Section A-Research paper
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Exploring Taste Masking Potential of Hot Melt Coating Technique

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Abstract

In the present investigation, the hot melt coating technique has been assessed for its taste masking potential of tenofovir. Drug was fabricated into pellets by extrusion and spheronization method and coated with using Gelucire 43/01 and Precirol. The prepared pellets were evaluated for flowability, physicochemical properties and taste masking ability. Taste masking ability of technique was characterized by spectrophotometric and taste panel methods. The coated pellets were with good to excellent flowing ability and acceptable physicochemical properties. The threshold bitterness of drug was found to be 250 µg/ml. All the coated pellet formulations mask the bitter taste for minimum first 1-1.5 min indicating completely masking of the drug taste. Taste masking evaluation of pellets indicates that 80% volunteer reported slight bitter taste at 2% w/w level of hot melt coating agent and 3 & 5% w/w coating levels were qualified to mask the bitter taste. Both Precirol and Gelucire 43/01 shows excellent taste masking potential for masking taste of tenofovir.

Keywords: Tenofovir, Threshold bitterness, Precirol, Gelucire 43/01, Hot melt coating, Panel method

1. Introduction

The drugs are available in two types of dosage forms in the market namely solids or liquids. The solid dosage form includes beads, capsules, pellets, spherules, tablets, etc. The solids are most popular because they need low storage and transportation space cost. They are more stable than liquid dosage forms. They are frequently coated for numerous reasons, masking unwanted organoleptic properties, protection from environmental factors, protection from destruction by biological fluid of body, enhanced mechanical strength, improve aesthetic value, enhance flowing ability and achieve tailored drug release.[1]

Generally, the coating agents, pigments and excipients are dissolved or dispersed in a suitable solvent and sprayed over substrate and dried until smooth layer is formed. The coating is generally performed in fluidized bed coater for particulate systems or perforated pan coater for single unit systems. [2,3] Presently the solid dosage forms are coated by either aqueous and non-aqueous coating. The liquid coating can attain remarkably even smooth lustrous coating surface. Despite of that the aqueous coating may cause hydrolysis of few drugs and increase the microbial burden over the dosage form leads to decrease in the drug stability. The aqueous coating needs more time for drying and consume more energy. For non-aqueous

coating of dosage forms using organic solvents leads environmental pollution, solvent recycling cost and operator safety issues. [4] The organic solvents are generally than aqueous solvent costly.

The U.S. Environmental Protection Agency (EPA) in 1970 enforced the Clean Air act to reduce atmospheric solvent emissions.[5] In 1976, the Occupational Safety and Health Administration (OSHA) restricts the utility organic solvents to avoid exposure of industrial workers.[6] To circumvent the problems associated with use of solvents, the attempt was made to use the hot melt coating (HMC) technique.[7] The hot melt coating is solvent free technique where the drug and excipients are dissolved or dispersed in the molten material of interest and poured or sprayed on the substrate surface.[8, 9] The substrate like beads, capsules, microcapsules, minitablets, pellets and tablets can be coated using pan coating or fluidized bed coating[6,7]. The materials used for HMC technique are generally waxes. The waxes are generally cheaper as compared to the polymers employed in solvent-based coating. The great versatility of waxes in terms of their solubility and safety.[9] The literature shows that HMC is having wide variety of applications in the drug delivery systems.[10]

Tenofovir, is an acyclic phosphonate nucleotide analogue and base form of prodrug tenofovir disoproxil fumarate (TDF) used in combination with other antiretroviral drugs for the treatment of adult patients infected with HIV (Figure 1). The recommended dosage regimen of TDF is presented as once daily due primarily to its long biological half-life.[11,12] Tenofovir base has aqueous solubility of ~5 mg/mL in aqueous medium, the solubility of the prodrug TDF is ~2.5-fold higher at 13.4 mg/mL.[13,14] But the bitter taste of TDF reduces the patient compliance.[15] Hence, the objective of the present investigation was to assess the taste masking ability of HMC technique using a model drug, Tenofovir. The Gelucire 43/01 and Precitol ATO 5 were used as hot melt coating agents.[16]

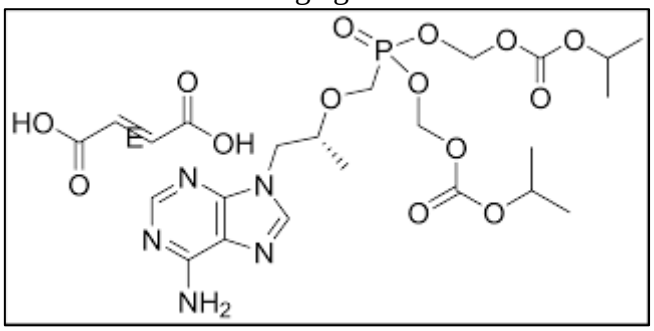

Figure 1: Structure of Tenofovir disoproxil fumarate

2. Materials and Methods

2.1 Materials

Tenofovir is a kind gift sample received from Mylan Laboratories Ltd., Aurangabad (MS), India. The Gelucire 43/01 and Precitol ATO 5 were free sample receive from Gattefose SAS, 69804 Saint-Prist Cedex, France. All other chemicals were of laboratory grade and used as received.

2.2 Methods

2.2.1 Preparation of Drug Pellets

TDF and excipients were blended in a double cone blender for 5 min. The Polyvinyl pyrrolidone solution (2% w/v) was poured slowly over powder blend. The cohesive mass was formed (Table 1). The mass was passed through 16 meshes to form extrudates. The wet extrudates charged into the extruder- spheronizer (Umang Pharmatek, India) and the spheronizer with cross-hatch plate of 1.2 mm was operated for 5 min at 850 rpm to produce TDF pellets.[17, 18] The pellets were dried at 60°C for 3 h and sifted to collect 16-20 mesh fractions.

Table 1. Formulation of TDF batches

Ingredient & Formulation code	F1	F2	F3	F4	F5	F6	F7	F8
Tenofovir disoproxil fumarate	300	300	300	300	300	300	300	300
Avicel PH 101	25	25	25	25	--	--	--	--
Spray dried lactose	--	--	--	--	25	25	25	25
Polyvinyl Pyrrolidone solution (2% w/v)	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
Coating composition								
Gelucire® 43/01	--	2	3	5	--	--	--	--
Precitol® ATO 5	--	--	--	--	--	2	3	5
α- Tocopherol	--	1	1	1	--	1	1	1

2.1.2 Hot Melt Coating of Pellets

The undersize and oversize pellets were rejected. TDF pellets were loaded into 10 inches diameter perforated coating pan equipped with 4 radially organized baffles and temperature regulation system. The drug pellets were rolled until pellet bed temperature of 60°C was attained. The molten Gelucire 43/01 and Precitol ATO 5 were used as coating materials. The molten coating mass was sprayed onto the rolling drug pellets in a slow stream. After the complete application of coating mass, the pellets were allowed to roll further for 10 min during which time the bed temperature was allowed to gradually come down. The pellets were then removed and cured in a dryer for 48 h.[19] The parameters employed for HMC of tenofovir pellets in coating pan are given in Table 2.

Table 2: Process parameters for hot melt coating[19, 20]

Parameter	Setting
Pellet weight	500 g
Pellet fraction	16 -20 mesh
Pan speed	20 rpm
Coating level	2, 3 and 5% w/w
Pellet bed temperature	60°C
Relative humidity	40% RH
Coating time	30 min
Curing time	30°C for 24 h

2.1.3 Evaluation of the Pellets

2.1.3.1 Pellet appearance

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

2.1.3.2 Mean Pellet Size (d_{mean})

The average size of pellets was carried out using sieving analysis technique. A sieve shaker and set of four active standard test sieves (#14, #16, #18 and #20) were used for the analysis.[19] Accurately weighed 100 g of drug pellets were placed in sieve arranged over decreasing order of aperture size from top to bottom. The sieve shaker was shaken for 5 min. The size distribution of pellets expresses the efficiency of the process of manufacture the uniform size pellets. The mean pellet size was calculated.

2.1.3.3 Angle of Repose (θ)

Accurately weighed 50 g of drug pellets were poured gently through glass funnel on a simple graph paper and encircle the pile circumference occupied by pellets.[19] The height (h) and radius (r) of the pile were recorded & angle of repose (θ) values were calculated.[20]

$$\text{Tan } \theta = (h/r)$$[21]

2.1.3.4 Bulk Density (ρ_b)

Bulk density is ratio of bulk weight and bulk volume. Accurately weighed 50 g of tenofovir coated pellet fraction of 16/20 mesh were poured gently through glass funnel into 100 ml calibrated measuring cylinder.[19] The surface was cautiously levelled with null pressure. The volume occupied by pellets was used for calculation of bulk density (g/ml). [21]

$$\rho b = (M/ V_b)$$

Where, ρb = bulk density, M = weight of the sample, and V_b = apparent volume of sample.

2.1.3.5 Tapped Density (ρ_t)

Bulk density is ratio of bulk weight and tapped volume. Tapped density was estimated in a similar way to that of bulk density. However, final volume was measured after tapping the cylinder from 3 inches until constant volume was obtained using Electrolab tapped density apparatus. The volume occupied by pellets after tapping was noted and tapped density (g/ml) was calculated. [19]

$$\rho t = (M/ Vt)$$

Where, ρt = tapped density, M = weight of the sample, and Vt = tapped volume of sample.

2.1.3.6 Carr Index (CI)

The external appearance of pellets and internal structure can alter material properties and porosity that greatly effect on pellet coating, flow and packing during tabletting or capsule filling. It also shows effect on drug release by affecting the capillary action of dissolved drug.[22] Using bulk density and tapped density values of tenofovir coated pellets the compressibility index can be calculated.[19]

2.1.3.7 Hauser Ratio (HR)

The bulk density and tapped density data were used for HR calculation.[8,9]

2.1.3.8 Hardness and Friability

The hardness tenofovir pellets was determined by Veego digital dial type hardness tester (Veego Scientific, India).[22] For the friability study, accurately weighed 10.0 g of tenofovir coated pellets (initial weight) with 25 glass beads of 3 mm diameter were placed in the revolving drum of Roche's friabilator (Veego Scientific, India) for 100 revolutions operated at 25 rpm speed.[19] The pellets were collected and placed on the sieve with 0.85 mm aperture and the smaller particles were allowed to pass through the sieve. The pellets were reweighed (Final weight) and % weight loss data were considered as % friability. [19]

2.1.3.9 Drug Content

Accurately weighed 500 mg of hot-melt coated pellets were grind carefully in the mortar. A total of 50 mg of this powder was transferred carefully to 100 ml volumetric flask and add 30 ml of methanol and ultrasonicated using laboratory sonicator (ISP Technologies, India) for 15 min to extract the tenofovir. Final volume was made with double distilled water and diluted suitably.[19] The diluted sample were scanned at 260 nm using double distilled water as blank using Ultraviolet- visible (UV) spectrophotometer (UV1800, Shimadzu, Japan). The drug content was calculated.[23]

2.1.3.10 In-vitro Dissolution

In-vitro release from tenofovir pellets was carried out using United States Pharmacopoeia (USP) XXV apparatus I (Basket Type), model Electrolab, 6 vessel assembly at 100 rpm. The dissolution medium consisted of 900 ml of double distilled water for 1 h at 37 ± 0.5°C and 5ml aliquots were withdrawn at predetermined time intervals.[24] An equivalent amount of fresh dissolution fluid equilibrated. Aliquots were diluted suitably, filtered and analyzed. All release studies were conducted in triplicate and the mean values were plotted versus time with a standard deviation less than three indicating reproducibility of result. The percent cumulative drug release against time was plotted. [19]

2.1.3.8.11 In-vitro Taste Evaluation

Hot melt coated pellets equivalent to 50 mg of drug were placed in test tube containing 10 ml of double distilled water maintained at 37±1°C, stirred gently to simulate conditions of mouth cavity. After every 30 sec collect aliquot of 1 ml and replace with fresh medium maintained at 37±1°C. Each aliquot was diluted to 100 ml and the absorbance of diluted solution was recorded at 260 nm using UV-visible spectrophotometer. Taste evaluation was performed for 10 min.[25]

2.1.3.12 Determination of Threshold Bitter Taste

To taste the sensory bitter taste of drug twelve human volunteers were selected and coded. They were asked to thoroughly rinse the mouth cavity with purified water. The dilutions of drug concentration range 50-500 µg/ml were prepared. Each volunteer was informed to hold 5 ml solution for 10 min and spat out. The volunteers were asked to rinse the mouth cavity with purified water after every treatment to avoid carryover effect of previous treatment. The score of bitterness given to each solution against the distilled water was recorded. The minimum concentration which was judged as bitter taste by volunteer was considered as bitter threshold. [26, 27]

2.1.3.13 Taste Panel Method

To taste the bitter taste of and efficacy of hot melt coating for taste masking of drug twelve human volunteers were selected. They were asked to thoroughly rinse the mouth cavity with purified water. They were provided with the 50 mg of pellets over tongue for 10 sec. Taking the taste of pure drug solution as standard, the degree of bitterness was judged by volunteers according to bitterness scale.[28]

2.1.3.14 Stability Test

The pellets equivalent to unit dose were filled hard gelatin capsule shells of '000' size and placed in amber coloured bottles and wrapped with aluminum foils. They were stored at temperature 40 ± 2°C and relative humidity (RH) 75 ± 5% for 3 months in the stability chamber (Remi Laboratory Instrument, CHM-6). The pellets were evaluated for any changes in physical appearance and percent drug content after every month.[19] Result obtained was compared with data obtained at zero time and pellets stored at 28±2°C and 42±2% RH.[29, 30]

3. Results and Discussion

The coating was performed with ease and rapidly. The percent yield of coated pellets was excellent as no agglomeration was observed.[22] This may be due to non-tacky nature of coating composition that facilitated free rolling of pellets.

3.1 Surface Morphology

The pellets prepared by extrusion and spheronization were spherical in shape and uniform in size.[22] The coated pellets were smooth in appearance than the uncoated pellets (Figure 2).

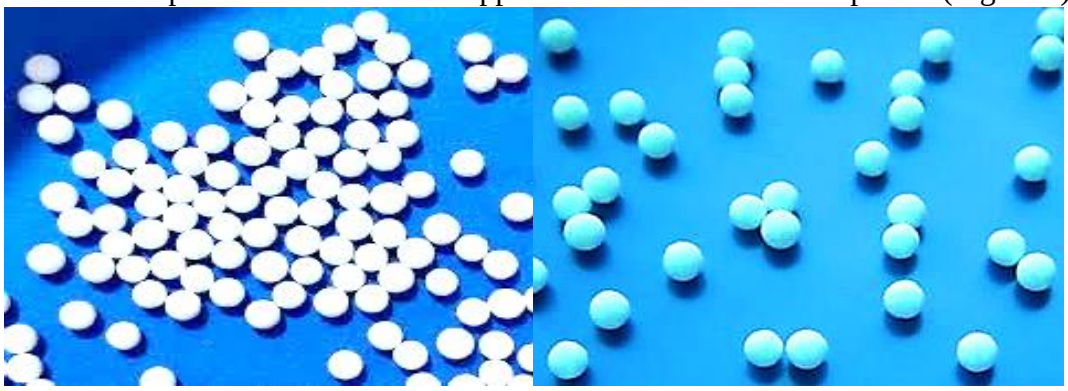

Figure 2: Photomicrograph of uncoated and coated tenofovir pellets.

3.2 Flowability of Pellets

The angle of repose values of uncoated pellets was found to be 26.38° and 27.92° indicates good flowability.[19] The angle of repose value for coated pellets was found to be in the range of 18.26° to 23.88° indicates good to excellent flowability of coated pellets than uncoated pellets. [31] With increase in the coating level the imperfections on pellet surface were found to decrease (Table 3).

The bulk density and tapped density of the uncoated pellets, formulation F1 were found to be 0.714 ± 0.002 and 0.787 ± 0.002 g/ml respectively. The bulk density and tapped density of the uncoated pellets, formulation F5 were found to be 0.698 ± 0.003 and 0.786 ± 0.002 g/ml respectively. The bulk density of coated formulations was range from 0.723 ± 0.001 to 0.764 ± 0.001 g/ml. The tapped density of coated formulations was range from 0.723 ± 0.001 to 0.764 ± 0.001 g/ml (Table 3).[19]

The Hausner ratio for formulation F1 and F5 were found to be 1.102 ± 0.002 and 1.126 ± 0.001 indicates good to excellent flowability. The coating of pellets reduce the Hausner ratio of pellets indicates improvement in flowing ability due to coating (Table 3). The Carr index for formulation F1 and F5 were found to be 9.275 ± 0.002 and 11.195 ±0.001 indicates good to excellent flowability. The results show that as the coating level increase from 2% towards 5% the Carr index value decreases. The coated pellet formulation shows excellent flowing ability (Table 3). [32]

Table 3: Flowability of coated and uncoated tenofovir pellets

Formulation Code	Angle of Repose† (°)	Bulk Density* (g/ml)	Tapped Density* (g/ml)	Carr Index* (%)	Hausner Ratio
F1	26.38	0.714 ± 0.002	0.787 ± 0.002	9.275 ± 0.002	1.102 ± 0.002
F2	23.88	0.723 ± 0.001	0.789 ± 0.001	8.365 ± 0.001	1.091 ± 0.003
F3	21.92	0.753 ± 0.001	0.807 ± 0.003	6.691 ± 0.002	1.072 ± 0.004
F4	19.71	0.749 ± 0.003	0.798 ± 0.002	6.210 ± 0.002	1.065 ± 0.001
F5	27.92	0.698 ± 0.003	0.786 ± 0.002	11.195 ±0.001	1.126 ± 0.001
F6	19.63	0.761 ± 0.003	0.813 ± 0.004	6.396 ± 0.004	1.068 ± 0.003
F7	18.26	0.757 ± 0.002	0.803 ± 0.003	5.728 ± 0.003	1.061 ± 0.003
F8	18.34	0.764 ± 0.001	0.816 ± 0.003	6.372 ± 0.001	1.068 ± 0.001

Where * and † indicates value in (Mean ± S.D.) and mean respectively where sample were analyzed in triplicate.[33]

3.3 Physicochemical Properties of Pellets: The pellets were with narrow size distribution and the mean size of pellets was range from 852 to 890 µm. The pellets were with acceptable crushing strength (±0.5 kg/cm^2) and friability (< 1%). The drug content was found to be within acceptable limits (Table 4).[34]

Table 4: Physicochemical properties of coated and uncoated tenofovir pellets

Formulation Code	Mean size† (µm)	Hardness* (kg/cm^2)	Friability* (%)	Drug content* (%)
F1	852	2.65 ± 0.05	0.248 ± 0.001	98.86 ± 1.26
F2	858	2.80 ± 0.10	0.232 ± 0.002	100.26 ± 2.06
F3	867	3.05 ± 0.05	0.168 ± 0.001	99.54 ± 0.84
F4	880	3.10 ± 0.10	0.215 ± 0.003	101.35 ± 1.98
F5	863	3.10 ± 0.15	0.228 ± 0.004	99.02 ± 3.13
F6	879	3.05 ± 0.15	0.235 ± 0.003	98.91 ± 0.57
F7	885	2.45 ± 0.10	0.358 ± 0.005	100.65 ± 2.53
F8	890	3.05 ± 0.10	0.228 ± 0.004	98.68 ± 0.21

Where * and † indicates value in (Mean ± S.D.) and mean respectively where sample were analyzed

in triplicate.[33]

3.4 In-vitro Release Study

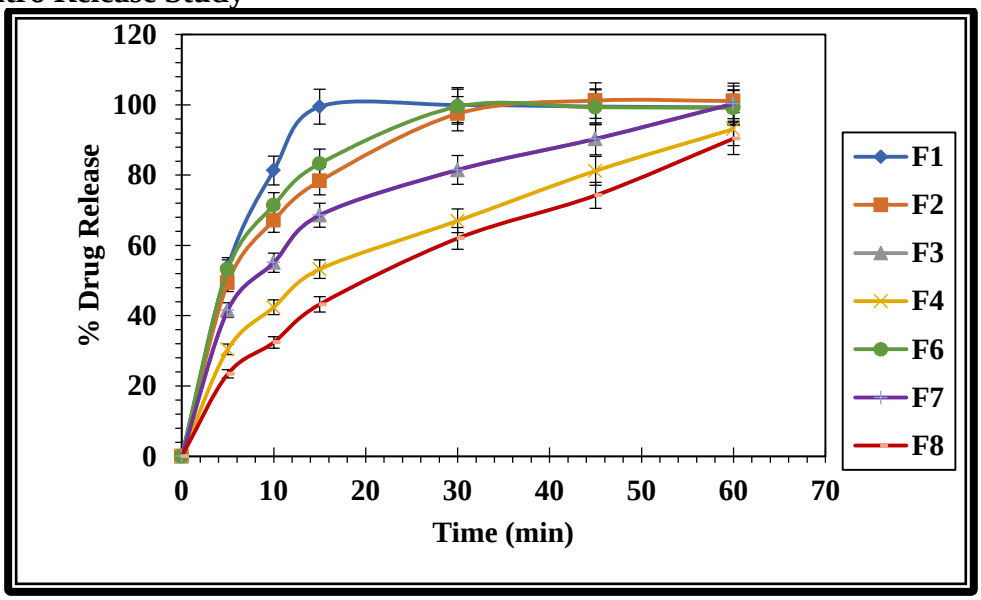

Figure 3 In-vitro drug release study

The in-vitro drug release was found to be dependent upon coating composition and coating level dependent. With increase in the coating level, the drug release decreases. Formulation F3 and F7 shows complete release in 30 min. The 5% coating level release drug very slow than the required.[35]

3.5 Threshold Bitter Taste Determination

The threshold bitterness of drug was found to be 250 µg/ml.[36]

3.5 In-vitro Taste Evaluation

The in-vitro taste evaluation of pellet formulation shows that the pellets coated with 2% w/w of HMC were unable to mask the bitter taste of pellets as the absorption of UV light was observed from 30 sec.[16] The 3% w/w coating level Gelucire 43/01 and Precirol can able to mask the bitter taste of pellets since the solution does not show UV light absorption in first half minute. The 5% w/w coating level Gelucire 43/01 and Precirol shows no UV light absorption in 10 min. It indicates the 3% w/w coating level Gelucire 43/01 and Precirol can able to mask the bitter taste while 5% w/w coating level delay the disintegration time of pellets and may affect rate of drug absorption through gastrointestinal tract (Table 5).

Table 5: In-vitro taste masking of pellets

Formulation Code	Time (min)							
	0.5	1.0	1.5	2.0	2.5	3.0	5.0	10.0
F1	+	+	+	+	+	+	+	+
F2	-	-	+	+	+	+	+	+
F3	-	-	-	-	+	+	+	+
F4	-	-	-	-	-	-	-	-
F5	+	+	+	+	+	+	+	+
F6	-	-	-	+	+	+	+	+
F7	-	-	-	-	+	+	+	+
F8	-	-	-	-	-	-	-	-

Where, + = UV absorbance and - = No UV absorbance

3.6 Panel Method

The volunteer study shows that uncoated pellets were found very bitter than the standard solution. The pellets coated with 2% w/w of Gelucire 43/01 and Precirol were unable to mask

the bitter taste of pellets. About 3% w/w of Gelucire 43/01 and Precirol were able to mask the bitter taste of pellets (Table 6).[36]

Table 6: Taste masking evaluation of pellets

Formulation Code	Volunteer Code							
	V_1	V_2	V_3	V_4	V_5	V_6	V_7	V_8
F1	++++	++++	++++	++++	++++	++++	++++	++++
F2	+	+	+	+	+	++	+	++
F3	-	-	-	-	-	-	-	-
F4	-	-	-	-	-	-	-	-
F5	+++++	+++++	+++++	+++++	+++++	+++++	+++++	+++++
F6	+	+	++	+	+	+	+	+
F7	-	-	-	-	-	-	-	-
F8	-	-	-	-	-	-	-	-

Where, +++++ = very-very bitter, ++++ = very bitter, +++ = moderately bitter, ++ = bitter, + = slightly bitter and – = tasteless.

3.7 Stability Test

The F7 pellet formulation stored at 28±2°C & 60±5% RH and 40 ± 2°C & 75 ± 5% RH [29, 30] shows drug content 100.23 ± 1.98% and 99.79 ± 2.11% respectively. The F7 pellet formulation stored as per ICH guidelines were found to be stable as there were no significant changes was observed after 3 months in drug content and physical appearance in the optimized formulation.

4. Conclusions

From the present investigation, it can be concluded that both the hot melt coating agents employed are equally efficient to mask the bitter taste of the tenofovir disoproxil fumarate by hot-melt coating technique. The coating level above 3% w/w was found to be sufficient to achieve the objective. The HMC technique is rapid, competent, economic and eco-friendly for taste. The present technique can be suitable for other drugs to overcome their disagreeable organoleptic properties. But proper preformulation, formulation development, preclinical studies, clinical studies and regulatory approval will be essential before launching product into market.

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Conflict of Intrest: Nil

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