



Design and *In vitro* Characterization of Dolutegravir Sustained Release Matrix Tablets

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ABSTRACT

The purpose of this research was to develop Dolutegravir sustained release 200mg matrix tablets. Dolutegravir is a second-generation HIV integrase strand transfer inhibitor (INSTI) and the most recent antiretroviral drug approved for the treatment of HIV-1 infection. Six formulations of Dolutegravir 200mg were formulated by direct compression technique using different hydrophilic polymer grades such as Carbopol 971G, Benecel K 100M (HPMC K 100M) were used as rate controlling polymers in different concentrations and other ingredients are Micro crystalline cellulose, Talc, Sodium Stearyl Fumarate, before the formulation the granules are evaluated by pre-compression studies. The obtained tablets were evaluated with different post-compression parameters like hardness, friability, thickness, weight variation, drug content, *in vitro* dissolution studies. The formulation F4 was selected as an optimized formulation because it gives best results in terms of *in vitro* drug release in a sustained release manner and best fitted to first order model with R² value of 0.999. Short time stability studies indicates no appreciable changes in drug content and *in vitro* drug release of optimized formulation of F4.

Keywords: Dolutegravir, Sustained release tablets, Hydrophilic, Carbopol 971G.

INTRODUCTION

Dolutegravir is an antiretroviral (anti-HIV) that belongs to a class of drugs called integrase strand inhibitors (INSTIs). It is intended for the treatment of HIV-1 infection in adults and children aged 12 years and older weighing at least 40kg. It works by blocking enzyme integrase inhibitor. This drug does not cure AIDS or completely kills the HIV virus, but helps to prevent further damage by slowing down the production of new viruses. Dolutegravir is used together with other antiretroviral drugs to delay the progressions of HIV-1 infection.

Tablets are the solid oral dosage forms which offer the greatest capabilities of all oral dosage forms for the greatest precision and the least content variability. Oral route for the drug delivery is the most popular, desirable and widely used route of administration of drug products because it is natural, convenient and cost effective and offers greater flexibility in dosage form design.

Sustained release oral dosage form is designed to achieve prolonged therapeutic effect by continuously releasing drug over an extended period of time irrespective of concentration. Sustained release dosage forms decrease the frequency of drug administration, increase the patient compliance, obtaining the maximum availability with a minimum dose, both systemic and local side effects can be reduced and also maintains better drug control of plasma drug levels.

One of the least complicated approaches to the manufacture of sustained release dosage form involves the direct compression of blend of drug, retardant

material, and additives to form a tablet in which drug is embedded in a matrix core of the retardant.

Dolutegravir is an HIV-1 antiviral agent. It inhibits HIV integrase by binding to the active sites and blocking the strand transfer steps of retroviral DNA integration. This is an essential step of HIV replication cycle and results in an inhibition of viral activity. After oral administration peak plasma Dolutegravir concentrations are achieved in 2-3 hours. The average terminal half life is approximately 14 hours and steady state is achieved after approximately 5 days with repeated dosing.

The main objective of sustained release systems is to maintain drug concentration in the blood or in the target tissues at a desired level as long as possible.

MATERIALS AND METHODS

Materials

Dolutegravir was received as gift sample from Richer Pharma Pvt.Ltd.

Microcrystalline cellulose, Talc, Sodium Stearyl Fumarate, Benecel K100 M, Carbopol 971G was received as a gift sample from Richer Pharma Pvt. Ltd.

Methods

Formulation of Dolutegravir sustained release matrix tablets

Dolutegravir sustained release matrix tablets were prepared by direct compression method. Six formulations of tablets each containing 200mg dose of Dolutegravir



were prepared with different concentrations of various excipients which were shown in Table 1.

Dolutegravir and polymers such as Carbopol 971G, and Benecel k 100M were accurately weighed, mixed uniformly and passed through # 40 mesh. Microcrystalline cellulose is used as diluents and Benecel is also used as

binding agent both were weighed accurately and passed through #40 meshes. Both were mixed properly and the mixture of Talc and sodium Stearyl Fumarate 1:1 ratio was added and mix for few minutes. Then the above mixture was compressed in to tablets by using station rotary compressed machine with punch size of 9 mm.

Table 1: Composition of Different Formulations from F1 to F6

Ingredients/formula Code(mg/tab)	F1	F2	F3	F4	F5	F6
Dolutegravir	50	50	50	50	50	50
Micro crystalline cellulose (avicel ph102)	106	96	86	106	96	86
Carbopol (971G)	40	50	60	-	-	-
Benecel (k & m DC)	-	-	-	40	50	60
Talc	2	2	2	2	2	2
Sodium Stearyl Fumarate	2	2	2	2	2	2
Core tablet weight (mg)	200	200	200	200	200	200

Evaluation of Pre-Compression Blend

Before the compression the granules were evaluated for their flow and compressibility properties.

Angle of repose

Angle of repose is determined by passing the powder through a funnel fixed to a burette stand at a particular height. The height is adjusted in such a way that the tip of the funnel touches the apex of the heap. The accurately weighed powder is allowed to pass through the funnel freely on to the surface. The height and radius of powder cone was measured by using following equation:

$$\tan \theta = h/r$$

Where h is the height of the powder cone and r is the radius of the powder cone, θ is the angle of repose.

Bulk density

Bulk density is determined by pouring a weighed quantity of blend into graduated cylinder by using funnel and volume was measured. It is the ratio of weight of the blend to bulk volume of the blend.

$$\text{Bulk density} = \text{Weight of blend} / \text{Bulk volume of the blend}$$

Tapped density

Tapped density is defined as the ratio of mass of blend to tapped volume of blend. It is determined by placing a graduated cylinder containing a known mass of drug on a mechanical tapper apparatus which is operated for a fixed number of taps until the powder bed has reached a minimum.

$$\text{Tapped density} = \text{Weight of the blend} / \text{Tapped volume of the blend}$$

Carr's compressibility index

Carr's compressibility index is determined by using the values of bulk density and tapped density. The equation for Carr's compressibility index is given as

$$\text{Carr's compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Bulk density}} \times 100$$

Hausner's ratio

Hausner's ratio is defined as the ratio of tapped density to the bulk density. It indicates the flow properties of powder.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Evaluation of Dolutegravir Matrix Tablets

Physical appearance

Physical appearance of tablets is determined by visual identity which involves the measurement of number of factors such as tablet size, shape, colour, odour, taste, surface texture and any identification marks present on the tablet.

Thickness

Thickness of the tablets was determined by using vernier callipers. Twenty tablets were taken randomly from the sample and each tablet thickness is measured.

Hardness

Hardness is determined by using Monsanto hardness tester; it is also called tablet crushing strength. It is performed on six tablets from each batch and the average of six values was noted.

Friability test

Friability test is performed in order to know the % weight loss of tablets by using Roche Friabilator. From each batch 10 tablets were accurately weighed and placed in friability and reweighed. The acceptable limit of the weight loss should not be more than 1%.

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$



Weight variation

The weight variation test is performed by taking 20 tablets from each formulations and weighing the individual tablets by using electronic balance. Their average weight was calculated as

$$\% \text{ Weight variation} = (W_A - W_i) \times 100 / W_i$$

Where,

W_i = Individual weight of the tablets

W_A = Average weight of the tablet

Content uniformity

This test is performed in order to know how much % of drug present in the sample. Over 10 tablets were selected randomly and average weight was calculated. Tablets were crushed in a mortar and accurately weighed amount of tablets triturate was taken for analysis and it was diluted with buffer solution. The contents were kept for sonication for proper dissolving of drug. Appropriate dilutions were made; the drug content was estimated by recording the absorbance at 254nm.

In vitro dissolution studies

The *in vitro* dissolution test was performed by using USP-II (paddle) dissolution apparatus at 100rpm. The dissolution media consist of 900ml of phosphate buffer of p^H 6.8 maintained at $37 \pm 0.5^\circ$ C. An aliquot (5ml) was withdrawn at specific time intervals (1hr, 2hr, 4hr, 8hr, 12hr, 16hr) and drug content was determined by using Uv-Visible spectrometer at 259.8nm.

RESULTS AND DISCUSSIONS

The formulations prepared were subjected to various pre-formulation and post-formulation evaluation studies. The results obtained were within the pharmacopoeial limits.

Standard calibration curve of Dolutegravir

Calibration curve of the pure drug Dolutegravir was prepared in the concentration range from 2-10mcg/ml at the wavelength of 254nm by using 6.8 phosphate buffer solutions. A graph of absorbance Vs concentration was plotted which indicated in compliance to Beer's law in the concentration range. The calibration curve showed good

linearity and regression coefficient (r^2) value is 0.999, and intercept 0.005.

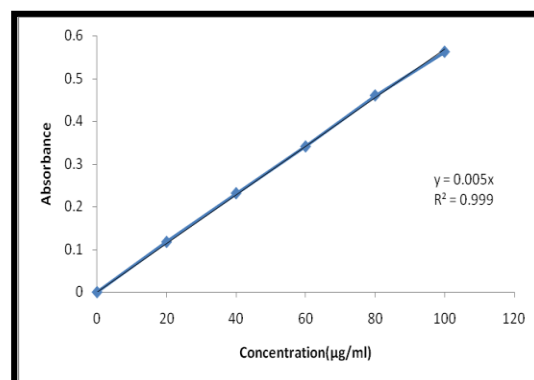


Figure 1: Calibration curve for Dolutegravir.

Pre-compression parameters**Angle of repose**

The values obtained for angle of repose of all the formulations are tabulated in Table 2, the values were found to be between 35.37° - 41.41° and it was observed to be within the pharmacopoeial limits.

Bulk density and Tapped density

Bulk density (0.366-0.410gm/cc) and Tapped density (0.517-0.590gm/cc) values were found to be within the pharmacopoeial limits indicating that the powder blend having the required flow for direct compression. The values for all the formulations are tabulated in Table 2.

Carr's compressibility index

Carr's index values ranges from (9.09-17.39%) which shows good flow property indicating that the powder blend have the required flow for direct compression. The values for all the formulations are tabulated in Table 2.

Hausner's ratio

Hausner's ratio values ranges from (1.312-1.439) which were found to be within the pharmacopoeial limits indicating that the powder blend have the required flow for direct compression. The values for all the formulation are tabulated in Table 2.

Table 2: Pre-compression parameters of Dolutegravir sustained release matrix tablets

Formulation	Bulk density(g/cc)	Tapped density (g/cc)	Hausner's ratio	Compressibility index (%)	Angle of repose (θ)
F1	0.386	0.551	1.428	13.04	35.37^0
F2	0.366	0.517	1.410	13.63	38.90^0
F3	0.395	0.558	1.412	9.09	38.86^0
F4	0.439	0.576	1.312	13.04	35.41^0
F5	0.397	0.571	1.438	13.63	41.41^0
F6	0.410	0.590	1.439	17.39	37.08^0

Post compression parameters**Weight variation**

All the tablets passed the weight variation test as the % variation was within the pharmacopoeial limits and weight of all the tablets was found to be uniform with least standard deviation. Drug content of all the batches were within the acceptable range which was shown in Table 3.

Hardness

Hardness was found to be within the range of (3.2-3.7) indicates that these tablets were within the pharmacopoeial limits shown in Table 3.

Friability

Friability values were found to be less than 1% and it was considered to be within the pharmacopoeial limits shown in Table 3.

Thickness

Thickness values were found to be within the range of (2.00-2.35) indicated that these were within the pharmacopoeial limits shown in Table 3.

Table 3: Post compression parameters of Dolutegravir sustained release tablets

Formula code	Hardness (kg/cm ²)	Thickness (mm)	Weight Variation (mg)	% Friability (% loss)	Assay (%)
F1	3.6	2.00	201.37	0.344	100
F2	3.4	2.10	200.24	0.160	100
F3	3.5	2.35	200.18	0.079	100
F4	3.5	2.12	200.01	0.184	99
F5	3.7	2.11	200.47	0.160	101
F6	3.2	2.20	219.99	0.129	99

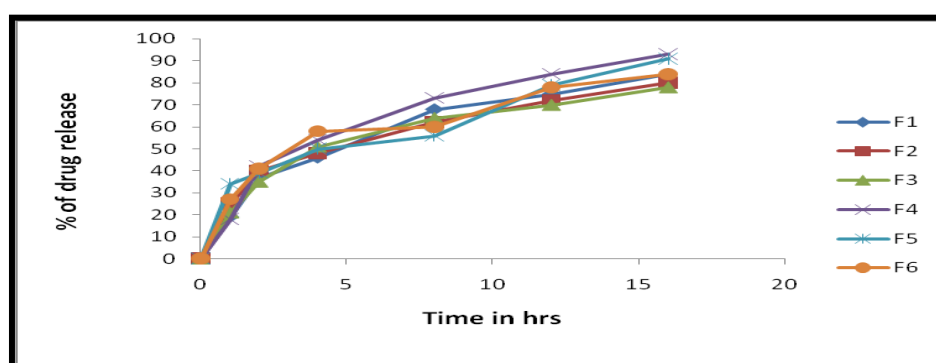
In vitro dissolution studies of Dolutegravir sustained release matrix tablets

In vitro dissolution studies were performed for sustained release tablets by using USP-II paddle dissolution

apparatus at 100 rpm in 900ml of phosphate buffer of pH 6.8 as a dissolution medium. The temperature was maintained at 37±0.5° C. The values obtained for different formulations are shown in Table 4.

Table 4: *In-vitro* drug release data of Dolutegravir formulations (F1 to F6)

Time in hours	% Cumulative Drug release						Pure drug
	F1	F2	F3	F4	F5	F6	
0	0	0	0	0	0	0	0
1	19.24	25.29	21.85	18.20	34.14	27.19	21.7
2	37.12	40.07	35.31	42.12	39.46	41.22	43.5
4	46.09	48.18	51.02	54.72	50.11	58.38	60.9
8	68.25	62.44	64.18	73.09	56.28	60.90	75.6
12	75.20	72.76	70.62	84.22	79.35	78.39	87.8
16	84.10	80.91	78.14	93.37	91.42	84.47	95.5

**Figure 2:** Drug release profile of sustained release tablets of Dolutegravir.

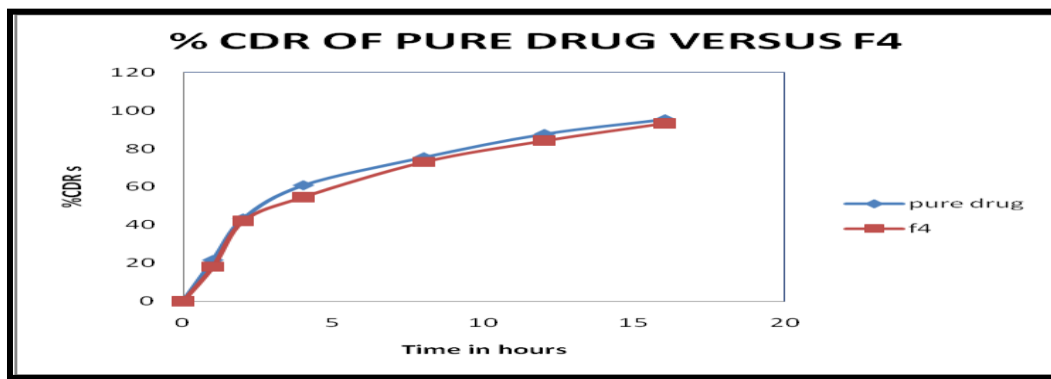


Figure 3: In vitro Drug Release Profile of Optimized Formulation (F4) Versus Pure Drug Dolutegravir

DISCUSSION

The pure drug Dolutegravir % drug release was found to be 95.5% at the end of 16th hour, when compared to pure

drug release the F4 formulation showed 93.37% drug release at the end of release time.

Table 6: Kinetic values obtained from different plots of formulation F4

Formulation	Zero order (R ²)	First order (R ²)	Higuchi (R ²)	Peppas (R ²)
F4	0.859	0.989	0.962	0.926

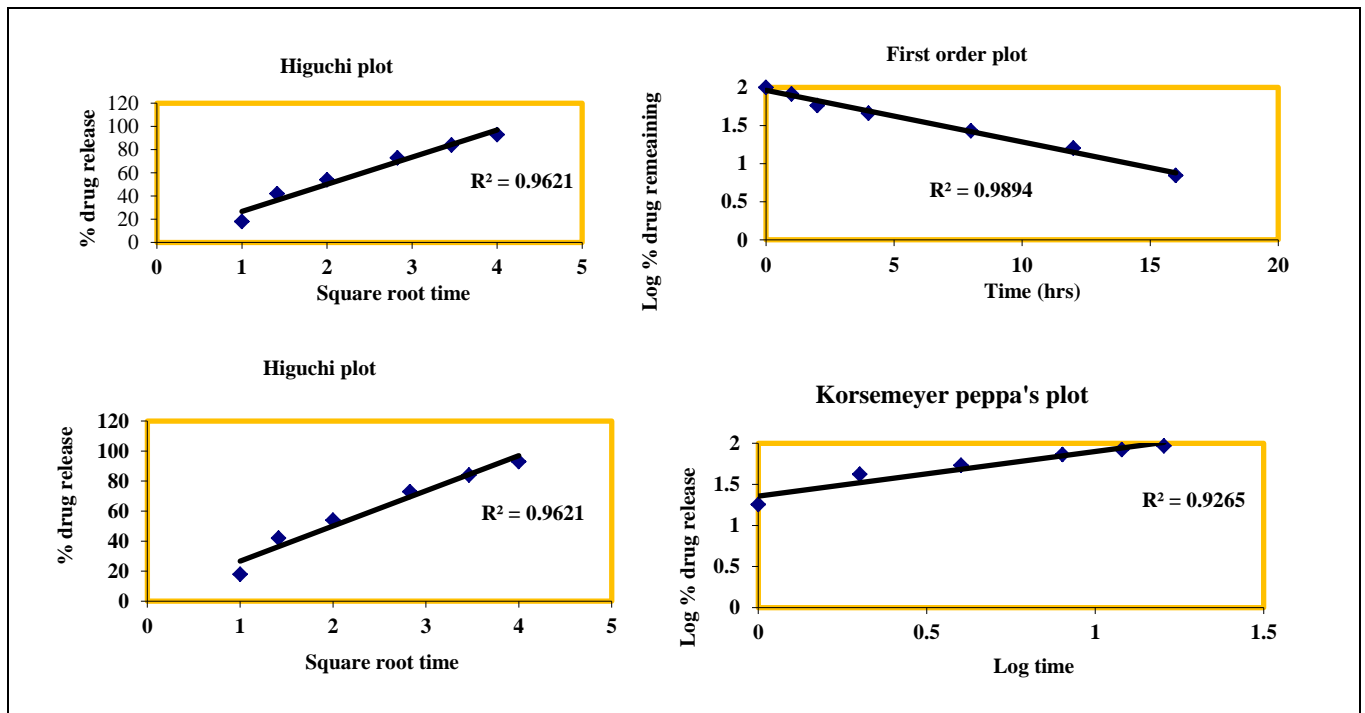


Figure 4: Dissolution kinetics studies of optimized formulation F4.

CONCLUSION

Dolutegravir was chosen as the model candidate for this study since it possess near ideal characteristics that a drug must have in formulating a sustained drug delivery system. It has high lipid solubility, effective in low plasma concentration and high degree of first pass metabolism. In this present study the tablets were prepared by using direct compression technique. All the formulations were evaluated for physical characteristics, pre-compression and post-compression, in-vitro dissolution studies. The pure drug Dolutegravir % drug release was found to be 95.5% at the end of 16th hour, when compared to pure

drug release the F4 formulation showed 93.37% drug release at the end of release time. Finally we have found that from all the formulations (F1-F6) only F4 formulation has successfully attained the sustained drug release for 16th hour.

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REFERENCES

1. Ansel's Pharmaceutical Dosage form and drug delivery system, eight editions, 227-260.
2. Aulton's Pharmaceutics, The design and manufacture of medicines Biopharmaceutics and Pharmacokinetics. A treatise, Second edition, Vallabhs prakashan, 315-384.
3. Lachmann L, Lieberman HA, Konig L. (1991); The theory and practice of Industrial pharmacy, Fourth edition, CBS Publishers and Distributors Pvt. Ltd; New Delhi: 467-488.
4. Bramhankar DM, jaiswal SB; Controlled release medications, In; BPPK Treatise, Vallabhs Prakashan; 1995, 3333- 375.
5. Chein Yie W (1992) ; Textbook of Novel drug delivery system, Second edition, Marcel Deker Inc; New York: 2.
6. K P Sampath Kumar, Debjit Bhomik, Shweta srivastava, Shravan paswan and A.S Dytta; Sustained release drug delivery system potential. The Pharma Innovation Vol 1 (2), 2012.
7. Sandy Griffith, Tamara Newman, Carlos Brites; Dolutegravir versus raltegravir in antiretroviral-experienced, integrase – inhibitors- naïve adults with HIV; Vol382, August24, 2013, 700-708.
8. Jose Vicente Fernande- Montero, Pablo Barrerio, Pablo Labarg; Dolutegravir, abacavir and lamivudine as HIV therapy, 15(7), 2014, 1051-1057.
9. Korsemeyer RW, Gurny R, Doelker E, Buri P. Peppas NA ; Mechanism of solute release from porous hydrophilic polymers; Int J Pharm, 15, 1983, 25-35.
10. Avinash H. Hosmani, Yogesh S. Thorat, Kature ; Carbopol and its pharmaceutical significance, Research gate, January 2006.

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