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Formulation Development and Evaluation of Tenofovir Disoproxil Fumarate Controlled Release Tablets

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Abstract

Tenofovir is a nucleoside reverse-transcriptase inhibitor that is currently being investigated as a potential HIV microbicide candidate, with a recent phase IIb study of a 1% (w/w) tenofovir gel reducing HIV acquisition by 39% in sexually active women. Tenofovir is nucleotide analogue reverse transcriptase inhibitors (nRTIs), which block reverse transcriptase, an enzyme crucial to viral production in HIV-infected people. Tenofovir disoproxil fumarate (a prodrug of tenofovir) film coated tablets contain 150 mg, 200 mg, 250 mg, and 300 mg of tenofovir disoproxil fumarate, distributed by Gilead Sciences with trademark of VIREAD. The objective of present investigation was to formulate and evaluate the controlled release tablets of Tenofovir using high molecular weight water-soluble poly (ethylene oxide) polymers and natural gums like Guar gum, Gum Kondagogu. A combination of natural hydrophilic polymers with synthetic hydrophilic polymers like poly (ethylene oxide) was also used in the preparation of matrix tablets and evaluated for their influence on controlled drug release. Matrix tablets were prepared by direct compression method using Tenofovir Solid dispersion as an active component which was prepared by solvent evaporation method using carrier poloxamer P188(in the ratio of 1:2). The matrix tablets were evaluated for hardness, weight variation, friability and for in-vitro release of the drug. The tablets containing Polyox-WSR 303 (TF6 with drug: polymer ratio 1:1.5) and combination of natural polymer gum kondagogu and Polyox-WSR 303 (TF9 with drug: polymer ratio 1:1.5) exhibited controlled release for a prolonged period of time. All the physical characteristics evaluated for the tablets were found to be within the acceptable limits.

Keywords

Guar gum, Gum Kondagogu, Matrix Tablet, poly (ethylene oxides), Tenofovir.

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1. INTRODUCTION

Acquired Immunodeficiency Syndrome (AIDS) continues to be one of the main public health problems around the world, especially in countries with the fewest resources. Tenofovir is a drug that acts by blocking reverse transcriptase activity in HIV infection. It is currently being investigated for its potential microbicidal effect against HIV. Solid

formulations have the advantage of high dose accuracy and long-term stability, as compared to semi-solid systems [1,2,3].

Oral route has been one of the most popular routes of drug delivery due to its ease of administration, patient compliance and flexible design of dosage forms [4]. The currently employed CR technologies for oral drug delivery are diffusion-controlled systems in which the polymer may undergo relaxation process in the presence of media so that the polymer chains become more flexible and the matrix swells [5]. This could allow the encapsulated drug to diffuse more rapidly out of the matrix. On the other hand, it would take more time for drug to diffuse out of the matrix since the diffusion path is lengthened by matrix swelling [6,7]. Moreover, it has been widely known that swelling and diffusion are not the only factors that determine the rate of drug release [8]. For dissolvable polymer matrix, polymer dissolution is another important mechanism that can modulate the drug delivery rate. While either swelling or dissolution can be the predominant factor for a specific type of polymer, in most cases drug release kinetics is a result of a combination of these two mechanisms [9].

Among the variety of hydrophilic polymers, poly (ethylene oxide) (PEO) is one of the most important material used in the pharmaceutical industries mainly because of its non-toxicity, high water-solubility [10] and swellability, insensitivity to the pH of the biological medium and ease of production. Natural gums like guar gum and Gum Kondagogu from natural sources [11] hydrate and swell on contact with water and these have been used for the preparation of controlled release dosage forms and also due to their cost effectiveness and regulatory acceptance.

The current study demonstrates that, to determine the release reading efficiency of the different polymers such as Polyox-WSR 301, Polyox-WSR 303, Gum kondagogu and guar gum on controlled release of matrix tablets containing Tenofovir solid dispersions [12,13,14,15,18].

2. MATERIALS AND METHODS

2.1 MATERIALS

Tenofovir disoproxil fumarate was obtained as a Gift sample (from Shilpa Medicare Limited, Raichur), Polymers PEO's [Polyox WSR 301 & Polyox WSR 303] were obtained from Dow chemicals Asia Pvt., Ltd. guar gum and Gum Kondagogu were procured commercially from Vasundhara gums & chemicals, Rajasthan. Micro crystalline cellulose and Talc was obtained from Signet Chemical Corporation Pvt. Ltd. Mumbai and Magnesium stearate is of analytical grade and procured commercially. All other chemicals were of analytical grade was used in the formulation.

All the carriers used were of analytical grade. Equipment's used in the formulation study are Analytical Precision Balance and UV Visible Spectrophotometer (PERKIN ELMER LAMBDA 35)

2.2 METHODOLOGY

Formulation and Evaluation of Tenofovir Disoproxil Fumarate Controlled Release Tablets was prepared using hydrophilic polymers, poly (ethylene oxide) (PEO) [16] and Natural gums like guar gum and Gum Kondagogu [17] in various ratios. The details are as follows;

2.2.1 Preparation of matrix tablets.

The matrix tablets containing Tenofovir Solid dispersions [18] were prepared by a direct compression method. The formulations consisted of a drug & polymer were in different ratios. Polyethylene oxides (Polyox WSR 301 and Polyox WSR 303), guar gum and gum kondagogu were used as a swellable hydrophilic polymers that controls drug release rates. The diluent Microcrystalline Cellulose (Avicel PH 102) was added with different proportions to the matrix tablets to achieve uniform weight of all the matrix tablets. Magnesium stearate was used as a lubricant and talc was used as a glidant. The selected drug solid dispersion, polymers, diluent and gildant were screened through #40 mesh and blended in a lab scale double cone blender. The premix blend was mixed thoroughly with selected lubricant to get uniform flow and better compressibility. The powder blend was characterized for flow properties as mentioned in below table 2. The lubricated blend was compressed using cadmach double sided rotary tablet press using flat round punches. The CR tablets were compressed with different compositions as mentioned in the table 1.

Table 1: Compositions of various matrix tablet formulations using tenofovir solid dispersion.

Ingredients [mg/tablet]	Formulation code with Drug: Polymer ratio											
Formulation code with Drug: Polymer ratio	**TF1 [1:0.5]**	**TF2 [1:1]**	**TF3 [1:1.5]**	**TF4 [1:0.5]**	**TF5 [1:1]**	**TF6 [1:1.5]**	**TF7 [1:0.5]**	**TF8 [1:1]**	**TF9 [1:1.5]**	**TF10 [1:0.5]**	**TF11 [1:1]**	**TF12 [1:1.5]**
Tenofovir SD Equivalent to 150mg of Tenofovir [Drug]	450	450	450	450	450	**450**	450	450	**450**	450	450	450
Polyox-WSR 301 [Polymer]	75	150	225	-	-	**-**	-	-	**-**	-	-	-
Polyox-WSR 303 [Polymer]	-	-	-	75	150	**225**	37.5	75	**112.5**	37.5	75	112.5
Gum kondagogu [Polymer]	-	-	-	-	-	**-**	37.5	75	**112.5**	-	-	-
Guar Gum [Polymer]	-	-	-	-	-	**-**	-	-	**-**	37.5	75	112.5
Microcrystalline Cellulose (Avicel PH 102) [Diluent]	120	45	70	120	45	**70**	120	45	**70**	120	45	70
Magnesium Stearate [Glidant]	2.5	2.5	2.5	2.5	2.5	**2.5**	2.5	2.5	**2.5**	2.5	2.5	2.5
Talc [[Lubricant]	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total Weight of tablet (mg)	**650**	**650**	**750**	**650**	**650**	**750**	**650**	**650**	**750**	**650**	**650**	**750**

2.2.2 Evaluation of Tablets [19]:

The prepared tablets were evaluated for different parameters which includes description, individual weight variation of tablets (n=20), hardness, drug content, diameter, thickness, friability and Dissolution rate characteristics.

Description:

Five tablets from different batches were randomly selected and observed visually the shape, nature of the edges, presence of foreign matter, chipping, capping and mottling color uniformity. Description of the tablets were found to be good.

Hardness:

The hardness of the five matrix tablets from each batch was determined by using a Monsanto tablet hardness tester (Electro lab, EH-01P).

Friability:

The friability of a sample of 20 tablets was measured using a friabilator ((Electro lab, EF-1W). Tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

Drug content:

Drug content was determined by taking an accurately weighed amount of blend (equivalent to 100 mg of drug substance) from the tablets by crushing using mortar and pestle. The powder was dissolved in 50 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and measured drug content by UV spectrophotometer at λ max of 260 nm using of 0.1 N HCl as blank.

Uniformity of weight:

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

Dissolution rate studies [20]:

The prepared tablets were evaluated for in vitro drug release. The drug release studies were carried out using USP type II (paddle) dissolution apparatus at 50

rpm in 900 mL of 0.1 N HCl at 37±0.5°C. Dissolution studies were carried out in triplicate, maintaining the sink conditions for all the formulations. A 5 ml aliquot of samples were withdrawn at regular time intervals, filtered and assayed at 260 nm using UV visible spectrophotometer. Samples were withdrawn at different time intervals and replaced with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 10ml by using 0.1N HCl. The release of drug was calculated with the help of Standard curve of Tenofovir disoproxil fumarate. To analyze the mechanism of drug release from the matrix tablets, data obtained from the drug release studies were analyzed according to the following equations of the First-order model, Higuchi model and the Korsmeyer-Peppas model [21,22] respectively. The observations of drug release for the drug in formulations are tabulated in Table 3 & Table 6.

Table 2: Result of pre-compression properties for the prepared granules of Tenofovir CR tablets

Formulation code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's Compressibility index (%)	Hausner's ratio	Angle of repose (θ)
TF1	0.41	0.49	16.33	1.20	23.55
TF2	0.42	0.50	16.00	1.19	23.74
TF3	0.44	0.52	15.38	1.18	20.80
TF4	0.43	0.49	12.24	1.14	22.31
TF5	0.42	0.49	14.29	1.17	23.53
TF6	0.43	0.51	15.69	1.19	24.65
TF7	0.43	0.51	15.69	1.19	20.31
TF8	0.45	0.54	16.67	1.20	22.30
TF9	0.44	0.52	15.38	1.18	21.35
TF10	0.45	0.52	13.46	1.16	24.50
TF11	0.44	0.51	13.73	1.16	22.38
TF12	0.43	0.51	15.69	1.19	21.23

Table 3: Post compression parameters for the prepared matrix tablets

Formulation code	Average Weight (mg)	Hardness (Kg/cm^2)	Friability (%w/w)	Drug Content (%)
TF1	651.2	9.5	0.20	99.8±0.2
TF2	649.3	10.2	0.13	99.6±0.2
TF3	750.5	10.3	0.16	99.5±0.2
TF4	652.8	10.4	0.23	99.9±0.2
TF5	653.6	9.7	0.25	97.5±0.2
TF6	750.9	10.5	0.16	96.8±0.2
TF7	649.5	9.2	0.17	96.9±0.2
TF8	648.7	10.6	0.25	98.2±0.2
TF9	751.3	9.8	0.23	98.3±0.2
TF10	655.5	9.7	0.18	99.4±0.2
TF11	652.9	10.8	0.19	98.7±0.2
TF12	751.8	10.2	0.17	99.7±0.2

Determination of calibration curve:

The Tenofovir disoproxil fumarate was scanned in UV for determination of λ max. UV spectrum of tenofovir disoproxil fumarate was found to be at 260nm in 0.1N HCl

The Stock solution of Tenofovir was prepared by accurately dissolving 100mg in 100ml of 0.1N HCl. From this 10ml was taken and diluted up to 100ml with 0.1N HCl. From this 10µg/ml solution was prepared by diluting 10ml to 100ml with 0.1N HCl. From this 2, 4, 6 & 8 to 10ml with 0.1N HCl. Absorbance were measured at 260 nm and results were tabulated in table

Table 4: Calibration Curve for the Estimation of Tenofovir

S. No	Concentration	Absorbance
1.	0	0
2.	2	0.123
3.	4	0.249
4.	6	0.376
5.	8	0.486
6.	10	0.592

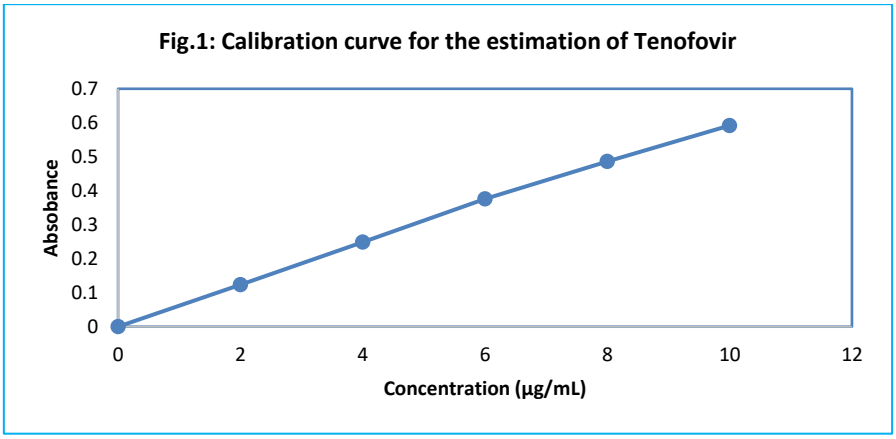

Fig 1: Calibration curve for Tenofovir

Table 5: Cumulative % drug release of Tenofovir CR Tablets 150mg formulations (TF1-TF12).

Tenofovir CR Tablets 150mg Formulation Cumulative % drug release												
Time (Hrs)	**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
1	26.65	17.43	13.54	12.56	8.67	**9.24**	21.67	12.43	**10.39**	18.56	19.89	12.85
2	41.23	34.86	25.56	26.33	19.56	**19.22**	40.44	26.98	**20.65**	39.67	41.38	28.56
4	65.78	59.55	45.53	38.67	30.45	**29.49**	60.55	41.36	**29.87**	62.45	68.79	44.44
6	98.54	78.98	61.26	49.65	36.54	**38.59**	83.56	53.34	**39.53**	78.63	88.56	59.47
8		97.98	75.58	59.89	48.67	**47.54**	98.23	64.32	**48.42**	90.54	100.1	71.22
10			85.63	72.54	61.45	**61.22**		77.8	**61.93**	100		82.42
12			98.98	87.88	73.45	**75.78**		90.6	**76.57**			93.8
14				99.85	87.87	**85.76**		99.48	**85.28**			100
16					98.94	**93.54**			**93.93**			
18						**99.88**			**99.02**			

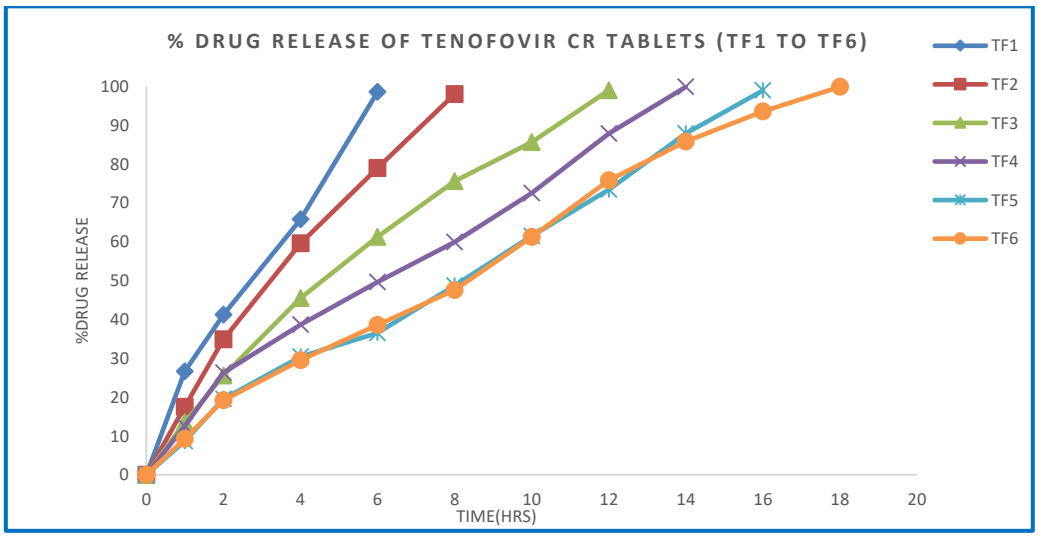

Fig 2: In-vitro drug release data for Tenofovir CR tablets (TF1-TF6).

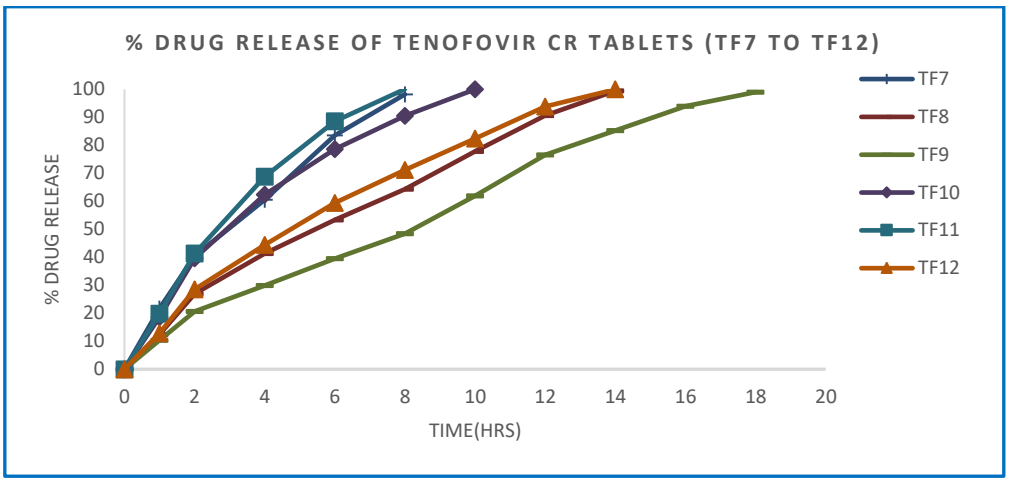

Fig 3: In-vitro drug release data for Tenofovir CR tablets (TF7-TF12).

Table 6: Dissolution Parameters of formulations (TF1-TF12).

Tenofovir CR Tablets							
Formulation code	**First order**		**Zero order**		**Higuchi**	**Peppa's**	
	K	**R^2**	**K**	**R^2**	**R^2**	**R^2**	**n value**
TF1	0.264	0.998	23.260	0.985	0.974	0.991	0.716
TF2	0.259	0.991	18.072	0.985	0.999	0.932	0.886
TF3	0.189	0.987	12.105	0.981	0.998	0.998	0.845
TF4	0.153	0.928	10.061	0.987	0.978	0.979	0.725
TF5	0.129	0.902	8.915	0.994	0.960	0.981	0.794
TF6	**0.126**	**0.929**	**8.344**	**0.992**	**0.975**	**0.990**	**0.776**
TF7	0.291	0.976	17.886	0.971	0.997	0.993	0.741
TF8	0.141	0.984	10.283	0.989	0.992	0.980	0.767
TF9	**0.125**	**0.937**	**8.246**	**0.990**	**0.976**	**0.989**	**0.730**
TF10	0.258	0.998	14.645	0.940	0.992	0.979	0.875
TF11	0.359	0.980	18.772	0.957	0.994	0.989	0.895
TF12	0.167	0.990	10.525	0.967	0.999	0.979	0.837

Differential Scanning Calorimetry (DSC)

The DSC thermograms of the pure drug and the tablet powder containing drug and the excipient was observed as shown in below figures.

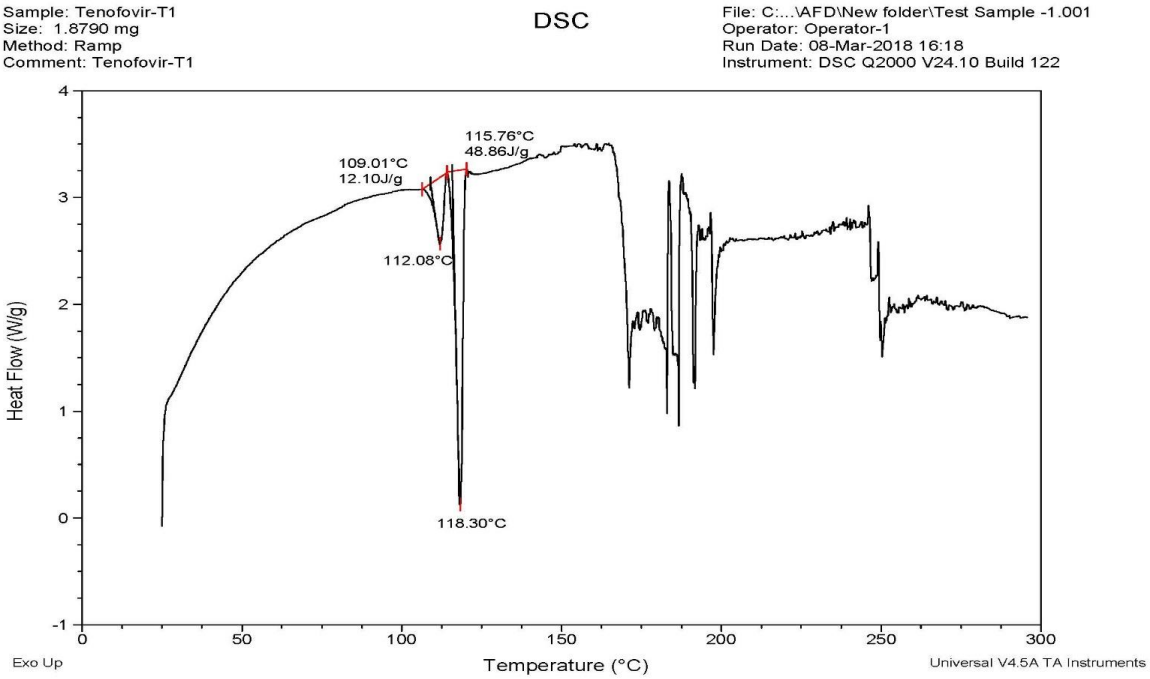

Fig 4: DSC thermograms of the pure drug Tenofovir

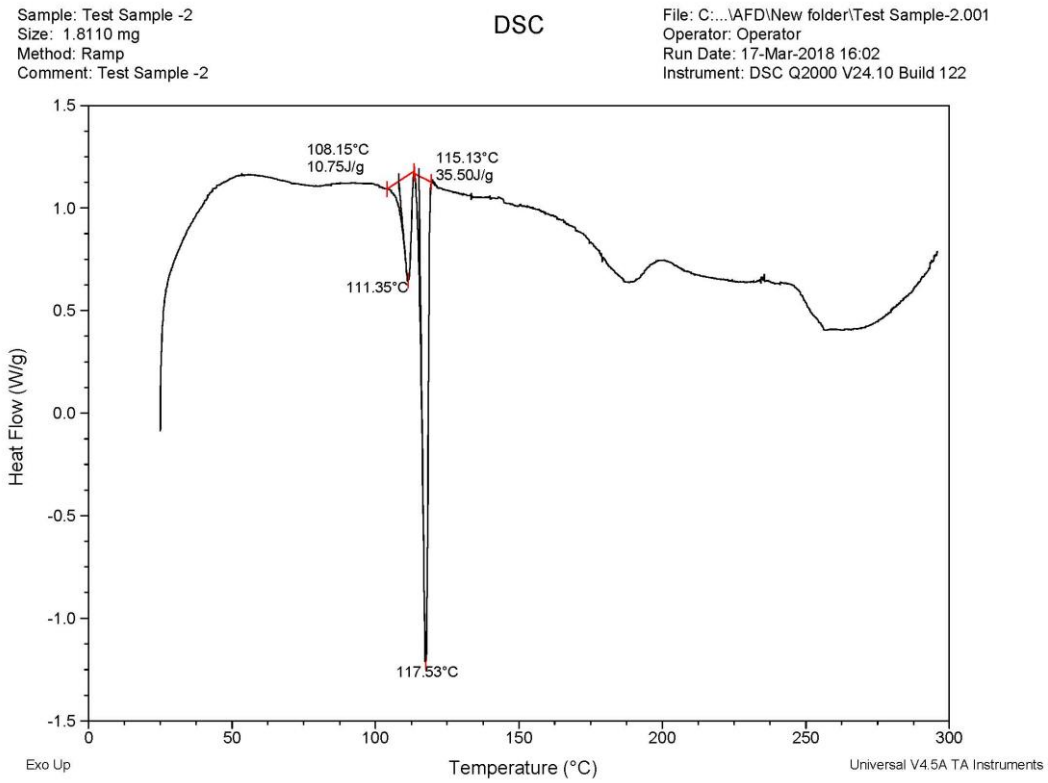

Fig 5: DSC thermograms of the Formulation (TF6)

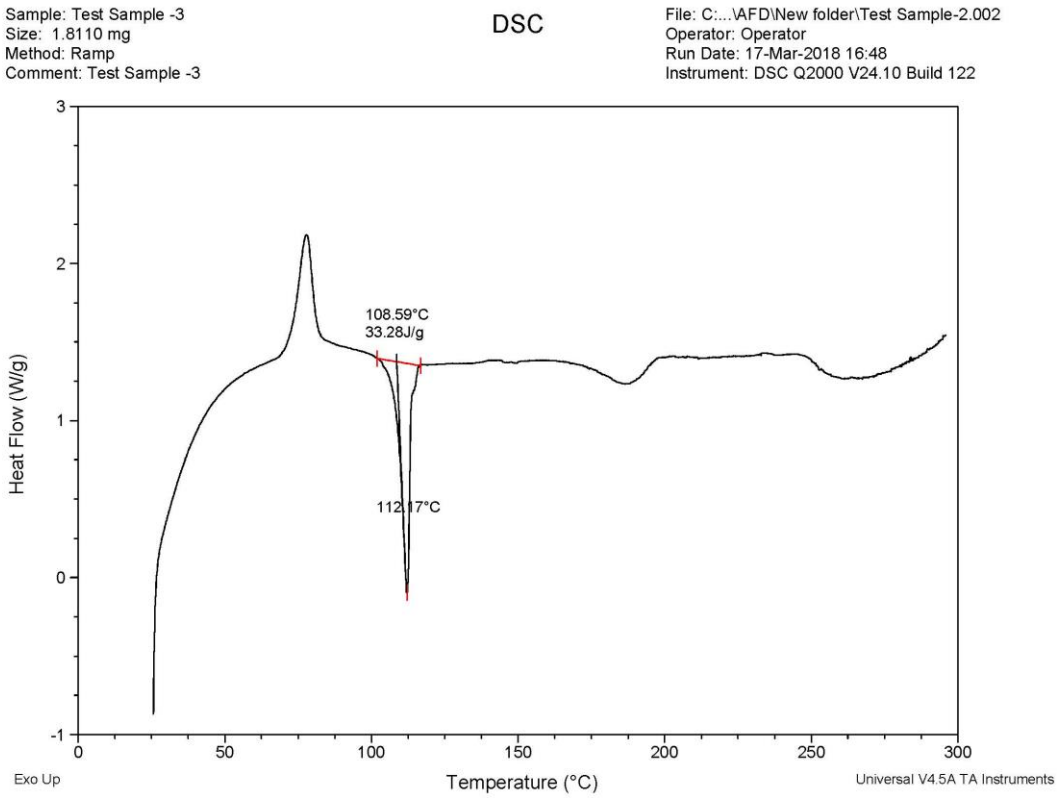

Fig 6: DSC thermograms of the Formulation (TF9)

2.3 RESULTS AND DISCUSSION.

1. Pre-compression properties for the prepared granules for Tenofovir CR tablets was characterized. Based on the results of flow properties, flow of the granules was found be good.
2. All the matrix tablets formulated employing selected polymers were of good quality with regard to drug content, hardness and friability and fulfilled the official (IP/USP) requirements of compressed tablets with regard to the above-mentioned physical properties.
3. All the formulations of Tenofovir CR tablets with different polymer compositions were within the weight range of 649.3 to 751.8 mg. Friability loss for all the formulations were in the range of 0.13% to 0.25% and the drug content in all the formulations was uniform and was in the range of 96-99 %. The hardness of all the formulations were maintained in the range of 9.0 to 10.0 (Kg/cm²).
4. DSC studies indicated no interaction between drug and selected polymer in the formulation.
5. The in vitro drug release studies were conducted for all the matrix tablet formulations. From the In vitro dissolution studies, it was observed that high molecular weight poly (ethylene oxide) i.e. Polyox WSR 303 alone in the drug: polymer ratio of 1:1.5 (**Formulation TF-6**) and combination of Polyox WSR 303 with gum kondagogu in the drug: polymer ratio of 1:1.5 (**Formulation TF-9**) effectively controlled the release rate of the drug for an extended period of time up to 18hrs than the low molecular weight Polyox WSR 301 and other polymer combinations.
6. Further, to understand the drug release mechanism, the data were fitted to korsmeyer-Peppas model for determining the drug release mechanism for these formulations. All the matrix tablets followed non-fickian diffusion mechanism (as per Table 3: $0.45<n<0.89$) which indicates the drug release through diffusion and polymer relaxation.
7. It was also observed that increase in the concentration of polymers, the drug release was extended. This is due the hydrophilic nature of the poly (ethylene oxide) and gums. The critical value of 'n' calculated for these formulations indicated non-fickian diffusion i.e., the drug release is by diffusion from the hydrated matrix and by polymer erosion.

3.0 CONCLUSION:

Tenofovir controlled release matrix tablets were successfully formulated employing poly (ethylene oxides) alone and with combinations of poly (ethylene oxide) and natural gums for control the release rate of the drug over an extended period of time. Developed CR tablets possessed the required physicochemical properties such as hardness, friability, weight variation, drug content. Based on the above discussion, this study demonstrates that high molecular weight synthetic polymer Polyox WSR 303 and combination of hydrophilic natural gums (gum kondagogu) with PEO's (Polyox WSR 303) having high molecular weight shown prolonged release of the drug up to 18 hrs. An important feature of this system is the potential for generating constant drug release. Therefore, it was concluded that the most satisfactory formulations are TF6 and TF9.

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