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FORMULATION DEVELOPMENT AND *IN VITRO* EVALUATION OF TENOFOVIR DISOPROXIL FUMARATE (TDF) IMMEDIATE RELEASE TABLETS

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Abstract:

In the present work, an attempt has been made to develop immediate release tablets of Tenofovir Disoproxil Fumarate (TDF). In the present work Sodium starch glycollate and Cross carmellose sodium were employed as super disintegrating agents for the selected drug molecule.. All the formulations were prepared by wet granulation method. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F9 formulation showed maximum % drug release i.e., 99.3 % in 25 min hence it is considered as optimized formulation.

Keywords: ***Tenofovir Disoproxil Fumarate (TDF),*** *Immediate release tablets, Sodium starch glycollate , and Cross carmellose sodium.*

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INTRODUCTION:

Immediate Release Drug Delivery Systems [1-3]:

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Also solid oral delivery systems do not require sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Excipients and equipments choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in the drug discovery such as genomics. Injections generally are not favoured for use by patients unless facilitated by sophisticated auto injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generate predominantly chemical entities with low molecular weights.

Introduction to Aids (Acquired Immuno Deficiency Syndrome) HIV [4-6]:

HIV is an RNA retrovirus. The two forms are known.HIV-1 is the organism is responsible for human AIDS.The HIV-2 organism is similar to the HIV-1 virus in that it also causes immune suppression,but it is less virulent.HIV-1 is distributed around the world, whereas the HIV-2 virus is confined to parts of Africa.

In 1983, HIV was isolated from a patient with lymphadenopathy and by 1984 it was demonstrated clearly to be causative agent of AIDS. Definition according to center of disease control and prevention(CDCP) all HIV infected people with CD4+ T Cells lower than 200 cells per cubic millimeter of blood. The retroviruses, which make a large family (Retroviridae), infect mainly vertebrates. These viruses' have a unique replication cycle where by their genetic information is encoded by RNA rather than DNA. Retroviruses contain RNA –dependent DNA polymerase (a reverse transcriptase) that directs the synthesis of a DNA form of the viral genome after infection of a host cell.The United States government and health organizations both endorse the *ABC Approach* to lower the risk of acquiring AIDS during sex: Abstinence or delay of sexual activity, especially for youth, Being faithful, especially for those in committed relationships, Condom use, for those who engage in risky behavior.

MATERIALS AND METHODS:

Tenofovir Disoproxil Fumarat (API), Croscarmellose sodium, Pregelatinized starch, Calciumsilicate, Opadry II blue(Y-30-1070) and all other chemicals wer laboratory grade were used.

Experimental Methodology

Preparation of standard calibration curve of Tenofovir Disoproxil Fumarate

100mg of Tenofovir disoproxil fumarate was accurately weighed and transferred to previously dried 100ml volumetric flask.Drug was dissolved in 100ml methanol.The solution was suitably diluted with 0.1N HCL solution to get standard concentration of 2,4,6,8,10,12,14,16,18 and 20 mcg/ml.Absorbance was measured at 260nm using UV-Visible Spectrophotometer.

Table 1: Formulation composition of TDF Immediate release Tablets (F1-F3) containing 3% Calcium silicate superdisintegrant

S.No	Materials	F1(mg)	F2 (mg)	F3 (mg)
1	Tenofovir Disoproxil Fumarate	300	300	300
2	Micro crystalline cellulose pH (102)	116	115	114
3	Mannitol	25	25	25
4	Pre gelatinized starch	20	20	20
5	Calcium silicate	14	15	16
6	Sodium starch Glycolate	-	-	-
7	Croscarmellose sodium	-	-	-
8	Purified water	Q.S	Q.S	Q.S
9	Magnesium sterate	10	10	10
10	Lactose Mono hydrate	15	15	15
	Core Tablet Weight	500	500	500
11	Opadry II blue	10	10	10
	Total weight(in mg) per one tablet	510	510	510

Table 2: Formulation composition of TDF Immediate release Tablets (F4-F6) containing 3% Sodium starch glycolate superdisintegrant

S.No	Materials	F4 (mg)	F5 (mg)	F6 (mg)
1	Tenofovir Disoproxil Fumarate	300	300	300
2	Micro crystalline cellulose pH (102)	116	115	114
3	Mannitol	25	25	25
4	Pre gelatinized starch	20	20	20
5	Calcium silicate	-	-	-
6	Sodium starch Glycolate	14	15	16
7	Croscarmellose sodium	-	-	-
8	Purified water	Q.S	Q.S	Q.S
9	Magnesium sterate	10	10	10
10	Lactose Mono hydrate	15	15	15
	Core Tablet Weight	500	500	500
11	Opadry II blue	10	10	10
	Total weight(in mg) per one tablet	510	510	510

Table 3: Formulation composition of TDF Immediate release Tablets (F7-F9) containing 3% Croscarmellose sodium

S.No	Materials	F7 (mg)	F8 (mg)	F9 (mg)
1	Tenofovir Disoproxil Fumarate	300	300	300
2	Micro crystalline cellulose pH (102)	116	115	114
3	Mannitol	25	25	25
4	Pre gelatinized starch	20	20	20
5	Calcium silicate	-	-	-
6	Sodium starch Glycolate	-	-	-
7	Croscarmellose sodium	14	15	16
8	Purified water	Q.S	Q.S	Q.S
9	Magnesium sterate	10	10	10
10	Lactose Mono hydrate	15	15	15
	Core Tablet Weight	500	500	500
11	Opadry II blue	10	10	10
	Total weight(in mg) per one tablet	510	510	510

Preparation of tenofovir disoproxil fumarate tablets:

Wet granulation method:

Wet granulation is a process of using a liquid binder to lightly agglomerate the powder mixture. The amount of liquid has to be properly controlled, as over-wetting will cause the granules to be too hard and under-wetting will cause them to be too soft and friable. Aqueous solutions have the advantage of being safer to deal with than solvent-based systems but may not be suitable for drugs which are degraded by hydrolysis.

Table 4: Film Coating Of Tenofovir Disoproxil Fumarate Immediate ReleaseTablets:

S.no	Ingredients	Quantity /tablet
1. 2.	Opadry II blue Methanol	10 mg q.s

Film Coating Of Tenofovir Disoproxil Fumarate Immediate Release Tablets

Opadry II blue was dissolved in Methanol and stir for 20min.to get homogenous solution.

The solution was sprayed on a optimized formulation by a auto coater to form a film on the surface of tablets , to maintain the physical and chemical stability of tablets .

The Coating Process Parameters Are As Follows:

Table 5: The Coating Process Parameters

S.NO	Parameters	Limits
1	Pan speed	14 to 18 rpm
2	Inlet air temperature	50 to 70^{0}c
3	Exhaust air temperature	40 to 60^0 c
4	Bed temperature	40^{0}c
5	Atomizing air pressure	2 to 4 kg/cm^2
6	Spray gun nozzle diameter	9.8 mm
7	Spray rate	4.5ml/min

Evaluation of Pre Compression Parameters

Performulation studies:

Performulation step is the first step in the dosage forms of a drug substance by any of technique. It can be defined as an investigation of physical and chemical properties of a drug substance useful to the formulator in developing stable and bioavailable dosage form, which can be mass-produce alone and when combined excipients. The overall of Preformulation studies is to generate information.

Evaluation of Tablets:

The evaluation of tablets includes, the nature of the active ingredient (identification), expected amount (assay),purity (related compounds),and uniformity of the amount of drug from tablet to tablet(uniformity of dosage units).

Stability Studies [8]

The International Conference of Harmonization (ICH) Guidelines titled, "stability testing of new drug substance and products" describes the stability test requirements for drug registration application in the European Union, Japan and the United States of America. ICH specifies the length of study and storage conditions as shown below

Long-term testing: - 25^0 C ± 2^{0}C / 60% RH ± 5% for 12 months.

Intermediate testing:- 30^{0}C ± 2^{0}C / 60% RH ± 5% for 6months.

Accelerated testing: - 40^{0}C ± 2 ^{0} C/ 75% RH± 5% for 6 months.

The optimized formulations were stored at at 40^{0}C / 75% RH for 3months in the humidity chamber the samples were withdrawn and analysed for physical parameters like hardness, disintegration time, drug content and in-vitro drug release were analyzed.

RESEARCH & DISCUSSIONS:

Preformulation Studies

Drug and Excipient Compatibility By FTIR

Drug excipient Interaction studies showed that there was no interaction or physical change between the drug and excipients. So the selected excipients were found to be compatible with the drug. The results were shown in Figure below.

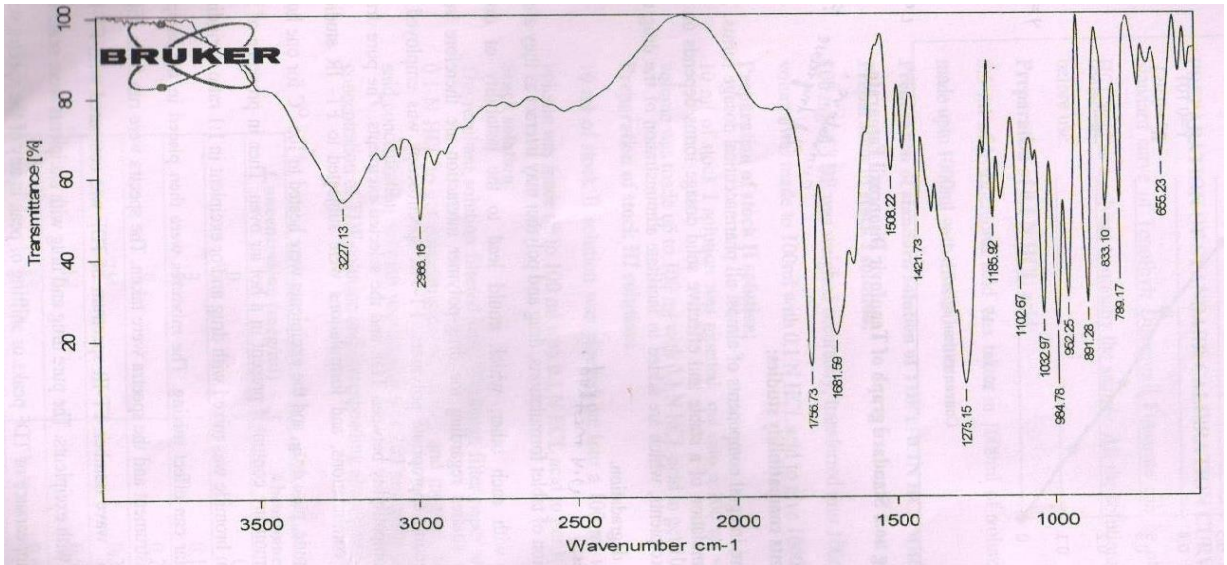

Fig 1: FTIR spectrum of pure drug of Tenofovir Disoproxil Fumarate

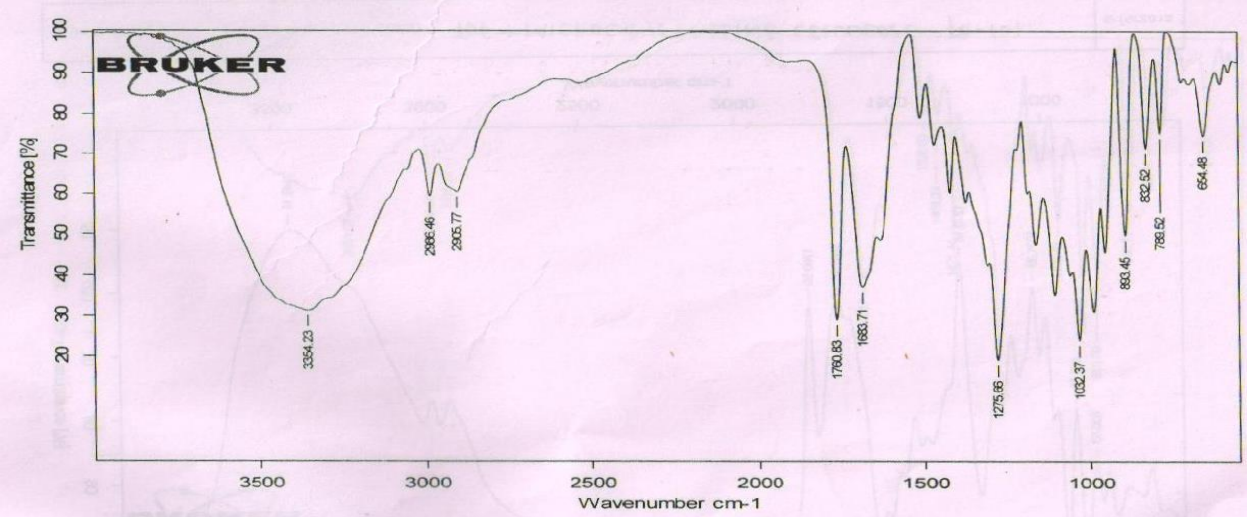

Fig 2: FTIR spectrum of pure drug of TDF+Croscarmellose sodium

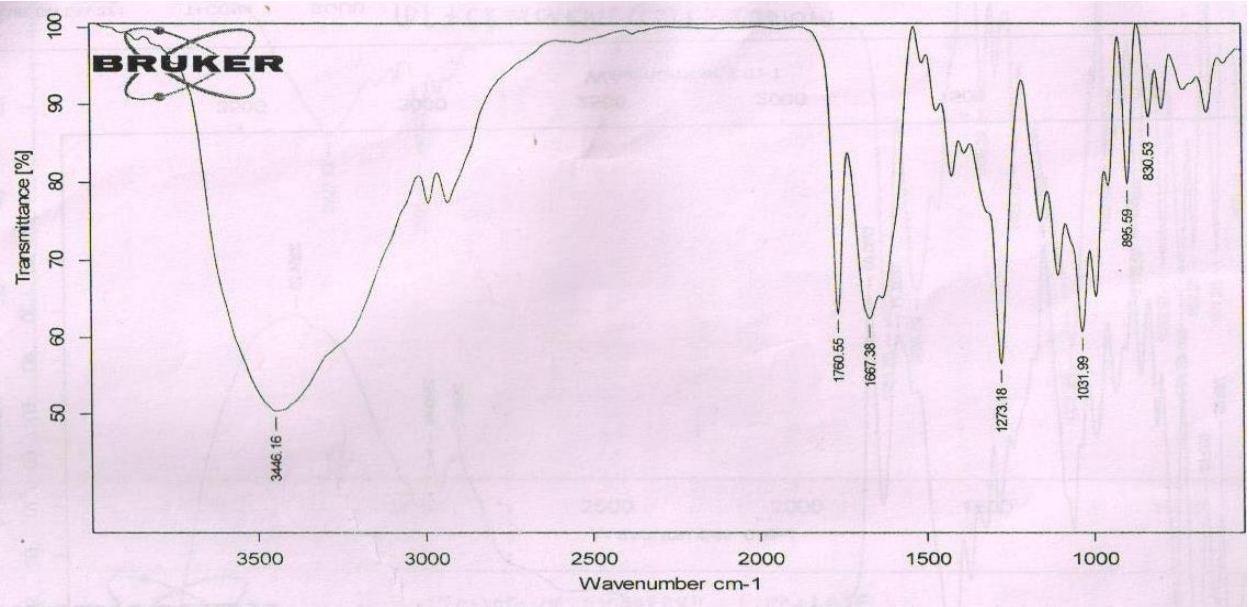

Fig 3: FTIR spectrum of pure drug of TDF+MCC

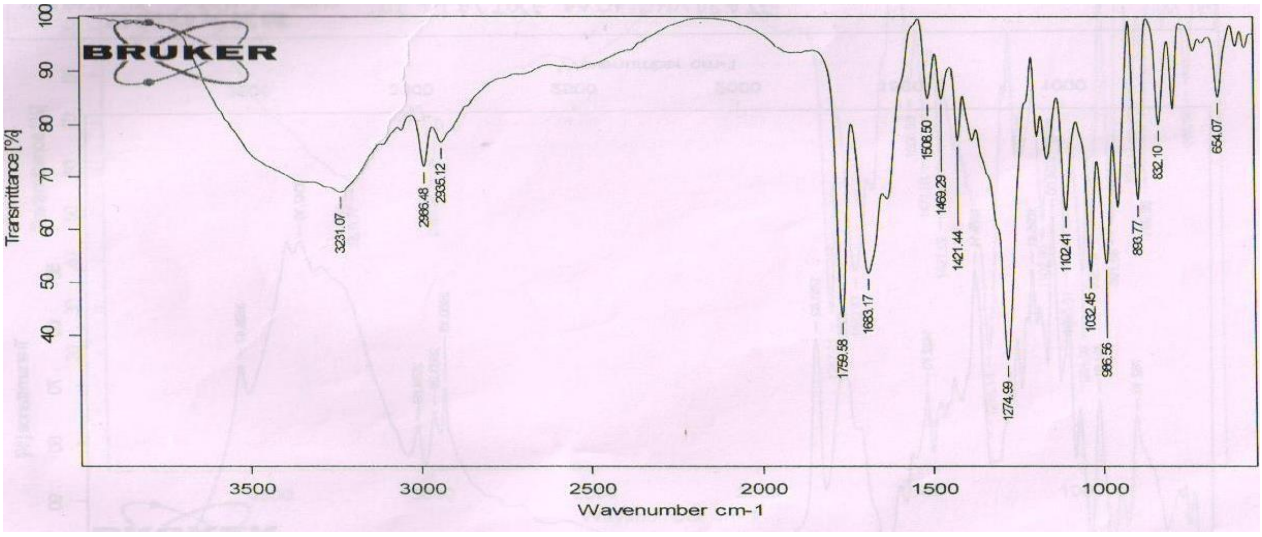

Fig 4: FTIR spectrum of pure drug of TDF+Pre gelatinized starch

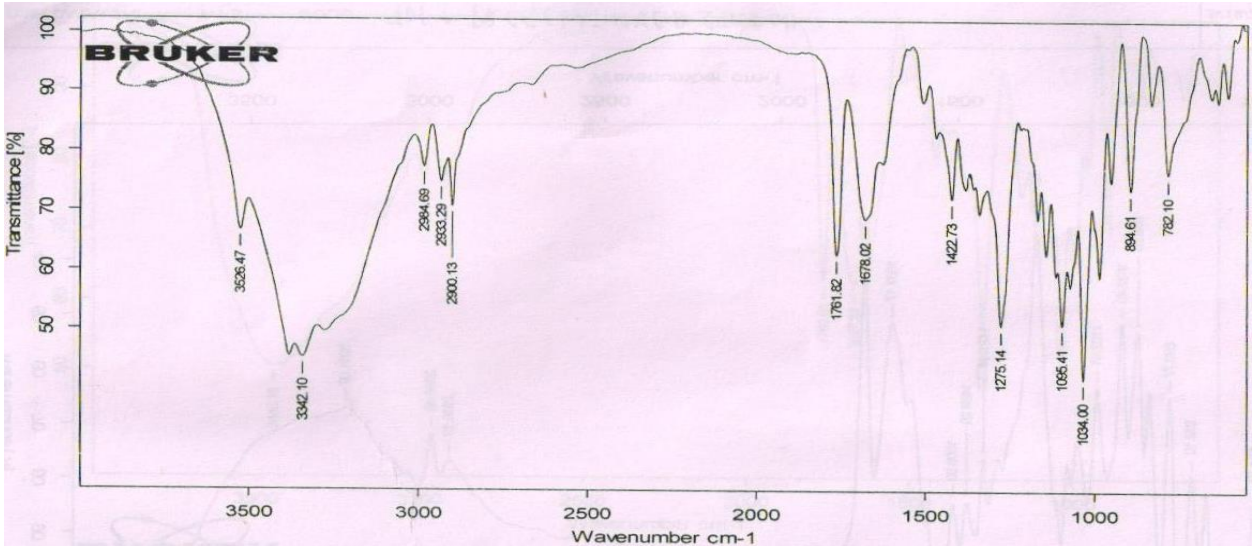

Fig 5: FTIR spectrum of pure drug of TDF+Ca.silicate

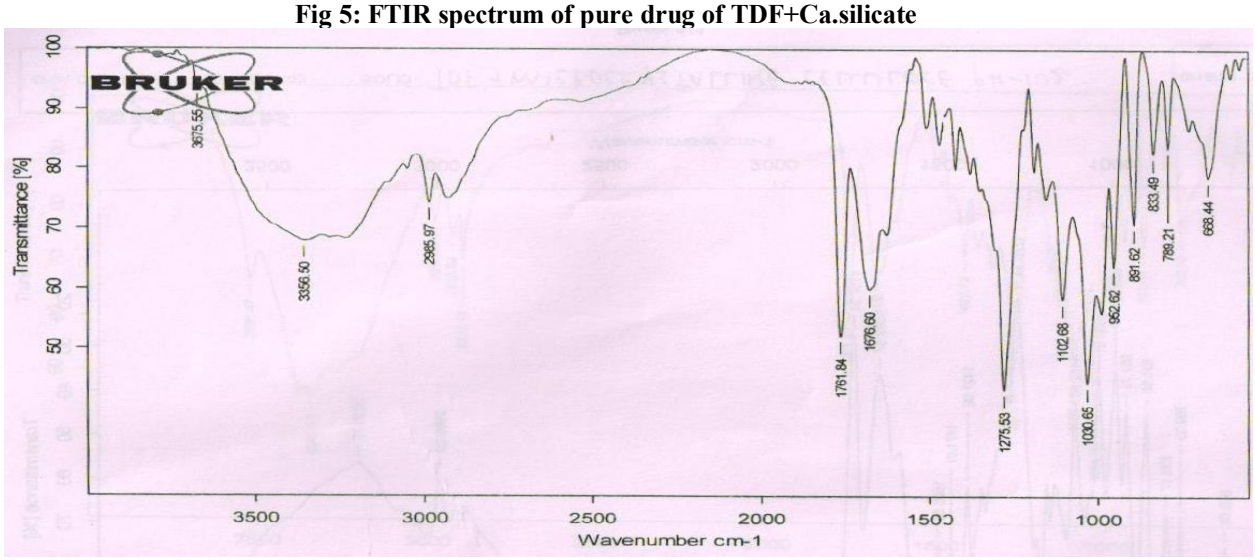

Fig 6: FTIR spectrum of pure drug of TDF+Opadry blue

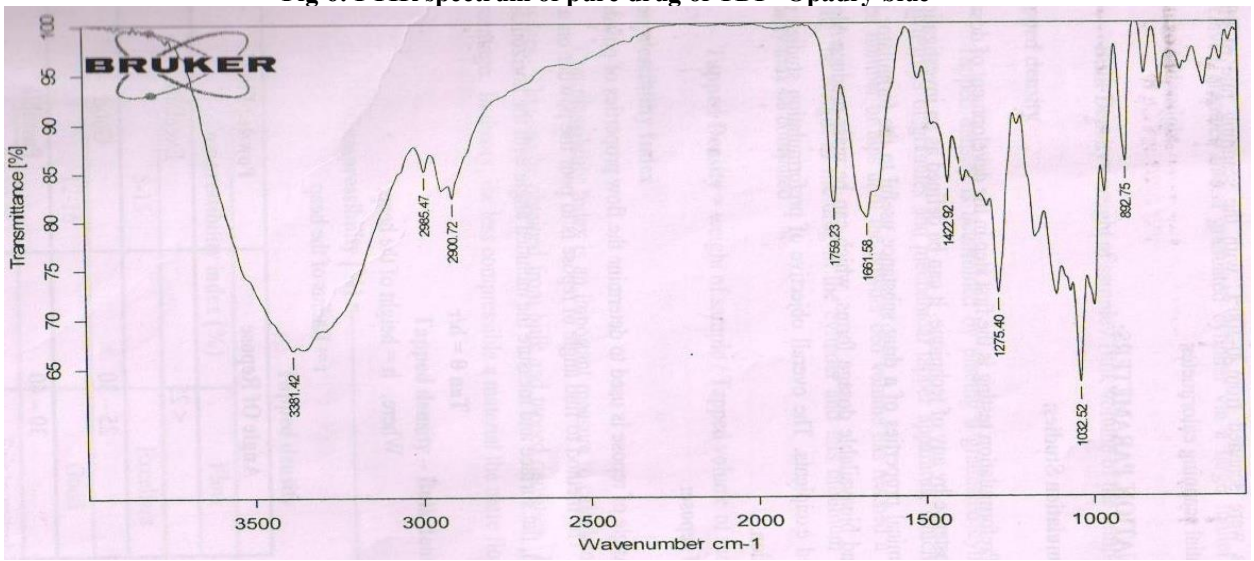

Fig 7: FTIR spectrum of pure drug of TDF+excipients

Table 6: Preparation of Standard Calibration Curve:

Concentration (mcg/ml)	Absorbance(260nm)
0	0
3	0.129
6	0.267
9	0.368
12	0.520
15	0.648
18	0.760

Standard calibration curve of TenofovirDisoproxilFumarate at 260nm.

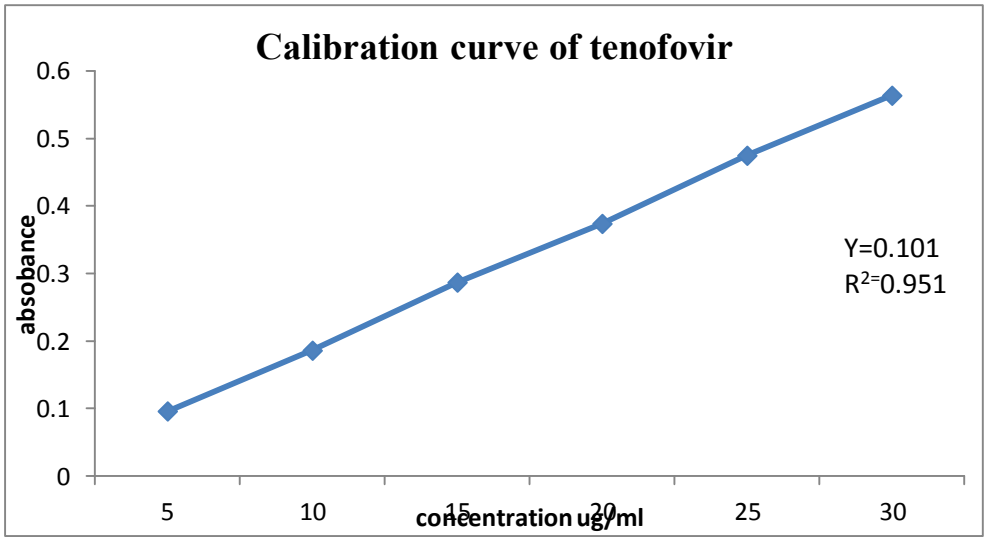

Fig 8: Standard Calibration curve of Tenofovir Disoproxil Fumarate

Evaluation of Pre compressed powder Blend of formulations F1 to F9

Table 7: Evaluation of Pre Compressed Powder Blend

Formulation code	Bulk Density(g/cc) Mean±S.D	Tapped Density(g/cc) Mean±S.D	Carr's Index (%) Mean±S.D	Hausner's Ratio Mean±S.D	Angle Of Repose (Ɵ) Mean±S.D
F_1	0.56±0.18	0.62±0.01	22.0±0.10	1.18±0.31	28.36±0.06
F_2	0.58±0.11	0.71±0.04	23.1±0.61	1.17±0.50	30.12±0.26
F_3	0.62±0.06	0.64±0.02	20.6±0.79	1.15±0.26	31.07±0.18
F_4	0.60±0.07	0.59±0.06	22.2±0.52	1.18±0.25	34.06±0.15
F_5	0.54±0.02	0.56±0.13	19.1±0.56	1.16±0.51	32.08±0.24
F_6	**0.65±0.09**	0.60±0.07	22.8±0.19	1.14±0.20	29.43±0.35
F_7	0.57±0.13	**0.66±0.01**	21.2±0.56	**1.18±0.45**	34.06±0.09
F_8	0.62±0.01	0.57±0.08	19.1±0.56	1.16±0.21	32.08±0.14
F_9	0.52±0.03	0.56±0.01	**22.8±0.19**	1.14±0.20	**29.43±0.17**

Post compression Evaluation of Tenofovirdisoproxilfumarate immediate release tablets (F1 to F9)

Table 8: Post Compression Evaluation of Tenofovir Disoproxil Fumarate Immediate Release Tablets

Formulation code	Hardness (kg/cm^2) Mean±S.D	Friability (%)Mean±S.D	Average Weight (mg) Mean±S.D	Thickness(mm) Mean±S.D	Disintegration time (mins) Mean±S.D	%Drug content uniformity Mean±S.D
F_1	4.24±0.17	0.23±0.06	509.3±0.7	6.34±0.02	7.4±0.18	97±0.29
F_2	4.34±0.12	0.28±0.01	508.0±0.3	6.56±0.08	6.96±0.12	98.2±0.82
F_3	4.29±0.23	0.25±0.04	510.1±0.11	6.24±0.04	6.54±0.18	99.8±0.56
F_4	4.45±0.24	0.25±0.03	509.2±0.18	6.28±0.06	5.76±0.12	99.5±0.75
F_5	4.48±0.22	0.24±0.04	508.6±0.02	6.45±0.02	5.54±0.34	100.12±0.47
F_6	4.36±0.23	0.22±0.01	509.0±0.14	6.10±0.03	5.20±0.66	99.9±0.88
F_7	4.41±0.24	**0.24±0.03**	**510.2±0.08**	6.34±0.02	5.12±0.71	99.6±0.82
F_8	**4.56±0.22**	0.25±0.04	508.6±0.12	**6.56±0.08**	5.10±0.39	100.8±0.56
F_9	4.10±0.23	0.25±0.01	509.0±0.41	6.24±0.04	**4.80±0.26**	**100.16±0.75**

Table 9: *In vitro* dissolution data of TenofovirDisoproxilFumaratetablets formulated with Calcium silicate.

Time(min)	*F1*	*F2*	*F3*
0	*0*	*0*	*0*
5	*31.2±0.54*	*28.02±0.56*	*32.87±0.52*
10	*39.1±0.54*	*37.28±0.23*	*42.22±1.24*
15	*47.7±0.57*	*49.32±0.38*	*56.28±0.46*
20	*56.6±0.47*	*60.22±0.48*	*64.22±0.62*
25	*65.8±0.36*	*71.73±0.75*	*73.73±0.75*
30	*76.1±0.67*	*80.27±0.81*	*80.30±0.81*

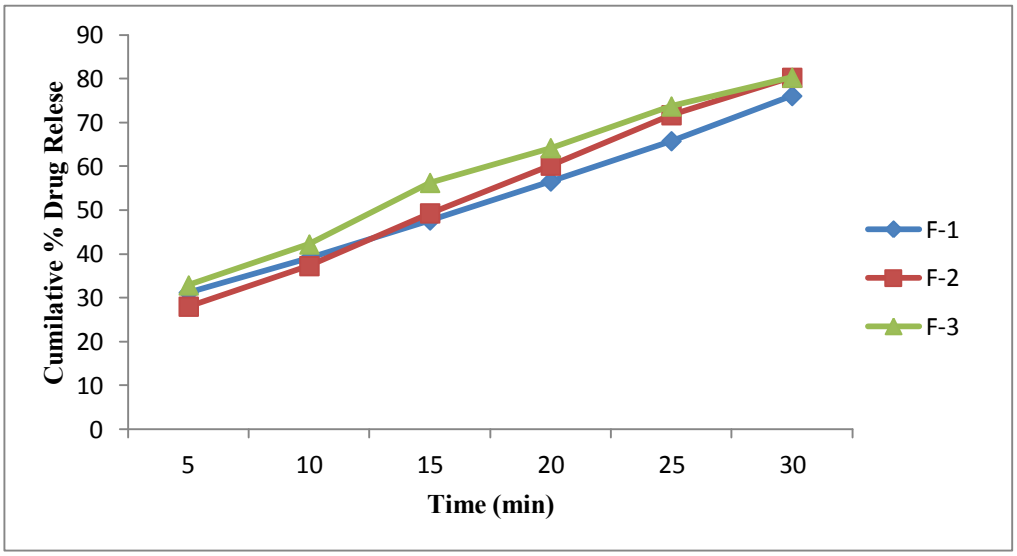

Fig 9: Dissolution profile of TenofovirDisoproxilFumarate tablets formulated with Calcium silicate in 0.1N HCl.

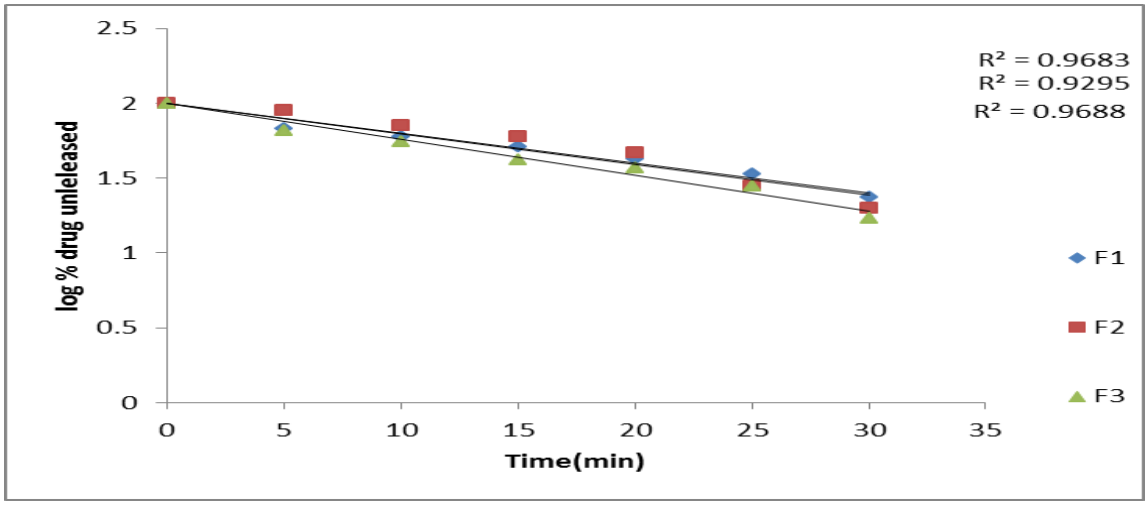

Fig 10: First order plots of Tenofovir Disoproxil Fumarate tablets formulated with Calcium silicate

Table 10: Dissolution Kinetics Tenofovir Disoproxil Fumarate Tablets with Calcium silicate

Formulation code	Correlation coefficient		K(min^{-1})	T_{50}(min)	T_{90}(min)	% DE_{30}
	Zero order	First order				
F_1	0.928	0.968	0.041	16.73	55.62	46.4
F_2	0.926	0.929	0.043	15.85	52.70	47.78
F_3	0.926	0.968	0.055	12.55	41.72	51.66

Table 11: *In vitro* dissolution data ofTenofovir Disoproxil Fumaratetablets formulated with Sodium starch glycolate.

Time(min)	*F4*	*F5*	*F6*
0	*0*	*0*	*0*
5	*28.10±0.32*	*20.34±0.56*	*21.92±0.52*
10	*34.3±0.38*	*28.03±0.73*	*33.62±0.74*
15	*38.7±0.77*	*35.93±0.38*	*45.14±0.46*
20	*43.4±0.47*	*49.51±0.48*	*65.57±0.62*
25	*60.9±0.36*	*68.05±0.75*	*77.12±0.75*
30	*73.24±0.67*	*77.12±0.81*	*82.70±0.81*

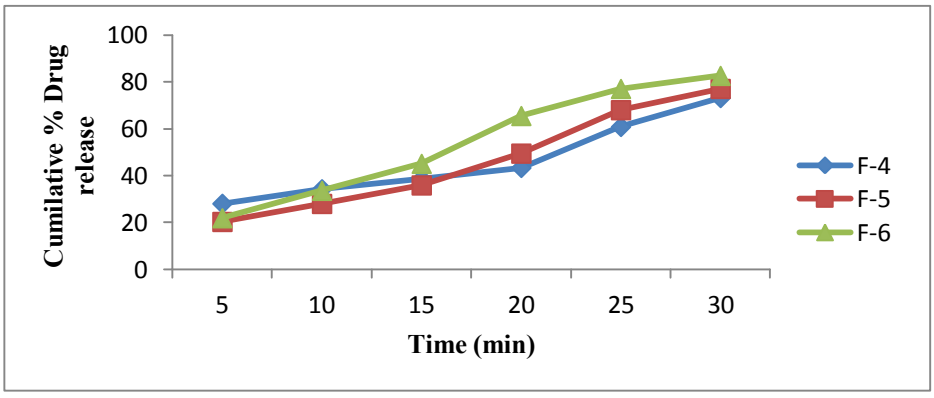

Fig 11: Dissolution profile of TenofovirDisoproxilFumaratetablets formulated with Sodium starch glycolate in 0.1N HCl.

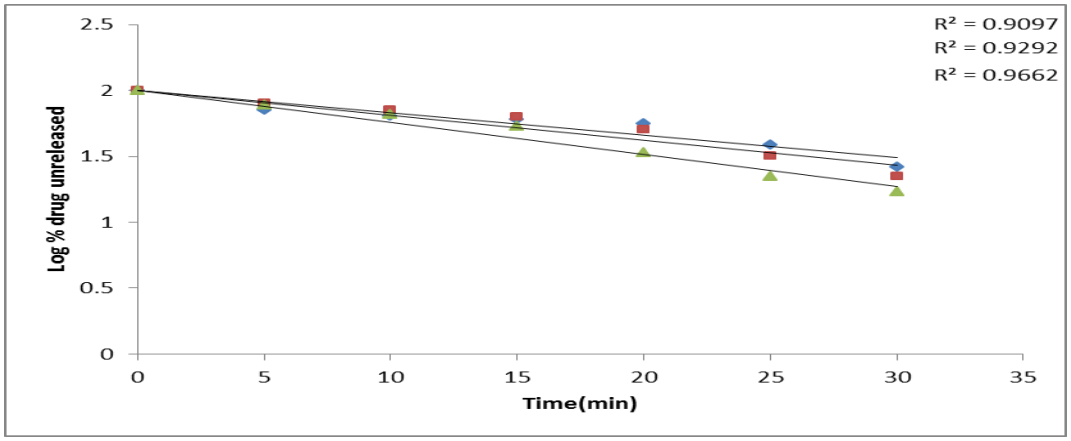

Fig 12: First order plots of Tenofovir Disoproxil Fumarate tablets formulated with Sodium starch glycolate in 0.1N HCl

Table 12: Dissolution Kinetics of Tenofovir Disoproxil Fumarate Tablets with Sodium starch glycolate

Formulation code	Correlation coefficient		K(min^{-1})	T_{50}(min)	T_{90}(min)	% DE_{30}
	Zero order	First order				
F_4	0.881	0.909	0.036	19.25	63.97	40.33
F_5	0.729	0.929	0.043	16.11	53.55	40.07
F_6	0.740	0.966	0.055	12.60	41.87	47.45

Table 13: *In vitro* dissolution data of Tenofovir Disoproxil Fumarate tablets formulated with Croscarmellose

Time(min)	F_7	F_8	F_9
0	*0*	*0*	*0*
5	*33.16±0.85*	*41.67±0.94*	*45.6±0.8*
10	*47.32±0.58*	*56.72±0.58*	*63.8±0.54*
15	*59.32±0.61*	*65.12±0.61*	*81.8±0.78*
20	*65.22±0.59*	*73.54±0.24*	*94.4±0.75*
25	*70.32±0.42*	*80.78±0.53*	*98.0±1.52*
30	*72.12±0.32*	*91.75±0.85*	*99.0±1.22*

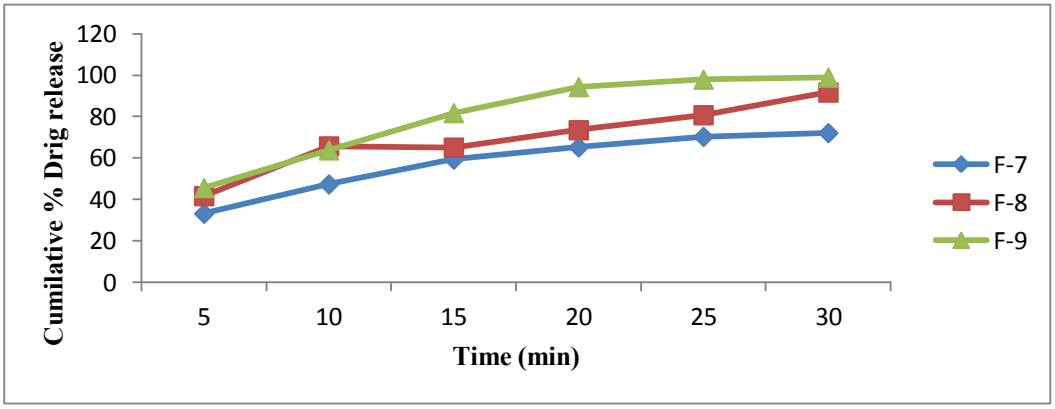

Fig 13: *In vitro* dissolution data of Tenofovir Disoproxil Fumarate tablets formulated with Croscarmellose

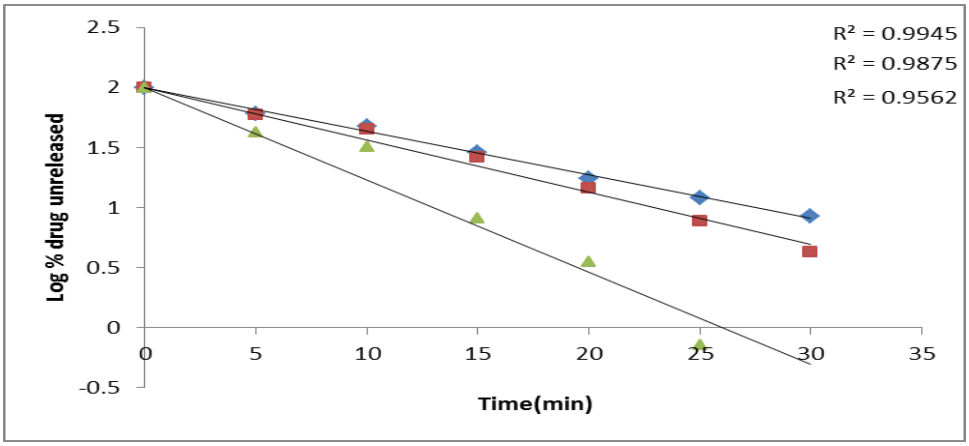

Fig 14: Dissolution Kinetics of Tenofovir Disoproxil Fumarate Tablets with Croscarmellose

Table 14: Dissolution Kinetics of Tenofovir Disoproxil Fumarate Tablets with Croscarmellose

Formulation code	Correlation coefficient		K(min^{-1})	T_{50}(min)	T_{90}(min)	% DE_{30}
	Zero order	First order				
F_7	0.928	0.994	0.082	8.45	28.08	62.77
F_8	0.926	0.986	0.099	7.00	23.26	65.66
F_9	0.926	0.957	0.142	4.88	16.21	72.45

Table 15: Post Compressional Parameters Of Coated Tablets:

Paremeter	F9	Marketed product
Average weight (mg)	510.8±4.3	509.4±1.6
Hardness (kg/cm^2)	6.9±0.052	4.80±0.33
% Friability	0.28±0.02	0.27±0.01
Thickness (mm)	6.52±0.02	6.10±0.1
Disintegration time(mins)	4.8±0.04	5.2±0.02
% Drug content	100.30	100.16

Table 16: Comparison of *In-Vitro* Release Profile of Optimized Formulation (F_9) with Marketed Product.

Time (min)	Cumulative % drug released	
	F_9	Market product
0	*0*	0
5	*45.6±0.8*	41.12±0.43
10	*63.8±0.54*	59.20±0.79
15	*81.8±0.78*	75.54±0.57
20	*94.4±0.75*	89.23±0.98
25	*99.0±1.52*	93.12±0.67
30	*100.2±1.22*	99.1±0.78

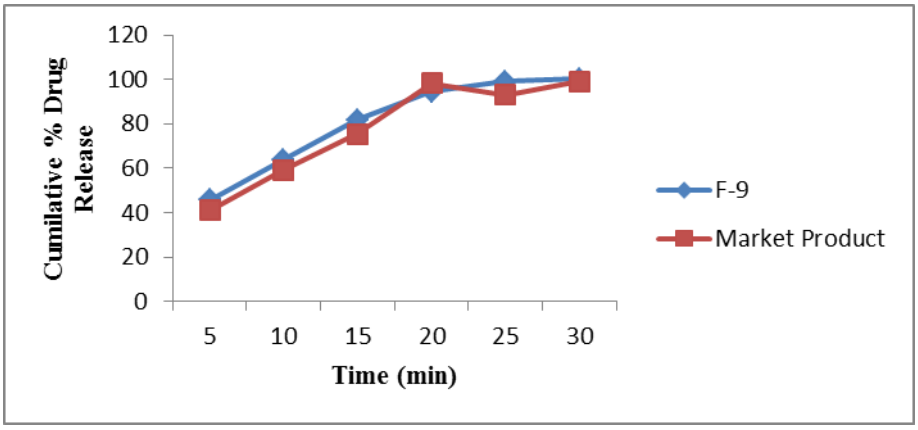

Fig 15: Comparative drug release profile of best formulation F_9 with marketed Product

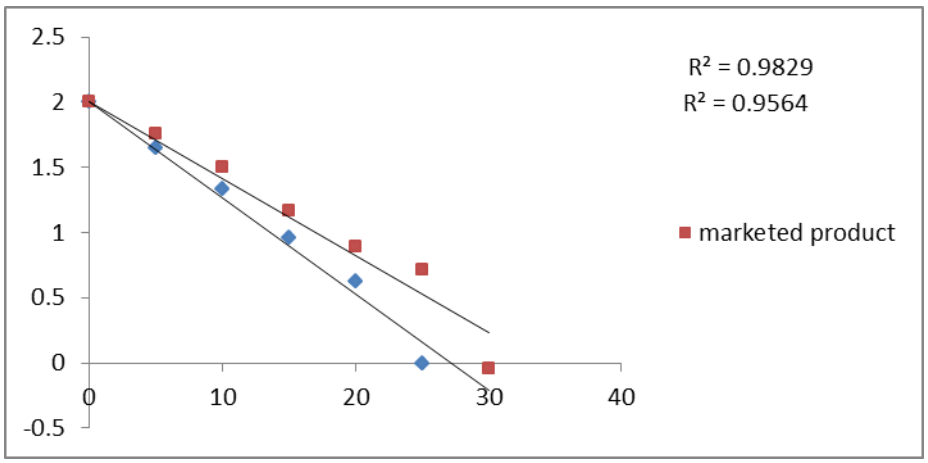

Fig 16: First order release profile of best formulations with Marketed formulation.

Table 17: Dissolution kinetics of best formulation and marketed formulation

Formulation code	Correlation coefficient		K(min^{-1})	T_{50}(min)	T_{90}(min)
	Zero order	First order			
F_9	0.937	0.982	0.124	6.37	18.57
Marketed product	0.918	0.956	0.101	8.8	20.93

Table 18: Accelerated Stability Studies

S.No	Test	Specification	Initial	After 1 month	After 2 months	After 3 months
1.	Description	Round Biconvex film coated pink colored Plain on both sides	Complies	Complies	Complies	Complies
2.	Average weight	510±2 mg	509.17mg	509.01mg	509.17mg	509.12mg
3.	Hardness	NLT 3.0 Kg/cm2	5.9kg/cm2	5.8kg/cm2	5.9Kg/cm2	5.7kg/cm2
4.	Disintegration Time	NMT 15 mins	5.10mins	5.4mins	5.0mins	4.9mins
5.	Dissolution	NLT 80% in 30mins	100.2%	99.1%	99.1%	99.0 %
6.	Assay (By HPLC)	NLT 90.0% & NMT 110.0%	100.4%	100.3%	99.8%	99.2%

SUMMARY AND CONCLUSION:

The objective of the present investigation is to formulate and evaluate the Tenofovir disoproxil fumarate I.R tablets. Tenofovir Disoproxil fumarate is an anti-retroviral agent shown to be effective in the treatment of HIV. The oral route remains the preferred route of drug administration due to its convience, good patient compliance and low medicine production costs. The drug is rapidly and completely absorbed from the gastrointestinal tract with a bioavailability of about 100%.

Recent advances in novel drug delivery system aims to provide rational drug therapy by enhanced safety and efficacy of drug molecule by formulating convient dosage form to administration. one such approach is immediate release tablets. The commonly used superdisintegrants used are Sodium starch glycolate ,Crosscarmellose sodium,these principally effects the rate of disintegration and dissolution. So,studies were undertaken to enhance dissolution rate by using super disintegrants at different concentrations by wet granulation method. The formulation F1 to F3 with calciumsilicate its shows the bad flow of powder and disintegration time was also very low.

The formulations F4 to F6 formulation is planned to improve the disintegration time by increasing the concentration of disintegrant of Sodium starch glycolate showed disintegration time was low and F7 to F9 formulation is planned to improve the disintegration time by changing the disintegrant with Crosacrmellose sodium showed optimum drug release at the end of 30 mins prepared by wet granulation .So ,these formulations were selected as better formulations along all the prepared tablets. These formulated tablets coated with opadry II blue solution and F9 formulation showed similar release profile as that of marketed formulation.

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