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Research Article

FORMULATION AND EVALUATION OF EMTRICITABINE AND TENOFOVIR DISOPROXIL FUMARATE FILM COATED TABLETS

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ABSTRACT

The objective of the present study is to formulate and evaluate once daily an immediate release tablet of Emtricitabine and Tenofovir disoproxil fumarate, which belong to class of anti-retroviral drugs known as nucleotide analogue reverse transcriptase inhibitors. Preformulation studies were performed prior to compression. The tablets were compressed by using dicalcium phosphate, lycatab-C, sodium starch glycolate, isopropyl alcohol, glyceryl distearate and ideal blue (Y-30-1070) was used for coating the tablets. Physical properties for granules such as angle of repose, bulk density, tapped density, hausner's ratio, compressibility index and post compression characteristics like weight variation, thickness, hardness, friability, disintegration time and drug release were studied. Formulations were evaluated for *in-vitro* drug release in 0.01N HCl over a period of 45 min revealed that sodium starch glycolate is found to be the better disintegrant when compared to lycatab-C. Wet granulation was found to be the best method of choice for formulation of these tablets when compared to direct compression. The results obtained from the present study indicates that, the prepared tablets of Emtricitabine and Tenofovir disoproxil fumarate could perform therapeutically with improved efficacy and better patient compliance by reducing pill burden.

Keywords: Dicalcium phosphate, Lycatab-C, Tenofovir disoproxil fumarate, Emtricitabine.

1. INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. Among the different routes of administration, the oral administration is the most preferred route due to various advantages including ease of ingestion, avoidance of pain and most importantly patient compliance. For many drug substances, conventional immediate release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patient[1]. Immediate release tablets have started gaining popularity and acceptance because they are easy to administer and lead to better patient compliance[2]. Despite of phenomenal advances in the other route of administration, the unavoidable truth is that the oral drug delivery remains well preferred delivery route.

Emtricitabine and Tenofovir disoproxil fumarate belong to class of antiretroviral drugs known as nucleotide analogue reverse transcriptase inhibitors exhibiting inhibitory activity against HIV-1 reverse transcriptase. Both the drugs are having less protein binding (less than 4% and 0.7% respectively) and with elimination half life 10 hours and 17 hours respectively. The main objective of this study is to formulate and evaluate once daily an immediate release tablet of Emtricitabine and Tenofovir disoproxil fumarate by reducing the dosing frequency and increasing patient compliance.

2. MATERIALS AND METHODS

2.1. Materials: Emtricitabine (Natco Pharma Ltd, Hyderabad), Tenofovir disoproxil fumarate (Natco Pharma Ltd, Hyderabad) were received as Gift sample. Dicalcium phosphate (Signet Chemical Corporation Pvt.Ltd.), Pregelatinized Starch (Signet Chemical Corporation Pvt. Ltd), Sodium starch glycolate (Signet Chemical Corporation Pvt. Ltd), Isopropyl alcohol (Merck), Glyceryl distearate (Roquette India Pvt.Ltd.), and Ideal blue (Y-30-1070) (Colorcon Asia Pvt.Ltd.) were commercially procured and used for this study.

2.2. Method of preparation: Formulation of Emtricitabine and Tenofovir disoproxil fumarate tablets were prepared by direct compression and wet granulation method employing various excipients like dicalcium phosphate as diluent, sodium starch glycolate and lycatab-C as disintegrating agent and glyceryl distearate as lubricant as shown in Table No: 1. Dicalcium phosphate and sodium starch glycolate or lycatab-C (5-8%) was passed through #40 and the above blend was mixed with Emtricitabine and Tenofovir disoproxil fumarate and passed through #24. The blended mixture was granulated with purified water and isopropyl alcohol ratio and the granules were passed through #12 and dried at 25±5^{0}C. These dried granules were passed through #18 and were lubricated with glyceryl distearate which was previously passed through #40. Finally the lubricated granules were compressed using 19×8.5mm capsule shaped punches. The compressed tablets were coated with Ideal blue (Y-30-1070), 15%w/w coating suspension of ideal blue in solvent isopropyl alcohol and water in 80:20 ratio. Ideal blue consists of HPMC E3 as film former, PEG 6000 as plasticizer, titanium dioxide as opacifier and FD&C2 blue aluminium lake as coloring agent. The parameters maintained for coating includes pan rpm with 18-20, peristaltic pump rpm with 1-2, set and bed temperatures with 55^{0}C and 38-41^{0}C and air pressure 1.8kg/cm^2. Different formulations were prepared and evaluated for thickness, hardness, friability, disintegration time and *in-vitro* drug release. Tablets were evaluated for *in-vitro* drug release in 0.01N HCl over a period of 45 min.

2.3. Drug-excipient compatibility studies: They provide the framework for the drugs in combination with the excipients in the fabrication of the dosage form and establish that the active drug has not undergone degradation, by carrying out infrared light absorption scanning spectroscopy studies (IR), DSC and by HPLC.

The pure drug and its formulation were subjected to IR studies by potassium bromide disc (pellet) method[3].

A Differential scanning calorimetry was used to study physical and chemical interaction between the drug and excipients used. Samples of the pure drug and optimized formulation were taken in flat bottomed aluminium pans and heated over a temperature range of 30 to 300^{0}C at a rate of 10^0/min with purging of nitrogen (50mL/min) using alumina as a reference standard, recorded on DSC-60, Shimadzu instrument.

Drug-excipient compatibility studies by HPLC were performed by placing the drug and excipient mixture in glass vials and sealed with aluminum foil and stored at elevated temperatures as 40^{0}C/75%RH and 55^{0}C/60%RH in capped vials for initial, 14 and 28 days. At the end the samples were analyzed for interaction between the active drug and excipient mixture

2.4. Evaluation of physical characteristics of granules

Angle of repose: Angle of Repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane and it was determined by the funnel method. The powder blend which was accurately weighed was taken in the funnel and the height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the blend[4]. The powder blend was allowed to flow through the funnel and diameter of the powder cone was measured. Angle of repose (θ) was calculated using the formula[5].

$$\text{Angle of Repose } (\theta) = \tan^{-1}(h/r)$$

Where, h = height of pile
r = radius of the base of the pile
θ = angle of repose

Bulk density determination: Weighed quantity of the powder was taken in a graduated measuring cylinder and volume (V_0) is measured and bulk density is calculated using the formula[6].

$$\text{Bulk density (BD)} = \frac{\text{Weight of the powder}}{\text{Volume of powder}}$$

Tapped density determination: Weighed quantity of powder was taken in a graduated cylinder and the volume is measured (V_0). The

graduated cylinder was fixed in the 'Tapped Densitometer' and tapped for 500, 750 and 1250 times until the difference in the volume after consecutive tappings was less than 2%. The final reading was denoted by (V_f).

$$\text{Tapped density (TD)} = \frac{W}{V_f}$$

Hausner ratio: Hausner ratio indicates the flow properties of the powder and measured by the ratio of tapped density to bulk density. Hausner ratio was calculated by using the formula.

$$\text{Hausner Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \text{ or } \frac{V_f}{V_o}$$

Where V_0 = Initial volume and V_f = Final volume

Compressibility Index: The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is simple, quick and popular method of predicting powder flow characteristics. Carr's index was calculated by using the formula given below[7].

$$\text{Compressibility Index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

2.5. Evaluation of tablets

Average weight of tablets: 20 tablets were randomly selected and weighed. The average weight of tablets was calculated using the following formula.

$$\text{Average weight} = \frac{\text{Weight of 20 tablets}}{20}$$

Weight variation test: 20 tablets were randomly selected and weighed individually. The average weights of these tablets were determined. The weight variations of individual tablets were determined with respect to average weight and % weight variation[8]. The weight variation test would be a satisfactory method of determining the drug content uniformity. The percent deviation was calculated using the following formula.

$$\% \text{ Deviation} = \frac{(\text{Individual weight} - \text{Average weight})}{\text{Average weight}} \times 100$$

Friability: The friability test was performed by taking initial weights of 20 tablets and placed in the friabilator, rotating at 25rpm for 4min. The difference in the weight is noted and expressed as percentage. Friability should be preferably between 0.5 to 1.0% and was calculated using the following formula[9].

$$\% f = \left(1 - \frac{W}{W_o}\right) \times 100$$

Where W_0 and W are the weights of tablets before and after the test, respectively.

Hardness test: The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. Tablets were randomly picked from each formulation and the mean and standard deviation values were calculated[10].

Disintegration test: Disintegration time was measured using USP disintegration test apparatus. Randomly six tablets were selected from each batch for disintegration test and were performed in 900 ml distilled water at 37±0.5^{0}C.

Assay: Assay is carried out using HPLC equipped with UV detector and data handling system.

Chromatographic conditions

Column	: Purosphere star – RP18, 150 * 4.6 mm, 5µm
Flow rate	: 1.0 ml/min
Wavelength	: UV-254 nm
Column temperature	: 30^{0}C
Injection volume	: 20µl
Run time	: 12 min.

Mobile phase A: It was prepared by filtered and degassed mixture of phosphate buffer pH 3 and acetonitrile in ratio of 970:30 v/v respectively.

Mobile phase B: It was prepared by filtered and degassed acetonitrile-HPLC grade.

Diluent: It was prepared by mixing phosphate buffer pH 3 and acetonitrile in ratio of 60:40 v/v respectively.

Emtricitabine and Tenofovir disoproxil fumarate standard preparation: Accurately weighed and transferred about 20mg of Emtricitabine working standard and 30mg of Tenofovir working standard into a 250 ml volumetric flask. Add about 180ml of diluents, sonicated to dissolve and the solution was cooled to room temperature and diluted to 250ml with diluents. Transfer 2ml of above solution into a 100ml volumetric flask and diluted to 100ml with Mobile phase-A and mixed well.

Sample preparation: Sample solution was prepared by accurately weighing 20 tablets and crushed into a fine powder. Transfer an accurately weighed amount of the powder equivalent to 200mg of Emtricitabine into 250ml volumetric flask. Add 180ml of diluents and shaked for 10min in rotating shaker and sonicated for 30min with occasional shakings. The solution was cooled to room temperature and diluted to volume with diluents and mixed well. Centrifuge the solution to 3000rpm for 10min. Transfer 1ml of above centrifuged solution into 100 ml volumetric flask and diluted to 100 ml with mobile phase-A.

Procedure: Separately injected equal volumes (about 20µl) of the water as blank, standard preparation and sample preparation into chromatograph and record the chromatograms and measured the peak area response for analyte peak. The percentage content of Emtricitabine and Tenofovir disoproxil fumarate tablets was calculated using the following formula.

$$\%\ \text{content of drug} = \frac{TA}{SA} \times \frac{SW}{250} \times \frac{2}{100} \times \frac{250}{TW} \times \frac{100}{1} \times \frac{P}{100} \times \frac{\text{Avg Wt}}{LA} \times 100$$

Where, TA= Peak area response due to Emtricitabine/ Tenofovir disoproxil fumarate from sample preparation

SA= Peak area response due to Emtricitabine/ Tenofovir disoproxil fumarate from standard preparation

SW= Weight of Emtricitabine/ Tenofovir disoproxil fumarate working standard taken in mg.

TW= Weight of sample taken in mg.

P= Purity of Emtricitabine/ Tenofovir disoproxil fumarate working standard taken on, as is basis.

AVG WT= Average weight of tablets.

LA= Labelled amount of Emtricitabine/ Tenofovir disoproxil fumarate.

Dissolution: *In-vitro* drug release studies were carried out by using USP Type 2 (rotating paddle method). The dissolution medium consists of 900 mL of 0.01N HCl kept at 37°C ± 0.5°C. Tablets were placed in the baskets of dissolution apparatus rotating at 50 rpm and 5ml of samples were withdrawn at specified time intervals and the volume was replaced with fresh medium. The withdrawn samples were filtered by using filter paper and analyzed for drug content using HPLC equipped with UV detector at 254 nm.

Chromatographic conditions

Column : Purosphere star - RP18, 150 * 4.6 mm,5µm
Flow rate : 1.0 ml/min
Wavelength : UV-254 nm
Column temperature : 30^0C
Injection volume : 10µl
Run time : 12 min.

Emtricitabine and Tenofovir disoproxil fumarate standard preparation: Accurately weighed and transferred about 22.2mg of Emtricitabine working standard and 33.3mg of Tenofovir working standard into a 100 ml volumetric flask. Add about 60ml of diluents, sonicated to dissolve and the solution was cooled to room temperature and make up the volume with 0.01N HCl to 100 ml.

Sample preparation: Place one tablet in each of six dissolution flasks containing 900ml of dissolution medium, previously maintained at 37^0C ± 0.5^0C, taking care to exclude air bubbles from the surface of each dosage unit and immediately operate the apparatus for 45min. After completion of specified time interval, withdraw a portion of solution from zone midway between the surface of dissolution medium and top of rotating blade, not less than 1 cm from vessel wall and filtered it through o.45µm membrane filter. The percentage content of Emtricitabine/ Tenofovir disoproxil fumarate was calculated using the following formula.

$$\%\ \text{content of drug} = \frac{TA}{SA} \times \frac{SW}{100} \times \frac{900}{1} \times \frac{P}{100} \times \frac{100}{LA}$$

Where,TA= Peak area response due to Emtricitabine/Tenofovir disoproxil fumarate from sample preparation

SA= Peak area response due to Emtricitabine/Tenofovir disoproxil fumarate from standard preparation

SW= Weight of Emtricitabine/Tenofovir disoproxil fumarate working standard taken in mg.

P= Purity of Emtricitabine/Tenofovir disoproxil fumarate working standard taken on, as is basis.

LA= Labelled amount of Emtricitabine/Tenofovir disoproxil fumarate.

Mechanism of Drug Release: Various models were tested for explaining the kinetics of drug release. To study the mechanism of the drug release rate kinetics of the dosage form, the obtained results were fitted into Zero-order, First

order, Higuchi, Hixson-Crowell model and Korsmeyer-Peppas release model[4].

Similarity and Dissimilarity factors: The estimation of the dissimilarity factor (f1) and similarity factor (f2) is to compare the dissolution profile of optimized formulation with marketed product. The difference factor (f1) calculates the percent difference between marketed product and formulation trial at each time point. The FDA suggested that two dissolution profiles were declared similar if f2 value between 50-100 and f1 was 0-15. It was calculated using the following formula[11].

$$f1 = \{[\Sigma_{t=1}^{n} |R_t - T_t|] / [\Sigma_{t=1}^{n} R_t]\} \times 100$$

$$f2 = 50 \times \log \{[1 + (1/n) \Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100\}$$

where, n is the number of dissolution sample times,

R_t and T_t are the individual or mean percent dissolved at each time point, t, for the marketed and formulation trial dissolution profiles, respectively.

Therefore these factors directly compare the difference between percent drug dissolved per unit time for formulation trial and marketed product.

Stability Studies: The stability studies were carried out according to ICH to assess the drug formulation stability. Optimized formulation was sealed in aluminium packaging laminated with polyethylene. Samples were kept at 25^0C/60% RH, 30^0C/65% RH and 40^0C/75% RH for 3 months. At the end of the study, the formulation was observed for change in physical appearance, colour, drug content and drug release characteristics[12].

3. RESULTS AND DISCUSSION

Emtricitabine and Tenofovir disoproxil fumarate tablets were formulated by using wet granulation method using dicalcium phosphate as diluent, sodium starch glycolate and lycatab-C as disintegrating agent and glyceryl distearate as lubricant as shown in Table No: 1.

3.1. FT-IR Spectra: The FTIR Spectrums of Emtricitabine, Tenofovir disoproxil fumarate and optimized formulation were shown in Fig 1, indicated no interaction between Emtricitabine, Tenofovir disoproxil fumarate and excipients when compared with the infrared spectrum of pure drugs.

3.2. Differential Scanning Calorimetry (DSC): DSC thermograms were obtained for pure Emtricitabine, pure Tenofovir disoproxil fumarate and for optimized formulation containing Emtricitabine, Tenofovir disoproxil fumarate and other excipients were shown in Fig 2. Pure Emtricitabine and pure Tenofovir disoproxil fumarate showed a sharp melting endotherm at 156.9^0C and 268.31^0C respectively. DSC thermogram of optimized formulation of tablet showed a broad peak of melting endotherm in the temperature range at 80.68-156.66^0C and 258.62-285.76^0C. The DSC thermogram of optimized formulation containing the drug and exicipients showed no characteristic peaks of the excipients and the drug peak was still present but slightly shifted from their original position. It indicates that the drug and excipients are compatible with each other.

3.3. HPLC: The drug and excipient compatibility studies were performed by means of physical mixture of drug and excipients at elevated temperatures as 40^0C/75%RH and 55^0C/60%RH in capped vials for initial, 14 and 28 days and no interaction between the active drug and excipient mixture were observed. This indicates that the drug is compatible with the formulation components.

3.4. Evaluation of physical characteristics of granules: The blends were analyzed for the parameters such as bulk density, tapped density, compressibility index, Hausner's ratio, angle of repose and the results were found to be within the limits. Bulk density and tapped density values range between 0.28-0.67g/ml and 0.43-0.76g/ml and the values were found to be within limits. Compressibility index values ranges between 11.05-13.4% and Hausner's ratio values were in the range of 1.12-1.15 for all formulations except for F1 and F2. After evaluating the blend parameters, the good flow properties were found for F3 to F11 formulations and the values are tabulated in Table No: 2.

3.5. Evaluation of tablets: All the tablets of different formulations complied with the limits of uniformity of weight variation (±5%). The thickness of the tablet ranged from 6.8mm to 7mm. The hardness of the tablets for all formulations ranged from 7.7 to 8.3 kg/cm^2 and percentage friability of all formulations ranges from 0.1 to 0.25 % w/w and were within the limits. The disintegration time of all formulations was in the range of 9.58-13.5 min, except for F9,

F10 and F11 showed in the range of 27.16-27.25 min and the values are tabulated in Table No: 3.

Coated tablets of different formulations were within the limits of weight variation 1032-1038 mg, thickness 6.9-7.1 mm and disintegration time 11.16-14.83 min, except for F9, F10 and F11 showed 28.33, 28.25 and 29.17min respectively and the values are tabulated in Table No: 4.

The drug release was found to be ranged from 87.2% to 99.2% for Emtricitabine and 86% to 99.8% for Tenofovir disproxil fumarate (Figure 3-4). The F6 formulation is optimized and % drug release of emtricitabine was found to be 99% and for innovator it is 98.5%, for Tenofovir disoproxil fumarate was found to be 99.8% and for innovator it is 98.8% which showed similar % drug release profile. With reference to disintegrant, sodium starch glycolate is found to be the better disintegrant when compared to lycatab-C.

3.6. Mechanism of Drug Release: The data obtained from *in-vitro* dissolution studies were fitted to Zero order, First order, Higuchi, Hixson Crowell and Peppas equation. The data of the various models revealed that the optimized formulation F6 follows first order release model with Fickian diffusion mechanism and the values are tabulated in Table No: 5.

3.7. Similarity and Dissimilarity factors: The dissimilarity factor (f1) and Similarity factor (f2) obtained for Emtricitabine and Tenofovir disoproxil fumarate was found to be within the standards. The standards for similarity factor and dissimilarity factor are 50-100 and 0-15 and the values are tabulated in Table No: 6 and 7.

3.8. Stability studies: The stability studies were carried out according to ICH guidelines at different conditions for F6 formulation for 3 months. During the stability studies, all the parameters of the optimized batch F6 do not show any remarkable changes and the values are tabulated in Table No 8.

4. CONCLUSION

In the present investigation Emtricitabine and Tenofovir disoproxil fumarate film coated tablets were formulated and evaluated using sodium starch glycolate and lycatab-C disintegrants to achieve immediate release by employing wet granulation technique. Based on the results the best formulation F6 has shown disintegration time 9.58±0.03 min, in vitro drug release for 45min in 0.01N HCl was found to be 99% and 99.8% for Emtricitabine and Tenofovir disoproxil fumarate respectively and drug release kinetics follows first order release model with fickian diffusion mechanism. Stability studies were performed for F6 formulation according to ICH guidelines for 3 months. Drug release of F6 formulation complies with innovator product (Truvada) and was found to be stable. Based on the above results, it was concluded that optimized formulation (F6) complies with the innovator product and hence considered as an ideal formulation.

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Table 1: Formulation trials F1-F11

S. No.	Ingredients	Quantity per tablet (mg)										
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
1	Emtricitabine	200	200	200	200	200	200	200	200	200	200	200
2	Tenofovir disoproxil fumarate	300	300	300	300	300	300	300	300	300	300	300
3	Dicalcium phosphate	440	440	440	430	440	430	420	410	430	420	410
4	Sodium starch glycolate	50	---	50	60	50	60	70	80	---	---	---
5	Lycatab-C	---	50	---	---	---	---	---	---	60	70	80
6	Purified water	---	---	q.s.	q.s.	---	---	---	---	---	---	---
7	Isopropyl alcohol+Purified water (80:20)	---	---	---	---	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
8	Glyceryl distearate	10	10	10	10	10	10	10	10	10	10	10
9	Ideal Blue (Y30-1070)	30	30	30	30	30	30	30	30	30	30	30
	Total	1030	1030	1030	1030	1030	1030	1030	1030	1030	1030	1030

*F1and F2: Direct compression & *F3 to F11: Wet granulation

Table 2: Pre-compression parameters

Formulation Code	Angle of Repose	Bulk density(g/ml)	Tapped density(g/ml)	Compressibility Index %	Hausner's Ratio
F1	38.00±0.55	0.320±0.015	0.450±0.001	28.8±0.12	1.40±0.020
F2	40.36±0.20	0.280±0.004	0.435±0.001	35.6±0.05	1.55±0.020
F3	27.80±0.06	0.642±0.006	0.742±0.002	13.4±0.15	1.15±0.008
F4	27.36±0.01	0.650±0.006	0.748±0.004	13.10±0.10	1.15±0.008
F5	26.07±0.14	0.660±0.001	0.754±0.002	12.46±0.02	1.14±0.009
F6	25.20±0.08	0.676±0.002	0.760±0.001	11.05±0.01	1.12±0.005
F7	25.71±0.51	0.670±0.002	0.758±0.002	11.60±0.06	1.13±0.010
F8	25.40±0.01	0.665±0.006	0.760±0.001	12.5±0.06	1.14±0.015
F9	26.56±0.05	0.656±0.007	0.738±0.001	11.11±0.01	1.12±0.003
F10	27.07±0.03	0.649±0.003	0.740±0.001	12.29±0.02	1.14±0.013
F11	26.81±0.03	0.652±0.004	0.736±0.003	11.41±0.03	1.12±0.005

Table 3: Core tablet parameters

Formulation Code	Weight Variation(mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%w/w)	Disintegration time (min)
F3	1000.0±2.1	6.9±0.01	8.0±0.5	0.18±0.010	13.51±0.09
F4	1000.5±1.8	7.0±0.06	7.8±0.9	0.11±0.005	9.60± 0.07
F5	1000.5±1.9	6.8±0.03	8.0±0.5	0.24±0.005	13.50±0.11
F6	1000.1±1.5	6.9±0.07	7.9±0.5	0.13±0.010	9.58±0.03
F7	1000.4±1.6	7.0±0.01	7.7±0.5	0.19±0.005	9.66±0.02
F8	1000.6±1.8	6.9±0.03	7.8±0.9	0.24±0.005	9.60±0.01
F9	1000.2±2.3	7.0±0.07	8.3±0.4	0.25±0.010	27.25±0.62
F10	1000.6±1.8	7.0±0.20	7.7±0.5	0.23±0.005	27.16±0.17
F11	1000.0±1.5	6.8±0.08	8.3±0.2	0.21±0.010	27.20±0.08

Table 4: Coated tablet parameters

Formulation Code	Weight Variation(mg)	Thickness (mm)	Disintegration time (min)
F3	1033±1.95	7.0±0.01	14.83±0.01
F4	1032±1.88	7.1±0.06	11.16±0.04
F5	1035±0.99	6.9±0.03	14.82±0.02
F6	1032±1.49	7.0±0.07	11.16±0.02
F7	1034±1.41	7.1±0.01	11.25±0.01
F8	1035±1.15	7.0±0.03	11.6±0.06
F9	1038±1.15	7.1±0.07	28.33±0.23
F10	1036±1.69	7.1±0.20	28.25±0.62
F11	1037±1.63	6.9±0.08	29.17±0.19

Table 5: *In-vitro* release kinetics for formulation F6

F.C	ZERO ORDER R(CvT)		FIRST ORDER TvsLog% Remaining		HIGUCHI R(Cv√T)		HIXSO CROWELL $Tvs(Q_o^{1/3}-Qt^{1/3})$		PEPPAS LogTvsLogC		
	R^2	K	R^2	K	R^2	K	R^2	K	R^2	K	n
EMT	0.782	1.972	0.993	0.101	0.955	15.55	0.975	0.079	0.902	3.054	0.485
TDF	0.754	1.975	0.983	0.135	0.943	15.76	0.977	0.089	0.889	2.91	0.465

Table 6: Calculation of similarity (f2) and dissimilarity (f1) factors for Emtricitabine

N (min)	Innovator (R_t)	F6 (T_t)	$\lvert R_t-T_t \rvert$	$\lvert R_t-T_t \rvert^2$	Similarity Factor (f2)	Dissimilarity Factor (f1)
5	31	32.5	1.5	2.25	78	2
10	64.4	63.8	0.6	0.36		
15	73.2	70.5	2.7	7.29		
30	92.2	93.9	1.7	2.89		
45	98.5	99	0.5	0.25		

Table 7: Calculation of similarity (f2) and dissimilarity (f1) factors for Tenofovir disoproxil fumarate

N (min)	Innovator (R_t)	F6 (T_t)	$\lvert R_t-T_t \rvert$	$\lvert R_t-T_t \rvert^2$	Similarity Factor (f2)	Dissimilarity Factor (f1)
5	33.1	32.5	0.6	0.36	75	2
10	65.8	63.8	2	4		
15	73.9	70.5	3.4	11.56		
30	95.6	93.9	1.7	2.89		
45	98.8	99	0.2	0.04		

Table 8: Parameters at different conditions after stability studies

S.N0	Parameters		Conditions			
			Initial	25^0C/ 60%RH	30^0C/ 65%RH	40^0C/ 75%RH
			0 Day	3 month	3month	3 month
1	Average weight (mg)		1032	1032	1032	1032
2	Thickness (mm)		7.1	7.1	7.1	7.1
3	Disintegration time (min)		9.58	9.57	9.56	9.56
4	Assay (%w/w)		99.8	99.8	99.7	99.6
5	% Drug release	EMT	99.0	98.8	98.6	98.5
		TDF	99.8	99.4	99.2	99.0

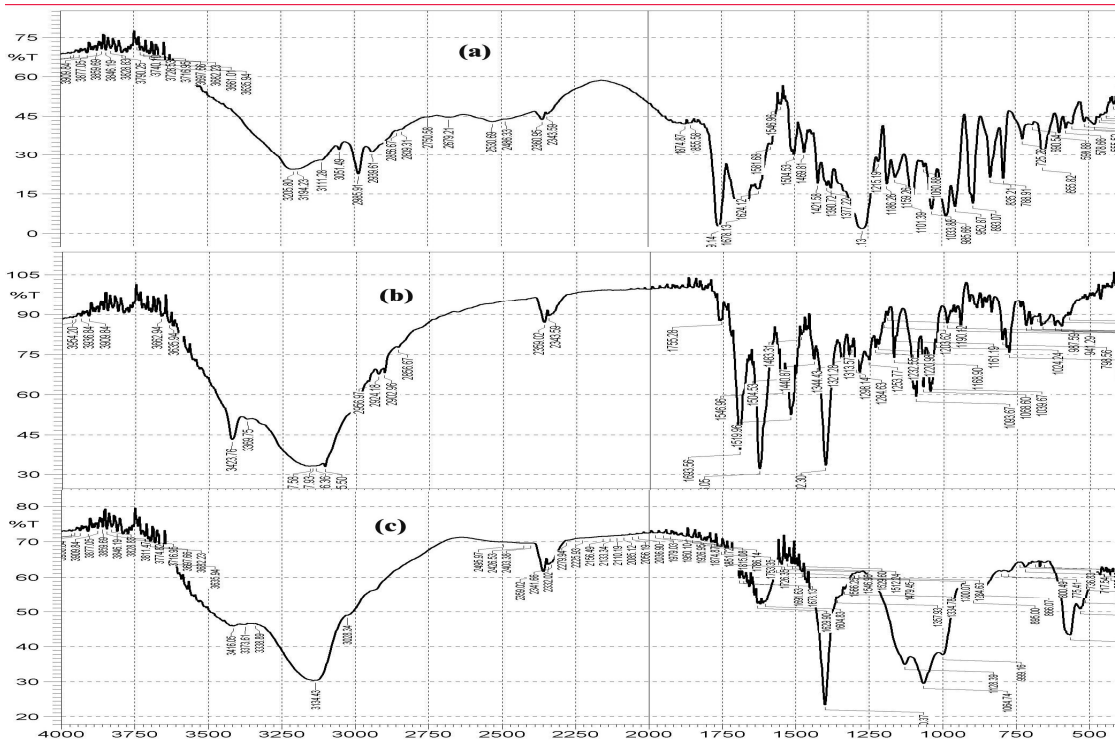

Fig. 1: FTIR spectra of drugs and optimized formulation. (a) Tenofovir disoproxil fumarate, (b) Emtricitabine, (c) optimized formulation

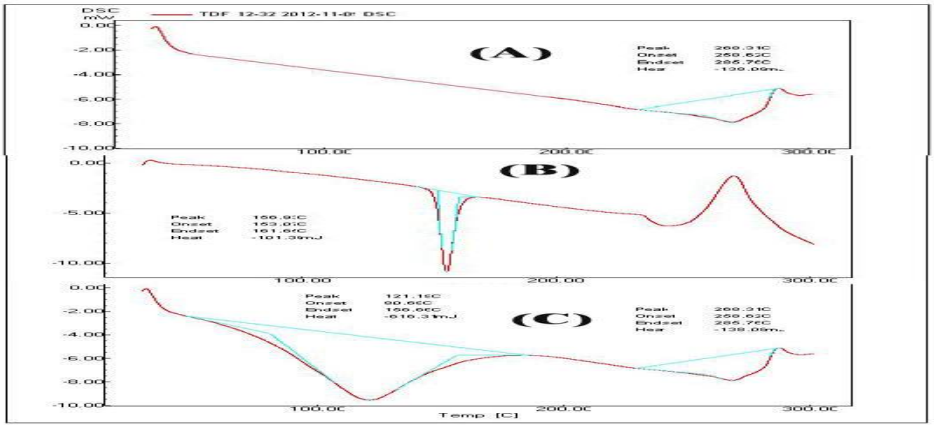

Fig. 2: DSC thermogram of drugs and optimized formulation.
(A) Tenofovir disoproxil fumarate, (B) Emtricitabine, (C) optimized formulation

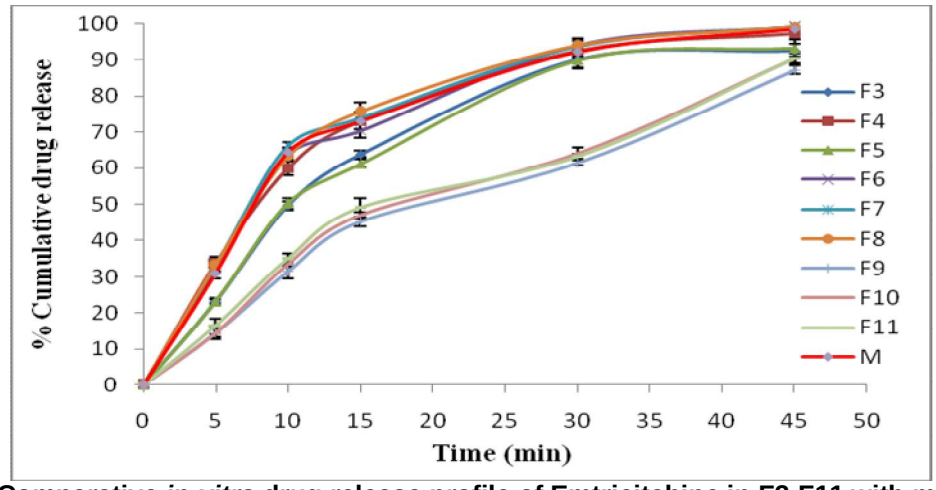

Fig. 3: Comparative *in-vitro* drug release profile of Emtricitabine in F3-F11 with marketed formulation

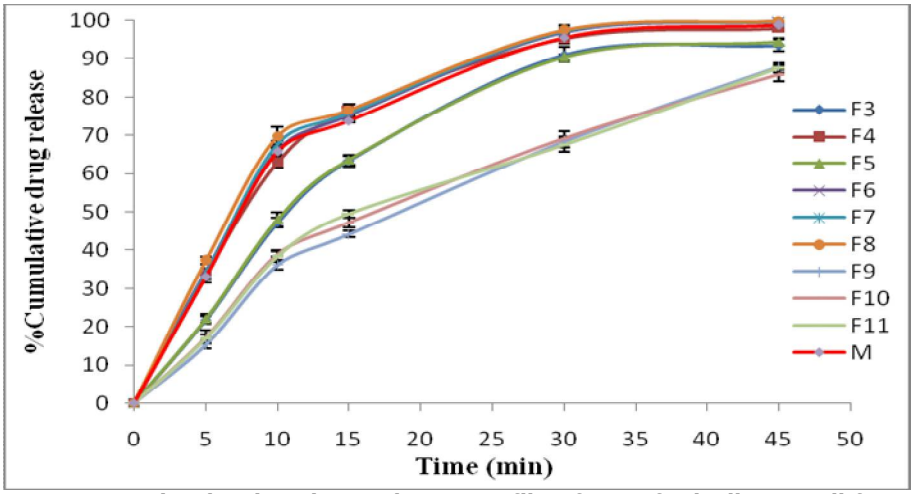

Fig. 4: Comparative *in-vitro* drug release profile of Tenofovir disoproxil fumarate in F3-F11 with marketed formulation

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