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FORMULATION AND EVALUATION OF TENOFOVIR DISOPROXIL FUMARATE IMMEDIATE RELEASE TABLETS

P. Rama Krishna Reddy[1]*, Dr. Pankaj Kumar Sharma[2], Dr. Jaya Sharma[2] and B. Chandana[3]

[1]Research Scholar- Pacific University, Pacific Hills, Pratapnagar Extn., Airport Road, Debari, Udaipur – 313003.

[2]School of Pharmaceutical Sciences, Jaipur National University, Jaipur.

[3]Assistant Professor, Tirumala College of pharmacy, Tirumala Nagar, Bardipur (V), Dichpally (M), Dist. Nizamabad-503 230. Telangana.

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***Corresponding Author**
P. Rama Krishna Reddy
Research Scholar- Pacific University, Pacific Hills, Pratapnagar Extn., Airport Road, Debari, Udaipur - 313003.

ABSTRACT

The present study was carried out for developing the formulation of tenofovir disoproxil fumarate IR layer was compressed as direct compression method. were evaluated for pre and post compression studies. Those all studies were found to be within limits. From the dissolution data of Tenofovir Immediate release. Formulation was shown maximum drug release at 20min. i.e., 99.67%. Hence IR23 was concluded as optimised formulation for IR layer.

KEYWORDS: Tenofovir, IR Tablets.

INTRODUCTION

Oral delivery of drugs is by far the most preferred route of drug delivery due to ease of administration, patient compliance, and flexibility in formulation. From immediate release to site- specific delivery, oral dosage form has really progressed. It is evident from the recent scientific and patented literature that an increased interest in novel dosage forms that are retained in the stomach for prolong and predictable period of time exist today in academic and industrial research groups. Various attempts have been made to develop Gastro retentive delivery systems.[1]

Floating Drug Delivery Systems and Its Mechanism

Floating drug delivery systems

Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the Surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positives ideas shown in fig. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.[2]

$$F = F_{buoyancy} - F_{gravity}$$

$$= (DF - Ds)\, gv \quad \text{---} (1)$$

Where, F= total vertical force, DF = fluid density,

Ds= object density, v = volume and g = acceleration due to gravity.

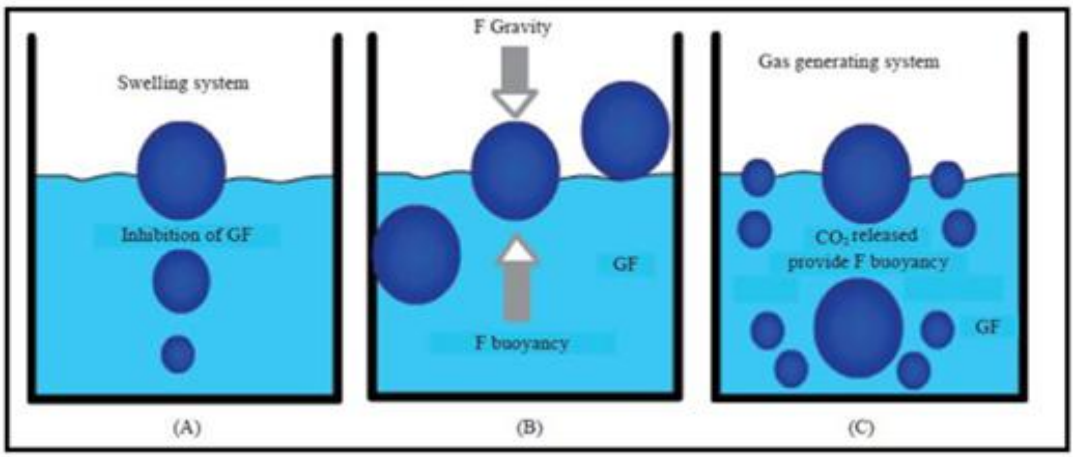

Fig. 1. Mechanism of Floating System.

Effervescent System FDDS

These are matrix type of system. Prepared with the help of sellable polymer such as methylcellulose and Chitosan and various effervescent compounds.

Ex: sodium bicarbonate, tartaric acid, citric acid.

These are formulated in such a way that when they come in contact with gastric content, co2 is liberated and gets entrapped in swollen hydrocolloid which provides buoyancy to dosage form. The design of delivery system was based on swellable asymmetric triple layer tablet approach.[3]

Gas Generating Systems

These are low density FDDS is based on the formation of co2 within the device following contact with body fluids. The materials are fabricated so that upon arrival in stomach, co2is librated by acidity of the gastric content and is entrapped in the gellified hydrocolloid this produce upward motion of the dosage form and maintain its buoyancy.

Decrease in specific gravity cause dosage form to float on the chyme the co2 generating components may be intimately mixed within the tablet matrix in which case a single layer or bilayered is produced which contain the gas generating mechanism in one hydrocolloid containing layer and the drug in the other layer formulated for a sustained release effect.[4-6]

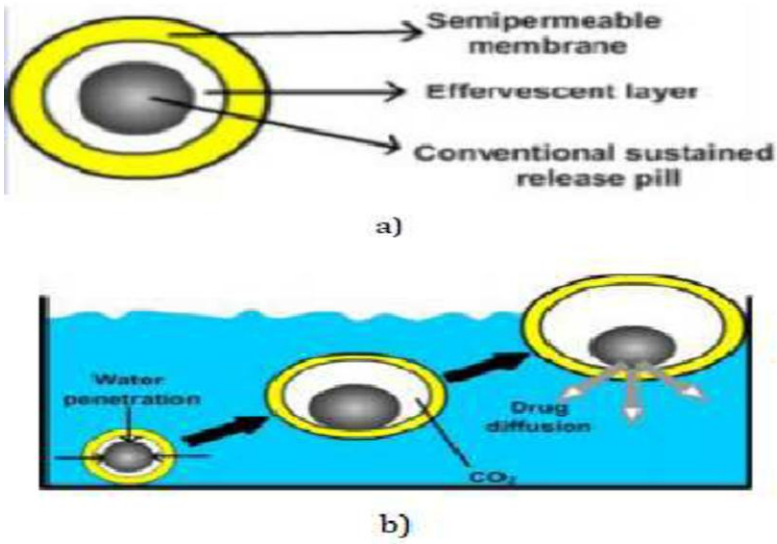

Fig. 2: Different layers Semi-permeable membrane, Effervescent layer Core pill layer. Mechanism of floatation via CO2 liberation.

Volatile Liquid Containing Systems (Osmotically Controlled DDS)

As an Osmotically controlled floating system, the device comprised of a hallow deformable unit that was convertible from a collapsed position after an extended period of time. A housing was attached to the deformable unit and it was internally divided into a first and second chamber with the chambers separated by an impermeable, pressure responsive

movable bladder. The first chamber contain an active drug, while the second chamber contain a volatile liquid, such as cyclopentane or ether that vaporises at physiological temperature to produce a gas, enabling the drug reservoir to float. To enable the unit to exit from the stomach, the device contained a bioerodible plug that allowed the vapour to escape.[7]

Non-Effervescent FDDS

Non-Effervescent FDDS use a gel forming (or) swellable cellulose type of hydrocolloids, Polysaccharide, matrix forming polymer like polycarbonate, polymethacrylate and polystyrene. One of the formulation methods involves the mixing of the drug with gel forming hydrocolloids which swell in contact with gastric fluid after oral administration and maintains integrity of shape and a bulk density barrier, the air trapped by swollen polymer confer buoyancy to the dosage forms.[8]

Colloidal Gel Barrier Systems (Hydrodynamic Balanced Systems)

Such system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption site in the solution form for ready absorption, this system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid e.g. (HPMC), polysaccharides and matrix forming polymer such as polycarbophil, polystyrene and polyacrylate. On coming in the contact with GI fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface.[9]

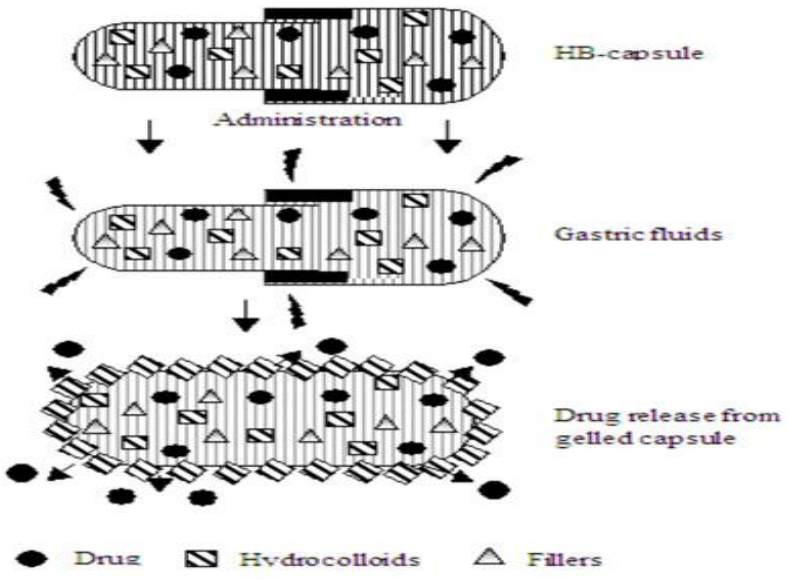

Fig: 3 Working Principle of Hydrodynamically Balanced tablets.

Microporous Compartment Systems

This technology is based on the encapsulation of a drug reservoir inside a Microporous compartment with pores along its top and bottom walls. The peripheral wall of the drug reservoir compartment is completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the gastric fluid to an extent that it prevents their exist from the drug and carrier the dissolved drug for continuous transport across the intestine for absorption.[10]

Floating Microspheres / Micro balloons

Hallow microspheres are considers as most promising buoyant system as they are more advantageous because of central hallow space inside the microsphere. Hallow microsphere is loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent Diffusion method.[11]

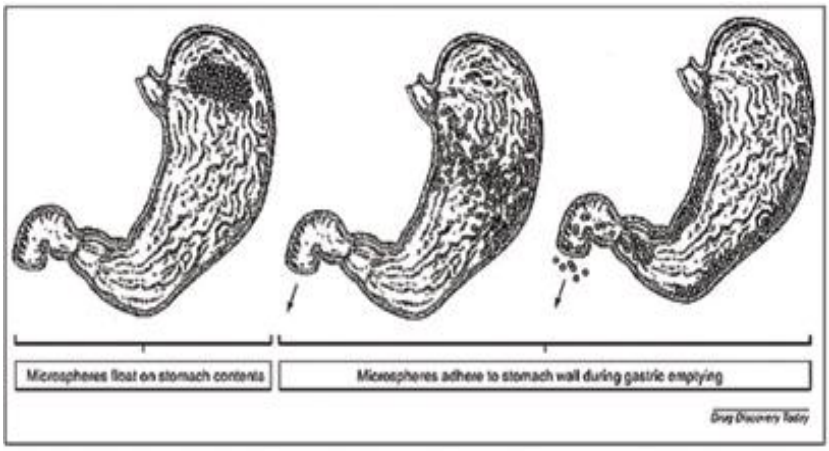

Fig.4: Release of drug from Floating tablets.

Alginate Beads / Floating Beads

Multi-unit floating dosage forms have been developed from freeze calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride. Causing the precipitation of calcium alginate. The beads are than separated, snap-frozen in liquid nitrogen and freeze-dried at 400C for 24 h, leading to the formation of a porous system, this can maintain a floating force for over 12 h. these floating beads gave a prolonged residence time of more than 5.5 h.

Raft forming systems

Raft forming system have received much attention for the delivery of antacid and drug delivery for gastro infection and disorders on contact with gastric fluid a gel forming solution swells and forms a viscous cohesive gel containing entrapped co2 bubbles. Which forms raft layer on top of gastric fluid which releases drug slowly in stomach. (Often used for gastro esophageal reflux treatment.[12]

Fig. 5: Schematic picture for raft forming system.

Advantages of FDDS

FDDS is highly advantageous in the treatment of the disorders related to the stomach. As the prime objective of such systems is to produce a gastro retentive product or a product which has an enhanced retention time in the stomach.[13]

- Drugs with considerably short half life can be administered in this manner to get an appreciable therapeutic activity.
- Enhancement of the bioavailability for drugs which can metabolized in the upper GIT.
- They also have an advantage over the conventional system as it can be used to overcome the adversities of gastric retention time as well as the gastric emptying time.
- The duration of treatment through a single dose, which releases the an active ingredient over an extended period of time.
- The active entity is delivered specifically to the site of action, thus minimizing or eliminating the side effects.

AIM AND OBJECTIVES

The aim of the study is to formulate and evaluate Immediate Release Tablets of Tenofovir Disoproxil Fumarate. To develop a pharmaceutically equivalent stable, cost effective and

quality improved formulation of Immediate Release tablets and to compare with that of the Marketed dosage form.

PLAN OF WORK

1. Literature Survey
2. Selection and Procurement of suitable Drug candidate and Excipients.
3. Preparation of standard graph of Tenofovir Disoproxil Fumarate I n 0.1 N HCL.
4. Drug and Excipient compatibility studies using FTIR.
5. Formulation of floating tablets of Tenofovir Disoproxil Fumarate.

A. Optimisation of sodium bicarbonate Concentration.

B. Formulation development of Tenofovir Disoproxil Fumarate Immediate Release tablets using polymers.

6. Precompression studies of Formulation blend of

A. Angle of repose

B. Bulk density

C. Tapped density

D. Carr's index

E. Hausner's ratio

7. Preparation of the Floating tablets of Tenofovir Disoproxil Fumarate.

8. Post Compression Evaluation of prepared floating tablets of Tenofovir Disoproxil Fumarate

A. Weight variation

B. Tablet Thickness

C. Tablet Hardness

D. Friability

E. Assay

F. *In-vitro* buoyancy studies

i. Floating lag time.

ii. Total Floating time.

G. *In vitro* release studies

9. Selection of optimised formulation.

10. Kinetic analysis of Optimised dissolution data**.**

RESULTS AND DISCUSSION

Analytical Method

Determination of absorption maxima

The standard curve is based on the spectrophotometry. The maximum absorption was observed at 260nm.

Calibration curve

Table: 1 Graphs of Tenofovir Disoproxil Fumarate was taken in 0.1N HCL (pH 1.2).

Conc [µg/mL]	Absorbance
0	0
5	0.114
10	0.225
15	0.312
20	0.411
25	0.513

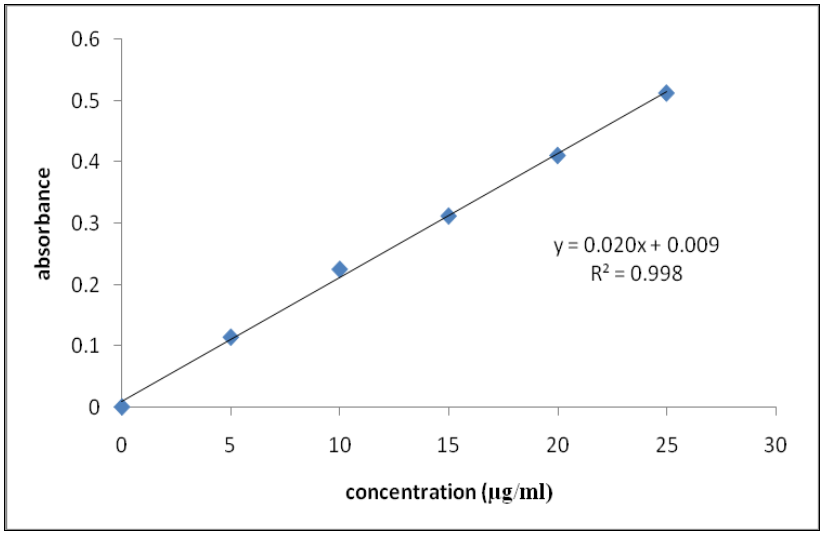

Fig 6: Standard graph of Tenofovir Disoproxil Fumarate in 0.1N HCL

Standard graph of Tenofovir Disoproxil Fumarate was plotted as per the procedure in experimental method and its linearity is shown in Table and Fig. The standard graph of Tenofovir Disoproxil Fumarate showed good linearity with R^2 of 0.998, which indicates that it obeys "Beer- Lamberts" law.

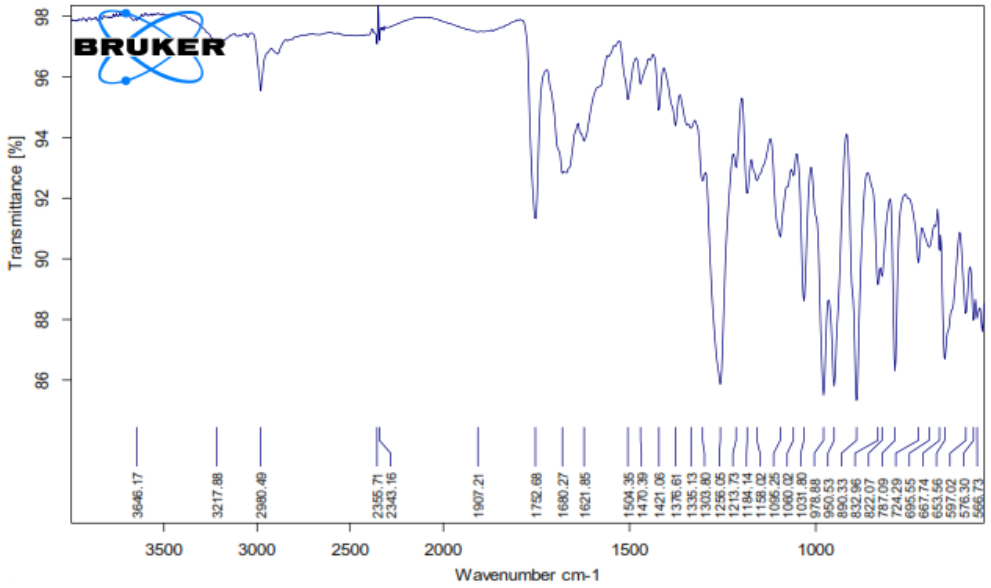

Fig. 7: FTIR Spectrum of pure drug.

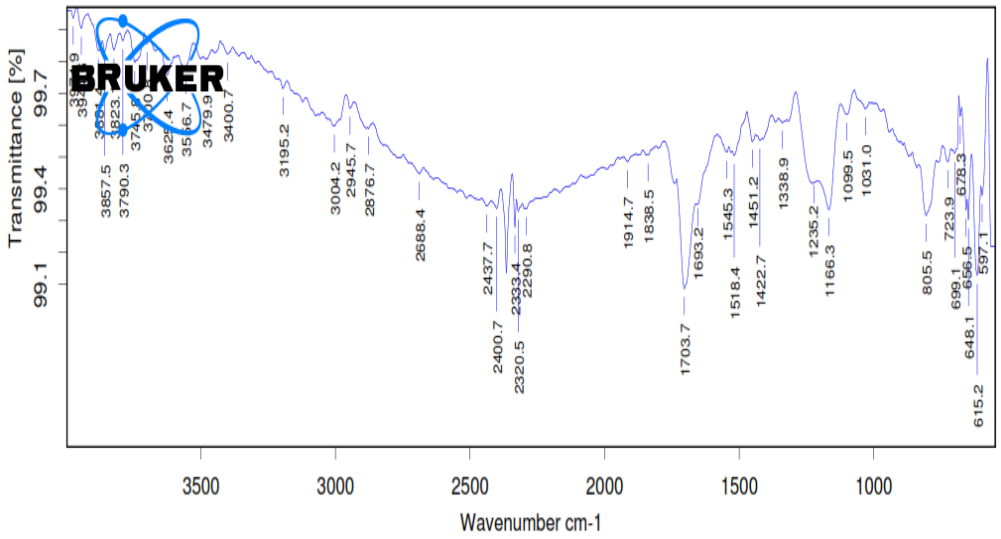

Fig: 8 Graph: Ft-Ir Graph of Optimised Formulation.

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

Tenofovir Disoproxil Fumarate is also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug

Table: 2 Pre formulation parameters of powder blend.

Formulation Code	Angle of Repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
IR1	26.01	0.49	0.57	14.03	1.16
IR2	24.8	0.56	0.65	13.84	1.16
IR3	22.74	0.57	0.68	16.17	1.21
IR4	25.33	0.54	0.64	15.62	1.18
IR5	26.24	0.55	0.67	17.91	1.21
IR6	26.12	0.56	0.66	15.15	1.17
IR7	25.12	0.59	0.67	11.86	1.11
IR8	26.8	0.48	0.54	12.5	1.12
IR9	23.74	0.56	0.66	17.85	1.17
IR10	26.33	0.44	0.55	18.18	1.18
IR11	25.21	0.48	0.57	16.66	1.16
IR12	27.18	0.51	0.59	15.68	1.15
IR13	24.29	0.46	0.56	17.85	1.21
IR14	26.01	0.50	0.59	15.25	1.18
IR15	25.27	0.44	0.56	16.66	1.21
IR16	25.28	0.41	0.57	15.88	1.21
IR17	26.25	0.42	0.52	16.78	1.21
IR18	23.24	0.44	0.53	15.89	1.21
IR19	23.22	0.47	0.54	15. 45	1.21
IR20	22.28	0.49	0.55	16.66	1.21
IR21	24.89	0.48	0.57	16.66	1.21
IR22	22.38	0.43	0.58	16.66	1.21
IR23	23.98	0.42	0.59	16.66	1.21
IR24	22.59	0.41	0.53	16.66	1.21
IR25	21.47	0.46	0.52	16.66	1.21

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.41 to 0.59 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.52 to 0.68 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 18 which shows that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 1.12 to 1.22 indicating the powder has good flow properties.

Quality Control Parameters For tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, Drug content and drug release studies were performed for floating tablets.

Table: 3 *In-vitro* quality control parameters for IR tablets.

Formulation codes	Average Weight (mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	*In Vitro* Disintegration Time (sec)
IR1	495.5	4.5	0.52	3.5	99.76	32.14
IR2	502.4	4.0	0.54	3.3	97.45	23.19
IR3	497.6	4.4	0.51	3.1	98.34	14.52
IR4	499.6	4.5	0.55	3.4	99.87	32.13
IR5	502.4	4.4	0.56	3.2	99.14	25.27
IR6	500.7	4.2	0.45	3.4	97.56	16.35
IR 7	498.95	4.2	0.45	3.1	98.3	35.14
IR 8	499.15	4.7	0.54	3.2	99.3	26.21
IR 9	500.26	4.2	0.55	3.3	98.2	15.30
IR 10	505.36	4.0	0.56	3.5	99.2	12.15
IR 11	497.25	4.2	0.48	3.1	99.3	14.28
IR 12	496.26	4.1	0.45	3.2	97.2	25.36
IR 13	502.5	4.3	0.51	3.3	102.3	45.3
IR 14	503.63	4.4	0.52	3.3	103.5	42.8
IR 15	505.85	4.5	0.53	3.4	10.3	43.8
IR 16	496.74	4.1	0.45	3.2	99.5	33.7
IR 17	501.36	4.3	0.49	3.0	102.3	42.1
IR 18	502.58	4.2	0.50	3.1	99.8	29.6
IR 19	499.9	4.2	0.52	3.2	99.7	25.5
IR 20	499.3	4.3	0.53	3.5	99.8	33. 1
IR 21	496.7	4.4	0.56	3.1	99.9	36.9
IR 22	497.8	4.6	0.49	3.3	99.3	37.8
IR23	498.3	4.9	0.47	3.4	98.9	36.5
IR24	497.2	4.2	0.57	3.6	99.4	27.9
IR25	497.4	4.1	0.53	3.5	99.7	28.3

All the parameters such as weight variation, friability, hardness, thickness, drug content were found to be within limits.

***In Vitro* Drug Release Studies**

Table: 4 Dissolution data of Immediate release Layer by using Natural superdisintegrant i.e., Locustbean gum.

TIME (Min)	IR1	IR2	IR3	IR4	IR5
0	0	0	0	0	0
5	25.3	30.81	45.74	37.31	26.56
10	38.7	36.74	66.26	47.63	37.3
15	48.6	56.26	78.98	73.42	52.21
20	64.2	87.42	95.86	84.74	63.57
30	76.2	98.52		97.32	71.83
45	96.4				82.49
60	96.4				92.35

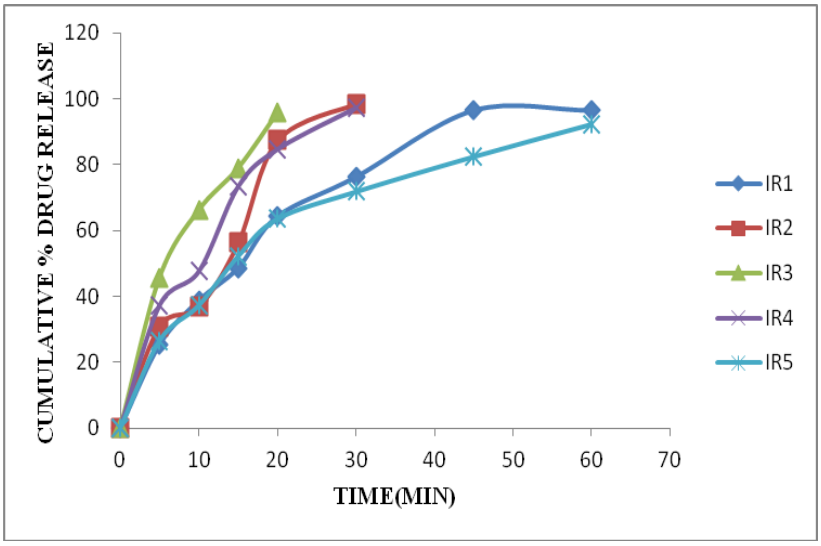

Fig: 9.

Table: 5 Dissolution data of Immediate release Layer by using Natural superdisintegrant i.e., Plantago ovata seed powder.

TIME(Min)	IR6	IR7	IR8	IR9	IR10
0	0	0	0	0	0
5	10.79	12.34	13.51	26.75	22.32
10	20.08	24.56	25.37	45.30	27.18
15	25.72	35.63	36.54	63.72	33.37
20	48.86	41.23	44.07	79.31	42.16
30	55.73	58.84	61.95	94.48	59.70
45	68.87	71.46	74.03		75.24
60	84.72	86.88	90.77		87.31

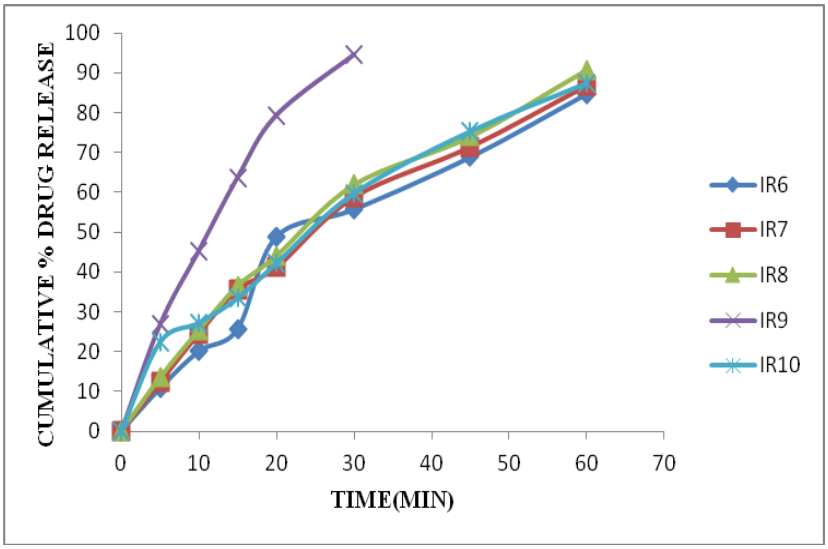

Fig: 10.

Table: 6 Dissolution data of Immediate release Layer by using Synthetic superdisintegrant i.e., Sodium starch glycolate.

TIME(Min)	IR11	IR12	IR13	IR14	IR15
0	0	0	0	0	0
5	23.55	34.94	17.83	14.65	12.47
10	48.13	62.36	26.57	22.88	28.9
15	63.54	76.21	47.9	37.11	31.50
20	85.88	92.89	75.33	47.78	43.23
30	90.12		89.44	74.51	57.41
45				87.74	69.36
60					78.57

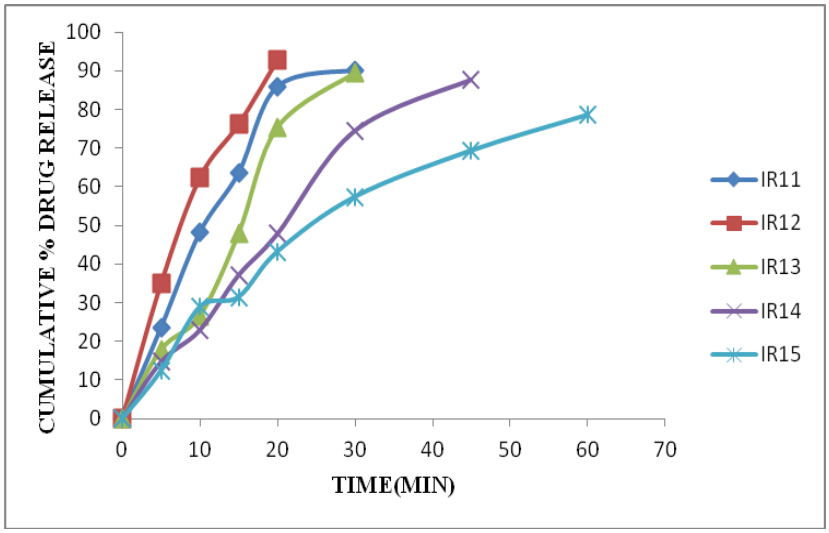

Fig: 11.

Table: 7 Dissolution data of Immediate release Layer by using Synthetic superdisintegrant i.e., Croscaramellose sodium.

TIME(Min)	IR16	IR17	IR18	IR19	IR20
0	0	0	0	0	0
5	17.11	24.30	22.57	32.47	37.48
10	24.30	32.56	38.87	42.81	52.44
15	36.66	48.80	47.65	64.17	74.50
20	54.90	57.10	61.35	83.67	98.74
30	62.57	65.78	78.80	95.33	
45	70.10	72.60	92.70		
60	86.64	88.20			

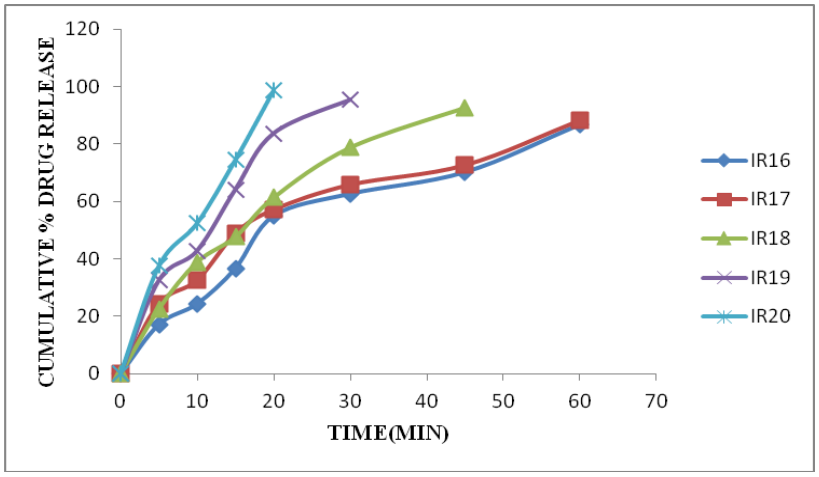

Fig: 12.

Table: 8 Dissolution data of Immediate release Layer by using Synthetic superdisintegrant i.e., Crospovidone.

TIME(Min)	IR21	IR22	IR23	IR24	IR25
0	0	0	0	0	0
5	8.23	12.44	29.05	27.66	16.25
10	19.65	26.39	58.96	61.35	28.39
15	27.32	57.21	89.38	87.89	62.04
20	42.38	74.32	99.67	95.64	91.23
30	63.54	86.55			
45	82.69	93.22			
60	91.36				

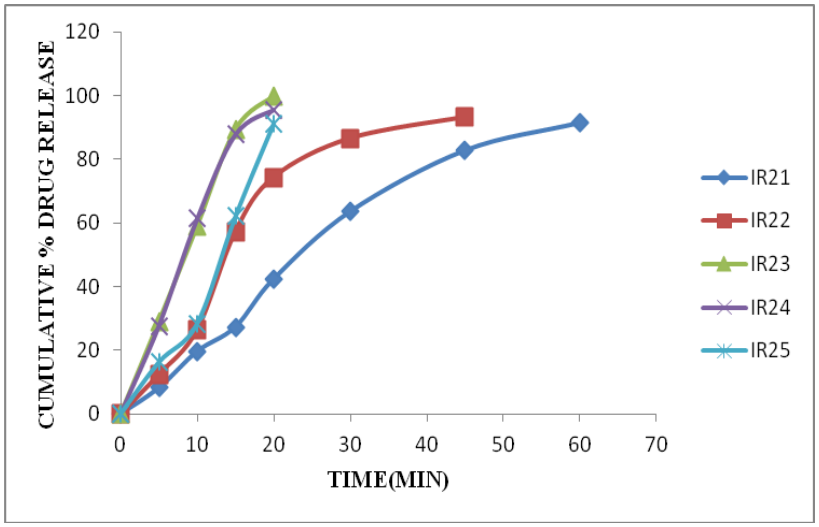

Fig: 13.

From the dissolution data of Tenofovir Immediate release Layer, IR23 formulation was shown maximum drug release at 20min. i.e., 99.67%. Hence IR23 was concluded as optimised formulation for IR layer.

CONCLUSION

Immediate release Tablet powder blends were subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.49 to 0.56 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.68 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 18 which shows that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

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