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Formulation and *In vitro* evaluation of elvitegravir solid dispersion

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Abstract
The present study deals with the formulation and evaluation of elvitegravir solid dispersions to improve the oral bioavailability of poorly water soluble drug. They are usually presented as amorphous products, mainly obtained by two major different methods, for example, fusion and solvent evaporation. Among the different methods of preparation of solid dispersion, fusion method was found to be most effective. FTIR studies were performed to identify the physicochemical interaction between drug and carriers and found to be compatible. Solid dispersion of elvitegravir was prepared with PEG 6000, Urea and Mannitol in different drug: carrier ratio using different methods. The prepared solid dispersions were evaluated for solubility analysis, drug content, *In-vitro* drug release studies and SEM studies. The formulation FSDPN3 containing PEG 6000 showed highest drug release within 20mins.

Keywords: elvitegravir; solid dispersions; bioavailability; fusion method; solvent evaporation

1. Introduction
The formulation of hydrophobic drugs as solid dispersions is a significant area of research aimed at improving the dissolution and bioavailability of hydrophobic drugs [1]. Solid dispersions consisting of two components in the solid state are referred to as binary systems. The two components are a water-soluble carrier and a hydrophobic drug dispersed in the carrier substance [2]. Chiou and Riegelman [3] defined the term solid dispersion as 'the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting- solvent method'. Several insoluble drugs have been shown to improve their dissolution character when incorporated into solid dispersion. It releases the drug through different mechanisms, and the rate of release of drug to the surrounding fluid is mainly dependent on the type of solid dispersion formed [4]. Solid dispersion technique has been widely employed to improve the dissolution rate, solubility and oral adsorption of poorly water soluble drugs [5]. Management of the drug release profile using solid dispersions is achieved by manipulation of the carrier and solid dispersion particles properties [6]. Parameters, such as carrier molecular weight and composition, drug crystallinity and particle porosity and wettability, when successfully controlled, can produce improvements in bioavailability [7, 8]. The aim of the present work is to enhance the oral bioavailability of poorly water soluble drug like Elvitegravir by enhancing aqueous solubility which is achieved by preparing solid dispersion and then developing a fast dissolving drug delivery system for the prepared solid dispersion.

2. Materials and Methods
2.1 Materials: Elvitegravir was obtained from Chandra labs, Hyd. Polyethylene glycol and mannitol were procured from ESSEL fine chem. Mumbai. Cross povidone, Sodium starch glycolate and Cross caramellose sodium were purchased from MYL CHEM Mumbai. Lactose monohydrate, Urea, Magnesium stearate and talc were purchased from S.D. Fine Chem. Ltd, Mumbai, India.

2.2 Methods
Preparation of Solid Dispersion [9, 10]
Solid dispersions were prepared by different methods like solvent evaporation and fusion method and the compositions as given in table-1 and 2.

Solvent evaporation method: Elvitegravir and each of water soluble carrier PEG 6000, Urea and Mannitol were weighed accurately in various ratios (1:1, 1:2 and 1:3) and transferred to

beaker containing sufficient quantity of acetone to dissolve. The solvent was evaporated at room temperature. The resulting solid dispersion was stored for 24 hrs in a desiccator to congeal. Finally, dispersion were passed through sieve no.85 and stored in desiccator till further use.

Fusion Method: Each of water soluble carrier PEG 6000, Urea and Mannitol were weighed accurately in various ratios (1:1, 1:2 and 1:3) and melted in a porcelain dish at 80-85ºC and to this calculated amount of Elvitegravir was added with thorough mixing for 1-2 minutes followed by quick cooling. The dried mass was then pulverized by passing through sieve no.85 and stored in a dessicator until used for further studies.

Table 1: Composition of Elvitegravir solid dispersions by Fusion method

Solid dispersion Composition	Method	Drug-Polymer Ratio	Formulation Code
Elvitegravir: Urea	Fusion method	1:1	FSDUN1
		1:2	FSDUN2
		1:3	FSDUN3
Elvitegravir: PEG 6000	Fusion method	1:1	FSDPN1
		1:2	FSDPN2
		1:3	FSDPN3
Elvitegravir: Mannitol	Fusion method	1:1	FSDMN1
		1:2	FSDMN2
		1:3	FSDMN3

Table 2: Composition of Elvitegravir solid dispersions by Solvent evaporation method

Solid dispersion composition	Method	Drug-Polymer Ratio	Formulation Code
Elvitegravir: Urea	Solvent evaporation method	1:1	SSDUN1
		1:2	SSDUN2
		1:3	SSDUN3
Elvitegravir: Mannitol	Solvent evaporation method	1:1	SSDMN1
		1:2	SSDMN2
		1:3	SSDMN3

Characterization of Solid Dispersions:

Drug content

An accurately weighed quantity of solid dispersion equivalent to 20mg of Elvitegravir was taken into a 100ml volumetric flask, dissolved in acetone and suitably diluted with 6.8pH Phosphate buffer. The content of Elvitegravir was determined spectrophotometrically at 313 nm against suitable blank using UV-visible spectrophotometer (1601, Shimadzu, Kyoto, Japan) [11].

Solubility Studies

Solubility studies were performed according to method reported by Higuchi and Connors. Excess (usually more than 1mg/ml concentration) of solid dispersions were added to 25ml of distilled water taken in stopper conical flasks and mixtures were shaken for 24hrs in rotary flask shaker. After shaking to achieve equilibrium, 2ml of aliquots were withdrawn at 1hr intervals and filtered through whatmann filter paper. The filtrate was diluted if necessary and analyzed by UV-spectrophotometer at 244nm. Shaking was continued until three constitutive readings were same [12].

***In-vitro* dissolution studies**

The quantity of solid dispersion equivalent to 20mg of Elvitegravir was filled in colourless hard gelatin capsule by hand filling method. The dissolution study of capsules was conducted using dissolution testing USP apparatus 1 (basket method) in 900 ml of 6.8pH Phosphate buffer at 37±0.5ºC and at a speed of 50 rpm. Aliquot of 5ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume after each sampling and analyzed spectrophotometrically at 313 nm against suitable blank using UV-visible spectrophotometer (1601, Shimadzu, Kyoto, Japan) [13, 14].

3. Results and Discussion

Drug content results for solid dispersions: The drug content in the solid dispersions was almost same and the assay was in the range and the assay did not drop in the solid dispersion the value was above 97% for all formulations and the results are represented in the tables-3-6.

Table 3: Percentage of drug content in Elvitegravir solid dispersions by fusion method using urea

FSDUN1	FSDUN2	FSDUN3
97.5±0.25	97.6±0.26	98.4±0.29

Table 4: Percentage of drug content in Elvitegravir solid dispersions by fusion method using PEG 6000

FSDPN1	FSDPN2	FSDPN3
98.3±0.17	98.4±0.51	98.2±0.61

Table 5: Percentage of drug content in Elvitegravir solid dispersions by fusion method using mannitol

FSDMN1	FSDMN2	FSDMN3
97.6±0.81	97.3±0.51	97.4±0.56

Table 6: Percentage of drug content in Elvitegravir solid dispersions by solvent evaporation method

SSDUN1	SSDUN2	SSDUN3	SSDMN1	SSDMN2	SSDMN3
87.6±0.16	89.6±0.19	89.0±0.29	91.6±0.31	93.8±0.45	94.2± 0.64

The drug content in the solid dispersions was almost same and the assay was in the range and the assay did not drop in the solid dispersion the value was above 87% for all formulations.

Solubility results for solid dispersions: Practically insoluble in water, DMSO ≥86mg/mL, Ethanol ≥85mg/mL.

Scanning Electron Microscopy (SEM)

SEM studies as shown in the figure-1 revealed the surface morphological properties of the solid dispersion indicating that the solid dispersion was in amorphous state.

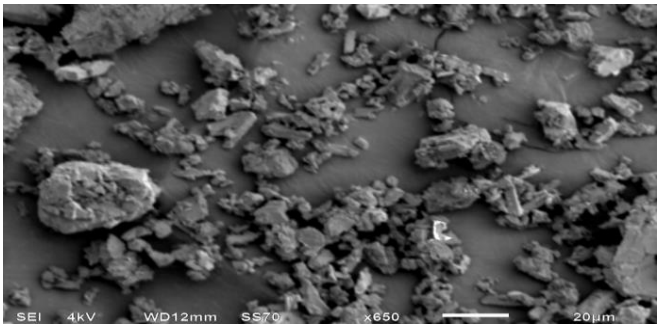

Fig 1: SEM studies for optimised formulation

***In-vitro* dissolution results for Solid Dispersions:**

Drug release in solid dispersion by fusion method: *In-vitro* dissolution test results indicate complete dissolution of drug from all its solid dispersion within 20min figure. Among the different methods of preparation of solid dispersion, fusion method was found to be most effective. The formulation FSDPN3 showed highest drug release within 20min.

Table 7: Cumulative percentage drug release with Urea

Time (minutes)	Cumulative percentage drug release with Urea		
	FSDUN1	FSDUN2	FSDUN3
5	49.3±0.18	53.21±0.20	68.28± 0.12
10	52.2± 0.24	58.52±0.29	77.65±0.16
15	66.5±0.25	69.43±0.20	84.34±0.25
20	75.36±0.20	79.65± 0.18	86.47± 0.27

Table 8: Cumulative percentage drug release with PEG 6000

Time (minutes)	Cumulative percentage drug release with PEG 6000		
	FSDPN1	FSDPN2	FSDPN3
5	45.21±0.16	52.18±0.15	65.11±0.54
10	59.32±0.24	65.15±0.14	77.32±0.24
15	75.58±0.18	78.16±0.199	85.35±0.26
20	97.69±0.18	98.17± 0.16	**100.1±0.17**

Table 9: Cumulative percentage drug release with Mannitol

Time (minutes)	Cumulative percentage drug release with Mannitol		
	FSDMN1	FSDMN2	FSDMN3
5	36.12±0.48	38.11±0.26	40.0±0.16
10	51.47±0.64	56.54±0.24	65.21±0.18
15	69.85±0.27	73.26±0.23	79.58±0.19
20	85.15±0.18	89.32±0.29	94.64±0.58

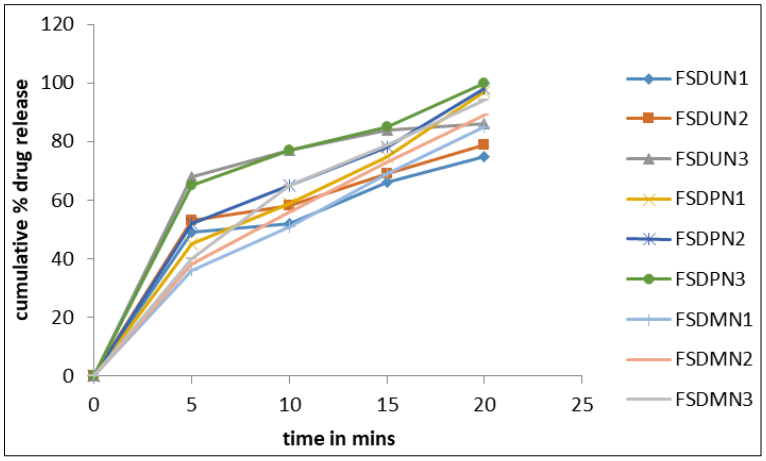

Fig 2: Drug release profile for solid dispersions of Elvitegravir with Urea, PEG 6000 and Mannitol

Drug release in solid dispersion by solvent evaporation method

Table 10: Cumulative percentage drug release with Urea

Time (minutes)	Cumulative percentage drug release with Urea		
	SSDUN1	SSDUN2	SSDUN3
5	45.21±0.13	49.32± 0.18	64.21± 0.87
10	59.36±0.18	54.24±0.24	78.35±0.78
15	65.35±0.24	67.54±0.65	82.36±0.45
20	78.31± 0.22	83.25±0.96	87.31±0.28

Table 11: Cumulative percentage drug release with Mannitol

Time (minutes)	Cumulative percentage drug release with Mannitol		
	SSDMN1	SSDMN2	SSDMN3
5	32.18±0.18	37.12±0.74	42.16±0.18
10	49.15±0.19	54.25±0.47	67.24±0.45
15	67.16±0.54	70.45±0.75	74.27±0.26
20	84.14±0.78	86.25± 0.45	90.22±0.98

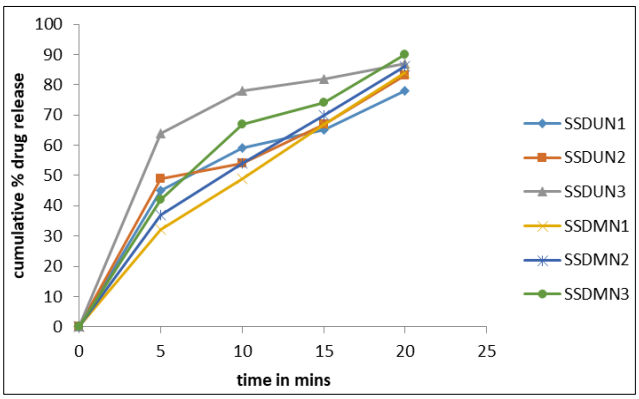

Fig 3: Drug release profile for solid dispersions of Elvitegravir with Urea and Mannitol

Analysing the release profile it was found FSDPN3 formulation with Elvitegravir and PEG6000 with ratio 1:3 has shown maximum release compared with others.

4. Conclusion

Solid dispersions were successfully prepared by fusion method and solvent evaporation method for an anti-viral drug Elvitegravir by using polymers such as Urea, Mannitol and PEG 6000. Among the various solid dispersions prepared, the formulation i.e., the solid dispersion of Elvitegravir with PEG 6000 prepared by fusion method FSDPN3 showed faster dissolution rate ie, within 20mins. Thus it is considered as an optimized formulation which fulfil the objective of the study.

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