4.4 Tapped Density (ρ_t)

Bulk density is ratio of bulk weight and tapped volume. Tapped density was estimated in a similar way to that of bulk density. However, final volume was measured after tapping the cylinder from 3 inches until constant volume was obtained using Electrolab tapped density apparatus. The volume occupied by pellets after tapping was noted and tapped density (g/ml) was calculated using the equation[4]

$$\text{Tapped density} = \frac{\text{Weight of pellets}}{\text{Tapped volume of pellets}}$$ …… (6.6)

6.4.5 Carr Index (CI)

The external appearance of pellets and internal structure can alter material properties and porosity that greatly effect on pellet coating, flow and packing during tabletting or capsule filling. It also shows effect on drug release by affecting the capillary action of dissolved drug. Using bulk density and tapped density values of tenofovir coated pellets the compressibility index can be calculated using equation.

$$\text{Carr Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

……..… (6.7)

The flow ability of prepared pellets can be decided based on the standard values

Table 6.20 : Standard Carr's Index Flowability Chart

Carr's index	Flowability
10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Very very poor

6.4.6 Hardness and Friability

The hardness tenofovir pellets was determined by digital dial type hardness tester (Veego Instruments Corporation, India). For the friability study, accurately weighed 10.0 g of tenofovir coated pellets (initial weight) with 25 glass beads of 3 mm diameter were placed in the revolving drum of Roche's friabilator (Veego Instruments Corporation, India) for 100 revolutions operated at 25 rpm speed. The pellets were collected and placed on the sieve with 0.85 mm aperture and the smaller particles were allowed to pass through the sieve. The pellets were reweighed (Final weight) and % weight loss data were considered as %friability and calculated using equation [26]

$$\text{Friability (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

……. (6.8)

6.4.7 Drug Content

Accurately weighed 500 mg of hot-melt coated pellets were grind carefully in the mortar using pestle and sieved from 80 sieve. Accurately weighed 50 mg of this powder was transferred carefully to 100 ml volumetric flask and add 30 ml of methanol and ultrasonicated using laboratory sonicator (ISP Technologies, India) for 15 min to extract the tenofovir. Final volume was made with phosphate buffer pH 6.8 and diluted suitably. The diluted sample were scanned at 260 nm using double distilled water as blank using Ultraviolet- visible (UV) spectrophotometer (UV1800, Shimadzu, Japan). The drug content was calculated using standard calibration curve.[22]

6.4.8 In-vitro Drug Release Study

In-vitro drug release from Tenofovir pellets was carried out using United States Pharmacopoeia (USP) apparatus I (Basket Type), model Electrolab, 6 vessel assembly at 100 rpm. The 900 ml of 0.1N hydrochloric acid was used as dissolution medium since it can maintain sink condition during dissolution. Temperature of dissolution medium was maintained at 37 ± 0.5°C. The dissolution was conducted for an hour. Aliquots of 5 ml were withdrawn at predetermined intervals. An equivalent amount of fresh dissolution fluid equilibrated at the same temperature. Aliquots withdrawn were diluted suitably (1 ml to 20 ml), filtered and analyzed. All dissolution studies were conducted in triplicate and the mean values were plotted versus time with a standard deviation less than three indicating reproducibility of result. The percent cumulative drug release against time was plotted.[30, 31]

Table 6.21 : In-vitro Dissolution Study Conditions for Tenofovir Pellets

Sr. No.	Parameters	Specifications
1.	Dissolution apparatus	USP Type I (Basket)
2.	Speed	100 rpm
3.	Temperature	37± 0.5°C
4.	Time	30 min
5.	Dissolution medium	0.1N hydrochloric acid
6.	Volume of dissolution medium	900 ml
7.	Sampling time	5, 10, 15, and 30 min

6.4.9 In-vitro Taste Evaluation

Hot melt coated pellets equivalent to 50 mg of drug were placed in test tube containing 10 ml of double distilled water maintained at 37±1°C, stirred gently to simulate conditions of mouth cavity. After every 30 sec aliquot of 1 ml was collected and replaced with fresh medium to maintain dissolution medium at 37±1°C. Each aliquot was diluted to 100 ml and the absorbance of diluted solution was recorded at 260 nm using UV-visible spectrophotometer. Taste evaluation was performed for 10 min.[32]

6.4.10 Determination of Threshold Bitter Taste

To taste the sensory bitter taste of drug twelve human volunteers were selected and coded. They were asked to thoroughly rinse the mouth cavity with purified water. The dilutions of drug concentration range 50-500 µg/ml were prepared. Each volunteer was informed to hold 5 ml solution for 10 sec and spat out. The volunteers were asked to rinse the mouth cavity with purified water after every treatment to avoid carryover effect of previous treatment. The score of bitterness given to each solution against the distilled water was recorded. The minimum concentration which was judged as bitter taste by volunteer was considered as bitter threshold.[33,34]

6.4.11 Taste Panel Method

To taste the bitter taste of and efficacy of hot melt coating for taste masking of drug twelve human volunteers were selected. They were asked to thoroughly rinse the mouth cavity with purified water. They were provided with the 50 mg of pellets over tongue for 10 sec. Taking the taste of pure drug solution as standard, the degree of bitterness was judged by volunteers according to bitterness scale.[35]

6.4.12 Stability Test

The pellets equivalent to unit dose were filled in self-sealing Aluminium pouch. They were stored at temperature 25±2°C & 60±5% RH and 40 ± 2°C & 75 ± 5% RH for 6 months in the stability chamber (Remi Laboratory Instrument, CHM-6). The pellets were evaluated for any changes in physical appearance and percent drug content after every month. The results obtained were compared with data obtained at zero time and pellets stored at 25±2°C and 60±5% RH. The pellets were evaluated for any changes in physical appearance, drug content and in-vitro drug release after every month. The results obtained were compared with data obtained at zero time and pellets stored at 25±2°C & 60±5% RH and 40 ± 2°C & 75 ± 5% RH[36,37].

6.5 Compression of Tablets

Each blend was prepared using two different fillers and two different hot melt-coated pellets. The compression was performed on three different hardness, low, medium and high hardness. Moreover, final blend of un-coated pellets was also compressed for comparative taste masking evaluation.

Table 6.22: Hot Melt Coated Pellets Using Gelucire® 43/01

Ingredients/Parameters		Formulation Code							
		F38	F39	F40	F41	F42	F43	F44	F45
Tenofovir Disoproxil Fumarate		300	300	300	300	300	300	300	300
Microcrystalline Cellulose (Avicel PH 101)		25	25	25	--	--	--	25	--
Spray-dried Lactose (DCL-11)		--	--	--	25	25	25	--	25
Polyvinyl Pyrrolidone (K-30) (2% w/v)		q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
Hot melt coating (%)	Gelucire® 43/01 (%)	3	3	3	3	3	3	--	--
	α- Tocopherol (%)	1	1	1	1	1	1	--	--
Silicified MCC		60	60	60	60	60	60	60	60
Talc		8	8	8	8	8	8	8	8
Crospovidone		5	5	5	5	5	5	5	5
Magnesium Stearate		2	2	2	2	2	2	2	2
Hardness		L	M	H	L	M	H	M	M

L: Low Hardness, M: Medium Hardness, H: High Hardness

Table 6.23 : Hot Melt Coated Pellets Using Precirol® ATO 5

Ingredients/Parameters	Formulation Code							
	F46	F47	F48	F49	F50	F51	F52	F53
Tenofovir Disoproxil Fumarate	300	300	300	300	300	300	300	300
Microcrystalline Cellulose (Avicel PH 101)	25	25	25	--	--	--	25	--
Spray-dried Lactose(DCL-11)	--	--	--	25	25	25	--	25
Polyvinyl Pyrrolidone (K-30) (2% w/v)	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.

Ingredients/Parameters		Formulation Code							
		F46	F47	F48	F49	F50	F51	F52	F53
Hot melt coating (%)	Precirol® ATO 5 (%)	3	3	3	3	3	3	--	--
	α- Tocopherol (%)	1	1	1	1	1	1	--	--
Silicified MCC		60	60	60	60	60	60	60	60
Talc		8	8	8	8	8	8	8	8
Crospovidone		5	5	5	5	5	5	5	5
Magnesium Stearate		2	2	2	2	2	2	2	2
Hardness		L	M	H	L	M	H	M	M

Brief Manufacturing Process:

1. The final blending of hot melt coated pellets of Gelucire® 43/01 or Precirol® ATO 5 or un-coated pellets were mixed with extragranular materials, Silicified Microcrystalline Cellulose (Cushioning agent), talc and magnesium stearate were mixed.
2. The compression of tablets using 10 station rotatory tablet punching (Riddhi Pvt. Ltd., India) using 8 mm circular biconcave punches by adjusting hardness. Tablets were compressed at Low, Medium and High hardness. Hardness levels 4±0.5 kg/cm^2 to 7±0.5 kg/cm^2 were evaluated.

6.6 Evaluation of Tablets

6.6.1 Organoleptic Properties

The prepared tablets were observed for appearance, colour, odour and taste.

6.6.2 Weight Variation Test

Twenty tablets were selected randomly and weighed. The average weight was determined. Then individual tablets were weighed and was compared with average weight. The comparison variation within the limits, prepared tablet batches pass the weight variation test.

Table 6.24: Standards for Uniformity of Weight

Sr. No.	Average weight	Percent deviation
1.	130 mg or less	10
2.	130 to 324 mg	7.5
3.	325 or More	5

Note: Limits as per US Pharmacopoeia

6.6.3 Tablet Hardness Test

The resistance of tablets to delivery or breakage under state of capacity, transportation and dealing with before utilization depends on its hardness. The hardness of tablet of every formulation can be estimate by Monsanto tester, Pfizer tester and Erweka Hardness Tester. The hardness was measured in terms of kg/cm^2. Tablet crushing strength (Fc) or hardness, the force required to break a tablet in a diametric compression, was measured using Monsanto tablet hardness tester. Randomly selected six tablets were used for evaluation from each batch. Each tablet was placed between anvil and the screw was rotated to apply pressure. The pressure required to break tablet was recorded on scale. The mean and standard deviation value were recorded.

6.6.4 Thickness

The thickness of individual tablets was measured using micrometer screw gauge, which permits accurate measurements and provides information of the variation between tablets.

6.6.5 Tablet Friability

The friability of the tablets was measured in a friability test apparatus. Tablets of a known weight (W0) (sample quantity approx. 6.5 g tablets) were dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %. Determination was made in triplicate.

$$\text{Friability (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \quad \ldots (6.9)$$

6.6.6 Drug Content

Twenty tablets were weighed and taken in mortar and crushed to make powder. A quantity of powder weighing equivalent to 300 mg of TDF was taken in 1000 ml volumetric flask and 100 ml ethanol was added. Final volume was adjusted using distilled water with occasional shaking. The resultant solution was sonicated in Ultrasonicator (ISP Technologies, India) for 5 minutes. The solution was filtered using membrane filter 0.45µm and then the solutions absorbance was measured at 260 nm using UV visible spectrophotometer. Then the amount of drug present was calculated using standard graph.

6.6.7 In-vitro Disintegration Test

The disintegration test was carried out using 6 tablets using tablet disintegration test apparatus (Electrolab India Pvt Ltd., India). Distilled water was used as medium for test at 37ºC ± 2ºC. The time required for complete disintegration of the tablets was recorded. No palpable mass remain on mesh was recorded as disintegration time.

6.6.8 In-vitro Drug Release Study

In-vitro dissolution studies for prepared tablets and the marketed available tablets was carried out using USP apparatus I (Basket Type), model Electrolab, 6 vessel assembly at 100 rpm in 900 ml of distilled water as dissolution media, maintained at 37 ± 0.5°C. After predetermined interval 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium. The solution was cooled down to room temperature filtered using membrane filter 0.45µm and then the solutions absorbance was measured at absorption maxima using UV visible spectrophotometer. The cumulative percentage of drug release was calculated and represent graphically. The similarity and difference factor were used to confirm the uniformity in release profile between Tablet B formulation and marketed formulation (Vired 300 Tablets).[29,30]

Table 6.25: In-vitro Dissolution Study Conditions for Tenofovir Tablets

Sr. No.	Parameters	Specifications
1.	Dissolution apparatus	USP Type I (Basket)
2.	Speed	100 rpm

Sr. No.	Parameters	Specifications
3.	Temperature	37± 0.5°C
4.	Time	30 min
5.	Dissolution medium	Distilled water
6.	Volume of dissolution medium	900 ml
7.	Sampling time	5, 10, 15 and 30 min

6.6.9 In-vitro Taste Evaluation

To taste the bitter taste of and efficacy of compressed tablets for taste masking of drug, twelve human volunteers were selected and coded them. They were asked to thoroughly rinse the mouth cavity with purified water. They were provided with one over tongue for 10 sec. Taking the taste of pure drug solution as standard, the degree of bitterness was judged by volunteers according to bitterness scale.[35]

6.6.10 Similarity Factor (f_2):

Different dissolution profiles were compared to establish the effect of formulation or process variables on the drug release as well as comparison of the test formulations to the theoretical release profile. The dissolution similarity was assessed using the Food and Drug Administration (FDA) recommended approach (f_2, similarity factor). The similarity factor is a logarithmic, reciprocal square root transformation of the sum of squared errors, and it serves as a measure of the similarity of two respective dissolution profiles. [38,39]

$$f_2 = 50.\ \text{Log}\ \{[1+ (1/n)\ \Sigma^{n}_{t=1}(R_t-T_t)^{2}]^{-0.5} \times 100\} \qquad (6.10)$$

Where, n = number of sample points,

R_t = percent of marketed product observed and

T_t = percent of test formulations release observed

FDA has set a published standard for similarity factor (f_2) value (50-100) for indication of similarity between two dissolution profiles. To use mean data, the coefficients of variation for mean dissolution profile of a single batch should be less than 10%. The average difference at any dissolution sampling point should not be greater than 15% between test and reference products. If the drug release is more than 85% in 15 minutes, the dissolution profiles are considered similar.[38,39]

6.6.11 Stability Test

The stability of the active ingredient is a major criterion in determining acceptance or rejection of batch. During stability study, the product was exposed to accelerated as well as long term stability conditions of temperature and humidity. The final formulation was filled in polycarbonate bottles sealed with Aluminium foil and kept in the humidity chamber maintained at 25ºC±2 ºC /60% ± 5%RH and 40ºC±2 ºC /75% ± 5%RH conditions for six months as per International Council of Harmonization (ICH) guidelines.[36,37]

Part B

6.7 Materials and Methods for Sitagliptin Phosphate Monohydrate

6.7.1 Materials and Equipment for SPM

Table 6.26: List of Material and Suppliers

Sr. No.	Chemical	Supplier
1.	Sitagliptin Phosphate Monohydrate	Mylan Laboratories Limited, India
2.	Stearic acid	S.D. Fine Chemicals, India
3.	Palmitic acid	S.D. Fine Chemicals, India
4.	Polyvinyl Pyrrolidone (K-30)	Thomas Baker Chemical Pvt. Ltd. India
5.	Dicalcium phosphate	Thomas Baker Chemical Pvt. Ltd., India
6.	Titanium dioxide	S.D. Fine Chemicals, India
7.	Polyethylene glycol-4000	Gem9 Envirotech Supplier, India
8.	Colloidal Silicon Dioxide (Aerosil)	S.D. Fine Chemicals, India
9.	Talc	Themis Laboratories, India
10.	Spray Dried Lactose (DCL-11)	S.D. Fine Chemicals, India
11.	Sodium Starch Glycolate	S.D. Fine Chemicals, India
12.	Microcrystalline Cellulose (Avicel PH 101)	S.D. Fine Chemicals, India

All the other chemicals were of analytical and laboratory grade used as procured.

Table 6.27: List of Equipment and Make

Sr. No.	Equipment	Make
1.	UV- Visible spectrophotometer	Schimadzu®, Japan
2.	USP dissolution test apparatus	Electrolab®, India
3.	Sieve shaker	Toshiwal and Company®, India
4.	Digital hardness tester	Veego Scientific®, India
5.	Roche friabilator	Veego Scientific®, India
6.	Ultrasonicator	ISP technologies®, India
7.	Stability chamber	Electrolab®, India
8.	Pan coater	Adinath International, India
9.	Bulk density apparatus	Electrolab India Pvt Ltd., India
10.	Friability test apparatus	Veego Instruments Corporation, India
11.	Disintegration test apparatus	Electrolab India Pvt Ltd., India
12.	Dissolution test apparatus	Electrolab India Pvt Ltd., India
13.	Tablet punching machine	Riddhi Pvt. Ltd., India
14.	pH Meter	Global electronics, India
15.	Analytical balance	Denver instrument, Germany
16.	Hardness tester	Veego Instruments Corporation, India

6.7.2 Methods for SPM

6.7.2.1 Preformulation Studies for SPM

6.7.2.1.1 Organoleptic Properties

The organoleptic properties of Sitagliptin Phosphate Monohydrate (SPM) like colour, odour and taste were determined. The appearance of the sample SPM was observed under microscope.

6.7.2.1.2 Melting Point:

Determination of melting point of drug is preliminary test for the determination of purity of the drug. Lowering or widening of melting point range indicates presence of impurity in the pure drug. The melting behavior was determined using a Mettler-Toledo MP70 melting point system (Greifensee, Switzerland). A capillary was used with a closed bottom, applying a heating rate of 10°C min^{-1} up to a temperature limit

of 400°C.[15]

The DSC analysis was performed in a Shimadzu® DSC-60 calorimeter (Kyoto, Japan). The samples were analyzed in an aluminum crucible containing around 2.0 mg of sample under dynamic synthetic air atmosphere (50 mL min−1) with a heating rate of 10°C min−1 and temperature range of 30°C to 400°C. The instrument was calibrated with indium and zinc (reference standards). The purity was determined using aluminum crucibles with approximately 2.0 mg of sample at a heating rate of 2 °C min−1 from 30°C to 400 °C. The purity of the sample was measured in triplicate using TASYS software (version 1.14, Shimadzu®), based on the Van't Hoff equation:

$$X2 = (To - Tm)\Delta Hf/RTo^{2} \quad \text{.....(6.11)}$$

Where, the purity is determined from the molar percentage of impurities present in the sample, X2 represents the mole fraction of impurities, Tm is the sample melting temperature, To is the melting point of the pure substance (°K), R is a gas constant and ΔHf is the heat of fusion of the main component (J mol−1).[16,17]

6.7.2.1.3 Identification (Fourier Transform Infrared (FTIR) Spectroscopy)

The infrared spectra were recorded on a Bruker Alpha-P FTIR spectrometer (Ettlingen, Germany) using attenuated total reflection (ATR) in the wavelength range of 3500 to 500 cm^{-1}, with a nominal resolution of 4 cm^{-1} and accumulation of 32 scans.[18]

6.7.2.1.4 Spectrophotometric Method for Measurement of Sitagliptin

Instrument: Instrument used UV-Visible double beam spectrophotometer, Shimadzu Corporation (Japan), Model UV-1800 with a bandwidth of 0.5nm and a pair of 1cm matched quartz cells. Analytical balance (Denver instrument, Germany) and sonicator (Electro quip Ultra sonicator, Texas), pH meter (Global electronics, India) was used in the study. Calibrated glass wares used throughout the work.

Chemicals:

The drug (Sitagliptin phosphate) supplied by Mylan was used. The chemicals used were Methanol (AR Grade, S.D. Fine Chemicals, Mumbai, India) and distilled water.

Method:

Standard Graphs of Sitagliptin

Preparation of Stock Solution: Accurately weighed 10 mg of sitagliptin phosphate was taken in a 100 ml volumetric flask and dissolved in 5 ml of methanol. The volume was made up to 100 ml with double distilled water, which constitute stock solution of 100 µg/ml concentration.

Preparation of Working Solution: The stock solution was suitably diluted with double distilled water to prepare the working solutions of 10, 20, 30, 40, 50, and 60 µg/ml.

Estimation of Absorption Maxima (λmax): A 100 µg/ml solution of sitagliptin phosphate was scanned between 200-400 nm to determine the absorption maxima (λmax) of sitagliptin.

Determination of Absorbance: The working solutions were analyzed for their absorbance using UV-Visible spectrophotometer, at λmax about 267 and a standard graph was plotted. The procedure repeated to construct the standard graph of sitagliptin in 0.01N hydrochloric acid, phosphate buffer pH 4.5 and phosphate buffer pH 8 (USP). [19-21]

6.7.2.1.5 Solubility Analysis:

Solubility is one of the most important parameters about achieving the desired concentration of the drug in systemic circulation to obtain the required pharmacological response. Poorly water-soluble drugs with a slow absorption, for instance, may show inadequate bioavailability.[22,23]

Solubility analysis of sitagliptin phosphate monohydrate was carried out by adding 257 mg SPM in different medium like 0.01N hydrochloric acid, 0.01M sodium citrate, 0.01 M sodium carbonate, acetate buffer (pH 4.5) and distilled water (pH 7.0) in volumetric flasks of 50 ml capacity. The overall solubility analysis was performed at 25°C. The buffer used were with pH not deviated than 0.5 units after addition of drug. The pH was recorded initially and after 24 hours shaking with wrist action shaker and the solutions were analyzed for dissolved drug substances. Solution was filtered through 0.45 µ membrane, and filtrate was analyzed spectrophotometrically. [24-26]

The solubility of SPM was also estimated in organic solvents like in acetone, acetonitrile, ethanol, methanol, isopropyl alcohol, isopropyl acetate, dimethyl sulfoxide and N, N-dimethyl formamide in the similar way.[27]

6.7.2.1.6 Partition Coefficient

Sitagliptin phosphate partition coefficient was determined in n-octanol-water system. A 500 mg of sitagliptin phosphate was transferred to a bottle containing 500 ml of n-octanol. The bottles were capped and agitated for 24h at room temperature to achieve complete equilibration. The phases were allowed to separate in a separating funnel. The aqueous layer containing the drug was analyzed at a maximum wavelength of 267 nm using UV-Visible spectrophotometer. The drug concentration in the aqueous layer was obtained from the calibration graph.[28] The partition coefficient of the drug was calculated using the equation:

$$K_{o/w} = C1\text{-}Cw/Cw\ (Vw\text{-}Vo) \quad \text{.....(6.12)}$$

Where, Ko/w = partition coefficient; C1 = total concentration of sitagliptin phosphate; Cw = concentration of sitagliptin phosphate in aqueous phase; Vw = volume of the aqueous phase; Vo = volume of the organic phase. The determination was done in triplicates.

6.7.2.1.7 pH Determination:

A 2% saturated solution of Sitagliptin Phosphate was prepared in distilled water and pH was measured by a digital pH meter.[29]

6.7.2.1.8 Loss on Drying (%)

Accurately weighed 2 g of SPM previously screened through sieve number 80 was placed in dry weighing bottle and transfer the bottle in hot air oven maintained below 10°C temperature than the melting point of SPM for 1-2 hours hot air oven till constant weight was observed. The acceptance criteria as per United States Pharmacopoeia is not more than 2%.[30]

6.7.2.2 Excipient Compatibility Studies

To evaluate the compatibility of selected excipients with sitagliptin phosphate monohydrate (SPM) API, a binary mixture of API and excipients were prepared with 1:1 ratio and exposed at 50 ± 2°C in glass vials closed with a rubber stopper with

aluminum cap sealing for 7 days. The samples were evaluated for physical characteristics (physical appearance).

Table 6.28 : Excipient Compatibility Studies- Binary Mixture

Binary mixture
Sitagliptin Phosphate Monohydrate (API)
Sitagliptin Phosphate Monohydrate + Stearic acid
Sitagliptin Phosphate Monohydrate + Palmitic acid
Sitagliptin Phosphate Monohydrate + Polyvinyl Pyrrolidone (K-30)
Sitagliptin Phosphate Monohydrate + Dicalcium Phosphate
Sitagliptin Phosphate Monohydrate + Titanium Dioxide
Sitagliptin Phosphate Monohydrate + Polyethylene lycol-4000
Sitagliptin Phosphate Monohydrate + Colloidal Silicon Dioxide (Aerosil)
Sitagliptin Phosphate Monohydrate + Talc
Mixture of Sitagliptin Phosphate Monohydrate + All above excipients

6.7.3 Formulation Development for Sitagliptin Phosphate Monohydrate

6.7.3.1 Process Selection

Sitagliptin phosphate monohydrate API has good flow characteristics, hence direct compression method was chosen.

6.7.3.1.1 Initial Risk Assessment of the Process Variables

The initial risk assessment of the formulation variables and justification for the risk assessment are presented in table below.

Table 6.29 : Initial Risk Assessment of the Process Variables

Drug Product CQAs	Process Variables		
	Blending	Compression	HMC and Drying
Moisture	Low	Low	Low
Assay	High	High	High
Dissolution	Low	High	High

Table 6.30 : Justification for the Initial Risk Assessment of the Process Variables

Process Variables	Drug Products CQAs	Justification
Blending	Moisture	The blending process has no direct impact on the Dissolution and Moisture of the final product.
	Dissolution	
	Assay	Blending process parameters such as blending time, blender speed are impacts on uniform mixing of API with other excipients. The uneven distribution impacts the assay of finished product. Hence, risk is considered as High.
Compression	Moisture	The compression stage has no direct impact on Moisture of the final product. Hence, risk is low.
	Assay	The compression process involves the conversion of final blend into unit dosage at a predefined target tablets weight. The individual tablets weight uniformity of tablets have impact on assay and the hardness has impact on the dissolution of tablets.
	Dissolution	
HMC and Drying	Moisture	The HMC coating process has no direct impact on moisture as it does not involve aqueous vehicle.
	Assay	HMC coating process involves heating of tablets and application of hot (molten) coating agent. The drug may degrade due to heat. Hence, risk is high.

Process Variables	Drug Products CQAs	Justification
	Dissolution	HMC coating process involves application of hydrophobic coating agents, which may impact on drug release. Hence, risk is high.

6.7.3.2 Selection of Filler:

Three different fillers were evaluated for suitability. Blending was performed using Microcrystalline Cellulose, Spray Dried Lactose, and Dicalcium phosphate as filler. All three final blends were compressed.

Table 6.31 : Formulation of Sitagliptin Batches- Selection of Filler

Ingredients	Formulation code		
	B1	B2	B3
Sitagliptin Phosphate Monohydrate	65	65	65
Dicalcium Phosphate	60	--	--
Microcrystalline Cellulose (Avicel PH101)	--	60	--
Spray Dried Lactose (DCL-11)	--	--	60
Talc	2	2	2
Croscarmellose Sodium	2	2	2
Colloidal Silicon Dioxide (Aerosil)	1	1	1

Brief Manufacturing Process:

1. Sitagliptin, Dicalcium phosphate or Microcrystalline Cellulose (Avicel PH 101) or Spray-dried Lactose (DCL-11) were sifted through #20 sieve.
2. The remaining materials Talc, Croscarmellose sodium, and Colloidal Silicon Dioxide (Aerosil) were sifted separately through #20 sieve.
3. Sifted materials of step 1 were loaded into a double cone blender and mixing was performed for 20 mins at 24 RPM.
4. Sifted materials of step 2 were loaded into a double cone blender and mixing was performed for 5 mins at 24 RPM.
5. Compressed the final blend (three blends of three different fillers) using a 10-station rotary tablet machine with 6-mm standard biconcave circular punches.

6. The tablets were tested for physical appearance, hardness, and disintegration time.

6.7.3.3 Selection of Disintegrant:

Two different Disintegrants were evaluated for suitability. Optimization was performed using Microcrystalline Cellulose (Avicel PH 101), as filler. Both the blends were compressed.

Table 6.32 : Formulation of Sitagliptin Batches- Selection of Disintegrant

Ingredients	Formulation code	
	B4	B5
Sitagliptin Phosphate Monohydrate	65	65
Microcrystalline Cellulose (Avicel PH101)	60	60
Talc	2	2
Sodium Starch Glycolate	2	--
Croscarmellose Sodium	--	2
Colloidal Silicon Dioxide (Aerosil)	1	1

Brief Manufacturing Process:

1. Sitagliptin, Microcrystalline Cellulose Avicel PH 101 were sifted through #20 sieve.
2. The remaining materials Talc, Croscarmellose sodium or Sodium Starch Glycolate, and Colloidal Silicon Dioxide (Aerosil) were sifted separately through #20 sieve.
3. Sifted materials of step 1 were loaded into a double cone blender and mixing was performed for 20 mins at 24 RPM.
4. Sifted materials of step 2 were loaded into a double cone blender and mixing was performed for 5 mins at 24 RPM.
5. Compressed the final blend (two blends of two different disintegrants) using a 10-station rotary tablet machine with 6-mm standard biconcave circular punches.
6. The tablets were tested for physical appearance, hardness, and disintegration time.

6.7.3.4 Selection of Glidant and Lubricant:

Colloidal Silicon Dioxide (Aerosil) was selected as a glidant, and Talc was selected as a lubricant in the above experiments for the selection of filler and disintegrant. The performance of the blend during compression was found satisfactory in all experiments. Hence, the same glidant and lubricants were identified as suitable for the formulation. The optimized formula for core tablets is as below:

Table 6.33 : Optimized Formulation of Sitagliptin Batches

Ingredient & Formulation code	mg/tablet
Sitagliptin Phosphate Monohydrate	65
Microcrystalline Cellulose (Avicel PH101)	60
Talc	2
Croscarmellose Sodium	2
Colloidal Silicon Dioxide (Aerosil)	1

6.7.3.5 Preparations of SPM core tablets:

Tablet containing 65 mg of Sitagliptin Phosphate Monohydrate equivalent to 50 mg of Sitagliptin were prepared. Compression was carried out using a 10-station rotary tablet machine with 6-mm standard biconcave circular punches.[31]

6.7.3.6 Selection of coating agents:

The suitability and performance of Gelucire® 43/01 and Precirol® ATO 5 as a hot melt coating agents were already evaluated for Tenofovir formulation; hence it was decided to assess alternate hot melt coating agents.

The experiments were designed to optimize and identify suitable hot melt coating ingredients and process parameters. The natural origin hot melt coating agents, stearic acid and palmitic acid were used for coating.[32]

Table 6.34 : Formulation of Hot Melt Coating Composition

Ingredients	Formulation Code							
	F1	F2	F3	F4	F5	F6	F7	F8
Stearic acid	4.00	3.75	3.5	3.25	--	--		
Palmitic acid	--	--	--	--	4.00	3.75	3.5	3.25
Polyethylene Glycol 4000	--	0.25	0.5	0.75	--	0.25	0.5	0.75
Titanium dioxide	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
α-tocopherol	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

Brief Manufacturing Process:

1. Each batch of 400 SPM tablet cores equivalent 50 g of tablet were loaded into a 5-inch coating pan equipped with 4 radially organized baffles and a temperature regulation system.
2. The tablet cores were rolled at 40 rpm in the coating pan until tablet bed temperature was attained 60°C.
3. The hot melt coating agents, Stearic acid and palmitic acid were separately molt at 80°C.
4. Alpha-tocopherol was used as oil soluble antioxidant and Polyethylene Glycol 4000 (PEG 4000) was employed as pore former to achieve immediate release were added into the above molten hot melt coating solution. The Titanium dioxide were added into above solution under continuous stirring.
5. The molten coating mass was sprayed onto the rolling SPM tablets in slow stream by atomizing the coating solution (spray gun 100 ml S68; pilot at 15-psi pressure).
6. After the complete application of coating mass, the coated tablets were allowed to roll further for 15 min during which time the bed temperature was allowed to gradually come down.
7. The parameters employed for HMC of SPM in coating pan are given below table and followed same procedure for all formulations.[32]

Table 6.35 : Coating Variables for SPM Core

Sr. No.	Coating parameters	Tablets 400 (50 g)
1.	Spray rate	1.5 ml/min
2.	Atomizing air pressure	15 psig
3.	Tablet bed temperature	40-65°C
4.	Pan diameter	5 inches
5.	Pan speed	40-60 rpm
6.	Air flow	80-120 cfm
7.	Inlet air temperature	35- 45°C
8.	Outlet air temperature	40- 60°C
9.	Number of baffles	4
10.	Relative humidity	40%

6.7.3.7 Physico-Chemical Properties of Tablets:

6.7.3.7.1 Appearance:

Many pharmaceutical tablets use color as a vital means of rapid identification and consumer acceptance. But it must be uniform within a single tablet, from tablet to tablet and from lot to lot. The presence of an odor in a batch of tablets could indicate a stability problem e.g. the characteristic odor of acetic acid in degrading aspirin tablets or could be characteristic of the drugs e.g. vitamins have a characteristic odor. Taste is important in consumer acceptance of chewable tablets. The tablet cores were visually observed for any capping, chipping and lamination. The coated tablets were also checked for coating defects.[33]

6.7.3.7.2 Hardness:

For this test type of the Monsanto hardness tester to evaluate tablet hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with the tablet and zero reading is taken. The upper plunger is then forced against a spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is recorded in kilogram. For each formulation the hardness values for 6 tablets were determined using Monsanto hardness tester.[34]

6.7.3.7.3 Thickness:

The thickness of a tablet is the only dimensional variable related to the process. Thickness of individual tablets may be measured by a micrometer. Other techniques involve placing 5 tablets in a holding tray, where their total thickness may be measured by a sliding caliper scale. Tablet thickness should be controlled within a ± 5 % variation of a standard. Thickness must be controlled to facilitate packaging. It is expressed in mm. Average thickness was calculated.[34]

6.7.3.7.4 Percent Weight Gain:

Weight gain by tablet is one of the important parameters monitored during formulation, process and scale up development. Weight gain was calculated from the difference in the tablet weight before and after coating.[35]

6.7.3.7.5 Weight Variation Test:

This test examines uniformity in accordance with the formulation of each batch of tablets, which illustrates its content. In this study, we selected 20 tablets of SPM, which were weighed individually and collectively. Tablets were weighed individually. The average weight was calculated and compare the individual tablet weight. The tablet passes the U.S.P. test if not more than 2 tablets are outside the percentage limit and if the number of tablets differs by more than 2 times the percentage limit then test fails.[36]

The weight variation was calculated using the formula –

Weight variation (%) = (Initial weight - Average weight)/Average weight × 100…..(6.13)

It is meant to compare the USP limits and the data were recorded in table format.[37]

Table 6.36 : USP Limits for Weight Variation of Tablets

Sr. No.	Weight	Limit (%)
1	130 mg or less	10
2	130 mg to 324mg	7.5
3	More than 324 mg	5

6.7.3.7.6 Friability Test

As per USP standards, the friability test was performed using the Roche friabilator. It checks the tendency of the tablet to crumble, chip, or break upon abrasion or compression. It is important to check the friability of a tablet for complete dissolution in the gastrointestinal tract. The test checks the sturdiness of a tablet, and a loss of 1% tablet mass is acceptable during the process.[38]

6.7.3.7.7 Disintegration Test

As per USP standards, the SPM tablets are disintegrated into small granules to increase the surface area. It involves the disintegration of the tablets in a liquid medium as stated in the monograph under experimental conditions and recorded as disintegration time. The test is crucial, as it provides critical safety data in regard to the bioavailability of the solid dosage form of the drug. During this test, six tablets from batch were randomly selected and one tablet was placed in each tube with a mesh size of 10 basket as per USP standards. The basket was placed in a 1liter beaker containing phosphate buffer solution of pH 6.8 at 37°C. The apparatus was operated at 28-32 cycles/minutes and, simultaneously, a stopwatch was started. When all the particles passed from each test tube into the beaker, the finishing time was noted as the disintegration time. This disintegration test was a quantitative test, as time was measured during the test.[38]

6.7.3.7.8 In-vitro Dissolution Study of Marketed Products:

In-vitro dissolution of marketed film coated tablets of sitagliptin phosphate monohydrate was conducted to select the suitable dissolution medium for the study. It was used as yard sticks to prove the suitability of the dissolution conditions for the drug in study, whether sink conditions are maintained or not. In vitro dissolution of twelve marketed tablets.[39, 40]

Table 6.37 : In-vitro Dissolution Study Conditions for Marketed Products

Sr. No.	Parameters	Specifications
1.	Dissolution apparatus	USP Type II (Paddle)
2.	Paddle speed	100 rpm
3.	Temperature	37± 0.5°C

Sr. No.	Parameters	Specifications
4.	Time	1 hr
5.	Dissolution medium	Phosphate buffer pH 6.8
6.	Volume of dissolution medium	900 ml
7.	Sample volume	1 ml
8.	Sampling time	15, 30, 45 and 60 min
9.	Dilution factor	20

The sample solutions were filtered through Whatman filter paper (45 µm), from this filtered solution, 0.5 mL solution was taken into 10 mL volumetric flask and volume was made up with 6.8 pH buffer and solutions were analyzed at 267 nm by UV Spectrophotometer. The release in the dissolution medium was determined by software (PCP Disso v 2.08).

6.7.3.7.9 Drug Content:

Twenty tablets from each formulation were selected for the estimation of drug content. The tablet was weighed, triturated and transferred the powder to a 100 ml flask containing 50 ml of 0.1N HCL. The content of the flask was filtered through a filter, kept in a 100 ml volumetric flask. The residue was washed with another 40 ml of 0.1N HCL and the volume was made up to the mark. The sample was suitably diluted and analyzed spectrophotometrically against blank (0.1N HCL) at 267 nm using double beam UV- visible spectrophotometer.[41]

6.7.3.7.9.1 Procedure for Assay of SPM Formulations

Twenty tablets of SPM formulations were weighed and powdered. A quantity of tablet powder equivalent to 50 mg of SPM was transferred to 50 mL volumetric flask. Accurately measure 5 ml of methanol was transferred to 50 mL volumetric flask and ultrasonicated for 20 min and volume was made up to the mark with distilled water. The solution was then filtered through a Whatmann filter paper grade. The filtrate was appropriately diluted further. The absorbance of the resulting solution was measured at 267 nm and the amount of SPM was computed from its calibration plot.[42]

6.7.3.7.10 Moisture Uptake

A number of methods have been developed to test the moisture uptake of pharmaceutical dosages. The most commonly used approach is to measure the weight increase of the dosages at various constant temperature and humidity conditions. Typically, both coated and uncoated dosages are evaluated for their moisture uptake at these different humidity conditions created by a saturated salt solution, such as potassium chloride or sodium chloride. According to the United States Pharmacopeia (USP), for equilibrium moisture determinations, weighing should be carried out every hour until achievement of consecutive readings corresponding to a recorded mass change of less than 0.25%.[43]

6.7.3.7.11 Similarity Factor (f_2):

Different dissolution profiles were compared to establish the effect of formulation or process variables on the drug release as well as comparison of the test formulations to the theoretical release profile. The dissolution similarity was assessed using the Food and Drug Administration (FDA) recommended approach (f_2, similarity factor). The similarity factor is a logarithmic, reciprocal square root transformation of the sum of squared errors, and it serves as a measure of the similarity of two respective dissolution profiles.

$$f_2 = 50.\ \text{Log}\ \{[1+ (1/n)\ \Sigma^{n}_{t=1}(R_t-T_t)^{2}]^{-0.5} \times 100\} \ldots\ldots\ldots\ldots\ldots (6.14)$$

Where, n = number of sample points,

R_t = percent of marketed product observed and

T_t = percent of test formulations release observed

FDA has set a published standard for similarity factor (f_2) value (50-100) for indication of similarity between two dissolution profiles. To use mean data, the coefficients of variation for mean dissolution profile of a single batch should be less than 10%. The average difference at any dissolution sampling point should not be greater than 15% between test and reference products. If the drug release is more than 85% in 15 minutes, the dissolution profiles are considered similar.[44,45]

6.7.3.7.12 Stability Test

The stability of the active ingredient is a major criterion in determining acceptance or rejection of batch. During stability study, the product was exposed to accelerated as

well as long term stability conditions of temperature and humidity. The final formulation was packed in well- sealed Alu-alu package and kept in the humidity chamber maintained at 25ºC/60% RH and 40ºC/75% RH conditions for six months as per International Council of Harmonization (ICH) guidelines.[46]

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CHAPTER – VII

RESULTS AND DISCUSSION

7. Results and Discussion

Part A: Tenofovir Disoproxil Fumarate

7.1 Preformulating Studies

7.1.1 Organoleptic Properties of TDF

The organoleptic properties of TDF like color, odor, and taste were observed and recorded as shown below.

Table 7.1 : Organoleptic Properties of TDF

Sr. No.	Parameter	Standard	Observed
1.	Color	White to off-white	Off-white
2.	Odor	Characteristic	Characteristic
3.	Taste	Bitter	Bitter

Inference: The organoleptic properties of TDF match with the standard reference TDF.

7.1.2 Density and Flow Properties

Density and flow properties of Tenofovir disoproxil fumarate API was evaluated and the results are given in the following table,

Table 7.2 : Density and Flow Properties of Tenofovir Disoproxil Fumarate API

Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)
0.35	**0.51**	**30.85**

Inference: Tenofovir disoproxil fumarate (TDF) API showed poor to very poor flow characteristics.

7.1.3 Solubility

The solubility of TDF in different solvents mentioned below,

Table 7.3 : Solubility Data of TDF

Solvent	Solubility (mg/ml)
0.1 N HCl	77.86 ± 2.06
Distilled water	13.27 ± 0.45
pH 6.8 phosphate buffer	68.33 ± 1.96

Solvent	Solubility (mg/ml)
Ethanol	97.42 ± 3.57
Methanol	80.09 ± 2.81
Dimethyl Sulfoxide	101.55 ± 3.32

Inference: The highest solubility among aqueous media is in 0.1 N acid and the lowest is in distilled water. Among the organic solvents, the highest solubility is found in DMSO.

7.1.4 Melting Point

The melting point of TDF was determined using capillary technique using mineral oil and differential scanning calorimetry.

Table 7.4 : Melting Point of TDF

Method	Melting Point (°C)
Capillary technique	115-118°C
Differential scanning calorimetry	115.67°C (peak)

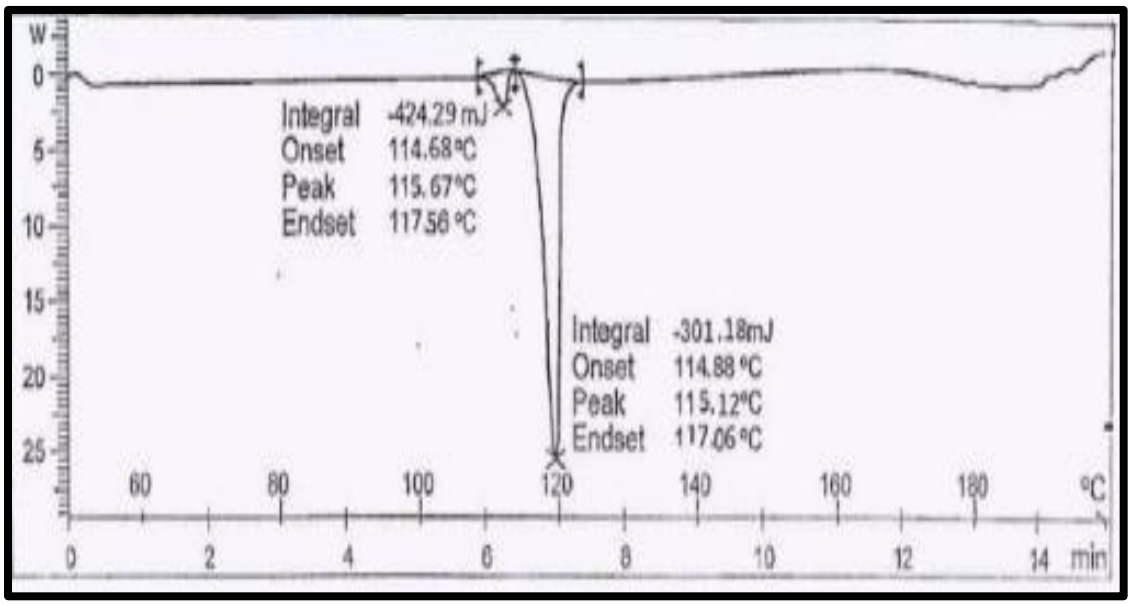

Fig. 7.1 : DSC Thermogram of TDF

Inference: The melting point is found to be complying with the acceptance criteria as per reference

7.1.5 Loss on Drying

The percent loss on drying was estimated using hot air oven till constant weight was obtained.

Inference: The % loss on drying for TDF sample was found to be 1.23 ± 0.004%.

The % LOD is found to be complying with the acceptance criteria as per Indian Pharmacopoeia i.e. NMT 3.5%.

6.2 UV-spectrophotometric Method for Measurement of TDF

Estimation of the Absorption Maxima (λmax)

The 5µg/ml solution of TDF was scanned for estimating the absorption maxima (λmax) between 200 to 400 nm. The absorption maxima were observed at 260 nm as shown below

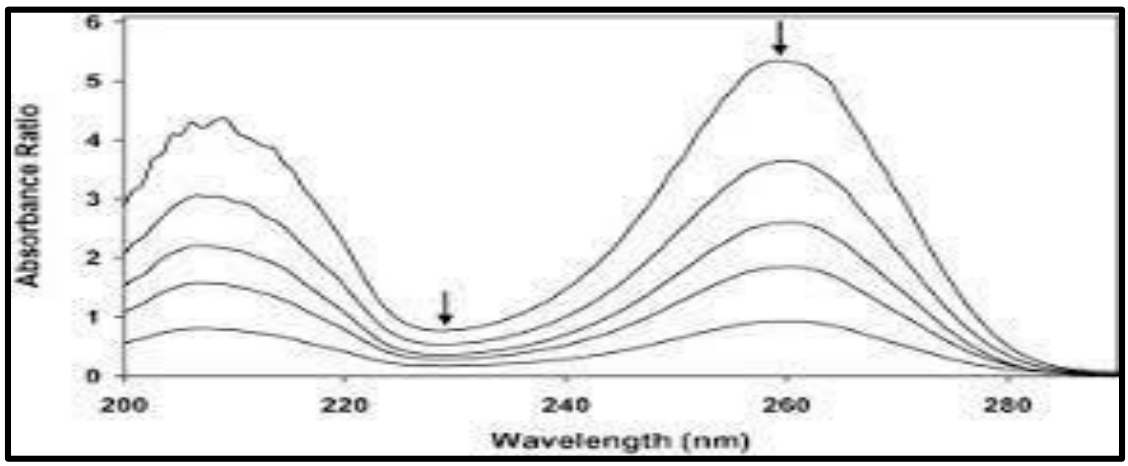

Fig. 7.2 : UV Spectrum of TDF Showing Absorption Maxima

Standard Graphs of TDF in 0.1 N Hydrochloric Acid

The working solutions of 5, 10, 15, 20, 25, 30, and 35 µg/ml concentration of TDF were prepared in 0.1N hydrochloric acid. They were scanned at 260 nm using UV-Visible spectrophotometer using 0.1N hydrochloric acid as blank. The absorbances of working solutions were recorded and tabulated against the concentration (µg/ml). A standard graph was plotted between concentration of TDF in µg/ml (x-axis) against absorbance (y-axis).

Table 7.5 : Standard Graphs of TDF in 0.1 N Hydrochloric Acid

Sr. No.	Concentration of TDF (µg/ml)	Absorbance
1.	5	0.111
2.	10	0.225
3.	15	0.343
4.	20	0.456
5.	25	0.561
6.	30	0.678
7.	35	0.796

The calibration curve of TDF in 0.1 N HCl is shown below. The straight line was obtained after plotting the curve between the concentration of TDF in µg/ml (x-axis) against absorbance (y-axis). The equation of the straight line and regression coefficient (r^2) was found to be y = 0.0227x - 0.0013 and 0.9998 respectively. The value of the regression coefficient was closer to 1 indicating the best-fitted line.

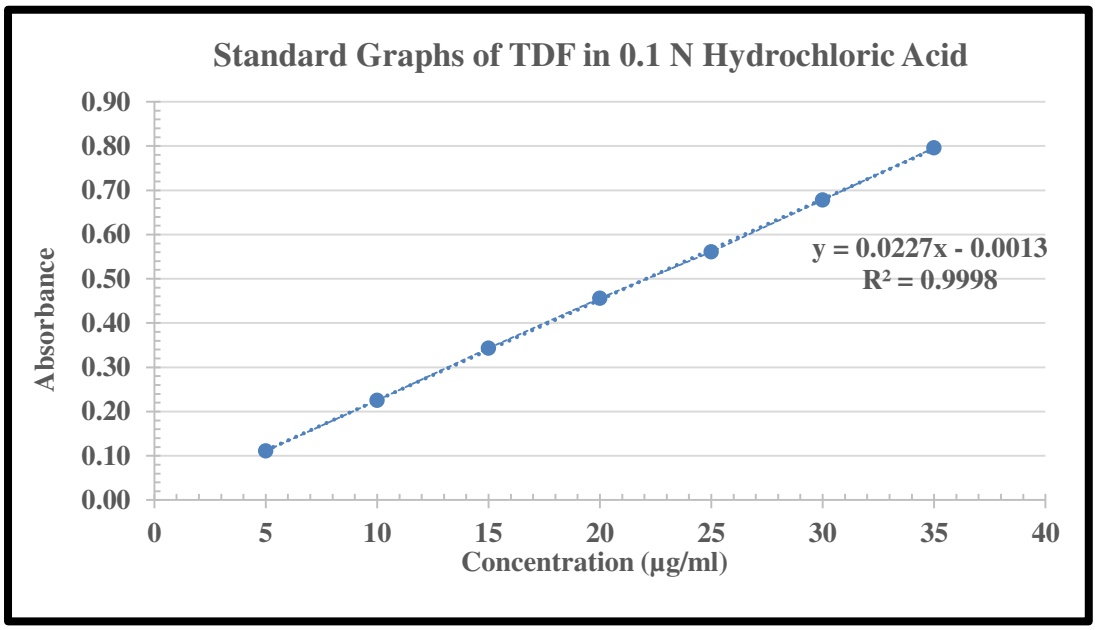

Fig. 7.3 : Standard Graph of TDF in 0.1N HCl

Standard Graphs of TDF in Distilled Water

The working solutions of 5, 10, 15, 20, 25, 30, and 35 µg/ml of TDF were prepared in distilled water. They were scanned at 260 nm using UV-Visible spectrophotometer

using distilled water as blank. The absorbances of working solutions were recorded and tabulated against the concentration (µg/ml). A standard graph was plotted between concentration of TDF in µg/ml (x-axis) against absorbance (y-axis).

Table 7.6 : Standard Graphs of TDF in Distilled Water

Sr. No.	Concentration of TDF (µg/ml)	Absorbance
1.	5	0.121
2.	10	0.231
3.	15	0.349
4.	20	0.463
5.	25	0.576
6.	30	0.687
7.	35	0.807

The calibration curve of TDF in distilled water is shown below. The straight line was obtained after plotting the curve between the concentration of TDF in µg/ml (x-axis) against absorbance (y-axis). The equation of straight line and regression coefficient (r^2) were found to be y = 0.0228x + 0.0053 and 0.9999 respectively. The value of regression coefficient (r^2) was closer to 1 indicating the best-fitted line.

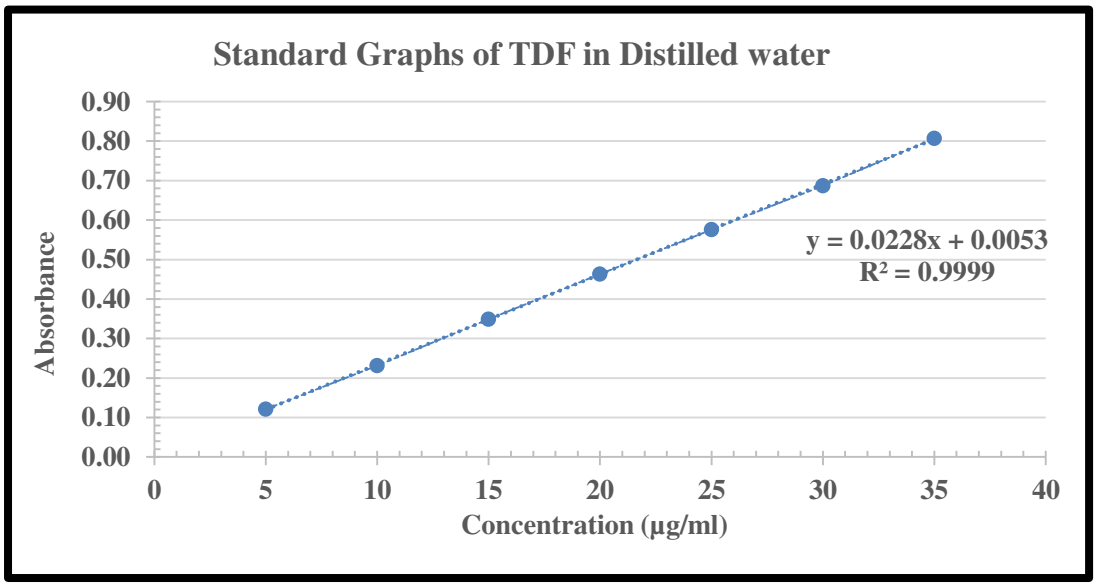

Fig. 7.4 : Standard Graph of TDF in Distilled Water

Standard Graphs of TDF in Phosphate Buffer pH 6.8

The working solutions of 5, 10, 15, 20, 25, 30, and 35 µg/ml of TDF were prepared in phosphate buffer pH 6.8 were scanned at 260 nm using UV-Visible spectrophotometer using distilled water as blank. The absorbances of working solutions were tabulated against the concentration (µg/ml). A standard graph was plotted between concentration of TDF in µg/ml (x-axis) against absorbance (y-axis).

Table 7.7: Standard Graphs of TDF in Phosphate Buffer pH 6.8

Sr. No.	Concentration of TDF (µg/ml)	Absorbance
1.	5	0.119
2.	10	0.236
3.	15	0.354
4.	20	0.472
5.	25	0.589
6.	30	0.698
7.	35	0.814

The calibration curve of TDF in phosphate buffer pH 6.8 is shown below. The straight line was obtained after plotting the curve between the concentration of TDF in µg/ml (x-axis) against absorbance (y-axis). The equation of straight line and regression coefficient (r^2) were found to be y = 0.0232x + 0.0054 and 0.9999 respectively. The value of regression coefficient (r^2) was closer to 1 indicating the best fitted line.

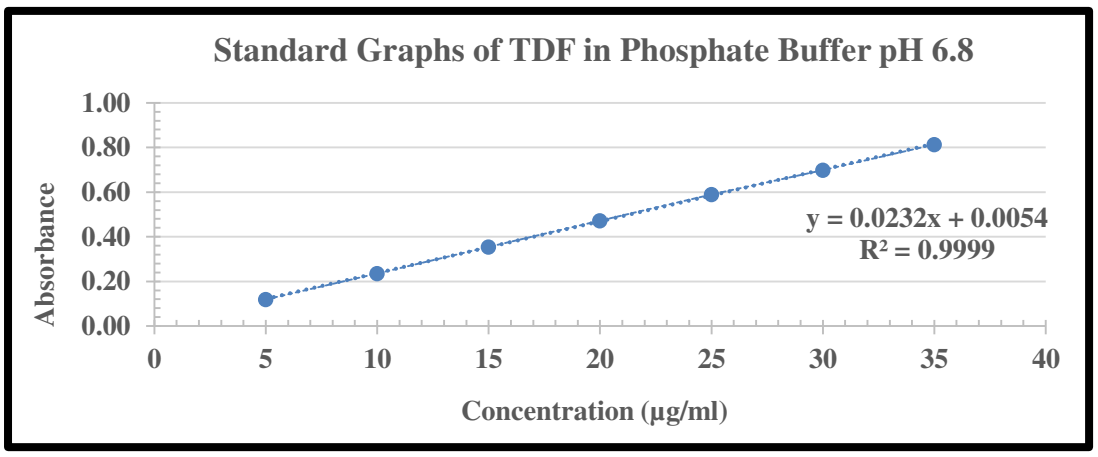

Fig. 7.5 : Standard Graph of TDF in Phosphate Buffer in pH 6.8

The above standard graphs of TDF were used for the estimation of drug content, % drug release, solubility, etc. in the further part of the research.

7.3 Excipient Compatibility Studies

The samples were evaluated for physical characteristics (physical appearance) and results of the compatibility study are reported in the following tables.

Table 7.8 : Details of Excipient Compatibility Studies

Binary mixture	Observation at Initial (0 days)	Observation after 7 days
Tenofovir Disoproxil Fumarate (API)	Off white powder	No discoloration.
Tenofovir Disoproxil Fumarate + Microcrystalline cellulose (Avicel PH101)	Off white powder	No discoloration.
Tenofovir Disoproxil Fumarate + Spray dried Lactose (DCL-11)	Off white powder	No discoloration.
Tenofovir Disoproxil Fumarate + Mannitol	Off white powder	No discoloration.
Tenofovir Disoproxil Fumarate + Polyvinyl Pyrrolidone (K-30)	Off white powder	No discoloration.
Tenofovir Disoproxil Fumarate + Hydroxypropyl cellulose (HPC-L)	Off white powder	No discoloration.
Tenofovir Disoproxil Fumarate + Magnesium stearate	Off white powder	No discoloration.
Tenofovir Disoproxil Fumarate + Talc	Off white powder	No discoloration.
Tenofovir Disoproxil Fumarate + Gelucire	Off white powder	No discoloration.
Tenofovir Disoproxil Fumarate + Precirol	Off white powder	No discoloration.
Tenofovir Disoproxil Fumarate +	Off-white wet mass	No discoloration.

Binary mixture	Observation at Initial (0 days)	Observation after 7 days
Cross Povidone		
Tenofovir Disoproxil Fumarate + Silicified Microcrystalline Cellulose (PROSOLV)	Off-white wet mass	No discoloration.
Tenofovir Disoproxil Fumarate + Alpha-tocopherol	Off white powder	No discoloration.
Mixture of Tenofovir Disoproxil Fumarate +All above excipients	Off white powder	No discoloration.

Inference: There was no change in the physical observations of the binary mixture when exposed at 50°C±2°C for 7 days. Further finalized formulation will be evaluated for accelerated stability study using all these excipients. Hence, it can be concluded that the above excipients are compatible with the drug substance.

7.4 Preparation of Drug Pellets

7.4.1 Selection of Filler

Three different fillers Microcrystalline Cellulose, Spray Dried Lactose, and Mannitol were evaluated.

Table 7.9 : Selection of Filler

Study Outcome	Formulation code		
	F1	F5	F9
Good Pellets (Fraction #16/20) quantity (%)	92	95	83
Endpoint observation remark	Good	Good	Fair

Inference:

- The manufacturing process was feasible for use of all three fillers.
- The good pellet fraction was observed more than 90% for pellets formulated using Microcrystalline Cellulose and Spray Dried Lactose. Hence, these two fillers were selected for further optimization.

7.4.2 Selection of Binder

Two binding agents, Polyvinyl Pyrrolidone (K-30) and Hydroxypropyl Cellulose (HPC-L) were evaluated for suitability of pellets formulation.

Table 7.10 : Selection of Binder

Study Outcome	Formulation code			
	F1A	F1B	F5A	F5B
Good Pellets (Fraction #16/20) quantity (%)	93	75	94	62
Endpoint observation remark	Good	Poor	Good	Poor

Inference:

- The manufacturing process was feasible for use of Polyvinyl Pyrrolidone (K-30) as binder. However, consistent extrudes were not able to produced for trials formulated using Hydroxypropyl Cellulose (HPC-L) as binder. Additionally, more fragile pellets were produced. Hence, Polyvinyl Pyrrolidone (K-30) selected as binder.
- The good pellet fraction was observed more than 90% for pellets formulated using Microcrystalline Cellulose (Avicel PH 101) and Spray Dried Lactose (DCL-11). Hence, these two fillers were selected for further optimization.

7.4.3 Optimization of Fluid Uptake

Two different fluid uptake levels were evaluated using a Polyvinyl Pyrrolidone (K-30) (2% w/v). Optimization was done using formulations of Microcrystalline Cellulose (Avicel PH 101) and Spray Dried Lactose (DCL-11).

Table 7.11 : Optimization of Fluid Uptake

Study Outcome	Formulation code			
	F1C	F1D	F5C	F5D
Good Pellets (Fraction #16/20) quantity (%)	93	88	94	86
Endpoint observation remark	Good	Fair	Good	Fair

Inference:

- The feasibility of forming extrudes and further spheronization was better with 8% fluid uptake for trials manufactured with fillers, Microcrystalline Cellulose and Spray Dried Lactose. A slightly sticky nature was observed for extrudes formulated with 12% fluid uptake.
- Hence, 8% fluid uptake was finalized for further optimization.

7.4.4 Optimization of Screen Size for Preparation of Extrudes.

Two different sieve sizes were selected for optimization. The type of binder and Fluid uptake levels were kept constant. Optimization was done using formulations of Microcrystalline Cellulose (Avicel PH 101) and Spray Dried Lactose (DCL-11).

Table 7.12 : Optimization of Screen Size for Preparation of Extrudes

Study Outcome	Formulation Code			
	F1E	F1F	F5E	F5F
Good Pellets (Fraction #16/20) quantity (%)	95	85	92	81
Endpoint observation remark	Good	Fair	Good	Fair

Inference:

- The good pellets fraction was observed higher for screen size #16 at extrusion stage, Hence, the use of #16 sieve for extrusion was selected.

7.4.5 Optimization of Spheronization Process

Three different spheronizer cross-hatch plates of 1.0, 1.2, and 1.5 mm sizes were selected for optimization. The type of binder, Fluid uptake levels and extrusion screen were kept constant. Optimization was done using formulations of Microcrystalline Cellulose (Avicel PH 101) and Spray Dried Lactose (DCL-11)

Table 7.13 : Optimization of Spheronization Process

Study Outcome	Formulation Code					
	F1G	**F1H**	**F1I**	**F5E**	**F5F**	**F5I**
Good Pellets (Fraction #16/20) quantity (%)	84	92	71	82	93	77
Endpoint observation remark	Fair	Good	Fair	Fair	Good	Fair

Inference:

- There was observation of higher fines (#20 pass) using Spheronizer cross-hatch plates 1.0 mm. On the other hand, coarser pellets were produced using 1.5 mm plate, this lead to higher oversize on #16 mesh.
- Hence, for optimum size of pellets in the fraction of #16 passed and #20 retained, Spheronizer cross-hatch plates 1.2 mm selected.

7.4.6 Optimization of Drying Process for Pellets

Two different drying time were selected for optimization. The type of binder, Fluid uptake levels, extrusion screen and cross-hatch plate size were kept constant. Optimization was done using formulations of Microcrystalline Cellulose (Avicel PH 101) and Spray Dried Lactose (DCL-11).

Table 7.14: Optimization of Drying Process for Pellets

Study Outcome	Formulation Code			
	F1J	F1K	F5J	F5K
Good Pellets (Fraction #16/20) quantity (%)	93	91	94	90
Endpoint observation remark	Good	Good	Good	Good

Inference:

- The fraction of good pellets was comparable (>90%) irrespective of drying time (1 h and 3 h).
- The LOD of pellets was checked. The LOD of the pellets at drying times of 1 hour and 3 hour were checked.

- The LOD of pellets dried for 1 hour was 2.10%-2.57% and for 3 hour was 1.82%-1.94%. This indicates a uniform drying of pellets is achieved in 3 hours.
- On the basis of observed data, 3 hour drying time was considered.

7.4.7 Hot Melt Coating of Pellets:

7.4.7.1 Optimization Hot Melt Coating Agent and Level of coating

The TDF pellets based on Microcrystalline Cellulose (Avicel PH 101) and Spray-dried Lactose (DCL-11) were utilized for coating optimization. Two hot melt coating agents, Gelucire® 43/01 and Precirol® ATO 5 were used for coating evaluation, along with α- Tocopherol as an antioxidant for the coating agent. The coating levels of 3, 4 and 5% were evaluated.

Table 7.15: Optimization Hot Melt Coating Agent and Level of Coating

Test	Formulation Code											
	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20	F21
Appearance	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Mean particle size	850	855	867	838	857	874	843	862	873	847	859	891
Bulk Density (g/mL)	0.714 ± 0.002	0.723 ± 0.001	0.753 ± 0.001	0.749 ± 0.003	0.731 ± 0.003	0.761 ± 0.003	0.757 ± 0.002	0.764 ± 0.001	0.710 ± 0.001	0.733 ± 0.001	0.746 ± 0.001	0.769 ± 0.001
Tapped Density (g/mL)	0.787 ± 0.002	0.789 ± 0.001	0.807 ± 0.003	0.798 ± 0.002	0.813 ± 0.004	0.816 ± 0.003	0.788 ± 0.002	0.790 ± 0.002	0.801 ± 0.002	0.783 ± 0.002	0.799 ± 0.002	0.805 ± 0.002
Carr's Index	9.27	8.36	4.80	5.54	8.05	4.51	5.25	3.29	11.58	8.94	6.63	4.94
Hardness	2.85 ±0.05	2.97 ± 0.10	3.35 ± 0.05	2.98 ± 0.10	3.02 ± 0.15	3.41 ± 0.15	3.05 ± 0.10	3.11 ± 0.10	3.43 ± 0.10	3.00 ± 0.12	3.08 ± 0.10	3.51 ± 0.05
Friability	0.248 ± 0.01	0.232 ± 0.002	0.168 ± 0.001	0.215 ± 0.003	0.228 ± 0.004	0.235 ± 0.003	0.358 ± 0.005	0.228 ± 0.004	0.175 ± 0.011	0.215 ± 0.003	0.228 ± 0.004	0.235 ± 0.003
Drug content	99.86 ± 1.26	100.26 ± 2.06	99.54 ± 0.84	101.35 ± 1.98	99.02 ± 3.13	98.91 ± 0.57	100.65 ± 2.53	98.68 ± 0.21	99.34 ± 3.18	98.71 ± 0.77	101.65 ± 2.76	99.98 ± 2.29
Dissolution (%) (N=6)												
5 mins	72±7.67	66± 6.25	50± 0.12	70± 4.16	69± 6.93	59± 2.65	69 ± 5.21	64± 7.64	54± 4.15	68±7.91	68 ± 8.54	62± 4.15
10 mins	89±4.21	85 ± 3.67	79± 5.15	90± 3.12	86 ± 4.98	77± 6.84	93 ± 2.82	89 ± 5.18	85± 8.73	89±5.12	86 ±7.40	80± 8.13
15mins	96 ±2.76	93 ± 2.76	87 ± 4.72	97 ± 2.97	95 ± 3.33	84 ± 4.26	98 ± 2.01	98 ± 4.11	91 ± 5.54	99 ± 3.56	93 ±5.91	91± 7.91
30 mins	101±0.26	99 ± 0.96	98 ± 1.04	102±0.86	100± 1.16	92±3.04	102±1.20	102± 0.88	97± 4.37	101±2.05	100±4.88	98± 4.59

Inference:

- Gelucire® 43/01 and Precirol® ATO 5 with different concentration by using hot melt coating process, all the trials found feasible.
- The evaluation outcomes such as mean particle size, bulk density, tapped density, hardness, friability and drug content for all the trials were found comparable. However, the dissolution profile exhibit differences due to coating weight build-up.
- The drug release is found directly proportional to weight build.
- Dissolution of pellets having weight gain 3 and 4% gives better dissolution results than 5% weight gain. Hence 3 and 4% weight gain was selected for further evaluation.

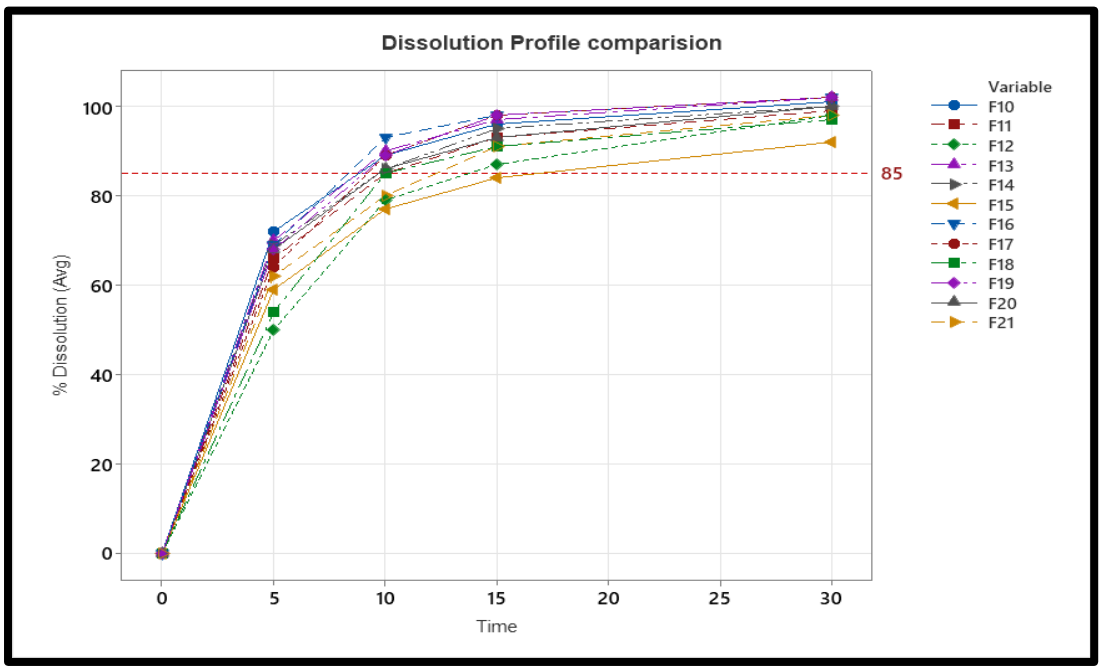

Fig. 7.6 : Dissolution Profile of Hot Melt Coated Pellets

7.4.7.2 Taste Evaluation

The taste evaluation was performed by implementing two methods,

- In-vitro Taste method
- Taste Panel Method.

The taste method evaluation was conducted on pellets coated with 3 and 4%. The uncoated pellets were used as positive control. The outcomes were tabulated as below-

The In-vitro Taste evaluation UV spectrometer was used to indicate the time after which the pellets exhibit UV absorbance at 250 nm. The UV absorbance indicates bitterness. A delay in absorbance above 2 minutes is considered effective taste masking as the time taken to swallow is generally less than 2 minutes.

Table 7.16: Taste Evaluation of Pellets

Test	Formulation Code									
	F1	**F5**	**F10**	**F11**	**F13**	**F14**	**F16**	**F17**	**F19**	**F20**
UV absorbance time (mins)	0'30''	0'30''	1'00''	2'30''	1'30''	3'00''	1'00''	2'30''	1'00''	2'30''
Taste Panel Method										
V1	+++++	+++++	+	-	-	-	++	-	-	-
V2	+++++	++++	++	-	-	-	+	-	+	-
V3	+++++	+++++	+	-	+	-	-	-	++	-
V4	++++	+++++	-	-	-	-	+	-	+	-
V5	+++++	+++++	+	-	-	-	-	-	-	-
V6	+++++	++++	+	-	-	-	+	-	-	-
V7	+++++	+++++	-	-	-	-	-	-	-	-
V8	+++++	+++++	+	-	+	-	-	-	+	-
V9	++++	+++++	+	-	-	-	-	-	-	-
V10	+++++	+++++	+	-	+	-	+	-	+	-
V11	+++++	++++	-	-	-	-	-	-	-	-
V12	+++++	+++++	++	-	-	-	+	-	+	-

Where, +++++ = very-very bitter, ++++ = very bitter, +++ = moderately bitter, ++ = bitter, + = slightly bitter, – = tasteless and V= Volunteer

Inference:

- The Taste panel of 12 volunteers indicated that the pellets coated with 3% coating lowered the bitterness potential of the pellets, however, complete masking was achieved with 4% coating level.
- Hence, pellets coated with 4% weight gain was taken for tableting.

7.4.7.3 Optimization of Coating Process Parameters: Pan Speed

The TDF pellets based on Microcrystalline Cellulose (Avicel PH 101) and Spray-dried Lactose (DCL-11) were utilized for coating optimization. Two Hot Melt Coating agents, Gelucire® 43/01 and Precirol® ATO 5 were used for coating evaluation, along with α- Tocopherol. The experiments were conducted with two different pan speeds keeping coating weight build-up constant.

Table 7.17: Optimization of Coating Process Parameters: Pan Speed

Study Outcome	Formulation Code							
	F22	F23	F24	F25	F26	F27	F28	F29
Mean particle size	849	810	855	826	858	801	867	819
Hardness	2.92 ±0.05	2.55 ± 0.10	3.18 ± 0.05	2.69 ± 0.10	3.16± 0.06	2.49 ± 0.11	3.09 ± 0.05	2.72 ± 0.13
Appearance	Good	Fines	Good	Fines	Good	Fines	Good	Fines

Inference:

- The hot melt coating process was found to be feasible for pan 15 rpm, as for 20 rpm fines were visually observed in coating pan.
- The coating was observed uniform on visual monitoring for 15 rpm, same was confirmed with surface morphology.
- The mean particle size and hardness data for 20 rpm was comparatively lower indicates the generation fines due to attrition in coating pan.

Surface morphology of pellets:

- The hot melt coated pellets on 15 rpm were spherical in shape and uniform in size.

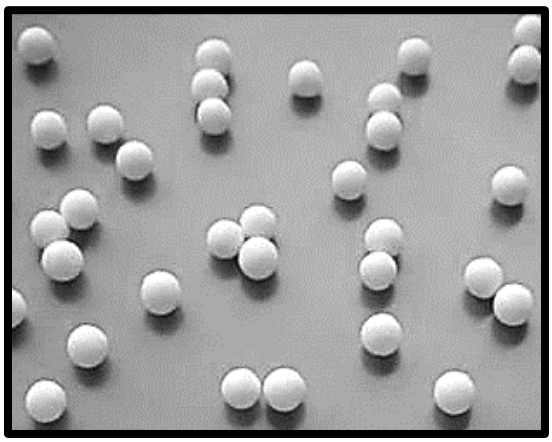

Fig. 7.7 : Surface Morphology of Hot Melt Coated Pellets

7.4.7.4 Optimization of Coating Process Parameters: Temperature

The TDF pellets based on Microcrystalline Cellulose (Avicel PH 101) and Spray-dried Lactose (DCL-11) were utilized for coating optimization. Two hot melt coating agents, Gelucire® 43/01 and Precirol® ATO 5 were used for coating evaluation, along with α- Tocopherol. The experiments were conducted with two different bed temperatures keeping pan rpm and coating weight build up constant.

Table 7.18: Optimization of Coating Process Parameters: Temperature

Study Outcome	Formulation Code							
	F30	F31	F32	F33	F34	F35	F36	F37
Appearance	Agglomeration	Good	Agglomeration	Good	Agglomeration	Good	Agglomeration	Good

Inference:

- The hot melt coating process was found to be feasible for 60º C bed temperature, as 40º C agglomeration of pellets was observed in the coating pan. The agglomeration is due to rapid solidification of the coating agent on lower temperature.

7.4.7.5 Stability Evaluation

- Stability charged experimental Batches: F31, F33, F35 and F37

- Pack: Equivalent to unit dose were filled in the self-sealing Aluminium pouch.
- Stability Condition: At temperature 25±2°C & 60±5% RH and 40 ± 2°C & 75 ± 5% RH for 6 months in the stability chamber (Remi Laboratory Instrument, CHM-6).
- Frequency:
    - For 40 ± 2°C & 75 ± 5% RH: Initial, 1month, 2 Month, 3 month and 6 months
    - For 25±2°C & 60±5% RH : Initial, 1month, 2 Month, 3 month , 6 months.
- Testing: Physical appearance, drug content and in-vitro drug release.

Table 7.19: Accelerated Stability Data (Pellets)

40 ± 2°C & 75 ± 5% RH				
Formulation code	**Station**	**Appearance (White to off-white pellets)**	**Drug Content (%) (90.0 -110.0)**	**Drug Release (%) (NLT 80%(Q) in 30 mins)**
F31	Initial	Complies	100.3	98
	1 M	Complies	99.0	95
	2M	Complies	98.3	97
	3M	Complies	101.0	95
	6M	Complies	100.0	93
F33	Initial	Complies	98.0	94
	1 M	Complies	102.0	96
	2M	Complies	99.8	97
	3M	Complies	97.9	91
	6M	Complies	99.5	98
F35	Initial	Complies	101.1	100
	1 M	Complies	99.0	98
	2M	Complies	98.7	95
	3M	Complies	100.0	101
	6M	Complies	96.9	94
F37	Initial	Complies	97.8	99

40 ± 2°C & 75 ± 5% RH				
Formulation code	**Station**	**Appearance (White to off-white pellets)**	**Drug Content (%) (90.0 -110.0)**	**Drug Release (%) (NLT 80%(Q) in 30 mins)**
	1 M	Complies	102.4	102
	2M	Complies	101.0	101
	3M	Complies	100.2	99
	6M	Complies	99.8	99

Table 7.20: Long Term Stability Data (Pellets)

25±2°C & 60±5% RH				
Formulation Code	**Station**	**Appearance (White to off-white pellets)**	**Drug Content (%) (90.0 -110.0)**	**Drug Release (%) (NLT 80%(Q) in 30 mins)**
F31	Initial	Complies	99.8	99
	1 M	Complies	98.6	100
	2M	Complies	100.2	98
	3M	Complies	98.7	97
	6M	Complies	99.2	99
F33	Initial	Complies	100.6	98
	1 M	Complies	98.8	98
	2M	Complies	97.9	97
	3M	Complies	98.2	100
	6M	Complies	98.0	101
F35	Initial	Complies	102.1	99
	1 M	Complies	99.5	98
	2M	Complies	100.4	97
	3M	Complies	99.7	100
	6M	Complies	98.3	99
F37	Initial	Complies	100.5	101

25±2°C & 60±5% RH				
Formulation Code	**Station**	**Appearance (White to off-white pellets)**	**Drug Content (%) (90.0 -110.0)**	**Drug Release (%) (NLT 80%(Q) in 30 mins)**
	1 M	Complies	99.4	99
	2M	Complies	98.7	98
	3M	Complies	96.9	102
	6M	Complies	99.5	98

Inference:

- The accelerated stability data up to six months indicates that Hot Melt Coated pellets in designated packs were stable, without any borderline compliance. This gives assurance of product quality.
- The long-term stability data was also found consistent.
- Based on overall stability data, it can be assured to provide the quality product with new technology of taste masking i.e. hot melt coating.

7.5 Compression of Tablets

The TDF pellets coated at 4% weight build-up were blended with extragranular material and compressed into tablets. The evaluation was performed for pellets manufactured using Microcrystalline Cellulose (Avicel PH 101) and Spray Dried Lactose (DCL-11) as a filler. Both types of pellets were compressed at low, medium and High hardness. The study was repeated for both the coating agents. Below is the tabulated compilation of experiment outcomes,

Table 7.21: Hot Melt Coated Pellets Using Gelucire® 43/01

Study Outcome	**Formulation Code**							
	F38	**F39**	**F40**	**F41**	**F42**	**F43**	**F44***	**F45***
Hardness	L	M	H	L	M	H	M	M
Weight Variation (%) (n=10)	-0.9% to 2.1%	-1.8% to 0.5%	-2.0% to 1.6%	-1.9% to 1.3%	-1.0% to 2.3%	-1.6% to 1.9%	-2.1% to 1.7%	-1.1% to 1.4%

Limit: 413 mg ±5%								
Hardness (n=10) (kg/cm2)	6.1 ± 0.2	9.2 ± 0.1	11.8 ± 0.3	5.5 ± 0.3	8.8 ± 0.2	12.1 ± 0.4	9.0 ± 0.3	9.2 ± 0.2
Thickness (mm) (n=10)	3.41 ± 0.22	3.34 ± 0.19	3.26 ± 0.28	3.44 ± 0.30	3.37 ± 0.24	3.25 ± 0.14	3.24 ± 0.20	3.20 ± 0.16
Friability (%) (6.5 g, Triplicate)	0.29 ± 0.12	0.18 ± 0.15	0.11 ± 0.12	0.34 ± 0.27	0.26 ± 0.60	0.14 ± 0.18	0.36 ± 0.46	0.43 ± 0.36
Disintegration time (mins) (n=6)	Max. 4	Max. 6	Max. 7	Max. 5	Max. 7	Max. 8	Max. 6	Max. 5
Drug content (%)	99.2± 1.2	97.7± 1.4	101.0± 0.9	101.3 ± 0.2	100.2± 0.6	98.9± 0.6	102.1 ± 0.2	101.6± 0.7
Dissolution (NLT 80Q% in 30 mins)	96± 2	95± 1	92± 4	95± 2	94± 4	93± 2	97± 1	96± 3
Taste Evaluation – UV absorbance time (mins)	>10	>10	>10	>10	>10	>10	2	2

*Compressed tablets weight 400 mg, being uncoated pellets.

L: Low Hardness, M: Medium Hardness, H: High Hardness

Table 7.22: Hot Melt Coated Pellets Using Precirol® ATO 5

Study Outcome	Formulation Code							
	F46	**F47**	**F48**	**F49**	**F50**	**F51**	**F52***	**F53***
Hardness	L	M	H	L	M	H	M	M
Weight Variation (%) (n=10) Limit: 413	-2.1% to 2.3%	-1.9% to 1.6%	-2.0% to 1.3%	-2.5% to 2.1%	-2.2% to 1.5%	-0.8% to 2.2%	-1.4% to 0.7%	-1.6% to 1.4%

Study Outcome	Formulation Code							
	F46	**F47**	**F48**	**F49**	**F50**	**F51**	**F52***	**F53***
mg ±5%								
Hardness (n=10) (kg/cm2)	5.9 ± 0.3	8.6 ± 0.1	10.7 ± 0.3	4.9 ± 0.5	9.2 ± 0.1	11.7 ± 0.3	9.7 ± 0.2	9.6 ± 0.3
Thickness (mm) (n=10)	3.51 ± 0.31	3.43 ± 0.34	3.55 ± 0.17	3.49 ± 0.22	3.34 ± 0.23	3.21 ± 0.28	3.37 ± 0.33	3.32 ± 0.21
Friability (%) (6.5 g, Triplicate)	0.39 ± 0.17	0.14 ± 0.25	0.12 ± 0.14	0.37 ± 0.22	0.29 ± 0.51	0.20 ± 0.28	0.34 ± 0.16	0.37 ± 0.13
Disintegration time (mins) (n=6)	Max. 5	Max. 7	Max. 8	Max. 4	Max. 6	Max. 8	Max. 7	Max. 5
Drug content (%)	101.3 ± 0.9	99.2± 0.8	100.1±1.3	99.3± 0.7	99.4± 1.6	97.9± 0.5	101.3 ± 0.4	100.6± 1.1
Dissolution (NLT 80Q% in 30 mins)	97± 2	98± 1	96± 4	99± 2	96± 4	93± 2	96± 1	94± 3
Taste Evaluation – UV absorbance time (mins)	>10	>10	>10	>10	>10	>10	2	2

*Compressed tablets weight 400 mg, being uncoated pellets.

L: Low Hardness, M: Medium Hardness, H: High Hardness

Inference:

- The compression process for hot melt coated pellets found to be feasible.
- Tablets compressed at different hardness are found to have acceptable friability, disintegration time, and dissolution.
- The tablets manufactured with coated pellets of both the coating materials exhibit taste-masking ability at all three hardness levels.

7.6 In-vitro Dissolution Study

The in-vitro drug release study from tablets prepared with coated pellets and marketed tablets was performed. Drug release is found to be complete within 30 min which complies with the Pharmacopoeial standards. The drug release from marketed tablets and tablets prepared from hot melt coated pellets was found to similar, which was confirmed from similarity factor (f_2). The values of similarity factor were found to be >50 using marketed sample (Viread 300) as reference sample. It indicates similar drug release profile.

Table 7.23: Similarity Factor (f2) Data

Reference batch (Viread 300)	**Test Batch**			
Reference	Test_F39	Test_F42	Test_F47	Test_F50
(f2)	70	74	66	80

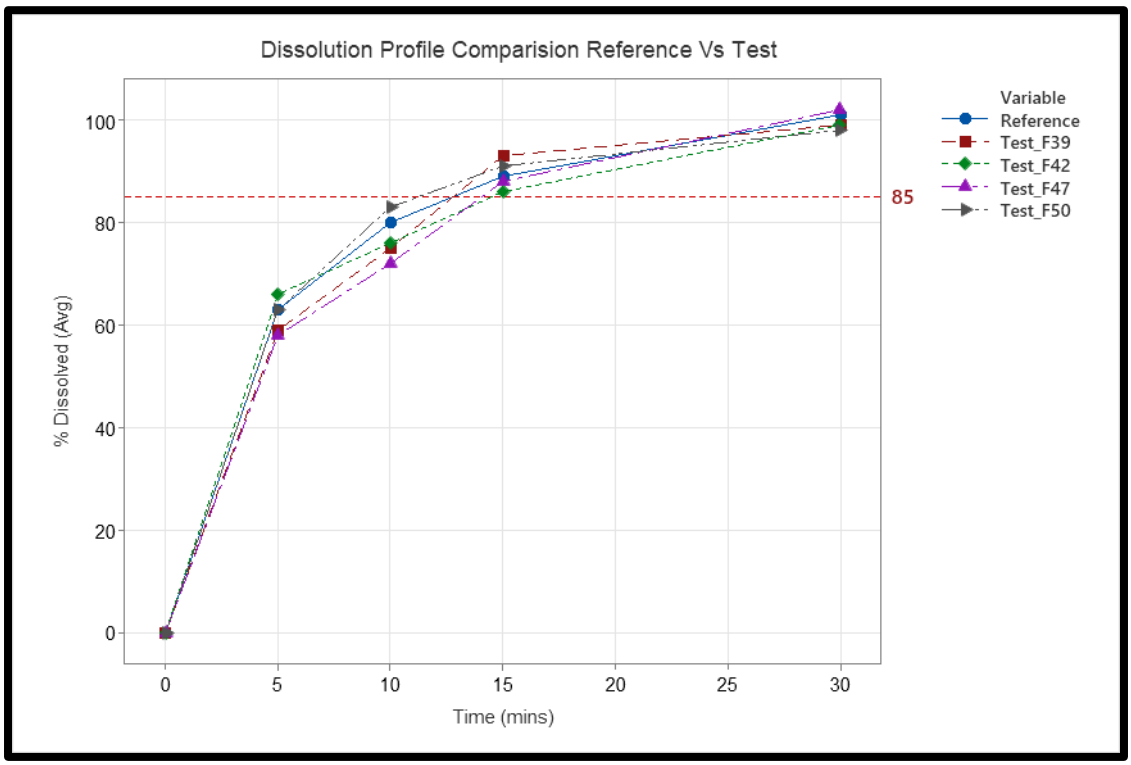

Fig. 7.8 : Comparison of Dissolution Profile of Reference (Viread) and Developed Formulations (Test)

Inference:

- Dissolution profile of reference batch against test batches found comparable.
- The f2 value > 50 shows that dissolution profile of both reference batch and test batches are similar.

7.7 Taste Evaluation

The taste evaluation was performed by implementing Taste Panel Method on volunteers.

The taste method evaluation was conducted on tablets with optimized HMC coated pellets. The tablets manufactured using un-coated pellets were used as positive control. The outcomes were tabulated as below-

Table 7.24: Taste Evaluation by Taste Panel Method

Volunteers Code	Formulation Code						
	F52	F53	Viread 300	F39	F42	F47	F50
V1	++++	++++	-	-	-	-	-
V2	++++	++++	-	-	-	-	-
V3	+++++	+++	-	-	-	-	-
V4	++++	++++	-	-	-	-	-
V5	++++	++++	-	-	-	-	-
V6	+++++	++++	-	-	-	-	-
V7	+++	++++	-	-	-	-	-
V8	++++	++++	-	-	-	-	-
V9	++++	++++	-	-	-	-	-
V10	+++++	+++++	-	-	-	-	-
V11	+++++	++++	-	-	-	-	-
V12	+++++	+++++	-	-	-	-	-

Where, +++++ = very-very bitter, ++++ = very bitter, +++ = moderately bitter, ++ = bitter, + = slightly bitter, – = tasteless and V= Volunteer

Inference:

- The Taste panel of 12 volunteers indicated that the tablets prepared with coated pellets are capable of bitter taste masking similar to the marketed coated tablet product.

7.8 Stability Evaluation

- Stability charged experimental Batches: F39, F42, F47 and F50
- Pack: Polycarbonate bottles sealed with Aluminum foil.
- Stability Condition: At temperature 25±2°C & 60±5% RH and 40 ± 2°C & 75 ± 5% RH for 6 months in the stability chamber (Remi Laboratory Instrument, CHM-6).
- Frequency:

- For 40 ± 2°C & 75 ± 5% RH: Initial, 1month, 2 Month, 3 month and 6 months
- For 25±2°C & 60±5% RH : Initial, 1month, 2 Month, 3 month , 6 months.

- Testing: Physical appearance, drug content and in-vitro drug release.

Table 7.25: Accelerated Stability Data

40 ± 2°C & 75 ± 5% RH				
Formulation Code	**Station**	**Appearance (White to off white tablets)**	**Drug Content (%) (90.0 -110.0)**	**Drug Release (%) (NLT 80% (Q) in 30 minutes)**
F39	Initial	Complies	101.2	100
	1 M	Complies	91.0	100
	2M	Complies	98.3	98
	3M	Complies	100.0	94
	6M	Complies	99.0	98
F42	Initial	Complies	99.9	93
	1 M	Complies	98.0	99
	2M	Complies	98.8	98
	3M	Complies	96.9	95
	6M	Complies	100.5	98
F47	Initial	Complies	102.1	99
	1 M	Complies	98.0	99
	2M	Complies	98.8	98
	3M	Complies	100.9	100
	6M	Complies	99.4	96
F50	Initial	Complies	98.8	97
	1 M	Complies	101.9	101
	2M	Complies	99.0	99
	3M	Complies	99.2	101
	6M	Complies	101.8	100

Table 7.26: Long-term Stability Data

25±2°C & 60±5% RH				
Formulation Code	**Station**	**Appearance (White to off white tablets)**	**Drug Content (%) (90.0 -110.0)**	**Drug Release (%) (NLT 80% (Q) in 30 minutes)**
F39	Initial	Complies	99.7	100
	1 M	Complies	99.3	99
	2M	Complies	11.2	95
	3M	Complies	99.7	99
	6M	Complies	100.2	99
F42	Initial	Complies	101.6	95
	1 M	Complies	100.8	99
	2M	Complies	99.8	99
	3M	Complies	98.9	99
	6M	Complies	97.9	101
F47	Initial	Complies	100.1	100
	1 M	Complies	100.5	95
	2M	Complies	100.4	99
	3M	Complies	98.9	101
	6M	Complies	98.9	98
F50	Initial	Complies	102.5	99
	1 M	Complies	100.4	100
	2M	Complies	99.6	101
	3M	Complies	99.8	100
	6M	Complies	99.9	99

Inference:

- The final product (tablets) formulated with hot melt coated pellets (agent – Gelucire and Precirol) shown the consistent results on accelerated stability

condition up to six months. This indicates that, the formulated product is capable to withstand up to its shelf life (target 24 months) in the designated pack.

- The long-term stability data up to six moth shows no negative trends.
- Based on overall stability data, it can be assured to provide the quality product with new technology of taste masking i.e., hot melt coating.

Part B: Sitagliptin Phosphate Monohydrate

7.9 Preformulating Studies

7.9.1 Organoleptic Properties

The organoleptic properties of SPM like color, odor and taste were observed. The shape of the crystal was observed under microscope. The observations were tabulated in below table.

Table 7.27 : Organoleptic Properties of SPM

Sr. No.	Parameter	Observation
1.	Description	Crystalline, off-white in powder
2.	Bulk density	0.461 g/ml
3.	Tapped density	0.579 g/ml
4.	Carr's index	20.4 (Fair)

Inference: The organoleptic properties of SPM were compared with the Pharmacopoeial standards and were matches with the standard reference indicates that SPM sample.

7.9.2 Melting point

The melting point is traditionally used as a measure of purity. The change in the melting point value than the standard affect quality and purity of the model drug. The melting behavior was determined using a Mettler-Toledo MP70 melting point system (Greifensee, Switzerland). A capillary was used with a closed bottom, applying a heating rate of 10°C min^{-1} up to a temperature limit of 400°C. The melting point of sitagliptin phosphate monohydrate was found to be 216.48°C which closely matches with Pharmacopoeial standard.

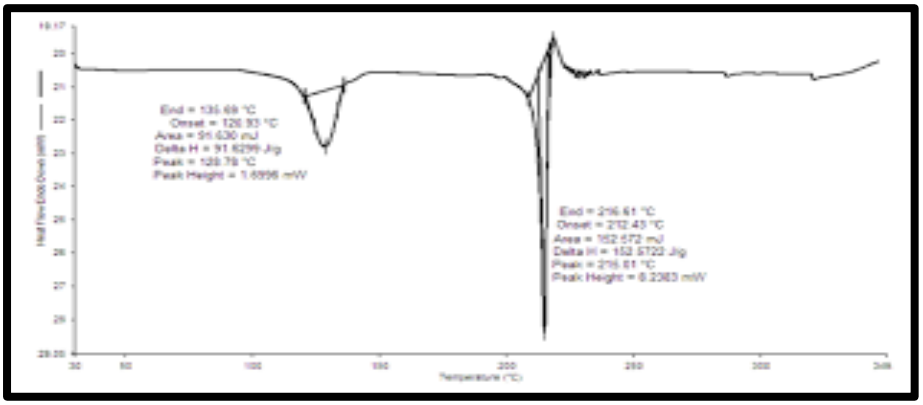

Fig. 7.9: DSC Thermogram of SPM

The sitagliptin phosphate monohydrate differential scanning calorimetry studies indicated a sharp peak at 216.61 °C with an enthalpy change of 131.5 J/ g, corresponding to the melting of pure sitagliptin phosphate monohydrate. So, it was inferred that the given sample of the drug was pure. The DSC thermogram of Sitagliptin phosphate monohydrate showed a characteristic sharp endothermic peak at 135.69 ºC due to water liberation from the drug as it is a monohydrate salt.

7.9.3 Identification by Fourier Transform Infrared (FTIR) Spectroscopy

The infrared spectra were recorded on a Bruker Alpha-P FTIR spectrometer (Ettlingen, Germany) using attenuated total reflection (ATR) in the wavelength range of 4000 to 400 cm^{-1}, with a nominal resolution of 4 cm^{-1} and accumulation of 32 scans.

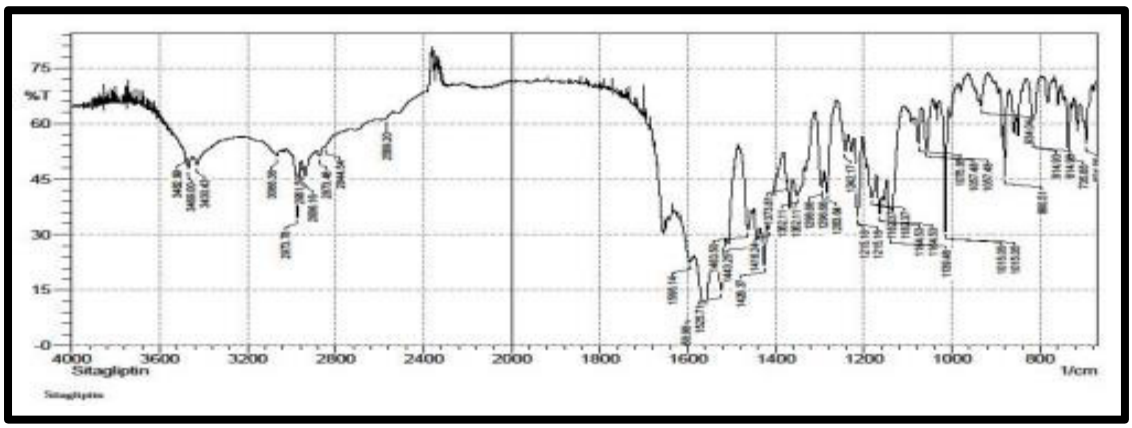

Fig. 7.10: IR spectrum of Sitagliptin Phosphate Monohydrate

Interpretation of FTIR Spectrum: The table below shows the peaks observed at different wave numbers and the functional group associated with these peaks. The major peaks are identical to the functional group of Sitagliptin phosphate monohydrate. Hence, the sample was confirmed as Sitagliptin phosphate monohydrate used for the study purpose.

Table 7.28 : Interpretation of FTIR Spectrum of Sitagliptin Phosphate Monohydrate

Sr. No.	Functional Groups	Wave number (cm^{-1})
1	O-H Stretching	3430
2	N-H stretching	3307
3	C -H stretching (Aromatic)	3049
4	C-O stretching	1631
5	C-N stretching	1517
6	N-H bending	1580
7	C-H bending	742

7.9.4 UV Spectrophotometric Method for Measurement of SPM

7.9.4.1 Estimation of the Absorption Maxima (λmax)

The 10 µg/ml SPM solution was scanned to estimate the absorption maxima (λmax) between 200 to 400 nm. The absorption maxima were observed at 267 nm.

7.9.4.2 Standard Graph of SPM in Distilled Water

The working solutions of 10, 20, 35, 40, and 50 µg/ml concentrations of SPM were prepared in distilled water. They were scanned at 267 nm using a UV-visible spectrophotometer using double distilled water as blank. The absorbances of working solutions were recorded and tabulated against the concentration (µg/ml). A standard graph was plotted between the concentration of SPM in µg/ml (x-axis) against absorbance (y-axis).

Table 7.29: Standard Graph of SPM in Distilled Water

Sr. No.	Concentration of SPM(µg/ml)	Absorbance
1.	10	0.196
2.	20	0.374
3.	35	0.559
4.	40	0.640
5.	50	0.754

The calibration curve of SPM in double distilled water is shown in the figure. The straight line was obtained after plotting the curve between the concentration of SPM in µg/ml (x-axis) against absorbance (y-axis). The equation of straight line and regression coefficient (r^2) were found to be y = 0.0138x + 0.0763 and 0.9944 respectively. The value of regression coefficient was closer to 1 indicating the best fitted line.

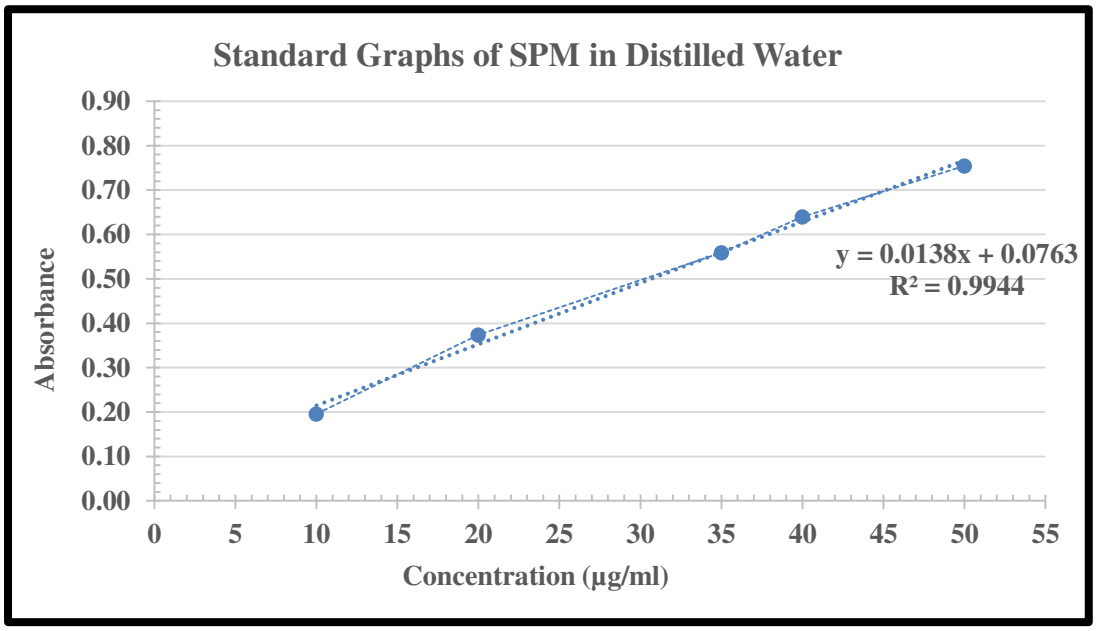

Fig. 7.11: Standard Graph of SPM in Distilled Water

7.9.4.3 Standard Graph of SPM in 0.01 M Hydrochloric Acid

The working solutions of 10, 20, 35, 40 and 50 µg/ml concentration of SPM were prepared in 0.01M hydrochloric acid. They were scanned at 267 nm using UV-Visible spectrophotometer using 0.01M hydrochloric acid as blank. The absorbances of working solutions were recorded and tabulated against the concentration (µg/ml). A

standard graph was plotted between concentration of SPM in µg/ml (x-axis) against absorbance (y-axis).

Table 7.30: Standard Graph of SPM in 0.01 M Hydrochloric Acid

Sr. No.	Concentration of SPM(µg/ml)	Absorbance
1.	10	0.192
2.	20	0.379
3.	35	0.669
4.	40	0.755
5.	50	0.913

The calibration curve of SPM in 0.01 M HCl is shown in the figure. The straight line was obtained after plotting the curve between the concentration of SPM in µg/ml (x-axis) against absorbance (y-axis). The equation of straight line and regression coefficient (r^2) were found to be y = 0.0183x + 0.0158 and 0.9983 respectively. The value of the regression coefficient was closer to 1 indicating the best-fitted line.

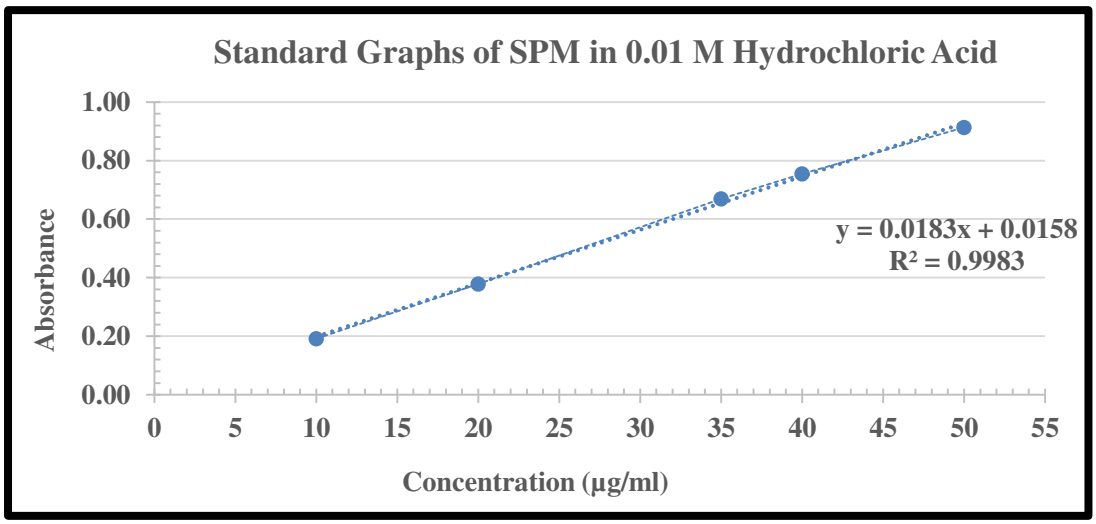

Fig. 7.12 : Standard Graph of SPM in 0.01M HCl

7.9.4.4 Standard Graph of SPM in Phosphate Buffer pH 4.5

The working solutions of 10, 20, 35, 40, and 50 µg/ml concentration of SPM were prepared in phosphate buffer pH 4.5. They were scanned at 267 nm using UV-Visible spectrophotometer using phosphate buffer pH 4.5 as blank. The absorbances of working solutions were recorded and tabulated against the concentration (µg/ml). A

standard graph was plotted between the concentration of SPM in µg/ml (x-axis) against absorbance (y-axis).

Table 7.31: Standard Graph of SPM in Phosphate Buffer pH 4.5

Sr. No.	Concentration of SPM(µg/ml)	Absorbance
1.	10	0.194
2.	20	0.385
3.	35	0.573
4.	40	0.749
5.	50	0.921

The calibration curve of SPM in phosphate buffer pH 4.5 is shown in below figure. The straight line was obtained after plotting the curve between the concentration of SPM in µg/ml (x-axis) against absorbance (y-axis). The equation of straight line and regression coefficient (r^2) were found to be y = 0.0183x + 0.0184 and 0.9988 respectively. The value of the regression coefficient was closer to 1 indicating the best fitted line.

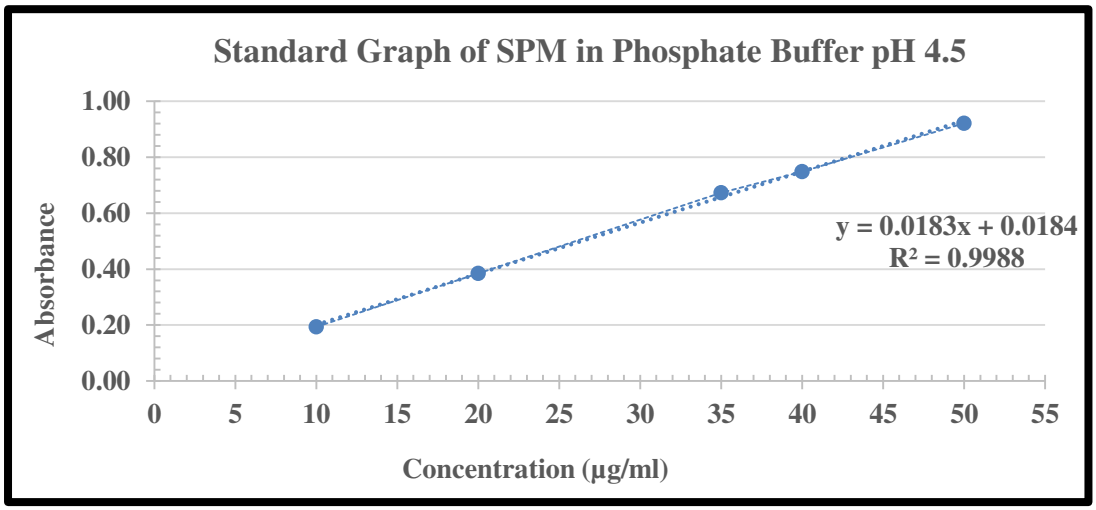

Fig. 7.13 : Standard Graph of SPM in Phosphate Buffer pH 4.5

7.9.4.5 Standard Graph of SPM in PB pH 8.0

The working solutions of 10, 20, 35, 40, and 50 µg/ml concentration of SPM were prepared in phosphate buffer pH 8.0. They were scanned at 267 nm using UV-Visible spectrophotometer using phosphate buffer pH 8.0 as blank. The absorbances of

working solutions were recorded and tabulated against the concentration (µg/ml). A standard graph was plotted between concentration of SPM in µg/ml (x-axis) against absorbance (y-axis).

Table 7.32: Standard Graph of SPM in Phosphate Buffer pH 8.0

Sr. No.	Concentration of SPM(µg/ml)	Absorbance
1.	10	0.191
2.	20	0.382
3.	35	0.620
4.	40	0.699
5.	50	0.899

The calibration curve of SPM in phosphate buffer pH 8.0 is shown in below figure. The straight line was obtained after plotting the curve between the concentration of SPM in µg/ml (x-axis) against absorbance (y-axis). The equation of straight line and regression coefficient (r^2) were found to be y = 0.0173x + 0.0221 and 0.9979 respectively. The value of regression coefficient was closer to 1 indicates best fitted line.

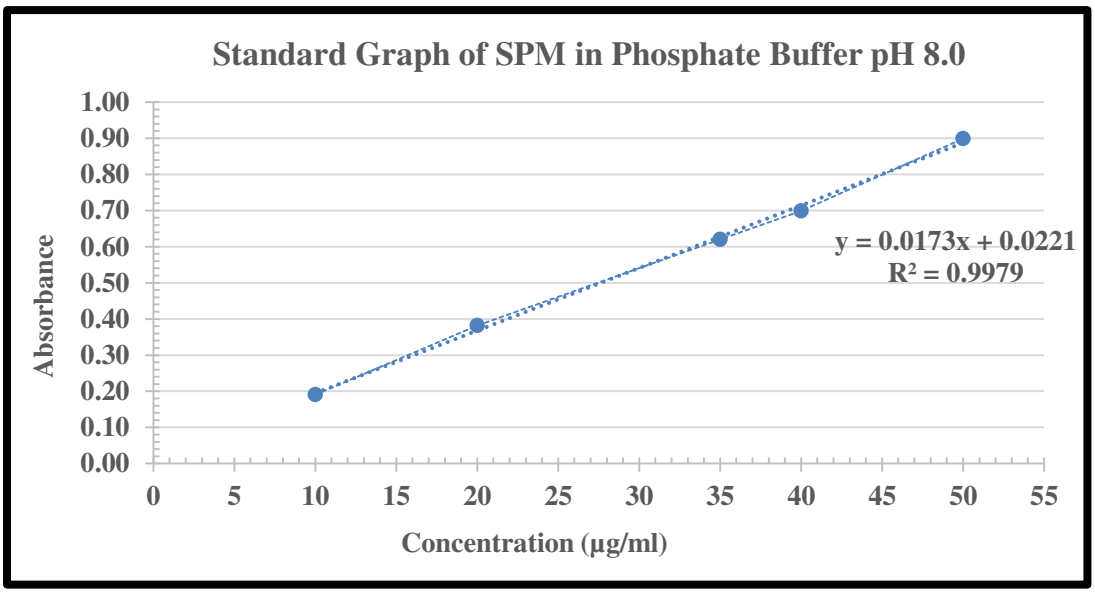

Fig. 7.14 : Standard Graph of SPM in Phosphate Buffer in pH 8.0

7.9.5 Solubility

Solubility is one of the most important parameters in relation to achieving the desired concentration of the drug in systemic circulation in order to obtain the required pharmacological response. Poorly water-soluble drugs with a slow absorption, for instance, may show inadequate bioavailability. The solubility of sitagliptin phosphate monohydrate in various solvent was determined at 25°C.

Table 7.33 : Solubility Study of SPM

Sr. No.	Solvent	Solubility (mg/ml)
1	Distilled water	69.53±0.02
2	Hydrochloric acid (0.01M)	68.19 ±0.01
3	Sodium citrate solution (0.1M)	67.07 ±0.009
4	Sodium carbonate (0.1M)	41.77±0.03
5	Phosphate buffer pH 4.5	49.6 ± 0.01
6	Phosphate buffer pH 8.0	72.631 ±0.006
7	Dimethyl Sulfoxide	90.33 ±0.025
8	Ethanol	0.01 ±0.002
9	Methanol	0.04 ±0.001
10	Acetonitrile	0.003±0.0002

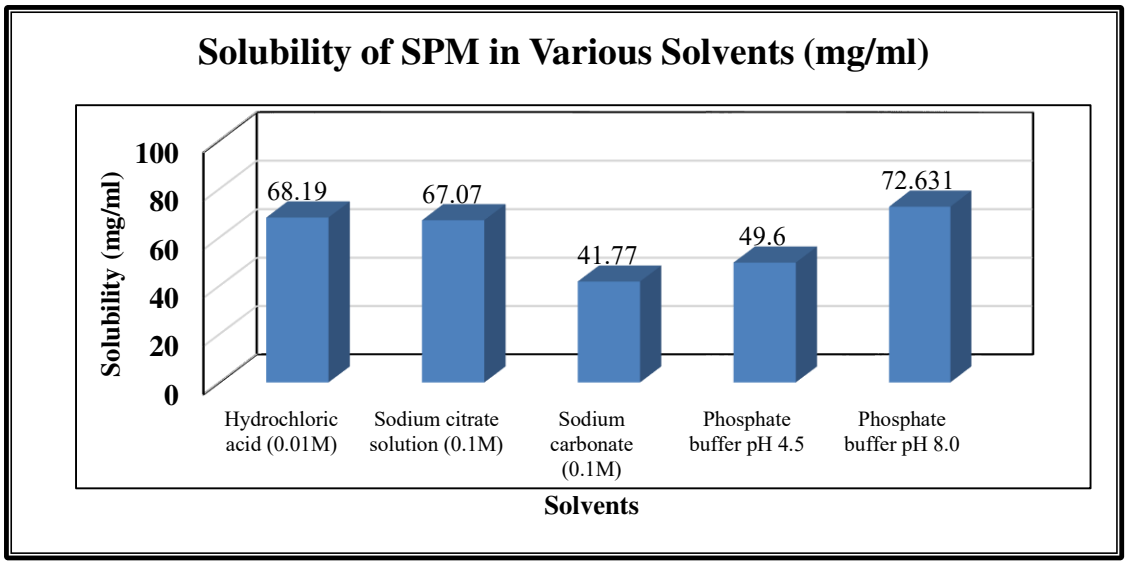

Fig. 7.15: Solubility of SPM in Various Solvents

The saturation solubility values of SPM in various solvents shows that SPM shows pH dependent solubility. As solubility was pH dependent the partition coefficient was also found to be pH dependent.

It was confirmed that Sitagliptin phosphate monohydrate had relatively higher solubility in distilled water compared with solutions of lower pH. Overall, sitagliptin phosphate monohydrate was confirmed as a soluble material at higher pH.

Sitagliptin phosphate monohydrate was found to be soluble in organic solvents like dimethyl sulfoxide and N, N-dimethyl formamide. Sitagliptin phosphate monohydrate was practically insoluble in ethanol, methanol and acetonitrile according to USP <1296>.

7.9.6 Partition Coefficient (Ko/w)

The octanol/water distribution coefficient (Ko/w) of sitagliptin is dependent on pH as the SPM shows pH dependent solubility. The Ko/w values at pH 4.5 (PB), 8.0 (PB) and 7.0 (water) were found to be -1.07 ±0.002, -0.02 ±0.001and 1.14±0.002 respectively for triplicate determination. A partition coefficient of SPM for octanol and water system reported in the literature is 1.8. The experimental value matches with the reference value.

7.9.7 pH of 2% Solution

The pH of 2% solution of Sitagliptin Phosphate Monohydrate was determined for triplicate and found to be 8.72 ±0.02.

7.9.8 Loss on Drying (%)

Accurately weighed 2 g of SPM previously screened through sieve number 80 was placed in dry weighing bottle and transfer the bottle in hot air oven maintained below 10°C temperature than the melting point of SPM for 1-2 hours hot air oven till constant weight was observed. The loss on drying value for the SPM sample was found to be 2.71±0.032 for triplicate determination. The acceptance criteria as per United States Pharmacopoeia (USP) is not more than 3.3 to 3.7%. It indicates that the sample meets the criteria for Loss on Drying.

7.10 Excipient Compatibility Studies

The samples were evaluated for physical characteristics (physical appearance) and results of the compatibility study are reported in the following tables.

Table 7.34 : Excipient Compatibility Outcome for SPM

Binary mixture	Observation	
	Initial (0 days)	After 7 days
Sitagliptin Phosphate Monohydrate (API)	Off white powder	No discoloration.
Sitagliptin Phosphate Monohydrate + Stearic acid	Off white powder	No discoloration.
Sitagliptin Phosphate Monohydrate + Palmitic acid	Off white powder	No discoloration.
Sitagliptin Phosphate Monohydrate + Polyvinyl Pyrrolidone (K-30)	Off white powder	No discoloration.
Sitagliptin Phosphate Monohydrate + Dicalcium phosphate	Off white powder	No discoloration.
Sitagliptin Phosphate Monohydrate + Titanium dioxide	Off white powder	No discoloration.
Sitagliptin Phosphate Monohydrate + Polyethylene glycol-4000	Off white powder	No discoloration.
Sitagliptin Phosphate Monohydrate + Colloidal Silicon Dioxide (Aerosil)	Off white powder	No discoloration.
Sitagliptin Phosphate Monohydrate + Talc	Off white powder	No discoloration.
Mixture of Sitagliptin Phosphate Monohydrate + All above excipients	Off-white wet mass	No discoloration.

Inference: There was no change in the physical observations of the binary mixture when exposed at 50°C±2°C for 7 days. Further, the finalized formulation will be evaluated for accelerated stability study using all these excipients. Hence, it can be concluded that the above excipients are compatible with the drug substance.

7.11 Formulation Development

7.11.1 Selection of Filler

Three different fillers were evaluated for suitability. Blending was performed using Microcrystalline Cellulose (Avicel PH 101), Spray Dried Lactose (DCL-11), and Dicalcium Phosphate as filler. All three final blends were compressed.

Table 7.35 : Formulation of Sitagliptin Batches- Selection of Filler

Study Outcome	Formulation code		
	B1	**B2**	**B3**
Physical appearance	Free from defects	Free from defects	Minor sticking
Hardness (kg/cm2)	4.8±0.10	5.3±0.15	5.2±0.11
Disintegration time (min-sec)	11’22”	5’45”	5’30”

Inference:

- The compression activity for the above trials was found satisfactory, except for formulation code B3 (Spray Dried Lactose as filler), where minor sticking was observed.
- The hardness for all three trials was found comparable, but for the same hardness higher disintegration time was noted for formulation code B1 (Dicalcium phosphate as filler).
- Hence based on the overall observation of the above trials, Microcrystalline Cellulose (Avicel PH 101) was selected as a suitable filler for further optimization.

7.11.2 Selection of Disintegrant:

Two different Disintegrants (Sodium starch glycolate and Croscarmellose sodium) were evaluated for suitability. Optimization was performed using Microcrystalline Cellulose (Avicel PH 101), as filler. Both the blends were compressed.

Table 7.36 : Formulation of Sitagliptin Batches- Selection of Disintegrant

Study Outcome	Formulation code	
	B4	B5
Physical appearance	Free from defects	Free from defects
Hardness (kg/cm2)	5.5±0.14	5.4±0.15
Disintegration time (min-sec)	7'22"	5'40"

Inference:

- The disintegration time for both trials was almost comparable, however being an immediate release dosage form, Croscarmellose sodium with lesser disintegration time was selected as a disintegrant.

7.11.3 Selection of Glidant and Lubricant:

The outcome of above trials (selection of filler and disintegrants) indicates suitability for the use of Colloidal Silicon Dioxide (Aerosil) and Talc as glidant and lubricant in the finalized formulation.

Table 7.37 : Formulation of Sitagliptin Batches- Selection of Glidant and Lubricant

Study Outcome	Formulation code	
	B2	B5
Physical appearance	Free from defects	Free from defects
Hardness (kg/cm2)	5.3±0.15	5.4±0.15
Disintegration time (min-sec)	5'45"	5'40"

Inference:

- The compression process and outcome of formulation codes B2 and B5 were found to be defect free and smooth, thus Talc and Colloidal Silicon Dioxide (Aerosil) were selected in the final formula.

7.11.4 Preparation of SPM Tablets

The tablets were prepared by direct compression method using a 10-station rotatory tablet compression machine using 6 mm standard biconcave circular punches. The

hardness was adjusted to 5 kg/cm^2. The prepared tablet cores were evaluated for quality control tests and results were recorded.

7.11.5 Preparation of Coated SPM Tablets

The tablet cores were coated using hot melt coating agents as per the coating composition and using coating parameters described in the material and method section. The coated tablets were evaluated for quality control tests.

7.12 Evaluation of SPM Coated Tablets

The different experiments were conducted with varying concentration of hot melt coating agents, stearic acid or Palmitic acid. Accordingly, pore former Polyethylene Glycol 4000 (PEG 4000) concentration was varied. The hot melt-coated tablets in comparison with core tablets were analysed for weight variation, Thickness, Hardness, Weight gain, Disintegration time, Friability, Drug content and Moisture uptake.

Table 7.38: Evaluation of SPM Uncoated and Coated Tablets

Study Outcome	Formulation Code								
	Core	F1	F2	F3	F4	F5	F6	F7	F8
Weight variation (mg)*	130.12±0.18	135.45±0.19	135.36±1.04	134.27±0.43	135.42±2.29	134.34±1.18	133.87±2.35	134.04±1.08	134.43±0.18
Thickness (mm)@	2.83±0.011	2.91±0.013	2.89 ±0.008	2.90 ±0.011	2.84 ±0.016	2.89 ±0.009	2.84 ±0.012	2.87 ±0.018	2.91±0.021
Hardness (kg/cm^2) @	5.0±0.2	5.2±0.10	5.1±0.15	5.0±0.2	4.8±0.15	5.1±0.2	5.0±0.10	5.0±0.2	4.9±0.15
Disintegration time (min) @	5	13	10	7	5	14	10	7	4
Friability (%)$	0.32	0.15	0.17	0.20	0.18	0.13	0.14	0.13	0.16
Drug content (%)*	99.29 ±1.39	99.87±2.91	100.21±2.15	98.93 ±3.11	99.06 ±0.73	98.76±2.65	100.11±1.13	99.57±2.68	98.32 ±2.62
Moisture uptake (%)@	0.38 ±0.09	0.09 ±0.01	0.10 ±0.01	0.12 ±0.02	0.13 ±0.03	0.05 ±0.01	0.07 ±0.02	0.08±0.03	0.11 ±0.03

Where, *,@ and $ indicates sample size (n) 20, 06 and 10 respectively.

Inference:

- The weight variation, hardness, and thickness data of all experiments for the hot melt coated tablets indicate that the coating was uniform across individual tablets.
- The moisture uptake for all hot melt coated tablets was comparatively better than that of the core tablets.
- The disintegration time decreases as the level of hot melt coating and the quantity of pore former PEG 4000 increases in coating composition.

- The formulation F1 (Stearic acid -HMC agent) and F5 (Palmitic acid -HMC agent) having higher disintegration time (>10 mins), moreover formulation F4 and F8 has lower disintegration (≤ 5 mins).
- **In-vitro Dissolution Test of Prepared SPM Tablets:** An in-vitro dissolution test was conducted on the SPM tablet core, and the SPM tablets coated with stearic acid and palmitic acid. As stearic acid and palmitic acid level in the coating composition increases drug release decreases proportionally.
- Formulation F4 and F8 follows the acceptance criteria as per USP and hence selected as suitable formulations. These formulations (F4 and F8) releases more than 80% drug in 30 min and more than 90% drug in 45 min. The SPM core tablets release more than 90% drug within 15 min.

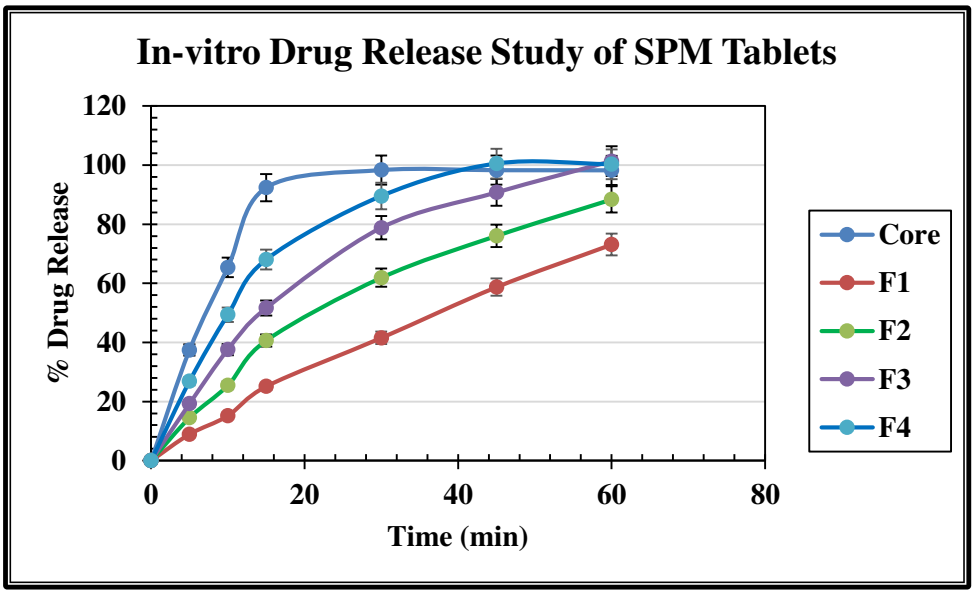

Fig. 7.16 : In-vitro Drug Release Study of Uncoated Tablet and Stearic Acid Coated Tablets

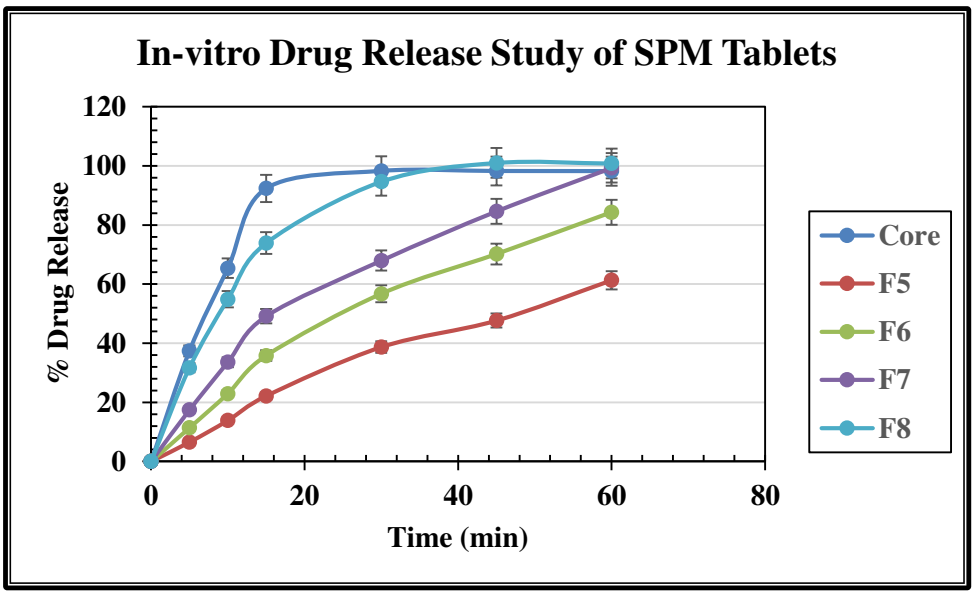

Fig. 7.17: In-vitro Drug Release Study of Uncoated Tablet and Palmitic Acid Coated Tablets

- Formulation F8 shows smoother surface and low water uptake value than formulation F4. The in-vitro drug release profile from F8 was found to be faster than F4 formulation. Therefore, dissolution profile of F8 formulation was compared with innovator product.
- **In-vitro Dissolution Study of Marketed Product:** In-vitro dissolution of marketed film coated tablets of sitagliptin phosphate monohydrate (Jankey® by Cadila Pharmaceutical Ltd., India) was conducted on twelve marketed tablets. As per United States Pharmacopoeia (USP) chapter <711> USP dissolution apparatus II (Paddle type) using 900 ml phosphate buffer pH 6.8 at 37± 0.5°C operated at 50 rpm. The samples were collected at 5, 10, 15, 30, 45 and 60 min and diluted suitably and analyzed using UV-Visible spectrophotometer. The sample solutions were filtered through Whatman filter paper (0.45 µm), from this filtered solution, 0.5 mL solution was taken into 10 mL volumetric flask and volume was made up with 6.8 pH buffer and solutions were analyzed at 267 nm by UV Spectrophotometer. The release in the dissolution medium was determined by software (PCP Disso v 2.08).
- **Acceptance criteria reported in USP-** Not less than 80% of labelled amount should release in 30 min and not less than 90% of labelled amount should release

in 45 min. The in-vitro dissolution test marketed sample, Jankey® were conducted and as per acceptance criteria given in USP reference tablets passes the test. Hence the same conditions were used for the in-vitro dissolution of prepared formulations.

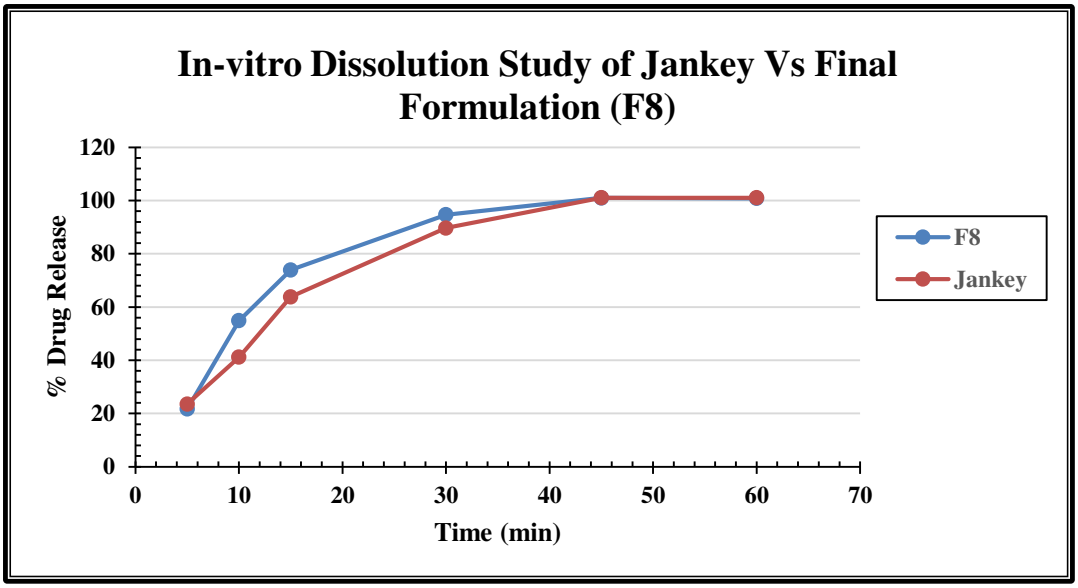

Fig. 7.18: In-vitro Dissolution Study of Marketed Product and Final Formulation

- **Similarity Factor (f_2) :** The dissolution profile of F8 formulation was compared with both innovator sample, where Similarity factor (f_2) was found to be 55. Hence F8 was considered as suitable formulation for stability study.

7.13 Stability Evaluation

- Stability-charged experimental Batch: F8
- Pack: Alu-Alu Blister pack.
- Stability Condition: At temperature 25±2°C & 60±5% RH and 40 ± 2°C & 75 ± 5% RH for 6 months in the stability chamber (Remi Laboratory Instrument, CHM-6).
- Frequency:
    - For 40 ± 2°C & 75 ± 5% RH: Initial, 1month, 2 Month, 3 month and 6 months
    - For 25±2°C & 60±5% RH : Initial, 1month, 2 Month, 3 month , 6 months.

- Testing: Physical appearance, drug content, moisture uptake and in-vitro drug release.

Table 7.39: ACC Stability Data for SPM Tablets

40 ± 2°C & 75 ± 5% RH					
Formulation Code	**Station**	**Appearance**	**Drug Content (%) (90.0 -110.0)**	**Moisture Uptake (%)**	**Drug Release (%) (NLT 80% (Q) in 30 minutes)**
Core Tablets	Initial	White	99.2	0.38	98
	1 M	Slightly off white	97.8	0.47	97
	2M	Off white	95.3	0.69	98
	3M	Off white to yellow	94.7	1.16	94
	6M	Light Yellow	91.2	2.13	92
F8	Initial	Yellowish white	98.3	0.11	93
	1 M	Yellowish white	98.2	0.15	94
	2M	Yellowish white	98.0	0.13	92
	3M	Yellowish white	97.7	0.22	92
	6M	Yellowish white	98.3	0.43	93

Table 7.40: Long-Term Stability Data for SPM Tablets

25±2°C & 60±5% RH					
Formulation Code	Station	Appearance (White tablets)	Drug Content (%) (90.0 - 110.0)	Moisture Uptake (%)	Drug Release (%) (NLT 80% (Q) in 30 minutes)
Core Tablets	Initial	White	99.2	0.38	98
	1 M	Slightly off white	98.8	0.39	98
	2M	Off white	97.9	0.44	96
	3M	Off white	96.5	0.55	95
	6M	Off white	94.6	1.10	94
F8	Initial	Yellowish white	98.3	0.11	93
	1 M	Yellowish white	97.9	0.19	92
	2M	Yellowish white	97.3	0.13	95
	3M	Yellowish white	97.0	0.23	92
	6M	Yellowish white	98.0	0.38	94

The appearance of the uncoated tablet was found to be change from white to off-white to yellowish in uncoated tablets. In case of coated tablets, the color of coated tablet was retained as yellowish white due to palmitic acid in coating composition.

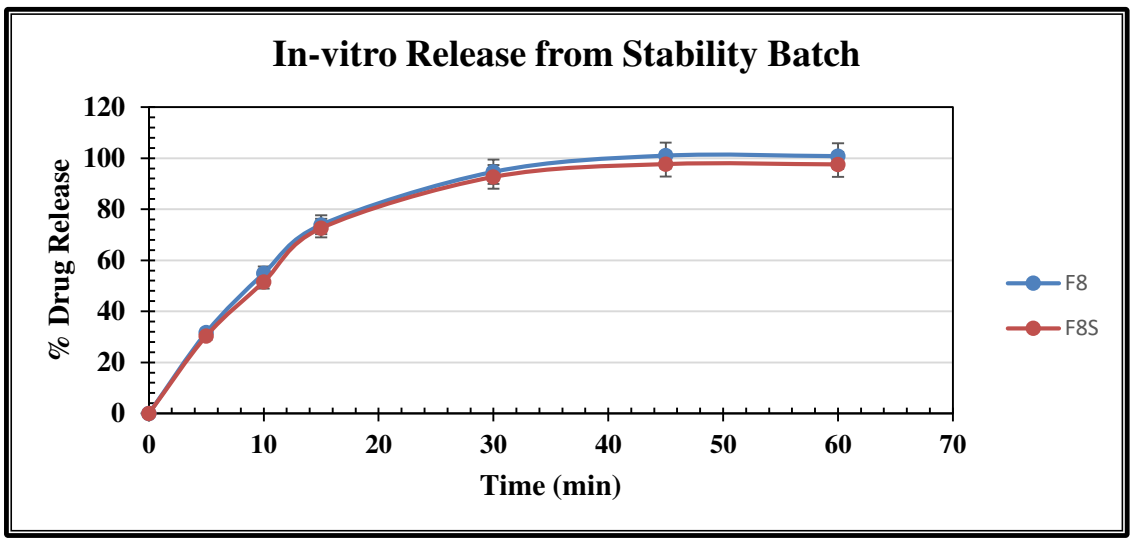

Fig. 7.19: In-vitro Release from Stability Batch

The in-vitro drug release from F8 formulation on the next day of preparation was compared with stability batch stored at accelerated conditions (40 ± 2°C & 75 ± 5% RH) after 6 months. No significant change in drug release was observed indicates F8 formulation was found to be stable. And after application of hot melt coating with hydrophobic coating agent like palmitic acid can protect core from moisture and resist the absorption of moisture by sitagliptin phosphate monohydrate and hence improve the stability.

CHAPTER – VIII

CONCLUSIONS

Conclusions

Tenofovir Disoproxil Fumarate (TDF) can be successfully designed using Hot Melt Coating technique in Pellets and also compressed as Tablets.

TDF is a slightly water-soluble drug with a bitter taste used in the treatment of Hepatitis and HIV. The bitter taste of TDF reduces patient acceptance and compliance with the dosage regimen. The commercially available formulation is a coated tablet. However, the coating process has various limitations such as time-consuming process, higher cost of production, product stability, environmental concerns, and health hazards due to the usage of aqueous or organic solvents. Hence, the present study has demonstrated an alternate technique of Hot-Melt Coating for Taste-masking.

In the given method Gelucire®43/01 and Precirol® ATO 5 were used as hydrophobic Hot-Melt Coating agents to reduce direct contact with saliva while given orally. Hot-Melt Coating comparatively is faster process and need lesser coating agent in comparison to film and sugar coating. It is the technique, not utilizing water and hence enhance the stability as well as not using organic solvents provides environment safety.

It is noteworthy to mention that the method is simple and does not require specialized equipment and costly coating agents. The prepared pellets were spherical, smooth, elegant with uniform & narrow size distribution and good to excellent flowability. Also, they pass the parametric tests namely hardness, friability, and drug content as per specifications.

The in-vitro taste evaluation of pellet formulation shows that the pellets coated with 3% w/w of HMC were unable to mask the bitter taste of pellets as the absorption of UV light was observed after 30 seconds. The coating level of 4% w/w using Gelucire 43/01 and Precirol can mask the bitter taste of pellets since the solution does not show UV light absorption in 2 minutes.

The volunteer study shows that uncoated pellets were found very bitter than the standard solution. The pellets coated with 3% w/w of Gelucire 43/01 and Precirol were unable to mask the bitter taste of the pellets. About 4% w/w of Gelucire and Precirol were able to mask the bitter taste of pellets**.** The formulation stored as per

ICH guidelines shows stability when the appearance, drug content, and in-vitro drug release were evaluated.

The developed taste-masked pellet formulation can be useful for the treatment of pediatric patients or patients facing difficulty in swallowing.

Further, the pellets were compressed into tablet dosage form, which is the most common dosage form due to its ease of handling and better stability profile. The tablet formulations were evaluated for the effectiveness of taste masking. The taste-masking ability was evaluated using the volunteer panel method. The study indicates that there is no impact on the bitterness taste masking efficacy of the HMC-coated pellets compressed into tablets.

The study performed as per ICH guidelines shows good stability.

Further, an in-vivo study must be carried out before commercialization of the product into the market.

A successful attempt was made to improve the stability of Sitagliptin Phosphate Monohydrate (SPM) using the hot melt coating technique. The Sitagliptin Phosphate Monohydrate was prepared by direct compression using a rotatory tablet punching machine. The SPM tablets core prepared were circular biconvex in shape and had smooth surfaces. The Sitagliptin Phosphate Monohydrate tablets were coated in a conventional coating pan with slight modifications and proved to be successful. Further in-vivo study is needed before the commercialization of the product into the markets.

In the present study has demonstrated that Palmitic acid proved their role in improving the stability of Sitagliptin Phosphate Monohydrate from the moisture. As per literature stability Sitagliptin is affected by moisture and leads to degradation at higher rate. Therefore, it is worthy of mentioning that proposed technique uses Palmitic acid for Hot Melt Coating due to their hydrophobic nature resist the entry of water in tablets containing SPM. The result of present study proved that Palmitic acid as Hot Melt Coating agent can constitute an excellent alternative to recently used conventional coating. Both Hot Melt Coating agents are obtained naturally from the

food component were not produce any allergic reactions in humans or animals and hence included in the Generally Regarded As Safe (GRAS) list. The Hot Melt Coating technique can be an eco-friendly, economical, efficient, simple and rapid tool for the design of moisture sensitive drugs. It is excellent alternative compared to conventional coating technique where solvent evaporation, recovery, treatment and disposal could become very costly and time consuming. It is also the excellent alternative for aqueous based coatings where coating is needed for water sensitive drugs.

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Exploring Taste Masking Potential of Hot Melt Coating Technique

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Abstract

In the present investigation, the hot melt coating technique has been assessed for its taste masking potential of tenofovir. Drug was fabricated into pellets by extrusion and spheronization method and coated with using Gelucire 43/01 and Precirol. The prepared pellets were evaluated for flowability, physicochemical properties and taste masking ability. Taste masking ability of technique was characterized by spectrophotometric and taste panel methods. The coated pellets were with good to excellent flowing ability and acceptable physicochemical properties. The threshold bitterness of drug was found to be 250 µg/ml. All the coated pellet formulations mask the bitter taste for minimum first 1-1.5 min indicating completely masking of the drug taste. Taste masking evaluation of pellets indicates that 80% volunteer reported slight bitter taste at 2% w/w level of hot melt coating agent and 3 & 5% w/w coating levels were qualified to mask the bitter taste. Both Precirol and Gelucire 43/01 shows excellent taste masking potential for masking taste of tenofovir.

Keywords: Tenofovir, Threshold bitterness, Precirol, Gelucire 43/01, Hot melt coating, Panel method

1. Introduction

The drugs are available in two types of dosage forms in the market namely solids or liquids. The solid dosage form includes beads, capsules, pellets, spherules, tablets, etc. The solids are most popular because they need low storage and transportation space cost. They are more stable than liquid dosage forms. They are frequently coated for numerous reasons, masking unwanted organoleptic properties, protection from environmental factors, protection from destruction by biological fluid of body, enhanced mechanical strength, improve aesthetic value, enhance flowing ability and achieve tailored drug release.[1]

Generally, the coating agents, pigments and excipients are dissolved or dispersed in a suitable solvent and sprayed over substrate and dried until smooth layer is formed. The coating is generally performed in fluidized bed coater for particulate systems or perforated pan coater for single unit systems. [2,3] Presently the solid dosage forms are coated by either aqueous and non-aqueous coating. The liquid coating can attain remarkably even smooth lustrous coating surface. Despite of that the aqueous coating may cause hydrolysis of few drugs and increase the microbial burden over the dosage form leads to decrease in the drug stability. The aqueous coating needs more time for drying and consume more energy. For non-aqueous

coating of dosage forms using organic solvents leads environmental pollution, solvent recycling cost and operator safety issues. [4] The organic solvents are generally than aqueous solvent costly.

The U.S. Environmental Protection Agency (EPA) in 1970 enforced the Clean Air act to reduce atmospheric solvent emissions.[5] In 1976, the Occupational Safety and Health Administration (OSHA) restricts the utility organic solvents to avoid exposure of industrial workers.[6] To circumvent the problems associated with use of solvents, the attempt was made to use the hot melt coating (HMC) technique.[7] The hot melt coating is solvent free technique where the drug and excipients are dissolved or dispersed in the molten material of interest and poured or sprayed on the substrate surface.[8, 9] The substrate like beads, capsules, microcapsules, minitablets, pellets and tablets can be coated using pan coating or fluidized bed coating[6,7]. The materials used for HMC technique are generally waxes. The waxes are generally cheaper as compared to the polymers employed in solvent-based coating. The great versatility of waxes in terms of their solubility and safety.[9] The literature shows that HMC is having wide variety of applications in the drug delivery systems.[10]

Tenofovir, is an acyclic phosphonate nucleotide analogue and base form of prodrug tenofovir disoproxil fumarate (TDF) used in combination with other antiretroviral drugs for the treatment of adult patients infected with HIV (Figure 1). The recommended dosage regimen of TDF is presented as once daily due primarily to its long biological half-life.[11,12] Tenofovir base has aqueous solubility of ~5 mg/mL in aqueous medium, the solubility of the prodrug TDF is ~2.5-fold higher at 13.4 mg/mL.[13,14] But the bitter taste of TDF reduces the patient compliance.[15] Hence, the objective of the present investigation was to assess the taste masking ability of HMC technique using a model drug, Tenofovir. The Gelucire 43/01 and Precitol ATO 5 were used as hot melt coating agents.[16]

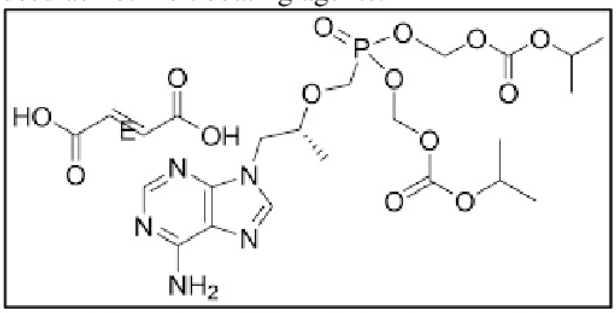

Figure 1: Structure of Tenofovir disoproxil fumarate

2. Materials and Methods

2.1 Materials

Tenofovir is a kind gift sample received from Mylan Laboratories Ltd., Aurangabad (MS), India. The Gelucire 43/01 and Precitol ATO 5 were free sample receive from Gattefose SAS, 69804 Saint-Prist Cedex, France. All other chemicals were of laboratory grade and used as received.

2.2 Methods

2.2.1 Preparation of Drug Pellets

TDF and excipients were blended in a double cone blender for 5 min. The Polyvinyl pyrrolidone solution (2% w/v) was poured slowly over powder blend. The cohesive mass was formed (Table 1). The mass was passed through 16 meshes to form extrudates. The wet extrudates charged into the extruder- spheronizer (Umang Pharmatek, India) and the spheronizer with cross-hatch plate of 1.2 mm was operated for 5 min at 850 rpm to produce TDF pellets.[17, 18] The pellets were dried at 60°C for 3 h and sifted to collect 16-20 mesh fractions.

Table 1. Formulation of TDF batches

Ingredient & Formulation code	F1	F2	F3	F4	F5	F6	F7	F8
Tenofovir disoproxil fumarate	300	300	300	300	300	300	300	300
Avicel PH 101	25	25	25	25	--	--	--	--
Spray dried lactose	--	--	--	--	25	25	25	25
Polyvinyl Pyrrolidone solution (2% w/v)	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
Coating composition								
Gelucire® 43/01	--	2	3	5	--	--	--	--
Precitol® ATO 5	--	--	--	--	--	2	3	5
α- Tocopherol	--	1	1	1	--	1	1	1

2.1.2 Hot Melt Coating of Pellets

The undersize and oversize pellets were rejected. TDF pellets were loaded into 10 inches diameter perforated coating pan equipped with 4 radially organized baffles and temperature regulation system. The drug pellets were rolled until pellet bed temperature of 60°C was attained. The molten Gelucire 43/01 and Precitol ATO 5 were used as coating materials. The molten coating mass was sprayed onto the rolling drug pellets in a slow stream. After the complete application of coating mass, the pellets were allowed to roll further for 10 min during which time the bed temperature was allowed to gradually come down. The pellets were then removed and cured in a dryer for 48 h.[19] The parameters employed for HMC of tenofovir pellets in coating pan are given in Table 2.

Table 2: Process parameters for hot melt coating[19, 20]

Parameter	Setting
Pellet weight	500 g
Pellet fraction	16 -20 mesh
Pan speed	20 rpm
Coating level	2, 3 and 5% w/w
Pellet bed temperature	60°C
Relative humidity	40% RH
Coating time	30 min
Curing time	30°C for 24 h

2.1.3 Evaluation of the Pellets

2.1.3.1 Pellet appearance

The coated and uncoated were snapped using digital microscope connected with personal computer.

2.1.3.2 Mean Pellet Size (d_{mean})

The average size of pellets was carried out using sieving analysis technique. A sieve shaker and set of four active standard test sieves (#14, #16, #18 and #20) were used for the analysis.[19] Accurately weighed 100 g of drug pellets were placed in sieve arranged over decreasing order of aperture size from top to bottom. The sieve shaker was shaken for 5 min. The size distribution of pellets expresses the efficiency of the process of manufacture the uniform size pellets. The mean pellet size was calculated.

2.1.3.3 Angle of Repose (θ)

Accurately weighed 50 g of drug pellets were poured gently through glass funnel on a simple graph paper and encircle the pile circumference occupied by pellets.[19] The height (h) and radius (r) of the pile were recorded & angle of repose (θ) values were calculated.[20]

$$\text{Tan } \theta = (h/r)$$[21]

2.1.3.4 Bulk Density (ρ_b)

Bulk density is ratio of bulk weight and bulk volume. Accurately weighed 50 g of tenofovir coated pellet fraction of 16/20 mesh were poured gently through glass funnel into 100 ml calibrated measuring cylinder.[19] The surface was cautiously levelled with null pressure. The volume occupied by pellets was used for calculation of bulk density (g/ml). [21]

$$\rho b = (M/ V_b)$$

Where, ρb = bulk density, M = weight of the sample, and V_b = apparent volume of sample.

2.1.3.5 Tapped Density (ρ_t)

Bulk density is ratio of bulk weight and tapped volume. Tapped density was estimated in a similar way to that of bulk density. However, final volume was measured after tapping the cylinder from 3 inches until constant volume was obtained using Electrolab tapped density apparatus. The volume occupied by pellets after tapping was noted and tapped density (g/ml) was calculated. [19]

$$\rho t = (M/ Vt)$$

Where, ρt = tapped density, M = weight of the sample, and Vt = tapped volume of sample.

2.1.3.6 Carr Index (CI)

The external appearance of pellets and internal structure can alter material properties and porosity that greatly effect on pellet coating, flow and packing during tabletting or capsule filling. It also shows effect on drug release by affecting the capillary action of dissolved drug.[22] Using bulk density and tapped density values of tenofovir coated pellets the compressibility index can be calculated.[19]

2.1.3.7 Hauser Ratio (HR)

The bulk density and tapped density data were used for HR calculation.[8,9]

2.1.3.8 Hardness and Friability

The hardness tenofovir pellets was determined by Veego digital dial type hardness tester (Veego Scientific, India).[22] For the friability study, accurately weighed 10.0 g of tenofovir coated pellets (initial weight) with 25 glass beads of 3 mm diameter were placed in the revolving drum of Roche's friabilator (Veego Scientific, India) for 100 revolutions operated at 25 rpm speed.[19] The pellets were collected and placed on the sieve with 0.85 mm aperture and the smaller particles were allowed to pass through the sieve. The pellets were reweighed (Final weight) and % weight loss data were considered as % friability. [19]

2.1.3.9 Drug Content

Accurately weighed 500 mg of hot-melt coated pellets were grind carefully in the mortar. A total of 50 mg of this powder was transferred carefully to 100 ml volumetric flask and add 30 ml of methanol and ultrasonicated using laboratory sonicator (ISP Technologies, India) for 15 min to extract the tenofovir. Final volume was made with double distilled water and diluted suitably.[19] The diluted sample were scanned at 260 nm using double distilled water as blank using Ultraviolet- visible (UV) spectrophotometer (UV1800, Shimadzu, Japan). The drug content was calculated.[23]

2.1.3.10 In-vitro Dissolution

In-vitro release from tenofovir pellets was carried out using United States Pharmacopoeia (USP) XXV apparatus I (Basket Type), model Electrolab, 6 vessel assembly at 100 rpm. The dissolution medium consisted of 900 ml of double distilled water for 1 h at 37 ± 0.5°C and 5ml aliquots were withdrawn at predetermined time intervals.[24] An equivalent amount of fresh dissolution fluid equilibrated. Aliquots were diluted suitably, filtered and analyzed. All release studies were conducted in triplicate and the mean values were plotted versus time with a standard deviation less than three indicating reproducibility of result. The percent cumulative drug release against time was plotted. [19]

2.1.3.8.11 In-vitro Taste Evaluation

Hot melt coated pellets equivalent to 50 mg of drug were placed in test tube containing 10 ml of double distilled water maintained at 37±1°C, stirred gently to simulate conditions of mouth cavity. After every 30 sec collect aliquot of 1 ml and replace with fresh medium maintained at 37±1°C. Each aliquot was diluted to 100 ml and the absorbance of diluted solution was recorded at 260 nm using UV-visible spectrophotometer. Taste evaluation was performed for 10 min.[25]

2.1.3.12 Determination of Threshold Bitter Taste

To taste the sensory bitter taste of drug twelve human volunteers were selected and coded. They were asked to thoroughly rinse the mouth cavity with purified water. The dilutions of drug concentration range 50-500 µg/ml were prepared. Each volunteer was informed to hold 5 ml solution for 10 min and spat out. The volunteers were asked to rinse the mouth cavity with purified water after every treatment to avoid carryover effect of previous treatment. The score of bitterness given to each solution against the distilled water was recorded. The minimum concentration which was judged as bitter taste by volunteer was considered as bitter threshold. [26, 27]

2.1.3.13 Taste Panel Method

To taste the bitter taste of and efficacy of hot melt coating for taste masking of drug twelve human volunteers were selected. They were asked to thoroughly rinse the mouth cavity with purified water. They were provided with the 50 mg of pellets over tongue for 10 sec. Taking the taste of pure drug solution as standard, the degree of bitterness was judged by volunteers according to bitterness scale.[28]

2.1.3.14 Stability Test

The pellets equivalent to unit dose were filled hard gelatin capsule shells of '000' size and placed in amber coloured bottles and wrapped with aluminum foils. They were stored at temperature 40 ± 2°C and relative humidity (RH) 75 ± 5% for 3 months in the stability chamber (Remi Laboratory Instrument, CHM-6). The pellets were evaluated for any changes in physical appearance and percent drug content after every month.[19] Result obtained was compared with data obtained at zero time and pellets stored at 28±2°C and 42±2% RH.[29, 30]

3. Results and Discussion

The coating was performed with ease and rapidly. The percent yield of coated pellets was excellent as no agglomeration was observed.[22] This may be due to non-tacky nature of coating composition that facilitated free rolling of pellets.

3.1 Surface Morphology

The pellets prepared by extrusion and spheronization were spherical in shape and uniform in size.[22] The coated pellets were smooth in appearance than the uncoated pellets (Figure 2).

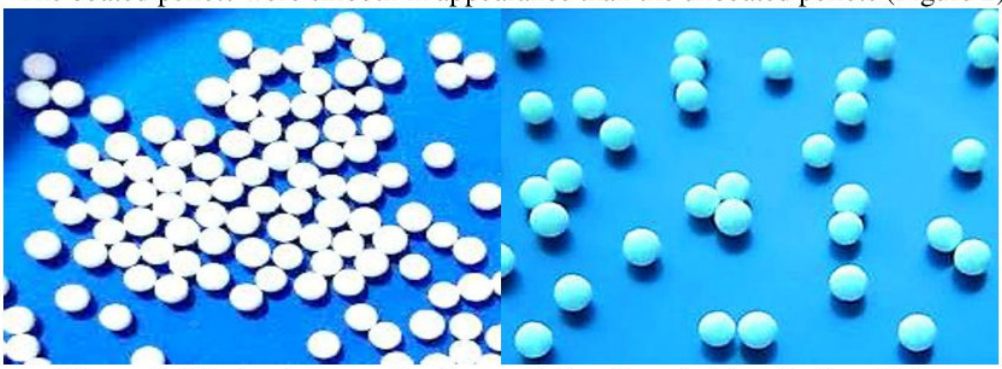

Figure 2: Photomicrograph of uncoated and coated tenofovir pellets.

3.2 Flowability of Pellets

The angle of repose values of uncoated pellets was found to be 26.38° and 27.92° indicates good flowability.[19] The angle of repose value for coated pellets was found to be in the range of 18.26° to 23.88° indicates good to excellent flowability of coated pellets than uncoated pellets. [31] With increase in the coating level the imperfections on pellet surface were found to decrease (Table 3).

The bulk density and tapped density of the uncoated pellets, formulation F1 were found to be 0.714 ± 0.002 and 0.787 ± 0.002 g/ml respectively. The bulk density and tapped density of the uncoated pellets, formulation F5 were found to be 0.698 ± 0.003 and 0.786 ± 0.002 g/ml respectively. The bulk density of coated formulations was range from 0.723 ± 0.001 to 0.764 ± 0.001 g/ml. The tapped density of coated formulations was range from 0.723 ± 0.001 to 0.764 ± 0.001 g/ml (Table 3).[19]

The Hausner ratio for formulation F1 and F5 were found to be 1.102 ± 0.002 and 1.126 ± 0.001 indicates good to excellent flowability. The coating of pellets reduce the Hausner ratio of pellets indicates improvement in flowing ability due to coating (Table 3). The Carr index for formulation F1 and F5 were found to be 9.275 ± 0.002 and 11.195 ±0.001 indicates good to excellent flowability. The results show that as the coating level increase from 2% towards 5% the Carr index value decreases. The coated pellet formulation shows excellent flowing ability (Table 3). [32]

Table 3: Flowability of coated and uncoated tenofovir pellets

Formulation Code	Angle of Repose† (°)	Bulk Density* (g/ml)	Tapped Density* (g/ml)	Carr Index* (%)	Hausner Ratio
F1	26.38	0.714 ± 0.002	0.787 ± 0.002	9.275 ± 0.002	1.102 ± 0.002
F2	23.88	0.723 ± 0.001	0.789 ± 0.001	8.365 ± 0.001	1.091 ± 0.003
F3	21.92	0.753 ± 0.001	0.807 ± 0.003	6.691 ± 0.002	1.072 ± 0.004
F4	19.71	0.749 ± 0.003	0.798 ± 0.002	6.210 ± 0.002	1.065 ± 0.001
F5	27.92	0.698 ± 0.003	0.786 ± 0.002	11.195 ±0.001	1.126 ± 0.001
F6	19.63	0.761 ± 0.003	0.813 ± 0.004	6.396 ± 0.004	1.068 ± 0.003
F7	18.26	0.757 ± 0.002	0.803 ± 0.003	5.728 ± 0.003	1.061 ± 0.003
F8	18.34	0.764 ± 0.001	0.816 ± 0.003	6.372 ± 0.001	1.068 ± 0.001

Where * and † indicates value in (Mean ± S.D.) and mean respectively where sample were analyzed in triplicate.[33]

3.3 Physicochemical Properties of Pellets: The pellets were with narrow size distribution and the mean size of pellets was range from 852 to 890 µm. The pellets were with acceptable crushing strength (±0.5 kg/cm^2) and friability (< 1%). The drug content was found to be within acceptable limits (Table 4).[34]

Table 4: Physicochemical properties of coated and uncoated tenofovir pellets

Formulation Code	Mean size† (µm)	Hardness* (kg/cm^2)	Friability* (%)	Drug content* (%)
F1	852	2.65 ± 0.05	0.248 ± 0.001	98.86 ± 1.26
F2	858	2.80 ± 0.10	0.232 ± 0.002	100.26 ± 2.06
F3	867	3.05 ± 0.05	0.168 ± 0.001	99.54 ± 0.84
F4	880	3.10 ± 0.10	0.215 ± 0.003	101.35 ± 1.98
F5	863	3.10 ± 0.15	0.228 ± 0.004	99.02 ± 3.13
F6	879	3.05 ± 0.15	0.235 ± 0.003	98.91 ± 0.57
F7	885	2.45 ± 0.10	0.358 ± 0.005	100.65 ± 2.53
F8	890	3.05 ± 0.10	0.228 ± 0.004	98.68 ± 0.21

Where * and † indicates value in (Mean ± S.D.) and mean respectively where sample were analyzed

in triplicate.[33]

3.4 In-vitro Release Study

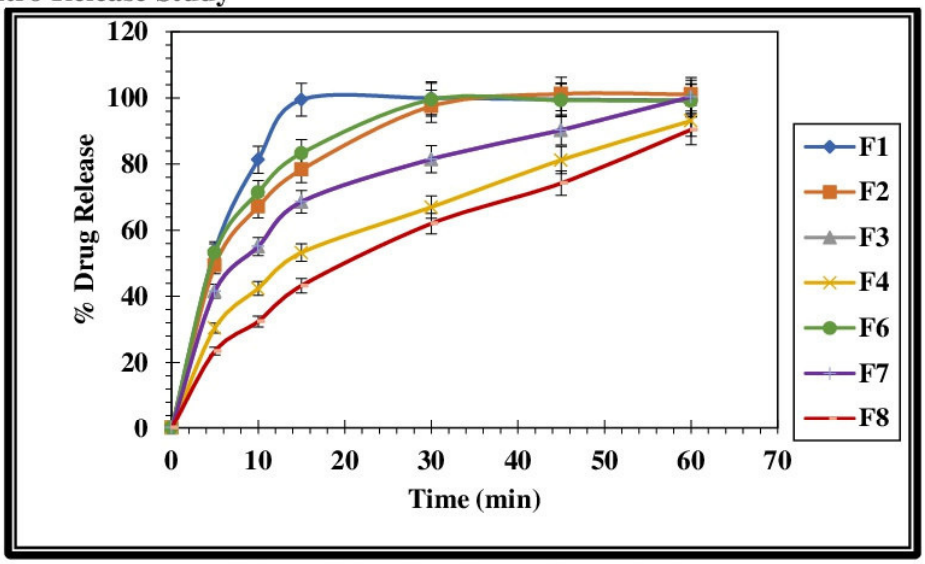

Figure 3 In-vitro drug release study

The in-vitro drug release was found to be dependent upon coating composition and coating level dependent. With increase in the coating level, the drug release decreases. Formulation F3 and F7 shows complete release in 30 min. The 5% coating level release drug very slow than the required.[35]

3.5 Threshold Bitter Taste Determination

The threshold bitterness of drug was found to be 250 µg/ml.[36]

3.5 In-vitro Taste Evaluation

The in-vitro taste evaluation of pellet formulation shows that the pellets coated with 2% w/w of HMC were unable to mask the bitter taste of pellets as the absorption of UV light was observed from 30 sec.[16] The 3% w/w coating level Gelucire 43/01 and Precirol can able to mask the bitter taste of pellets since the solution does not show UV light absorption in first half minute. The 5% w/w coating level Gelucire 43/01 and Precirol shows no UV light absorption in 10 min. It indicates the 3% w/w coating level Gelucire 43/01 and Precirol can able to mask the bitter taste while 5% w/w coating level delay the disintegration time of pellets and may affect rate of drug absorption through gastrointestinal tract (Table 5).

Table 5: In-vitro taste masking of pellets

Formulation Code	Time (min)							
	0.5	1.0	1.5	2.0	2.5	3.0	5.0	10.0
F1	+	+	+	+	+	+	+	+
F2	-	-	+	+	+	+	+	+
F3	-	-	-	-	+	+	+	+
F4	-	-	-	-	-	-	-	-
F5	+	+	+	+	+	+	+	+
F6	-	-	-	+	+	+	+	+
F7	-	-	-	-	+	+	+	+
F8	-	-	-	-	-	-	-	-

Where, + = UV absorbance and - = No UV absorbance

3.6 Panel Method

The volunteer study shows that uncoated pellets were found very bitter than the standard solution. The pellets coated with 2% w/w of Gelucire 43/01 and Precirol were unable to mask

the bitter taste of pellets. About 3% w/w of Gelucire 43/01 and Precirol were able to mask the bitter taste of pellets (Table 6).[36]

Table 6: Taste masking evaluation of pellets

Formulation Code	Volunteer Code							
	V_1	V_2	V_3	V_4	V_5	V_6	V_7	V_8
F1	++++	++++	++++	++++	++++	++++	++++	++++
F2	+	+	+	+	+	++	+	++
F3	-	-	-	-	-	-	-	-
F4	-	-	-	-	-	-	-	-
F5	+++++	+++++	+++++	+++++	+++++	+++++	+++++	+++++
F6	+	+	++	+	+	+	+	+
F7	-	-	-	-	-	-	-	-
F8	-	-	-	-	-	-	-	-

Where, +++++ = very-very bitter, ++++ = very bitter, +++ = moderately bitter, ++ = bitter, + = slightly bitter and – = tasteless.

3.7 Stability Test

The F7 pellet formulation stored at 28±2°C & 60±5% RH and 40 ± 2°C & 75 ± 5% RH [29, 30] shows drug content 100.23 ± 1.98% and 99.79 ± 2.11% respectively. The F7 pellet formulation stored as per ICH guidelines were found to be stable as there were no significant changes was observed after 3 months in drug content and physical appearance in the optimized formulation.

4. Conclusions

From the present investigation, it can be concluded that both the hot melt coating agents employed are equally efficient to mask the bitter taste of the tenofovir disoproxil fumarate by hot-melt coating technique. The coating level above 3% w/w was found to be sufficient to achieve the objective. The HMC technique is rapid, competent, economic and eco-friendly for taste. The present technique can be suitable for other drugs to overcome their disagreeable organoleptic properties. But proper preformulation, formulation development, preclinical studies, clinical studies and regulatory approval will be essential before launching product into market.

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Conflict of Intrest: Nil

Source of Support: Not declared

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Hot Melt Coating: An Ecofriendly Technology In Pharmaceutical Product Development

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Abstract:
The objective of review is to explore various aspects hot melt coating (HMC) technology in the drug product manufacture. Global market drivers for oral solid dosage (OSDs) forms are generic market, newer indications of existing drugs, new combinations, life cycle extension of available drugs etc. To meet the needs of market and regulatory bodies, the melt coating technology can resolve the drug related issues of bioavailability, economy, formulation, stability and scalability. The HMC is rapid, reliable, cost-effective and environment friendly technique. Neither aqueous nor organic solvents are required for drug product design in this technique. The regulatory bodies are currently focusing on environment sustainability and safety issues which are strictly followed by this technology. The simple pan coaters or fluidized bed coaters with minor modification were deployed in this technology. It offers several applications in dosage form design. It is user friendly as most of lipid materials are used for coating which facilitate easy gliding of dosage form into gastrointestinal tract (GIT).

Key-words: Hot melt coating, Ecofriendly, Stability, Lipid, Solventless, Generic

Introduction

Majority of medicines and dietary supplements are orally administered. The OSD market is growing at higher pace due to several motives. Recently, the formulation and development scientists from pharmaceutical industries are manipulating available drugs into innovative delivery systems utilizing advanced technologies to provide better quality, safe, stable and efficient remedies than the currently available in the global market.[1] Many drugs are with several undesirable characteristics like-

1. Unacceptable color, odour and taste
2. Light, moisture or oxygen sensitive
3. Rapid dissolution causing irritation in GIT
4. Instability in stomach pH
5. Need tailored drug release profile from drug products
6. Poor bioavailability and flowing ability

Several techniques were reported to circumvent above issues. The coating of the OSDs is oldest practice to overcome all above problems. By choosing apt coat former the tailored drug release profile can be attained like the immediate release, delayed release, controlled release, regioselective release etc.[2] The coating can protect the GIT from hostile effects of active pharmaceutical ingredients (API) and vice- versa. It also shields medicament from light, heat, moisture and other environmental factors. The coated substrate has enhanced flowing ability that fascinates in accurate dosing of API.[3]

Need of Hot Melt Coating

The water based coating and organic solvent-based coating were most common. The coating agents are either dissolved or dispersed in aqueous or organic solvents with additives and sprayed or poured over the substrate or substrate sometimes dipped into coating solution for encapsulation of core. The residual moisture after aqueous coating may surge microbial burden over dosage form and residual organic solvent traces may cause solvent associated toxicity to patients. Leaving the organic solvents in environment leads to global warming

(greenhouse effect) and produce harm to industry workers. In contrast, the organic solvent recovery and treatment are inflated processes. The regulatory bodies like the United States Food and Drug Administration (US FDA), Environmental Protection Agency (EPA) and Occupational Safety and Health Administration (OSHA) are stalwartly confining the usage of organic solvents in pharmaceutical manufacture. Due to the several demerits of aqueous or organic solvent-based coating, researchers are in the need of simple, efficient, precise, scalable, economic and regulatory acceptable coating technology.[4,5]

Hence in 1940, the HMC was first employed in paper and textile industries and in 1980 onwards was continued in pharmaceuticals. The molten coating agents are either sprayed or poured over the substrate. The molten droplets are spread and solidify on the solid surface.[6] The beads, capsules, drops, granules, powders, pellets, spherules, tablets, etc. are usually used as substrate. Since last 60 years, HMC were utilized on industrial scale but at limited extent.[7,8]

Merits

1. Organic solvent free and environment friendly technique[9]
2. Bypasses steps like solvent disposal, treatment/ recovery associated with organic solvent[9]
3. Speedy process trails on regulatory directives for usage of organic solvents[9]
4. No or low risk of bacteriological contamination as water- free technique[10]
5. No chances of hydrolysis of drug or additives as no aqueous medium is used[10]
6. Tailored drug release profile can be attained using suitable coating composition
7. No need of costly equipments as pan/ fluid bed coater can be exploited
8. Regularity benefits like extension of patent life and product line
10. Opportunity of patenting and registration of invention to international marketplace

Demerits

1. Not suit for thermolabile therapeutic actives & additives and thus limits formulation development
2. Limited molten mass can be coated on substrate
3. Multilayer coating is difficult (superior layer coat former should have low MP than inferior)[11]
4.Thermal behaviour and compatibility of drug and excipients must be considered[12]
6. Polymorphic nature of HMC agents may alter dissolution profile among the batches[13]
7. Use of hygroscopic additive may affect thickness and moisture absorbed by coat. This is having direct influence on stability of drug[14]
7. The safety of operator is very critical since operation require higher temperature[5]
8. High energy is needed for melting of coat former
9. Complete toxicity study data of hot melt coating agent is necessary along with dosage form[4]
10. Suitable modification in coating machines is required

Applications

The substrates are coated to achieve several objectives (Table 1).

Table 1: Application of Hot Melt Coating in Drug Product

Sr. No.	Utility	Active Pharmaceutical Ingredient
1	Taste masking[3]	Aspirin,[16] Paracetamol,[17-19] Bromhexine hydrochloride,[20] Salbutamol sulphate. [20]
2	Reduces acidity	Vitamins[21]
3	Improve stability	Hygroscopic or light sensitive or oxidizable drugs[14, 22, 23]
4	Improve flowability	Drug with poor flowability[24]
5	Modified release	Ambroxol, [25] Cefuroxime axetil, [1] Chlorpheniramine maleate, [26, 27] Chloroquine, [28] Diclofenac sodium, [29-31] Metoprolol tartrate,[32] Nifedipine, [33] Paracetamol, [16] Propranolol hydrochloride, [34] Theophylline, [3, 35, 36] Ranolazine, [37] Ibuprofen, [38] Chlorpheniramine maleate, [39] Verapamil hydrochloride, [39] Diltiazem hydrochloride[39]
6	Enhance shelf-life	Probiotics and herbal extracts[40]
7	Incompatible drugs	Multi-component drug delivery systems

Hot melt coating agents [41, 42]

All coating agents employed in conventional film coating or sugar coating are not apt for HMC. The ideal characteristics of coating agent for HMC are-

1) The required viscosity should be less than 300 millipoises at its melting point.
2) They should have spreadability over substrate.
3) They should have narrow and precise melting point range.
4) The melting point of HMC agent should be 60-80°C to facilitate ease in flow.
5) They should not show polymorphic transformation during product manufacture or storage.
6) The uniform substrate dimensions are prerequisite for batch-to-batch uniformity.

The lipids from natural origin (bees wax, cetyl alcohol, caurnava wax and spermaceti wax), hydrogenated oils (castor oil, sesame oil and arachis oil), polyoxy glycerides and partial glycerides/ surfactants are used in HMC. The summary of the HMC agents is given in Table 2.

Table 2: Hot Melt Coating Agents and their applications

Coating Agent and Meting Point	Chemical Nature	Application(s)	Example(s)
Animal fats ≈ 80 °C	Clarified butter	Sustained release	Cow ghee
Fatty acids ≈ 60-90 °C	Long chain unbranched saturated or unsaturated aliphatic fatty acids	Prolonged release and enteric coating	Behenic acid, Stearic acid, & Palmitic acid
Fatty alcohols ≈ 50-55 °C	Long chain fatty aliphatic alcohol containing 8 to 20 carbon atoms	Modified release, & Taste-masking	Cetyl alcohol, & Wool alcohol
Partial glycerides ≈ 55-75 °C	Mono-, di-, and triglycerides mixture. Based on physicochemical properties required substitutions were made	Modified release, Taste-masking, & Lubrication	Compritol® 888 ATO, Myvaplex™ 600, & Precirol® ATO 5
Polyoxy glycerides (Partially digestible) ≈ 50 °C	Mixture of glycerides and esters of fatty acid and PEG	Immediate release, & Modified release	Gelucire® 50/02, & Gelucire® 50/13
Vegetable oils (Generally digestible) ≈ 60-70 °C	Mixture of triglycerides, free fatty acids, phospholipids	Taste-masking, & Modified release	Hydrogenated cottonseed oil, Hydrogenated palm oil, & Hydrogenated soybean oil
Waxes (Lipophilic) ≈ 62–86 °C	Long chain alcohols and their esters with fatty acids	Modified release	White and yellow beeswax, Carnauba wax, Candelilla wax, paraffin wax, hydrogenated Jojoba oil, Rice bran wax
Polyethylene glycols (PEG), Propylene glycols and polyglycerol (Variable based on molecular weight)	Based on the average molecular weight, PEGs are available in various grades i.e., liquid, semisolid and solid. They are available in variety grades with vary in their physical properties.	Taste-masking, sealant & Modified release	PEG 1450 and 3350 molecular weights. Higher molecular weight PEG are not suitable since their melt have higher viscosity

Hot Melt Coating Method

The HMC is usually performed using conventional coating pan or fluidized bed coater with slight augmentations. The pan coating is executed by pan pour or pan spray method. The fluidized bed coater can be achieved by top spray, bottom spray, tangential spray method, turbo- jet coating or solid dispersion technique. The direct blending and spouted bed techniques are least common methods employed in HMC.[43]

1. Pan Coating: The modified conventional pan coater is employed for pan spray or pan pour HMC technique. The substrate is coated either by pouring or spraying the molten coat former in a coating pan equipped with baffles or other augmentations and temperature regulating systems. The coating agent is heated slightly above

its' melting point (5-10°C) and other excipients are mixed in the melt with stirring. The substrates are rolled in the coating pan and heated until substrate temperature reach to 10°C below melting point of coat former. The molten mass is loaded onto the hot rolling substrates in as a slow stream or sprayed with controlled rate with insulated spray nozzle from optimized distance using appropriate spray pattern. The substrates are allowed to roll for 10-20 min during which the bed temperature bring gradually down. The coated substrates are removed and cured in a dryer for few hours. The pan spray coating is more efficient and that provides controlled release of medicament due to uniform film formation, while pan pour method demonstration variation in the drug release profile with in same batch of product because of uneven coating. Therefore, pan pour technique is used in modifying organoleptic drug products, improving flowability, and reducing acidity of drugs.[29]

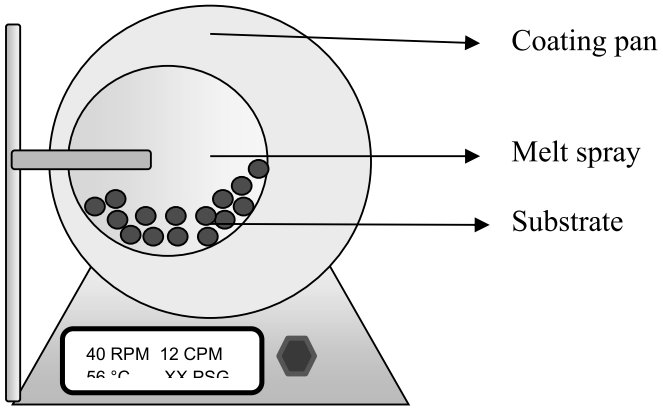

Fig.1 Pan coating.

2. Spouted Bed Coating: The well-defined fluid dynamics was reported to coat tablets in a prism shaped spouted bed made up of transparent stainless steel and borosilicate glass with adjustable horizontal air vents. Generally, the coating is performed at maximum height maintain air flow above 40% as minimum air velocity in spouted bed using air compressor provided with orifice meter. The weighed substrate is placed in spouted bed and the temperature and air flow rate are adjusted. Once the temperature of substrate become steady, the coating agents are added from the top at one time in column of equipment. The content is spouted for optimized period. The heating is stopped and coated substrate is allowed to cool to room temperature. Further spouting of coated substrate is continued to avoid aggregation of substrate. The coated substrate was collected and weighed to estimate coating efficiency using initial weight and final weight of substrate along with coating material added for coating.[44]

$$Coating\ efficiency\ (\%) = \frac{Final\ weight\ of\ coated\ core - Initial\ weight\ of\ core}{Coating\ material\ loaded} \times 100$$

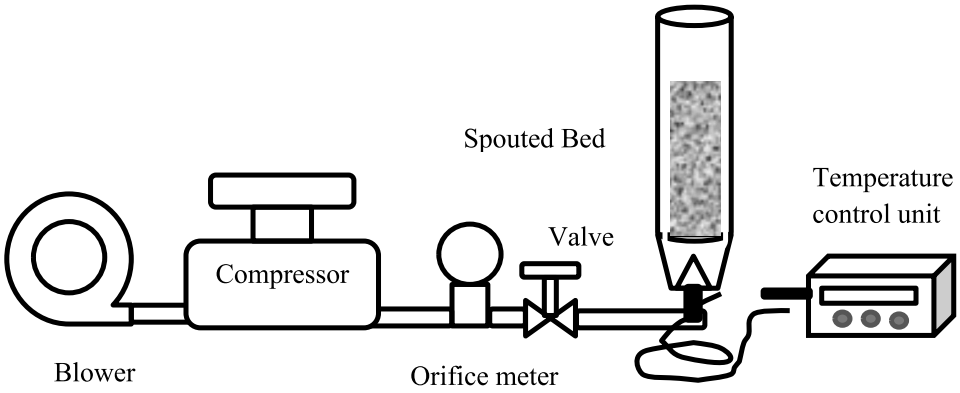

Figure 2. Spouted bed coating

3. Fluidized Bed Coating (FBC): The various types of substrates can be coated with top spray, bottom spray and tangential spray using fluidized bed coater provided with specially designed triaxial nozzles. The molten coat former is passed through central tube of nozzle edged by high pressure and low volume air valve. The both coaxial tubes are covered with large air space through heated automized air. The nozzle is normally fixed closed to the surface of substrate bed to reduce the distance so as to prevent congealing of molten mass before touching the substrate surface. The spray nozzle and tank with hot melt coating material is insulated to maintain uniform temperature throughout coating.

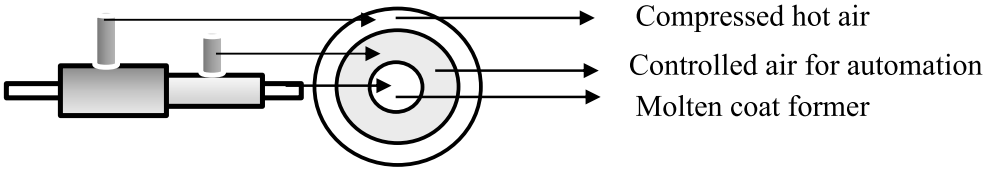

Figure 3. Modified nozzle for HMC for fluidized bed coating coater

Types of Fluidized Bed Coating:

3A. Top spray Fluidized Bed Coating

It is common, efficient and standard technique used for HMC of pellets, particles and granules. During the coating operation, upward moving substrates are coated with downward moving molten coating mass. The substrate temperature is kept below 10-20°C than the melting point of melting agent of coat former. It has limitation of fluidity and flow. The top spray coating involves three steps: i) melting of coat former, ii) spraying of melt over substrate and iii) congealing of coated substrate.

3B. Bottom Spray Fluidized Bed Coating: An alternate technique to top spray fluid bed coating that is employed for coating of small substrates like beads, granules, larger particles, pellets and spherules. This technique provides well-organized air and coating mass flow. It is effective for hot melt coating on small scale. The coating on large scale can be possible at the disbursement of PT/MP ratio.

Bottom spray coating instrument comprise of an air handling unit, distribution plate and spray nozzle at the bottom. The distribution plate is perforated plate that facilitates the uniform distribution of fluidizing substrate in the coating region by the virtue of large volume of air. When substrate is suspended in coating zone, the molten hot melt mass is sprayed over substrate and the coated substrate fall on peripheral part of coating zone on distribution disc. The disc used for HMC are more perforated and with higher hole diameter than the conventional solvent-based coating for providing more efficient air distribution. This will avoid agglomeration of substrate during coating. It the height of coating zone is doubled; the substrate coating will be reduced coating thickness.

The substrates with poor flowability such as larger particles and/or particles of higher density that are difficult to coat with the top spray technique, and hence, the bottom spray method should be preferred in that case. The add-on critical parameters associated with equipment includes the height of the partition area (determined by the size, density and the desired substrate speed), and the type of distribution disc, which is chosen according to the substrate nature (particles of 50 μm, pellets or tablets).[46]

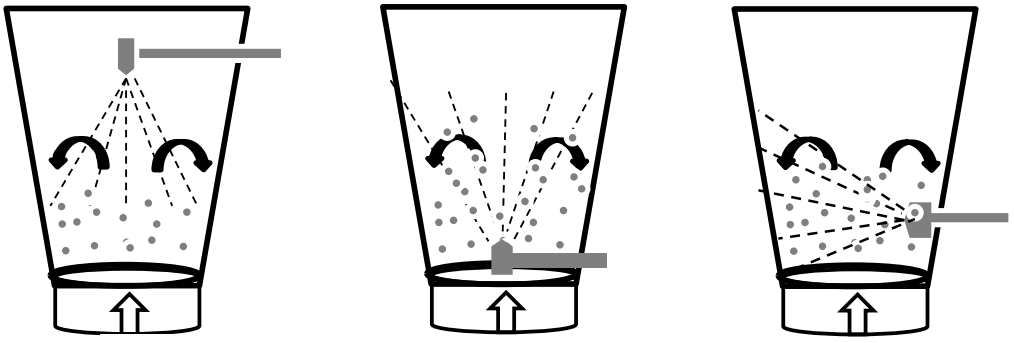

Figure 3: Types of (A) Top spray, (B) Bottom spray and (C)Tangential spray

3C. Tangential-spray fluid bed coating: It is an innovative fluid bed coating technique where the rotating dispersion disc is employed for spraying and smoothing of the coat. The higher coating levels are possible at expense of PT/MP ratio. It is mainly used to produce pellets by powder layering (alone, in suspension or in solution). The rotor system features the spray nozzle, which is located laterally to the substrate, and the rotating disk (rotor) based at the bottom of the tank. Three mechanical forces cause particle motion, mixing and granulation. The centrifugal force developed by the rotating disk projects the substrate to the periphery where the fluidization air suspends and particles gravimetrically fall back on the disk. The substrate is exposed to higher mechanical stress than former two fluidized bed coating techniques. Hence, the substrate that are highly resistant to these forces are well suited for this process. Similar to the top or bottom fluid bed systems, the spray nozzle is heated through compressed air and insulated to prevent re-melting of the lipid coat. However, as particle adhesion to the tank is likely the product temperature is kept lower compared to the top-spray system. This technique has limited coating capacity.

3D. Solid dispersion: The solid dispersion technique was acquainted by Kennedy et al which devoid of spraying process and hence nozzle spray system. Hence, method is least complicated. In this method, the substrate is combined with coating agent in the fluid bed chamber undergo four simple steps: (i) warming up of chamber, (ii) preheating core, (iii) coating agent melting & mixing other additives and (iv) spreading and congealing. But, the series of weak-points may be found in this process like conventional method. The cores and coating melt are kept into a chamber at high temperature is not feasible. It was reported that, the porosity and density of substrate affected reproducibility of the technique. When the nonpareil-sugar beads are used for coating tend to agglomerate, if the particle size is smaller than 40 mesh for coating agents PEG 1450-8000 and MPEG 2000 and 5000. For the uniform spreading of hot melt coating, the optimal viscosity of the coating agent is less than 300 centipoises. This technique allows coating up to 2.5-5% w/w. In fact, in real cases a higher percentage of coating is required to be deposited.

Kennedy et al., improved technique by coating the drug beads with two different coating agents by one by another. But he specified that the difference between melting points of two coating agents should be at least 15°C. In this respect, fluidized bed coaters are preferred for coating due to the inherent advantages of the technology such as high flowability of particulate materials, temperature homogeneity, more uniform coating due to very good solids mixing and lower process time due to high heat transfer.[27]

The quality of the fluidized bed coating can be assessed in both macroscopic and microscopic levels. In the former case, the production time, practical yield, energy consumption and material required are considered based on the coating performance. In the later case, the coating quality is characterized mainly as a function of two factors, coat uniformity, coat morphology and measured by both the standard achieved and its repeatability for properties or specifications of it, like appearance, assay of the active ingredient, dissolution profile, particle size distribution and shelf-life. The product yield is simply the ratio of the mass of the product which meets the required specifications to the total material mass used in the process. The difference represents the product losses that occur during coating. In the fluidized bed coating process, product losses, occurring generally due to improper process planning, are mainly composed of raw materials entraining out of the system before being coated and agglomerated particles whose particle size and specifications are not within the acceptable particle size range. It affects also the quality of the coating. Therefore, the correct planning and precise control of the process parameters is of paramount importance. However, this indeed is not an easy task as the fluidized bed coating process is a complex process with many interrelated process variables. As stated by Jones nearly 20 products and process variables are involved in the fluidized bed coating. These variables can be classified as apparatus variables, product variables and process variables. The instrument variables, such as geometry of the unit, distribution grid, spray nozzle characteristics, filter mechanism etc. are determined by the equipment used. Product variables depend on the formulation used.[47]

Scherzinger and Schmidt pointed that, the process parameters are the most important and easily variable parameters and knowledge and determination of these parameters is essential for achieving a controllable and successful process. Although, the fluidized bed coating process has been investigated and used in different industries for years, trial and error together with experience is still the most preferred method for determining the optimum values of these parameters in the pharmaceutical industry. Therefore, there is still limited number of studies in the literature on the investigation of the effect of the process variables on the performance of different fluidized bed systems. [48]

3E. Turbo Jet Coating: This process is adapted to coat solid particles by suspending them in a spiral of ascending air that provides the homogeneous distribution of individual particles. The molten lipid is dispersed from the bottom of the tank and tangential to the particle flow. Here, lipid crystallization within the nozzle expansion is prevented by a micro-environment surrounding the nozzle out-let.[49] The merit of this technique is its ability to suspend particles within the ascending air stream, allowing the coating of very fine particles.

4. Hot-melt coating by direct blending: It is the one of the simplest ways to make coat particles. This technique does not require complicated equipment, the obtained results are quite surprising and it can be applied for a wide range of different size substrates as well as multiple coated layers. The method comprises of five steps: (i) melting of coating agent, (ii) drug dissolution or dispersion of other excipients into molten coating, (iii) mixing of the substrate and molten coating agent, (iv) cooling with continued stirring of the mixture, and (v) congealing the coated particles. The active ingredient can be deposited in the core by a granulating method, and then coated out-side by a coating layer. The drug also can be dispersed into the coating agent and then the mixture is coated outside the coating core. Ready-made sugar beads of various sizes are commercially available.

Wax formulations for coating drug-loaded sugar beads have been investigated by Bhagwatwar and Bodmeier.[50] The sugar beads are homogenous in size and shape and easily adhere to waxes. The smaller the size of substrate, the larger is the surface area available for coating agent to deposit onto. In this technique, very small modification is done that is molten coating material contains less than 10% solvent.[51] Weight gain during coating can reach a high value. However, extremely tiny particles are likely to agglomerate which increases the variability of the coated beads mixing and coating must be appropriately controlled to avoid variability. To obtain high weight gains with readymade substrates, the process is most simple if the core has a large enough surface area but is not too small in size (so as to avoid agglomeration).

In other words, it is desirable that the coated beads contain a large amount of drug but the variability is reduced to a minimum value. For laboratory scale research projects, it was found that the size range of sugar beads 30-60 mesh work excellently. The coated beads then are loaded into hard gelatin capsules which are the final and complete dosage form. Coated beads may be used to compress into tablets, too. There are no documents that list waxes that should be applied in the coating process to obtain slow drug release. The reason behind that is the waxes with high molecular weight and hydrophobicity are likely to reduce the drug dissolution rate in water. Conversely, substances which are hydrophilic or increase the wetting characteristics of the drug are likely to increase the rate of drug dissolution like PEG. All the waxes need to be hard enough to congeal at room temperature.

Nifedipine is sensitive to light, yet there are no reports on the behavior of nifedipine at high temperature. Thus, it is obligatory to investigate carefully the stability of the active substance to heat. Moreover, sugar beads are made of sucrose which is easily burned at high temperature. So that, the limiting temperature is 100°C. Hot melt direct blending coating, involves application of a molten coating material onto beads or capsules in a heated tablet coating pan. In the hot-melt pan coating cetyl alcohol and Gelucire® (Gelucire) 50/13 were used as coating agents.[33]

Conclusions

In pharmaceutical industries, the safety and protection of the workers and environment are considered at highest priority along with drug product safety and efficacy. Therefore, now a day, industries are in the search of solvent free processes and production. HMC offers a novel and smart option to pharmaceutical manufacturers. HMC technique presents economic, easy, efficient, ecofriendly, and rapid technique in comparison to conventional coating methods where solvent evaporation, recovery and treatment can become very expensive, time consuming and may harm operators of industry and environment. Definitely, even if the spraying rate of coating agent is slower than conventional coating, but the HMC agents are not diluted with solvents, which results in higher and uniform application rates when compared to other techniques.

Furthermore, the equipments of choice for HMC are fluid bed coater and modified conventional coating pan. HMC provides several utility including modifications of drug release, reduces acidity of vitamins and few drugs, masking objectionable drug characteristics, (with immediate release obtained by the addition of surfactants to the lipid coating agent), drug protection and the lubrication of particles exhibiting a large specific surface area. However, the progress of these innovative systems remains more challenging than that of traditional methods and hence collective efforts progressively address the issue.

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Research Article

Improving Stability Of Sitagliptin Using Hot Melt Coating Technique

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ABSTRACT

Objective: To improve the stability of sitagliptin using hot melt coating technique. Method: Sitagliptin phosphate monohydrate (SPM) tablets were prepared using direct compression. They were coated with stearic acid and palmitic acid as hot melt coating agents using pan spray method under optimized coating conditions. The prepared tablets were evaluated for Pharmacopoeial specifications like appearance, thickness, hardness, weight variation, friability, disintegration test, drug content, weight gain, water uptake and in-vitro dissolution study. The uncoated sitagliptin tablets and coated sitagliptin tablets were placed at accelerate conditions for stability study. Results: The prepared tablets pass the tests as per United States Pharmacopoeia (USP). Formulation F8 having similar drug release profile as that of marketed formulation and follows the acceptance criteria as per United States Pharmacopoeia. F8 was found to be stable at accelerated conditions as per International Council of Harmonization (ICH) guidelines. No significant change in appearance, drug content and drug release were observed in the stability batch (F8S). Conclusion: The hot melt coating using hydrophobic agents can successfully improve the stability of sitagliptin phosphate monohydrate. And adding the pore formers in variable quantities in coating composition the target drug release profile can be tailored.

Keywords: Hot melt coating, Sitagliptin, Stearic acid, Palmitic acid, Stability, Water uptake

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INTRODUCTION

Diabetes is a chronic metabolic disease, arises due to inability of the pancreas to produce adequate quantities of insulin (Type 1 diabetes) or the inability of the body to utilize insulin efficiently (Type 2 diabetes) to regulate blood sugar levels. Uncontrolled diabetes results in high blood sugar, commonly referred to as hyperglycaemia, which can cause serious damage to many vital organs, especially the nerves, kidneys, eyes and blood vessels. In 2016, World Health Organization (WHO) estimated that the diabetes was the seventh major cause of global death burden, with approximately 1.6 million deaths resulting directly from diabetes. A 5% increase in premature mortality from diabetes was reported between 2000 and 2016.[1]

Sitagliptin, (7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl) butyl]-5,6,7,8-tetrahydro-3- (trifluoromethyl)-1,2,4-triazolo[4,3-a] pyrazine) is a potent, safe, effective and selective inhibitor of dipeptidyl peptidase-4 (DPP-4). It is prescribed as alone or in combination with other antihyperglycemic agents for the treatment of type 2 diabetes in adult patients. Sitagliptin is administered once daily. It has a low propensity for pharmacokinetic drug-drug interactions, with a very low potential to cause hypoglycaemia.[2]

Sitagliptin is available as the phosphate monohydrate, malate and tartrate salts in tablet dosage forms. The original innovator (Januvia® marketing authorization hold by Merck and Dohme Corporation) uses sitagliptin phosphate monohydrate (SPM).[3-5] The hydrate form was mostly preferred in the industry as hydrates are relatively stable. It is included in

Biopharmaceutical Classification System (BCS) class I was supported by various regularity bodies.[6-9] It was approved in 2006 by the Food and Drug Administration (FDA).[10,11] It was undergoes decomposition at the faster rate in presence of water and ultraviolet light.[12-14]

Applying the melted excipient, which are usually a lipid, on a solid substrate needs no evaporation or drying phase, and there is no risk of solvent exposure. Subsequently, this leads to a more cost-effective and environment friendly process. [15, 16]. To obtain HMC layer, usually only one excipient would suffice. The most widely used excipients for HMC are lipids of vegetable origin, most of them with Generally Recognized as Safe (GRAS) status and approved for oral use.[16] The driving force for the implementation of HMC is to evade the use of solvents and all the resulting constrains of their use.[17, 18] Therefore, pan coaters, fluid beds and spouted beds can be adapted to atomize molten coating formulations, and coat diverse substrates from drug crystals to tablets or capsules. [19-22]

Hence an attempt was made to improve the stability of sitagliptin phosphate monohydrate by coating with hot melt coating technique using hydrophobic coating agents like stearic acid and palmitic acid.[23-25]

MATERIALS AND METHODS

MATERIALS

Sitagliptin phosphate monohydrate was a kind gift sample obtained from Cadila Pharmaceutical Limited, India. Stearic acid, palmitic acid, and titanium dioxide were purchased from S.D. Fine Chemicals, India. All other materials used were of laboratory and analytical grade.

METHODS

Preparations of SPM core tablets: Each tablet containing 65 mg of sitagliptin phosphate monohydrate equivalent to 50 mg of sitagliptin base were prepared by direct compression. All the ingredients were weighed accurately and transferred to double cone blender to mix geometrically **(Table 1)**. The mixing was performed after addition of each ingredient for 7 min. The mixed bulk was taken out and characterized for various precompression parameters. The hardness of tablets was maintained at about 5 kg/cm^2. The tablet compression was carried out using 10 station rotary tablet machine with 6 mm standard biconvex circular punches.[26]

Table 1. Formulation of SPM Core

Sr. No.	Ingredient	Quantity per Tablet (mg)
1.	Sitagliptin phosphate monohydrate	65
2.	Dicalcium phosphate	53
3.	Sodium starch glycolate	2
4.	Talc	2
5.	PEG 8000	2
6.	Aerosil	1
	Tablet weight	125 mg

Coating of SPM core tablets

Four hundred SPM tablet core were loaded in coating pan. Hot melt coating composition was maintained at 80°C. The coating variables are shown in **(Table 2).** The tablet cores were rolled in pan until tablet bed temperature was attained 60°C temperature. The molten stearic acid and palmitic acid were used as hot melt coating agents. Alpha-tocopherol was used as oil soluble antioxidant and Polyethylene glycol 4000 (PEG 4000) was employed as pore former to achieve immediate release. The molten coating mass was sprayed onto the rolling SPM tablets in slow stream. The coated tablets were allowed to roll further for 15 min by reducing the tablet bed temperature gradually. Tablets were then removed and cured in a dryer for 24 h.[27]

Table 2. Coating variables for SPM Core

Sr. No.	Coating parameters	Tablets 400 (50 g)
1.	Spray rate	1.5 ml/min
2.	Atomizing air pressure	15 psig
3.	Tablet bed temperature	40-65°C
4.	Pan diameter	10 inches
5.	Pan speed	40-60 rpm
6.	Air flow	80-120 cfm
7.	Inlet air temperature	35- 45°C
8.	Outlet air temperature	40- 60°C
9.	Number of baffles	4 radially arranged
10.	Relative humidity	40%
11.	Curing temperature	24 h at 25 °C

Table 3. Formulation of Hot Melt Coating Composition

Sr. No.	Composition	F1	F2	F3	F4	F5	F6	F7	F8
1.	Stearic acid	5	4.75	4.5	4.25	--	--		
2.	Palmitic acid	--	--	--	--	4.00	3.75	3.5	3.25
3.	PEG 4000	--	0.25	0.5	0.75	--	0.25	0.5	0.75
4.	Titanium dioxide	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
5.	α-tocopherol	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
All weights were taken in mg									

Evaluation of Tablets

Appearance

The tablet cores were visually observed for any capping, chipping and lamination. The coated tablets were also checked for coating defects.[28]

Thickness

The thickness of a tablet is the only dimensional variable related to the process. Thickness of individual tablets was measured by a micrometre screw gauge. Tablet thickness should be controlled within ± 5 % variation of a standard. Average thickness and standard deviation were calculated.[29]

Hardness

The Monsanto tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet and zero reading was taken. The upper plunger was then forced against a spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture was recorded in kilogram. For each formulation the hardness values for 6 tablets were determined and recorded.[29]

Weight Variation Test

We have selected 20 tablets of SPM, which were weighed individually and collectively. The average weight was calculated and compare the individual tablet weight. The tablet passes the USP test if not more than 2 tablets are outside the percentage limit and if number of tablets differs by more than 2 times the percentage limit then test fails.[30,31]

The weight variation was calculated using the formula –

Weight variation (%) = (Initial weight - Average weight)/Average weight × 100.

Friability Test

As per USP, the friability test was performed by placing previously weighed 6.5 g tablets in the Roche friabilator and operating for 100 revolutions at 25 rpm. The test checks the tendency of the tablet to crumble, chip, or break upon abrasion or compression and sturdiness of a tablet, and a loss of 1% tablet mass is acceptable during the process.[32]

Disintegration Test

Six tablets from each batch were randomly selected and one tablet was placed in each tube with a mesh size with basket as per USP standards. The basket was placed in 1liter beaker containing phosphate buffer solution of distilled at 37±2°C. One disc was placed in each tube and disintegration apparatus was operated at 29-32 cpm. When all the particles passed from each test tube into the beaker, the time was noted as the disintegration time. This disintegration test was a quantitative test.[32]

Weight gain (%)

Weight gain by tablet is one of the most important parameters monitored during formulation, process and scale up development. Weight gain was calculated from the difference in the tablet weight before and after coating.[33]

In-vitro dissolution study

In-vitro dissolution of marketed film coated tablets of sitagliptin phosphate monohydrate was conducted to select the equivalent formulation from the prepared formulations. The in-vitro dissolution study of prepared formulation was carried out using following dissolution study conditions (**Table 4**). In-vitro dissolution of six marketed tablets and prepared tablets.[34, 35]

Table 4. In-vitro dissolution study conditions

Sr. No.	Parameter	Specifications
1.	Dissolution apparatus	USP XXV Type II (Paddle)
2.	Paddle speed	50 rpm
3.	Temperature	37± 0.5°C
4.	Time	1 h
5.	Dissolution medium	Phosphate buffer pH 6.8
6.	Volume of dissolution medium	900 ml
7.	Sample volume	1 ml
8.	Sampling time	5, 10, 15, 30, 45 and 60 min
9.	Dilution factor	20

The sample solutions were passed through membrane filter paper (0.45 µm) and suitably diluted with 6.8 pH phosphate buffer and solutions were analyzed at 267 nm by UV Spectrophotometer.

Drug content

Twenty tablets from each formulation were selected for the estimation of drug content. The tablets were weighed, triturated and transferred the powder into 100 ml volumetric flask containing 50 ml of 0.01N HCL. The content of the flask was filtered through a membrane filter and kept in a 100 ml volumetric flask. The residue was washed with another 40 ml of 0.01N HCL and the volume was made up to the mark. The sample was suitably diluted and analyzed spectrophotometrically against blank (0.01N HCL) at 267 nm using double beam UV- visible spectrophotometer.[36]

Moisture Uptake

Both coated and uncoated tablets are evaluated for their moisture uptake by placing in a desiccator containing saturated potassium chloride solution (80% RH). According to the USP, for equilibrium moisture uptake determined, by weighing sample every hour until achievement of consecutive readings corresponding to a recorded mass change of less than 0.25%.[37]

2.5.4 Stability study

The uncoated tablets and coated tablets (selected formulation) were stored at the conditions as per directed by ICH guidelines in Alu Alu blister packing and stored at 25±2°C & 60±5% RH and 40±2°C & 75±5% RH. They were compared for organoleptic properties, drug content and in-vitro drug release after every month up to 3 months and at 6 months.[38]

RESULTS AND DISCUSSION

Preparation of SPM Tablets

For the preparation of the SPM tablets, the dicalcium phosphate was used as directly compressible diluent. It is a type of inorganic water insoluble diluent. The PEG 8000 was used as water soluble lubricant; talc was used as anti-adherent and silicon dioxide was used as glidant. The bulk powder was characterized for flow properties and precompression parameters were determined and recorded **(Table 5)**.

Table 5. Precompression parameters for bulk powder

Sr. No.	Parameter	Observed value	Remark
1	Angle of repose (°) *	24°.18’	Good
2	Bulk density (g/ml) $	0.877 ± 0.014	--
3	Tapped density (g/ml) $	1.021 ± 0.009	--
4	Carr’s Index (%) $	14.10 ± 0.011	Good
5	Hausner Ratio$	1.165 ± 0.003	Good

Where, * and $ indicates values in mean and mean± SD for triplicate determination respectively.

The angle of repose for bulk was found to be 24°.18’ (between 20-30°) indicates good flow property. The Carr index and Hausner ratio values were between 11-15 and 1.12- 1.18 respectively indicates good flow properties and compressibility. The tablets were successfully prepared by direct compression using ten station rotatory tablet compression machine using 6 mm diameter standard biconcave circular punches. The hardness was adjusted to 5 kg/cm^2. The prepared tablet cores were evaluated for quality control tests and results were recorded in **Table 6**.

2.6.15 Preparation of coated SPM Tablets

The prepared tablet cores were coated successfully using hot melt coating agents as per the coating composition and using coating parameters.

The coated tablets were evaluated for quality control tests.

Evaluation of SPM coated tablets

Appearance

The tablet cores and coated tablets were visually observed for defects. No tablet defects were observed. Biconvex circular tablets & cores with slightly yellowish white to yellowish colour and characteristic odour were successfully prepared by direct compression.

Weight Variation Test

All the tablet prepared uncoated tablets and coated tablets shows weight within the official limits as per USP, it passes the weight variation test **(Table 6)**.

Hardness

The force required to break the tablet was recorded using Monsanto tester in kilogram **(Table 6)**. From each formulation 6 tablets were used for the determination of hardness and the mean ± SD were reported. All coated SPM tablets and SPM tablet core were passing the test for hardness as per USP.

Thickness

Tablet thickness was determined using micrometre screw gauge and the average thickness ± standard deviation of tablets was reported. The thickness of SPM uncoated tablet was found to be 2.83±0.011 mm. The thickness of SPM coated tablets was found in the range of 2.84 ±0.012 to 2.91±0.021 mm. All coated SPM tablets and SPM tablet core were passing the test for thickness **(Table 6)** indicating suitability for packaging.

Friability Test

During friability test the % weight loss from SPM uncoated tablets was found to be 0.32% and for hot melt coated tablets the value ranges from 0.13 to 0.18% indicates coating prevent weight loss from tablets during test and provide strength to the tablets.

Disintegration Test

The disintegration time for uncoated and coated tablets was found to be less than 14 min. **(Table 6)** indicates all formulations passes the disintegration test as per USP. As the coating level increases the disintegration time also increases **(Table 6)**.

Drug content

It is used as gold standard test for dosage form because it affects safety and efficacy of drug product. The drug content in SPM core tablets was found to be 99.29 ±1.39% and SPM coated tablets was found in the range of 98.32 ±2.62 to 100.21±2.15%. They were found to be within acceptable limit as per USP **(Table 6).**

Moisture Uptake

The water uptake by SPM tablet core when placed in desiccator containing saturated solution of potassium chloride was found to be 0.38 ±0.09%. The water uptake by SPM coated tablets was recorded in the range of 0.09 ±0.01 to 0.13 ±0.03% **(Table 6)**. As the level of stearic acid or palmitic acid in coating composition increases, the water uptake decreases. As the concentration PEG in coating composition increases water uptake increases.

Table 6. Evaluation of SPM uncoated and coated tablets

Parameter	Core	F1	F2	F3	F4	F5	F6	F7	F8
Weight variation (mg)*	124.12±0.18	130.45±0.19	129.36±1.04	130.27±0.43	129.42±2.29	131.34±1.18	128.87±2.35	132.04±1.08	129.43±0.18
Thickness (mm)[@]	2.83±0.011	2.91±0.013	2.89 ±0.008	2.90 ±0.011	2.84 ±0.016	2.89 ±0.009	2.84 ±0.012	2.87 ±0.018	2.91±0.021
Hardness (kg/cm^2) [@]	5.0±0.2	5.2±0.10	5.1±0.15	5.0±0.2	4.8±0.15	5.1±0.2	5.0±0.10	5.0±0.2	4.9±0.15
Weight gain[@] (%)	--	4.94	3.49	4.21	3.54	5.07	3.09	5.63	3.54
Disintegration time (min) [@]	5	13	10	7	5	14	10	7	4
Friability (%) [$]	0.32	0.15	0.17	0.20	0.18	0.13	0.14	0.13	0.16
Drug content (%) *	99.29 ±1.39	99.87±2.91	100.21±2.15	98.93 ±3.11	99.06 ±0.73	98.76±2.65	100.11±1.13	99.57±2.68	98.32 ±2.62
Moisture uptake (%) [@]	0.38 ±0.09	0.09 ±0.01	0.10 ±0.01	0.12 ±0.02	0.13 ±0.03	0.05 ±0.01	0.07 ±0.02	0.08±0.03	0.11 ±0.03

Where, *, [@] and [$] indicates sample size (n) 20, 06 and 10 respectively.

In-vitro dissolution study of marketed products

Acceptance criteria reported in USP describe that not less than 80% of labelled amount should release in 30 min and not less than 90% of labelled amount should release in 45 min. The in-vitro dissolution test of marketed samples, Sitenali® & Jankey® were conducted and as per acceptance criteria given in USP reference tablets passes the test. Hence the same conditions were used for the in-vitro dissolution of prepared formulations **(Figure 1)**.

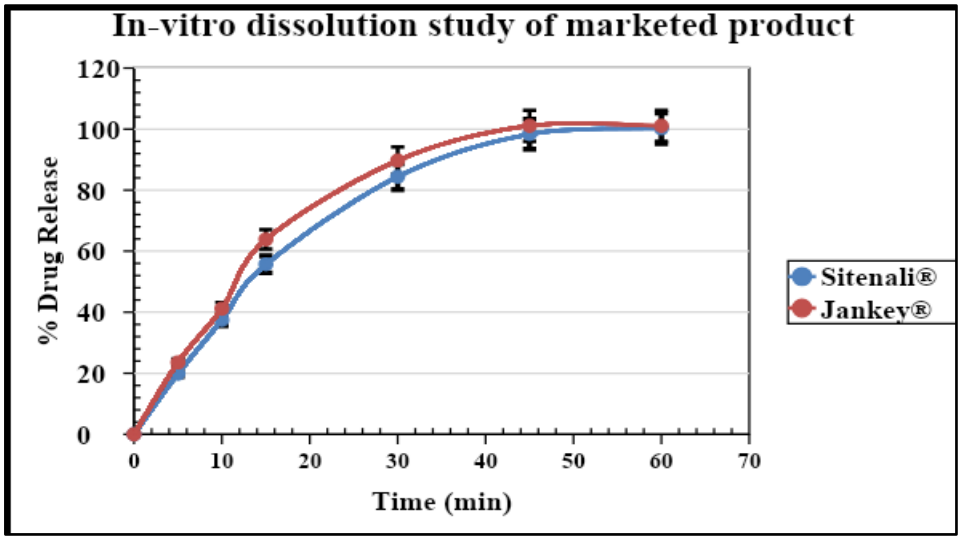

Figure 1. In-vitro dissolution study of marketed products.

In-vitro dissolution test of prepared SPM tablets

In-vitro dissolution test was conducted and SPM tablets coated with stearic acid is shown in **Figure 2**. As stearic acid level in the coating composition increases drug release decreases proportionally. Formulation F4 follows the acceptance criteria as per USP and hence selected as best formulation. The SPM core tablets release more than 90% drug within 15 min.

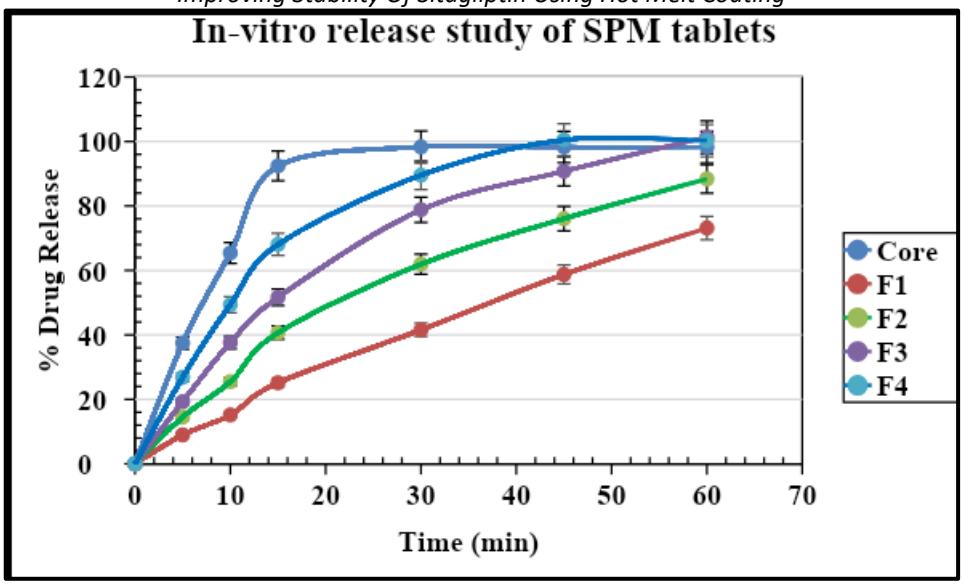

Figure 2. In-vitro release study of SPM uncoated tablet and stearic acid coated tablets

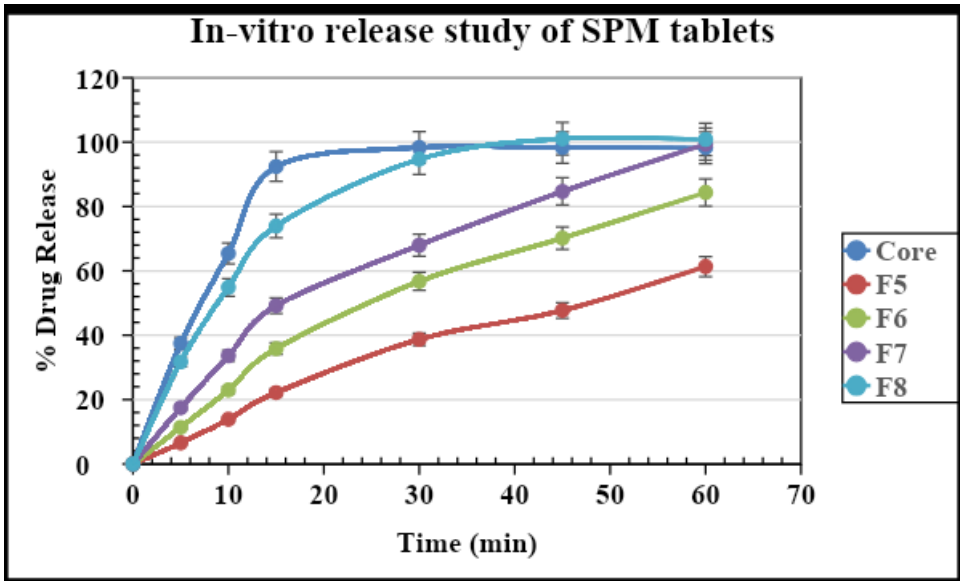

Figure 3. In-vitro release study of SPM uncoated tablet and palmitic acid coated tablets

In-vitro dissolution test conducted SPM tablet core and SPM tablets coated with palmitic acid is shown in **Figure 3**. As palmitic acid level in the coating composition increases drug release decreases proportionally. Formulation F8 follows the acceptance criteria as per USP and hence was selected as best formulation. F8 formulation releases more than 80% drug in 30 min and more than 90% drug in 45 min.

Formulation F8 shows smoother surface and low water uptake value than formulation F4. The in-vitro drug release profile from F8 was found to be faster than F4 formulation. Therefore, it was compared with innovator product (Jankey) whose release profile closer to F8 formulations as shown in Figure 4 and which was confirmed by calculating similarity factor (f_2) and difference factor (f_1). The similarity factor (f_2) and difference factor (f_1) for F8 formulation was found to be 56 and 15 respectively when compared with innovator product (Jankey). Hence F8 was considered as best formulation for stability study.[39]

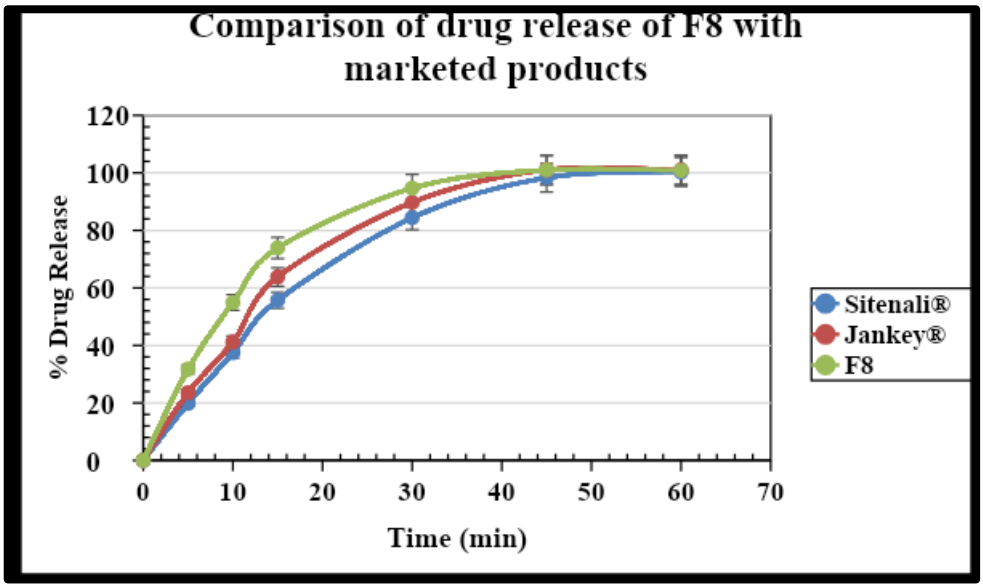

Figure 4: Comparison of F8 drug release with marketed products

Stability study

The drug content of SPM uncoated tablets was found to be significantly affected at accelerated conditions as per ICH guidelines **(Table 7).** It was found that drug content in F8 formulation was found to be within significant limit. It shows that the hot melt coating enhances the stability of SPM in coated tablets. Further it was confirmed by performing in-vitro drug release study.

Table 7. Drug content in SPM uncoated tablets and F8 tablets stored for stability

Storage period	Drug Content (%)			
	25±2°C & 60±5% RH		40 ± 2°C & 75 ± 5% RH	
	Tablet core	F8	Tablet core	F8
Initial	99.29 ±1.39	98.32 ±2.62	99.29 ±1.39	98.32 ±2.62
1 Month	98.81 ±0.96	98.24± 1.57	97.86 ±1.32	97.92± 0.67
2 Months	97.92 ±2.18	98.09 ± 2.11	95.38±2.32	97.39 ± 1.18
3 Months	96.58 ±2.43	97.78 ± 2.08	92.71 ±1.03	97.07± 1.52
6 Months	95.86 ±1.89	97.14 ± 1.74	90.47 ±2.41	96.53 ±0.89

Where, values shown were as mean ± SD for triplicate determination.

The colour of the uncoated tablets was found to be change from white to off-white. In case of coated tablets, the colour of coated tablet was retained as yellowish white due to palmitic acid in coating composition **(Table 8)**.

Table 8: Appearance of SPM uncoated tablets and F8 tablets stored for stability

Storage period	Appearance			
	25±2°C & 60±5% RH		40 ± 2°C & 75 ± 5% RH	
	Tablet core	F8	Tablet core	F8
Initial	White	Yellowish white	White	Yellowish white
1 Month	Slightly off-white	Yellowish white	Off-white	Yellowish white
2 Months	Slightly off-white	Yellowish white	Off-white	Yellowish white
3 Months	Off-white	Yellowish white	Off-white	Yellowish white
6 Months	Off-white	Yellowish white	Off-white	Yellowish white

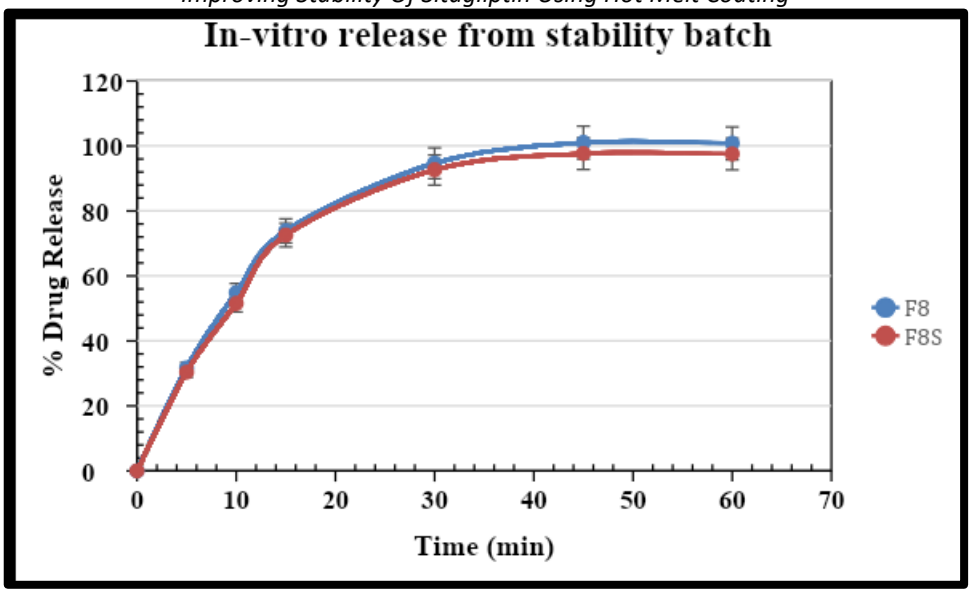

Figure 5. In-vitro release from stability batch

The in-vitro drug release from F8 formulation on the day of preparation was compared with stability batch stored at accelerated conditions (40 ± 2°C & 75 ± 5% RH) after 6 months. No significant change in drug release was observed indicates F8 formulation was found to be stable **(Figure 5)**. And after application of hot melt coating with hydrophobic coating agent like palmitic acid can protect core from moisture and resist the absorption of moisture by sitagliptin phosphate monohydrate and hence improve the stability.

CONCLUSIONS

The sitagliptin phosphate monohydrate was reported as moisture sensitive drug. It was recommended as safe drug in the type 2 diabetes for adults with low incidences of side effects when given orally. Both stearic acid and palmitic acid shown good hot melt coating agent ability. The tablets were prepared by direct compression successfully and coated with stearic acid and palmitic acid independently. The tailored release can be achieved by fabricating the series of formulations. Hot melt coated tablets pass the Pharmacopoeial tests as per United State Pharmacopoeia. The water uptake test demonstrates that hot melt coating with these hydrophobic agents reduce the moisture uptake. The formulation F8 drug release profile was found to be similar with marketed product (Jankey). Formulation F8 was found to be stable as per ICH guidelines for 6 months accelerated stability study. The hot melt coating retains the drug contain than uncoated sitagliptin tablets indicating improving the stability of sitagliptin. Further in-vivo study needs to be carried out before launching the product to market.

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