

**FORMULATION AND EVALUATION OF IMMEDIATE RELEASE EMTRICITABINE & TENOFOVIR DISOPROXIL FUMARATE TABLET****\*Kotta Kranthi Kumar<sup>1</sup>, Sravanthi.Morae<sup>1</sup>, M. Sabareerh<sup>2</sup>**<sup>1</sup>Department of Pharmaceutics, SKU College of Pharmaceutical Sciences, S.K.University' Anantapur, India<sup>2</sup>A.P, Krishna Teja Pharmacy College Tirupathi, India**Received 10 August 2013; Revised 25 August 2013; Accepted 1 September 2013****ABSTRACT**

The main purpose of the present study is to formulate and evaluate once daily an immediate release tablet of Emtricitabine and Tenofovir disoproxil fumarate using different disintegrants. Preformulation studies were performed prior to compression. The tablets were compressed using Dicalcium phosphate, sodium starch glycolate, Lycatab-C, isopropylalcohol, glyceryl distearate and HPMC, Ideal blue (Y-30-1070) was used for coating the tablets. The fabricated tablets were evaluated for various properties like thickness, hardness, friability, disintegration time. Formulations were evaluated for the release of Emtricitabine and Tenofovir disoproxil fumarate over a period of 45 min using United States Pharmacopoeia (USP) type-II dissolution apparatus. The in-vitro drug release study, T-VI exhibited satisfactory drug release. Sodium starch glycolate is found to be the better disintegrant when compared to Lycatab-C. Compared to the direct compression, wet granulation was found to be the best method of choice for formulation of these tablets.

**KEY WORDS:-**, HPMC, Dicalcium Phosphate, Sodium Starch Glycolate.**INTRODUCTION:****Immediate-Release Preparations:<sup>1,2</sup>**

A dosage form that is intended to release the entire active ingredient on administration with no enhanced, delayed or extended release effect. 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 pre-gastric absorption, convenience in drug administration to dysphasic patients. Conventional Immediate Release 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. (Tablets: -<sup>3,4</sup>)

Tablet is solid dosage form 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 Pharmaceutical excipients tablets are the dominant dosage forms for drug delivery, occupying two thirds of the global market. Generally, they are produced by compressing dry powder blends consisting of a number of components with

different functionalities in a die. With advancement in technology and increase in awareness towards modification in standard tablet to achieve better acceptability as well as bioavailability, newer and more efficient tablet dosage forms are being developed. The main reasons behind formulation of different types of tablets are to create a delivery system that is relatively simple and in expensive to manufacture, provide the dosage form that is convenient from patient's perspective and utilize an approach that is unlikely to add complexity during regulatory approval process.

**IMMEDIATE RELEASE FILM COATING SYSTEMS FOR TABLETS:<sup>5</sup>**

The pigmented and non-pigmented film coatings are used for immediate release solid dosage forms. These film coating formulas produce attractive, elegant coatings on even the most challenging tablet surfaces and can be used in both aqueous and organic coating procedures. An extensive selection of polymer blend formulations provides the user with the ability to impart many beneficial features to a solid oral dosage formulation.

**These benefits include:**

1. Reduced coating process time
2. Superior adhesion on difficult to coat cores

3. Less stressful processing conditions for heat sensitive, friable or high drug content cores
4. Sharper logo definition, even at higher weight gains
5. Better gloss and smoothness compared to conventional tablets
6. Improved colour stability.

Aqueous film coating is the quickest and least expensive method for enhancing the tablet appearance and unlike other methods, will not affect dissolution or disintegration profiles. The dry-blend systems consist of polymers, plasticizers and pigments combined in one, easy-to-use and this dry powder system which is

rehydrated quickly with water. Dry coating technology provides benefits such as improved adhesion, reduced processing times and application of the tablet coating at wider process parameters.

The aim of present work is to formulate film coated tablets of Emtricitabine combination with Tenofovir disoproxil fumarate comparable to the marketed product which could perform therapeutically, with improved efficacy.

**MATERIALS:**

List of Materials

Table: 1

Material	Category	source
Emtricitabine	API	Natco Pharma Ltd.
Tenofovir disoproxil Fumarate	API	Natco Pharma Ltd,
Microcrystalline Cellulose pH 102	Diluent	Vijilak Pharma
Dicalcium phosphate A-tab	Buffering Agent	Signet Chemical Pvt Ltd
Hydroxy propyl cellulose LH-II	Polymer	Vijilak Pharma
Pregelatinized starch Lycatab-c	Disintegrant	Signet Chemical Corporation Pvt Ltd
Sodium starch glycolate	Disintegrant	Signet Chemical Corporation Pvt Ltd
Magnesium Stearate	Lubricant	Signet Chemical Corporation Pvt Ltd
Ideal Blue (Y-30-1070)	Colouring agent	Signet Chemical Corporation Pvt Ltd

**MANUFACTURING METHODS:** <sup>6,7</sup>

Pharmaceutical products are processed all over the world using the direct compressing, wet granulation or dry granulation methods. Method is chosen depend on the ingredients individual characteristics like flow property,

compressibility. Choosing a method requires thorough investigation of each ingredient in the formula, the combination of ingredients, and how they work with each other. Then the proper granulation process can be applied.

Table: 2

S.NO	INGREDIENTS	Quantity per tablet (mg)												
		T-I	T-II	T-III	T-IV	T-V	T-VI	T-VII	T-VIII	T-IX	T-X	T-XI	T-XII	T-XIII
1	Emtricitabine	200	200	200	200	200	200	200	200	200	200	200	200	200
2	Tenofovir disoproxil fumarate													
3	Dicalcium phosphate	440	440	440	430	440	430	420	410	430	420	410	430	430
4	Sodium starch glycolate	50	---	50	60	50	60	70	80	---	---	---	60	60
5	Lycatab-C	---	50	---	---	---	---	---	---	60	70	80	---	---
6	Purified water	---	---	q.s.	q.s.	---	---	---	---	---	---	---	---	---
7	Isopropyl alcohol+ Purified water (80:20)	---	---	---	---	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

8	Glyceryl distearate	10	10	10	10	10	10	10	10	10	10	10	10	10
9	Ideal Blue (Y-30-1070)	30	30	30	30	30	30	30	30	30	30	30	30	30

10-20

**EVALUATION OF TABLETS:**

To design tablets and later monitor tablet production quality, quantitative evaluation and assessment of tablet chemical, physical and bioavailability properties must be made. The important parameters in the evaluation of tablets can be divided into physical and chemical parameters.

**Physical appearance:**

The general appearance of tablets, its visual identity and overall elegance is essential for consumer acceptance. The control of general appearance of tablet involves measurement of number of attributes such as tablet size, shape, colour, presence or absence of odour, taste, surface texture and consistency of any identification marks.

**Tablet size and Thickness:**

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by Vernier Callipers scale. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter. Tablet thickness should be controlled within a  $\pm 5\%$ . In addition thickness must be controlled to facilitate packaging.

**Average weight of Tablets:**

Take randomly 20 tablets and weigh accurately 20 tablets and calculate the average weight.

$$\text{Average weigh} = \frac{\text{weight of 20 tablets}}{20}$$

**Weight variation test:**

It is desirable that all the tablets of a particular batch should be uniform in weight. If any weight variation is there, that should fall within the prescribed limits:

$\pm 10\%$  for tablets weighing 130mg or less

$\pm 7.5\%$  for tablets weighing 130mg-324mg

$\pm 5\%$  for tablets weighing more than 324mg

The test is considered correct if not more than two tablets fall outside this range. When 20 tablets are taken for the test and not more than 1 tablet fall outside this range when only 10 tablets are taken for the test. The difference of weight in tablets can lead to

variation in doses. For carrying out this test 20 tablets at random are taken and weighed. The weights of individual tablets are then compared to be equal to average weight.

**All the results are mentioned in table no: 4**

**Friability:**

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these are placed in the friabilator, rotating at 25rpm for 4min. The difference in the weight is noted and expressed as percentage. It should be preferably between 0.5 to 1.0%.

**All the results are mentioned in table no: 4**

**Hardness test:**

This is to force required to break a tablet in a diametric compression. A tablet requires a certain amount of mechanical strength to withstand the shocks of handling in its manufacturing, packing, shipping and dispensing. Hardness of the tablet is determined by Stock's Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moves along the gauze in the barrel fracture.

**All the results are mentioned in table no: 4**

**Disintegration test:**

For most tablets the first important step toward solution is break down of tablet into smaller particles or granules, a process known as disintegration. This is one of the important quality control tests for disintegrating type tablets. Six tablets are tested for disintegration time using USP XXII apparatus.

**All the results are mentioned in table no:4**

**Dissolution:**

Dissolution is a process in which a solid substance solubilises in a given solvent i.e. mass transfer from the solid surface to the liquid surface. It 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.

**Dissolution (By HPLC method):****Dissolution conditions:**

Medium: 0.01 N HCl

Volume: 900 ml

Apparatus: USP Type 2 paddle

RPM: 50

Temperature:  $37 \pm 0.5^{\circ}\text{C}$  Time interval: 45 min

#### Chromatographic conditions:

Column: Purosphere star – RP18, 150 \* 4.6 mm, 5 $\mu\text{m}$

Flow rate: 1.0 ml/min

Wavelength: UV-254 nm

Column temperature:  $30^{\circ}\text{C}$

Injection volume: 10 $\mu\text{l}$

Run time: 12 min.

#### All the results are mentioned in table no: 5

#### ASSAY (content uniformity):

Although the specifications for assay results differ from product to product, generally the expected range for individual active ingredient is to be within 90%–110% of the labelled amount.

#### Instrument:

HPLC equipped with UV detector and data handling system.

#### Chromatographic conditions:

Column: Purosphere star –RP18, 150 \* 4.6 mm, 5 $\mu\text{m}$

Flow rate: 1.0 ml/min

Wavelength: UV-254 nm

Column temperature:  $30^{\circ}\text{C}$

Injection volume: 20 $\mu\text{l}$

Run time: 12 min.

#### 1. Emtricitabine and Tenofovir disoproxil fumarate standard preparation:

Accurately weigh and transfer about 20mg of Emtricitabine working standard and 30mg of Tenofovir working standard into a 250 ml volumetric flask. Add about 180ml of diluents and sonicate to dissolve. Cool the solution to room temperature and dilute to volume with diluents (0.08 mg/ml of Emtricitabine and 0.12 mg/ml of Tenofovir). Transfer 2ml of above solution into a 200ml volumetric flask, mix well and dilute to volume with Mobile phase –A and mix.

#### 2. Sample preparation:

Weigh and finely powder not fewer than 20 tablets. Transfer an accurately weighed portion of the powder equivalent to 200 mg of emtricitabine into 250ml volumetric flask. Add 180ml of diluents. Shake for 10min with rotating shaker and sonicate for 30min with

occasional shakings. Cool the solution to room temperature and dilute to volume with diluents and mix. Centrifuge the solution to 3000 rpm for 10 min. Transfer 1ml of above centrifuged solution into 100ml volumetric flask and dilute with Mobile phase A.

#### System suitability:

Chromatograph the standard preparation (six replicate injections), measure the peak area response for the analyte peak and evaluate the system suitability parameters as directed.

#### Acceptance criteria:

1. %RSD for replication of peak area response due to emtricitabine and tenofovir peak from the standard preparation should be not more than 2.0
2. The tailing factor for emtricitabine and tenofovir peak should be not more than 2.0
3. The number of theoretical plates for emtricitabine and tenofovir peak should be not less than 2000.

#### Procedure:

Separately inject equal volumes (about 20 $\mu\text{l}$ ) of the water as blank, standard preparation and sample preparation into chromatograph and record the chromatograms and measure the peak area response for analyte peak. Calculate the percentage content of Emtricitabine and Tenofovir disoproxil fumarate tablets taken by formula.

#### Percentage content of Emtricitabine / Tenofovir disoproxil fumarate:

$$= \frac{\text{TA}}{\text{SA}} * \frac{\text{SW}}{250} * \frac{2}{20} * \frac{250}{\text{TW}} * \frac{100}{1} * \frac{\text{P}}{100} * \frac{1}{\text{AVG WT/LA}} * 100$$

Where,

TA= Peak area response due to Emtricitabine / Tenofovir disoproxil fumarate from sample preparation

SA= Peak area response due to Emtricitabine / Tenofovir disoproxil fumarate from standard preparation

SW= Weight of Emtricitabine / Tenofovir disoproxil fumarate working standard taken in mg.

TW= Weight of sample taken in mg.

P= Purity of Emtricitabine / Tenofovir disoproxil fumarate working standard taken on, as is basis.

AVG WT= Average weight of tablets.

LA= Labelled amount of Emtricitabine / Tenofovir disoproxil fumarate.

#### DRUG RELEASE KINETICS: <sup>21-30</sup>

To analyse the mechanism of the drug release rate kinetics of the dosage form, the data were plotted as:

**Zero order release rate kinetics:**

To study the Zero order release kinetics the release rate data were **fitted** to the following equation.

$$F = K t$$

Where, 'F' is the fraction of drug release, 'K' is the release rate constant, and 't' is the release time.

When the data is plotted as Cumulative percent drug released versus time, if the plot is linear then the data obeys Zero order release kinetics, with slope equal to K.

**All the results are given in table: 33, 34, and 35.**

**First order kinetics:**

A First order release would be predicated by the following equation.

$$\log C = \log C_0 - K t$$

Where C = Amount of drug remained at time 't' Co = initial amount of drug

$$K = \text{First order rate constant (hr}^{-1}\text{)}$$

When the data is plotted as Cumulative percent drug remaining versus time yields a straight- line, Indicating that the release follows First order kinetics .The constant 'K' can be obtained by multiplying 2.303 with slope values.

**Higuchi release model:**

To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = K. t^{1/2}$$

Where, 'F' is the amount of drug release 'K' is the release rate constant, and 't' is the release time.

When the data is plotted as Cumulative drug released Versus Square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism .The slope is equal to 'K'.

**Korsmeyer and peppas release model:**

The release rate data were **fitted** to the following equation.

$$M_t / M_\infty = K. t^n$$

Where,  $M_t / M_\infty$  is the fraction of the drug release, 'K' is the release rate constant, 't' is the release time, and 'n' is the diffusional exponent for the drug release that is dependent on the shape of the matrix dosage form. When the data is plotted as Log of drug released Versus log time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from Y-intercept.

**Diffusion mechanisms based on (n):**

Table: 3

<i>Diffusion exponent (n)</i>	<i>Overall solute diffusion mechanism</i>
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

**Similarity and Dissimilarity factors:**

Similarity Factor (f2) stresses on the comparison of closeness of two comparative formulations. Generally similarity factor in the range of 50-100 is acceptable according to US FDA. It can be computed using the formula

$$f_2 = 50 \times \log \left\{ \left[ 1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

Where, n is the number of dissolution sample times, Rt and Tt are the individual or mean percent Dissolved at each time point, t, for the reference and test dissolution profiles, respectively.

Dissimilarity factor (f1) focuses on the difference in percent dissolved between marketed d product and formulation trials at various time intervals. It can be

mathematically computed by using  $f_1 = \left\{ \left[ \sum_{t=1}^n |R_t - T_t| \right] / \left[ \sum_{t=1}^n R_t \right] \right\} \times 100$  Therefore the factors directly compare the difference between percent drug dissolved per unit time for the formulation trials and marketed product.

**Stability studies:**

The stability studies were carried out according to ICH to assess the drug formulation stability. Optimized FV formulation was sealed in aluminium packaging laminated with polyethylene. Sample were kept at 40 °C and 75% RH for 3 months. At the end of the study period, the formulation was observed for change in physical appearance, colour, and drug content and drug

release characteristics.

## RESULTS:

Table: 4

Trial batches	Weight (mg)	Thickness (mm)	Hardness (kg)	Friability (%w/w)	Disintegration time(min)
Innovator	1000	7.10	24	0.12	11min 30sec
T-I	1004	7.16	21.4	0.18	14min 50sec
T-II	1002	7.10	22.0	0.11	11min 10sec
T-III	1005	7.19	20.5	0.24	14min 50sec
T-IV	1002	7.10	22.1	0.13	11min 10sec
T-VI	1004	7.16	21.4	0.19	11min 15sec
T-VII	1005	7.19	20.5	0.24	11min 36sec
T-VIII	1008	7.22	20.0	0.25	28min 20sec
T-IX	1006	7.20	20.4	0.23	28min 15sec
T-X	1007	7.21	20.3	0.21	29min 10sec
T-XI	1003	7.14	21.8	0.20	11min 5sec
T-XII	1002	7.10	22.2	0.14	10min 20sec
T-XIII	1002	7.10	22.3	0.10	10min 55sec

## DISCUSSION:

From the above table post compression parameters like thickness, hardness and friability of T-VI are found to be greater than innovator. Disintegration time of T-VI, are found to be less than innovator.

## DISSOLUTION PROFILE OF TRIAL BATCHES:

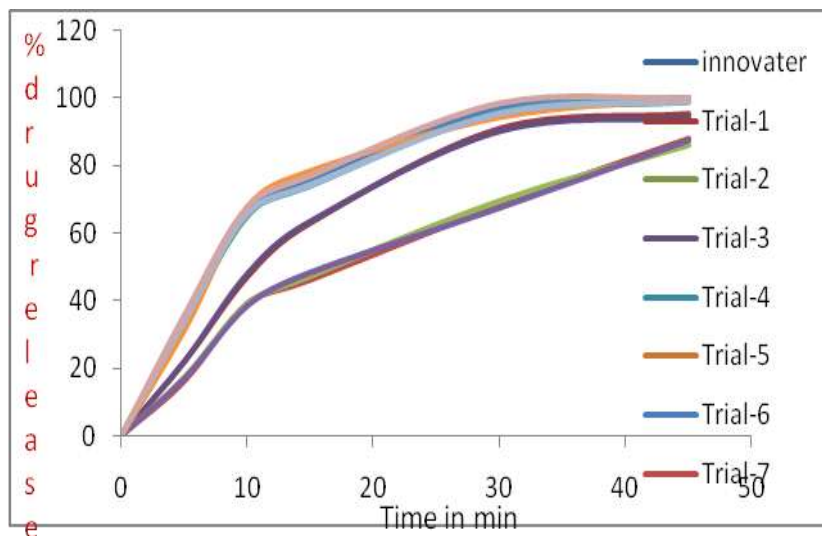
**In-vitro release of Tenofovir disoproxil fumarate formulations:**

Table: 5

Trails	Time(min)					
	0 min	5min	10min	15min	30min	45min
T-I	0	21.9	47.2	63.2	91.1	95.5
T-II	0	33.9	65.2	76.2	95.4	99.0
T-III	0	22.1	48.1	63.6	90.4	94.4
T-IV	0	34.5	66.2	75.2	96.9	100.0
T-V	0	33.1	65.9	74.9	97.2	99.9
T-VI	0	33.9	67.2	75.6	97.4	100.2
T-VII	0	16.2	39.2	46.2	68.3	88.0
T-VIII	0	17.2	39.0	47.2	69.4	86.0
T-IX	0	16.9	38.5	48.3	67.5	87.5
T-X	0	33.2	65.6	74.2	95.9	99.6
T-XI	0	31.2	67.6	78.2	94.2	99.8

<b>T-XII</b>	0	34.0	66.0	74.5	95.6	99.2
<b>T-XIII</b>	0	35.8	67.8	76.9	98.3	99.8
<b>Innovator</b>	0	32.5	64.8	73.8	95.3	98.0

Figure: 1



**DISCUSSION:**

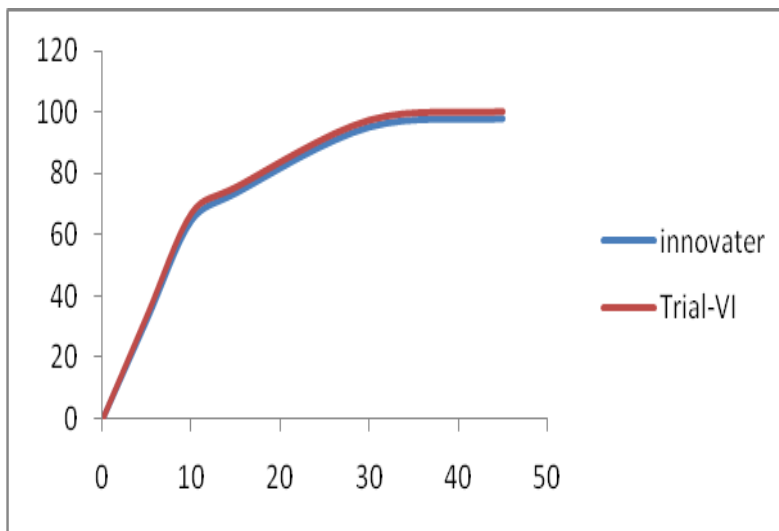
From the above table % drug release of T-VI showing better results compared with innovator.

**COMPARATIVE DISSOLUTION PROFILE OF OPTIMISED BATCHE (T-VI) & INNOVATOR:**

Table: 6

Time(min)	innovator	Trial-VI
0	0	0
5	32.5	33.9
10	64.8	67.2
15	73.8	75.6
30	95.3	97.4
45	98	100.2

Figure: 2



**STABILITY STUDIES:**

**Stability studies results of optimized batch:**

Table: 7

S. No.	Parameters	CONDITIONS				
		Initial	40c & 75% RH			25 <sup>0</sup> C&60%RH
		0 Day	1 month	2month	3month	3 month
1	ASSAY	99.8	99.8	99.6	99.5	99.5
2	INNOVATOR	98.4	98.4	98.1	98.0	98.0

**DISCUSSION:**

During the stability studies, assay values of the optimized batch when compared with innovator do not show any remarkable changes in the dose. Test Frequency: Initial, 1 Month & 3MonthsIt is found to be all

the physical and chemical parameters are satisfactory based on initial stability data. Photo stability studies have shown that the medicinal product is non-light sensitive.

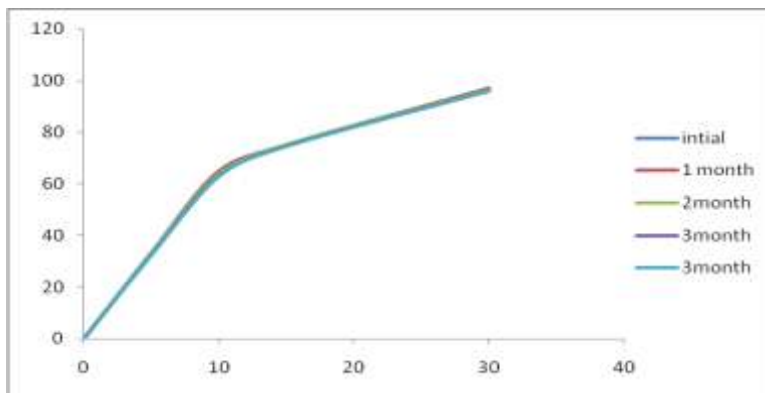
**Dissolution Profile of optimized batch (T-VI):**

Table: 8

Time (min)	Optimized batch dissolution profile storage Conditions				
	Initial	40c & 75% RH			25 <sup>0</sup> C&60%RH
	0 Day	1 month	2month	3month	3 month
0	0	0	0	0	0
5	33.2	33.2	33.0	32.6	32.5
10	64.8	64.8	63.8	63.0	63.0
15	75.0	75.0	75.0	74.7	74.5
30	96.9	96.9	96.2	96.0	96.0
45	100.2	100.2	100.0	99.4	99.0

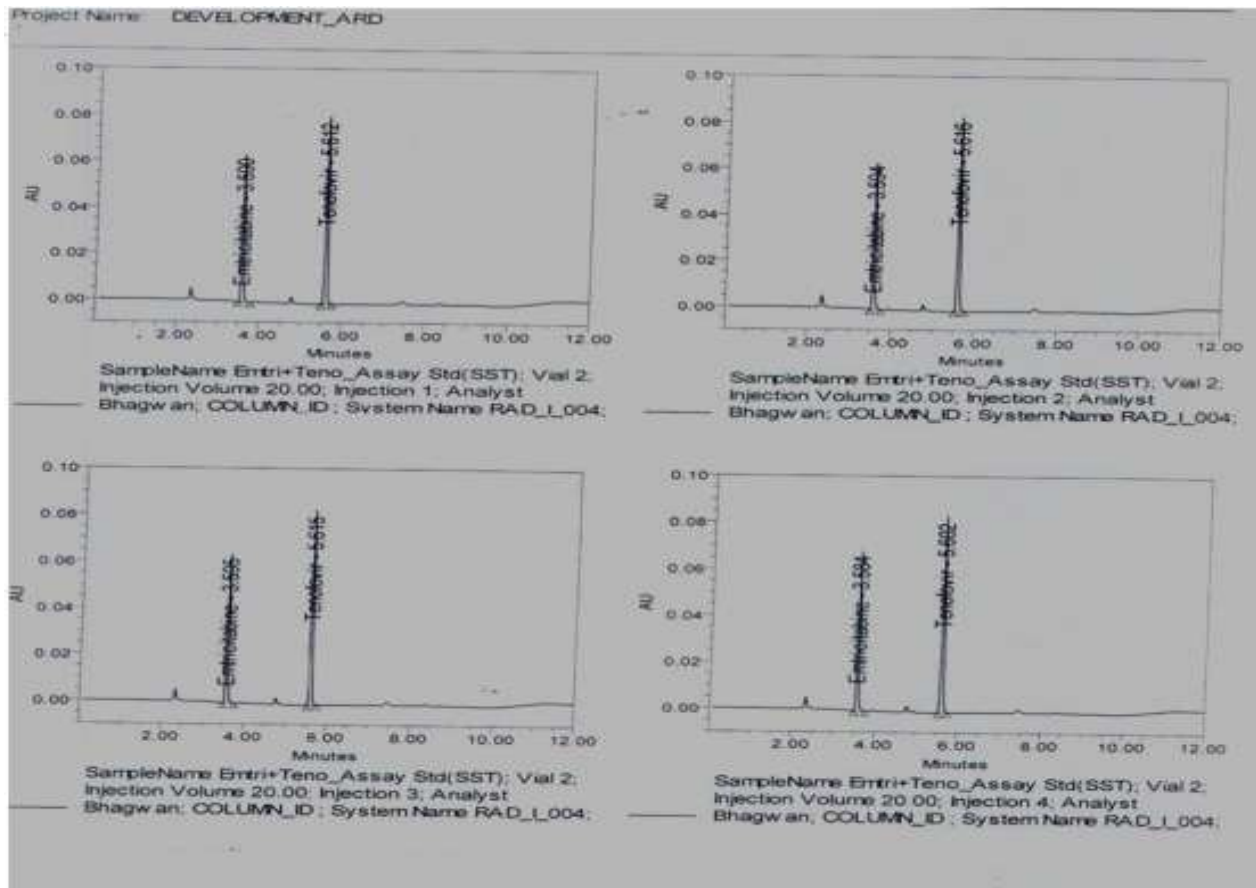
**Dissolution profiles comparison after stability studies:**

Figure: 3



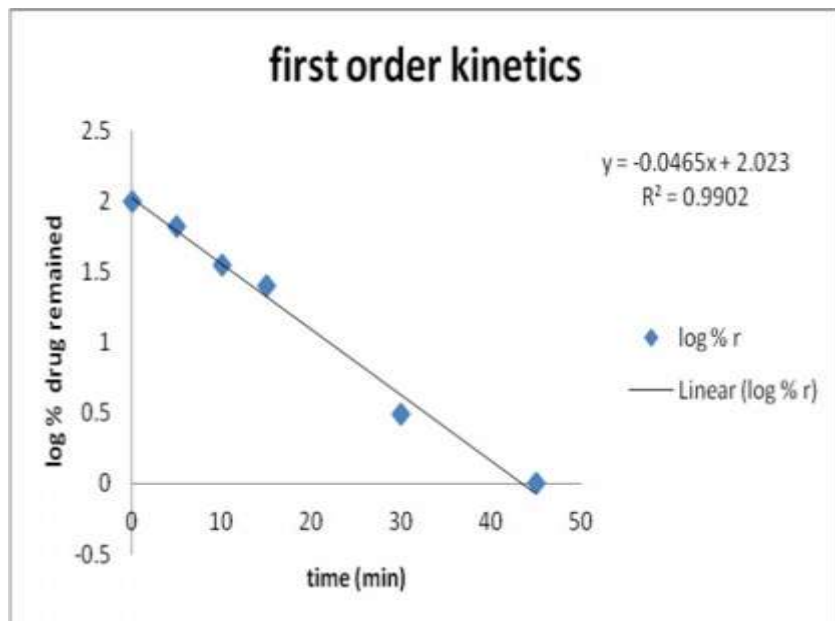
**CONTENT UNIFORMITY:  
ASSAY OF OPTIMISED BATCH:**

Figure: 4



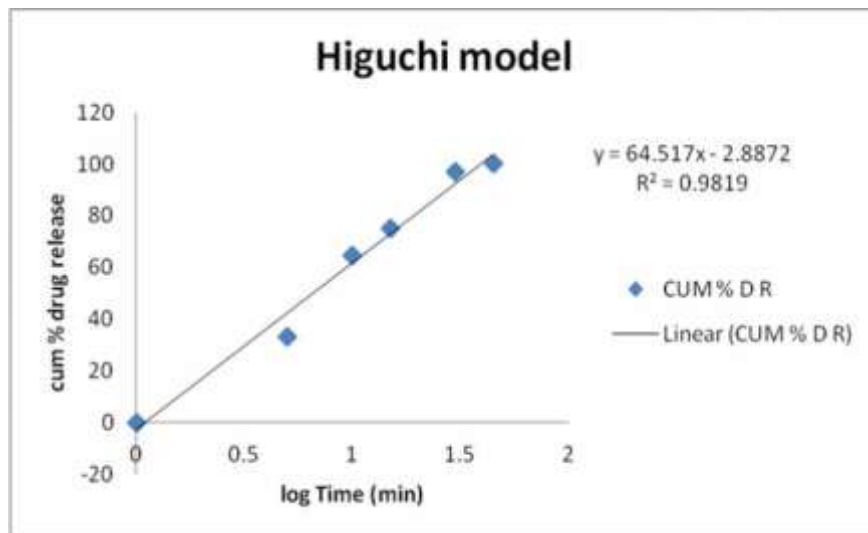
**First Order Release Plots  
First order kinetics of optimized batch (T-VI)**

Figure: 5



**HIGUCHIS PLOTS:  
Higuchis model for optimized batch (T-VI):**

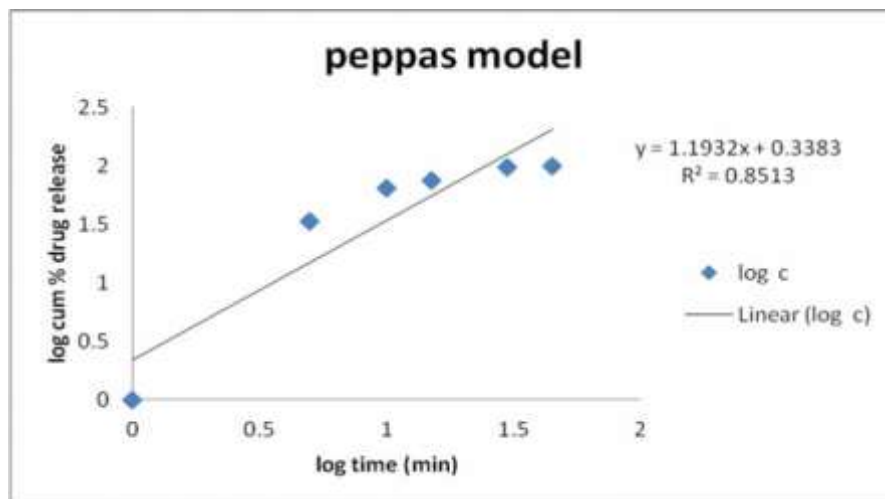
Figure: 6



**KORSMEYER PEPPAS KINETICS MODELS:**

Korsmeyer peppas kinetics model for optimized batch (T-VI):

Figure: 7



**SIMILARITY AND DISMILARITY FACTORS:**

Similarity and dissimilarity factors of optimized batch:

Table: 9

N	Innovator (R <sub>t</sub> )	trial-VI (T <sub>t</sub> )	(R <sub>t</sub> -T <sub>t</sub> )	(R <sub>t</sub> -T <sub>t</sub> ) <sup>2</sup>	Similarity factor(f <sub>2</sub> )	Dissimilarity factor(f <sub>1</sub> )
0	0	0	0	0	77.32	1.50850
5	32.5	33.2	-0.7	0.49		
10	64.8	64.8	0	0		
15	73.8	75.0	-1.2	1.44		
30	95.3	96.9	-1.6	2.56		
45	98.2	100.2	-2	4		

Table: 10

Parameters	Limits	Optimized(T-VI)
F1	0-15	1.5
F2	>50	77.32

**DISCUSSION:**

From the results the formulation may pass in in- vivo studies.

**CONCLUSION:**

The optimized batch trial (T – VI) is having more drug release and stability when compared with innovator. Therefore, it was concluded that the T – VI trial was the satisfactory formulation that could perform therapeutically with improved efficacy.

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