PUBLICATIONS

Section A-Research paper
ISSN 2063-5346

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]

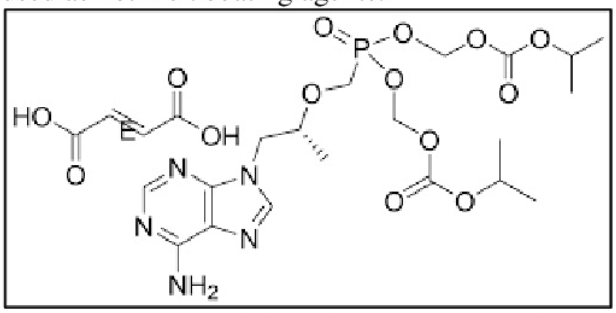

Figure 1: Structure of Tenofovir disoproxil fumarate

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).

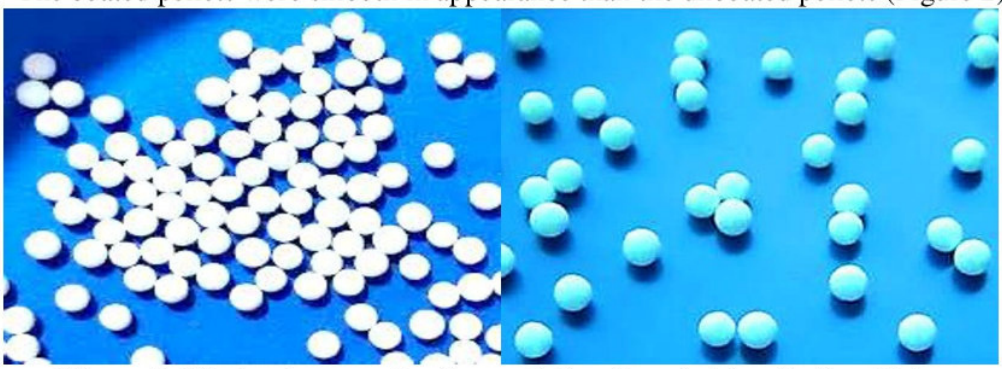

Figure 2: Photomicrograph of uncoated and coated tenofovir pellets.

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

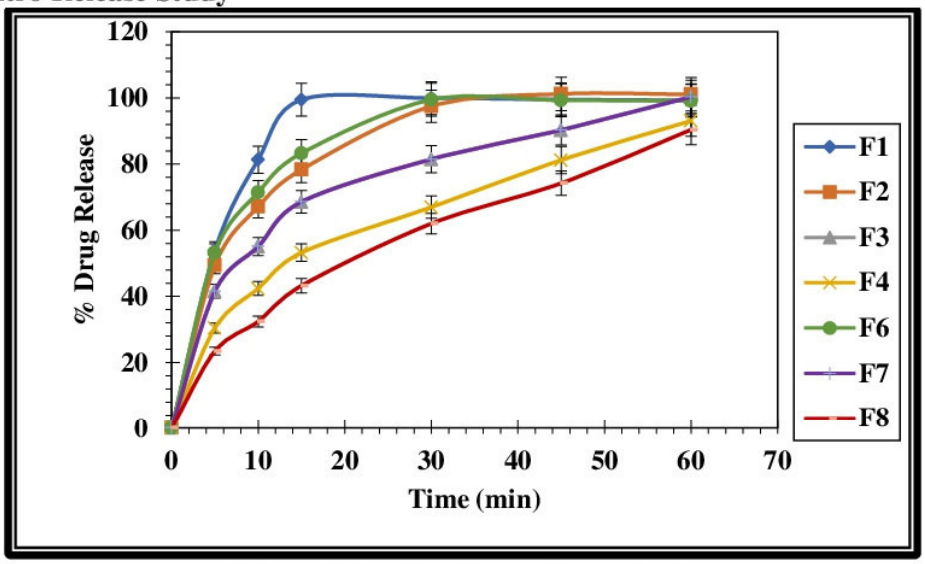

Figure 3 In-vitro drug release study

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.

Acknowledgement: Authors thanks the management and the Principal of Satara College of Pharmacy, Satara for providing the facilities to perform the research work.

Conflict of Intrest: Nil

Source of Support: Not declared

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Latin American Journal of Pharmacy
(formerly *Acta Farmacéutica Bonaerense*)

Lat. Am. J. Pharm. **43** (4): (2024)

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]

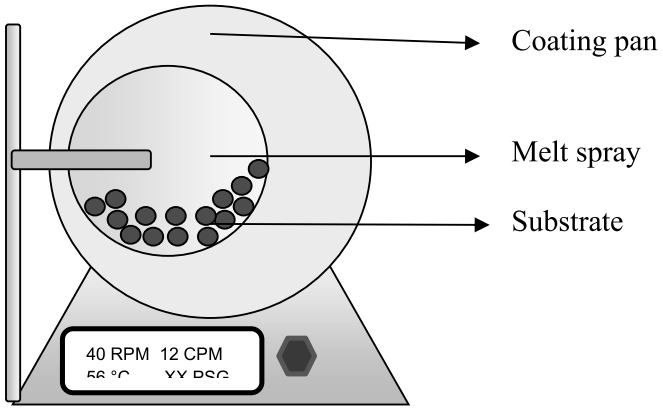

Fig.1 Pan coating.

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]

$$Coating\ efficiency\ (\%) = \frac{Final\ weight\ of\ coated\ core - Initial\ weight\ of\ core}{Coating\ material\ loaded} \times 100$$

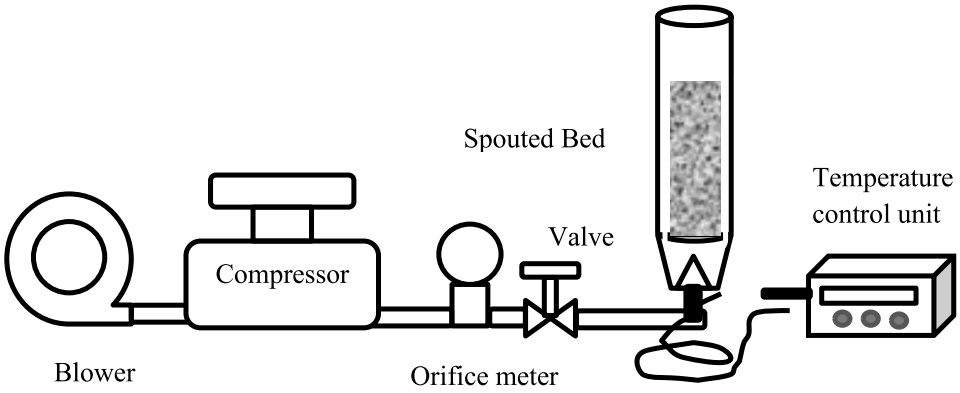

Figure 2. Spouted bed coating

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.

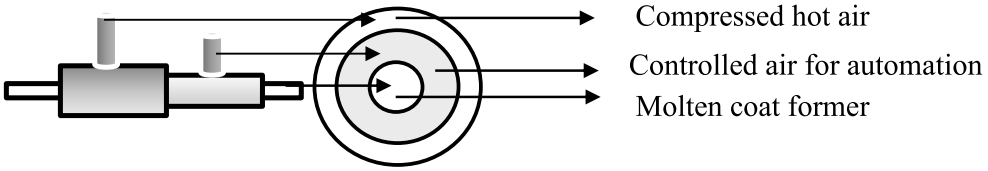

Figure 3. Modified nozzle for HMC for fluidized bed coating coater

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]

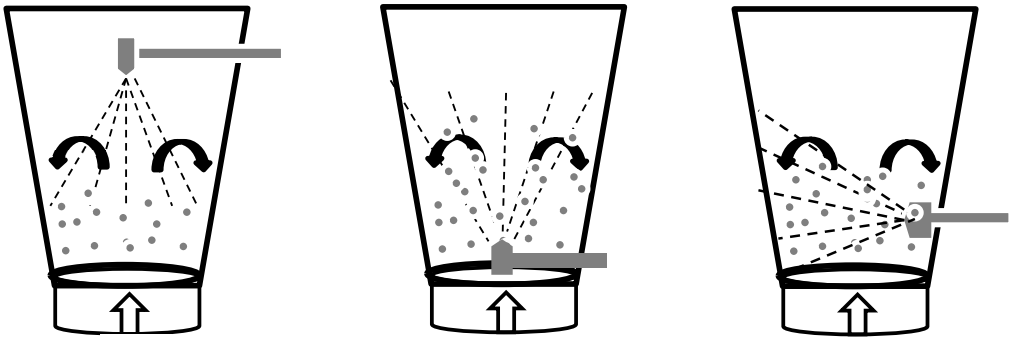

Figure 3: Types of (A) Top spray, (B) Bottom spray and (C)Tangential spray

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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Afr. J. Biomed. Res. Vol. 27 (September 2024); 110-118

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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Receiving Date: 10/07/2024 Acceptance Date: 20/08/2024

DOI: https://doi.org/10.53555/AJBR.v27i1S.1319

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)**.

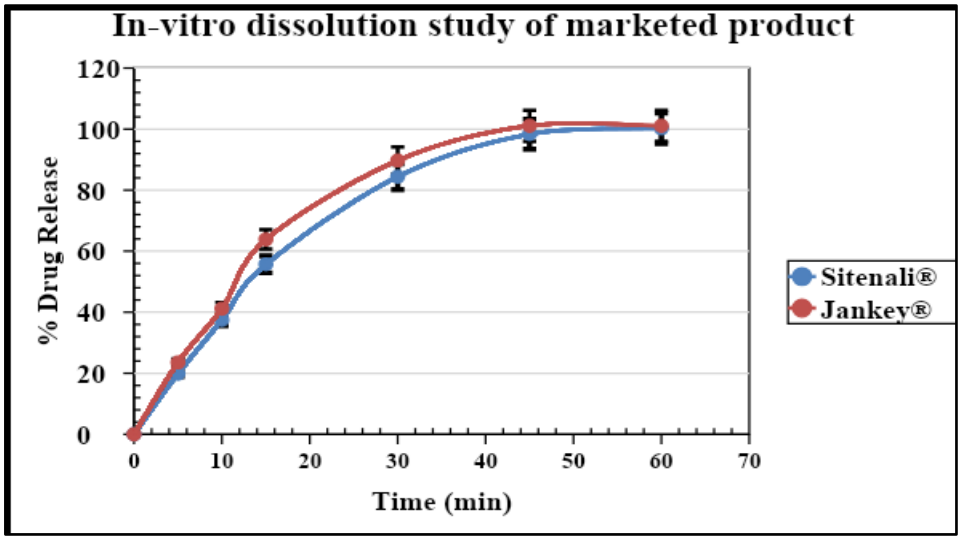

Figure 1. In-vitro dissolution study of marketed products.

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.

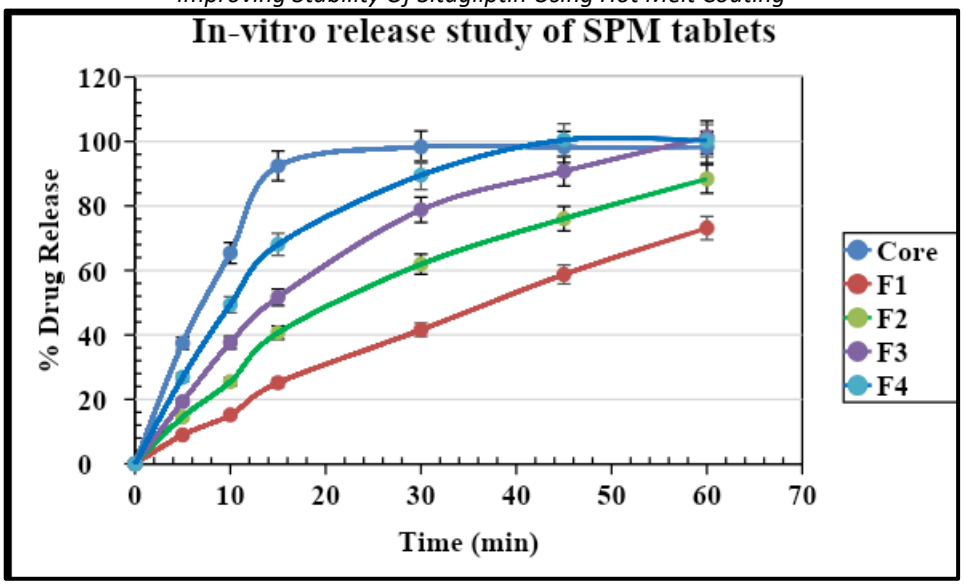

Figure 2. In-vitro release study of SPM uncoated tablet and stearic acid coated tablets

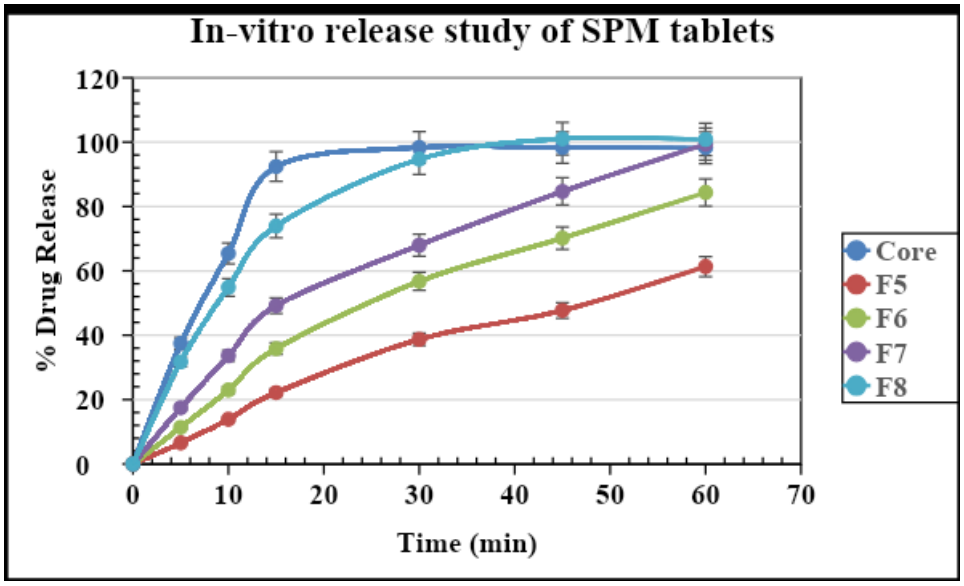

Figure 3. In-vitro release study of SPM uncoated tablet and palmitic acid coated tablets

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]

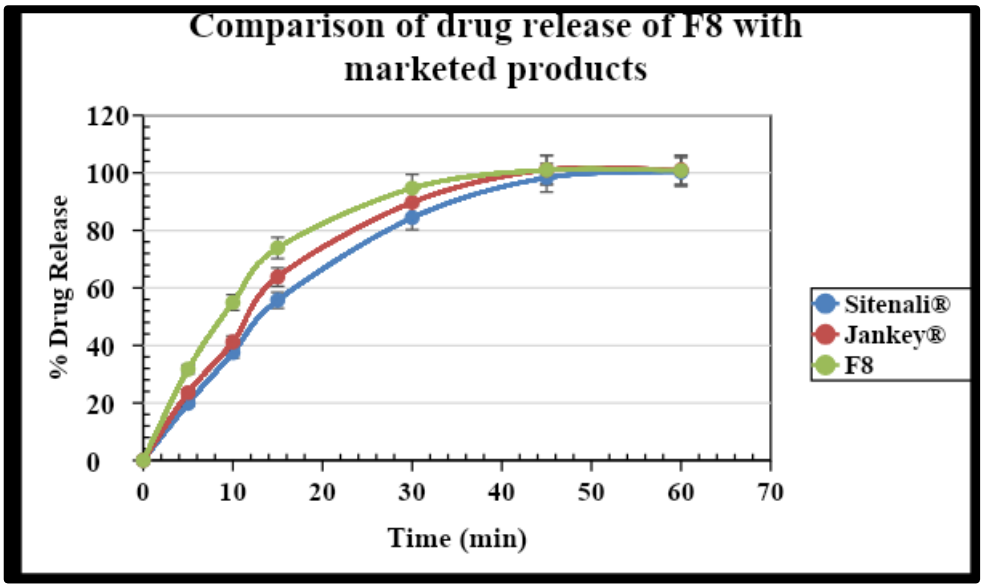

Figure 4: Comparison of F8 drug release with marketed products

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

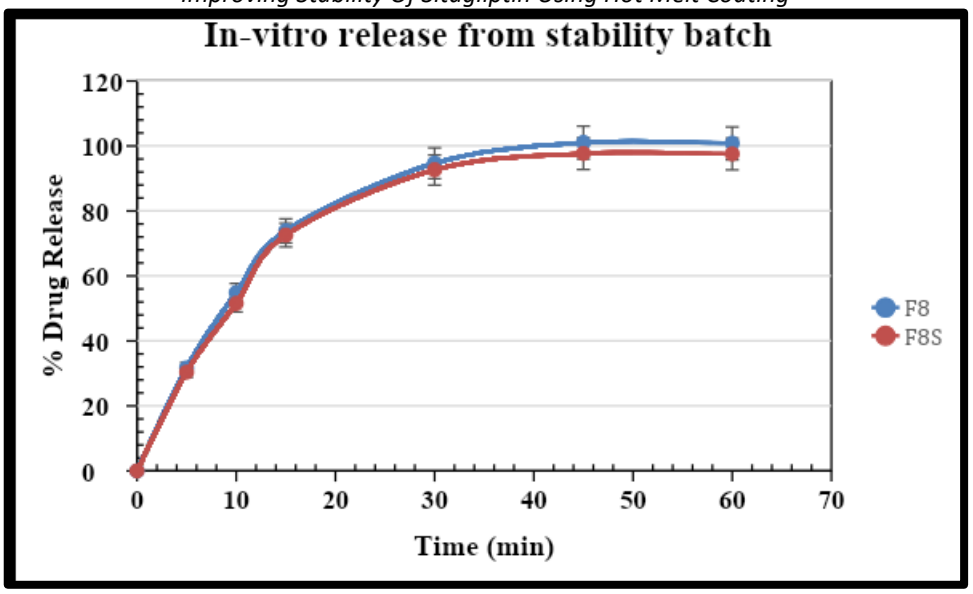

Figure 5. In-vitro release from stability batch

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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Acknowledgement: Authors thanks Gaurishankar Education Society's Satara College of Pharmacy, Satara and Dr. Rajendra Gode College of Pharmacy, Amravati for providing support to conduct the research work.

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