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 using the formula:

\[ \theta = \tan^{-1}\left(\frac{h}{r}\right) \]
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.

\[
\text{Carr's Index} = \frac{\text{Tapped density} - \text{Poured density}}{\text{Tapped density}} \times 100
\]

Hausner’s ratio

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

\[
\text{Hausner’s Ratio} = \frac{\text{Tap density}}{\text{Bulk density}}
\]

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 Whatmann 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 300+*) 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 | T½ (min) | DDE% | First order rate constant | Hicson crowell cube root plot |
|-------------|---------------------------|----------|-------|---------------------------|-------------------------------|
| DD          | 13.34                     | >60      | 6.50  | 0.0019                    | 0.0016                        |
| DS1         | 47.11                     | >60      | 26.25 | 0.0092                    | 0.971                         |
| DS2         | 58.88                     | >60      | 32.50 | 0.0128                    | 0.901                         |
| DS3         | 73.21                     | >60      | 42.50 | 0.0199                    | 0.906                         |
| DS4         | 61.19                     | 19.87    | 33.75 | 0.0133                    | 0.978                         |
| DS5         | 49.18                     | >60      | 28.75 | 0.0092                    | 0.996                         |
| DS6         | 43.16                     | >60      | 23.12 | 0.0085                    | 0.906                         |
| DS7         | 50.63                     | >60      | 59.25 | 0.0100                    | 0.906                         |
| DS8         | 58.58                     | 19.70    | 34.37 | 0.0123                    | 0.994                         |
| DS9         | 52.64                     | 29.55    | 28.12 | 0.0108                    | 0.901                         |
| DS10        | 46.01                     | >60      | 23.75 | 0.0087                    | 0.904                         |
| DF1         | 64.55                     | 15.84    | 36.87 | 0.0151                    | 0.900                         |
| DF2         | 75.22                     | 10.37    | 43.75 | 0.0202                    | 0.922                         |
| DF3         | 86.33                     | 05.18    | 53.12 | 0.3065                    | 0.998                         |
| DF4         | 77.08                     | 09.76    | 46.25 | 0.0219                    | 0.933                         |
| DF5         | 66.32                     | 14.64    | 40.00 | 0.0157                    | 0.905                         |
| DF6         | 56.99                     | 20.32    | 32.5  | 0.0120                    | 0.962                         |
| DF7         | 64.22                     | 15.43    | 40.00 | 0.0147                    | 0.941                         |
| DF8         | 77.53                     | 09.89    | 46.25 | 0.0220                    | 0.920                         |
| DF9         | 70.05                     | 10.57    | 42.50 | 0.0172                    | 0.939                         |
| DF10        | 60.08                     | 16.48    | 27.50 | 0.0123                    | 0.919                         |

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=O 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=O-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=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.

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

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 371.78°C, 380°C and 3890°C. A sharp endothermic peak for poloxamer-188 was observed at 59.50°C. Sharp and broad peaks for DF3 were observed at 57.470°C, 345.80°C and 373.680°C. 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 Shimaizu and DSC-60, Germany for all the samples using Nickel filter, CuKα 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 poloxamer-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.

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.

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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