Research Article

Formulation and Evaluation of Taste Masked Oro-dispersible Tablets of an Anti-HIV Drug

Arifa Begum. Shaik*[1], Rajini. Gongati[2], Padmalatha. Kantamneni[3]

*[1]Department of Pharmaceutics, Chalapathi Institute of Pharmaceutical Sciences, Chalapathi Nagar, Lam, Guntur, Andhra Pradesh, India.
[2]Department of Pharmaceutics, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada, Andhra Pradesh, India.
[3]Department of Pharmacology, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada, Andhra Pradesh, India.
***Corresponding author's E-mail:** arifashaik2007@gmail.com

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ABSTRACT

Tenofovir disoproxil fumarate is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. Tenofovir exhibits activity against HIV-1 reverse transcriptase. Tenofovir disoproxil fumarate is the water soluble (BCS class – III drug) diester prodrug of the active ingredient tenofovir. The oral bioavailability in fasted patients is approximately 25%. The drug is incompletely absorbed from gastrointestinal tract. Formulation of tenofovir disoproxil fumarate into an oro-dispersible dosage form can provide fast relief with greater bioavailability. The bitter taste of drug should be masked in order to formulate it in a palatable form. In the current research work, an attempt was made to mask the bitter taste of tenofovir by complexation technique, with a formulation into oro-dispersible tablets, using superdisintegrants sodium starch glycolate (SSG), crospovidone (CP) and croscarmellose sodium (CCS) in different concentrations. The complexes of tenofovir disoproxil fumarate with β-cyclodextrin were prepared by co-grounding method in various drug: complex ratios. The prepared solid inclusion complexes were analysed for taste masking and characterized by FT-IR. Using the optimized drug: β-cyclodextrin complex (1:1 molar ratio), oro-dispersible tablets were prepared and evaluated for thickness, weight variation, hardness, friability, drug content, wetting time, water absorption ratio, *in vitro* dispersion time, *in vitro* disintegration time and *in vitro* dissolution rate. The maximum drug release of 99.85% was obtained from the formulation F6 containing the highest concentration of CP and therefore formulation F6 was considered as the optimized formulation.

Keywords: Tenofovir disoproxil fumarate, β-cyclodextrin, Taste-masking, Co-grounding, Oro-dispersible tablets.

INTRODUCTION

Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is the difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis.[1]

For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Orodispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people. Fast dissolving tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, Orodispersible tablets, porous tablets, quick dissolving etc.[2]

Cyclodextrins are cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity. On account of their relatively hydrophobic interiors, CDs have the ability to form inclusion complexes with a wide range of substrates.[3] This complex-forming ability of CD have been widely exploited in the pharmaceutical field for various applications, including taste-masking of bitter drugs.[4-6] The use of CD as a taste-masking agent has been widely reported.[7-9]

Tenofovir disoproxil fumarate (a prodrug of tenofovir) which is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. *In vivo* tenofovir disoproxil fumarate is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Tenofovir exhibits activity against HIV-1 reverse transcriptase. Tenofovir disoproxil fumarate is the water soluble (BCS class – III drug) diester prodrug of the active ingredient tenofovir. The oral bioavailability in fasted patients is approximately 25%.[10] The drug is incompletely absorbed from gastrointestinal tract, hence there is a need to develop a suitable formulation of tenofovir disoproxil fumarate to improve its bioavailability. When a single oral dose (300 mg) is given to HIV-1 infected subjects in the fasted state, the maximum serum concentration was achieved in 1.0 ± 0.4 h (T_{max}).

Tenofovir disoproxil fumarate is a drug with bitter taste. Complexation with β-CD will mask the bitter taste of tenofovir disoproxil fumarate. It would be advantageous to formulate taste masked, orodispersible tablets of

tenofovir disoproxil fumarate to overcome the problems of its bitter taste and low oral bioavailability due to low permeability. The formulation of orodispersible tablets will show rapid onset of action with improved oral bioavailability.

The objective of the current research was to develop an oral patient friendly taste masked orodispersible tablets of an anti-HIV drug, tenofovir disoproxil fumarate using cyclodextrin and superdisintegrants by direct compression method with rapid dissolution and improved bioavailability.

MATERIALS AND METHODS

MATERIALS

Tenofovir disoproxil fumarate was received as a gift sample from Hetero Drugs Pvt. Ltd., Hyderabad, India. Sodium starch glycolate was purchased from Loba Chemie Pvt., Ltd. Crosscarmellose sodium, Flavour and Talc were obtained from Nice Chemicals Pvt., Ltd. Aspertame, Mannitol and β-cyclodextrin were procured from Himedia Laboratories Pvt., Ltd. Crospovidone and Magnesium stearate were obtained from Oxford Laboratories Pvt., Ltd.

METHODS

Drug - Excipients Compatibility Studies

Fourier Transformation Infra-Red (FTIR) Analysis[11]

The objective of the compatibility study was to determine the compatibility of the drug and the polymer or excipients. An FT-IR spectrophotometer was used for infrared analysis of samples. About 4-5 mg of sample was mixed with dry potassium bromide (KBr) and the sample was examined at transmission mode over the wave number range of 4000 cm^{-1} - 400 cm^{-1}.

Formulation Development

Calibration of Standard Curve of Tenofovir Disproxil Fumarate

Preparation of Standard Graph

100 mg of tenofovir disoproxil fumarate was weighed accurately and dissolved in 100 ml of phosphate buffer, pH 6.8 in 100 ml volumetric flask. The resulting solution had a concentration of 1 mg/ml (1000 µg/ml). From the stock solution, 10 ml of stock solution was further diluted to make up to 100 ml using 6.8 pH phosphate buffer with concentration 100 µg/ml. Different aliquots of 1 ml, 2 ml, 3 ml, 4 ml, 5 ml were diluted up to 10 ml with buffer to give concentrations in the range of 10 µg/ml, 20 µg/ml, 30 µg/ml, 40 µg/ml, 50 µg/ml concentration of tenofovir disoproxil fumarate respectively. The absorbance of each solution was measured by UV - visible spectrophotometer at 210 nm using the phosphate buffer solution, pH 6.8 as blank. The graph of concentration versus absorbance was plotted.

Preparation of Solid Complexes

Total four solid complexes of tenofovir disoproxil fumarate with β-cyclodextrin (1:1, 1:2, 1:3 and 1:4 molar ratios) were prepared by co-grounding method as followed: The drug was triturated with a minimum quantity of ethanol in a glass mortar until it gets dissolved. β-cyclodextrin was then added, and the thick slurry was triturated rapidly at room temperature until the solvent was evaporated. Finally, the obtained powder was sieved through # 44 sieve and stored in desiccators. The physical mixtures of tenofovir disoproxil fumarate and β-cyclodextrin in 1:1, 1:2, 1:3 and 1:4 molar ratios were also prepared by mixing together the milled powders (#100) using a mortar and pestle.

Evaluation of Taste of the Prepared Solid Complexes

The samples of drug-β-cyclodextrin complexes were subjected to sensory evaluation by a panel of 5 members regarding the bitter taste; the check was carried out by categorizing the bitter taste into the following 5 classes.

Class 5: Very strong bitter taste
Class 4: Strong bitter taste
Class 3: Moderately bitter taste
Class 2: Slightly bitter taste
Class 1: No bitter taste

The pure drug tenofovir disoproxil fumarate was used as a standard control, with a mean bitter taste of 5.0. Written consent was obtained from the panel members and the procedure involved in testing the taste of complexes was explained. Each of the panel members was given the control, *i.e.*, the pure drug - tenofovir disoproxil fumarate. The panel members were asked to compare the bitterness of each of the ratios of the complex with that of the control, indicating the level of bitterness perceived by them. The panel members were asked to gargle and wait for 20 min before another sample was given to them for taste evaluation. The mean bitterness value of each of the ratios was calculated based upon the level of bitterness sensed by each individual member of the panel.

Formulation of Oro-dispersible Tablets of Tenofovir Disoproxil Fumarate

Tablets consisting of 600 mg drug-β cyclodextrin complex (1:1 molar ratio) equivalent to 300 mg of the drug using different concentrations of superdisintegrants such as sodium starch glycolate (SSG), crospovidone (CP) and crosscarmellose sodium (CCS) were prepared by direct compression technique as mentioned in Table 1. The drug- β cyclodextrin complex, excipients, superdisintegrants, sweetener and flavor were passed through a # 40 sieve. All the above ingredients were properly mixed together in a polybag. Talc and magnesium stearate were passed through # 80 sieve and then blended with the initial powder mixture in a polybag. Finally, the powder blend obtained was

compressed into tablets on an 8-station rotary tablet machine (Karnavathi).

Table 1: Formulation of Tenofovir Disoproxil Fumarate Oro-dispersible Tablets

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug-β cyclodextrin complex (1:1) (mg)	600	600	600	600	600	600	600	600	600
Microcrystalline celluiose (mg)	59	49	39	59	49	39	59	49	39
SSG (mg)	20	30	40	-	-	-	-	-	-
CP (mg)	-	-	-	20	30	40	-	-	-
CCS (mg)	-	-	-	-	-	-	20	30	40
Aspertame (mg)	1	1	1	1	1	1	1	1	1
Flavor (mg)	2	2	2	2	2	2	2	2	2
Magnesium stearate (mg)	2	2	2	2	2	2	2	2	2
Talc (mg)	6	6	6	6	6	6	6	6	6
Mannitol (mg)	10	10	10	10	10	10	10	10	10
Total weight of tablet (mg)	700	700	700	700	700	700	700	700	700

Evaluation of Flow Properties of Blend Powder

Bulk Density[12]

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this, the bulk density was calculated according to the formula mentioned below. It is expressed in g/ml and is given by,

$D_b = M / V_b$

Where, M = Mass of powder,

V_b = Bulk volume powder,

D_b = Bulk density of powder.

Tapped Density (D_t)

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2% (in a bulk density apparatus). It is expressed in g/ml and is given by

$D_t = M / V_t$

Where, M = Mass of powder,

V_t = Tapped volume of powder.

Carr's index (or) % compressibility index

It indicates powder flow properties. It is expressed in percentage and is given by, Carr's index (or) % compressibility index.

$$CI = \frac{D_t - D_b}{D_t} X\ 100$$

D_t = Tapped density of the powder,

D_b = Bulk density of the powder.

Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula,

$$Hausner's\ Ratio = \frac{D_t}{D_b}$$

Where, D_t is the tapped density,

D_b is the bulk density.

Lower Hausner's ratio (< 1.25) indicates better flow properties than higher ones (> 1.25).

Angle of Repose (Θ)

The friction forces in a loose powder can be measured by the angle of repose (Θ). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane

$\Theta = \tan^{-1} (h / r)$

Where, Θ = Angle of repose, H = Height in cm

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. This explains relationship between angle of repose and powder flow properties.[13]

Post-Compression Analysis

Thickness

20 tablets were randomly taken from each formulation and their thickness was measured using a Vernier calipers. The mean ± S.D. values were noted. The tablet thickness must be controlled within a ± 5% variation of the standard value.[14]

Weight variation

Twenty tablets were selected randomly from each formulation batch and weighed individually in order to check for the weight variation. Tablets are designed to contain a specific quantity of the drug in a specific quantity of tablet formula, weight of the tablet being prepared is routinely determined to ensure that a tablet consists of the drug in proper amount. Average weight of 20 tablets was computed using an electronic balance. Individual weight of each tablet was calculated and compared with that of average weight. The mean ± SD were noted. The tablets meet United States Pharmacopoeia (USP) specifications if no more than 2 tablets outside the % limit and if no tablet differs by more than two times the % limit.[15]

Hardness

Hardness or tablet crushing strength, the force that is required to break a tablet in a diametric compression. Hardness of tablets from various formulations was measured using Monsanto tablet hardness tester and expressed in kg/cm^2. Usually, a minimum hardness of 4 kg is considered to be acceptable for uncoated tablets. The hardness for orally disintegrating tablets must be preferably 1-3 kg.[16]

Friability

Friability of the tablet was determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet from a height of 6 inches in each revolution. Pre-weighed sample of 10 tablets were placed in a plastic chambered friabilator attached to a motor and subjected to 100 revolutions or for 4 min. The tablets after subjection to friability test were dedusted using a soft muslin cloth and then reweighed. % loss of tablet weight was calculated. The percentage friability was given by the formula,

$$\%\ Friability = \frac{(W_1 - W_2)}{W_1}\ X\ 100$$

Where,

W_1 = Initial weight of the 10 tablets,

W_2 = Final weight of the 10 tablets.

Friability values less than 1% are generally considered to be acceptable.

Uniformity of content

10 tablets were selected randomly from each formulation batch and finely powdered. The amount of powder equivalent to one tablet was added to 100 ml of phosphate buffer, pH 6.8 in a conical flask. The conical flask was placed on a rotary shaker and an aliquot of solution was subjected to centrifugation and the supernatant was filtered through a 0.22 µ filter. The absorbance of the resultant supernatant solution was measured using UV - visible spectrophotometer at the λ_{max} of 210 nm against phosphate buffer, pH 6.8 as blank. The concentrations were calculated with the help of the standard graph and the total amount of drug present in the formulation was determined.

Wetting time

In a small petridish consisting 6 ml of water, a piece of tissue paper which is folded twice was kept. To the petridish a water soluble phenolphthalein dye was added. The dye solution was used in order to identify the complete wetting of the tablet surface.[17] A tablet from each formulation batch was placed carefully on the surface of folded tissue paper in petridish at room temperature. The time taken for water to reach the upper surface of the tablets and fully wet them was noted as the wetting time. To check for reproducibility, the measurements were determined in replicates (n=3). The wetting time was recorded with the help of a stop watch.

Water absorption ratio

The tablet weight before placement in the petridish was noted (W_b) using digital balance (Darvin& Sansui). The wetted tablet from the petridish was taken and then reweighed (W_a) using the same. The Water absorption ratio (R) was calculated according to the below mentioned equation.

$$Water\ Absorption\ Ratio\ (R) = \frac{(W_a - W_b)}{W_b}\ X\ 100$$

Where, W_b and W_a = Weight of tablet before and after water absorption respectively.

In vitro disintegration time

Disintegration time is considered as one of the important parameter in choosing the best formulation. In order to achieve correlation between disintegration time *in vitro* and *in vivo*, several methods were proposed, developed and followed at their convenience. Disintegration times for rapid dissolving tablets of antiretroviral drug were determined using USP tablet disintegration apparatus with phosphate buffer, pH 6.8 as the medium. The volume of medium was 900 ml and temperature was 37 ^{0}C ± 2 ^{0}C. The time (sec) taken for complete disintegration of the tablets with no palpable mass remaining in the apparatus was measured.

In-vitro drug release (dissolution) studies

The *in-vitro* drug release study was performed for all the formulations using USP type II dissolution apparatus under the following conditions. Dissolution test parameters: Dissolution medium: 900 ml of phosphate buffer, pH 6.8, Stirring speed: 50 rpm, Temperature: 37 ± 0.5 ^{o}C, Sampling time: 5, 10, 15, 20, 25, 30, 40, 50 & 60 min. At predetermined time intervals aliquot samples (5 ml) were collected and replenished with same volume of fresh medium. The aliquot samples (5 ml) were diluted appropriately and the drug content was estimated by using UV - visible spectrophotometer at λ_{max} 210 nm.

Stability studies

The stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physicochemical, therapeutic & toxicological specifications. In the present study, stability studies were carried out at 25^{o}C / 60% RH and 40^{o}C / 75% RH for a specific time period up to 90 days for optimized formulations.

RESULTS AND DISCUSSION

Drug - Excipients Compatibility Studies

FT-IR Analysis

The interaction studies were carried out to ascertain any kind of interaction of drug with the excipients used in the preparation of fast dissolving tablets.

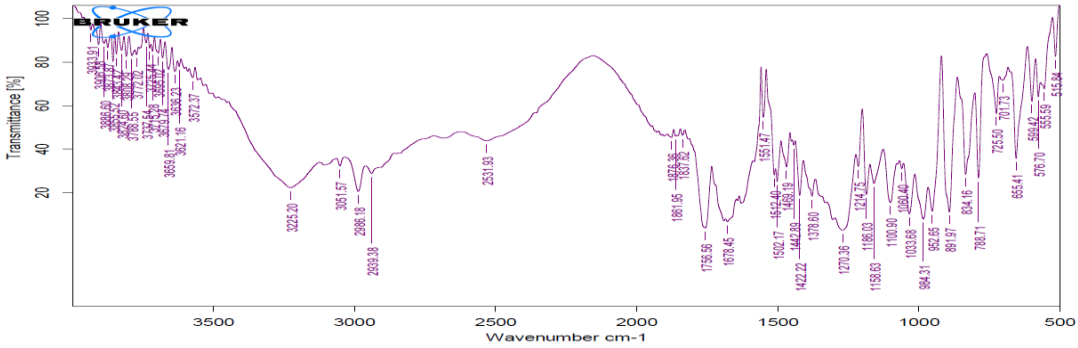


Figure 1: FT-IR Spectra for Tenofovir Disoproxil Fumarate

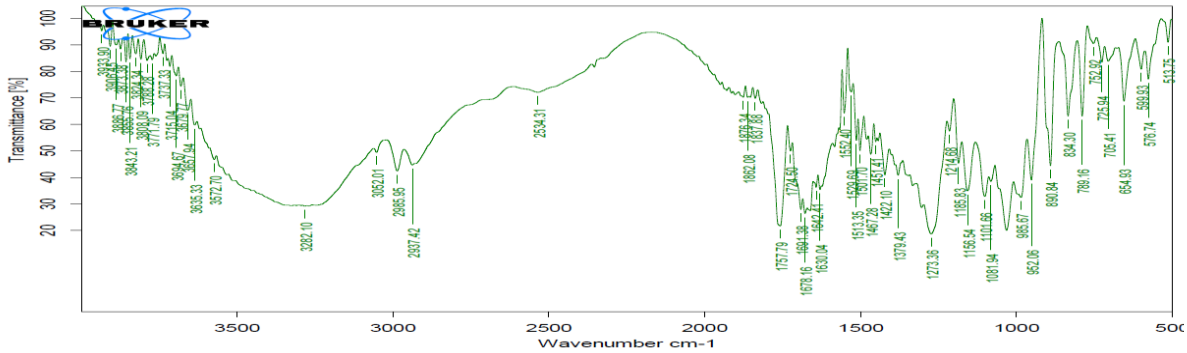
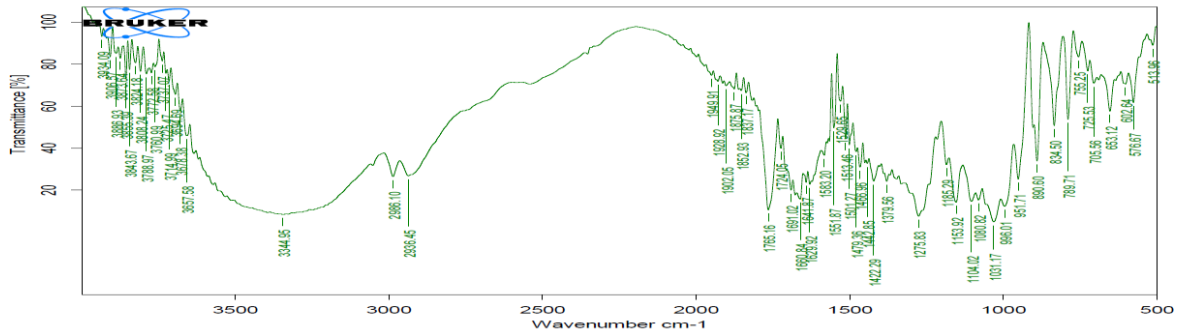


Figure 2: FT-IR Spectra for Tenofovir Disoproxil Fumarate – β-Cyclodextrin Physical Mixture



Figur 3: FT-IR Spectra for Formulation F6

Inference

The CH and OH stretching modes were observed at regions having high wave number in the FT-IR spectrum of tenofovir disoproxil fumarate. The CH stretching bands were found between 2986.18 cm^{-1} and 3051 cm^{-1} in FT-IR spectrum of pure drug. The CH stretching modes in ring as

well as methylene groups were identified and their effect in tenofovir was examined. Physical mixture of drug with β cyclodextrin, physical mixtures of formulations F3, F6 and F9 clearly showed the retention of characteristic peaks of tenofovir disoprixil fumarate and thus revealing no interaction between the selected drug tenofovir, β cyclodextrin and other excipients.

Formulation Development

Standard Curve of Tenofovir Disoproxil Fumarate

The standard curve of tenofovir disoproxil fumarate plotted as concentration Vs absorbance followed a linear relationship in the range of 10 µg/ml – 50 µg/ml and the correlation coefficient (R^2) value in phosphate buffer, pH 6.8 at 210 nm was observed to be 0.999 indicating that the method obeyed Beer-Lambert's law.

Evaluation of Taste of the Prepared Solid Complexes

The bitter taste of tenofovir disoproxil fumarate was masked after complexation with β cyclodextrin. In co-grounding method, the drug- complex (1:1 ratio) resulted in maximum masking of bitter taste of tenofovir with a mean bitterness value of 2 during the taste evaluation process.

Preparation of Tenofovir Disoproxil Fumarate Oro-dispersible Tablets

The current study was undertaken to formulate rapid dissolving tablets of tenofovir disoproxil fumarate by direct compression method using SSG, CP & CCS as superdisintegrants. Total nine batches were formulated (F1, F2, F3, F4, F5, F6, F7, F8 and F9).

Evaluation of Pre-Compression Parameters

Angle of Repose

The prepared blend for all the formulations were evaluated for the flow properties (Table 2). The angle of repose of all the formulations was within the range of 23.31^{o} ± 1.31 –28.08^{o} ± 0.06. These values indicate that the powder blend exhibited good flow properties.

Bulk density and tapped density

The prepared powder blends for all the formulations were evaluated for bulk density and tapped density by using bulk density apparatus and the results obtained were shown in Table 2. The bulk density was found in the range of 0.28 g/cm^3 ± 0.03 - 0.58 g/cm^3 ± 0.04. The tapped density ranged between 0.33 g/cm^3 ± 0.02 – 0.80 g/cm^3 ± 0.04.

Carr's Index and Hausner's Ratio

The Carr's index of all the formulations existed in the range of 08.75 ± 0.03 to 15.38 ± 0.04 as shown in the Table 2. The result of the Hausner's ratio of all the formulations was between 1.09 ± 0.03 & 1.16 ± 0.03. These values indicate that the prepared powder blend of oro-dispersible tablets exhibited good flow properties.

Table 2: Flow Properties of Tenofovir – β Cyclodextrin Complex Blend

Formulation	Angle of Repose (^{o})	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index	Hausner's Ratio
F1	26.14 ± 0.04	0.49 ± 0.06	0.56 ± 0.07	12.50 ± 0.06	1.14 ± 0.06
F2	27.62 ± 0.03	0.48 ± 0.05	0.54 ± 0.06	14.28 ± 0.04	1.16 ± 0.06
F3	26.35 ± 0.07	0.46 ± 0.06	0.53 ± 0.02	13.20 ± 0.05	1.15 ± 0.07
F4	23.31 ± 1.31	0.73 ± 0.02	0.80 ± 0.04	08.75 ± 0.03	1.09 ± 0.03
F5	25.47 ± 0.06	0.53 ± 0.07	0.60 ± 0.02	11.66 ± 0.02	1.13 ± 0.05
F6	26.38 ± 1.52	0.58 ± 0.04	0.65 ± 0.07	10.76 ± 0.07	1.12 ± 0.04
F7	28.08 ± 0.06	0.55 ± 0.05	0.63 ± 0.05	12.69 ± 0.04	1.14 ± 0.02
F8	24.10 ± 0.08	0.52 ± 0.07	0.60 ± 0.04	15.38 ± 0.04	1.15 ± 0.08
F9	27.62 ± 0.05	0.28 ± 0.03	0.33 ± 0.02	14.40 ± 0.01	1.16 ± 0.03

Note: Mean ± S.D. of three determinations

Evaluation of Post-Compression Parameters

The prepared oro-dispersible tablets of taste masked tenofovir disoproxil fumarate by direct compression method were evaluated for various post-compression parameters. The results of post-compression evaluation of prepared tablets were represented in Table 3. The tablets were evaluated for the physical appearance, thickness, diameter, weight variation, hardness, friability & drug content. The prepared tablets of all the 9 formulations were observed to be in white in color, smooth in texture; round and slightly convex in shape. Thickness & diameter values for all the formulations were observed to be 6 mm ± 0.2 and 10 mm ± 0.1 respectively. Weight variation values for all the 9 formulations were found to be within the limits. Hardness for all the nine formulations was in the range of 2.4 ± 0.48 to 3.6 ± 0.16 kg/cm^2. Friability was found in the range of 0.32% ± 0.01 - 0.89% ± 0.07 & the drug content values were in range of 92.95% ± 0.01 - 99.82% ± 0.01 indicating the compliance with limits of Indian Pharmacopoeia.

Wetting Time and Water Absorption Ratio

The wetting time was least and rapid in formulations with CP as the superdisintegrant followed by CCS and SSG. It was found that, as the concentration of disintegrant increased, time taken for wetting was reduced. The wetting time was observed to be in the range of 58 ± 1.04 sec to 99 sec ± 1.16. Water absorption ratios of all nine formulations were in the range of 136 ± 0.84 to 212 ± 1.28. The results were mentioned in Table 3.

In Vitro Dispersion Time & *In Vitro* Disintegration Time

The *in-vitro* dispersion time and *in-vitro* disintegration time in all formulations (F1 to F9) were observed and found to be in the range 24 sec ± 0.46 to 44 sec ± 1.72 and 98 sec ± 0.82 to 127 sec ± 1.40 respectively. The results were tabulated in Table 3.

Table 3: Evaluation of post-compression parameters

Formulation	Hardness (kg/cm^2)	Friability (%)	Drug Content (%)	Wetting time (sec)	Water Absorption Ratio	*In-vitro* Dispersion Time (sec)	*In-vitro* Disintegration Time (sec)
F1	2.8 ± 0.42	0.52 ± 0.02	95.45 ± 0.02	96 ± 1.13	212 ± 1.28	42 ± 1.26	127 ± 1.40
F2	2.6 ± 0.31	0.46 ± 0.03	98.05 ± 0.01	99 ± 1.16	119 ± 1.85	44 ± 1.72	124 ± 1.46
F3	2.4 ± 0.45	0.32 ± 0.01	98.95 ± 0.03	94 ± 1.10	208 ± 1.56	38 ± 1.61	126 ± 1.58
F4	2.7 ± 0.52	0.68 ± 0.04	97.13 ± 0.02	58 ± 1.04	136 ± 0.84	24 ± 0.46	108 ± 1.04
F5	2.9 ± 0.46	0.84 ± 0.06	98.46 ± 0.02	62 ± 1.13	152 ± 0.42	28 ± 0.52	105 ± 1.03
F6	2.5 ± 0.15	0.44 ± 0.04	99.82 ± 0.01	55 ± 1.36	141 ± 1.62	22 ± 0.42	98 ± 0.82
F7	3.2 ± 0.10	0.89 ± 0.07	92.95 ± 0.01	62 ± 1.18	159 ± 1.81	31 ± 0.62	120 ± 1.84
F8	3.6 ± 0.16	0.49 ± 0.03	94.82 ± 0.04	70 ± 1.06	157 ± 1.95	33 ± 1.03	122 ± 1.10
F9	2.4 ± 0.48	0.52 ± 0.02	99.65 ± 0.02	68 ± 1.12	156 ± 1.32	36 ± 1.25	117 ± 1.92

Note: Mean ± S.D. of three determinations

In-Vitro Drug Release Studies

The *in-vitro* drug dissolution studies of all nine formulations (F1 to F9) were carried out and the results were represented in Table 4 & Fig. 4. The amount of tenofovir released from various formulations F1, F2, F3, F4, F5, F6, F7, F8 and F9 at end of 60 min were 81.15%, 85.37%, 87.28%, 96.25%, 97.21%, 99.85%, 91.44%, 92.08% and 94.91% respectively. For formulations F1, F2 & F3, SSG was employed as the superdisintegrant. In case of formulations F4 - F6, CP was employed as the superdisintegrant. In formulations F7 to F9, CCS was used as the superdisintegrant. The maximum drug release of 99.85% was obtained from the formulation F6 containing the highest concentration of CP and therefore formulation F6 was considered as the optimized formulation. Minimum drug release of 81.15% was shown by F1 formulation which contained SSG as the superdisintegrant in the lowest concentration. Moreover, the initial dissolution rate for the optimized formulation F6 was observed to be 32.41% / 5 min. From the results obtained, it was evident that the drug release from the formulations found to increase with the increase in the amount of superdisintegrant added in each formulation.

Table 4: *In-Vitro* Release Studies of Tenofovir Oro-dispersible Tablets

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	18.98 ± 0.72	19.78 ± 0.57	18.12 ± 0.71	27.54 ± 0.65	29.03 ± 0.32	32.41 ± 0.15	25.26 ± 0.25	29.32 ± 0.13	30.92 ± 0.31
10	22.42 ± 0.43	21.67 ± 0.34	24.93 ± 0.81	36.97 ± 0.54	38.43 ± 0.79	40.74 ± 0.52	29.91 ± 0.51	34.04 ± 0.34	35.83 ± 0.42
15	60.12 ± 0.71	61.24 ± 0.71	65.43 ± 1.00	70.23 ± 0.21	82.47 ± 0.52	85.56 ± 0.24	68.14 ± 0.95	69.26 ± 0.64	70.23 ± 0.72
20	64.89 ± 0.77	65.43 ± 1.16	68.76 ± 0.93	83.31 ± 0.42	87.54 ± 1.05	92.14 ± 0.41	80.92 ± 1.42	81.18 ± 0.81	83.17 ± 0.98
30	66.54 ± 0.57	70.08 ± 0.93	72.03 ± 0.61	85.12 ± 0.82	92.14 ± 0.84	93.46 ± 0.74	87.26 ± 0.51	89.56 ± 0.24	90.12 ± 1.05
40	77.92 ± 0.71	79.14 ± 0.97	81.81 ± 0.21	90.74 ± 1.54	94.01 ± 0.25	96.92 ± 0.81	88.56 ± 0.62	90.27 ± 1.24	91.96 ± 0.49
50	80.78 ± 0.86	82.39 ± 1.00	83.54 ± 0.82	94.32 ± 0.51	96.14 ± 0.46	98.04 ± 0.29	90.91 ± 0.62	91.29 ± 0.84	93.47 ± 0.36
60	81.15 ± 0.68	85.37 ± 0.71	87.28 ± 0.24	96.25 ± 0.92	97.21 ± 1.05	99.85 ± 0.32	91.44 ± 0.27	92.08 ± 1.17	94.91 ± 0.45

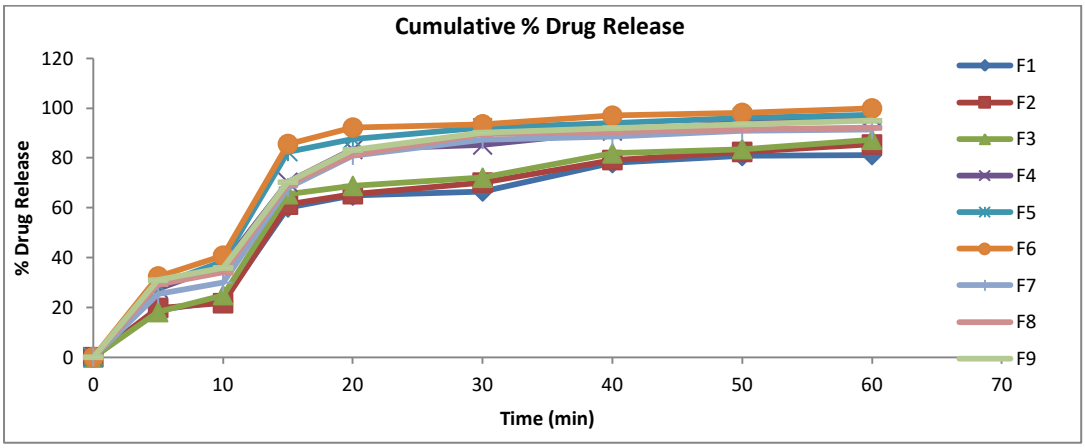


Figure 4: Drug Release Profiles for taste masked tenofovir disoproxil fumarate oro-dispersible tablets (F1-F9)

Stability studies

The stability study was performed for the taste masked tenofovir disoproxil fumarate oro-dispersible formulations F3, F6 & F9 at 25 ^{0}C / 60% RH and 40 ^{0}C / 75% RH for a period of up to 90 days. Results of stability study revealed that there were no significant changes in the drug content and % drug release in case of the best formulations at the end of 90 days. Hence, the formulations were found to be stable for a period of 3 months.

CONCLUSION

Tenofovir disoproxil fumarate, a bitter drug, could be successfully taste-masked employing β-cyclodextrin by co-grounding technique. The taste-masked drug complex was used to prepare oro-dispersible tablets. The tablets formulated with crospovidone (5.7%) as superdisintegrant showed rapid disintegration as well as drug release. The developed formulation offered significant results in terms of improving the taste and bioavailability.

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