CHAPTER – I

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].

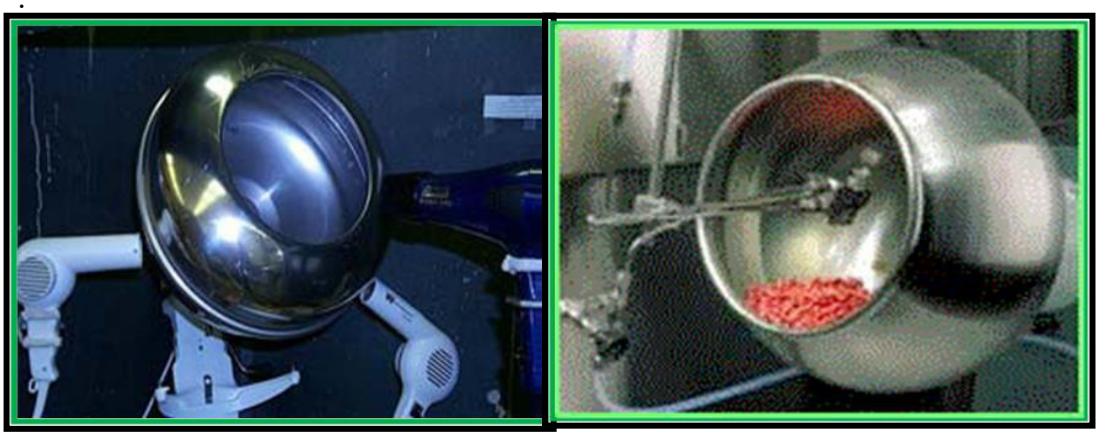
1.5 Hot Melt Coating Equipment

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

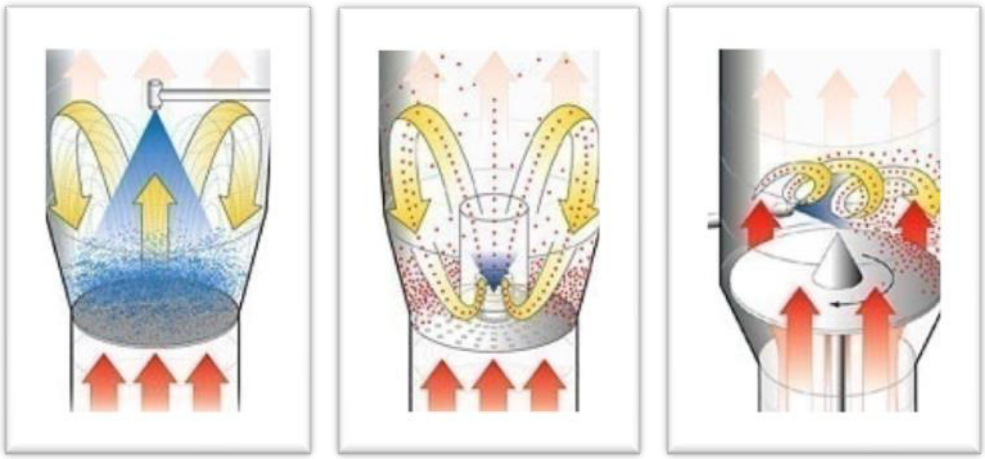
The basic fluid dynamic properties for tablet spouting were obtained using a prismatic spouted bed setup. The equipment was made of clear acrylic glass with two horizontal and adjustable gas inlets. The coating was applied at the maximum spouted bed height, with an air flow rate 40% higher than the lowest 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].

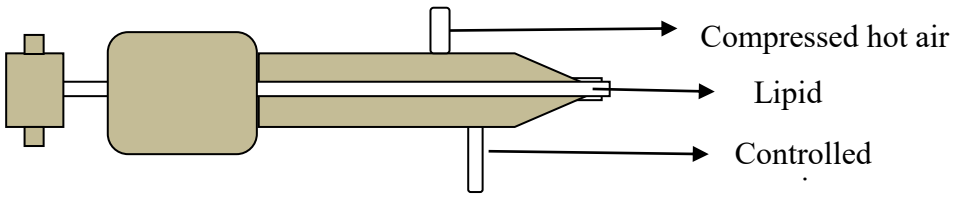


Fig. 1.3: Nozzle for Hot Melt Coating

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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