ijlpr 2021; doi 10.22376/ijpbs/lpr.2021.11.5.P51-59

International Journal of Life science and Pharma Research

ISSN 2250-0480

Research Article

Pharmaceutics for effective drug dosage

Formulation and Optimization of Dolutegravir Fast Dissolving Tablets Using Various Solubility Enhancement Methods

Martha Srinivas [*1] and Dr. Anoop singh[2]

[1]*ResearchScholar, Department of Pharmaceutics, Bhagwant University, ajmer, Rajastan, 305004.*

[1]*Faculty , Department of Pharmaceutics, Joginpally B R Pharmacy College, Hyderabad.500075.*

[2]*ResearchSupervisor, Department of Pharmaceutics, Bhagwant University, ajmer, Rajastan, 305004.*

Abstract: Dolutegravir is a HIV-1 antiviral agent to control HIV/AIDS. In the present study Dolutegravir solid dispersion has been subjected to improve the solubility and dissolution rate performance by formulating as fast dissolving tablets, in which PEG 6000 and Poloxamer 407 were used as polymers. Solid dispersions of Dolutegravir were prepared with different carriers in different ratios of drug and carriers such as PEG 6000 and Poloxamer 407 (1:1, 1:2 and 1:3) by solvent evaporation and fusion method. The pre-compression and post-evaluation parameters were studied and the results were shown. All the results were within acceptable IP limits Finally, by comparing all the dissolution profile of solid dispersions , formulation F3 containing Dolutegravir + PEG 6000 (1:3) showed better results by solvent evaporation method at the end of 60 min with maximum drug release, hence it is selected as the best formulation. From the obtained optimized solid dispersion formulation, the fast dissolving tablets were prepared by using different concentrations of various super disintegrants. The *in-vitro* drug releases of the formulated Dolutegravir tablets were performed using a 6.8 pH Phosphate buffer as dissolution medium. The optimized DF3 formulation containing Sodium starch glycolate (SSG) (6% w/w) as super disintegrant, and it showed 98.04±1.9 % percentage drug release at 25 min. Characterization in solid-state were done by analytical methods such as UV-Visible, FT-IR studies. The optimized formulation followed first order release kinetics.

Keywords: Dolutegravir, PEG 6000, Poloxamer 407, Super disintegrants, Sodium starch glycolate, Solvent evaporation, FT-IR.

***Corresponding Author**

Martha Srinivas , ResearchScholar, Department of Pharmaceutics, Bhagwant University, ajmer, Rajastan, 305004.

Received On 23 April, 2021
Revised On 16 September, 2021
Accepted On 17 September, 2021
Published On 22 September, 2021

Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

Citation Martha Srinivas , Dr. Anoop singh , Formulation and Optimization of Dolutegravir Fast Dissolving Tablets Using Various Solubility Enhancement Methods.(2021).Int. J. Life Sci. Pharma Res.11(5), 51-59 http://dx.doi.org/10.22376/ijpbs/lpr.2021.11.5.P51-59

1. INTRODUCTION

The oral bioavailability of a medicinal substance is based on its solubility and/or rate of dissolution and may be the rate of bioavailability decides the treatment operation. Efforts are also needed to improve drug dissolution. The methods used for improving the dissolution rate includes the formation of salt, micronization, and adding solvents or active agents to the surface. Solid dispersion is one of the process which include dispersion in a solid internal carrier or matrix prepared by a melting process, dissolution by a solvent system, or a melting solvent method of one or more active ingredients. As an effective method to improve the properties of dissolution and the bioavailability of poor water-solution drugs, solid dispersions have been historically used since 1961, and a number of researchers have investigated poorly water-soluble Solid Dispersions (SDs) of drugs with different pharmacologically inert carriers are commercially useful to improve the dissolution and oral absorption of poorly water-soluble drugs.[1]Dolutegravir[2] is an important recent addition to the expanding list of antiretroviral drugs for treating HIV-1 infection in adults and adolescents. Dolutegravir (Active pharmaceutical ingredient) 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.[3]The average terminal half-life is approximately 14 hours and steady state is achieved after approximately 5 days with repeated dosing. Dolutegravir (DTG) is a medication in the BCS Class-II category, as it has low solubility and high permeability. It must be improved in terms of solubility, dissolving rate, and oral bioavailability, hence solid dispersion mechanisms are the recent trend technologies for poorly soluble drugs as BCS Class II and BCS Class IV drugs to improve the solubility and rate of dissolution.[4-5] Solid dispersions (SDs) traditionally have been used for improving the dissolution rate properties and bioavailability of poorly water-soluble drugs.[6]Fast or immediate drug dissolution from solid dispersions has been observed due to increased wettability, improved dispersibility of drug particles, and the existence of the drug in amorphous form with improved solubility, and absence of aggregation of drug particles. Literature study results showed that the solvent evaporation method has been used for the preparation of solid dispersions for dissolution improvement. Earlier studies shown that solid dispersion systems increased the drug dissolution due to improved solubility, wettability, and dispersibility using hydrophilic carriers.[7] This method requires a minimal amount of solvent in dissolving the drug. The dissolution of a medicament depends upon its release from the dosage form and subsequent mixing into physiological fluids. It has been estimated that nearly 35-40 % of the drugs effect from poor aqueous solubility, thereby affecting their absorption from the gastrointestinal tract, which leads to poor oral bioavailability, high intra-, and inter-subject variability, enhance in dose, reduction in therapeutic efficiency, and finally failure in formulation development. Solid dispersions (SDs) are defined as the dispersion of one or more medicaments in an active hydrophilic carrier or matrix in a solid-state, and are prepared by the fusion, solvent-fusion method.[8] This technique enables decreasing particle size to a nearly molecular level, offers a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems of poorly water-soluble drugs that are cost-effective and significantly reduced in dosage. It has been widely demonstrated that a hydrophilic carrier dissolves rapidly, exposing the drug particles to the dissolution medium as fine particles facilitating fast dissolution and absorption. The mechanisms for enhanced dissolution rate may include reduction of crystallite size, solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability, and dispersibility of a drug from the dispersion, dissolution of the drug in the hydrophilic carrier, or conversion of the drug to an amorphous state.[9]The presented research study is aimed to develop fast disintegrating solid dispersion solid unit dosage forms of Dolutegravir using different water soluble polymers and super disintegrants.

2. MATERIALS AND METHODS

Dolutegravir (DTG) was purchased from B.M.R. Chemicals, Hyderabad, PEG 6000, Poloxamer 407 and Methanol were purchased from SD Fine Chemicals, Remaining Excipients Lycoat, Sodium starch glycolate, Lactose, Magnesium stearate, and talc were purchased from Oxford Laboratories, Mumbai. All the used ingredients and chemicals were analytical grades.

2.1 Method of Preparation of Solid Dispersions of Dolutegravir[9-10]

Dolutegravir Solid dispersions (SD's) were prepared by various methods such as solvent evaporation and fusion method. In this connection, it is worth-mentioning that polymers like PEG 6000 and Poloxamer 407 were used, shown in Table 1.

2.1.1 Solvent evaporation

In solvent evaporation method, the drug and carriers were i.e Dolutegravir, PEG 6000 mixed in 1:1, 1:2, and 1:3 ratios using methanol, Similarly the drug Dolutegravir and carrier Poloxamer 407 mixed with 1:1,1:2 and 1:3 ratios using solvents as methanol. The solvent was removed by evaporation under reduced pressure. The mass was pulverized and passed through sieve # 60 and now the obtained product was collected.

2.1.2 Fusion method

Carriers PEG 6000 and Poloxamer 407 were taken separately and heated to a molten state at 60 °C and to this mass, the weighed amount of the drug was added with continuous stirring with a glass rod until dissolved. The different ratio of drug was added and finally, solid dispersion (SD) was obtained in 1:1, 1:2, and 1:3 w/w ratios of drug to carriers showed in Table 1. Solidification was allowed to occur at room temperature. The product was stored in desiccators for 24 h and then pulverized using a porcelain mortar and pestle. The pulverized powder was passed through the #60 sieve to get a uniform particle size.[10-11]

Table 1: Solid dispersion codes of various methods and ratios of Drug: Polymers

SD Code	Solid Dispersion Method	Drug : Polymer	Drug Polymer ratios
F1,F2 & F3	Solvent evaporation method	Dolutegravir : PEG 6000	1:1,1:2 and 1:3
F4,F5 & F6	Solvent evaporation method	Dolutegravir : Poloxamer 407	1:1, 1:2 and 1:3
FF1, FF2 & FF3	Fusion method	Dolutegravir : PEG 6000	1:1, 1:2 and 1:3
FF4, FF5 & FF6	Fusion method	Dolutegravir : Poloxamer407	1:1, 1:2 and 1:3

2.2 *In vitro dissolution study of solid dispersions*

The prepared solid dispersions containing 50 mg weight equivalent of Dolutegravir was placed in a capsule and subjected to *in vitro* dissolution. The dissolution test was carried out using USP type I basket method [apparatus I]. The stirring rate was 50 rpm, 6.8 pH Phosphate buffer was used as a dissolution medium and this medium was maintained at 37±0.5°C. 5 ml of samples were withdrawn at regular intervals of time and replaced with same quantity of fresh dissolution medium at each time, The collected samples were analyzed using UV -Visible spectrophometry at 260 nm.[12]

Table 2: *Invitro* drug release studies for formulations (F1-F6)

Time (Min)	Percentage drug release					
	Dolutegravir : PEG 6000			Dolutegravir: Poloxamer 407		
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	29.66±0.5	38.21±0.9	45.75±2.5	26.65±1.6	30.17±0.8	39.72±1.8
10	43.74±1.2	49.78±1.8	59.33±2.0	35.19±1.9	43.74±1.3	56.31±2.1
15	49.78±1.9	61.84±2.1	68.38±3.2	45.25±2.1	56.31±2.1	63.85±2.4
30	61.84±2.1	73.41±2.4	83.46±2.7	56.31±2.4	65.86±3.2	79.44±1.5
45	75.42±0.9	81.45±1.6	90.50±1.9	63.35±3.1	78.43±2.4	86.48±2.9
60	86.48±1.4	91.51±1.4	98.54±1.5	73.41±2.3	86.48±2.6	95.53±1.2

Values were mean± SD; (n=3), P<0.0001

3. STATISTICAL ANALYSIS OF DATA

The values so obtained were reported in Table 2,using Graph Pad Prism software, version 9.1.2 (226), the prepared solid dispersions dissolutions were F1- F6 used for analysis of comparison studies, The obtained data were reported as mean ± standard deviation (SD), P value is <0.0001 was considered as significant. *Invitro* drug release of Dolutegravir solid dispersions[13] by solvent evaporation method with PEG 6000 and Poloxamer 407 in various ratios were observed, which shows at the end of 60 min, F3 formulation percent drug releases 98.54±1.5%,showed in Table 2.

Table 3: *In vitro* drug release studies for formulations (FF1-FF6)

Time (Min)	Percentage drug release					
	Dolutegravir : PEG 6000			Dolutegravir: Poloxamer 407		
	FF1	FF2	FF3	FF4	FF5	FF6
0	0	0	0	0	0	0
5	32.68±1.1	36.20±0.9	40.22±1.3	22.63±0.9	29.16±1.1	36.20±0.4
10	43.24±1.4	46.76±1.1	55.31±1.4	35.19±1.6	40.22±1.9	49.27±0.6
15	50.28±2.1	52.79±2.1	65.36±2.2	42.74±1.9	49.27±2.3	56.31±1.4
30	59.33±2.6	60.33±1.5	76.42±3.1	50.28±2.1	56.81±1.8	68.38±1.6
45	65.36±2.8	69.38±1.6	83.46±1.6	59.33±2.0	65.36±2.0	76.42±1.9
60	69.89±1.0	78.94±1.7	90.50±1.6	65.86±2.4	73.41±2.6	82.96±1.5

Values were mean± SD; (n=3), P<0.0001

3.1 *Statistical analysis of Dolutegravir solid dispersions data*

All the solid dispersions dissolution profile reports obtained by the GraphPad Prism software, version 9.1.2 (226), and the solid dispersions were tested in two way ANOVA with all the formulations i.e. FF1 to FF6 and have reported mean, standard deviation, n and p values showed in table 3. The level of significance for comparison was set as p less than 0.0001.*Invitro* drug release of Dolutegravir solid dispersions by using fusion method with PEG 6000 and Poloxamer 407 in various ratios were observed which showed at the end of 60 min, FF3 releases highest release 90.50±1.6% showed in Table 3.From the *invitro* drug release of various Dolutegravir solid dispersion methods, F3 formulation consists PEG 6000 by using solvent evaporation method which showed a maximum of 98.54±1.5% at the end of 60 min. So that F3 formulation was considered as an optimized formulation, and processed for further studies showed in Table 3.

4. RESULTS

4.1 *Calibration curve of Dolutegravir in 6.8 pH Phosphate buffer*

10 mg of Dolutegravir was taken in a 10 ml volumetric flask. The solution was made up to the mark with a 6.8 pH buffer to give 1000 µg /ml concentration. From s solution 1 ml is

diluted to 10 ml with, 6.8 pH buffer to give 100 µg /ml concentration. From the above stock solution subsequent dilutions containing 5 to 30 µg/ml solutions were prepared. The absorbance of each test solution was measured at λ_{max} i.e. 260 nm of Dolutegravir in UV/Visible spectroscopy against blank,the linearity studies were carried out for pure drug Dolutegravir. The coefficient correlation factor (r^2) was obtained, indicated the purity of drug with the standards.Showed inFigure 1.[14]

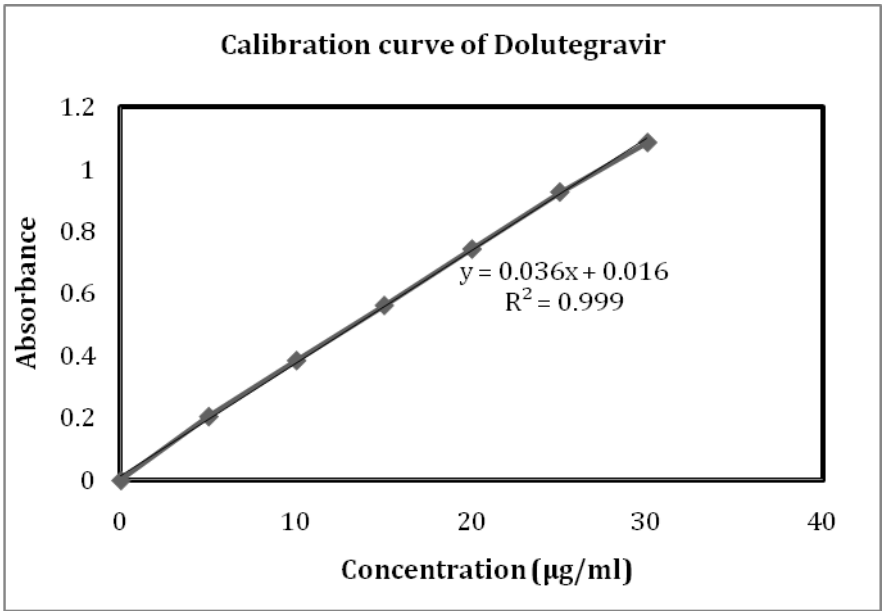

Fig 1: Calibration Graph of Dolutegravir

4.2 Preparation of Dolutegravir Tablets:

Equivalent weight of Dolutegravir was added with suitable excipients, and the tablets were formulated by direct compression according to the formulae showed in the Table 4.All the ingredients were passed through #40 mesh sieve separately. The drug, and Lactose were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside. Then the other ingredients were mixed in geometrical order and passed through coarse sieve (#40mesh) and the tablets were compressed using hydraulic press. Compression force of the machine was adjusted to obtain the hardness within the range of for all batches.[15]The weight of the tablets was kept constant for all formulations DF1 to DF6. tabulated in Table 4.

Table 4: Formulation of Dolutegravir tablets[16]

Ingredients (mg)	DF1	DF2	DF3	DF4	DF5	DF6
Dolutegravir (weight equivalent to Solid dispersion)	50	50	50	50	50	50
Sodium starch glycolate (SSG)	5	10	15	--	--	--
Lycoat	--	--	--	5	10	15
Lactose	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium stearate	2	2	2	2	2	2
Talc	2	2	2	2	2	2
Total weight(mg)	250	250	250	250	250	250

Mentioned values were mean± SD; (n=3), P < 0.0001

Table 5: % Cumulative drug release of formulations DF1-DF6

Time (min)/%CDR	DF1	DF2	DF3	DF4	DF5	DF6
0	0	0	0	0	0	0
5	39.68±0.3	46.38±0.6	56.38±1.4	35.24±0.8	43.95±1.1	55.36±1.2
10	56.32±1.1	65.67±1.1	75.96±1.6	56.33±1.1	62.16±1.5	68.12±0.9
15	65.34±1.4	79.35±1.6	88.07±1.8	69.83±1.6	73.95±1.7	75.63±0.5
20	70.61±2.1	86.81±1.8	95.18±0.9	75.26±2.3	79.42±2.0	83.62±1.6
25	79.05±2.4	90.24±2.0	98.04±1.9	79.17±1.4	86.34±2.3	90.24±2.1
30	86.34±1.9	93.58±2.2		82.34±2.8	90.42±3.1	96.38±1.8

4.3 Statistical analysis of Dolutegravir tablets dissolution profiles data

The observed reported values were analyzed by the Graph Pad Prism software, version 9.1.2 (226), and the acquired results of Dolute gravir tablets in-vitro dissolution profiles (DF1 to DF6) were tested two way ANOVA analysis with reported mean, standard deviations (SD), n and p values showed in table 5. The obtained p value is less than 0.0001 was considered as statistically significant.

5. DISCUSSION

5.1 *In Vitro* Drug Release of (DF1-DF6)

Invitro dissolution study was performed by using USP Type II apparatus (Paddle type) at 50 rpm. (Revolution per minute), 6.8 pH Phosphate buffer (900 ml) was used as a dissolution medium which is maintained at 37±0.5°C. Aliquots of dissolution medium (5 ml) were withdrawn at specific time intervals and filtered. An equal amount of fresh dissolution medium is replaced immediately following withdrawal of test sample. The percentage of drug released at various intervals was calculated by using Beer-lambert's law.[17] From the mentioned *in vitro* drug release studies of Dolutegravir (DF1-DF6) fast dissolving tablet formulations[18],it was observed that formulations showed drug release at the end of 30 mins, DF1 releases 86..34±1.9%, DF2 releases 93.58±2.2%, DF4 releases 82.34±2.8%, DF5 releases 90.42±3.1% , DF6 releases 96.38±1.8% but DF3 Dolutegravir formulation was released 98.04±1.9% at the time of 25 mins .The obtained cumulative percentage drug releases of Dolutegarvir tablets formulations DF1 to DF6 were showed in Table no 5.The formulations containing sodium starch glycolate (SSG) as a super disintegrant in different concentrations were 2%, 4%, and 6% (w/w) which reveals that the increased in the super disintegrant concentration, and decreases in the drug release time. The DF3 fast dissolving tablets[19]formulation containing Sodium starch glycolate SSG) 6% concentration showed maximum amount of 98.04±1.9 % drug release at the end of 25 min. Whereas formulations containing lycoat as a super disintegrants in different concentrations like 2%, 4%, and 6%, revealed that the increase in super disintegrant[20-23] concentration decreases the drug release time and the DF6 formulation containing lycoat 6% showed a maximum amount of drug release (96.38±1.8%) at the end of 30 min. The obtained p value is ≤0.0001 was considered as statistically significant Therefore, a favorable formulation, which increases the solubility and dissolution rate, hence it was used for the treatment of HIV/AIDS.[24-32] The reported percentage cumulative drug releases comparative studies were showed in the Figure no 2.

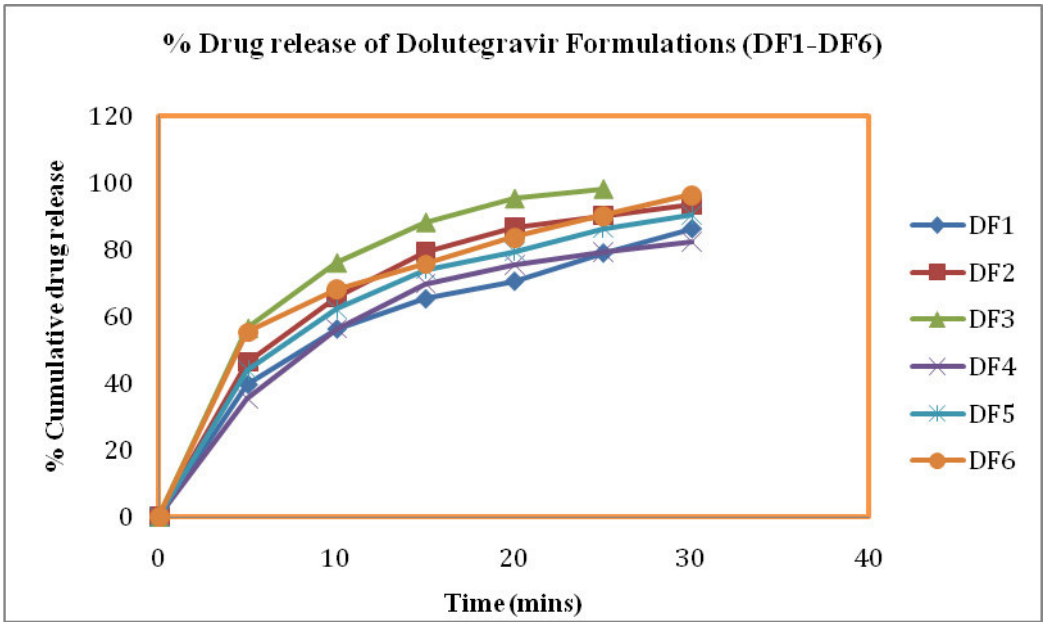

Fig 2: *Invitro* drug release of formulations DF1-DF6

5.2 FT-IR Studies

Drug and excipients compatibility[22] was confirmed by comparing spectra of FT-IR analysis of pure drug was showed in Figure 3 and pure drug with that of various pharmaceutical excipients used in the formulation were showed in Figure 4.Compatibility studies were performed using FT-IR spectrophotometer. The characteristic absorption peaks of Dolutegravir were obtained at different wavenumbers in different samples. The FTIR spectral investigations had been performed on Dolutegravir pure drug, poloxamer 407, and in this analysis the pure drug Dolutegravir exhibited a sharp peak at 2123.67 cm−1,1383.32 cm−1, 846.65 cm−1, and 875.53 cm−1 evidencing the presence of C-N stretching, C≡C stretching, C-O-C stretching, C-H bending, and Ar-H bending. For Poloxamer 407, sharp peaks at 2227.60 cm−1, 2155.00 cm−1, and 852.23 cm−1 indicated C-N stretching, C≡C stretching, and C-H bending. For DF3 stable solid dispersion, sharp peaks at 2127.12 cm−1, 2065.30 cm−1, 1291.18 cm−1, and 852.24 cm−1 indicated C-N stretching, C≡C stretching, C-O-C stretching, and Ar-H is bending. The remaining peaks were unaltered indicating that there has been no drug and excipients interaction. The detailed spectral elucidations were showed in Figure 3 and Figure 4 respectively. The peaks obtained in the spectrum of each formulation correlate with the peaks of drug spectrum. The mentioned FTIR studies represents that the drug was physically,chemically and therapeutically compatible with the pharmaceutical formulated components.

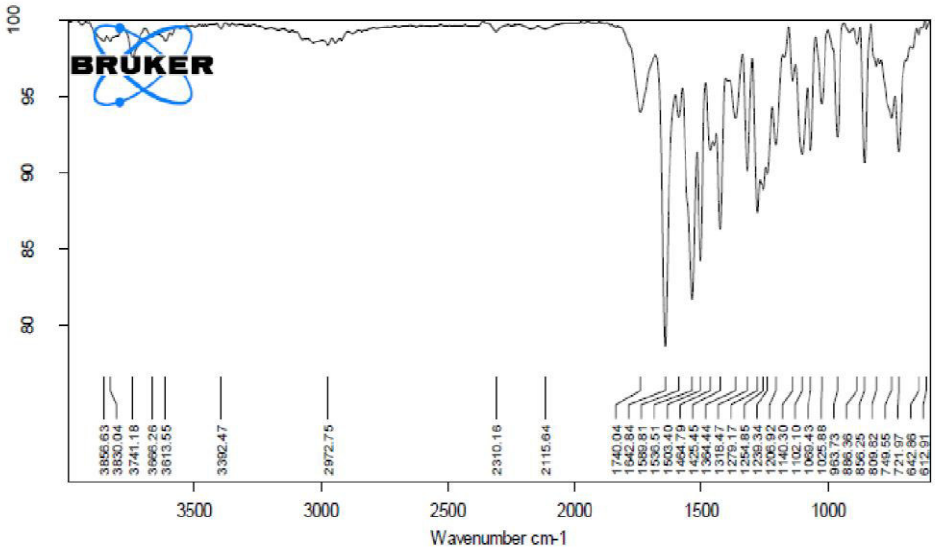

Fig 3: FTIR spectrum pure drug Dolutegravir

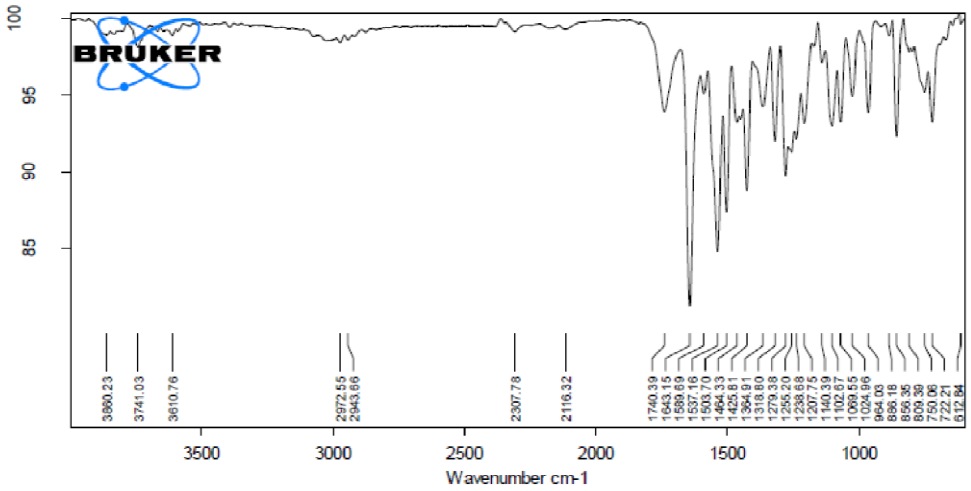

Fig 4: FTIR spectrum (Dolutegravir + Excipients)

From the drug excipient compatibility studies, we observed that there are no interactions between the pure drug (Dolutegravir) and optimized formulation (Dolutegravir: excipients) which indicates that there were no physical changes showed in Figure 4.

5.3 Drug release kinetics

The drug releases from the Dolutegravir fast dissolving tablets were explained by using mathematical model equations such as zero order, first order, Higuchi and Peppa's kosmeyer order of kinetics. Zero order of kinetics and first order of kinetics curves were showed in Figure 5, Figure 6 and Higuchi, Peppa's kosmeyer order of kinetics were showed in Figure 7, Figure 8 respectively. Based on the regression values, it was concluded that the optimized formulation DF3 follows first order kinetics correlation factor (r^2) value (0.995) was showed in Table 6. It is indicate that the rate of drug release is concentration dependent.

Table 6 : order of kinetic values of Formulation DF3

Order of kinetics	Zero Order	First Order	Higuchi OrderPeppa'sKorsmeyerOrder	
Regression values	0.908	0.995	0.971	0.858

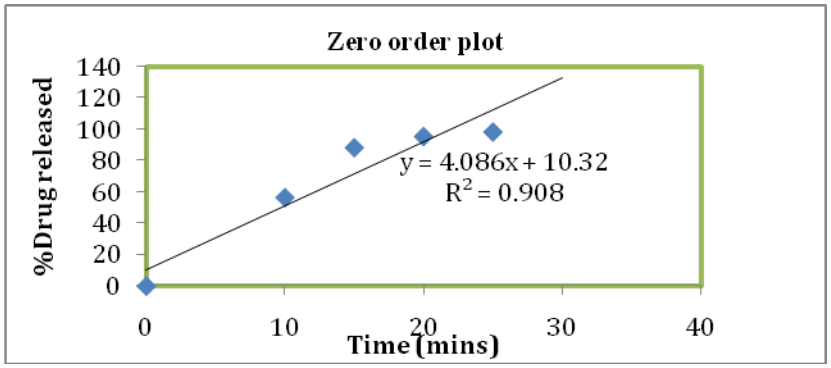

Fig 5: Zero order kinetics graph of DF3 formulation.

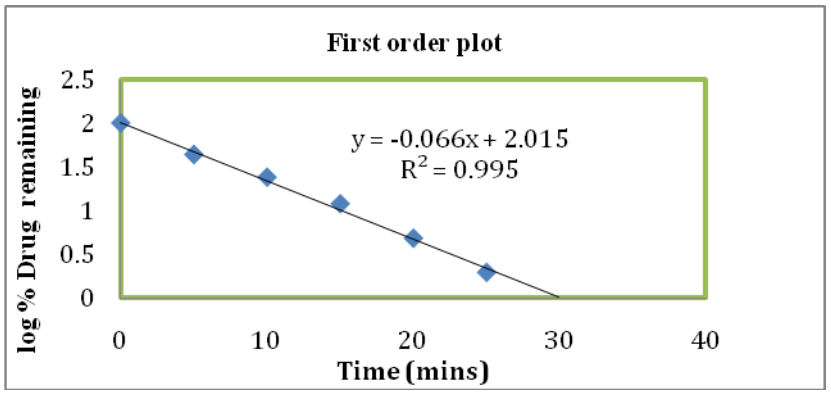

Fig 6: First order kinetics graph of DF3 formulation.

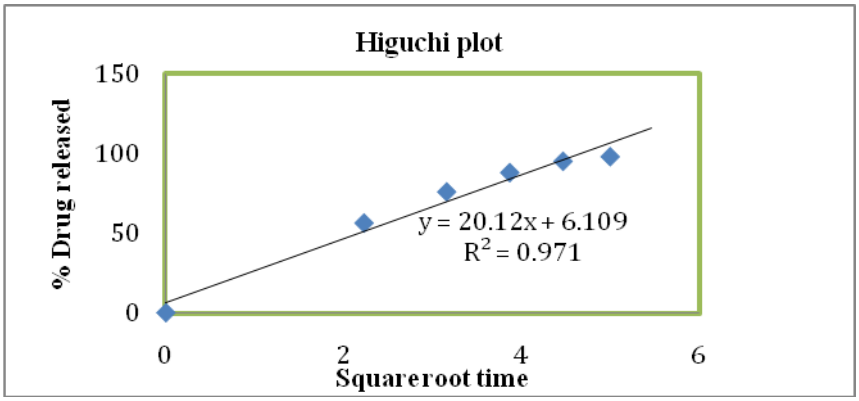

Fig 7: Higuchi order kinetics graph of DF3 formulation.

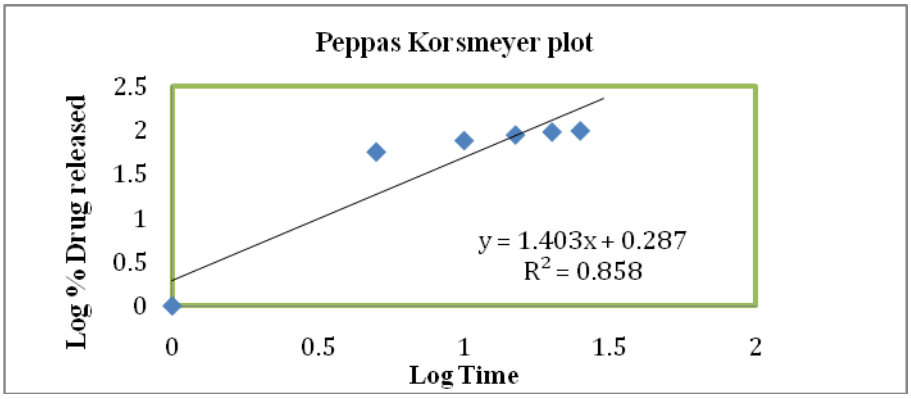

Fig 8: Peppa's korsmeyerorder kinetics graph of DF3 formulation.

6. CONCLUSION

In this present study, PEG 6000 and Poloxamer 407 polymers were used in the preparation of Dolutegravir solid dispersions by a solvent evaporation method, and Fusion method. Hence, based on the investigation of research work in comparison with fusion method, the solvent evaporation solid dispersion technique was more effective in enhancing the solubility, and dissolution rate of poorly soluble BCS class II drug i.e. Dolutegravir. All the prepared solid dispersions

were evaluated and the results were explained in the above-mentioned data. From that optimized formulation (F3), we prepared the Dolutegarvir Fast dissolving tablets using solid dispersion weight equivalent to 50 mg Dolutegravir, super disintegrants like sodium starch glycolate (SSG), lycoat, and other excipients. By observing the *in vitro* dissolution studies of Dolutegravir with Polymer PEG 6000 using solvent evaporation (1:3) ratio shown better drug release, and mentioned drug release formulation (DF3) consists sodium starch glycolate (6 % w/w) as super disintegrant showed 98.04±1.9 % of percent drug release at the end of 25 mins. Hence, it can be concluded the kinetics of the drug studies, optimized formulation (DF3) followed First order drug release. Poorly soluble drugs are slowly absorbed as compared with drugs with higher solubility. Consequently, and these kinds of BCS class II drugs had great challenges to further develop in fast dissolving tablet dosage forms. Hence it is important to enhance the aqueous solubility, dissolution rate, and bioavailability of these drugs from its oral solid dosage forms. In Solid dispersion techniques PEG 6000, Poloxamer 407 polymers have been used to improve the dissolution properties and bioavailability of poorly water soluble drugs. This research study has demonstrated the possibility of improving dissolution rate performance of Dolutegravir tablets by using solid dispersion technique.

7. ACKNOWLEDGEMENT

We thank the organization of Joginpally BR Pharmacy College, Hyderabad for their support and research facility. Special thanks to U.Vykuntam garu and our sincere thanks to Research Supervisor Dr. Anoop Singh, Bhagwant University for the support of research work.

8. AUTHORS CONTRIBUTION STATEMENT

The author Mr. Srinivas M confirms sole responsibility for the study conception, data collection, and formulation design regarding this research work. Dr. Anoop Singh contributed to performing the methods of preparations and interpretation of results. Prof Vykuntam U helped to draft the manuscript preparation. All the authors verified the results and accepted the final version of the Research manuscript.

9. CONFLICT OF INTEREST

Conflict of interest declared none.

10. REFERENCES

1. Sanjoy Kumar Das, SudiptaRoy, Yuvaraja Kalimuthu. Solid Dispersions: An Approach to Enhance the Bioavailability of Poorly Water-Soluble Drugs, International Journal of Pharmacology and Pharmaceutical Technology; 2011; 1:37-46.
2. McCormack, P.L. Dolutegravir: A Review of Its Use in the Management of HIV-1 Infection in Adolescents and Adults. 2014; 1241–1252.
3. Emmanuel Ndashimyea,b, Eric J. Artsa, Dolutegravir response in antiretroviral therapy naïve and experienced patients with M184V/I: Impact in low-and middle-income settings. International Journal of Infectious Diseases 2021; 298–303.
4. Srinivas Martha, Archana N, B Sindhu Vahini, Design and In vitro Characterization of Dolutegravir Sustained Release Matrix Tablets, International Journal of Pharmaceutical Sciences Review and Research2017; 46:136-141.
5. Athira R. Nair, YarlagaddaDaniLakshman, wapnil J. Dengale, Overview of Extensively Employed Polymeric Carriers in Solid Dispersion Technology, AAPS PharmSciTech 2020; 21: 309.
6. Arunachalam A, Karthikeyan M, Konam K, Prasad P, Sethuraman S, Ashutoshraman S. Solid dispersions: a review, CPR; 2010. p. 82-90.
7. XingwangZhang, HuijieXing, Zhiguo Ma, Dispersion Techniques for Dissolution and Bioavailability Enhancement of Poorly Water-Soluble Drugs, Pharmaceutics. 2018; Sep; 10(3): 74.
8. Patel PB, Prajapati ST, Patel NR, Patel NN, Patel CN. Solid dispersion: a method of improving bioavailability and taste masking. Inventi Rapid: Pharm Tech Vol 2013; 3:427-39.
9. Leunar C, Dreessan J. Improving drug solubility for oral delivery using solid dispersion. Eur J Pharm Biopharm 2000; 50:47-60.
10. PS Argade, DD Magar, RB Saudagar. Review article on solid dispersion as solubility enhancement technique for poorly water soluble drugs. J Adv Pharm Edu Res 2013; 3:427-39.
11. S.S. Dhanwate, Development and validation of analytical method for the estimation of Lamivudine and Dolutegravir sodium in dosage form J. Pharm. Sci. & Res. Vol. 11(8), 2019, 2886-2890.
12. Balasaheb, B.G., Balasaheb, A.K., Subhash, T.R., Jijabapu, K). Development and Validation of UV Spectrophotometric Method For Estimation of Dolutegravir Sodium in Tablet Dosage Form. Malaysian Journal of Analytical Sciences, 2015;19(6):1156-1163.
13. Sethia S. Solid dispersions-revival with greater possibilities and applications in oral drug delivery. Crit. Rev. Ther. Drug Carrier Syst., 20(2-3), 2003, 215-247.
14. Ujjwala A. Mulak, Dr.Sushil P. Narkhede, MadhaviP.Shinde, Development of Analytical Method for In-vitro Drug Dissolution Study of Dolutegravir Marketed Formulation, Journal of Pharmaceutical sciences and Research2018;10(11): 2726-2730.
15. SundeepMupparaju, VidyadharaSuryadevara, Ramu Anne, Formulation and Evaluation Of Dolutegravir Sodium Solid Dispersions And Fast Dissolving Tablets Using Poloxamer-188 and Jack Fruit Seed Starch As Excipients, Asian J Pharm Clin Res 2019; 12(6):181-190.
16. JogalaS,Glimepiride fast disintegrating tablets: formulation, evaluation & *in-vivo* disintegration and dynamic studies. Int J Pharm PharmSci 2016; 8(5): 615-21.
17. Biswajit B, Formulation & evaluation of fast dissolving tablets of cinnarizine using super disintegrant blends & subliming material. J Adv Pharm Tech Res 2011; 2(4): 266-73.
18. Mizumoto, Masuda Yoshinori, Yamamoto Takeshi, Yonemochi, Terada Katsuhide: Formulation design of a novel fast-disintegrating tablet. International Journal of Pharmaceutics 2005; 306:83–90.
19. Pekamwar S.S, Formulation and evaluation of solid dispersion of lopinavir by using different techniques. Int. Res. J. Pharm. 2015, 6(9).
20. RakeshPahwa and Nisha Gupta, Superdisintegrantsin the Development of Orally Disintegrating Tablets: A Review,

internataional journal of Pharmaceutical sciences and Research 2011; 2(11): 2767-2780.

21. PinumallaKavyaSree, Srinivas Martha, Sharma JVC. Formulation and evaluation of oral fast disintegrating tablets of Delafloxacin. International Journal of Pharmacy and Biological Sciences. 2019;9(3):1035-1044.
22. HaranathChinthaginjala, Hindustan Abdul Ahad, RahulraghavDasari , Formulation and In Vitro Evaluation of Fast Disintegrating Tablets of an Anti-Inflammatory Drug using Natural Super Disintegrating Agents..(2).Int. J. Life Sci. Pharma Res.2021 (11), 9-18 http://dx.doi.org/10.22376/ijpbs/lpr.2021.11.2.P9-18.
23. Kambhamvenkateswarlu and K.b.chandrasekhar, Formulation and in-vitro evaluation of lacidipine oral disintegrating tablets: enhancement of solubility and dissolution rate, int. J. Life sci. Pharma Res.2016 6(2), 15-25.
24. SwatiSareen, George Mathew, and Lincy Joseph, Improvement in solubility of poor water-soluble drugs by solid dispersion, Int J Pharm Investig. 2012; 2(1):12–177.
25. Srinivas, M, Singh, Anoop. (2021). Enhancement of solubility and dissolution rate of Bcs class-II Fluvoxamine tablets using solvent evaporation solid dispersion technique. *Journal of Pharmaceutical Research International*, *33*(31B), 44-53. https://doi.org/10.9734/jpri/2021/v33i31B31689
26. Nazemoon Reddy, SwarnalathaDugasani, Devanna Nayakanti , Fabrication and characterization of Lercanidipine Hydrochloride solid dispersions by fusion and solvent evaporation techniques. Int. J. Life Sci. Pharma Res.2021; 11(1):78-86. http://dx.doi.org/10.22376/ijpbs/lpr.2021.11.1.P78-86
27. Vaneetha G, Srinivas Martha, NagarajuPotnuri. Design and solubility enhancement of empagliflozin immediate release tablets by using solid dispersion method. International Journal of Pharmacy and Pharmaceutical Research. 2017;10(2):163-179
28. Shamsuddin, Fazil M, Ansari SH, Ali J. Development and evaluation of solid dispersion of spironolactone using fusion method. Int J PharmaInvestig 2016; 6:63-8.
29. Christopher vimalson, s. Parimalakrishnan, s. Anbazhagan1, solid dispersion technique to enhance the solubility and dissolution of febuxostat an Bcs class II drug, Int J App Pharm 2019; 11(1) : 241-246.
30. KS Remya, P Beena, PV Bijesh, and A Sheeba, Formulation Development, Evaluation and Comparative Study of Effects of Super Disintegrants in Cefixime Oral Disintegrating Tablets,J Young Pharm. 2010 ; 2(3): 234–239.
31. Ketan T. Savjani, Anuradha K. Gajjar, Jignasa K. Savjani, Drug Solubility: Importance and enhancement techniques, International Scholarly Research Network.,ISRN Pharmaceutics,2012: 195727.
32. Swapna Mane, Ritesh Bathe, SandhyaraniAwatade Formulation and evaluation of fast disintegrating tablets of atenolol using natural and synthetic super disintegrants, Journal of Drug Delivery & Therapeutics. 2019; 9(2):150-158.