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Formulation, Taste Masking and *In-Vitro* Evaluation of Tenofovir Disoproxil Fumarate Oral Disintegrating Tablets

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Abstract
Orally disintegrating tablets are intended to disintegrate fast in the mouth to provide dispersion before being swallowed where the active ingredient is intended for gastrointestinal delivery and absorption. Tenofovir exhibits activity for HIV-1 infection. The bitter taste of drug should be masked in order to formulate it in a palatable form. In the current study, an attempt was made to mask the bitter taste of Tenofovir by solid dispersion technique using mannitol by Fusion method and to develop oral disintegrating tablets of Tenofovir by direct compression method using the super disintegrants like Sodium starch glycolate, Croscarmellose sodium and Crospovidone. The formulations were characterized for their pre compression and post compression evaluations. The drug and polymer interaction by FTIR and DSC studies reveal the drug excipients compatibility. The blend of all the formulations showed good flow properties. The prepared tablets were shown to have good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. The optimized formulation F6 shows 99.85% drug release within 30 mins. Disintegration time, Invitro dispersion time for F6 was found to be 21±0.83 sec, 18.08±0.48, respectively. Water absorption ratio was 90.12±0.11 and wetting time 52.25±0.01sec showing high water absorbing ability. Results from stability studies indicate that the formulated Oral disintegrating tablets are stable for a period of 45 days under two different conditions at 25±2°C / 65±5%RH and 40±2°C / 75±5%RH.

Keywords
Tenofovir disoproxil fumarate, taste masking, solid dispersion, Oral disintegrating tablets, Direct Compression method

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INTRODUCTION
Orally Disintegrating Tablets (ODT's) are also called mouth dissolving tablets, orodispersible tablets, fast dissolving tablets, rapidly dissolving tablets, porous tablets and rapid melts. 'Orodispersible tablet', which disintegrates and disperses readily in the oral cavity within a period of three minutes, before swallowing. The faster the drug disintegrates into the solution, the quicker is the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form.

Taste-masking is of critical importance in the formulation of an acceptable ODT. Traditional tablet formulations generally do not address the issue of taste masking, because it is assumed that the dosage

form will not dissolve until passing the oral cavity. Elimination of the bitterness of the tablet can be achieved by adding flavors and sweetening agent or by sugar coating on the tablets. To increase the tablet disintegration, Super disintegrants are added in it, which are very helpful to increase the bioavailability of tablet and to increase the disintegration property of tablet in saliva. The patients can feel the normal disintegration time of ODT's from 5-30 seconds.

Tenofovir disoproxil fumarate is an Antiretroviral agent that belongs to the class of nucleotide reverse transcriptase inhibitors, approved by the Food and Drug Administration (FDA), for the treatment of wide range of viral infections, including HIV AIDS & Hepatitis. Furthermore, on account of the high aqueous solubility it is well-absorbed after oral administration. The absolute bioavailability is approximately 25% due to extensive hepatic metabolism.[1]

MATERIALS AND METHOD

Tenofovir Disoproxil Fumarate was obtained from Hetero Labs Pvt Ltd, Mannitol, Croscarmellose sodium, Crospovidone, Magnesium stearate and talc from SD fine chemicals, Mumbai, Microcrystalline cellulose from Merck Specialties Pvt. Ltd

Drug-Excipient Compatibility Study

FTIR Study:

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.[2]

DSC Study:

DSC-Thermogram of drug and excipients and their combination were recorded using DSC to study the incompatibility. All samples were weighed and heated in a closed pierced aluminium pan at a scanning rate of 10°C/min between 30°C and 300°C and 60 ml/min of nitrogen flow.[3]

Formulation Development

Preparation of Solid Dispersions by Fusion Method:

Tenofovir and water soluble carrier Mannitol was weighed accurately in various ratios (1:1, 1:2 and 1:3) and melted in a porcelain dish until completely melted followed by quick cooling on ice bath. The dried mass was then pulverized by passing through sieve no.60 and stored in a desiccator until used for further use.[4]

Characterization of Solid Dispersions

1. Drug content:

An accurately weighed quantity of solid dispersion equivalent to 10mg of Tenofovir was taken into a 10ml volumetric flask, dissolved in ethanol and suitably diluted with 6.8pH Phosphate buffer. The content of Tenofovir was determined spectrophotometrically at 260 nm against suitable blank using UV-visible spectrophotometer.[5]

2. *In-vitro* dissolution studies*:*

The quantity of solid dispersion equivalent to 100mg of Tenofovir was filled in colourless hard gelatin capsule by hand filling method. The dissolution study of capsules was conducted using dissolution testing USP apparatus 1 (basket method) in 900 ml of 6.8pH Phosphate buffer at 37±0.5ºC and at a speed of 50 rpm and sampling time: 5, 10, 15, 20, 25, 30 mins. Aliquot of 5ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume after each sampling and analyzed spectrophotometrically at 260 nm against suitable blank using UV-visible spectrophotometer.[6]

3. Taste evaluation of Solid Dispersions:

Sensory test on taste of all granule preparations was performed using 6 healthy adult volunteers from whome informed consent was first obtained. They rinsed their mouth cavities sufficiently before and after tasting. The prepared granules were kept in the volunteer's mouth for 30s and then spit out. The taste score was set to the range of 0-4 based on the degree of taste masking (0-Good,1-Taste less,2-Slightly bitter, 3-bitter ,4-very bitter).[7]

Formulation of Oro-dispersible Tablets of Tenofovir Disoproxil Fumarate

Table no. 1 showing the formulation of Tablets consisting of 600 mg drug-mannitol solid dispersions (1:3 molar ratio) equivalent to 150 mg of the drug using different concentrations of super disintegrants such as cross povidone (CP), crosscarmellose sodium (CCS) were prepared by direct compression technique as mentioned in Table. The drug - mannitol solid dispersion, excipients, super disintegrants, sweetener and flavour 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.[8]

Table -1: Formulation of Tenofovir Disoproxil Fumarate tablets (F1-F6).

Composition (mg)	F1	F2	F3	F4	F5	F6
Drug – Mannitol (1:3) (mg)	600	600	600	600	600	600
SSG	20	35	-	-	-	-
CCS	-	-	20	35	-	-
CP	-	-	-	-	20	35
MCC	70	55	70	55	70	55
Magnesium stearate	5	5	5	5	5	5
Talc	5	5	5	5	5	5
Total weight	700	700	700	700	700	700

Precompression Evaluations

Determination of Angle of repose: The angle of repose is determining by allowing mass of powdered to flow freely through an orifice from a certain height and form a conical heap on the horizontal surface. The angle of repose is determined by the formula

$\tan \theta = h/r$

Where,

θ is the angle of repose,

h is the height of the heap of powder and

r is the radius of the base of the heap of powder.

Determination of Bulk density tapped density, compressibility index and hausners ratio: A fixed quantity of the powder (W) was introduced into a 100 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using the following formulas:

Bulk density = W / V_0

Tapped density = W / Vf

- Where, W = weight of the powder; V0 = initial volume; Vf = final volume.

Compressibility index (Carr's index): Compressibility index is an important measure that can be obtained from the bulk and tapped densities.

Compressibility index, (CI) = 100 (V0 - Vf) / V0

Hausner's Ratio: It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.[9]

Hausner's Ratio = Tapped density/Bulk density

Evaluation of Tablets

1. Weight Variation test: Twenty tablets were selected from each formulation and the average weight was determined. The individual tablet weight was compared with the average weight.[10]

2. Friability: The friability of the tablets was evaluated using a Roche friabilator. It subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm for about 4minutes or 100 revolutions. Pre weighed sample(Wi) of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were deducted using a soft muslin cloth and reweighed (Wf). The friability (F) is given by the formula.[11]

$$F = (W_{initial} - W_{final} \times 100) / W_{initial}$$

3. Hardness: The hardness of the prepared tablets was estimated using Monsanto hardness tester. Three tablets from each formulation batch were selected and force is applied diametrically. It is expressed in kg/cm^2.[12]

4. Thickness: 20 tablets were randomly taken from each formulation and their thickness was measured using a Screw gauge. The mean ± S.D. values were noted. The tablet thickness must be controlled within a ± 5% variation of the standard value.[13]

5. Water absorption ratio: The tablet weight before placement in the Petri dish was noted (Wb) using digital balance. The wetted tablet from the Petri dish was taken and then reweighed (Wa) using the same. The Water absorption ratio (R) was calculated according to the below mentioned equation.[14]

Where, Wb and Wa = Weight of tablet before and after water absorption respectively.

6. Wetting Time: A piece of tissue paper folded twice was placed in a petri dish (i.d =6.5cm) containing 10ml of water, a tablet was put on the paper and the time for complete wetting was noted. Three trials from each batch were performed.[15]

7. In-vitro dispersion time: *In-vitro* dispersion time was measured by dropping a tablet in a measuring cylinder containing 6 ml of simulated saliva fluid (p^H 6.8). Three tablets from each formulation were randomly selected and *in-vitro* dispersion time was expressed in seconds.[16]

***8. In vitro* disintegration time:** Disintegration time is considered as one of the important parameter in choosing the best formulation. 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°C ± 2°C. The time (sec) taken for

complete disintegration of the tablets with no palpable mass remaining in the apparatus was measured.[17]

9.*In vitro* Dissolution Study:

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} 260 nm.[18]

10. 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 and 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 45 days for optimized formulations.[19,20]

RESULT AND DISCUSSIONS

Drug - Excipients compatibility studies by FT-IR:

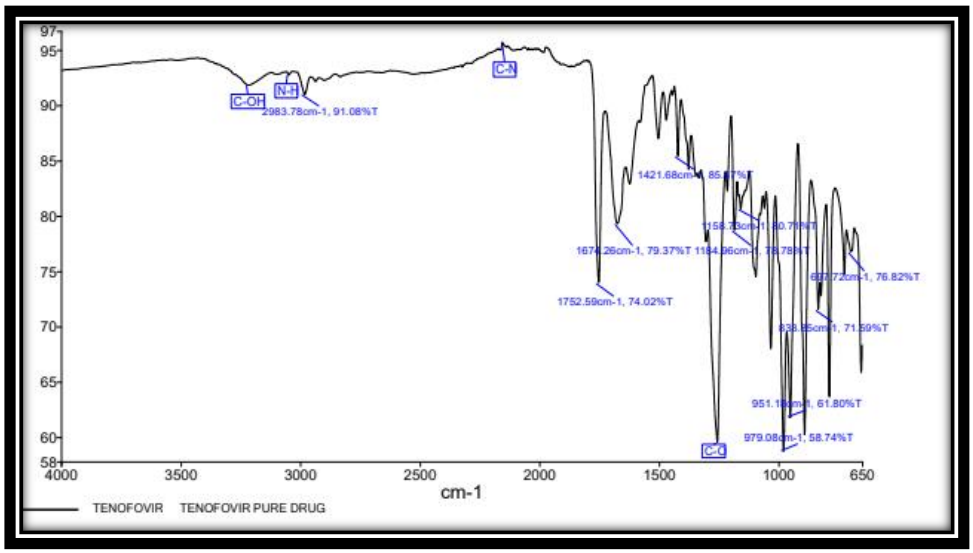

Figure-1: FT-IR interpretation of Pure drug

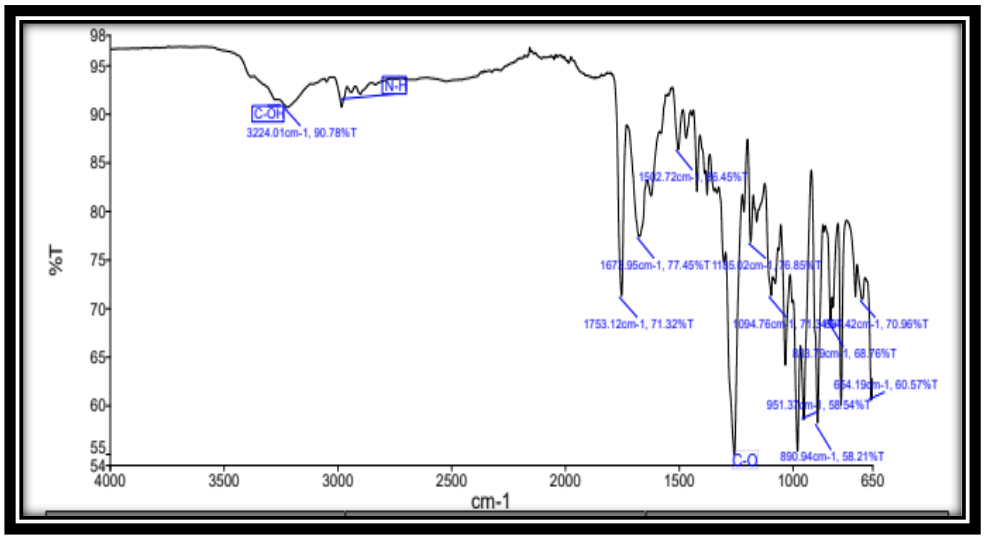

Figure-2: FT-IR of drug+ mannitol

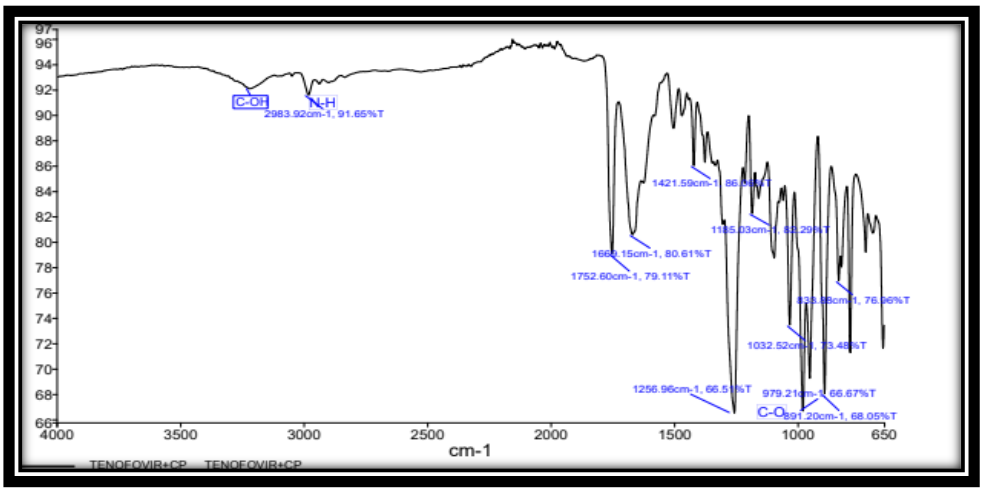

Figure-3: FT-IR of Tenofovir + CP

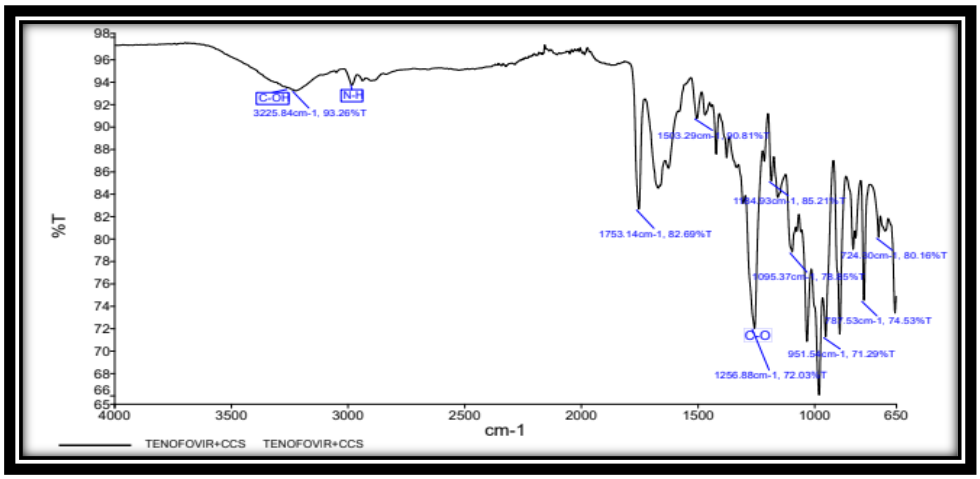

Figure-4: FT-IR of Tenofovir + CCS

Discussion: The figure no. 1,2,3,4 shows the FTIR of Pure drug and its combination with excipients. It was observed that, there was no disappearance or shift in peak position of Tenofovir Disoproxil Fumarate in any spectra of drug & excipients, which proved that drug and excipients were compatible and the study of spectra indicated no chemical reaction.

Drug - Excipients compatibility studies by DSC:

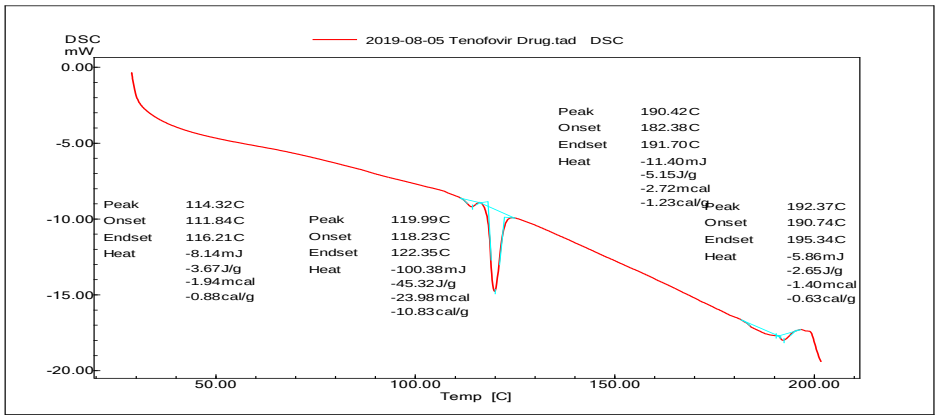

Figure-5: DSC interpretation of Pure drug Tenofovir Disoproxil Fumarate.

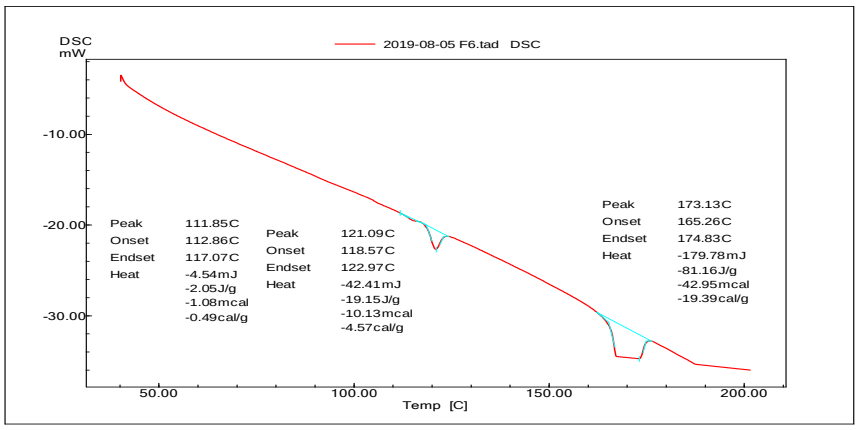

Figure-6: DSC interpretation of Optimised drug F6.

Discussion: The DSC thermogram of the pure drug Tenofovir disoproxil fumarate shows distinct endothermic peak at 119.99°C. The DSC analysis of the Optimised Formula (F6) revealed a negligible change from the endothermic peak of pure drug Tenofovir disoproxil fumarate. when compared with pure drug's Thermogram there was no interaction found between drug and other excipients as shown in figure no.5 and 6.

Characterisation of Solid Dispersions:

1. Drug Content:

Table no 2: Drug Content of Solid Dispersions

S.NO	SAMPLE	Drug-Carrier ratio	% Drug Content
1	SD1	1:1	75.05±0.29
2	SD2	1:2	86.32±0.54
3	SD3	1:3	97.41±0.81

All values are expressed in S.D (n=3)

Discussion: The drug content of SD3 is more than the other formulations as shown in table no.2

2. *In vitro* Dissolution Studies:

Table no 3: *In vitro* Dissolution study of solid dispersions

S.NO	Time (mins)	Cumulative %DR (SD1)	Cumulative %DR (SD2)	Cumulative %DR (SD3)
1	5	36.63±0.26	40.0±0.16	65.11±0.19
2	10	51.41±0.45	56.55±0.18	68.28±0.25
3	15	53.25±0.53	65.32±0.19	77.65±0.21
4	20	58.55±0.88	68.21±0.58	84.34±0.54
5	25	64.42±0.19	77.73±0.21	90.13±0.36
6	30	75.33±0.04	86.44±0.23	98.17±0.18

All values are expressed in S.D (n=3)

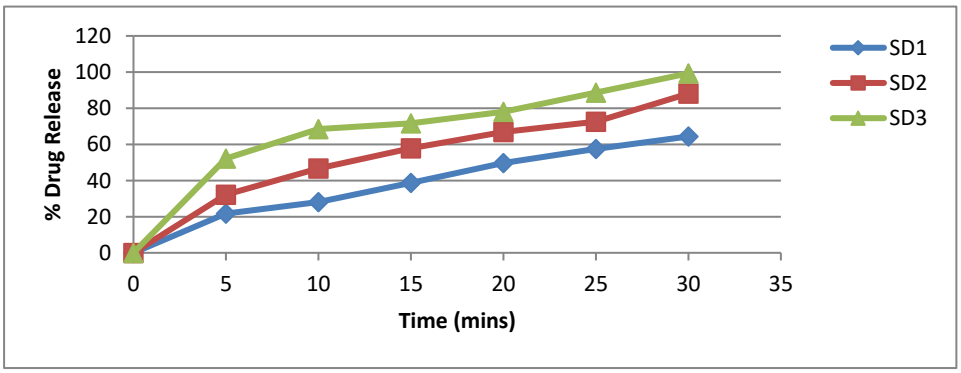

Figure-7: Comparative *In vitro* dissolution profile of Solid Dispersions

Discussion: The *In vitro* Dissolution study of solid dispersions is given in table no.3. The optimized solid dispersions (SD3) shows drug release of 98.17% within 30 mins which is more than the other formulations is shown in figure no.7. Thus due to fast release of drug it was chosen as best formulation.

3. Taste evaluation of solid dispersions

Table no 4: Scores of taste masking

Ratio	Scores given by six volunteers						Taste score
	I	II	III	IV	V	VI	
1:1	3	3	2	3	3	3	17
1:2	1	2	1	2	2	1	10
1:3	0	0	0	0	1	0	1

Discussion: A sensory test on taste of all solid dispersions was performed using 6 healthy adult volunteers. Then based on scores, the best taste masked (1:3) Drug: mannitol solid dispersions were selected as optimized as given in table no.4

Results of Pre-Compression Parameters:

Table no 5: Results of pre-compression parameters.

S.no	Formulations	Angle of repose (^{0})	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Compressibility Index (%)	Hausner's ratio
1	F1	22.08±0.75	0.43±0.01	0.63±0.01	14.22±0.08	1.48±0.04
2	F2	27.39±0.53	0.42±0.16	0.72±0.27	11.81±0.63	1.29±0.03
3	F3	26.58±0.64	0.45±0.01	0.70±0.03	14.38±0.34	1.38±0.07
4	F4	27.01±0.10	0.46±0.19	0.74±0.30	13.47±0.27	1.53±0.01
5	F5	26.41±0.28	0.44±0.02	0.69±0.02	15.26±0.38	1.42±0.01
6	F6	26.89±0.26	0.44±0.09	0.71±0.15	13.83±0.19	1.65±0.15

Discussion: From the table no.5 showing Pre-compression parameters it was clear evidence that powdered blend has good to fair flow properties and is suitable for direct compression.

Results of Post Compression Parameters

Table no 6: Results of post compression parameters.

Formulation	Weight variation (%)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)
F1	688.33±0.67	4.1±0.08	4.46±0.47	0.47±0.56	90.43±0.04
F2	677.43±0.36	3.83±0.12	4.56±0.03	0.35±0.01	91.72±0.98
F3	694.66±0.22	423±0.02	4.51±0.09	0.84±0.21	96.33±0.76
F4	691.33±0.03	4.05±0.15	4.33±0.01	0.65±0.03	92.82±0.49
F5	685.66±0.21	4.13±0.05	4.47±0.13	0.53±0.76	96.28±0.40
F6	685.58±0.19	4.07±0.06	4.43±0.05	0.48±0.02	98.65±0.39

All values are expressed in S.D (n=3)

Table no 7: Results of post compression parameters.

Formulations	Disintegration time (secs)	Dispersion time (secs)	Wetting time (secs)	Water absorption ratio (%)
F1	65.11±0.24	38.33±0.02	96.66±0.01	80.10±0.11
F2	57.36±0.79	31.12±0.13	92.12±0.05	80.01±0.09
F3	38.65±0.25	27.98±0.43	71.01±0.02	78.09±0.16
F4	30.87±0.45	23.35±0.02	63.33±0.04	75.21±0.12
F5	23.55±0.27	22.28±0.04	58.64±0.03	80.09±0.10
F6	21.83±0.95	18.08±0.48	52.25±0.01	90.12±0.11

All values are expressed in S.D (n=3)

Table no 8: Comparative In-vitro Dissolution study of formulations F1 to F6.

Time (mins)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	21.15±0.77	23.37±0.96	30.91±0.79	38.54±0.03	45.35±0.52	47.78±0.71
10	28.99±0.02	32.21±0.39	45.72±0.40	50.91±0.41	53.76±0.18	60.28±0.45
15	42.27±0.47	47.18±0.05	56.29±0.67	61.33±0.01	72.89±0.07	75.53±0.63
20	54.32±0.12	61.8±0.52	65.44±0.57	73.39±0.19	88.98±0.82	93.68±0.03
30	63.97±0.35	71.77±0.15	82.29±0.34	94.15±0.97	97.61±0.29	99.85±0.44

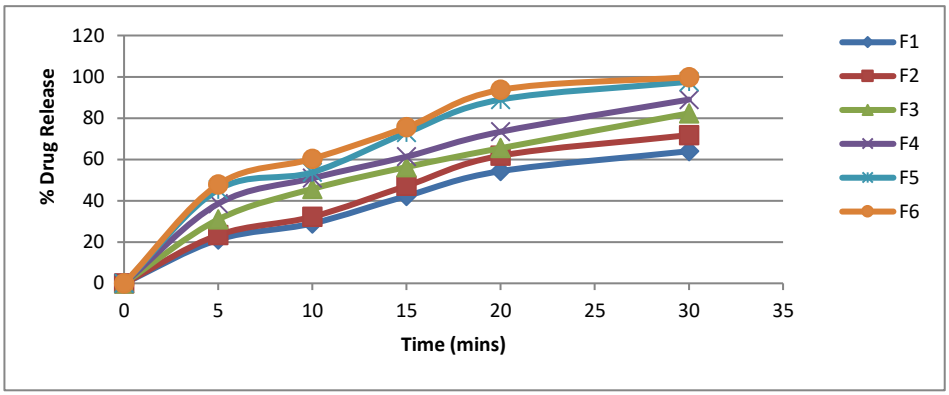

Figure-8: Comparative *In vitro* Dissolution study of formulations F1 to F6.

Discussion:

The values of hardness, thickness, friability, weight variation and drug content of all the formulations were found to be within the limits as stated in I.P as given in Table No.6. The optimized formulation (F6) showing disintegration time- 16±0.60, dispersion time- 18.02±0.60, wetting time- 18.20±0.05, and water absorption ratio- 98.02±0.16 was given in table no.7. The *In vitro* Dissolution study of Oral disintegrating tablets is given in table no.8. The optimized formulation F6 shows drug release of 99.85% within 30 mins which is more than the other formulations is shown in figure no.8. Thus due to fast release of drug it was chosen as best formulation.

Kinetic Analysis:

Table no 9: Drug release kinetics of optimized formulation (F6).

	ZERO	FIRST	HIGUCHI	PEPPAS
	%CDR Vs T	Log % CD Remain Vs T	%CDR Vs √T	Log %CDR Vs Log T
Slope	2.975	−0.166	0.053	1.571
Intercept	21.188	2.317	0.978	0.925
Correlation	0.762	−0.875	0.901	0.810
R^2	0.954	0.801	0.991	0.827

Graphs indicating drug release kinetics of optimized formulation (F6):

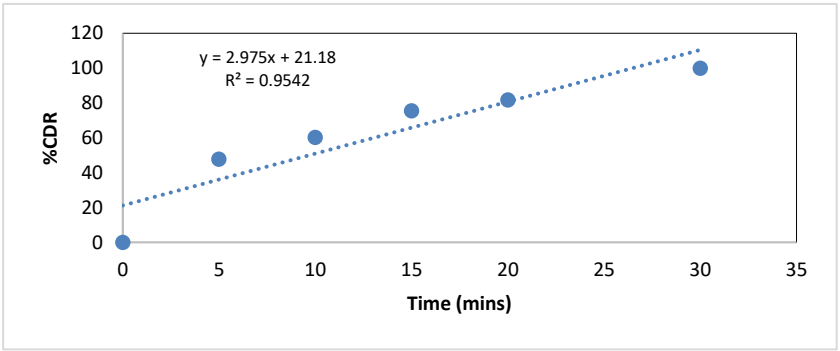

Figure-9: Zero order kinetics for F6 batch.

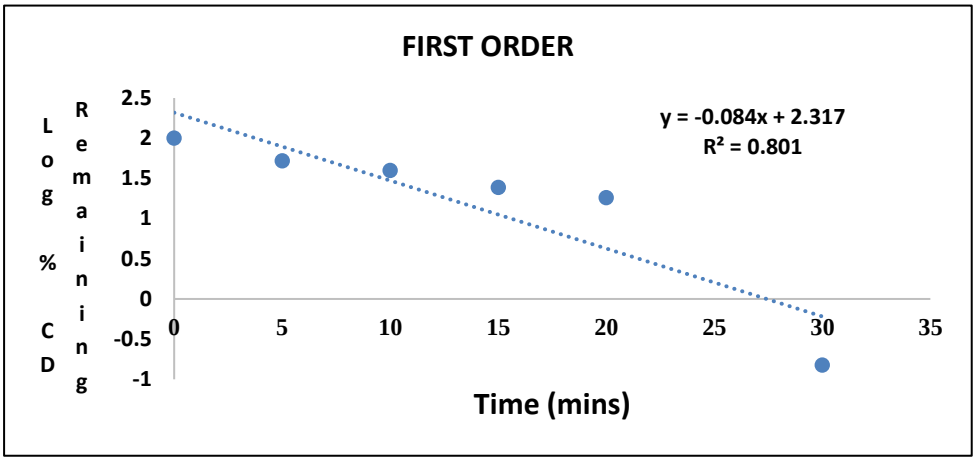

Figure-10: First order kinetics for F6 batch.

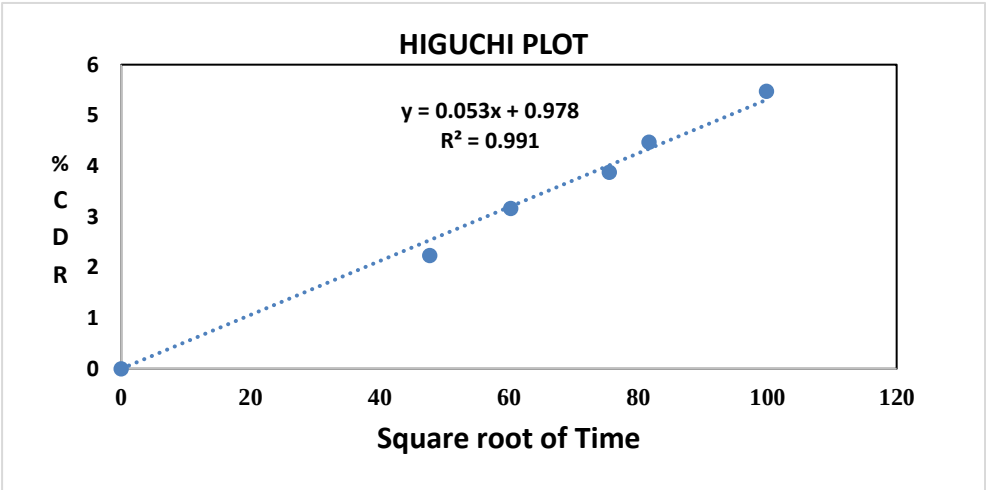

Figure- 11: Higuchi model for F6 batch.

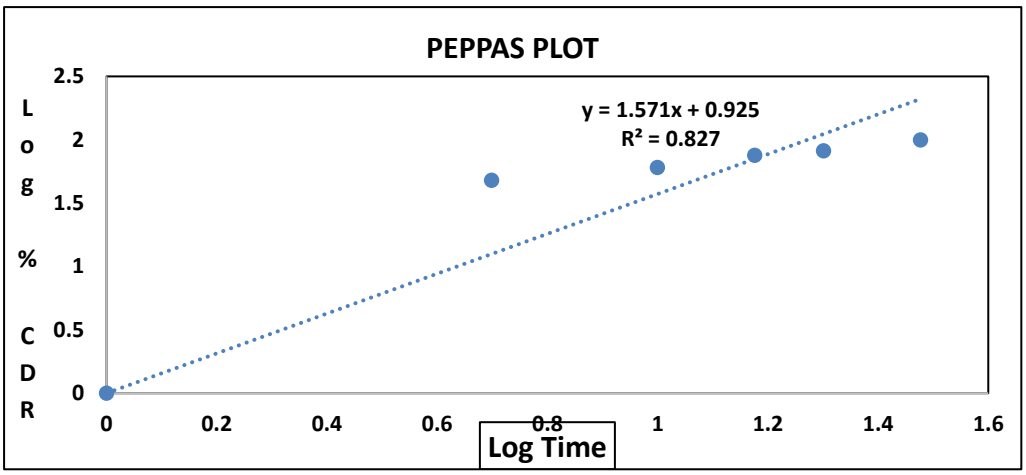

Figure- 12: Peppas model for F6 batch.

Discussion:

Drug release kinetics of optimized formulation (F6) is given in table no.9 and When the data was subjected to zero order and first order kinetic model, a linear relationship was observed with high r^2 value for the first order model as compared to zero order suggested that the formulation were fiirst order immediate release. Higuchi model when applied to

the In-vitro release data, high r^2 value suggested that the drug release from tablets followed non-fickian diffusion mechanism shown in figure no. 9,10,11&12. The correlation coefficient (R^2) indicate that the drug release was following First order release kinetics and non- fickian diffusion mechanism.

Stability Studies

Table no 10: Stability studies of optimized formulation (F6).

Time	Color	% drug content	Disintegration time	Cumulative % drug release	Cumulative % drug release
				25°± 2°/65±5%RH	**40±2°C / 75±5%RH**
First day	**White**	98.65±0.39	21.83±0.95	99.85±0.44	99.85±0.44
30 days	White	97.5±0.19	19.86±0.45	99.01±0.72	99.01±0.72
45 days	White	97.2±0.17	18.43±0.35	98.62±0.65	98.62±0.65

Discussion: The stability studies of optimized formulation F6 is given in table no.10. The studies concluded that, there were no remarkable changes during the period of storage as per ICH guidelines.

CONCLUSION

The present investigation successfully formulated Oral disintegrating tablets of Tenofovir by Direct compression method using Crospovidone, Croscarmellose sodium & Sodium starch glycolate to enhance the bioavailability & patient compliance. The blend of all the formulations showed good flow properties such as Angle of repose, Bulk density, Tapped density, Carr's index and Hausner's ratio. The FTIR and DSC studies revealed that there was no interaction found between the drug and the excipients. First the solid dispersions were prepared by fusion method to mask the bitter taste of the drug, then the tablets were formulated by Direct compression method using Crospovidone, Croscarmellose sodium and Sodium starch glycolate to enhance the bioavailability and patient compliance. Formulation F6 containing 5% Crospovidone was selected as optimised formulation as the disintegration time was 21±0.95 secs and in vitro drug release was 99.85±0.44 within 30 mins showing improved dissolution profile.

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