RESEARCH ARTICLE

Development and Evaluation of Dispersible Tablet comprising Tenofovir, Bictegravir and Emtricitabine

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ABSTRACT

Maximum Anti-HIV Drugs Dosage Forms are available as tablets or capsule dosage forms. Such Dosage Forms are not suitable for patient who is having difficulty to swallowing. Antiretroviral therapy for treatment of HIV Infection contains more than two drugs so dose of drugs are more and most of these drugs are having issues like high bitterness, low solubility, highly moisture sensitivity and drugs incompatibility issue so to formulate HIV drugs into dispersible tablet is challenging. In present research, fixed dose combination of Tenofovir, Bictegravir and Emtricitabine were used to formulate the dispersible bilayer tablet. Bictegravir sodium is BCS class II drug hence with this drug eight different formulation for solubility enhancement was performed. All the physicochemical parameters were evaluated for the granules, Dissolution, assay for the granules were determined. For second layer of Tenofovir, and Emtricitabine, disintegrant concentration was optimized with three different formulations and evaluation was done like flow properties of granules, DT, assay and dissolution. All the results were compared with the marketed product. The formulation F10 showed desirable DT, assay, and dissolution hence it was selected as best formulation.

Keywords: Bictegravir, Emtricitabine, Tenofovir, Anti-cancer Drugs, Dispersible tablet.

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INTRODUCTION

The solid dosage form is the most preferred drug delivery system invented by William Brockedon in 1842. Oral solid dosage is a form of essential administration dosage owing to being user friendly and production flexibility. Specifically route like oral is best as its non-invasiveness, high patient acceptance and thus maximum adherence to therapy. A dispersible tablet is a solid dosage form which upon administration generates a uniform suspension, making it easier to administer and swallow. It is especially beneficial for patients with swallowing difficulties, such as children and the elderly. Advantages include improved absorption, convenient dosing, and suitability for patients with restricted fluid intake.[1,2] Ideal dispersible tablets should disintegrate quickly in water, forming a uniform suspension for easy administration. They must have sufficient mechanical strength to withstand handling and packaging while ensuring rapid dispersion. The taste should be acceptable, with minimal bitterness or a suitable flavor masking. Additionally, they should provide consistent dosing and stability under standard storage conditions.[3] Dispersible tablets offer several advantages, making them a convenient dosage form. They dissolve in water to form a uniform suspension, making them easy to administer, especially for children, the elderly, and those with swallowing difficulties. It Avoids First Pass Metabolism due to pre-gastric absorption and it also improves bioavailability. These tablets provide quick onset of action due to faster absorption compared to conventional tablets. They are convenient for patients without access to water for swallowing pills and ensure accurate dosing. Additionally, they are cost-effective to produce and stable under normal storage conditions.[3]

The mechanism of drug release from dispersible tablets involves their rapid disintegration in water to form a fine suspension. The active drug particles are then dispersed, increasing the surface area for dissolution and absorption. This ensures faster drug release and quicker therapeutic action. the big size of oral solid formulation is challenging for patients with dysphagia, difficult to swallowing for patient like geriatric, pediatrics, psychiatric, stroke victim, pregnant women, condition like bedridden patient's, esophageal, ENT cancer, neurologic deterioration patient etc. thus, non adherence to treatment. So, health-care professionals do splitting of standard available pill for administration to such patients, which reduce absorptions, change pharmacokinetics and drug release kinetics, cause over or underdosing and thus incomplete virological suppression, increased adverse effects. Which successively promoted oral formulations dosage forms like Orodispersible Dosage Forms as Dispersible Tablet.[4, 5]

Currently maximum Anti-HIV Drugs Dosage Forms are available as tablet or capsules dosage form. Such Dosage Forms are not suitable for patient who is having difficulty to swallowing. Generally antiretroviral therapy for treatment of HIV Infection contains more than two drugs

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Table 1. Formulation trial batches for solubility enhancement of Bictegravir sodium

Raw material (mg) Dry mix	F1	F2	F3	F4	F5	F6	F7	F8
Bictegravir Sodium	52.88	52.88	52.88	52.88	52.88	52.88	52.88	52.88
Wet granulation	-	-	-	-	-	-	-	-
PEG 4000	52.88	-	-	-	-	-	-	-
PEG 6000	-	52.88	-	-	-	-	-	-
Gelucire 44/14	-	-	52.88	-	-	-	-	-
Propylene glycol	-	-	-	52.88	-	-	-	-
Kyron T 104	-	-	-	-	52.88		-	-
Poloxamer F127	-	-	-	-	-	20		-
Poloxamer F127	-	-	-	-	-	-	30	
Poloxamer F127	-	-	-	-	-	-	-	40
Acetone	24	30	24	28	40	26	21.42	21.42

so dose of drugs are more and most of these drugs are having issues like high bitterness, low solubility, highly moisture sensitivity and drugs incompatibility issue so to formulate HIV drugs into dispersible tablet is challenging. In present research, fixed dose combination of Tenofovir, Bictegravir and Emtricitabine were used to formulate the dispersible bilayer tablet.[6,7] Tenofovir belongs to the antiviral drug class, specifically a nucleotide reverse transcriptase inhibitor (NRTI). Tenofovir alafenamide falls under BCS Class III, which is defined by high solubility but low permeability.[8] In contrast, Bictegravir is categorized as BCS Class II, characterized by low solubility but high permeability. Bictegravir exhibits moderate solubility in aqueous media, with oral bioavailability around 35%, primarily constrained by its solubility. Meanwhile, Emtricitabine belongs to BCS Class I, noted for both high solubility and high permeability. It is highly water-soluble and demonstrates an oral bioavailability of approximately 93%, indicating efficient absorption.

Reason Behind Selecting Bilayer Tablet

Separating these drugs into different layers allows for the tailored delivery of each drug component. Emtricitabine, tenofovir alafenamide, and bictegravir have different pharmacokinetic properties, and their absorption and distribution in the body may need to be carefully controlled to achieve the desired therapeutic effect. In separate layers, the release profile of each drug can be optimized independently. These three drugs are hygroscopic, and due to this nature, it leads to drug-drug interactions in monolayer and also affects the dissolution of the drug. Physical stability and chemical stability may affect and lead to an alteration in the dissolution profile. If APIs are incompatible with each other, meaning they may react or interfere with each other's function, they can be separated into different layers to prevent interaction. Each drug in the combination has a different pharmacokinetic profile. By separating these drugs into different layers, it allows for the tailored delivery of each drug component. Each drug in the combination has a different Log P value. By separating these drugs into different layers, it ensures that each drug is released at the optimal rate for absorption. Bilayer tablets can reduce the number of tablets a patient needs to take, improving patient compliance.[9-11]

Table 2. Formulation trial batches for optimization of concentration of disintegrant (CCS) Layer I

S. No.	Ingredients	mg/ tablets		
Formulation Layer - I (Tenofovir and Emtricitabine) Dry Mix		F9	F10	F11
1	MCC PH-112	50.19	50.19	50.19
2	Tenofovir Alafenamide Hemi fumarate	28.32	28.32	28.32
3	Emtricitabine	200.49	200.49	200.49
4	Mannitol SD 200	20	20	20
5	Mannitol Pearlitol 25 C	20	20	20
6	Aspartame IP	25	25	25
7	Croscarmellose sodium	7.5	x	x
8	Croscarmellose sodium	x	10	x
9	Croscarmellose sodium	x	x	12.5
Binding				
10	Ethyl Cellulose N-7	5	5	5
11	MDC	q.s	q.s	q.s
Extra Granular Ingredients				
12	Croscarmellose sodium	7.5	x	x
13	Croscarmellose sodium	x	10	x
14	Croscarmellose sodium	x	x	12.5
15	Aspartame	20	20	20
16	Ponceu Colour	1	1	1
17	Syloids AL -1-FP	11	11	11
18	Strawberry Flavour	7	7	7
Lubrication				
19	Sodium stearyl fumarate	2	2	2
Total weight part-1		410 mg	410 mg	410 mg

Table 3: Formulation trial batches for optimization of concentration of disintegrant (CCS) Layer II

S. No.	Ingredients	mg/ tablets		
Formulation		F9	F10	F11
Layer – II (Bictegravir Sodium)				
Dry Mix				
1	MCC-PH-112	131.28	131.28	131.28
2	PVPK-30	5	5	5
3	Croscarmellose sodium	7.5	x	x
		x	10	x
		x	x	12.5
Binding				
4	Bictegravir Sodium	52.72	52.72	52.72
5	Acetone BP	Q.S	Q.S	Q.S
Extra granulation				
6	Poloxamer F-127	30	30	30
7	Croscarmellose sodium	10	10	10
8	Syloids AL -1-FP	5	5	5
Lubrication				
9	Sodium stearyl fumarate	2	2	2
	weight part-2	246	246	246
	Weight of core tablets	656.0	656.0	656.0
Coating				
1	Lecithin	2	2	2
2	HPMC – E-5	8.5	8.5	8.5
3	Titanium dioxide	0.5	0.5	0.5
4	Vanillin IP	2	2	2
5	Talc IP	0.5	0.5	0.5
6	PEG 6000	2.75	2.75	2.75
7	IPA	Q. S	Q. S	Q. S
8	MDC	Q. S	Q. S	Q. S
Total weight of tablets		672.25	672.25	672.25

Proposed dosage form of selected Anti-HIV Drugs developed by improving challenging parameters like solubility, permeability, bioavailability, bitterness and stability of anti-HIV drugs and their comparative evaluation studies like physical, chemical etc. parameters evaluations.

MATERIALS AND METHODS

Materials

Drugs Emtricitabine, tenofovir alafenamide, and bictegravir were received as a gift sample from Hetero Drugs. Microcrystalline cellulose used in the formulation development is Avicel pH112, supplied from DuPont Nutrition Ireland. The grade of Sodium starch glycolate, Ph. Eur. used in the formulation development is Primojel, supplied from DFE Pharma. Syloids AL1 FP was purchased from GRACE suppliers. Mannitol SD 200, Mannitol 25 C supplied from Roquette pharma,

Table 4. Organoleptic properties and melting points of drugs

Parameter	Bictegravir Sodium	Emtricitabine	Tenofovir Alafenamide
Description	A light yellow color powder	A White to off white powder	A white to off white powder
Melting point	124.5 ^{0}C	150.2 ^{0}C	132.3^{0}C

Table 5: Solubility Results of Bictegravir in Different pH media

Medium used	Solubility at 37^o C temperature			
	Solubility mg/ml	Mg/250 ml	Approx Vol. of Solvent in ml/g	Solubility criteria as per USP
Purified water	0.070	18.8	13333	Insoluble
50 mM citrate Ph 5.5	0.29	73.5	3401	Very slightly soluble
pH 6.8 Phosphate buffer	0.12	31.0	8064	Very slightly soluble

Table 6: Solubility Results of Emtricitabine

Medium used	Solubility (37^o C)			
	Solubility mg/ml	Mg/250 ml	Approx Vol. of Solvent in ml/g	Solubility criteria as per USP
Purified water	48.73	12182	20	Soluble
50 mM citrate Ph 5.5	46.95	11737	21	Soluble
pH 6.8 Phosphate buffer	43.70	10925	22	Soluble

Croscarmellose Sodium from JRS pharma, Aspartame, Ethyl Cellulose 7 CPS from KP Manish , Ponceau 4 R supra Colour purchased from Dynemic Product Ltd, Strawberry Flavor purchased from Fab flavours, Sodium Stearyl Fumarate, Povidone k 30, Poloxamer 407 (Plutonic F-127) , Lecithin, TPGS, HPMC - E-5 LV, Titanium Dioxide, Vanillin IP Snow orchid, Talc and PEG 6000 from signet excipients, KP Manish, Colourcon, DFE Pharma, DFE Pharma, Silaris Ingredients, Gattefosse, Flavaroma, JRS Pharma, Mitsuya, Prachin Chemical and Ankit Pulps these excipients used in the formulation development. Other chemicals used the formulation were of AR grade.

Organoleptic Properties

The received drug were evaluated for appearance and color. The tests were performed manually with reference to standard parameters.

Melting Point (MP)

Table 7: Solubility Results of Tenofovir alafenamide hemifumarate in Different pH media

Medium used	Solubility at 37° C temperature			
	Solubility mg/ml	Mg/250 ml	Approx Vol. of Solvent in ml/g	Solubility criteria as per USP
Purified water	12.74	3185	78	Sparingly Soluble
50 mM citrate pH 5.5	7.20	1800	138	Slightly Soluble
pH 6.8 Phosphate buffer	5.51	1377	181	Slightly Soluble

The MP was estimated with digital melting point apparatus having a temperature range up to 350^{0}C with heating speed of 0.1°C to 20°C/min. The sample under examination was filled in glass melting point capillaries and placed into the holder. Enabling working of digital instrument melting effect is studied and melting point investigation is performed. The MP obtained in the experiment was compared with the standard MP of drug reported in the literature or official compendia.

Solubility

Solubility, a crucial parameter in pre-formulation studies, was determined for every drug at 37°C over 24 hours. Different medium like purified water, 50 mM citrate pH 5.5, Phosphate buffer (pH 6.8) were used at constant temp of 37.0°C ± 0.5°C in water bath, with the samples placed on a shaker for continuous agitation. The process lasted for 18 to 24 hours followed by filtration using Millipore filter and then analysed spectrophotometrically.

DSC

A Hitachi 9020 model of DSC was used for the analysis and a thermogram was reported by using the same instrument.[12] Approx. 1-3 mg of the formulation was kept on a heated pan (50 ml/min Nitrogen flow rate) at a 10^{0}C/min. Thermal analysis of data was then conducted with a DSC thermogram.

Fourier Transformation Infrared (FTIR) Analysis

This study was performed to get information regarding functional groups available in the drugs and it also determines the interactions between drug and excipients.[12] The spectrum of drugs were analysed at 4000 – 900 cm^{-1} and compared with standard IR spectra to authenticate the drug molecule.

XRD Analysis

Philips PAN analytical expert Shimadzu XRD-7000 (Japan) was employed for the analysis. X-ray scattering measurements were conducted.

Drug Excipient Interaction

The analysis was performed at 40°C and 75% Relative Humidity condition.[13] Each API and co-processant were mixed at 1:1 and 1:10 ratios and kept in small glass vials in open and closed conditions and kept in a stability chamber for 30 days. The samples were examined after one month the physical observation and assay was

Table 8: Drug excipient compatibility study of Emitricitabine and Tenofovir

Sr. No.	Drug + Excipient	Physical Observation (Initial)	Physical Observation (40°C / 75 % RH) (1M)	Assay	Assay	
					Initial	40^{0}C/75 % RH (1M)
1	Tenofovir alafenamide hemi fumarate	White Powder	White Powder	Tenofovir	99.8	97.7
2	Emtricitabine	White Powder	White Powder	Emtricitabine	100	100.1
3	Tenofovir + Emtricitabine + Microcrystalline Cellulose PH 112	White Powder	White Powder	Tenofovir	100.8	97.5
				Emtricitabine	100.5	98.2
4	Tenofovir + Emtricitabine + Mannitol SD 200	White Powder	White Powder	Tenofovir	98.8	97.2
				Emtricitabine	99.1	96.5
5	Tenofovir + Emtricitabine + Mannitol 25 C	White Powder	White Powder	Tenofovir	100.1	96.4
				Emtricitabine	97.8	96.2
6	Tenofovir + Emtricitabine + Croscarmellose Sodium	White Powder	White Powder	Tenofovir	100.5	98.2
				Emtricitabine	100.7	97.5
7	Tenofovir + Emtricitabine + Aspartame	White Powder	White Powder	Tenofovir	100.5	98.7
				Emtricitabine	99.2	96.5
8	Tenofovir + Emtricitabine + Ethyl Cellulose 7 CPS	White Powder	White Powder	Tenofovir	99.4	97.4
				Emtricitabine	99.5	96.5
9	Tenofovir + Emtricitabine + Ponceau 4 R supra Colour	Light Pink Powder	Light Pink Powder	Tenofovir	100.7	97.8
				Emtricitabine	99.2	96.4

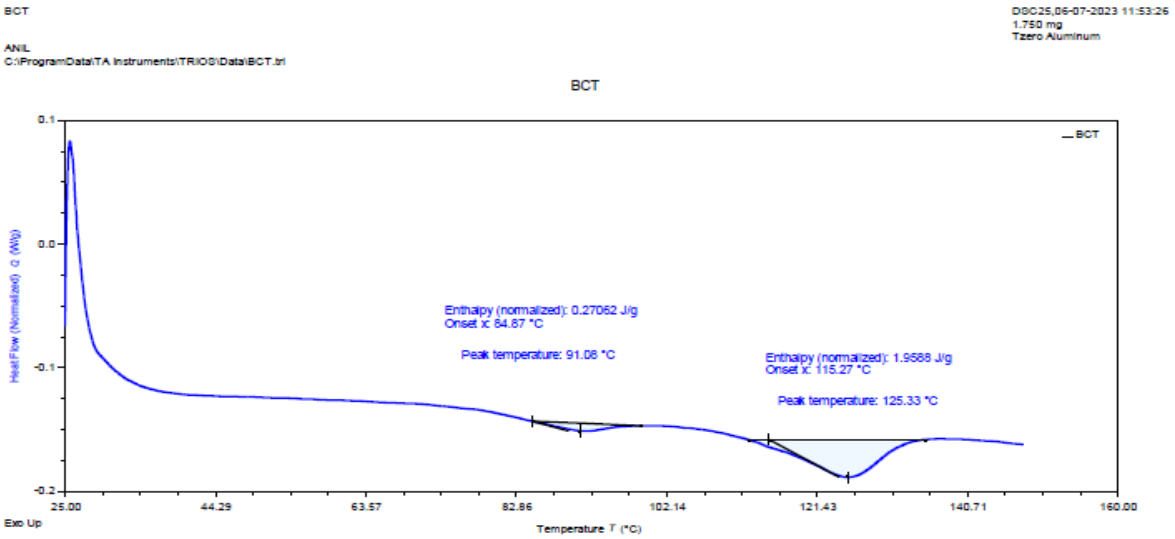

Figure 1: DSC thermogram of Bictagravir sodium

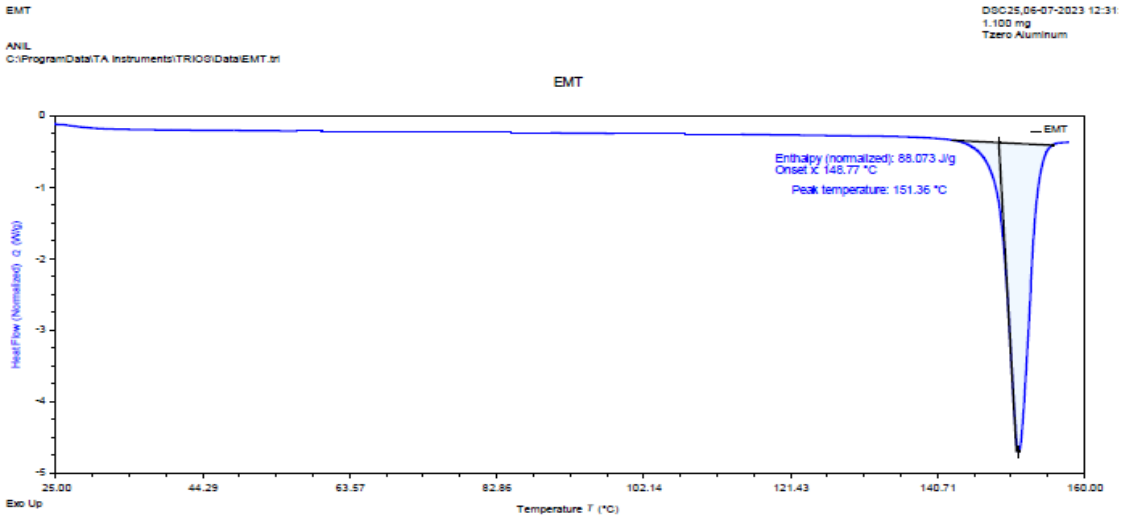

Figure 2: DSC thermogram of Emtricitabine

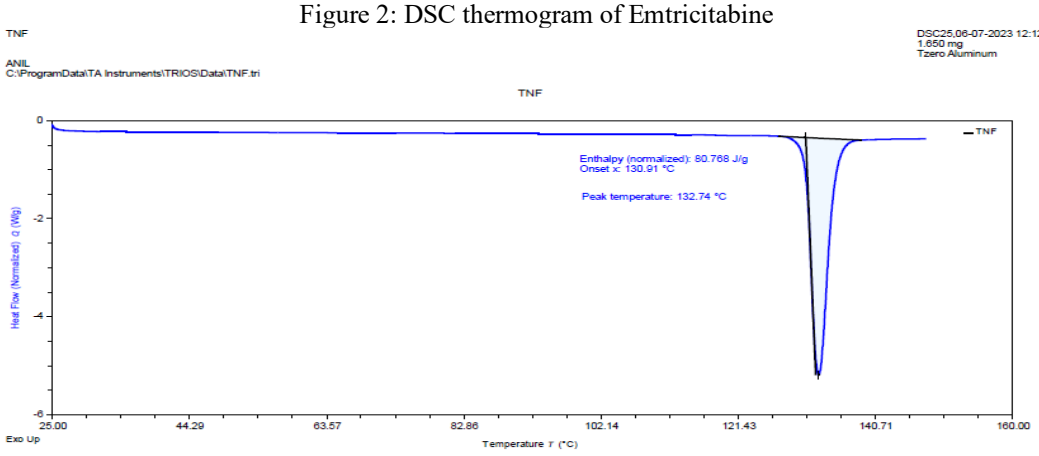

Figure 3: DSC thermogram of Tenofovir alafenamide hemifumarate

examined and compared with initial observations**.** Based on this comparison DEC was established.

Bulk Density

Accurately weighed drug sample was poured carefully without tapping in the graduated glass measuring cylinder. The untapped volume occupied by the drug in glass measuring cylinder was recorded. The BD of the drugs was determined using below equation.

$$\text{BD} = \frac{\text{Sample Weight (g)}}{\text{volume (ml)}}$$

Tapped Density (TD)

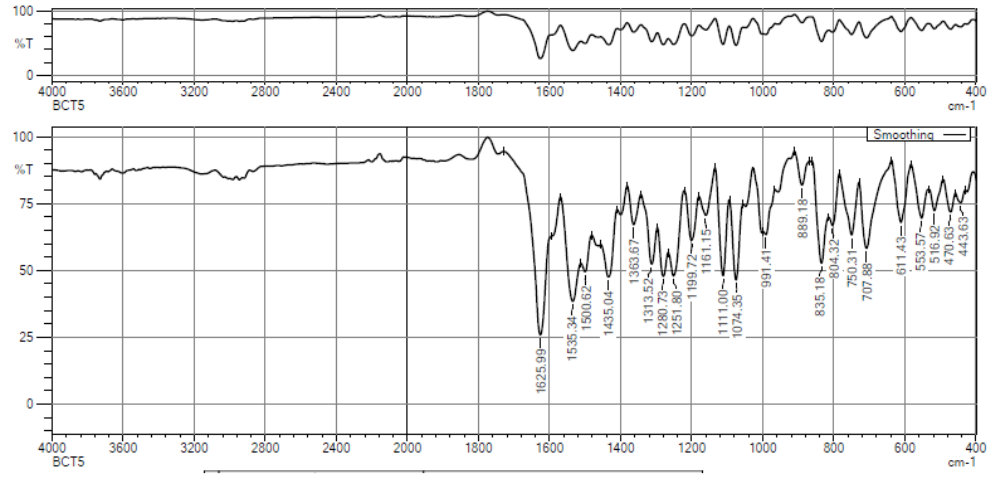

Figure 4: FT-IR spectra of Bictagravir sodium

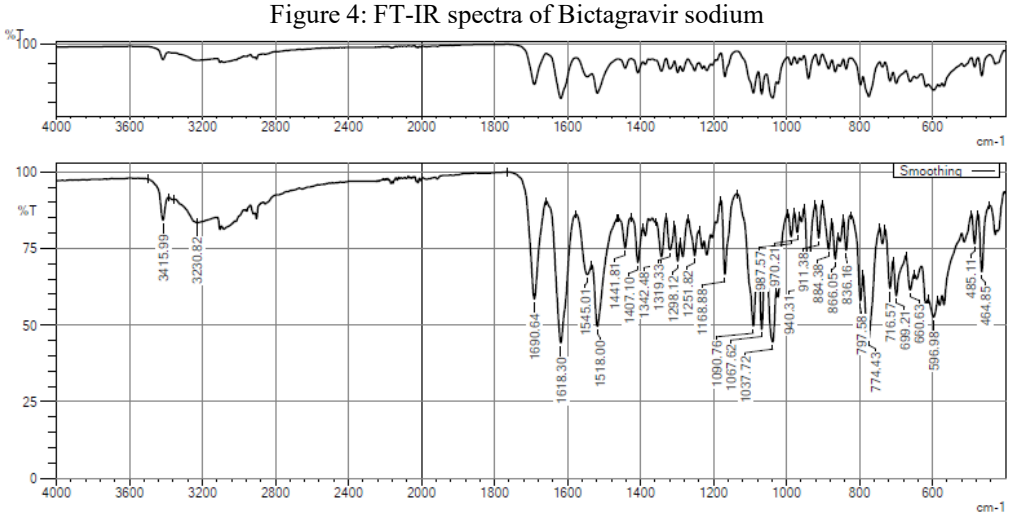

Figure 5: FT-IR spectra of Emtricitabine

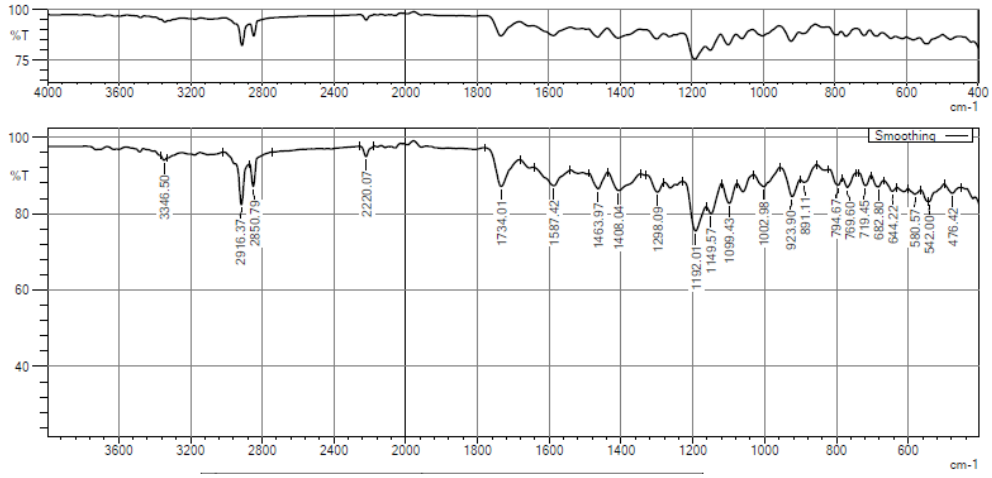

Figure 6: FT-IR spectra of Tenofovir

A similar procedure for BD was followed by providing a fixed number of tapping and tapped volume by drug was recorded and weighed again. The TD of the drug was determined using below equation

$$\text{TD} = \frac{\text{Sample Weight (g)}}{\text{tapped volume (ml)}}$$

Hausner's Ratio (HR)

Below equation was used to calculate the HR

$$\text{HR} = \frac{\text{TD}}{\text{BD}}$$

Carr's Index (CI)

Below equation gives the estimate CI

$$\text{CI} = \frac{\text{TD} - \text{BD}}{\text{TD}} \text{X } 100$$

Formulation of Bilayer Dispersible Tablet

Solubility Enhancement of Bictegravir Sodium

To formulate a dispersible bilayer tablet for the Fixed Dose Combination (FDC) of Bictegravir sodium,

Emtricitabine, and Tenofovir alafenamide, Bictegravir sodium should dissolve quickly and enhancing its solubility and absorption. To enhance the solubility of Bictegravir sodium, different solubilizer used and fluidized bed processor (FBP) was used. Different formulation trial batches were taken F1 to F9 shown in Table 1. Bictegravir Sodium was sifted through sieve 40. Acetone was taken in SS vessel and each solubilizer was added in vessel to add it. Stirred the solution for 30 min. By using wet granulation method, mixture was taken in fluidized bed dryer and granular mass was formed by setting all the parameters accurately. The formed granules were dried and LOD was checked it should NMT 2.5%. These granules were sifted from the 30 mesh and packed in double polythene bags.

Table 9: Drug excipient compatibility study of Emitricitabine and Tenofovir

Sr. No.	Drug + Excipient	Physical Observation (Initial)	Physical Observation (40ºC / 75 % RH) (1M)	Assay	Assay Initial	Assay 40^0C/75 % RH (1M)
1	Tenofovir + Emtricitabine + Syloid AL-1-FP	White Powder	White Powder	Tenofovir Emtricitabine	98.9 99.3	98.3 96.5
2	Tenofovir + Emtricitabine + Strawberry Flavor	White Powder	White Powder	Tenofovir Emtricitabine	98.7 100.0	97.8 98.4
3	Tenofovir + Emtricitabine + Sodium Stearyl Fumarate	White Powder	White Powder	Tenofovir Emtricitabine	100.3 100.2	98.6 98.2
4	Tenofovir + Emtricitabine + Lecithin	White Powder	White Powder	Tenofovir Emtricitabine	99.4 99.1	97.3 95.8
5	Tenofovir + Emtricitabine + HPMC - E-5 LV	White Powder	White Powder	Tenofovir Emtricitabine	99.9 100.0	97.2 95.6
6	Tenofovir + Emtricitabine + Titanium Dioxide	White Powder	White Powder	Tenofovir Emtricitabine	100.5 98.2	98.6 97.5
7	Tenofovir + Emtricitabine + Vanillin IP Snow orchid	White Powder	White Powder	Tenofovir Emtricitabine	100.7 100.4	98.1 98.5
8	Tenofovir + Emtricitabine + Talc	White Powder	White Powder	Tenofovir Emtricitabine	98.8 99.4	96.5 97.4
9	Tenofovir + Emtricitabine + all excipients	White Powder	White Powder	Tenofovir Emtricitabine	96.2 98.4	93.6 92.5

Table 10: Formulation Component compatibility study of Bictagravir

Sr. No	Drug + Excipient	Physical Observation (Initial)	40ºC / 75 % RH (1M)	Assay % Initial	Assay % 40^0C / 75 % RH (1 M)
1	Bictegravir sodium	White Powder	White Powder	99.7	97.9
2	Bictegravir sodium + Microcrystalline Cellulose PH 112	White Powder	White Powder	98.4	95.4
3	Bictegravir sodium + Croscarmellose Sodium	White Powder	White Powder	98.9	98.2
4	Bictegravir sodium + Syloid AL-1-FP	White Powder	White Powder	99.6	96.2
5	Bictegravir sodium + Sodium Stearyl Fumarate	White Powder	White Powder	99.4	95.6
6	Bictegravir sodium + Povidone k30	White Powder	White Powder	98.5	97.4
7	Bictegravir sodium + Poloxamer 407 (Plutonic F-127)	White Powder	White Powder	99.4	96.6
8	Bictegravir sodium + Lecithin	White Powder	White Powder	100.0	98.2
9	Bictegravir sodium + TPGS	White Powder	White Powder	99.3	96.5

Table 11: Formulation Component compatibility study of Bictagravir

Sr. No	Drug + Excipient	Physical Observation (Initial)	40ºC / 75 % RH (1M)	Assay % Initial	40^0C / 75 % RH (1 M)
1	Bictegravir sodium + HPMC - E-5 LV	White Powder	White Powder	98.6	97.5
2	Bictegravir sodium + Titanium Dioxide	White Powder	White Powder	98.5	97.2
3	Bictegravir sodium + Vanillin IP Snow orchid	White Powder	White Powder	100.0	96.5
4	Bictegravir sodium + Talc IP	White Powder	White Powder	99.1	97.8
5	Bictegravir sodium + PEG 6000	White Powder	White Powder	98.8	98.1
6	Bictegravir sodium + PEG 4000	White Powder	White Powder	96.5	93.0
7	Bictegravir sodium + Gelucire 44/14	White Powder	White Powder	97.3	94.5
8	Bictegravir sodium + PG	White Powder	White Powder	95.6	95.5
9	Bictegravir sodium + Kyron T 104	White Powder	White Powder	95.2	93.5
10	Bictegravir sodium + All excipients	White Powder	White Powder	98.7	94.8

Table 12: Flow properties of the drug Bictegravir sodium, Tenofovir and Emtricitabine

Parameter	Bictegravir Sodium	Emtricitabine	Tenofovir Alafenamide
Bulk Density (g/ml)	0.29	0.43	0.43
Tapped density (g/ ml)	0.425	0.73	0.77
Carr' Index	31.76	41.091	44.156
Hauser's ratio	1.46	1.697	1.79

Table 13. Evaluation of Bictagravir sodium granules

Parameters	F1	F2	F3	F4	F5	F6	F7	F8
Assay	97.6	98.4	97.5	98.8	99	99.4	98.6	100.6
B.D	0.28	0.26	0.25	0.24	0.27	0.45	0.48	0.5
T.D	0.4	0.33	0.37	0.42	0.4	0.53	0.56	0.57
Angle of Repose	64	57	56	60	58	32	31	31
C. Index	30	21	32	42	32	15	14	12
H.R	1.42	1.26	1.48	1.75	1.48	1.18	1.17	1.14
Flow	poor	passable	Very poor	Very Very poor	Very poor	Good	Good	Good

Evaluation of Bictegravir Sodium Granules

Angle of Repose

The fixed funnel method is employed to determine the angle of repose. In this technique, the sample is transferred into a funnel, ensuring that only the peak of the former drug heap comes into contact with the funnel's tip. The angle of repose is then calculated using the following formula, based on the measured height (H) and radius (R) of the heap.

Angle of repose (θ) = tan−1 (*h* /r)

Where, θ = angle of repose, h = height of heap, r = radius of base of heap circle

Bulk Density

Accurately weighed granule sample was poured carefully without tapping in the graduated glass measuring cylinder. The untapped volume occupied by the granules in the glass measuring cylinder was recorded. The BD of the granules was determined using below equation.

$$\text{BD} = \frac{\text{Sample Weight (g)}}{\text{volume (ml)}}$$

Tapped Density (TD)

A similar procedure for BD was followed by providing a fixed number of tapping and the tapped volume occupied by granules was recorded and weighed again. The TD of the granules was determined using below equation

$$\text{TD} = \frac{\text{Sample Weight (g)}}{\text{tapped volume (ml)}}$$

Hausner's Ratio (HR)

Below equation was used to calculate the HR

$$\text{HR} = \frac{\text{TD}}{\text{BD}}$$

Carr's Index (CI)

Below equation was used to estimate CI

$$\text{CI} = \frac{\text{TD} - \text{BD}}{\text{TD}} \text{X } 10$$

Solubility of Bictagravir Sodium Granules

Solubility study for all batches F1 to F8 (Bictagravir granules) was done in water and in phosphate buffer (pH 6.8 / pH 8).[12,13] Phosphate buffers 6.8, and 8 are used because they are the most important solvents for oral medication administration. These three primary atmospheric solvents are used to filter every preparation that we consume orally. It was done by taking the granules dissolving in one solvent at a time. Each formulation was dissolved in every solvent including phosphate buffer and sonicated for 5 minutes. Suitably diluted and make dilutions in concentrations like 1, 2, 3, 4, 5 µg per mL. The absorbance of each sample was determined.

Table 14: Solubility study for Bictegravir granules formulation F1 to F8

Formulation	Solubility mg/ml		
	Water	Phosphate buffer pH 6.8	Phosphate buffer pH 8
Pure drug	0.075	0.124	0.099
F1	0.15	0.248	0.198
F2	0.31	0.321	0.267
F3	0.51	0.496	0.396
F4	0.78	0.765	0.567
F5	0.91	0.991	0.667
F6	1.2	1.21	0.792
F7	2.8	2.9	3.167
F8	2.18	2.32	2.678

Assay (HPLC Method)

Tablet powder equivalent to about 50 mg was transferred into a 200 ml volumetric flask. About 140 ml of diluent added and sonicated it for not less than 10 minutes with occasional shaking. Diluted it to volume with diluent and mix. The solution was filtered through 0.45 µm membrane filter and discarded first few ml of the filtrate. RP-HPLC instrument equipped with UV detector was used (Schimadzu make, model-LC-2010 CHT). The stationary phase is Inertsil ODS 3V (250 mm x 4.6 mm x 5µm), flow rate 1.0 ml / minutes. Column temperature selected as at 30ºC and wavelength selected at 260 nm. Final concentration selected as 60 ppm for Bictegravir.

Dissolution (HPLC Method)

Citrate buffer pH 5.5 selected as dissolution medium, 900 ml volume, Apparatus Paddle and speed 50 RPM, Dissolution time selected as 15 minutes. Temperature sated as 37±5ºC. Placed one tablet into each of the six dissolution jars. At the end of the specified time withdraw 10 ml of the sample solution from each dissolution vessel and replaced the aliquots with equal volumes of dissolution medium maintained at 37.0±0.5°C. Filtered the solution through 0.45 µm filter and discarded few ml of the filtrate. Separately injected 10 µl of above prepared standard and sample solution in to the chromatographic system. Separately inject 20 µl of diluent as blank, standard solution (five injections) and sample solution into the chromatographic system. Record the chromatograms and measure the peak responses.

Optimization of Concentration of Disintegrant

Tenofovir and Emtricitabine Layer Formulation (Part I)

Accurately weighed and sifted MCC-PH-112, Pearlitol 25C, Mannitol SD 200 Croscarmellose sodium, Tenofovir Alafenamide Hemi fumarate, Emtricitabine and Aspartame IP through 40 # mesh. MDC was taken in SS vessel add ethyl Cellulose N-7 to get dissolve and stirrered for 30 minutes. blend was laoded in FBP & granulate it with step-2 solution, using Top spray assembly to form a granular mass. LOD should be NMT 2.5 % at 105 °C & sifted the dried granules through 30 # mesh. If any retained granules observed, milled it through multi mill using suitable screens. Dried granules were stored in double polythene bags sealed with triple laminated Alu pouches containing silica canisters (Table 2 and 3).

Sifting of Extra Granulation

Table 15: Dissolution study of different formulations in pH 5.5

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
5	60	75	80	83	84	86	90	89
10	65	87	89	92	93	89	93	91
15	78	92.5	96	95	95	95	98	95
30	88	94	96.8	97	98	96	99	98
45	96	95	97	98	99	98	102	100

Table 16: Evaluation of flow properties for formulation F9 to F12

Batch No	F9	F10	F11
B.D	0.45	0.46	0.52
T.D	0.52	0.51	0.54
Angle of Repose	31	31	32
C. Index	13	12	12
H.R	1.15	1.12	1.08
Flow	Good	Good	Good

Table 17: Characterization of Bilayer uncoated tablet for formulation F9- F11

S. No.	Parameter	F9	F10	F11
1	Average Weight (mg)	662	655	656
2	Thickness (mm)	5.55	5.57	5.60
3	Hardness (Kp)	14.2	12.8	11.5
4	Disintegration Time (minutes)	1 min 33 seconds	1 min 27 seconds	1 min 32 seconds
5	Friability (% w/w)	0.7	0.09	0.14

Aspartame, Croscarmellose sodium, Ponceau Color, Syloid AL-1 FP and Strawberry Flavor passed through mesh at # 40 and Sodium Steryl Fumarate pass through at # 60. Both blend mixed for 10 minutes in octagonal Blender.

Bictegravir Sodium (Part-II)

Accurately weighed and sifted MCC-PH-112, Croscarmellose sodium and PVPK-30 through 40 # mesh. Acetone was taken in SS vessel add Bictegravir sodium and stirrer for 30 minutes. Above mixture was blended in FBP & granulate it with step-2 solution, using Top spray assembly to form a granular mass.

Sifting of Extra Granulation

Sifted Syloid AL-1 FP, Poloxamer f 127 and Croscarmellose sodium pass through mesh at # 40 and Sodium Steryl Fumarate passed through at # 60. Blending was done for both 10 minutes in octagonal Blender.

Part I and II were punched using 17.5 X 8.0 mm, Capsule shaped, Concave, Bilayer, one side break other side is plain dies to formulate the tablets.

Coating of Tablets

Approximately 80% Isopropyl Alcohol was added to a cleaned S.S. vessel, followed by dispersing Hydroxyl

Table 18: Characterization of Bilayer coated tablet for formulation F9- F11

S. No.	Parameter	F9	F10	F11
1	Average Weight (mg)	675	668	677
2	Thickness (mm)	5.56	5.60	5.61
3	Hardness (Kp)	16.5	13.8	12.7
4	Disintegration Time (minutes)	1 min 26 seconds	1 min 21 seconds	1 min 27 seconds
5.	Assay	95.45	100.44	98.87

Propyl Methyl Cellulose and mixing. Dichloromethane was then incorporated. In a separate vessel, the remaining 20% Isopropyl Alcohol was used to disperse Lecithin, Vanillin, PEG 6000, Talc, and Titanium Dioxide. Both suspensions were milled using a Colloidal Mill, combined, and stirred with the remaining Dichloromethane. Tablets were warmed in a coating pan to 45°C ± 5°C, sprayed with the film coating suspension, and dried after achieving a mass gain of 2.50 ± 0.50% m/m.

Evaluation of Flow Properties of Granules for Layer 1

For flow properties of granules like, AOR, BD, TD, CI, HR, were evaluated.

Characterisation of Tablets

Average Weight

Approximately 20 tablets were randomly selected, and their weights were precisely measured in milligrams. The mean and standard deviation were then calculated.

Thickness

Thickness can be calculated digital Vernier Calliper. Ten tablets were randomly selected. The observations were noted in mm and the standard deviation was determined.

Hardness

This can be done by using ten tablets that were selected at random was assessed using the Stokes Monsanto hardness tester. The average, as well as the standard deviation (SD), was calculated.

Friability

In an automatic friabilator, 20 tablets were randomly sampled from different batches for this test, and 100 rotations of the test were performed. The dedusted tablets were weighed, and the average of three evaluations of friability was computed. Typically, tablets were regarded as appropriate when there was a weight loss of less than 1%.

Disintegration Test (DT)

The DT was checked for 6 sample tablets in DT apparatus filled with 900 ml of DW at 37 ± 0.5^0C. The DT in seconds was noted when no visible residue was observed in DW.

Assay

For assay, same procedure was applied using HPLC method as stated earlier.

Dissolution

For dissolution, same procedure was applied using HPLC method as stated earlier.

Comparative Study with Marketed Formulation

This test involves comparing various formulation parameters, including weight, color, shape, weight variation, friability, hardness, diameter, drug content, disintegration time, and % CDR. All these parameters are evaluated against those of the marketed formulation.

RESULTS

Preformulation Study

Organoleptic Properties

Bictegravir, Emtricitabine and Tenofovir alafenamide hemifumarate were examined for organoleptic properties and melting points their observations are recorded in Table 4.

Solubility

Solubility data of each drug in different medium is given below Table 5, Table 6 and Table 7.

DSC

Differential Scanning Calorimetry was used to carry thermal analysis of drug. DSC thermogram was reported using the Calorimetry for differential scanning (Hitachi

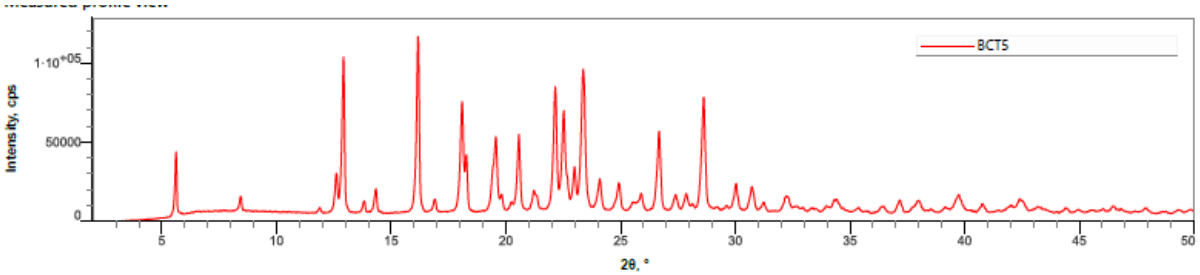

Figure 7: XRD spectra of pure drug Bictagravir

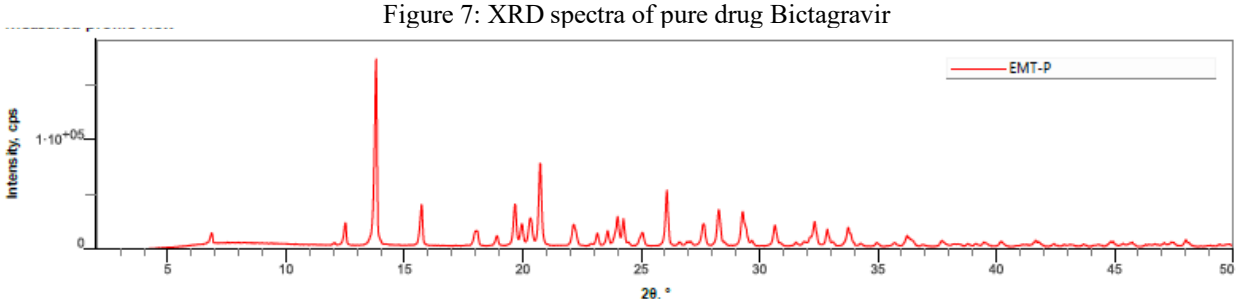

Figure 8: XRD spectra of pure drug Emtricitabine

Table 19: Dissolution for batch F9-F11

Dissolution profile									
	F9			F10			F11		
Time	B	E	T	B	E	T	B	E	T
5	88	101	96	85	100	97	84	100	95
10	89	102	98	90	103	101	89	102	99
15	91	102	98	91	102	101	90	102	99
30	94	102	98	93	102	101	92	102	99
45	95	101	98	95	102	101	94	102	99

Table 20: Comparative dissolution profile for reference product and optimised formulation

Time	Reference product			Optimised batch F10		
	B	E	T	B	E	T
0	0	0	0	0	0	0
5	40	64	56	86	100	97
10	66	98	101	90	103	101
15	79	99	101	91	102	101
30	93	103	105	93	102	101
45	98	102	105	95	102	101

Table 21: Comparative study with marketed formulation

Parameter	Reference product	Optimised Product
Shape	Capsule shaped	Capsule shaped
Average Weight (mg)	715	668
Thickness (mm)	5.62-5.75	5.6
Hardness (Kp)	19.7	13.8
Disintegration Time (minutes)	7min 45 sec	1min 21 sec
Dissolution (within 15 min)	B=79 E=99 T=101	B=91 E=102 T=101

9020). Sharp endothermic peak was visible in the DSC of the Bictagravir sodium at 125.33^{0}C (Figure 1), 151.36^{0}C for Emtricitabine (Figure 2) and 132.74 for Tenofovir alafenamide hemifumarate (Figure 3). which corresponds to the M.P. of respective sample. Through DSC study it was confirmed that the obtained sample of the drug was Bictagravir sodium, Emtricitabine and Tenofovir alafenamide hemifumarate.

FT-IR Analysis

The corresponding groups present in each drug sample were revealed by FTIR Spectroscopic testing. The IR spectra of drugs were recorded along 4000 – 400 cm^{-1}

The results showed (Figure 4) that the sample's size and position in relation to the spectrum's absorption maxima were identical. The characteristic bands of the drug are reported belwo and spectra are shown in figure 5. –C=o stretching observed at ~1650–1700 cm⁻¹. Strong peak here likely corresponds to amide or ketone groups in bictegravir. At ~1500–1600 cm⁻¹ showed N-H bending or C=C stretching (aromatic ring) indicates the presence of secondary amides and aromatic groups. C-N stretching observed at ~1200–1350 cm⁻¹. Aromatic C-H bending at ~700–900 cm⁻¹Confirms aromatic ring presence. The spectrum matches well with the expected functional groups in bictegravir, including amide, ketone, aromatic rings, and fluoro groups. The strong peaks at ~1650–1700 cm⁻¹ (C=O stretching) and ~1200–1350 cm⁻¹ (C-N and C-F stretching) confirm the presence of key structural features. No unexpected peaks suggest the absence of significant impurities.

The FTIR spectrum for Emtricitabine shows (Figure 5) ~3200–3400 cm⁻¹: Broad peaks indicate O-H and N-H stretching (hydroxyl and amine groups). ~1600–1700 cm⁻¹: Strong peak corresponds to C=O stretching (carbonyl group). ~1000–1200 cm⁻¹: Peaks represent C-O and C-F stretching, confirming the presence of fluorinated and hydroxyl groups. ~700–900 cm⁻¹: C-H bending confirms the aromatic system. The spectrum aligns well with emtricitabine's functional groups, supporting its structural identification.

The FTIR spectrum of tenofovir alafenamide (Figure 6) can be interpreted as ~3100–3500 cm⁻¹: Broad peaks indicate O-H and N-H stretching, suggesting the presence of hydroxyl and amine groups. ~2800–3000 cm⁻¹: Aliphatic C-H stretching, denotes towards alkyl chains in the structure. ~1700–1750 cm⁻¹: Strong peak indicates C=O stretching, confirming ester or amide groups. ~1000–1100 cm⁻¹: C-O and P-O-C stretching, associated with ester and phosphonate bonds. These peaks align well with tenofovir alafenamide's functional groups, validating its structure.

XRD

An XRD analysis was conducted to establish whether the pure drug was crystalline or amorphous. Sharp peaks at specific angles 6°, 13°, 16°,18°, 22° it confirms the crystalline nature and likely corresponds to its stable polymorphic form (Figure 7 and Figure 8)

Characteristic diffraction peaks for emtricitabine appeared at specific angles at ~8°, 14°, 18°, 20°, 22°, and 25°. These peaks correspond to specific lattice planes in the crystalline structure of emtricitabine.

Drug Excipient Interaction

The compatibility study of the formulation component was performed. The ratio of API Emitricitabine and Tenofovir (Table 8 and 9) and Bictegravir (Table 10 and 11) the excipients are given below. Results of Drug-Excipients Compatibility studies are provided here after. And it was found that drug excipient compatibility studies were found satisfactory. Compatibility studies conducted under accelerated conditions of 40°C / 75% RH for 30 days

revealed no significant changes in impurity levels or the description of the physical mixtures and API. Based on these results, the following excipients were chosen for formulation development experiments.

Evaluation Study of Drug

The bulk and tapped density as well as the flow ability of three substances were measured and presented in Table 12.

Evaluation of Bictegravir Sodium Granules

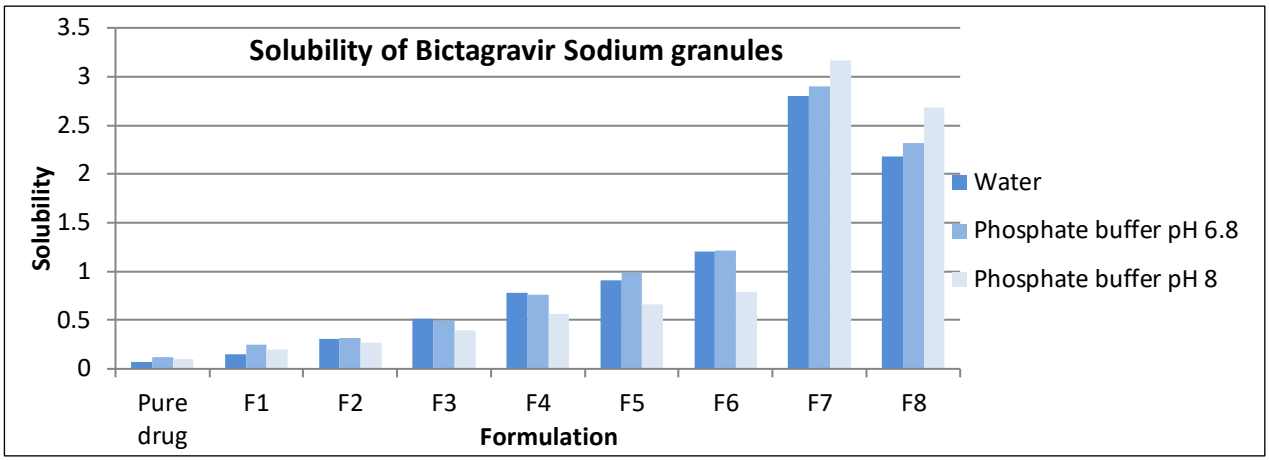

Figure 9: Solubility of pure drug and Bictagravir sodium granules in different media

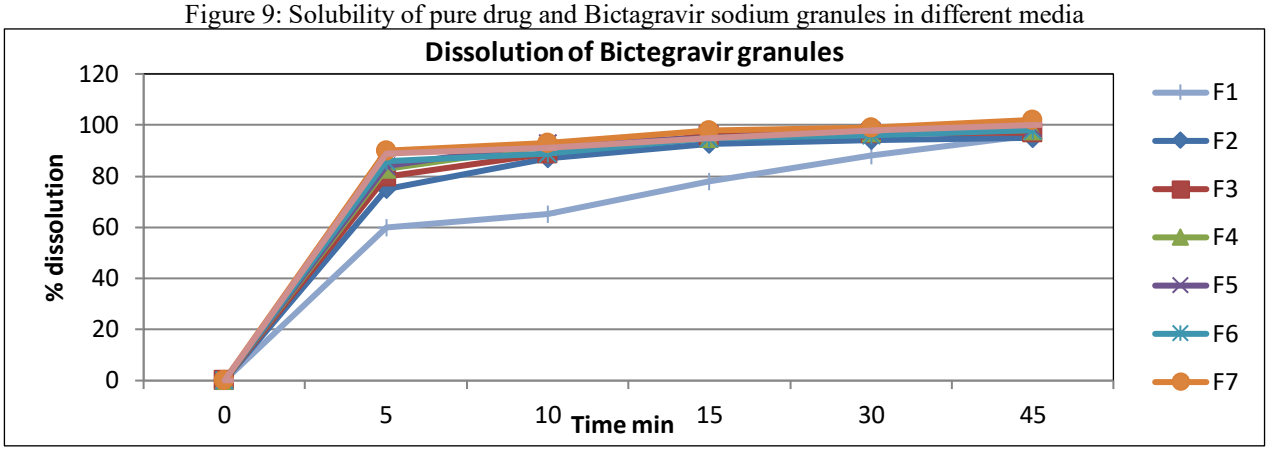

Figure 10: Dissolution study of Bictegravir granules

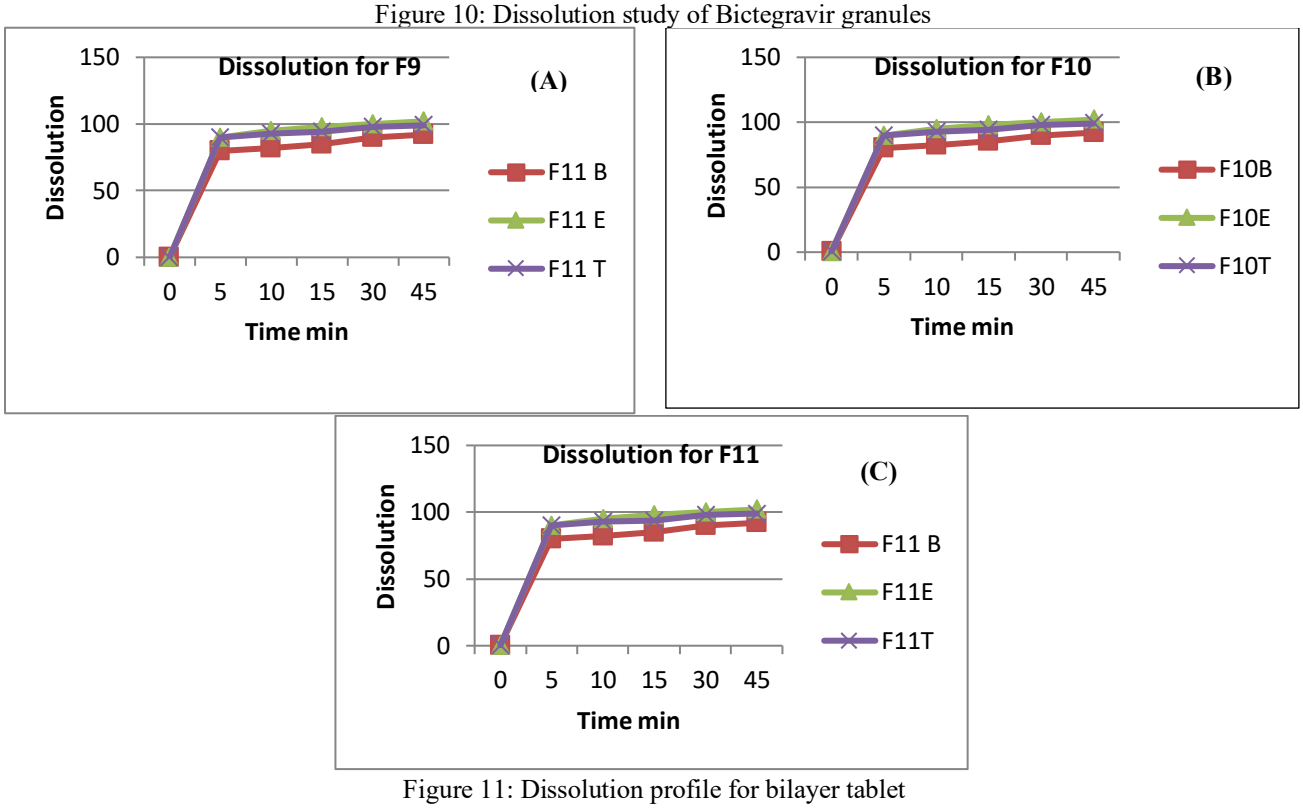

Figure 11: Dissolution profile for bilayer tablet

Flow properties were evaluated (**Table 13**) BD was found in the range of 0.24-0.48, TD was found in the range of 0.33-0.57, AOR, CI and HR for batches F6 to F8 was found satisfactory. Batch F7 was found to have good flowing properties. Assay for granules was found in the range between 97.5-100.6%. Batches F7 and F8 was having maximum drug content.

Solubility of Bictagravir Sodium Granules

Solubility study for all the batches were determined in water as well as in phosphate buffer pH 6.8 and 8 (Table 14). Pure drug was insoluble in water and its solubility was 0.075 mg/ml while in phosphate buffer pH 6.8 was 0.124 and in pH 8 phospahte buffer it was 0.099 mg/ml. In formulation different solubilizer used and granules were prepared by using fluidised bed dryer, hence solubility of the Bictegravir granules was found to be increased. In formulation F7 with use of Poloxamer 127 with concentration of 30 mg showed the maximum solubility as compare to pure drug. Formulation F7 showed maximum solubility in water, phosphate buffer pH 6.8 and pH 8.

Dissolution

Dissolution study of Bictegravir granules was performed in Citrate buffer pH 5.5. It was observed that formulation F7 shown the maximum dissolution within 5 minutes i.e 90%. Observations for dissolution for different formulations F1 to F8 is shown in Table 15 and Figure 10

Bilayer Tablet Formulation and Disintegrant Concentration Optimization

Evaluation of Flow Properties of Granules for Layer 1 (Tenofovir and Emtricitabine)

AOR, BD, TD, CI, HR was verified for the flowability of the granules. Observations for formulations F9 to F11 are shown in Table 16. All the parameters for batches F9, F10 and F11 were found to be satisfactory and can be conclude that flow of the granules was good. Formulation F10 showed AOR 31 and Carr's index was found to be12 which indicates the good flow property.

Characterisation of Tablets

In characterization, average weight, thickness, hardness, disintegration time and friability was determined. The results for formulation F9, F10 and F11 for uncoated tablets are shown in Table 17 and for coated tablets shown in Table 18. Average weight for F9, F10 and F11 was found to be 662 mg, 655 mg and 656 mg respectively. Thickness was found within range while hardness was found in acceptable range. For F10 of coated tablets hardness value was about 13.8 Kp and its disintegration time was found to be 1 min 21 seconds which is closer to marketed formulation and friability for uncoated tablet was also found within limit. Assay value for formulations was found in the range of 95.45 – 100.44 %

Dissolution

Dissolution for bilayer tablet was performed in Citrate buffer pH 5.5. Observations for dissolution of batch F9, F10 and F11 are shown in Table 19 and Figure 11 their respective graphs are shown in figure 11 a, b c. From dissolution profile F10 formulation showed longer dissolution time than other formulations.

Comparative dissolution profile for reference product and optimised formulation is shown in Table 20 and Figure 12 shows the comparative dissolution profile of marketed product and optimised batch F10. F10 formulation showed maximum drug release within 5 minutes than marketed product

Comparative Study with Marketed Formulation

Optimised formulation F10 was compared with different parameters with marketed formulation and observations for this study are given Table 21.

DISCUSSION

Currently maximum Anti-HIV Drugs Dosage Forms are available as tablet or capsules dosage form. Such Dosage Forms are not suitable for patient who is having difficulty to swallowing. Generally antiretroviral therapy for

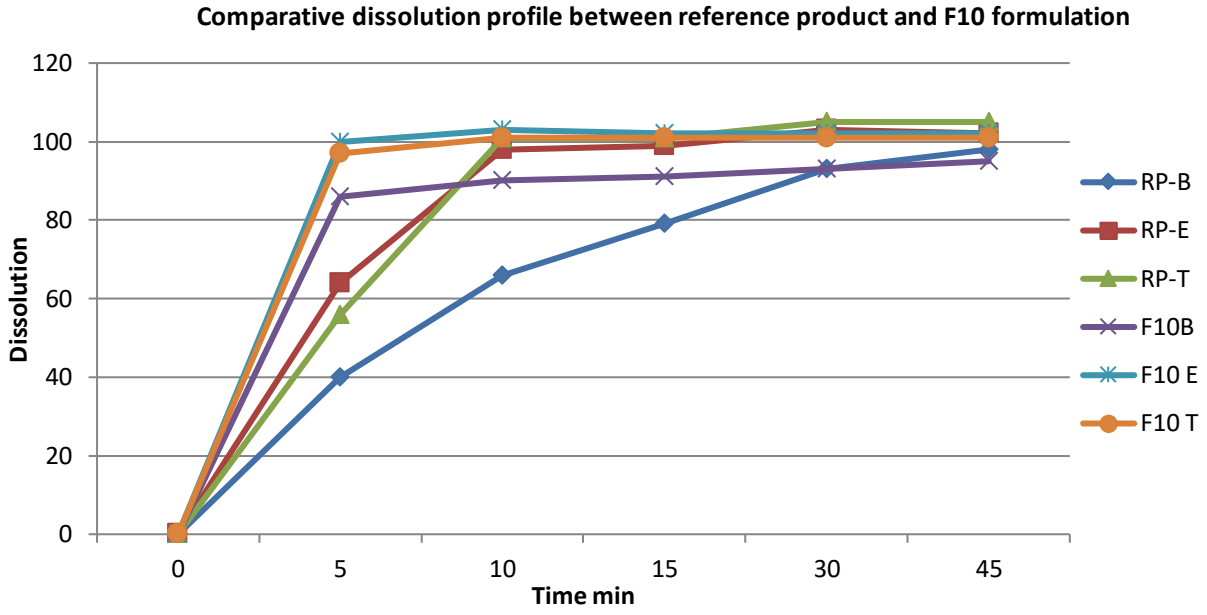

Figure 12: Comparative dissolution profile between reference product and F10 formulation

treatment of HIV Infection contains more than two drugs so dose of drugs are more and most of these drugs are having issues like high bitterness, low solubility, highly moisture sensitivity and drugs incompatibility issue so to formulate HIV drugs into dispersible tablet is challenging. In present research, fixed dose combination of Tenofovir, Bictegravir and Emtricitabine were used to formulate the dispersible bilayer tablet. Bictegravir Sodium, Emtricitabine, and Tenofovir alafenamide hermifumarate, these three drugs belong to different BCS classes i. e. class II, class I and class III respectively. In this research dispersible bilayer tablet of these three drugs were developed.

The research begins with preformulation study of all the three drugs with melting point and solubility in different medium like water, 50 mM citrate Ph 5.5, pH 6.8 Phosphate buffer. Results for this study shown in table 3, 4 and 5. For identification of drugs DSC was performed. Sharp endothermic peak was visible in the DSC of the Bictagravir sodium at 125.33^0C. 151.36^0C for Emtricitabine and 132.74 for Tenofovir alafenamide hemifumarate peaks were observed. Through DSC study it was confirmed that the obtained sample of the drug was Bictagravir sodium, Emtricitabine and Tenofovir alafenamide hemifumarate. The functional groups present in each drug sample were revealed by FTIR Spectroscopic testing for all the drug and it confirm the presence of key structural features. XRD analysis of drugs showed the sharp peaks at different diffraction angles proved the crystalline nature of drugs. Compatibility studies at both accelerated conditions. 40 ^{0}C / 75 % RH for 30 days showed no remarkable deviation in impurity and in description of the physical mixtures and API. Flow properties of drugs were determined and its result is mentioned in table 8.

The main challenge was to enhance the solubility of the Bictegravir drug. Therefore, different solublizers were used like PEG 4000, PEG 6000, Gelucire 44/14, Propylene glycol, Kyron T 104, Poloxamer F127 in different concentration (20mg, 30mg 40mg). To formulate the bictegravir granules fluidized bed dryer granulation technology was used. The FBD process for granule preparation involves spraying a solution of binder on a powder bed, where particles are suspended in an air stream. The binder wets the particles, and as they collide, liquid bridges form, followed by drying to produce granules.[12,13] The binder used in fluidized bed granulation helps in forming more homogenous mixtures of the drug and excipients, leading to consistent solubility across batches.[14,15] In this optimization, Formulation F7 showed maximum solubility of the granules. Poloxamer F127 at 30 mg concentration was finalised. All the flow properties of granules improved and solubility was checked and it was found that F7 formulation showed maximum solubility in water and in phosphate buffer pH 6.8 and 8. Dissolution was also found to be increased in F7.

For bilayer dispersible tablet formulation, all evaluation parameters for granules were found to be satisfactory. Flow property was improved for granules. Optimization of disintegrant concentration was performed. Three concentration was selected for cross carmellose sodium as 7.5 mg, 10 mg, and 12.5 mg. Amongst 10 mg was finalised as it showed DT very minimum than marketed product i.e.1 min 21 sec. And dissolution for the tablet was found desirable within 15 min dissolution for bictegravir, emtricitabine and tenofovir was found to be 91 %, 102 % and 101 % respectively. The formulation F10 showed desirable DT, assay, and dissolution hence it was selected as best formulation amongst all 11 formulation

CONCLUSION

This study involves the formulation of dispersible bilayer tablet of Bictegravir sodium, Emtricitabine and Tenofovir alafenamide hemifumarate where enhancement of solubility for Bictegravir sodium was successfully done with using different solubilizer and fluidised bed drying granulation technique. Bictegravir is a BCS class II drug having low solubility hence needed to improve solubility. In this method Poloxamer F127 with concentration of 30 mg was selected. Hence solubility of bictegravir increased than pure drug and also flow property enhanced. In another layer of Emtricitabine and Tenofovir alafenamide hemifumarate, disintegrant concentration was optimised by taking different trials where cross carmellose sodium with concentration of 10 mg was selected due to with disintegration decreased and dissolution of tablet increased than marketed product. The formulation F10 showed desirable DT, assay, and dissolution hence it was selected as best formulation amongst all 11 formulation.

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