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

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ABSTRACT

Emtricitabine and Tenofovir Disoproxil fumarate belongs to class of Anti-retroviral drugs known as nucleotide analogue reverse transcriptase inhibitors. The main objective of the present study is to formulate and evaluate an film coated tablet of Emtricitabine and Tenofovir Disoproxil fumarate using different disintegrates. Preformulation studies were performed prior to compression. The tablets were compressed using microcrystalline cellulose, lactose, pregelatinized starch, Crosscarmellose sodium, talc, sodium starch glycolate, magnesium stearate and opadry II blue was used for coating the tablets. The fabricated tablets were evaluated for various micromeritic properties like bulk density, tapped density, compressibility index, Hauser's ratio, angle of repose and post compression characteristics like thickness, hardness, friability, disintegration time and drug release. Crosscarmellose sodium is found to be the better disintegrate when compared to sodium starch glycolate in the formulation of film coated tablets of Emtricitabine and Tenofovir Disoproxil fumarate. Compared to the direct compression, wet granulation with pregelatinized starch as binder was found to be the best method of choice for formulation of these tablets. The absorbance of Emtricitabine and Tenofovir Disoproxil fumarate were screened in the UV region and the maximum absorbance was found to be 282 nm and 258nm respectively and this was used for HPLC analysis. The results of the present study indicates that, the prepared tablets of Emtricitabine and Tenofovir Disoproxil fumarate could perform therapeutically, with improved efficacy and better patient compliance like that of the marketed product.

Key Words:- Sodium starch glycolate, Magnesium stearate, opedryblue 2,Tenofovir disoproxil fumarate, Emtricitabine.

INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects (Diane J.Burgess and Anthony J. Hickey, 2007). For many substances, film coated formulation provide clinically effective therapy maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patients. The Indian National AIDS Control Organization (NACO) projects that there will be 90 lakh HIV cases by 2010 (Gowtham *et al*., 2011).

Emtricitabine (EM) is a nucleotide reverse transcriptase inhibitor (NRTI) with activity against Human Immunodeficiency Virus (Type I) (HIV-1) (Prasanth Sai *et al*., 2011). Chemically, it is 4-amino-5fluoro-1-[2-(hydroxymethyl]-1,3-oxathiolan-5-yl] pyrimidin -2- one.

Tenofovir disproxil fumarate (TDF) belongs to class of anti-retroviral drugs knows as nucleotide analogue reverse transcriptase inhibitors (NtRTIs) which blocks reverse transcriptase an enzyme crucial to viral production in HIV-infected people. Chemically, TDF is 9[(R)-2-[[bis [[(isopropoxycarbonyl) oxy] methoxy] phosphinyl]

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methoxy] propyl] adenine fumarate (Devanand Pinate *et al*., 2012).

Tenofovir is a nucleotide analog of deoxyadenosine monophosphate, while Emtricitabine, the fluorinated derivative of lamivudine, is an analog of deoxycitidine are active against HIV-1, -2 and hepatitis B virus. Their long half-lives in plasma and in peripheral blood mononuclear cells allow oncedaily dosing in a single tablet, thus providing the nucleotide backbone for once-daily dosing, as a component of highly active antiretroviral therapy (HAART) (Jain CP and Naruka PS, 2009).

The introduction of potent antiretroviral agents and the combined use of these drugs have markedly reduced the replication of HIV in many patients, and improved survival rates. HAART is now the standard of care in the treatment of HIV infection. It is successful in reducing viral load, extending the asymptomatic phase of infection and improving the quality of life for many infected individuals.

MATERIALS AND METHODS

Emtricitabine (Cipla Pvt. Ltd, India), Tenofovir disproxil fumarate (Matrix laboratories, India) were received as Gift sample. Microcrystalline cellulose 102 (Vijilak Pharma, India), Lactose monohydrate (Micro pellet, India), Pregelatinized Starch (Signet Chemical Corporation Pvt. Ltd), Croscarmellose sodium (Colorcon Asis Pvt. Ltd.), Talc (Ganesh Scientifics Ltd.), Sodium starch glycolate (Sigma chemicals India.), Magnesium Stearate (Amistri Drugs Ltd,) and Opadry II blue (Y-30-1070) (Colorcon Asia Pvt, Ltd.) were commercially procured and used for this study.

Formulation of Tablets

Formulation of Emtricitabine and Tenofovir disproxil fumarate tablets were prepared by direct compression and wet granulation method employing various excipients as mentioned in the Table 1. Emtricitabine, Tenofovir disproxil fumarate, lactose monohydrate, 50% microcrystalline cellulose and sodium starch glycolate or croscarmellose sodium were passed through #40 mesh and mixed well. Binding solution was prepared separately by dissolving weighed quantity of pregelatinized starch in the water. The blended mixture was granulated with the above prepared binding solution and granules were dried in tray drier at 60°C. The dried granules were passed through #20 mesh and magnesium stearate was individually passed through #60 mesh. The dried granules were lubricated with remaining 50% microcrystalline cellulose and magnesium stearate. The tablets were compressed using a 27 station tablet compression machine using 19.2 × 9 mm capsule shaped punches. (Rimek, Ahmedabad).

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 3000C at a rate of 100 /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 400C/75%RH and 550C/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

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. 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 (Martin A, 2001)

Angle of repose $\theta = \text{Tan-1 } (h/r)$

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 (V0) is measured and bulk density is calculated using the formula (Prasanth Sai *et al*., 2011)

Bulk Density (BD) = Weight of granules /untapped volume of granules

Tapped density determination: Weighed quantity of powder was taken in a graduated cylinder and the volume

is measured (V0). 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 (Vf).
Tapped Density (TD) = Weight of granules / tapped volume of granules

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 (Lachman *et al*., 1987)
Hausner's ratio = Tapped Density / Bulk Density.

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.
Average weight= 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 (Abbaraju Prasanna Lakshmi *et al*., 2012). The weight variation test would be a satisfactory method of determining the drug content uniformity.

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% (Bishwajit Bokshi and Aparajita Malakar, 2012).

Hardness test: The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm . Tablets were randomly picked from each formulation and the mean and standard deviation values were calculate (Lieberman *et al*., 1989).

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±0.50C (Lieberman *et al*., 1989).
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 : 300C
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.
Percentage content of emtricitabine/Tenofovir Disoproxil fumarate =TA/SA * SW/100 * 900/1 * p/100 * 100/LA
Where
TA = peak area response due to emtricitabine/Tenofovir Disoproxil fumarate from standard preparation
SW = weight of emtricitabine/Tenofovir fumarate working standard taken in mg.
P= purity of emtricitabine/ Tenofovir fumarate working standard taken on, as is basis.

LA= labeled 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 : 300C
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 370C ± 0.50C, 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.
Percentage content of emtricitabine/Tenofovir Disoproxil fumarate =TA/SA * SW/100 * 900/1 * p/100 * 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 mode.

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.

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 250C/60% RH, 300C/65% RH and 400C/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 .

RESULTS AND DISCUSSION

Emtricitabine and Tenofovir disoproxil fumarate tablets were formulated by using wet granulation method using lactose mono hydrate as diluent, sodium starch glycolate and Crosscarmellose sodium as disintegrating agent and Magnesium stearate as lubricant as shown in Table No: 1.

HPLC: The drug and excipient compatibility studies were performed by means of physical mixture of drug and excipients at elevated temperatures as 400C/75%RH and 550C/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.

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.

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/cm2 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 marketed product.

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.

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.

Figure 1. Structure of Emtricitabine Structure

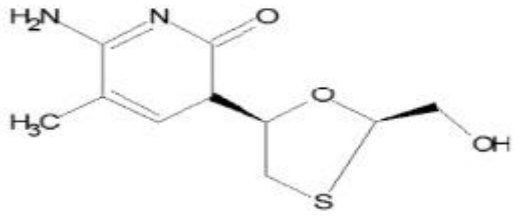

Figure 2. Structure of Tenofovir disproxil fumarate

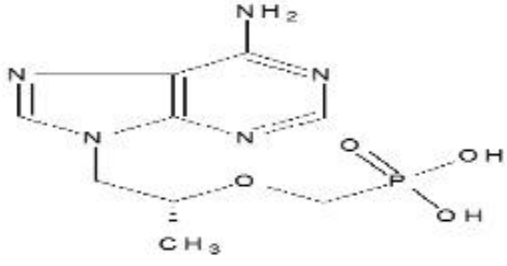

Figure 3. In vitro drug release profile for INNOVATOR product (emtricitabine and TDF)

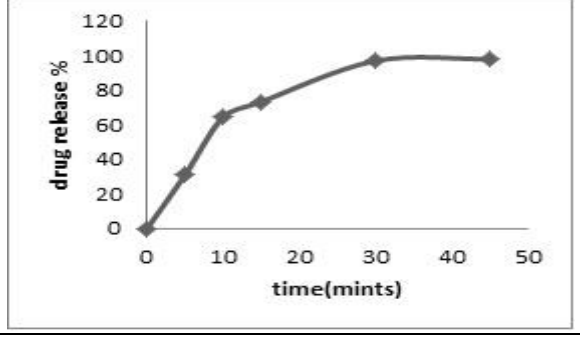

Figure 4. In vitro drug release profile for emtricitabine formulation

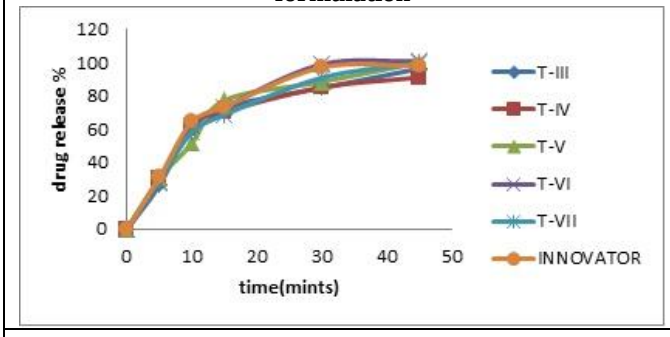

Figure 5. In vitro drug release profile for TDF formulation

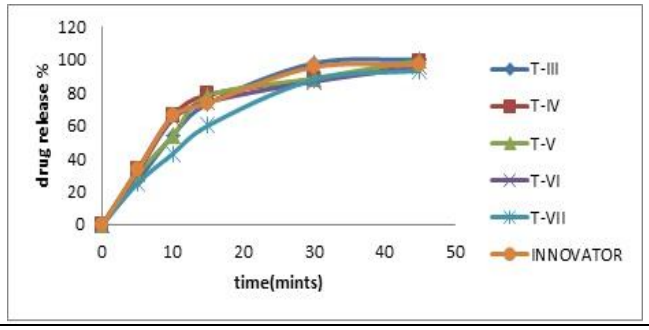

Figure 6. Zero order plot(emtricitabine)

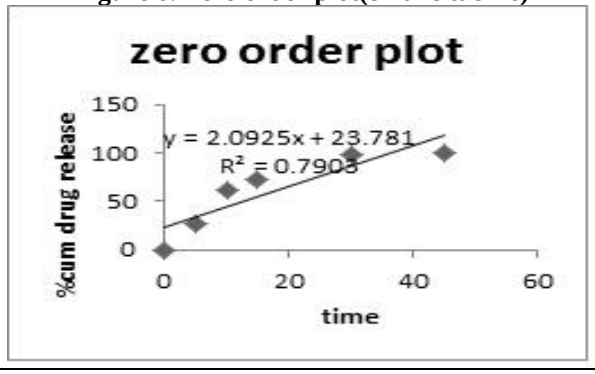

Figure 7. first order plot(emtricitabine)

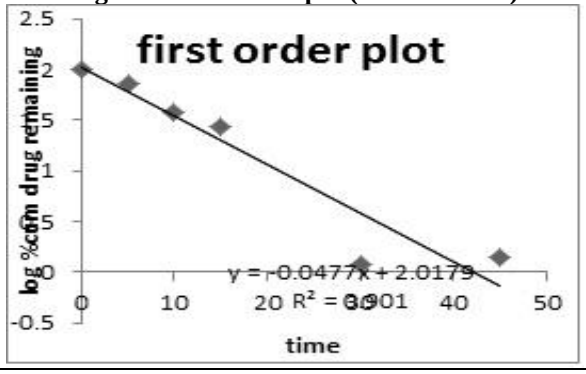

Figure 8. higuchi plot(emtricitabine)

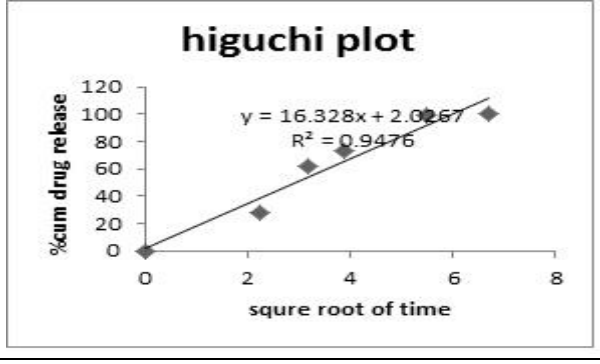

Figure 9. korsmeyer pepper plot(emtricitabine)

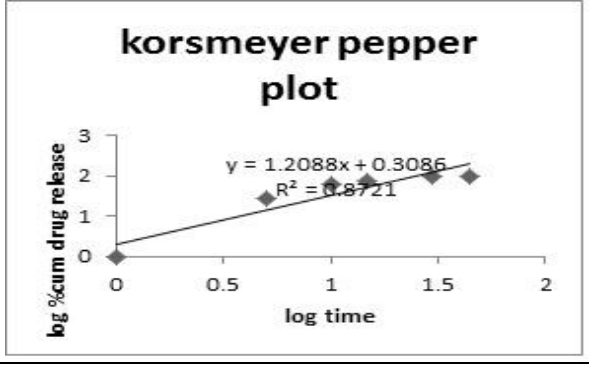

Figure 10. Zero order plot(TDF)

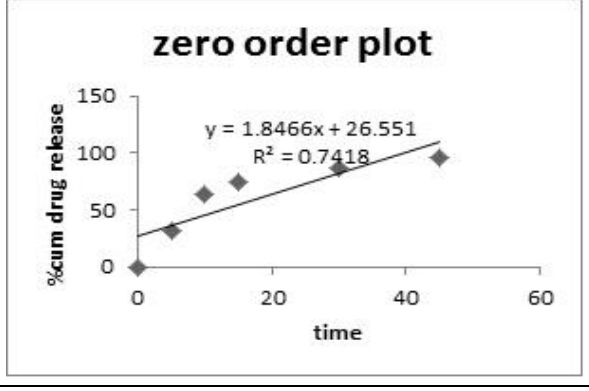

Figure 11. first order plot(TDF)

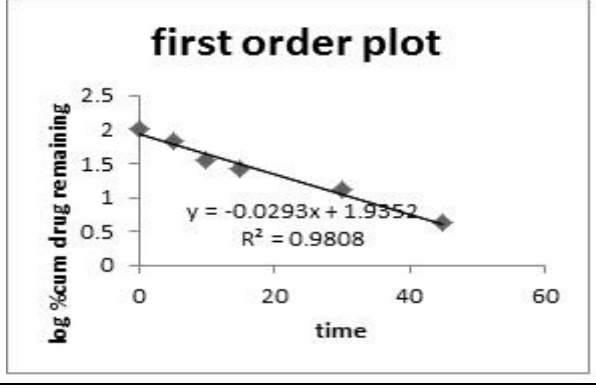

Figure 12. Higuchi plot(TDF)

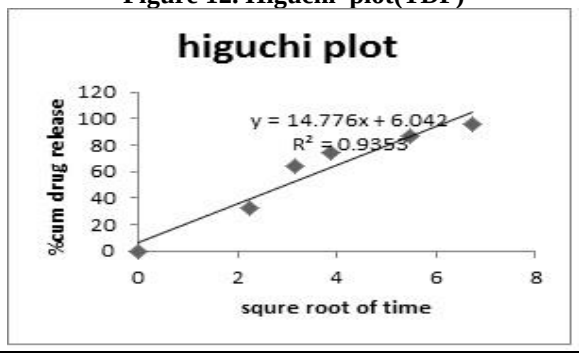

Figure13. Korsmeyer pepper plot (TDF)

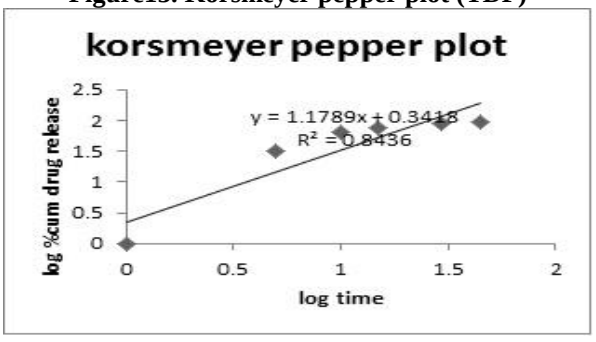

Table 1. Formulation Trials T1-TX

Ingredients	Quantity per tablet(mg)									
	T- I	T-II	T-III	T- IV	T-V	T- VI	T-VII	T-VIII	T- IX	T-X
Emtricitabine	200	200	200	200	200	200	200	200	200	200
Tenofovir Disoproxil fumarate	300	300	300	300	300	300	300	300	300	300
Pregelatinized starch	---	---	50	50	50	50	50	---	50	50
Lactose monohydrate	80	80	80	50	80	80	80	80	80	50
Microcrystalline cellulose pH102	355	355	305	295	305	295	285	355	305	295
Sodium starch glycolate	50	---	50	60	---	---	---	50	50	60
Crosscarmellose sodium	----	---	---	---	50	60	70	---	----	---
Magnesium stearate	15	15	15	15	15	15	15	15	15	15
Crospovidone	---	50	---	30	---	----	----	---	---	30
Purified water	---	----	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Opadry blue II	30	30	30	30	30	30	30	30	30	30
Total	1030	1030	1030	1030	1030	1030	1030	1030	1030	1030

Table 2. Lubricated blend parameters

S No	Angle of Repose	Bulk density (g/ml)	Tapped density(g/ml)	Carr's index (%)	Hausner's Ratio	LOD at 105^{0}C
T-I	35.0	0.323	0.547	40.95	1.693	-
T-II	35.89	0.312	0.521	38.38	1.66	3.21
T-III	32.7	0.42	0.59	28.81	1.404	2.17
T-IV	30.03	0.45	0.57	21.05	1.266	2.04
T-V	27.8	0.48	0.58	17.06	1.208	1.50
T-VI	25.4	0.5	0.6	16.66	1.2	1.77
T-VII	27.4	0.46	0.62	25.8	1.3	1.98
T-VIII	30.03	0.45	0.57	21.07	1.266	2.04
IX	35.0	0.323	0.547	41.01	1.693	3.21
X	26.1	0.51	0.578	16.98	1.277	3.22

Table 3. Core tablet parameters

S No	Weight variation (mg)	Thickness (mm)	Hardness (kp)	Friability (%w/w)	Disintegration time (mints)
T-I	1018±1.7	6.8±0.5	26±0.5	0.024±0.2	12min 40sec±3sec
T-II	1016±1.3	6.5±0.3	24±0.6	0.025±0.5	10min 30sec±5sec
T-III	1021±1.5	7.18±0.5	15.4±0.4	0.099±0.1	2min 57sec±2.5sec
T-IV	1023±0.5	7.11±0.5	18.4±0.3	0.078±0.05	6min 38sec±3.5sec
T-V	1017±1.5	6.35±0.8	24.4±0.9	0.028±0.07	8min 48sec±6.5sec
T-VI	1018±1.4	6.4±0.4	23±0.5	0.024±0.03	10min 50sec±6sec
T-VII	1014±1	6.6±0.5	24±0.3	0.021±0.05	9min 28sec±5sec
T-VIII	1025±0.5	7.19±0.2	25±0.4	0.024±0.05	10min 55sec±6sec
T-IX	1016±1.5	6.5±0.3	26±0.3	0.025±0.08	11min 39sec±8sec
T-X	1020±1	7.12±0.5	28±0.2	0.027±0.04	12min 49sec±5sec

Table 4. coated tablet parameters

S.No	Weight variation (mg)	Thickness(mm)	Hardness(kp)	Friability(%w/w)	Disintegration time (min)
T-III	1030±1.5	7.2±0.5	15±0.4	0.079±0.4	3min 26sec±2sec
T-IV	1039±0.8	7.27±0.9	19.4±0.4	0.068±0.03	7min 10sec±3sec
T-V	1036±2.5	6.9±0.4	22.4±0.9	0.023±0.07	10min 15sec±2sec
T-VI	1038±1.0	6.6±0.5	24±0.4	0.020±0.05	11min 40sec ±6sec
T-VII	1039±1.7	6.9±0.7	24.5±0.3	0.019±0.05	10min 40sec±7sec

Table 5. In-vitro drug release profile for Innovator (emtricitabine and TDF)

Time (minutes)	Cumulative percentage of drug release of TDF
0	0
5	33
10	65.8
15	73.9
30	95.6
45	96.8

Time (minutes)	Cumulative percentage of drug release of emtricitabine
0	0
5	31
10	64.4
15	73.3
30	97
45	98

Table 6. In vitro drug release profile for emtricitabine formulations

Time	T-III	T-IV	T-V	T-VI	T-VII
0	0	0	0	0	0
5	26.4	30	30.2	27.9	28.9
10	62	60	51.4	62	58
15	73.3	70.2	77.3	73	68.6
30	84.7	85	88.3	98.8	90.8
45	96.2	91	99.7	100.7	99.7

Table 7. In vitro drug release profile for TDF formulations

Time	T-III	T-IV	T-V	T-VI	T-VII
0	0	0	0	0	0
5	26.6	33.4	30.6	32	25
10	54.2	66.3	53.9	64	43
15	73.5	78.8	78.1	74.5	60.1
30	97.9	88.4	88.8	86.9	88
45	100.1	98.9	99.7	95.8	93.5

Table 8. kinetic values of emtricitabine

S No	Time(min)	Square root of time	Log time	Cum % drug release	Log Cum % drug release	Cum % drug remaining	Log Cum % drug remaining
1	0	0	0	0	0	100	2
2	5	2.23	0.698	27.9	1.45	72.1	1.86
3	10	3.16	1	62	1.79	38	1.58
4	15	3.87	1.17	73	1.86	27	1.43
5	30	5.48	1.47	98.8	1.99	1.2	0.08
6	45	6.71	1.65	100.7	2	0.7	0.15

Table 9. kinetic values of TDF

S No	Time(min)	Square root of time	Log time	Cum % drug release	Log Cum % drug release	Cum % drug remaining	Log Cum % drug remaining
1	0	0	0	0	0	100	2
2	5	2.23	0.698	32	1.51	68	1.83
3	10	3.16	1	64	1.81	36	1.56
4	15	3.87	1.17	74.5	1.87	25.5	1.41
5	30	5.48	1.47	86.9	1.94	13.1	1.12
6	45	6.71	1.65	95.8	1.98	4.2	0.62

CONCLUSION

The film coated tablets of emtricitabine combination with tenofovir disoproxil fumarate have been developed with wet granulation method with serial increasing disintegrant concentration ratio in each batch and it is compared with market (TRUVADA) tablets. Various trails were performed to get the optimized formula with disintigrents like sodium starch glycolate and crosscarmellose sodium. Among all the design formulations F-6 is showing optimized results with in USP limits. There is no undesirable change is found in accelerated stability condition for 1-3 months in optimized formulated batch. Stability studies were performed for these batches 1-3 months under accelerated and long term testing conditions. During that period the product was analysed for physical appearance, hardness, thickness, friability, loss of drying, dissolution, assay and related substances. The results were found to be with in specified limit.

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