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Original Article

PREPARATION AND EVALUATION OF DOLUTEGRAVIR SOLID DISPERSIONS

SUNDEEP MUPPARAJU[1,2], VIDYADHARA SURYADEVARA[1*], SANDEEP DOPPALAPUDI[1]

[1]Department of Pharmaceutics, Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Chandramoulipuram, Chowdavaram, Guntur, Andhra Pradesh, India 522019, [2]University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Nagarjuna Nagar, Guntur, Andhra Pradesh, India 522510
Email: svidyadhara@gmail.com

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ABSTRACT

Objective: The current work mainly focuses on solubility enhancement of dolutegravir which is a BCS (Biopharmaceutical Classification System) class-II drug using various excipients.

Methods: Solid dispersions of dolutegravir were prepared by solvent evaporation and fusion methods using carriers like poloxamer-188 and plasdone K-29/32 in different ratios (1:0.5 to 1:3.0). The amount of dolutegravir used was kept constant and the polymer concentrations were increased. Various physical parameters like angle of repose, carr's index, Hausner's ratio were calculated for the prepared solid dispersions. They were also evaluated for particle size and drug content uniformity along with *in vitro* drug release. Characterization studies like Fourier Transform Infra-Red spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), Scanning Electron Microscopy (SEM) and X-Ray Diffraction (XRD) were also done.

Results: Dolutegravir solid dispersions showed good to excellent flow properties. From *in vitro* dissolution studies, it was observed that the solid dispersion formulation DF3 containing dolutegravir and poloxamer-188 in 1:1.5 ratios prepared by fusion method showed better dissolution rate when compared with other formulations. The dissolution parameters were also evaluated. DF3 showed a higher drug release of 86.33% in 60 min. FTIR and DSC studies revealed that there were no major interactions between drug and excipients. XRD studies revealed the nature of formulations.

Conclusion: The solid dispersions prepared using poloxamer-188 by fusion method has enhanced the solubility of dolutegravir.

Keywords: Dolutegravir, Poloxamer-188, Plasdone K-29/32, Solid dispersions, Fusion method

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INTRODUCTION

Solubility is a major physicochemical factor which affects the drug absorption and its therapeutic efficiency. Solubility enhancement is the main area that researchers were focusing in recent days. Several methods like usage of polymers, superdisintegrants, preparation of formulations like solid dispersions and fast dissolving tablets has been employed in solubility enhancement. Of all these, preparation of solid dispersions is the best choice of researchers as they are easy to prepare, economic and time saving [1]. The term solid dispersion refers to a group of solid products consisting of at least two different components, a hydrophilic matrix and a hydrophobic drug [2]. They can be prepared by simple physical mixing, solvent evaporation and fusion techniques. Miscibility of polymers with the drug plays a key role in solubility enhancement of poorly water soluble drugs [3].

The present study was aimed to formulate dolutegravir solid dispersions using various polymers to improve the solubility and dissolution rate. Dolutegravir, an antiretroviral agent mainly acts by inhibiting the enzyme HIV integrase which is needed for viral replication process [4]. According to the Biopharmaceutical Classification Scheme, dolutegravir is considered as class II drug, i.e., water insoluble, lipophilic and highly permeable compound. Therefore, it is possible to improve its bioavailability by increasing apparent solubility in water through solid dispersion technology [5, 6]. The bioavailability of dolutegravir is approximately 34%. It is highly bound to plasma proteins. It has an approximate elimination half-life of 14h. Based on pharmacokinetic and pharmacodynamic parameters, Dolutegravir is selected as drug of choice for present study. The current study focused on the solubility enhancement of dolutegravir using solid dispersion technology.

MATERIALS AND METHODS

Procurement of materials

Dolutegravir was a gift sample from Dr. Reddy's Lab (Hyderabad, India). Poloxamer 188 and plasdone K-29/32 were gift samples from Pellets Pharma Ltd (Hyderabad, India).

Preparation of dolutegravir solid dispersions by solvent evaporation method

Specified quantities of dolutegravir and poloxamer-188 were taken in a china dish and to that few ml of methanol was added and slightly heated until both drug and polymer dissolves. Then the mixture was subsequently allowed to evaporate. The obtained mixture was dried, passed through the sieve no.80, packed in a wide mouthed amber colored glass container and was hermetically sealed and stored [7]. Similarly, the solid dispersions were prepared using plasdone K-29/32 as polymer. The results were given in table 1.

Preparation of dolutegravir solid dispersions by fusion method

Solid dispersions of Dolutegravir were prepared using poloxamer-188 and plasdone K-29/32 in different ratios by fusion method. Poloxamer-188 was placed in china dish and heated at 40 °C until it gets melted and then dolutegravir was added to it. After vigorous stirring in normal temperature, the mixture gets solidified. The solid mass was crushed, pulverized and sieved [8]. Similarly, the solid dispersions were prepared using plasdone K-29/32 as carrier. The granules obtained were stored in desiccator for further studies. The results were given in table 2.

Evaluation of physical parameters of dolutegravir solid dispersions

The prepared solid dispersions were evaluated for various physical parameters such as angle of repose, Carr's index, Hausner's ratio and particle size [9, 10]. The results were indicated in table 3.

Angle of repose

The powder flow properties were determined to know the good or bad material flow. The powder was taken into a funnel and poured through it. Below this, a graph sheet was placed to form a heap like structure for which, the radius and height of the heap was measured. Based on these, the angle of repose was calculated by using the formula;

$$\theta = \tan^{-1}(h/r)$$

Carr's index

A simple test was used to evaluate the flow ability of a powder by comparing the poured density and the tapped density of a powder and the rate at which it is packed down.

$$\text{Carr}'\text{s Index} = \frac{\text{Tapped density} - \text{Poured density}}{\text{Tapped density}} \text{ x } 100$$

Hausner's ratio

It is an indication of flow properties of the powder. Hausner's ratio can be calculated by using the formula;

$$\text{Hausner}'\text{s Ratio} = \frac{\text{Tap density}}{\text{Bulk density}}$$

Particle size

A set of sieves were taken, properly cleaned and are stacked in descending order of mesh size (increase in the sieve number). The solid dispersion was taken in the sieve number 18. The sieves are closed with lid and sieving was done for 5 min. The material retained on individual sieves were collected and weighed.

Drug content uniformity

Solid dispersions of dolutegravir equivalent to 50 mg was weighed and transferred into a 100 ml volumetric flask. To this, small quantity of methanol was added to dissolve. It was shaken occasionally for about 15 min and the volume was made up to 100 ml by methanol. The solution was filtered using Whattmann filter paper. The filtrate was subsequently diluted with 6.8pH phosphate buffer and the absorbance was measured at 258 nm using 6.8pH phosphate buffer as blank.

***In vitro* dissolution studies**

Dissolution studies for all solid dispersions were performed in a calibrated 8 station dissolution test apparatus (LABINDIA DS8000) equipped with paddles (USP apparatus II method) employing 900 ml of 6.8pH phosphate buffer as a dissolution medium. The paddles were operated at 50 rpm and temperature was maintained at 37±1 °C throughout the experiment [11]. The samples were withdrawn at 5, 10, 15, 20, 30, 45, 60 min and replaced with equal volume of same dissolution medium to maintain the sink conditions throughout the experiment. Samples withdrawn were suitably diluted with same dissolution medium and the amount of the drug dissolved was estimated by Lab India double beam U. V spectrophotometer (UV 3000+) at 258 nm. The dissolution profiles were indicated in fig. 1 and 2. Various dissolution parameters were calculated for the dispersions and were given in table 4.

Statistical analysis

The results obtained were statistically evaluated. As the procedures performed and the results obtained were in triplicates, the mean along with their standard deviations (SD) were calculated for drug content and drug dissolution profiles.

Characterization studies

Based on the dissolution studies, the optimized formulations were selected, and Fourier transfer infrared (FTIR) and differential scanning calorimetry (DSC) studies were performed to observe the drug-polymer interactions. X-Ray Diffraction (XRD) studies were performed to detect the nature of formulations. Scanning electron microscopy (SEM) analysis was performed on dolutegravir, poloxamer-188 and optimized solid dispersion to know surface characteristics. The results were shown in fig. 3, 4, 5 and 6.

RESULTS AND DISCUSSION

Preparation of dolutegravir solid dispersions by solvent evaporation method

Solid dispersions of Dolutegravir were prepared using poloxamer-188 and plasdone K-29/32 in different ratios by solvent evaporation method. The composition of dolutegravir solid dispersions prepared by solvent evaporation method is given the table 1.

Preparation of dolutegravir solid dispersions by fusion method

Solid dispersions of Dolutegravir were prepared using poloxamer-188 and plasdone K-29/32 in different ratios by fusion method. The composition of dolutegravir solid dispersions prepared by fusion method is given the table 2.

Table 1: Composition of dolutegravir solid dispersions prepared by solvent evaporation method

Solid dispersion	Drug: polymer ratio (Dolutegravir*: poloxamer-188)	Solid dispersion	Drug: polymer ratio (Dolutegravir*: plasdone K-29/32)
DS1	1:0.5	DS6	1:0.5
DS2	1:1.0	DS7	1:1.0
DS3	1:1.5	DS8	1:1.5
DS4	1:2.0	DS9	1:2.0
DS5	1:3.0	DS10	1:3.0

*One part is equal to 50 mg

Table 2: Composition of dolutegravir solid dispersions prepared by fusion method

Solid dispersion	Drug: polymer ratio (Dolutegravir*: poloxamer-188)	Solid dispersion	Drug: polymer ratio (Dolutegravir*: plasdone K-29/32)
DF1	1:0.5	DF6	1:0.5
DF2	1:1.0	DF7	1:1.0
DF3	1:1.5	DF8	1:1.5
DF4	1:2.0	DF9	1:2.0
DF5	1:3.0	DF10	1:3.0

*One part is equal to 50 mg

Evaluation of physical parameters of dolutegravir solid dispersions

Various physical parameters of dolutegravir solid dispersions were evaluated. The obtained results were indicated in table 3. Formulations prepared using dolutegravir and poloxamer-188 by fusion method showed good flow properties compared to others.

***In vitro* dissolution studies of dolutegravir solid dispersions**

Dolutegravir pure drug showed only 13.33% of drug release even after 60 min. This indicates its poor aqueous solubility as it is a BCS class II drug. Formulation DF3, prepared in 1:1.5 ratios of dolutegravir and poloxamer-188 showed maximum drug release of 86.33% in 60 min. It proves that solid dispersion technique

enhances drug release of poorly water soluble drugs as suggested by earlier studies [12, 13]. The fusion technique used for formulation of solid dispersions was also proved to be most advantageous as suggested earlier [14-16]. Usage of carriers increases the dissolution efficiency [17, 18]. Poloxamer-188 is a non-ionic surfactant which basically consists of both hydrophilic and lipophilic moieties. Hence the increase in drug release followed by decrease in drug release may be due to presence of high proportion of lipophilic moieties at higher concentration of polymer used in the dispersions [19, 20]. Apart from these, other polymers like PVP and PEG were also used in past studies to enhance solubility of BCS class-II drugs [21]. Thus solid dispersions DF3 containing drug to polymer ratio of 1:1.5 was found to be optimal concentration of the carrier for the preparation of solid dispersions. The dissolution profiles were indicated in fig. 1 and 2. The dissolution parameters were given in table 4. The first order plots revealed the linearity in drug release.

Table 3: Physical parameters of dolutegravir solid dispersions

Solid dispersion	Angle of repose (°)	Carr's index (%)	Hausner's ratio	Average particle size (µm)	Drug content (mg) (mean±SD)*
DD	32	19	1.22	35	49.45±0.66
DS1	28	15	1.17	179	48.71±0.59
DS2	26	14	1.15	171	49.63±0.17
DS3	24	12	1.13	165	50.20±0.77
DS4	25	13	1.15	174	48.92±0.81
DS5	25	14	1.15	176	48.45±0.59
DS6	29	15	1.18	181	49.16±0.17
DS7	27	13	1.16	175	49.08±0.54
DS8	26	13	1.14	169	48.66±0.41
DS9	26	12	1.16	173	49.25±0.77
DS10	28	14	1.16	176	48.82±0.81
DF1	25	14	1.16	171	48.35±0.54
DF2	23	13	1.14	164	49.62±0.41
DF3	21	12	1.12	158	50.08±0.77
DF4	23	13	1.14	165	48.73±0.81
DF5	25	14	1.15	169	48.12±0.59
DF6	27	15	1.18	177	49.08±0.17
DF7	25	14	1.16	172	50.23±0.54
DF8	22	13	1.15	166	49.24±0.41
DF9	24	12	1.17	171	48.07±0.77
DF10	25	13	1.17	175	48.65±0.81

*DD indicates Dolutegravir pure drug; n=3, SD: standard deviation

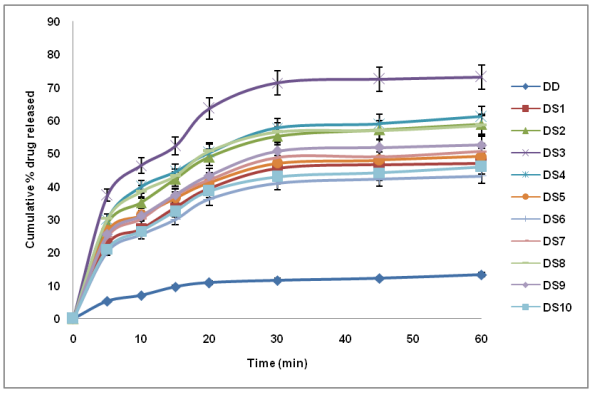


Fig. 1: Drug release profiles of dolutegravir solid dispersions prepared by solvent evaporation method (mean±SD; n=3)

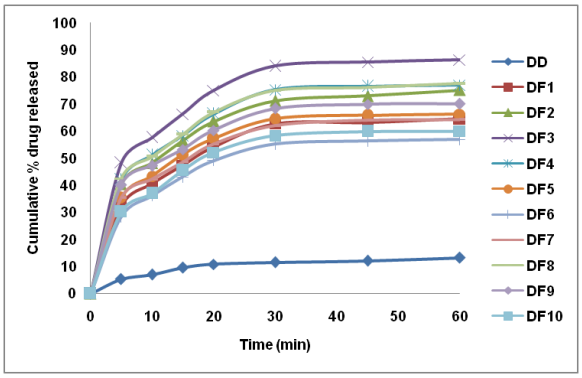


Fig. 2: Drug release profiles of dolutegravir solid dispersions prepared by fusion method (mean±SD; n=3)

Table 4: *In vitro* dissolution parameters of dolutegravir solid dispersions

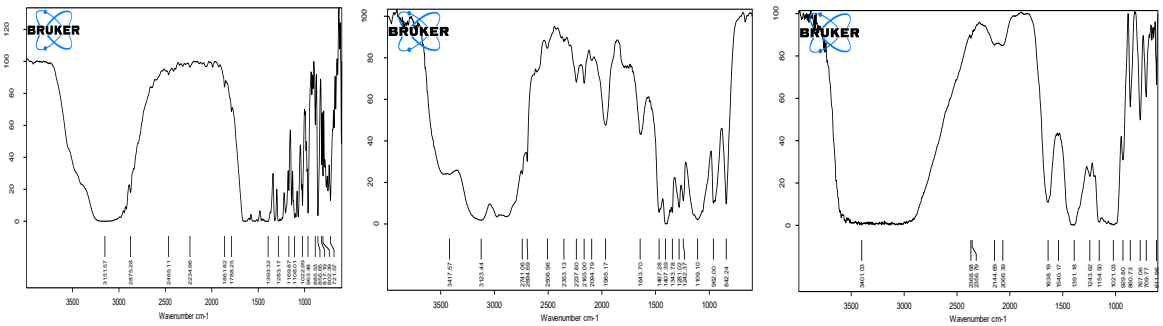
Formulation	% Drug released at 60 min	T_{50} (min)	DE_{20}%	First order rate constant		Hixson crowell cube root plot	
				K (min^{-1})	R^2	K ($min^{-1/3}$)	R^2
DD	13.34	>60	6.50	0.0019	0.711	0.0016	0.787
DS1	47.11	>60	26.25	0.0092	0.901	0.0071	0.915
DS2	58.88	20.44	32.50	0.0128	0.924	0.0095	0.960
DS3	73.21	10.78	42.50	0.0199	0.965	0.0138	0.978
DS4	61.19	19.87	33.75	0.0133	0.964	0.0096	0.931
DS5	49.18	>60	28.75	0.0092	0.933	0.0066	0.905
DS6	43.16	>60	23.12	0.0085	0.910	0.0063	0.922
DS7	50.63	59.25	28.12	0.0100	0.928	0.0075	0.935
DS8	58.58	19.70	34.37	0.0123	0.975	0.0087	0.944
DS9	52.64	29.55	28.12	0.0108	0.951	0.0082	0.901
DS10	46.01	>60	23.75	0.0087	0.904	0.0068	0.937
DF1	64.55	15.84	36.87	0.0151	0.900	0.0108	0.969
DF2	75.22	10.37	43.75	0.0202	0.922	0.0136	0.948
DF3	86.33	05.18	53.12	0.3065	0.988	0.0190	0.983
DF4	77.08	09.76	46.25	0.0219	0.933	0.0144	0.924
DF5	66.32	14.64	40.00	0.0157	0.905	0.0107	0.953
DF6	56.99	20.32	32.5	0.0120	0.962	0.0087	0.911
DF7	64.22	15.43	40.00	0.0147	0.941	0.0100	0.960
DF8	77.53	09.89	46.25	0.0220	0.920	0.0145	0.948
DF9	70.05	10.57	42.50	0.0172	0.939	0.0218	0.933
DF10	60.08	16.48	37.50	0.0133	0.919	0.0096	0.917

Characterization studies

Based on the dissolution studies performed on all the formulations, the optimized formulations were selected and following studies were done.

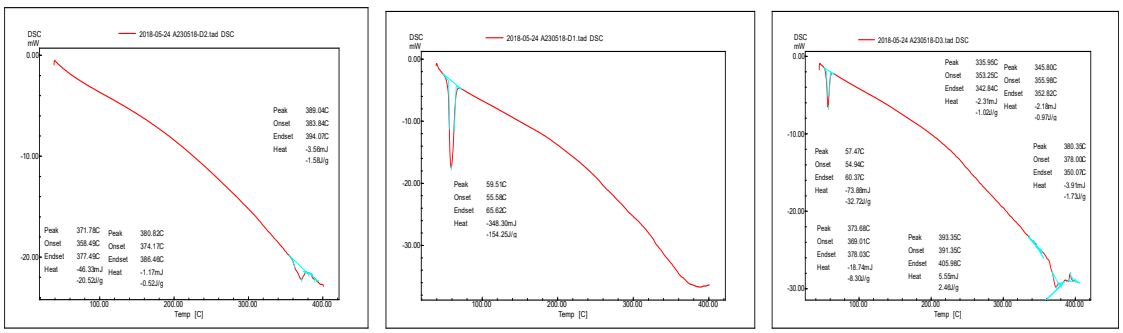
Fourier-transform infra-red (FT-IR) spectroscopic analysis

The FTIR spectral investigations were conducted on dolutegravir pure drug, poloxamer-188 and optimized dolutegravir solid dispersion. The pure drug dolutegravir exhibited sharp peak at 2234.96 cm^{-1}, 1393.32 cm^{-1}, 856.65 cm^{-1} and 885.53 cm^{-1} indicating the presence of C-N stretching, C≡C stretching, C-O-C stretching, C-H bending and Ar-H bending. For Poloxamer-188, sharp peaks at 2237.60 cm^{-1}, 2165.00 $cm^{-1}$and 842.24 cm^{-1} indicated C-N stretching, C≡C stretching and C-H bending. For DF3 solid dispersion, sharp peaks at 2237.12 cm^{-1}, 2165.40 cm^{-1}, 1391.18 $cm^{-1}$and 842.24 cm^{-1} indicated C-N stretching, C≡C stretching, C-O-C stretching and Ar-H bending. The remaining peaks were unaltered indicating that there were no drug and excipients interaction. The detailed spectral elucidations were shown in fig. 3.



(A) **(B)** **(C)**

Fig. 3: FTIR Spectra: (A) Dolutegravir pure drug (B) Poloxamer-188 (C) DF3 solid dispersion, DF3–solid dispersion of dolutegravir and poloxamer-188 in 1:1.5 ratio



(A) **(B)** **(C)**

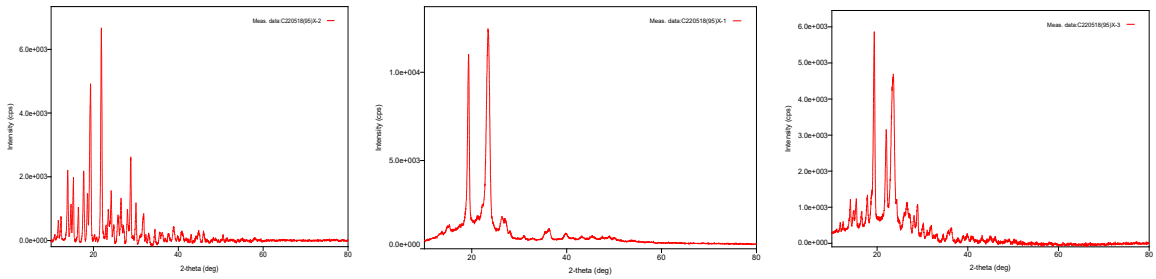
Fig. 4: DSC Thermograms: (A) Dolutegravir pure drug (B) Poloxamer-188, (C) DF3 solid dispersion, DF3–solid dispersion of dolutegravir and poloxamer-188 in 1:1.5 ratio

Differential Scanning Calorimetry (DSC):

A differential scanning calorimeter (DSC 200F3, Shimadzu) was used to obtain the DSC curves of dolutegravir pure drug, poloxamer-188 and solid dispersion DF3 representing the rates of heat uptake. The DSC results revealed that sharp peaks for dolutegravir were observed at 371.780C, 3800C and 3890C. A sharp endothermic peak for poloxamer-188 was observed at 59.50C. Sharp and broad peaks for DF3 were observed at 57.470C, 345.800C and 373.680C. These studies revealed that there were no drug and excipient interactions which were confirmed by obtaining similar thermographic peaks at respective temperatures. The detailed thermographs were shown in fig. 4.

Powder X-ray diffractometry (PXRD)

Powder X-ray diffraction (PXRD) patterns were traced employing X-ray diffractometer Shimadzu and DSC-60, Germany for all the samples using Nickel filter, CuK (α) radiation, a current of 20 mA and receiving slit of 0.2 inches. PXRD studies of dolutegravir showed several sharp peaks from 10 to 40 θ degrees. The PXRD studies for poloxamer-188 showed only two sharp peaks at 20 to 30 θ degree. The solid dispersion prepared by dolutegravir and polaxmer-188 revealed that sharp peaks corresponding to the polymer were observed at 20 to 30 θ degree. This indicated that the crystalinity of pure drug was greatly reduced by solid dispersion formulation having poloxamer 188. The powder x-ray diffraction patterns were shown in fig. 5.

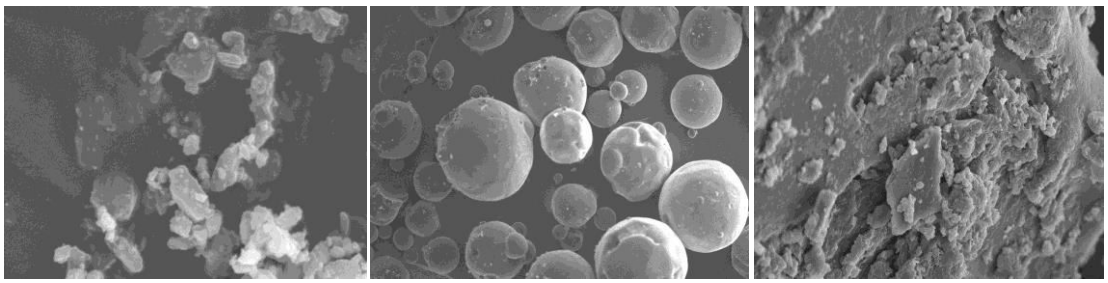


(A) **(B)** **(C)**

Fig. 5: XRD Diffractograms: (A) Dolutegravir pure drug (B) Poloxamer-188, (C) DF3 solid dispersion, DF3–solid dispersion of dolutegravir+poloxamer-188 in 1:1.5 ratio

Scanning electron microscopy

SEM images were taken for Dolutegravir pure drug, poloxamer-188 and solid dispersion DF3. SEM photographs of dolutegravir exhibited high crystalinity of drug with several planes of surface. Poloxamer-188 exhibited spherical shaped granular form of beads. Solid dispersion DF3 showed that the drug was absorbed on to the spherical beads and there by the crystalinity of drug is greatly reduced. The SEM images were clearly shown in the fig. 6.



(A) **(B)** **(C)**

Fig. 6: SEM Images: (A) Dolutegravir pure drug (B) Poloxamer-188 (C) DF3 solid dispersion, DF3–solid dispersion of dolutegravir and poloxamer-188 in 1:1.5 ratio

CONCLUSION

Dolutegravir solid dispersions were prepared using various concentrations of poloxamer-188 and plasdone K-29/32 using solvent evaporation and fusion methods and were subjected to *in vitro* dissolution studies. From these studies, it was observed that the proportion of carrier has influenced the dissolution parameters of various formulations. Poloxamer-188 has greatly modified the solubility of dolutegravir when solid dispersions were prepared by fusion method. The optimized solid dispersions when subjected to FTIR and DSC analysis, showed no drug-excipient interactions. Similarly, XRD studies were conducted to know the crystalline and amorphous nature of the samples.

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AUTHORS CONTRIBUTIONS

All the author has contributed equally.

CONFLICTS OF INTERESTS

The authors declare no conflicts of interest.

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