ORIGINAL RESEARCH PAPER

Pharmaceutical Science

FORMULATION DEVELOPMENT AND EVALUATION OF TENOFOVIR DISOPROXIL FUMARATE ORAL DISINTEGRATION TABLETS USING THE STARCH PHTHALATE

KEY WORDS: Tenofovir disoproxil fumarate, Oral disintegrating tablets, Direct compression technique, Super disintegrants

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ABSTRACT

The rationale of the current work was to formulate and evaluate Oral disintegrating tablets of Tenofovir disoproxil fumarate by direct compression technique with a vision to augment patient compliance and rapid onset of action. Twelve oral disintegrating formulations of Tenofovir disoproxil fumarate were formulated by direct compression method using starch phthalate& croscarmellose sodium, Avicel PH101 as the super disintegrants. The prepared formulations were evaluated for wetting time, drug content, in vitro disintegration time, dissolution time and also projected to kinetic treatment to know the pattern of drug release. Further, the discovered promising formulation was subjected to stability studies. Based on the results obtained, formulation F12 containing Avicel PH101 72.5 mg and Starch phthalate and croscarmellose sodium (1:1) 62.5 mg exhibited good wetting time, dispersion time, and disintegration time and drug release compared to Oral disintegrating tablets prepared with other super disintegrants. The stability studies piloted as per International Conference on Harmonisation guidelines on the promising formulation F12 disclosed no significant changes in the Disintegration time at Initial, 1 month , 2month, 3 months will be 5.2±0.43 5.1±0.54 5.1±0.23 5.1±0.12 min respectively. Oral disintegrating tablets of Tenofovir disoproxil fumarate were formulated successfully by employing direct compression technique. From the investigation, it can be reasonably concluded that F12 batch Oral disintegrating tablets of Tenofovir disoproxil fumarate with Avicel PH101 72.5 mg and Starch phthalate and croscarmellose sodium (1:1) 62.5 mg exhibited maximum cumulative drug release in 10 min.

INTRODUCTION

Oral drug delivery:

This is the most extensively used route of administration of all the ways investigated for systemic delivery of pharmaceuticals via pharmaceutical goods in various dosage forms. Because of its ease of administration, patient acceptance, and cost-effective manufacturing procedure, the oral route is regarded as the most natural, uncomplicated, convenient, and safe way. Conventional instant release formulations provide clinically effective therapy for numerous pharmacological substances while retaining the required balance of pharmacokinetic and pharmacodynamic characteristics with an acceptable level of patient safety[1,2].

For systemic effects, oral medication distribution is the most desirable and preferred form of administration. Furthermore, oral medication is often regarded as the first avenue studied in the research and development of new pharmacological entities, pharmaceutical formulations, owing to patient acceptance and ease of administration. The oral route of drug delivery is widely accepted, accounting for 50-60% of total dosage forms. Because of their simplicity of administration, correct dosage, self-medication, pain avoidance, and, most importantly, patient compliance, solid dosage forms are popular.

The most common approach for medication therapy is oral dose form. In the United States, oral dose forms are used for more than 80% of medications designed to have systemic effects[3].

The most popular solid dosage forms are tablets and capsules. The main disadvantage of these dose forms is their difficulty in swallowing. Tablets are the manufacturer's preferred dosage form over other oral dosage forms due to their low manufacturing and packaging costs.

Oral drug delivery system remains the most favourable approach for development of several drugs. Substantial progress has been occurred during the last few decades in the field of pharmaceutics and fine-technology that encourages the researchers to develop orally disintegrate tablets (ODTs) having greater patient amenability and suitability. These tablets (ODTs) are physically solid in nature but readily collapse and dissolve in the mouth deprived of chewing or no water is needed. It is very useful specially for those people who have difficulty in swallowing conventional tablets or capsules. It has been reported that dysphasia (difficulty in swallowing) is common among all age groups and more specific with pediatric and geriatric populations along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications. For these patients, ODTs are considered to be the best choice. ODTs with good taste and flavour have greater acceptability of bitter drugs by various groups of population.[3]

Orally disintegrating tablets are also called as oro-dispersible tablets or quick/ fast disintegrating tablet or porous tablets or mouth dissolving tablets or rapid/fast dissolving tablets or rapimelts. These all names of ODTs are accepted by United States pharmacopoeia (USP). In very recent time, the European Pharmacopoeia is using the name orodispersible tablets which disperse quickly (< 3 minutes) in mouth before intake[4].

According to USFDA, ODT is **"**A solid dosage form containing medical substance or active ingredient which disintegrates rapidly usually within a matter of seconds which when placed upon the tongue**"**. The disintegration time for ODTs generally range from several seconds to a minute[5].

Tenofovir disoproxil is an organic phosphonate that is the disoproxil ester of tenofovir. A prodrug for tenofovir, an HIV-1 reverse transcriptase inhibitor, tenofovir disoproxil is used as the fumaric acid salt in combination therapy for the treatment of HIV infection. It has a role as a prodrug, a HIV-1 reverse transcriptase inhibitor and an antiviral drug. It is functionally related to a tenofovir (anhydrous). It is chemically called as 9-[(R)]-2-[bis [(cisoproxycarbonyl) oxy] methoxy] propyl] adenine fumarate (1:1).6

Experimental work:

MATERIALS AND METHODS

Scanning of max[7]:

Preparation of Standard Stock Solution:

Standard solution containing 100 µg/ml of TD was prepared

by dissolving in 1ml methanol and the volume was made up to 100 ml with distilled water. From the stock, different aliquots were taken and diluted to 10 ml mark with same solvent to obtain series of concentrations. The solutions were scanned on spectrophotometer in the UV range 200-400 nm.

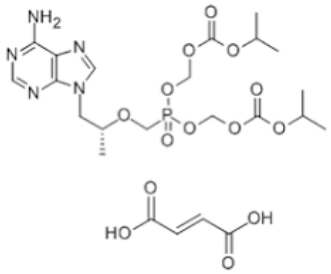

Figure1: Structure of Tenofovir disoproxil fumarate

Calibration curve: 100 mg of tenofovir was transferred into 100 ml volumetric flask. The powder was dissolved in 1 ml methanol and volume was made up with distilled water. This solution was brought into a concentration of 100 g/ml with distilled water. An appropriate aliquot was transferred to 10 ml volumetric flask, volume was adjusted to the mark and absorbance was recorded at 259 nm.

Preformulation studies:
Pre formulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.

Identification of drug by melting point:
The temperature at which the first particle of the substance completely melts is regarded as melting point of the substance. The temperature at which the first particle starts to melt and last particle completely melts is regarded as the range of melting point. Melting point of the drug was determined by capillary tube method.

Physicochemical parameters:
Organoleptic properties:[8]
The colour, odour and taste of the drug were recorded using descriptive terminology.

Solubility study:
It is important to know about solubility characteristic of a drug in aqueous system, since they must possess some limited aqueous solubility to elicit a therapeutic response. The solubility of drug was recorded by using various descriptive terminology specified in Indian pharmacopoeia, 2007.

Table No.2: Solubility specification

Descriptive terms.	Approximate volume of solvent in millilitres per gram of solvent.
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 1 to 30
Sparingly soluble	From 30to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 100 to 10,000
Practically insoluble	More than 10,000

Loss on drying:
Loss on drying is the loss of weight expressed as percentage w/w resulting from water and volatile matter of any kind that can be driven off under specified condition. The accurately weighed 1gm of sample was transferred in glass-stoppered, shallow weighing bottle and accurately weighed the bottle. The bottle was transferred in oven and substance was dried at 105°C for 3 hours. The bottle was removed from oven and reweighed; loss on drying was calculated by following equation,

$$\text{Lod} = \frac{\text{Initial wt of substance} - \text{Final weight of substance}}{\text{Initial wt of substance}} \times 100$$

Determination of Drug-Excipient compatibility:
A Compatibility study focuses on a binary mixture of drug substance and some selected excipients in a fixed ratio with or without added moisture. The mixture is stored at elevated temperature 40° C±2°C/75%±5%RH, 25°C± 2°C/60%±5%RH in capped vials. The result of the interaction between the active drug and excipients is determined by UV spectroscopy.

Procedure: Drug and Excipients mixture shall be prepared based on the information from Physician Desk Reference (PDR). The Drugs and Excipients individually and in combination shall be subjected for accelerated study conditions along with control samples and study at fixed intervals. The recommended drug- Excipients ratios for solid dosage forms are tabulated.

Differential scanning calorimetry (DSC):
Any possible drug Disintegrant interaction can be studied by thermal analysis. The DSC study was performed on pure drug, drug+ Croscarmellose sodium, drug+ Crospovidone and drug+ Starch phthalate. The study was carried out using a Shimadzu DSC 60, (Japan). The 2 mg of sample were heated in a hermetically sealed aluminium pans in the temperature range of 60°-180°C at heating rate of 10°c /min under nitrogen flow of 30ml/min.

Loose Bulk Density (LBD):
An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The loose bulk density (LBD) of powder blends was determined using the following formula.

Loose bulk density = Total weight of powder / Total volume of powder
Tapped bulk density (TBD):
An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The tapped bulk densities (TBD) of powder blends were determined using the following formula.

Tapped bulk density= Total weight of powder / Total volume of tapped powder

Hausner's Ratio:
Hausner's ratio was determined by following equation,

Hausner's Ratio= Tapped bulk density/Loose bulk density
A hausner ratio less than 1.25 indicates good flow while greater than 1.5 indicates poor flow.

Carr's Compressibility Index:
It is a simple index that can be determined on small quantities of powder. In theory, the less compressible a material the more flowable it is. The compressibility indices of the powder blends were determined using formula

Carr's Compressibility Index (%) = [(TBD-LBD)/ TBD] x100
Relationship between % compressibility and flowability is shown in the table

Table No.3: Carr's index flow property range

S. No.	Carr's index	Type of flow
1	5-15	Excellent
2	12-16	Good

Angle of repose:
The angle of repose was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured. The angle of repose was calculated using the following equation.

$\mathbf{Tan\theta = h/r}$

Where 'h' and 'r' are the height and radius respectively of the powder cone

Table No. 4: Standards for Angle of repose

S. No.	Flowability	Angle of repose (˚)
1	Excellent	<25
2	Good	25-30
3	Passable	30-40
4	Poor	37-45
5	Very poor	>45

Adding glidant for improving flow

pH: The pH is the measure of negative logarithm of hydrogen ion concentration of an aqueous solution. It is one of the most important factors from which the stand point of solubility, stability and physiochemical suitability of a formulation.

Procedure: Accurately Weighed 1 gm of Tenofovir disoproxil fumarate was dissolved in 100ml of demineralised water for preparing 1% of solution. The pH value of a solution was determined potentiometrically by means of a glass electrode.

Formulations:
Preparation of Starch Phthalate:
At first, phthalic anhydride (three parts) is dissolved in DMSO (two parts). The PH of the solution is maintained ~3.5 by dropwise adding NaOH solution (10M). Volume is made up to 50.0 mL. In this solution, starch obtained from potato (five parts) is mixed and stirred gently for sixteen hours. This dispersion is kept at 60 oC for 1 hour in the oven. The final product is washed with acetone followed by isopropyl alcohol to get rid of undesirable phthalic anhydride. The product starch phthalate is kept at 60o C in the oven for drying and sieved (120 sieve number).

Compare the native starch with SP samples for low values of the crystallinity, paste viscosity, retrogration and thermal degradation temperatures and high values of carbon residue in thermal decomposition, transparency and hydrophobicity for the films.

Preparation: Direct compression method 45-47
Different compositions of antiviral drug are prepared by using different ratios of starch phthalate as superdisintegrant (200 mg of drug with 20 to 25 mg of superdisintegrant). For the uniformity in particle size the ingredients are allowed to go through the column of 100 mesh sieve. A mixture containing SP, crospovidone, croscarmellose sodium, microcrystalline cellulose and starch is properly mixed followed by added to the desired drug (Antiviral drug). In the final step, Mg-stearate salt and Talc are mixed and is pressed mechanically.

Disintegration and dissolution studies are performed to the obtained oral disintegrating tablets prepared by using different ratios of superdisintegrants.

Table No. 5: Formulation tenofovir IR tablets

Ingredients	TF1	TF2	TF3	TF4	TF5	TF6	TF7	TF8	TF9	TF10	TF11	TF12
Tenofovir disoproxil fumarate	300	300	300	300	300	300	300	300	300	300	300	300
Avicel PH101	110	97.5	85	72.5	110	97.5	85	72.5	110	97.5	85	72.5
Starch Phthalate	25	37.5	50	62.5								
Croscarmellose sodium					25	37.5	50	62.5				
Starch phthalate+ croscarmellose sodium (1:1)									25	37.5	50	62.5
Mannitol	10	10	10	10	10	10	10	10	10	10	10	10
Aspartame	15	15	15	15	15	15	15	15	15	15	15	15
Sodium Bicarbonate	20	20	20	20	20	20	20	20	20	20	20	20
Citric acid	10	10	10	10	10	10	10	10	10	10	10	10
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5
Aerosil	5	5	5	5	5	5	5	5	5	5	5	5
Mint Flavors	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs

Evaluation of Tablets 12,13:
Tablet appearance:
- The tablets were visually observed for chipping, lamination and capping.

Thickness:
The thickness and diameter of tablets were important for uniformity of tablet size. The thickness and diameter of the tablets was determined using a Vernier callipers. Three tablets from each type of formulation were used and average values were calculated.

Hardness:
For each formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm2.

Disintegration time14,15:
The test was carried out on 6 tablets using Tablet disintegration tester. Distilled water at 37°C ± 2°C was used as a disintegration media and the time in seconds taken for complete disintegration of the tablet with no residual mass remaining in the apparatus was measured.

Table No. 6: Specifications of Disintegration time

Tablet Type	Time limit and Specifications
As per British Pharmacopoeia	
Uncoated	<15min
Coated Film coated Sugar Coated	 <30 min <60min, repeat in 0.1N HCl
Gastro resistant	>120min in 0.1N HCl <60min in 6.8 pH phosphate buffer
Effervescent	<5min in 200ml water
Soluble	<3min
Dispersable	<3min

% Friability16:
Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre weighed tablets was placed in Roche friabilator which was then operated for 100 revolutions. The tablets were then de dusted and reweighed. A loss of less than 1 % in weight is generally considered acceptable. Percent friability (% F) was calculated as follows

%F=(W1-W2)/W1×100
W1=Initial weight
W2=Final weight

Weight variation[17]:
To find out weight variation 20 tablets of each formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight.

Table No.7: Specifications of % weight variation allowed in tablets as per IP

S.No	Average wt of tablets(mg)	Max % deviation allowed
1	130 or less	±10
2	More than 130 and less than 324	±7.5
3	More than 324	±5

Content uniformity[18]:
it is performed to ensure that the tablets contain the proper amount of the active ingredient. This test is more important than the weight variation test therefore, when content uniformity test is done, there is no need to for weight variation test (but the reverse is not true). The following procedure is used for the content uniformity test:

- Take ten tablets randomly and assay them individually by a suitable technique.
- The tablets pass the test if only one of the ten tablets lies outside the range of 85-115% and no one is outside the range of 75-125%.
- If the above criteria are not met, another twenty are assayed individually and none of the twenty tablets fall outside the range of 85-115%

Invitro dissolution study[19]:
For each drug, there is a specific monograph in the USP or BP specifies all the required conditions to perform the dissolution test such as type of the medium to be used, its volume, speed of stirring, time intervals for sample withdrawal, method of analysis (UV, HPLC or titration), type of the apparatus (apparatus I or apparatus II) and so on. The conditions to test Tenofovir disoproxil fumarate IR tablets in USP are as follows: apparatus II, simulated gastric fluid 900 ml (0.1N HCl), 50 rpm and 40 min time interval. To pass the test successfully, the dissolved amount of drug after 40min is not less than 80% of the labelled amount assayed by UV spectroscopy.

Stability study[20]
Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of labelled potency and its physical characteristics have not changed appreciably or deleteriously.

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. The International Conference on Harmonization (ICH) Guidelines titled "Stability testing of New Drug Substances and Products (QIA) describes the stability test requirements for drug registration application in the European Union, Japan and the States of America.

Specifications:
Table No.8: ICH Specifications for Accelerated stability testing

S.NO	Study	Storage condition	Minimum Time Period
1	Long term	25°C± 2°C/60 %RH± 5%RH (or) 30C±2°C/ 65%RH±5%RH	12 months
2	Intermediate	30°C±2°C/65%RH±5%RH	6 months
3	Accelerated	40°C ±2°C / 75% RH ±5 % RH	6 months

In present study, the selected formulation F6 exposed up to 3 months stability studies at accelerated condition (40˚ C ±2˚C at 75% RH±5%RH) to find out the effect of aging on hardness, Disintegration time, drug content and In-Vitro drug released.

Stability studies were carried out at accelerated condition (40˚ C ±2˚ C at 75% RH ±5%RH) for the optimized formulation F6. The tablets were stored at 40˚ C ±20˚C at 75% RH ±5%RH for accelerated temperature in closed high density polyethylene bottles for 3 months. The samples were withdrawn after Pre determined Period of 1 month, 2 month and 3 months. The samples were analyzed for its hardness, Disintegration time, drug content and In-Vitro drug released.

RESULTS AND DISCUSSION

Scanning of λ max: The absorption maxima of the tenofovir disoproxil fumarate was measured in UV range 200-400 nm and the absorption maxima value was found to be 259nm observed In the Figure 2.

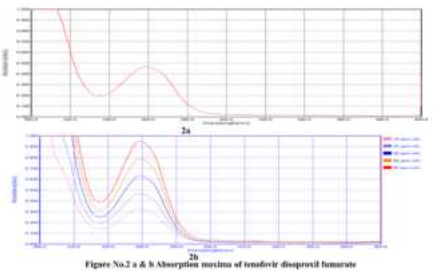

Figure No.2 a & b Absorption maxima of tenofovir disoproxil fumarate

Calibration curve: The standard curve for tenofovir disoproxil fumarate was generated by relating the concentration and absorbance. The linearity of curve was assessed using concentration ranging 10 to 50 µg/ml.

Table No.9: calibration of tenofovir disoproxil fumarate

S.NO	Concentration	Absorbance
1	0	0
2	10	0.315±0.25
3	20	0.473±0.34
4	30	0.630±0.62
5	40	0.788±0.47
6	50	0.945±0.44

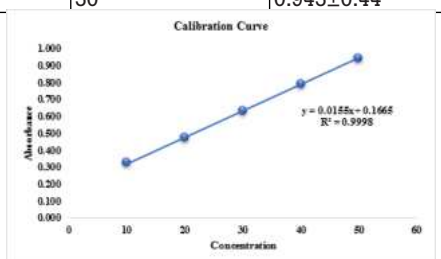

Figure No.3: calibration of tenofovir disoproxil fumarate

Pre-formulation studies:
Melting point: Melting point values of Tenofovir disoproxil fumarate sample was found to be in range of 113.2˚C to 119.57C using DSC. The reported melting point for Tenofovir disoproxil fumarate was 113.8˚C. Hence, experimental values were in good agreement with official values and the optimized formulation 167°C.

DSC Graphs:

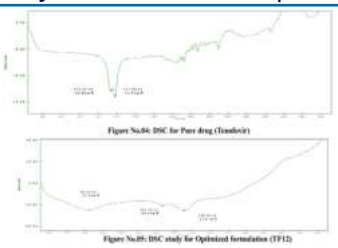

Figure No.04: DSC for Pure drug (Tenofovir)

Figure No.05: DSC study for Optimized formulation (TF12)

Physical compatibility study:

The pure drug and physical mixture of drug and excipients was used to measure the physical compatibility. The pure drug and binary mixture was stored in 40°C and 75%RH and observe up to two months and observe for colour and texture of the mixture observed in table.

Table No.10: physical compatibility for pure drug and binary mixture

S.No	Mixture	Observation		
		Initial	1Month	2 Month
1	Tenofovir (API)	White	White	White
2	Tenofovir +Starch phthalate	White	White	White
3	Tenofovir +Croscarmelose	White	White	White

FTIR study:

The compatibility study of the tenofovir disoproxil fumarate and various excipients used in the formulation was measured using FTIR (Fourier Transform Infrared Spectroscopy).

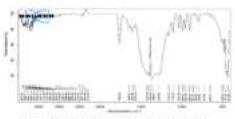

Figure No.06: FTIR Spectra for pure drug (TF)

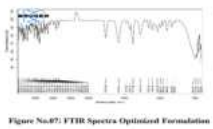

Figure No.07: FTIR Spectra Optimized Formulation

FTIR Interpretation of pure drug andoptimized formulation

Functional Group	Pure drug (Cm⁻¹)	Optimized formulation (Cm⁻¹)
N-H	3330.11	3337.40
C=O	1760.39	1761.58
P=O	1048.61	1042.82
NH_4 stretching band	1601.86	1378.89
C-N	1470.74	1423.49
C-H out of plane	900.600	900.600

Organoleptic properties:

- Colour:White to off white
- Odour: Odourless
- Nature: Crystalline powder

Solubility study: The solubility of tenofovir disoproxil fumarate was found in different solvents were tabulated.

Table No.12: Solubility of Tenofovir disoproxil fumarate

S.No	Name of Solvent	Solubility
1	Distilled water	Sparingly soluble
2	0.1N HCl	Soluble
3	Methanol	Freely soluble
4	DMF	Soluble

Loss on drying:

The loss on drying of the Tenofovir disoproxil fumarate was found after 3hrs was found to be

Table No.13: Percentage loss on drying of Tenofovir disoproxil fumarate

S.No	%LOD	Average
1	2.8	2.85±0.34
2	2.9	
3	2.8	

Physical characterization of API:

The physical characterization of like Loose Bulk Density, tapped density, Hausner's ratio, carr's index was found in the table.

Table No.14: Physical characteristics of API

S.No	Parameters	Results
1	Loose bulk density	0.481±0.02
2	Tapped density	0.712±0.01
3	Compressibility index	32.54±0.13
4	Hausner's ratio	1.480±0.01
5	Angle of repose	27.34±0.22

Physical characterization of blend:

Table No.15: Physical characteristics of lubricated blend

Formulation code	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of repose
TF1	0.483±0.01	0.690±0.01	30.00±0.24	1.429	26.43
TF2	0.494±0.02	0.685±0.03	27.88±0.21	1.387	26.12
TF3	0.477±0.02	0.655±0.02	27.17±0.16	1.373	25.32
TF4	0.481±0.01	0.673±0.02	28.52±0.18	1.399	24.22
TF5	0.485±0.03	0.699±0.01	30.61±0.13	1.441	27.13
TF6	0.489±0.02	0.692±0.01	29.33±0.17	1.415	26.55
TF7	0.493±0.01	0.696±0.03	29.16±0.27	1.412	25.46
TF8	0.496±0.03	0.674±0.01	26.40±0.25	1.359	24.41
TF9	0.479±0.02	0.694±0.03	30.97±0.22	1.449	27.12
TF10	0.499±0.01	0.684±0.02	27.04±0.21	1.371	25.43
TF11	0.498±0.03	0.675±0.01	26.07±0.18	1.355	25.12
TF12	0.487±0.02	0.665±0.02	27.17±0.19	1.366	24.65

Evaluation of tablets

Appearance: The tablets were observed visually, they did not show any defects such as capping, chipping and lamination.
Colour:White coloured
Shape: Round shape

Physical Characteristics:

The physical characteristics of Tenofovir disoproxil fumarate (TF1 to TF12) such as thickness, diameter, hardness, friability, weight variation and drug content were determined and results of the formulations TF1 to TF12 found to be within the limits specified in official books.

Table No.16: Physical characterization of TF 1-TF12

Formulation code	Thickness	Hardness	Friability	Weight variation	Disintegration time (sec)
TF1	5.46±0.26	5.4±0.12	0.16±0.01	0.22±0.03	34±0.22
TF2	5.32±0.36	5.5±0.08	0.14±0.12	0.19±0.01	32±0.19
TF3	5.38±0.22	5.5±0.09	0.17±0.09	0.17±0.01	31±0.11
TF4	5.44±0.44	5.6±0.11	0.21±0.02	0.16±0.02	29±0.19
TF5	5.42±0.43	5.3±0.07	0.12±0.05	0.18±0.01	33±0.21
TF6	5.36±0.54	5.7±0.08	0.14±0.07	0.20±0.01	32±0.24
TF7	5.45±0.43	5.6±0.10	0.18±0.08	0.21±0.03	31±0.32
TF8	5.43±0.33	5.8±0.13	0.17±0.09	0.19±0.02	32±0.34
TF9	5.42±0.21	5.7±0.12	0.15±0.01	0.18±0.01	37±0.29
TF10	5.46±0.43	5.4±0.13	0.17±0.02	0.17±0.03	39±0.30
TF11	5.39±0.32	5.3±0.10	0.12±0.05	0.21±0.01	31±0.12
TF12	5.41±0.25	5.5±0.06	0.19±0.04	0.19±0.01	22±0.43

Thickness and diameter:

Thickness and diameter specifications may be set on an individual product basis. There were no marked variations in the thickness and diameter of tablets within each formulation indicating uniform behaviour of granules throughout the compression process. The size width of the tablets of all formulations ranged between 5.32 to 5.46mm.

Tablet hardness:

A difference in tablet hardness reflects difference in tablet density and porosity. Which in turn are supposed to result in different release pattern of the drug by affecting the rate of penetration of dissolution fluid at the surface of the tablet and formation of gel barrier. The hardness of tablets was found to be in the range of 5.3 kg/cm2 to 5.7 kg/cm2. This indicates good tablet strength.

Percentage Friability:

Percentage friability of all the formulations was found between 0.12 to 0.21 %. This indicated good handling property of the prepared tablet.

Weight variation:
A tablet was designed to contain a specific amount of drug. When the average mass of the tablet was 500 mg the pharmacopoieal limit for percentage deviation was ±5%. The percentage deviation from average tablet weight for all the tablet was found to be within the specified limits and hence all formulations complied with the test for weight variation according to the pharmacopoieal specifications IP 2007.

In-Vitro Drug released Studies:
The In-Vitro Drug released Study of tenofovir disoproxil fumarate IR tablets done using USP-II apparatus, buffer 0.1N HCl (pH 1.2) and RPM 50RPM. The samples were collected at different time intervals 0, 5, 10, 20, 30, 40, 60 min and the absorbance measured using UV spectroscopy at 259nm and the amount was calculated.

Formulations TF1-TF4 was formulated using starch phthalate as super disintegrant. The mechanism of disintegration is swelling by water uptake immediately after intimate contact with water.

Formulations TF5-TF8 was formulated using starch phthalate as super disintegrant. The mechanism of disintegration is swelling and wicking action intimate contact with water. Wicking action where material-air or material-material interface is spontaneously replaced by material-water interface and thus helps in maintaining capillary flow.

Formulations TF9-TF12 was formulated using starch phthalate as super disintegrant. The mechanism of disintegration both swelling by water uptake and wicking action intimate contact with water. Wicking action where material-air or material-material interface is spontaneously replaced by material-water interface and thus helps in maintaining capillary flow.

Table No.17: Drug release study for the formulations TF1-TF12

Time (min)	Cumulative % drug release											
	TF1	TF2	TF3	TF4	TF5	TF6	TF7	TF8	TF9	TF10	TF11	TF12
0	0	0	0	0	0	0	0	0	0	0	0	0
2.5	14.34	15.45	20.23	21.68	13.24	16.44	20.72	22.35	20.14	24.45	25.35	32.73
5	30.24	32.43	43.45	45.45	29.21	34.44	46.35	46.46	44.45	55.45	57.64	62.16
7.5	54.68	59.68	64.68	69.56	48.68	62.63	66.78	67.55	59.34	69.73	72.34	88.93
10	66.43	72.46	79.48	81.39	61.43	77.44	78.48	82.32	81.37	89.46	91.47	99.57
15	88.73	89.61	93.43	90.68	78.73	89.21	92.41	91.64	98.53	98.34	98.93	
20	96.84	97.43	98.54	97.85	86.84	98.45	97.64	98.95				
25					98.45							

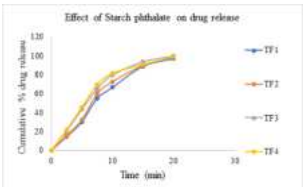

Figure No.8: Drug release study for formulation TF1-TF4

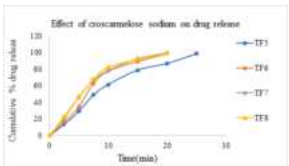

Figure No.9: Drug release study for formulation TF5-TF8

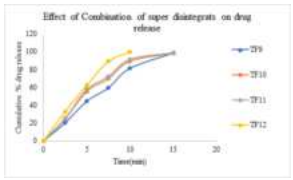

Figure No.10: Drug release study for formulation TF9-TF12

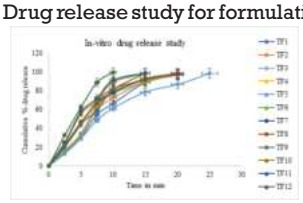

Figure No.11: Drug release study for formulations TF1-TF12

Drug Release kinetics:

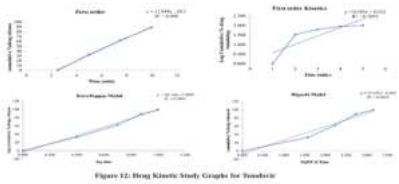

Table No.17: Regression values for optimised formulation of tenofovir

Order of kinetics	Zero order	First order	Higuchi plot	Kors-peppas Model
Regression value(r2)	0.998	0.7075	0.9614	0.9891

The drug release from the oral disintegrating tablets was explained by the using mathematical model equations such as zero order, first order methods. Based on the regression values it was concluded that the optimized formulation TF12 follows zero order kinetics drug release.

Stability study:
The best formulation TF12 was exposed to accelerated stability conditions and subjected to various evaluation parameters, and results were shown in table

Table No.18: Stability study data of optimised formulation (Tf12)

Parameter	Initial	1 month	2month	3 month
Description	White colour	White colour	White colour	White colour
Average wt	499.72±0.02	498.22±0.03	499.42±0.02	498.21±0.03
Hardness	5.5±0.03	5.4±0.05	5.3±0.05	5.3±0.05
Disintegration time	5.2±0.43	5.1±0.54	5.1±0.23	5.1±0.12

CONCLUSION
Tenofovir is antiviral drug used to treat infections like HIV. In this study initial all the preformulation studies like melting point physical stability and drug excipient compatibility studies were done for pure drug and excipients used in the formulation was shown no drug-excipient incompatibility between drug and polymer. IR tablets tenofovir were prepared using different disintegrants namely croscarmellose and starch phthalate and all pre compression parameters like bulk density, tapped density, carrs's index and angle of repose was measured for formulation mixtures (TF1-TF12) and post compression parameters like thickness and diameter, weight variation, hardness, friability, disintegration, drug dissolution studies was done for all formulations (TF1-TF12). The results shown that the thickness and diameter is in btween 5.32 to 5.46mm. Hardness of the tablets iin the range of 5.3 kg/cm2 to 5.7 kg/cm2, percentage friability 0.12 to 0.21 % and in drug release study Formulations TF1-TF4 was formulated using starch phthalate

as super disintegrant. The mechanism of disintegration is swelling by water uptake immediately after intimate contact with water. Formulations TF5-TF8 was formulated using starch phthalate as super disintegrant. The mechanism of disintegration is swelling and wicking action intimate contact with water. Wicking action where material-air or material-material interface is spontaneously replaced by material-water interface and thus helps in maintaining capillary flow. Formulations TF9-TF12 was formulated using starch phthalate as super disintegrant. The mechanism of disintegration both swelling by water uptake and wicking action intimate contact with water. Wicking action where material-air or material-material interface is spontaneously replaced by material-water interface and thus helps in maintaining capillary flow. Which showed that the formulation TF12which is the mixture of corscarmelose and starch phthalate was the best formulation with fast disintegration time and 22±0.43 sec and drug release 99.57 in 10 min respectively.

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