MALLA REDDY COLLEGE OF PHARMACY

(Affliated to osmania university)

FORMULATION AND EVALUATION OF ORAL DISINTEGRATING TABLET USING TENOFOVIR

In partial fulfillment of

BACHELOR OF PHARMACY

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ABSTRACT

- Orally Disintegrating tablets rapidly disintegrate or dissolve in the oral cavity without using water.
- Demand for ODI's has increased and the field has overgrown in the pharmaceutical industry,
- It is reported that ODI's have several advantages over other conventional tablets. Since , some of them absorbed from mouth, Pharynx and esophagus as the saliva passes down into the stomach.
- In such cases, the bio-availability of drug improves. Furthermore, The immediate release property of ODI's makes them a popular over dosage forms in patients with swallowing challenges due to its rapid onset of action. is an anti-viral drug , It can treat hepatitis-b ad HIV infection.
- It does not cure hepatitis-b , HIV or AIDS but may slow the progress of the disease . It belongs to anti-HBV reverse transcriptase inhibitor and HIV nucleoside analog reverse transcriptase inhibitor once in a day is taken and it is administered before

METHODOLOGY

- In this we are going to discuss regarding the formulation and evaluation of tenofovir in this different disintegrants are used such as microcrystalline cellulose , sodium starch glycolate , crosspovidone and sodium alginate. By direct compression tablets are formed and the evaluation test done are hardness, thickness, friability , weight variation, disintegration and dissolution studies.

RESULTS &DISCUSSION

- Formulation and evaluation of oral disintegrating tablets using tenofovir have been done and its evaluation parametres like weight variation test,hardness,thickness,friability ,disintegration time and dissolution studies were performed
- In most of the parameters the formulation F6 which containing microcrystalline cellulose and crosspovidine have been shown very less disintegration time i.e, 83 seconds ,friability of 0.09% and percentage of drug release also shown 96% of release in 40 mins which is very high when compare to that of other formulations .
- From the evalution we got a conclusion that formulations with combination of disintegrating agents shown good result .where as in individual disintegrating agent the crosspovidine shown good result.so we can say that by using this disintegrating agents we can achieve function of oral disintegrating nature in tablets.

LITERATURE REVIEW

- Anindita Behara., *et al.*, (2011) had developed the three simple Spectrophotometric methods for estimation of Emtricitabine and Tenofovir from tablet dosage form .They are Least square method, First order derivative spectroscopy and Area under curve method.

- Benjamin H Chi., *et al.*, (2007) had studied A single dose of Tenofovir and Emitricitabine at delivery reduced resistance to non- nucleoside reverse transcriptase inhibitors at 6 week safer delivery by half; therefore this treatment should be considered as an adjuvant to intrapartum nevirapine.

- Gupta, D.M. Barends., *et al.*, (2006) had studied the Review of global regulations concerning bio waivers for immediate releasesolid oral dosage forms. The regulations with respect to bio waivers for immediate release (IR) solid oral dosage forms in the USA, the EU, and Japan and from the World Health Organization (WHO) are summarized and compared.

- Giordano Madeddu., *et al.*, (2008) had studied both prevalence and incidence of nephro toxicity were low in patients receiving Tenofovir in a non-selected clinical setting. Renal injury in patients in patients receiving Tenofovir seems associated with the presence of co morbidities and with advanced HIV infection.

- Erno A. van Schaick., *et al.*, (2003) had developed Pharmacokinetic Comparison of Fast-Disintegrating and Conventional Tablet Formulations of Risperidone in Healthy Volunteers. The bioequivalence assessment was based on pharmacokinetic and statistical analysis of data from 37 subjects who completed both treatment periods. The fast disintegrating tablet and the conventional tablet showed bioequivalence with respect to the active moiety, Risperidone, and 9-hydroxy-risperidone.In this study in healthy subjects, a single administration of two 0.5mg fast-disintegrating Risperidone tablets was bioequivalent to a single administration of two 0.5-mg conventional Risperidone tablets
- Frampton James E., *et al.*, (2006) had developed Tenofovir / Emtricitabine double combination tablets. A new formulation combining fixed doses of the nucleoside reverse transcriptase inhibitors Emitricitabine (200mg) and Tenofovir disoproxil fumarate (300mg) represents the first once-daily, one- tablet antiretroviral regimen. Co-formulated Tenofovir disoproxil Fumarate/ Emtricitabine demonstrated bioequivalence to concomitant administration of the individual agents in a pharmacokinetic trial in healthy volunteers (n=48). Co-formulated Tenofovir disoproxil Fumarate/Emtricitabine has not been evaluated in clinicalHoratio
- B. Fung., *et al.*, (2002) had studied Tenofovir has exhibited anti-HIV activity in various HIV-infected cell lines and has produced a synergistic or additive effect against HIV when combined with other antiretroviral agents , Tenofovir appears to be a promising agent for the treatment of HIV infection

- Jessica Tan., *et al.*, (2008) had studied Tenofovir monotherapy is effective for patients with virologic break through or suboptimal response to ADV, but combination therapy with a nucleoside analogue should be considered in patients with ADV-resistance.

- Manikandan M., *et al.*, (2012) had Studied the formulation and evaluation of Tenofovir disoproxil fumarate and Emtricitabine immediate release tablets using different disintegrants like Croscarmellose sodium , Crosspovidone. The absorbance of Emtricitabine and Tenofovir was screened in the UV region and the maximum was found to be 282nm and258nm respectively and this was used for HPLC analysis.

INTRODUCTION:

- **TABLETS-**

DEFINATION-

Tablets are tamper proof solid unit dosage forms containing medicament or mixture of medicaments and excipients compressed or moulded into solid cylindrical shape having either flat or convex surfaces

PROPERTIES OF TABLET-

- Tablets must be elegant in appearance, characteristic shape, colour and other markings necessary to identify the product\
- Tablets must retain all these functional attributes which include drug stability and efficacy.
- The tablet must be sufficiently strong and resistant to shock, abrasion, should withstand handling during manufacturing, packing, shipping, and use. Hardness and friability tests measure this property.
- Tablet must be uniform in weight and in drug content of the individual tablet. This is measured by the weight variation and content uniformity tests.

ADVANTAGES AND DISADVANTAGES-

ADVANTAGES-

- High patient compliance.
- Their cost is lowest of all dosage forms
- Easiest and cheapest to packaging and shipment
- They are having best combined properties of chemical, mechanical andmicrobiological properties

- **DISADVANTAGES**
- A major disadvantage of capsules over tablets is their higher cost.
- It is difficult to convert a high dose poorly compressible API into a tablet of suitable size for human use.
- Slow onset of action as compared to parenterals, liquid orals and capsules.

GENERAL METHODS OF MANUFACTURING OF TABLETS

- There are four general methods for the manufacturing of the tablet
- They are :
    1. Direct compression
    2. Wet granulation
    3. Dry granulation
    4. Fluidized bed granulation

EXCIPIENTS USED IN TABLET:

- Excipients are inert substances used as diluents or vehicles for a drug. In the pharmaceutical industry it is a catch all terms which includes various sub-groups. Comprising diluents or fillers, binders or adhesives, disintegrants, lubricants, glidants or flavours, fragrances and sweeteners.

Criteria for selection of excipients-

- They must be physiological inert
- They must be acceptable to regulatory agencies
- They must be physiologically and chemically stable.
- They must be free of any bacteria considered to be pathogenic or otherwise objectionable.
- They must be not interfere with the bioavailability of the drug.

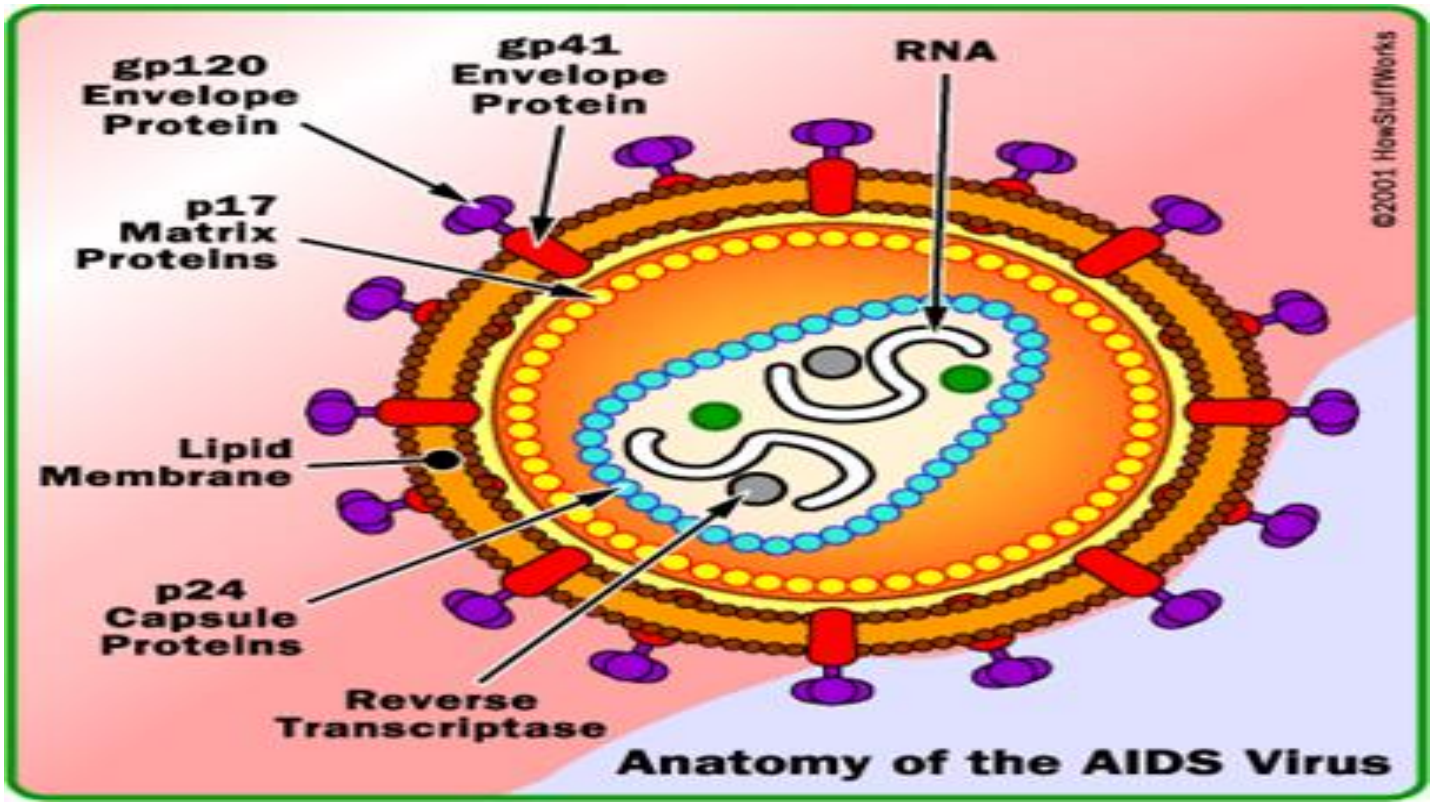
- **The tablet breaking mechanisms** -

- capillary action (Wicking)
- swelling
- Due to deformation
- Due to release of gases

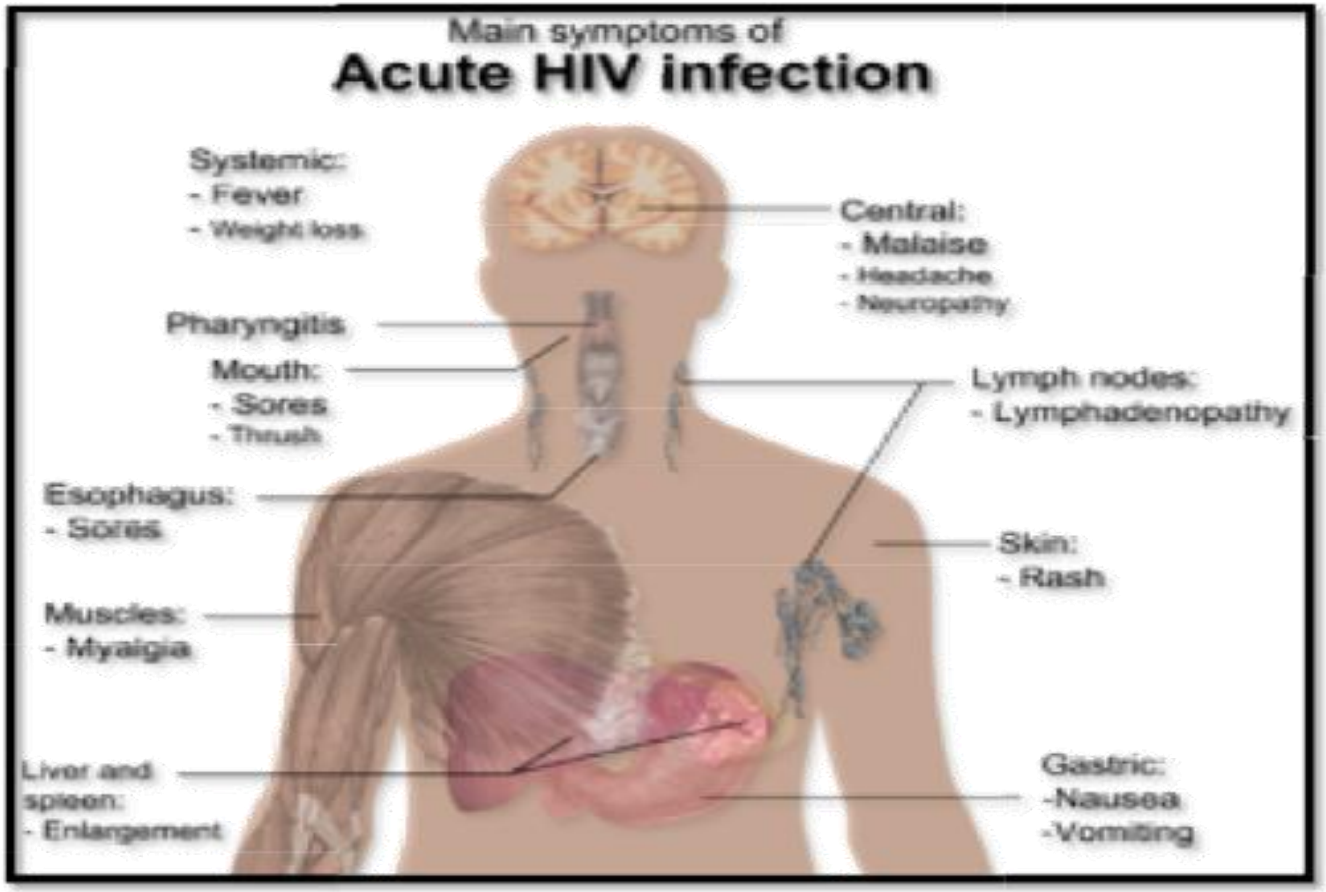
INTRODUCTION TO HIV

- HIV (Human Immunodeficiency Virus) infection has now spread to every country in the world. Approximately 40 million people are currently living with HIV infection, and an estimated 25 million have died from this disease. The scourge of HIV has been particularly devastating in sub-Saharan Africa, but infection rates in other countries remain high.
- HIV stands for the human immunodeficiency virus. It is one of a group of viruses known as retroviruses. After getting into the body, the virus kills or damages cells of the body's immune system. The body tries to keep up by making new cells or trying to contain the virus, but eventually the HIV wins out and progressively destroys the body's ability to fight infections and certain cancers
- AIDS stands for the Acquired Immuno Deficiency Syndrome. It is caused by HIV and occurs when the virus has destroyed so much of the body's defences that immune-cell counts fall to critical levels or certain life-threatening infections or cancers develop.

STRUCTURE OF HIV -



Signs &symptoms-



DIAGNOSIS-

HIV infection is commonly diagnosed by blood tests.

There are three main types of tests that are commonly used:

(1) antibody tests, (2) RNA tests, and (3) a combination test that detects both antibodies and a piece of the virus called the p24 protein. In addition, a blood test known as a Western blot is used to confirm the diagnosis.

- **CLASSIFICATION OF DRUGS-**

1.Nucleoside and nucleotide reverse transcriptase inhibitors

2.Non nucleoside reverse transcriptase inhibitors

3.Protease inhibitors

4.Integrase inhibitors

5.Viral entry inhibitors

6.Viral assembly inhibitors

NEED FOR EXPERIMENT -

- Tenofovir is an FDA Approved Prodrug for clinical use for the treatment of HIV infection, AIDS and AIDS related conditions either alone or in combination with other anti retroviral drugs.

- It is usually administered in a dose of 300 once daily in order to maintain effective concentration, and the main dose related adverse effect is renal toxicity, with increase in concentrations.

- Immediate release drug delivery systems for oral dosing are effective in achieving optimal therapy for the drugs that have longer half life.These preparations were able to release immediately with quicker on set of action and without dose dumping problem by incorporating super disintegrants like microcrystalline cellulose,Crospovidone.

OBJECTIVES-

- To formulate and evaluate Tenofovir immediate release Tablet.
- To study the effect of different superdisintegrants on drug release behaviour of the polymer.
- The objective of the present study is to developed a pharmaceutically equivalent, stable and quality improved formulation of immediate release Tenofovir Tablet which is Nucleotide reverse transcriptase inhibitors (NRTIs) and these were matched with that of the marketed dosage form
- Based on the Pre and post formulation parameters the best selected formulation was subjected to short term stability studies as per ICH guideline

MATERIALS AND EQUIPMENTS -

S.NO	EQUIPMENTS
1	Digital balance
2	Motor pestle
3	Tablet compression machine
4	Vernier calliper
5	Hardness tester
6	Disintegration apparatus USP
7	Mechanical stirrer
8	Dissolution apparatus USP
9	Ultra violet spectrometer
10	Infrared spectrometer

RAW MATERIALS

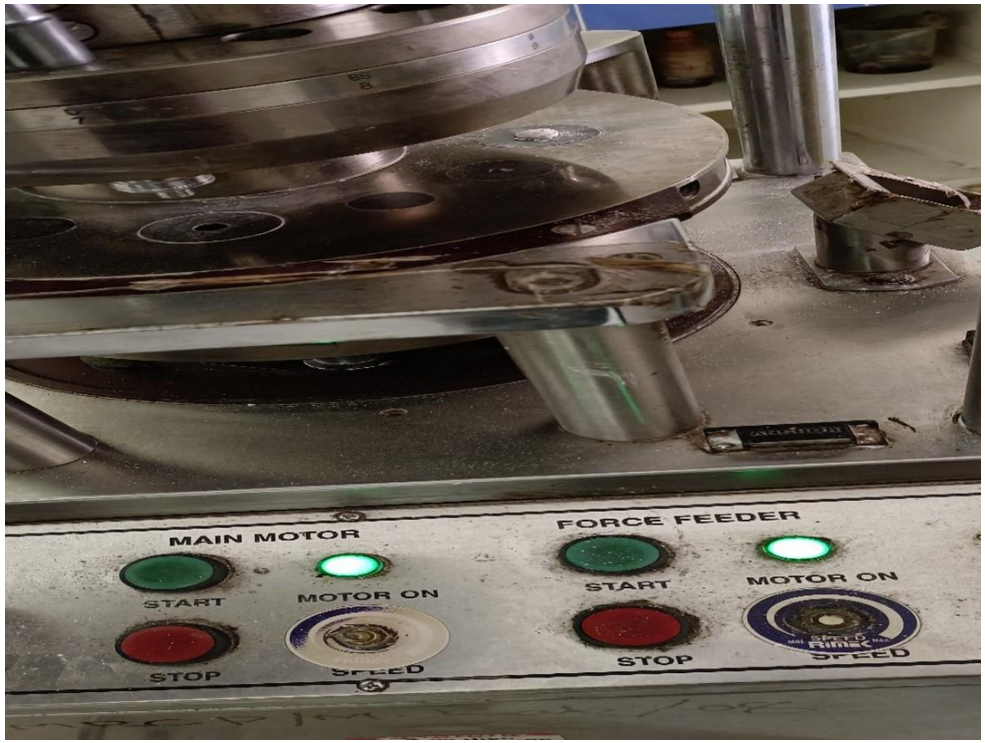
EXCIPIENTS	F1	F2	F3	F4	F5	F6	F7	F8
Tenofovir	300mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg
Calcium alginate	50mg	50mg	-	-	-	-	150mg	100mg
Microcrystalline cellulose	100mg	-	-	50mg	150mg	100mg	-	-
Crosspovidone	-	100mg	150mg	-	-	50mg	-	-
Sodium starch glycolate	-	-	-	100mg	-	-	-	50mg
Sodium saccharin	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg
Magnesium stereate	7mg	7mg	7mg	7mg	7mg	7mg	7mg	7mg
Mannitol	60mg	60mg	60mg	60mg	60mg	60mg	60mg	60mg
Flavour	4mg	4mg	4mg	4mg	4mg	4mg	4mg	4mg
Talc	20mg	20mg	20mg	20mg	20mg	20mg	20mg	20mg

METHODOLOGY-

1.Dry mixing

2.Direct compression-

The compression was done by using punches of size 16.5×8mm; oval shaped, D-tooling, plain surface on upper and lower punch

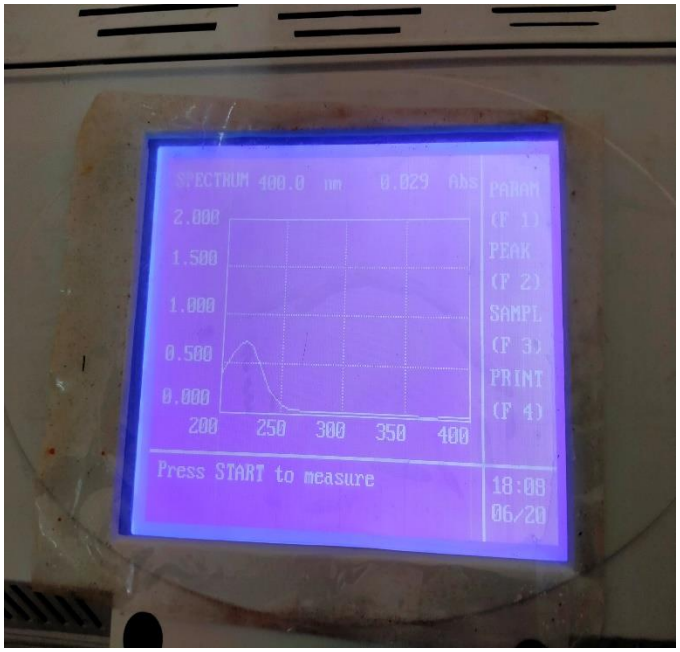


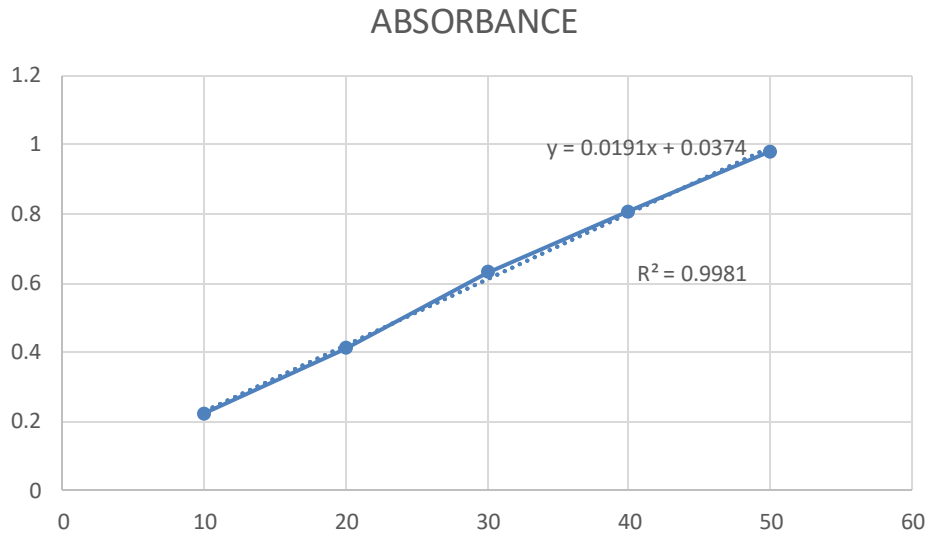
EVALUATION PARAMETERS -

- IR Spectroscopy
- UV Spectroscopy
- Physical appearance
- Weight variation test
- Thickness
- Hardness
- Friability
- Disintegration time
- Dissolution studies

IR Spectroscopy-

UV SPECTROSCOPY-The maximum wavelength =228nm





APPEARANCE-

The tablets were visually observed for capping, chipping, and lamination.

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 caliper. Three tablets from each type of formulation were used and average values were calculated.

THICKNESS VALUES-

Tablet number	Tablet thickness
F1	5.71mm
F2	5.71mm
F3	5.77mm
F4	5.67mm
F5	5.74mm
F6	5.74mm
F7	5.75mm
F8	5.74mm

WEIGHT VARIATION TEST-

- Total weight of the tablets
- Number of tablets
-
- =4395
- 8

- **Average weight of the tablet=549.375 mg**

Tablet number	Weight of the table
F1	550
F2	549
F3	548
F4	549
F5	549
F6	550
F7	550
F8	550
Total	4395

HARDNESS TESTING-

For each formulation, the hardness of tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between thetwo jaws of the tester. At this point, reading should be zero kg/cm2.

Tablet number	Hardness
F1	7.3 kg/cm^2
F2	7.1 kg/cm^2
F3	5.5 kg/cm^2
F4	6.5 kg/cm^2
F5	5.6 kg/cm^2
F6	6.4 kg/cm^2
F7	6.3 kg/cm^2
F8	6.2 kg/cm^2

PERCENTAGE FRIABILITY-

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.

Tablet number	Friability
F1	0.12%
F2	0.16%
F3	0.18%
F4	0.09%
F5	0.18%
F6	0.09%
F7	0.15%
F8	0.12%

DISINTEGRATION TEST-

The test was carried out on 6 tablets using Tablet disintegration tester. Distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in seconds taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured.

The fast disintegration taken place in f6 formulation

Tablet number	Disintegration
F1	3.28
F2	3.20
F3	2.28
F4	3.04
F5	2.24
F6	1.23
F7	1.34
F8	1.25

DISSOLUTION STUDIES -

- Dissolution is considered as one of the most important quality control tests performed on pharmaceutical dosage forms and is now developing into a tool for predicting bioavailability, and in some cases, replacing clinical studies to determine bioequivalence**.**

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F1 formulation-

Time	Absorbance	Concentration	Dilution	/5	/900	Add	×10	%drug
5min	0.04	1	1000	200	0.22	0.22	2.2	0.4%
10min	0.11	8	8000	1600	1.99	1.99	19.9	3.6%
15min	0.17	14	14000	2800	3.11	5.10	51.0	9.2%
20min	0.22	19	19000	3800	4.22	9.32	93.2	16.9%
25min	0.32	29	29000	5800	6.44	15.76	157.6	28.6%
30min	0.35	32	32000	6400	7.11	22.81	228.7	41.5%
35min	0.44	41	41000	8200	9.11	31.91	319.1	58.0%
40min	0.56	53	53000	10600	11.77	43.68	436.8	79.4%
45min	0.64	61	61000	12200	13.55	57.23	572.3	104%

F2 formulation-

Time	absorbance	Concentration	dilution	/5	/900	Add	×10	%drug
5min	0.07	4.0	4000	800	0.88	0.88	8.8	1.6%
10min	0.15	12.0	12000	2400	2.66	3.54	35.4	6.4%
15min	0.20	17.0	17000	3400	3.77	7.31	73.1	13.3%
20min	0.24	21.0	21000	4200	4.66	11.97	119.7	21.7%
25min	0.35	32.0	32000	6400	7.11	19.08	190.8	34.6%
30min	0.40	37.0	37000	7400	8.22	27.30	273.0	49.36%
35min	0.51	48.0	48000	9600	10.66	37.96	379.6	69.0%
40min	0.61	58.0	58000	11600	12.88	50.84	508.4	92.4%
45min	0.70	67.0	67000	13400	14.88	65.72	657.2	119.5%

F3 formulation-

Time	Absorbance	Concentration	Dilution	/5	/900	Add	×10	%drug
5min	0.05	2	2000	400	0.44	0.444	4.4	0.8%
10min	0.11	8.0	8000	1600	1.77	2.221	22.2	4.03%
15min	0.17	14.0	14000	2800	3.11	5.332	53.3	9.69%
20min	0.24	21.0	21000	4200	4.66	9.998	99.9	18.17%
25min	0.32	29.0	29000	5800	6.44	16.442	164.4	29.89%
30min	0.37	34.0	34000	6800	7.55	23.997	239.9	43.63%
35min	0.50	47.0	47000	9400	10.44	34.441	344.4	62.62%
40min	0.59	56.0	56000	11200	12.44	46.88	468.8	85.24%
45min	0.66	63.0	63000	12600	14.0	60.88	608.8	110.6%

F4 formulation-

Time	Absorbance	Concentration	Dilution	/5	/900	Add	×10	%drug
5min	0.07	4	4000	800	0.88	0.88	8.8	1.6
10min	0.15	12	12000	2400	2.66	3.54	35.4	6.4
15min	0.20	17	17000	3400	3.77	7.31	73.1	13.3
20min	0.26	23	23000	4600	5.11	12.42	124.2	22.5
25min	0.35	32	32000	6400	7.11	19.53	195.3	35.5
30min	0.40	37	37000	7400	8.22	27.75	277.5	50.4
35min	0.51	48	48000	9600	10.66	38.41	384.1	69.8
40min	0.61	58	58000	11600	12.88	51.49	514.9	93.6
45min	0.70	67	67000	13400	14.88	66.37	663.7	120.6

F5 formulation-

Time	Absorbance	Concentration	Dilution	/5	/900	Add	×10	%drug
5min	0.05	2.0	2000	400	6.44	0.44	4.4	0.8%
10min	0.11	8.0	8000	1600	1.77	2.21	22.1	4.03%
15min	0.17	14	14000	2800	3.11	5.32	53.2	9.67%
20min	0.23	20	20000	4000	4.44	9.76	97.6	17.7%%
25min	0.32	29	29000	5800	6.44	16.20	162.0	29.4%
30min	0.36	33	33000	6600	7.33	23.53	235.3	42.7%
35min	0.47	44	44000	8800	9.77	33.30	333.0	60.5%
40min	0.58	55	55000	11000	12.22	45.52	455.2	82.7%
45min	0.64	61	61000	12200	13.55	59.07	590.7	107.4%

F6 formulation-

Time	Absorbance	Concentration	Dilution	/5	/900	Add	×10	%drug
5min	0.089	5.0	5000	1000	1.11	1.11	11.1	2.02%
10min	0.162	13.2	13200	2640	2.93	4.04	40.4	8.08%
15min	0.204	17	17000	3400	3.77	7.81	78.1	14.21%
20min	0.284	25.4	25400	5080	5.67	13.45	134.5	24.4%
25min	0.362	33.2	33200	6640	7.37	20.82	208.2	37.8%
30min	0.412	38	38000	7600	8.44	29.24	292.4	53.1%
35min	0.522	49.2	49200	9840	10.93	40.17	401.7	73.04%
40min	0.621	59.1	59100	11820	13.13	53.30	533.03	96.91%
45 min	0.712	68.2	68200	13640	15.15	68.45	684.5	124.4%

F7 formulation-

Time	Absorbnce	Concentration	Dilution	/5	/900	Add	×10	%drug
5min	0.03	0	0	0	0	0	0	0%
10min	0.09	6	6000	1200	1.33	1.33	13.3	2.42%
15min	0.14	11	11000	2200	2.44	3.77	37.7	6.86%
20min	0.21	18	18000	3600	4.00	7.77	77.7	14.12%
25min	0.30	27	27000	5400	6.00	13.77	137.7	25.03%
30min	0.35	32	32000	6400	7.11	20.88	208.8	37.96%
35min	0.48	45	45000	9000	10.0	30.88	308.8	56.14%
40min	0.57	54	54000	10800	12.0	42.88	428.8	77.96%
45min	0.63	60	60000	12000	13.3	56.21	562.1	102.2%

F8 formulation-

Time	Absorbance	Concentration	Dilution	/5	/900	Add	×10	%drug
5min	0.04	1	1000	200	0.22	0.22	2.2	0.4%
10min	0.10	7	7000	1400	1.55	1.77	17.7	6.8%
15min	0.16	13	13000	2600	2.88	4.65	46.5	12.0%
20min	0.22	19	19000	3800	4.22	8.87	88.7	19.7%
25min	0.30	27	27000	5400	6.0	14.87	148.7	30.6%
30min	0.35	32	32000	6400	7.11	21.98	219.8	43.5%
35min	0.46	43	43000	8600	9.55	31.53	315.3	60.9%
40min	0.55	52	52000	10400	11.55	43.08	430.8	81.9%
45min	0.63	60	60000	12000	13.33	56.41	564.1	106%

CONCLUSION-

- A successful oral disintegrating drug delivery system was prepared with fast disintegrating mechanism which gives immediate onset of action.
- Tenofovir posses longer half life .Hence it was a good drug for oral disintegrating drug delivery system . The identification was carried out by disintegration, dissolution and its evaluation parameters .The analytical profile of drug was evaluated for development of standard curve and percentage release of drug .
- The powder blend was prepared and triturated and undergone for direct compression . A successful oral disintegrating drug delivery system was prepared with fast disintegrating mechanism which gives immediate onset of action.
- Tenofovir posses longer half life .Hence it was a good drug for oral disintegrating drug delivery system . The identification was carried out by disintegration, dissolution and its evaluation parameters .The analytical profile of drug was evaluated for development of standard curve and percentage release of drug . The powder blend was prepared and triturated and undergone for direct compression .

The study has revealed that by interchanging the disntegrant it is concluded that microcrystalline cellulose and crosspovidone in combination as disintegrating agents showing more amount of drug release when compared to other disintegrating agents.

However it needs further in depth in vivo release studies on suitable animal models with statistical clinical data for dependable and successful pharmaceutical marketing formulation.

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Thank You