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Formulation Development and Evaluation of Emtricitabine and Tenofovir Disoproxil Fumarate Film Coated Tablets

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Abstract

The present work is aimed to formulate the film coated tablets of Emtricitabine and Tenofovir disoproxil fumarate, drugs which are used in the treatment of HIV-1 infection. Tablets are prepared by wet granulation method using the different excipients, namely Sodium starch glycolate, Di calcium phosphate, starch 1500, ideal blue, Iso propyl alcohol. FTIR studies revealed that there are no incompatibilities between drugs and polymers used. The prepared tablets are evaluated for various properties. The In-vitro dissolution profiles of the formulations were compared with the innovator product TRUVADA. All the physical parameters are found to satisfactory for the formulation T-3 and the disintegration time was found to be 8 min 50 sec. *Invitro* drug release profile of formulation T-3 is matching with the *innovator.* Thus it can be concluded that the formulation T-3 is best formulation. The study can be extended to determine the in-vivo behaviour of the tablets.

Keywords: Film coated tablets, Emtricitabine, Tenofovir disoproxil fumarate, Wet granulation, Truvada, Innovator.

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1. Introduction

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. For many drug substances, conventional immediate release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patient [1].

Over the last 3 decades, many novel oral drug therapeutic systems have been invented along with the appreciable development of drug delivery technology. Based on the desired therapeutic objectives, Oral Drug Delivery Systems may be assorted into three categories[1]:

- Immediate-release preparations
- Controlled-release preparations and
- Targeted- release preparations

Immediate-Release Preparations:

These preparations are primarily intended to achieve faster onset of action for drugs such as analgesics, antipyretics, and coronary vasodilators. Other advantages include enhanced oral bioavailability through transmucosal delivery and pregastric absorption, convenience in drug administration to dysphagic patients, especially the elderly and bedridden patients. Conventional IR formulations include fast disintegrating tablets and granules that use effervescent mixtures, such as sodium carbonate (or sodium bicarbonate) and citric acid (or tartaric acid) and superdisintegrants, such as sodium starch glycolate, croscarmellose sodium and crospovidone. Current technologies in fast-dispersing dosage forms include modified tabletting systems, floss or Shearform technology, which employs application of centrifugal force and controlled temperature and freeze-drying.

Controlled Release Preparations:

The currently employed Controlled release technologies for oral drug delivery are diffusion-controlled systems; solvent activated systems and chemically controlled systems.

Targeted-Release Preparations:

Site-specific oral drug delivery requires spatial placement of a drug delivery device at a desired site within the GI tract. Although it is virtually possible to localize a device within each part of GI tract, the attainment of site-specific delivery in the oral cavity and the rectum is relatively easier than in the stomach and intestine. Tablet is a solid dosage forms each containing a unit dose of one or more medicaments. Tablets are solid, flat or biconvex discs prepared by compressing a drug or mixture of drugs with or without suitable excipients [2, 3, 4].

The tablet comprises at least one active ingredient. Suitable active ingredients broadly include pharmaceutically active ingredients, dietary supplements, nutritionals, nutraceuticals, and the like. More specifically these include analgesics, anti-inflammatory agents, decongestants, expectorants, antitussives, antihistamines, gastrointestinal agents, diuretics, bronchodilators, sleep-inducing agents, vitamins (such as vitamin D and vitamin K), minerals (such as calcium and magnesium), anti-infectives nutrients, and mixtures [8]. Conventional methods for tablet production include direct compression ("dry blending"), dry granulation followed by compression, and wet granulation followed by drying and compression [5,6,7,8].

The aim of present work is to formulate film coated tablets of Emtricitabine/Tenofovir disoproxil fumarate tablets. To develop a pharmaceutically stable, cost effective and quality improved formulation of Emtricitabine/Tenofovir disoproxil fumarate tablets. To produce better patient compliance with low dose of drug utilization. Newer NRTIs, such as Tenofovir and Emtricitabine, combine longer plasma half-lives with longer intracellular half-lives, prolonging exposure and the period of pharmacological activity [9-12].

2. Materials and Methods

Materials:

Emtricitabine and Tenofovir disoproxil fumarate were obtained as gift samples from Arch Pharmalabs Ltd. Dicalcium phosphate was obtained from Vijilak Pharma, Sodium starch glycolate was obtained from Signet Chemical Corporation Pvt Ltd, Magnesium Stearate was obtained from Amisti Drugs Ltd and Ideal blue was obtained from Colorcon Asia Pvt Ltd.

Drug – Polymer Interaction

It was carried out by taking FT-IR Infrared spectra of pure drug, and drug-polymer by KBr pellet technique and was recorded in the range of 4000 – 400 cm^{-1} using FT-IR Spectrophotometer.

Methods:

For direct compression: Di calcium phosphate, sodium starch glycolate were mixed sifted through #30 mesh. The above blend was mixed with Emtricitabine and Tenofovir disoproxil fumarate and passed through #24 mesh. The above blend lubricated with magnesium stearate. Lubricated material was compressed using 19.2 * 9mm oval shape punches.

For wet Granulation: Dicalcium phosphate, sodium starch glycolate were mixed sifted through #30 mesh. The above blend was mixed with Emtricitabine and Tenofovir disoproxil fumarate and passed through #24 mesh. The blend granulated with purified water and wet mass was passed through 12#mesh. Granules were dried in tray drier at 60^{o} c and dried granules were passed through 18#mesh. The dried granules were lubricated with magnesium stearate which was previously passed through 40#mesh.Compression: Lubricated granules were compressed using 19.2 * 9mm capsule shape punches and then coated by using ideal blue as a film former.

Table no. 1: Formulation for Emtricitabine and Tenofovir disoproxil fumarate tablet
Evaluation of prepared tablets

Ingredients	T-1	T-2	T-3	T-4	T-5	T-6	T-7
Emtricitabine	200	200	200	200	200	200	200
Tenofovir disoproxil fumarate	300	300	300	300	300	300	300
Di calcium phosphate	440	440	440	440	440	450	420
Sodium starch glycolate	50	50	50	-	-	40	70
Starch1500	-	-	-	50	50	-	-
Magnesium Stearate	10	10	10	10	10	10	10
Purified water	-	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Isopropyl alcohol	-	-	Q.S	Q.S	-	Q.S	Q.S
Ideal blue	30	30	30	30	30	30	30

Precompression parameters:
The prepared granules were evaluated for various parameters such as bulk density, tapped density, hausner's ratio and compressibility index to determine the flow properties of the granules.
Post compression Parameters:
The evaluation of tablets includes weight variation, friability, hardness, disintegration, etc. are conducted.
Friability: [13]
This test is intended to determine, under defined conditions, the friability of uncoated tablets, the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. Commercially available apparatus known as "friabilators" are used for the test. Generally, the test is done once. If cracked, cleaved, or broken tablets are obvious, then the sample also fails the test.
Hardness testing:
A tablet requires a certain amount of mechanical strength to withstand the shocks of handling in its manufacturing, packing, shipping and dispensing. Hardness and friability are most common measures used to evaluate tablet strength.
Disintegration test: [14, 15]
A disintegration test is a test to establish how fast a tablet disintegrates into aggregates and/or finer particle, the test is conducted using a specially designed instrument known as disintegration apparatus.
Dissolution: [16]
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.
***In-vitro* drug release profile:**

Dissolution Medium	: pH 0.01 Hcl Buffer
Volume (ml)	: 900
Apparatus	: USP Apparatus-II (Paddle)
Recommended Sampling times (Minutes)	: 5, 10, 15, 30 and 45 min
Speed (RPMs)	: 50

3. Results and Discussion

Drug–Polymer Interaction:
The characteristics absorption peaks of Emtricitabine and Tenofovir disoproxil fumarate was obtained at 1082, 1275, 1421, 1515and 1619 cm^{-1}.The peaks obtained in the spectras of each excipient correlate the peaks of drug spectrum. By correlation, it indicates that drug Emtricitabine and Tenofovir disoproxil fumarate is compatible with the components.
Precompression Parameters: The precompression parameters were determined and listed in the table 2. The results indicate good compressibility index for the powder blend of formulations. The BD and TD of the prepared granules ranged from 0.423 to 0.62 and 0.64 to 0.73 respectively. The compressibility (Carr's) index ranged from 15.2 to 34.62.

Table 2. Precompression parameters for the prepared granules

Formulation code	Bulk density (g/ml)	Tapped density(g/ml)	Compressibility index (%)	Hausner's ratio
T1	0.423	0.647	34.62	1.529
T2	0.6	0.72	16	1.22
T3	0.62	0.73	15.2	1.17
T4	0.59	0.7	15.7	1.18
T5	0.6	0.72	16.68	1.2
T6	0.56	0.72	22.2	1.2
T7	0.6	0.7	21.8	1.18

Post compression parameters:

Thickness: The thickness of the tablets was determined by Vernier calipers and was found in the range if 6.46-7.24 mm.

Hardness: It was found to be in the range of 7.5-10.4 kg/cm^2.

Friability: The % friability was less than 1% in all the formulations ensuring that tablets were mechanically stable.

Weight variation: Weight variation for the tablets of the all the batches was found to be in range of 1032.9-1039.9 mg. This ensure that it was within the limits of I.P ie., ± 5%.

Disintegration time: The disintegration time for the formulations was found to be in the range of 5min40sec-23 min 40 sec.

Table 3. Post compression parameters for the prepared tablets

Formulation code	Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%w/w)	Disintegtration time
T1	1039.9	7.24	8.66	0.069	8 min 50 sec
T2	1038.4	7.138	10.4	0.079	10min26sec
T3	1039.9	7.24	8.66	0.069	8 min 50 sec
T4	1036.6	6.66	9.33	0.093	11 min 20 sec
T5	1036.6	6.66	7.6	0.069	20 min20 sec
T6	1032.9	6.46	8.5	0.193	23 min 40 sec
T7	1037.1	6.46	7.5	0.219	5min40sec

Formulation Trial T-I was performed so as to select the method of preparation, primarily with direct compression. There was poor powder flow and capping was detected in this method. Trial- 2 was taken by changing the method of preparation as wet granulation, tablet came good, but impurities were observed. So the invitro dissolution studies were performed for the formulations T3-T7.

***In-vitro* drug Release Profile:**

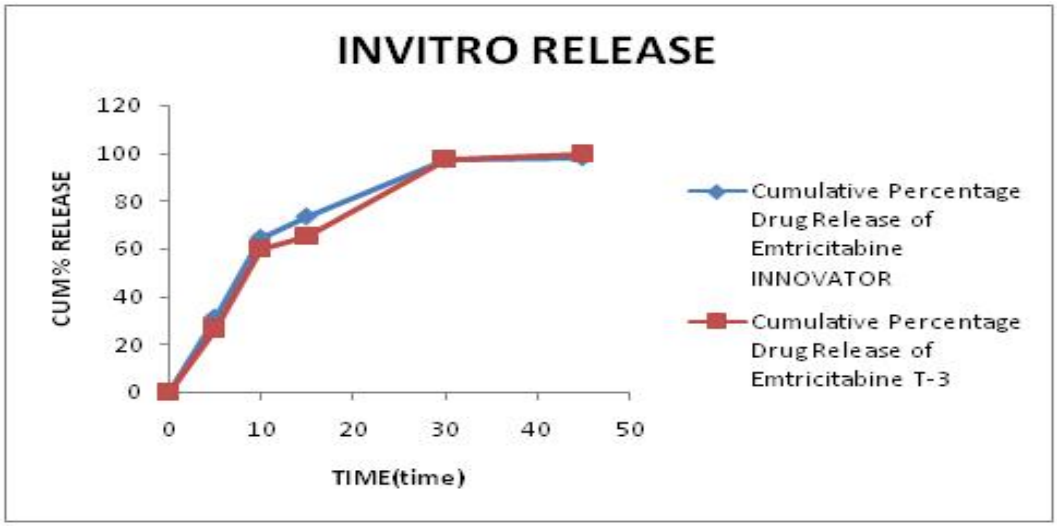

Figure 1. In-vitro drug release of T-3 Vs INNOVATOR (EMT)

Table 4. *In-vitro* drug Release Profile of T-3 and INNOVATOR (EMT)

Time (Minutes)	Cumulative Percentage Drug Release of Emtricitabine	
	Innovator	T-3
0	0	0
5	31.0	26.6
10	64.4	60
15	73.3	65
30	97.0	97.8
45	98.0	99.7

Table 5. In-*vitro* drug Release Profile of T-3 and INNOVATOR (TDF)

Time (Minutes)	Cumulative Percentage Drug Release of Tenofovir disoproxil fumarate	
	Innovator	T-3
0	0	0
5	33	32.2
10	65.8	64.5
15	73.9	72.3
30	95.6	85.6
45	96.8	96

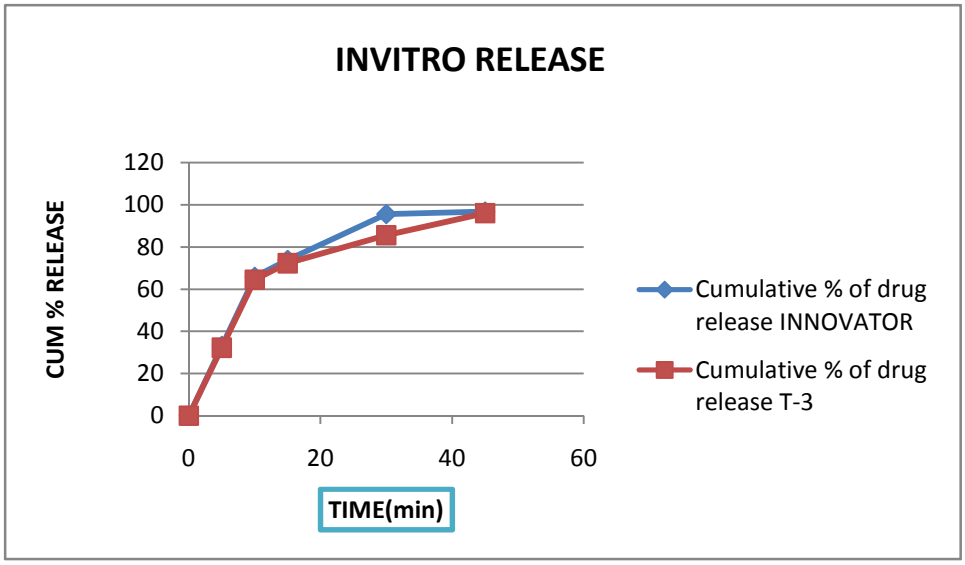

Figure 2. In-vitro drug release of T-3 Vs INNOVATOR (TDF)

Trial T-3 formulation is planned to prevent appearance of impurities by using Isopropyl alcohol and water used as vehicle in the ratio 80:20.All the physical parameters of tablets are found to be satisfactory dissolution profile also nearly matched with innovator. But still want to study the effect of other disintegrants on dissolution.

Table 6. *In-vitro* drug Release Profile of T-4 and INNOVATOR (EMT)

Time (Minutes)	Cumulative Percentage Drug Release of Emtricitabine	
	Innovator	T-4
0	0	0
5	31.0	26.4
10	64.4	62.0
15	73.3	73.3
30	97.0	84.7
45	98.0	96.2

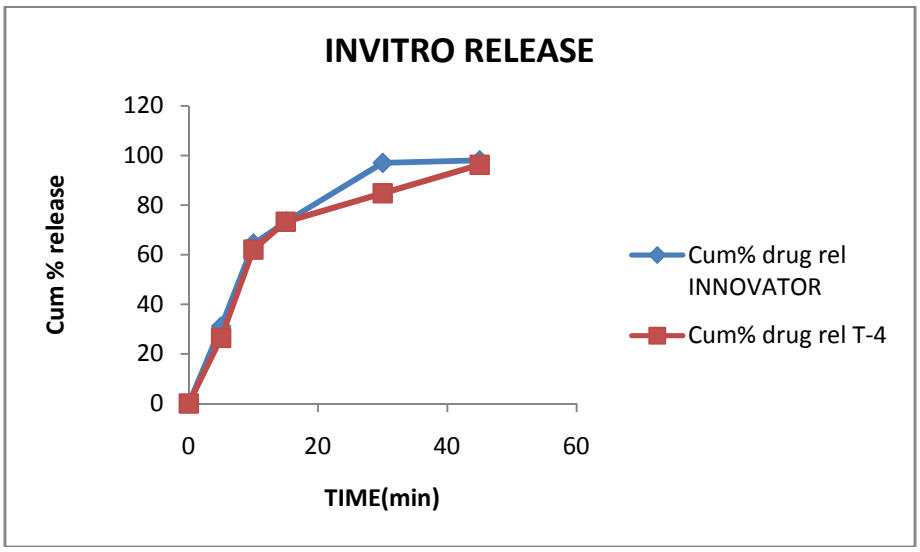

Figure 3. In-vitro drug release of T-4 Vs INNOVATOR (EMT)

Table 7. *In-vitro* drug Release Profile of T-4 and INNOVATOR (TDF)

Time (Minutes)	Cumulative Percentage Drug Release of Tenofovir disoproxil fumarate	
	INNOVATOR	*T-4*
0	0	0
5	33	26.6
10	65.8	54.2
15	73.9	73.5
30	95.6	97.9
45	96.8	100.1

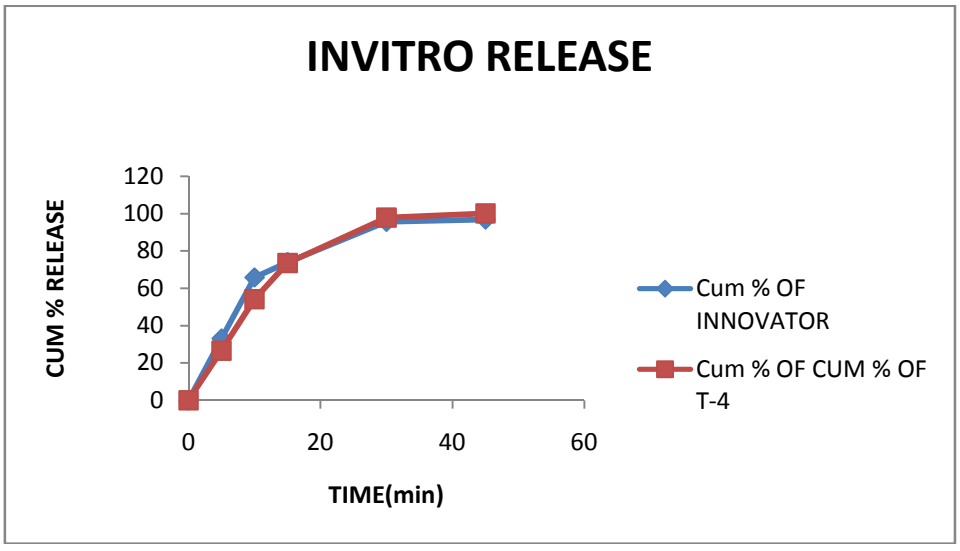

Figure 4. In-vitro drug release of T-4 Vs INNOVATOR (TDF)

Trial T-4 is planned to know the effect of other disintegrants on disintegration time by using STARCH1500 *disintegrant*. All the physical parameters of tablets are found to be satisfactory. *Invitro* dissolution profile was not matched with reference product and impurities were observed.

Table 8. *In-vitro* drug Release Profile of T-5 and INNOVATOR (EMT)

Time (Minutes)	Cumulative Percentage Drug Release of Emtricitabine	
	Innovator	T-5
0	0	0
5	31.0	29
10	64.4	40
15	73.3	55.5
30	97.0	70
45	98.0	83

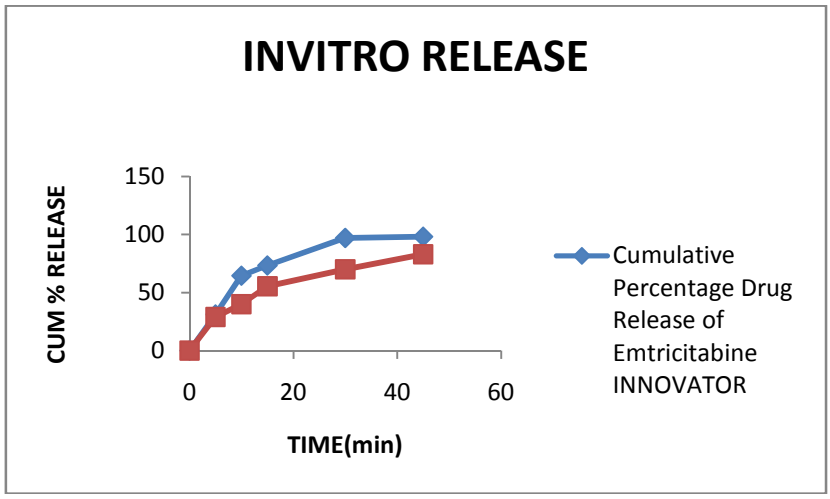

Figure 5. In-vitro drug release of T-5 Vs INNOVATOR (EMT)

Table 9. In-*vitro* drug Release Profile of T-5 and INNOVATOR (TDF)

Time (Minutes)	Cumulative Percentage Drug Release Tenofovir disoproxil fumarate	
	Innovator	T-5
0	0	0
5	33	20
10	65.8	30
15	73.9	51
30	95.6	71.1
45	96.8	82

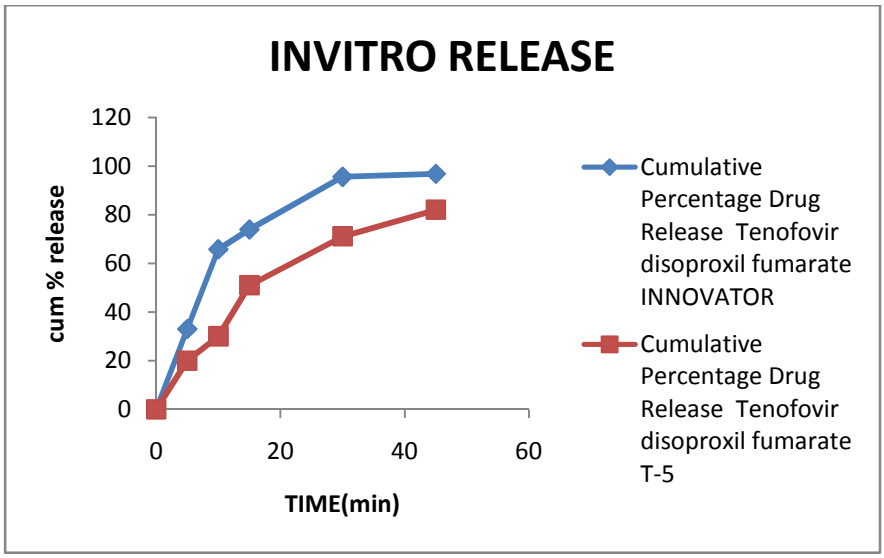

Figure 6. In-vitro drug release of T-5Vs INNOVATOR (TDF)

Formulation Trial T-5 is planned by changing the disintegrant.All the physical parameters of tablets are found to be satisfactory. *Invitro* drug release profile was not matching with the innovator.

Table 10. In-*vitro* drug Release Profile of T-6 and INNOVATOR (EMT)

Time (Minutes)	Cumulative Percentage Drug Release of Emtricitabine	
	Innovator	T-6
0	0	0
5	31.0	10
10	64.4	28
15	73.3	38
30	97.0	60
45	98.0	72

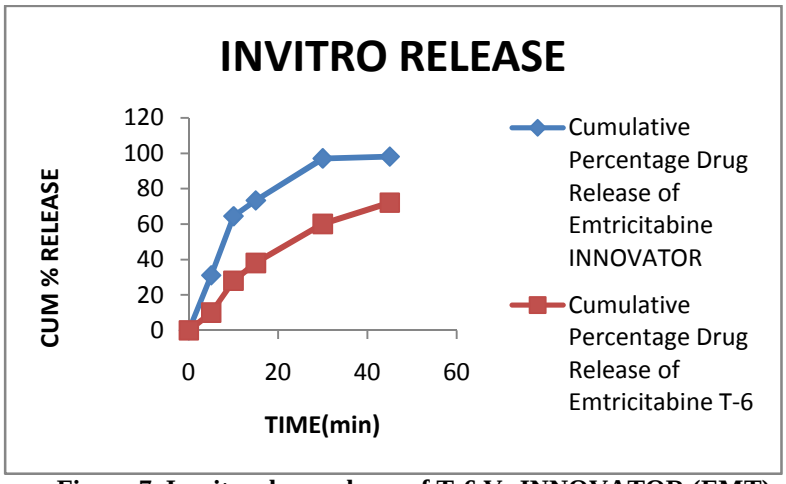

Figure 7. In-vitro drug release of T-6 Vs INNOVATOR (EMT)

Table 11. In-*vitro* drug Release Profile of T-6 and INNOVATOR (TDF)

Time (Minutes)	Cumulative Percentage Drug Release ot tenofovir disoproxil fumarate	
	Innovator	T-6
0	0	0
5	33	14
10	65.8	25
15	73.9	41.5
30	95.6	63
45	96.8	70.5

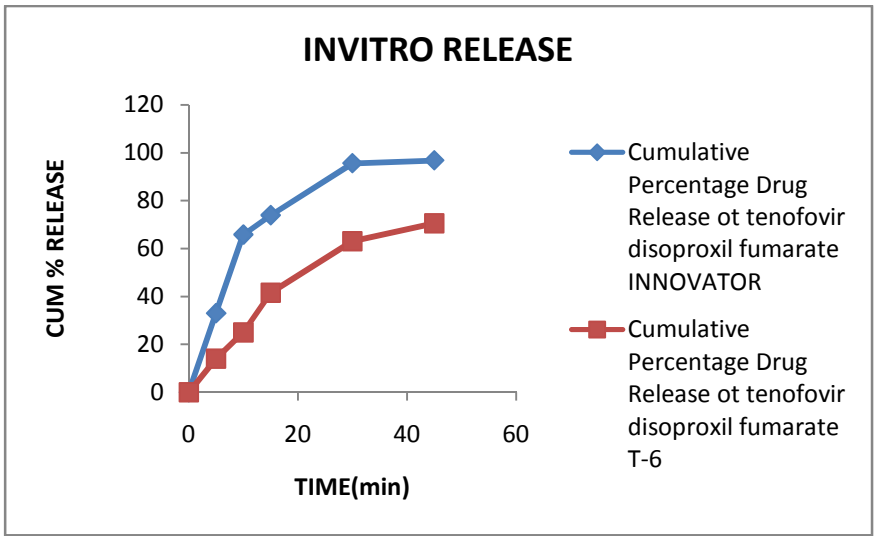

Figure 8. In-vitro drug release of T-6 Vs INNOVATOR (TDF)

Formulation Trial T-6 is planned to notice any change in the formulation on decreasing the disintegrant concentration.(Sodium starch glycolate). All the physical parameters are found to satisfactory *Invitro* drug release profile is not matching with the innovator.

Table 12. Invitro drug release of INNOVATOR and T-7(EMT)

Time (Minutes)	Cumulative Percentage Drug Release of Emtricitabine	
	Innovator	T-7
0	0	0
5	31.0	41
10	64.4	66.7
15	73.3	89
30	97.0	99.8
45	98.0	100.7

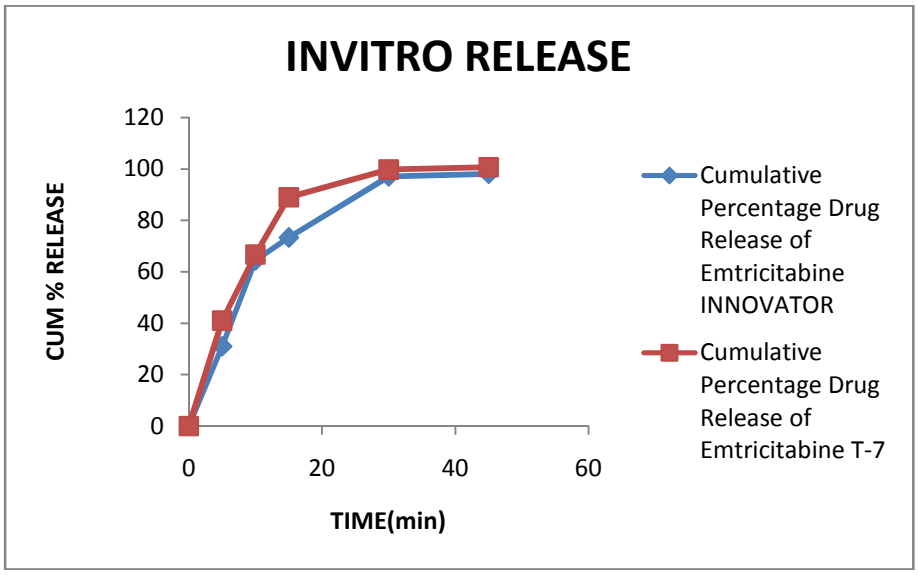

Figure 9. In-vitro drug release of T-7 Vs INNOVATOR (EMT)

Table 13. *In-vitro* drug Release Profile of T-7 and INNOVATOR (TDF)

Time (Minutes)	Cumulative Percentage Drug Release of Tenofovir disoproxil fumarate	
	Innovator	T-7
0	0	0
5	33	39.2
10	65.8	68.4
15	73.9	89.2
30	95.6	99.7
45	96.8	100.2

Formulation Trial T-7 is planned to notice any change in the formulation on increasing the disintegrant concentration (Sodium starch glycolate). All the physical parameters are found to satisfactory *Invitro* drug release profile is not matching with the *innovator*. According to all formulation trails Formula-3 shows the better outcome when compared with remaining trails.

4. Conclusion

The film coated tablets of Emtricitabine and Tenofovir disoproxil fumarate have been developed with wet granulation method and it is compared with that of TRUVADA tablets. Various trials were performed to optimize the disintegrants concentration of sodium starch glycolate. Amongst all the formulations, formulation containing sodium starch glycolate and di calcium phosphate (T3) is fulfilling all the parameters satisfactorily. It has shown excellent in vitro disintegration, in vitro dissolution, compared to other formulations. The hardness of core tablet (T3) was optimized to as 7-9 kg/cm^2 and coated tablets as 8 kg/cm^2. Dissolution studies were performed in media

pH 0.01 N Hcl buffer and found to be comparable with that of TRUVADA (*innovator*). The tablets passed Accelerated stability testing for 1 month in the condition 40°C/75%RH. During this period the product was analyzed for the physical appearance, hardness, thickness, friability, loss on drying, dissolution, assay, relative studies. The results were found to be within limit. The extension of this work can be carried for the *in vivo* studies of Emtricitabine and Tenofovir disoproxil fumarate.

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