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DEVELOPMENTAND EVALUATION OF FAST DISINTEGRATING TABLETS OF DOLUTEGRAVIR SODIUM

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ABSTRACT

Dolutegravir Sodium, a drug used to treat HIV infection, is the primary focus of the current study, as is its development and assessment in rapid disintegrating tablets (HIV). Using the physical approach and the kneading method, we formulated Dolutegravir Sodium as a solid dispersion in an effort to improve its solubility and dissolution rate. The adjusted solid dispersions were then used in the direct compression procedure to create orodispersable tablets with the addition of superdisintegrants such sodium starch glycolate and crospovidone. Dolutegravir Sodium, Sodium Starch Glycolate, and Crospovidone were all subjected to FTIR examinations to characterize their respective purity levels, and the resulting F6 formulation was found to have the best overall profile. The studies demonstrated that there was no interaction between the medication and the excipient. Dolutegravir Sodium tablets made utilising optimal solid dispersions (DK2) with PEG 6000 & Crospovidone as superdisintegrant were shown to be ideal for quick dispersion and for enhancing dissolving rate, which in turn boosts bioavailability, according to the study.

Keywords: Solid dispersions, fast disintegrating tablets, Dolutegravir Sodium and crospovidone.

INTRODUCTION

Fast disintegrating tablets are unit solid dose forms that, unlike traditional tablets, can be quickly dissolved in the mouth in the presence of saliva without the need for chewing or crushing[1-4]. Dolutegravir sodium is an antiretroviral drug that blocks the viral replication process by preventing the enzyme integrate, which is required for HIV replication. Dolutegravir falls within Biopharmaceutical Classification Scheme's Class II, which includes compounds that are water-insoluble, lipophilic, and extremely permeable. Therefore, solid dispersion technology can be used to increase apparent solubility in water, hence enhancing bioavailability [5-9].

The drug's solubility is a crucial physicochemical variable that influences both its bioavailability and its therapeutic efficacy. Now, researchers are trying to find ways to improve the drug's solubility in water so that it may be taken orally. Of these methods, preparing solid dispersions is among the most common. A group of solid products known as "solid dispersions" consist of a hydrophilic matrix and a hydrophobic medication[10, 12].

As part of the current study, Dolutegravir Sodium was formulated into fast-dissolving tablets via a direct compression method employing sodium starch glycolate and crospovidone as superdisintegrants in order to improve its solubility and dissolution rate.

MATERIALS AND METHODS

Free samples of PEG 6000 and dolutegravir sodium were provided by Aurbindo Pharma Ltd. in Hyderabad. Crospovidone and Sodium Starch Glycolate were purchased from a commercial supplier in Mumbai called Qualigens Fine Chemicals. The commercial magnesium stearate and talc used in this experiment came from yarrow Chem, Ltd. in Mumbai.

Dolutegravir Sodium saturated solubility studies

Dolutegravir Sodium solubility investigations were performed in a wide range of dissolving media. The medication was weighed out in increments of 10mg and then transferred to conical flasks containing 10ml of different dissolution media, such as water, 0.1N HCl at 6.8 pH, and a phosphate buffer at 7.2 pH, before being sealed. To incubate the conical flasks for 24 hours, we used a REMI incubator shaker set to 50 rpm at 37 1 °C. It was necessary to remove the conical flasks from the incubator shaker in order to filter the samples in whatman filter paper. To determine absorbance at 258 nm, we diluted the filtered-out solution with the right kind of dissolution media and used the matching dissolution media as blank solutions. The solubilities of Dolutegravir Sodium in various dissolution media were given in table 1.

Methods of preparation

Dolutegravir Sodium solid dispersions in PEG 6000 were prepared using physical mixing and the kneading process. Solid dispersions were given in table 2.

Physical Mixing

A measured amount of the drug and PEG 6000 were sieved through No. 80, collected, and then added to a clean, dry glass mortar for 5 minutes of trituration before being transferred to a suitable glass container, sealed hermetically, and stored at room temperature.

Kneading method

Triturating the drug and PEG 6000 separately in separate mortars yielded a fine powder in the correct quantities. The medication was placed in a mortar and then combined with the PEG 6000 and the requisite amount of water under high pressure for 2 minutes. The mixes were sieved through a No. 60 mesh screen, collected, and then placed in a sealed amber jar.

Evaluation of solid dispersions

Physical properties, including angle of repose, carr's index, average particle size, and drug content, were assessed, and found to be well within legal limits. The obtained data was showed in table 3.

Estimation of Dolutegravir Sodium solid dispersions

A few ml of methanol were added to the solid dolutegravir sodium dispersions that had been transferred to a 100 ml volumetric flask, and the mixture was agitated at regular intervals for 30 minutes. The final volume was made up by adding 6.8 pH Phosphate buffer to the flask. 10 ml of the solution were removed and centrifuged from the aforementioned flask. It was decided to collect and filter the supernatant solution. When the filtrate was diluted with a 6.8 pH Phosphate buffer, the absorbance at 258 nm was measured. Each formulation was tested six times (N=6).The estimation of Dolutegravir Sodium from all the formulations were showed in table 3

Dissolution studies on Dolutegravir Sodium solid dispersions

Solids dispersions were subjected to dissolution studies using USP paddle Type II apparatus with 900ml of dissolution medium containing 6.8 pH phosphate buffer. The samples were drawn up to 45 minutes. Samples were taken and suitably diluted with 6.8 pH phosphate buffer and the amount of dissolved drug was determined by ELICO SL-210 double beam spectrophotometer at 258 nm and simultaneously determined for the % cumulative drug released. The dissolution studies for all the formulation were performed in triplicate. The dissolution profiles for all the solid dispersions were shown in figures 1 . The release rate constants, T_{50} and T_{90}, were given in the table 4.

CHARACTERIZATION OF FAST DISINTEGRATING TABLETS

FTIR studies can be performed on Dolutegravir Sodium, Sodium starch glycolate and crospovidone and (F6) optimized formulations.

Fourier transforms infrared spectroscopy (FTIR)

The FTIR spectra of Dolutegravir Sodium, Sodium starch Glycolate, crospovidone and (F6) optimized formulations were obtained using Brucker FTIR spectrophotometer. The FTIR spectra were shown in Figures 2 to 5.

PREPARATION OF TABLETS WITH SOLID DISPERSIONS

Fast disintegrating tablets of Dolutegravir Sodium were created using the direct compression process and the optimised solid dispersions (DK2). The tablets were manufactured using an optimised solid dispersion (DK2), sodium starch glycolate, crospovidone, microcrystalline cellulose, talc, and magnesium stearate in the roles of diluent, glidant, and lubricant, respectively. A fixed ratio of medication to carrier was used, and the concentration of superdisintegrants was altered. Microcrystalline cellulose was used throughout all formulations to keep pill weights consistent. Table 5 displays the ingredients used in various tablet formulations.

After being separately weighed, the ingredients are blended for 15 minutes in a double cone blender, after each being passed through a sieve numbered 60. Tablets were made by directly compressing the powder combination using an ELITE 10 station micro press after lubrication with talc and magnesium stearate was applied. The Compositions of various Fast disintegrating tablets were given in table 5 .

Evaluation of physical parameters for Dolutegravir Sodium orodispersable tablets

Physical parameters such as weight uniformity, hardness, friability and drug content were evaluated for compressed tablets .The results were shown in table 6.

Dissolution studies on Dolutegravir Sodium Fast disintegrating tablets

All tablet formulations were subjected to dissolution tests in an 8-stage device using 900 ml of 6.8 pH phosphate buffer as the medium, with the paddles spinning at 50 rpm and the temperature held constant at 37 0.5 0C. For these tests, the volume of dissolving medium was kept constant by periodically taking samples and replacing them with a similar volume. The formulations' drug content was determined using a UV spectrophotometer set to 258 nm. The dissolution profiles of all tablet formulations were shown in figures 6**.** The release rate constants, T_{50} and T_{90}, were given in the table7.

ACCELERATED STABILITY STUDIES

Accelerated stability experiments were conducted on tablet formulations that performed well in vivo. The physical features of tablets and the chemical stability of medications contained in Fast dissolving tablets were studied. Accelerated stability investigations were performed on tablet formulations like F6. The above said formulations were kept in Petri dishes after preparation and stored in thermostated oven at a temperature and relative humidity of 25 ± 2^0c 60 ± 5% RH for 6 months and 40 ± 2^0c 75 ± 5% RH for 3 months. Then the samples of each type of formulations were evaluated for the earlier mentioned physical parameters. The dissolution profiles of optimized Dolutegravir Sodium formulations before and after stability studies were shown in Figure

RESULTS AND DISCUSSION

Water, 0.1N HCl, 6.8pH, and 7.2 pH Phosphate buffer were used in the solubility tests of sodium dolutegravir. According to the results of the present study, Phosphate buffer pH 6.8 was chosen as the dissolution medium for Dolutegravir Sodium because it shows the highest solubility in this buffer. The solubility values were shown in Table 1.

In order to create the Dolutegravir Sodium solid dispersions, the traditional methods of mixing and kneading were used. Modifying the PEG 6000 carrier concentration yielded these. The various compositions of solid dispersions prepared by various methods were shown in table 2. All dispersions were quite stable and showed excellent characteristics.

The angle of repose, Carr's index, average particle size and drug content values obtained for various solid dispersions were in the range of 23.45° – 25.88, 13.22 – 14.11%, 181± 4 to 155±2µm and.20.43 ±0.4 – 25.00± 0.1 mg. Thus all the solid dispersions were showed to be stable and suitable for preparation of tablets using direct compression technique. The obtained physical parameters were showed in table 3.

Dolutegravir Sodium solid dispersions were produced, and dissolving investigations were performed using a USP Type II dissolution apparatus. All solid dispersions were tested in triplicate for these analyses. When compared to pure Dolutegravir Sodium, the solubility rates of several solid dispersions of the drug were studied. All the solid dispersions were shown to have faster rates of solubility and dissolution.

Solid dispersions of Dolutegravir Sodium were prepared physical mixing and kneading method Among this solid dispersions prepared by Kneading method method were found to release the drug from 90.55±1.34% to 99.11±1.66% when compared to other method. The dissolution profiles of pure drug and prepared Dolutegravir Sodium dispersions were shown in figure no 9.

The T_{50}, T_{90} values are 6 min and 15 min for optimized DK2 solid dispersions respectively. The R^2 values attained for all the Solid dispersions of Dolutegravir Sodium were in the range of 0.944 – 0.999. Among the various methods used, Kneading method was showed complex formation between the drug and carrier. The order of rate of dissolution increased for various solid dispersions are kneading Method > Physical Mixing Method. Based on the *invitro* studies DK2 solid dispersions prepared by kneading method containing drug to carrier ratio of 1:2 was showed high dissolution rate, hence this optimized formulation DK2 was selected for preparation of FDTS by using various proportions superdisintegrants such as croscarmellose Sodium starch glycolate and

crospovidone were taken at 2, 4, 8, and 12% W/W of the tablet formulation and were prepared by direct compression technique. The compositions of Dolutegravir Sodium tablet formulations were given in table 5.

Later the FDTS were evaluated for physical parameters such as weight uniformity, hardness, friability, wetting time, dispersion test and drug content for finding the stability of tablets. These studies shown that total formulations were in the IP specified limits. The tablets hardness and weight uniformity of all batches were in the range of 3.5± 0.5kg/cm^2 and 199± 1.0 to 200± 3.0 mg. The friability loss and wetting time of different batches of tablets was given in the range of 0.18-0.20%. and 0.20 ±1.5-34.5±2.5sec. The drug content for all the batches of tablets were in the range of 23.22 to 24.68±0. All the tablet formulations were stable and complied I.P limits. The results were given in table no 6.

The prepared Dolutegravir Sodium Fast disintegrating tablets were subjected to USP Type II dissolution apparatus containing 900 ml of Phosphate buffer pH 6.8 maintaining at a temperature 37 ± 0.5^0 C with a paddle speed at 50 rpm. These studies shown that all the tablet formulations prepared by using various superdisintegrants were found to exhibit high solubility and dissolution rate than compared to tablets prepared without superdisintegrants. The dissolution profiles of Dolutegravir Sodium Fast disintegrating tablets were shown in figure 10.

The T_{50}, and T_{90} of F6 are 4 min, 9 min. The R^2 valves obtained for all the Dolutegravir Sodium Fast disintegrating tablets were linear in the range of 0.955 – 0.990. Fast disintegrating tablets of Dolutegravir Sodium prepared with 2% concentration of Crospovidone were showed high dissolution rate when compared to other tablet formulation, due to the increased wettability, and faster release of drug.

Fourier transform infrared spectral studies were used to know the interactions between drug with the excipients in the FDTS. The IR Spectra of drug Dolutegravir Sodium, SSG, CP and F6 optimized formulation were shown in figures 1 to 4. The FTIR interpretation shown that there were no interactions between drug and excipient used in the formulation.

The optimized formulation F6 containing Dolutegravir Sodium was conducted to accelerated stability studies. The results of these studies were shown in figures no 11. The results indicated that there were no physical changes observed in the tablets after storage. Based on these stability studies it was concluded that F6 FDTs tablet formulation were found to be stable.

CONCLUSION

Dolutegravir Sodium is only moderately soluble in water, however this work shows that solid dispersions prepared with PEG 6000 as carrier can significantly speed up the drug's dissolving time. Among the several techniques tried, the solid dispersions made by the Kneading method with a drug to carrier ratio of 1:2 show the highest rate of dissolution. Dolutegravir Sodium FDTS created by using several superdisintegrants also displays the quick drug release when compared with other formulations. Conclusions from the study suggest that solid dispersions of Dolutegravir Sodium including PEG 6000 and crospovidone as a superdisintegrant are optimal for quick dissolving and enhance bioavailability.

Table: 1 Saturation Solubility Studies of Dolutegravir Sodium in Different Dissolution Media

S. No	Dissolution Medium	Amount of Dolutegravir Sodium Soluble (µg/ml)
1	Distilled Water	214.12
2	6.8 pH phosphate buffer	467.54
3	7.2 pH phosphate buffer	339.92
4	0.1N HCl	298.33

Table 2: Compositions of various Dolutegravir Sodium Solid Dispersions

Method	Solid dispersion Code	Composition	Ratio	Concentration
Physical Mixing Method	DP1	D+ PEG 6000	1:1	25:25
	DP2	D+ PEG 6000	1:2	25:50
Kneading Method	DK1	D+ PEG 6000	1:1	25:25
	DK2	D+ PEG 6000	1:2	25:50

Table 3: Physical Parameters of Dolutegravir Sodium solid dispersions

S.NO	Solid Dispersion	Angle of Repose(o)	Carr's index (%)	Particle size (µm)	Drug content (mg)
1	DP1	23.45	13.22	181±5	20.43±0.1
2	DP2	24.58	14.45	176±4	23.01±0.3
3	DK1	23.11	13.90	166±1	22.26±0.2
4	DK2	25.88	14.11	155±6	25.68±0.3

Table 4: *Invitro* Dissolution Parameters of Dolutegravir Sodium Solid Dispersions

Formulation	T_{50} (Mins)	T_{90} (Mins)	K (Min^{-1})	R^2
DP1	16	45	0.0011	0.944
DP2	8	18	0.0013	0.969
DK1	4	24	0.0211	0.984
DK2	3	17	0.0377	0.999

Table 5: Compositions of various Dolutegravir Sodium Fast disintegrating tablets

Ingredients (mg/tab)	Formulations					
	D1	D2	D3	D4	D5	D6
Drug + carrier equivalent to 75 mg (1:2)	75	75	75	75	75	75
Sodium starch Glycolate (SSG)	4	8	12	-	-	-
Crospovidone (CP)	-	-	-	4	8	12
Avicel pH-102	111	107	105	111	107	105
Stevia powder (mg)	6	6	6	6	6	6
Talc (mg)	2	2	2	2	2	2
Magnesium stearate (mg)	2	2	2	2	2	2
Total Weight of Tablets (mg)	200	200	200	200	200	200

Table 6: Physical parameters of Dolutegravir Sodium Fast disintegrating tablets

Formulation	Weight Uniformity (mg)	Hardness (kg/cm^2)	Friability (%)	Drug Content (mg/Tablet)
D1	199± 1.0	3.3± 0.1	0.18	23.22±0.5
D2	197±1.0	3.4± 0.3	0.19	24.13±0.5
D3	198± 3.0	3.5± 0.3	0.16	22.35±0.7
D4	197± 1.0	3.4± 0.1	0.20	24.57±0.1
D5	199± 3.0	3.4± 0.2	0.17	23.87±0.2
D6	200± 3.0	3.5± 0.5	0.20	24.68±0.4

Table 7: *Invitro* dissolution parameters of Dolutegravir Sodium Fast disintegrating tablets

Formulation	T_{50} (Mins)	T_{90} (Mins)	K (Min^{-1})	R^2
F1	21	> 30	0.016	0.977
F2	16	> 30	0.022	0.956
F3	9	29.5	0.048	0.980
F4	10	29.5	0.090	0.966
F5	14	> 30	0.024	0.951
F6	4	11.5	0.311	0.989

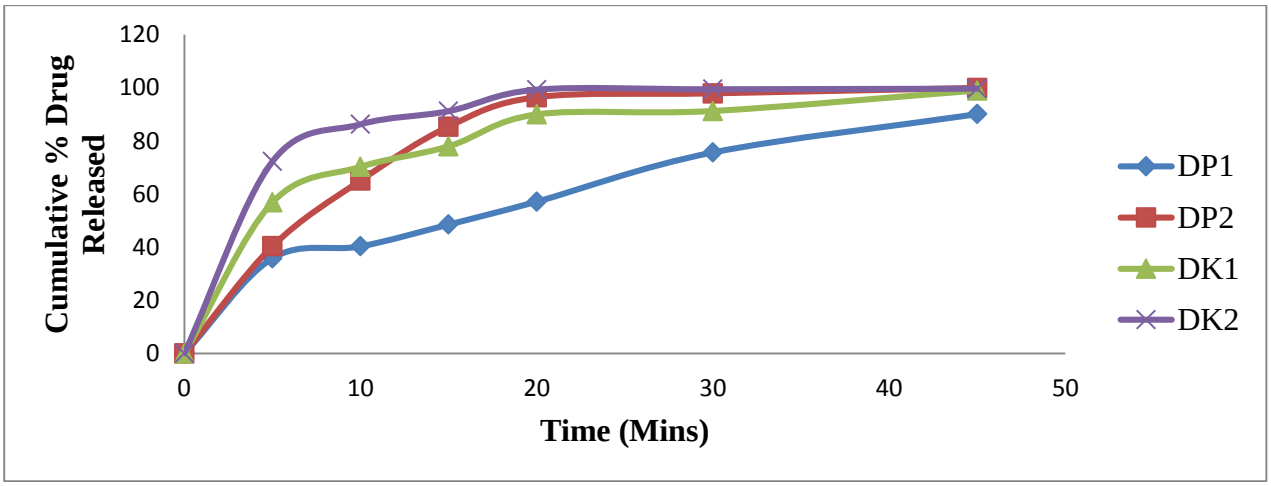

Fig. 1: Drug Release Profiles of Dolutegravir Sodium Solid Dispersions

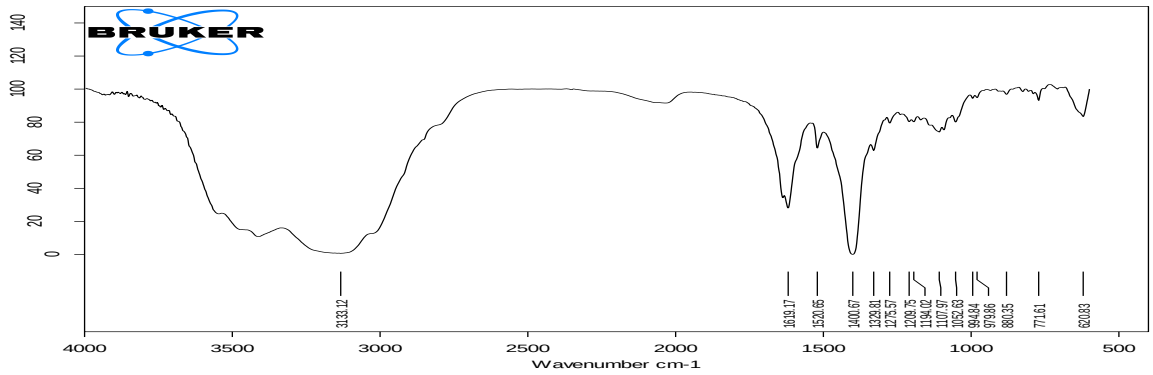

Fig. 2: FTIR Spectra of Dolutegravir Sodium Pure drug

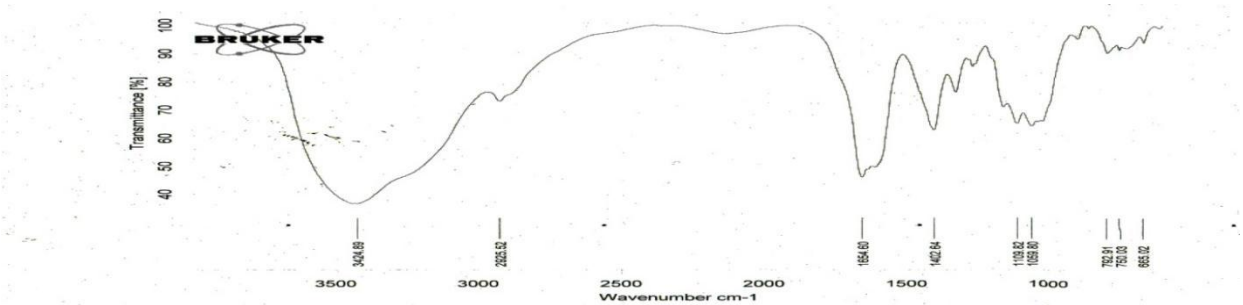

Fig. 3: FTIR Spectra of Sodium Starch Glycolate

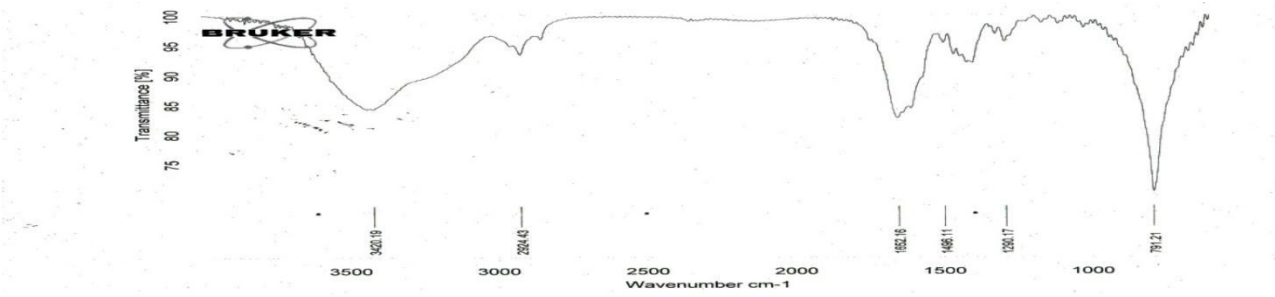

Fig. 4: FTIR Spectra of Crospovidone

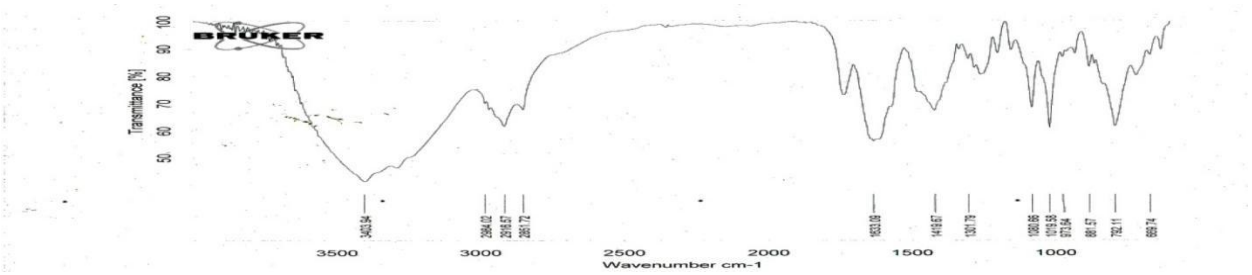

Fig. 5: FTIR Spectrum of Optimized Formulation D6

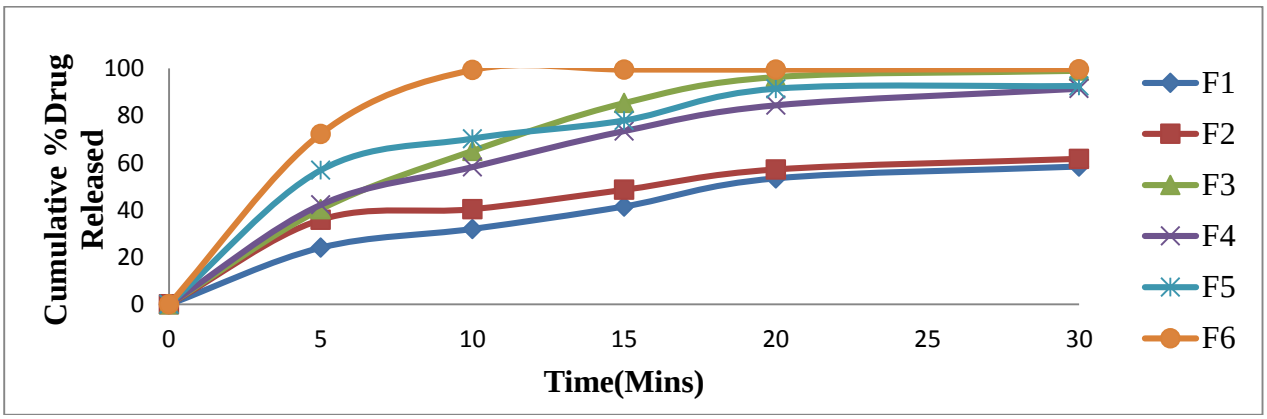

Fig. 6: Dissolution Profiles of Dolutegravir Sodium Fast disintegrating tablets

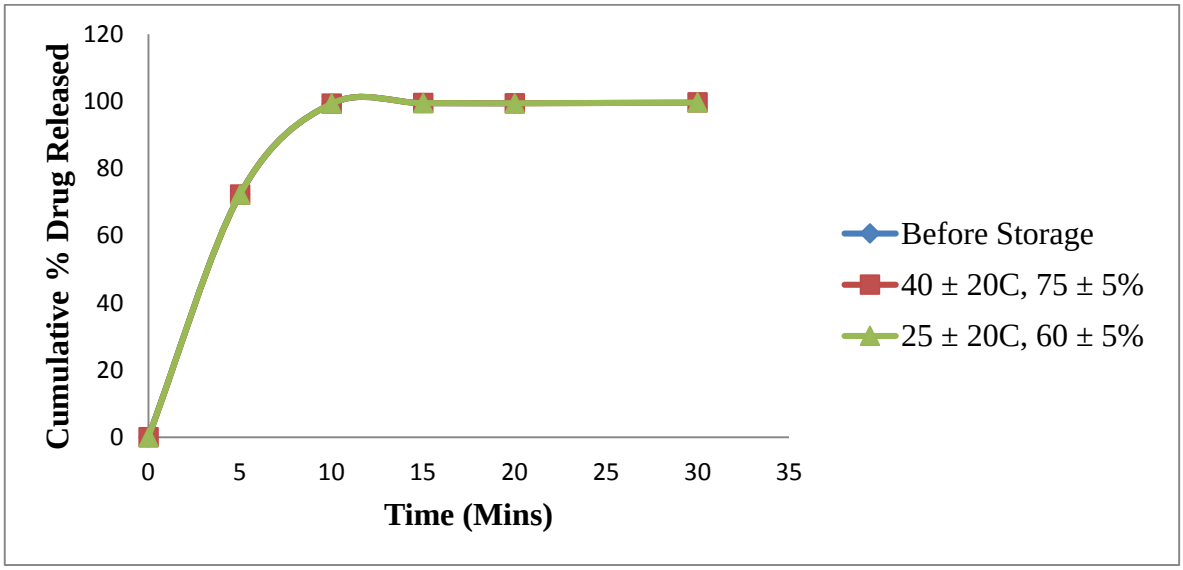

Fig. 7: Dissolution profiles of optimized Dolutegravir Sodium formulations before and after stability studies

REFERENCES

1. Tejvir Kaur P. a Mouth dissolving tablets. International journal of current pharmaceutical research. 2003;3:42-50.
2. Yang S, Jeong SH, Kimura S and Park K. Orally fast disintegrating tablets. Crit Rev Ther Dreg Carrier Syst. 2004;21:433–446.
3. Clotet B, Feinberg J, van Lunzen J, Khuong-Josses MA, Antinori A and Dumitru I. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. Lancet 2014;383:2222-31.

4. Elzi L, Erb S, Furrer H, Cavassini M, Calmy A and Vernazza P. Adverse events of raltegravir and dolutegravir. AIDS. 2017;31:1853-8. 5
5. Raffi F, Rachlis A, Stellbrink HJ, Hardy WD, Torti C and Orkin C. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, doubleblind, non-inferiority SPRING-2 study. Lancet. 2013;381:735-43.
6. Chauhan V, Kumar K and Teotia D. Fast dissolving tablets: A promising approach for drug delivery. Univ J Pharm Res. 2017;2:58-4.
7. Fateatun N, Jiaur RM, Sultan MM, Sorifa A, Aminul IT and Ahmed M. Physicochemical properties of flour and extraction of starch from Jack Fruit seed. Int J Nut Food Sci. 2014;3: 347-54.
8. Menaka T, Nagaraja G, Yogesh DB, Sunil Kumar US and Prakash L. Physicochemical properties of flour and isolated starch from Jackfruit seeds (Artocarpus Heterophyllus). Res J Pharm Sci. 2011;1:14-8.
9. Vidyadhara S, Sasidhar RL, Lakshmi HD, Vijetha P and Vijetha K. Studies on jack fruit seed starch as a novel natural superdisintegrant for the design and evaluation of Irbesartan fast dissolving tablets. Int Med Res. 2017; 6: 280-91.
10. Okunlola A and Odeku OA. Comparative evaluation of starches obtained from Dioscorea species as intragranular tablet disintegrants. J Drug Del Sci Technol. 2008;18:445-7
11. Hassan-Alin M, Andersson T, Bredgerg E and Röhss K. Eur J Clin Pharmacol. 2000;56:665–670.
12. Balakrishna T, Vidyadhara S, Murthy TEGK, Sasidhar RLC and Vikas S. Formulation and evaluation of lansoprazole orodispersable tablets using novel excipients. Der Pharmacia Lettre. 2016;8(17):73-82.