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Original Article

Formulation development and in-vitro evaluation of elvitegravir loaded solid dispersions to sustained release tablets

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ABSTRACT

The aim of the present study is to formulate Sustained release tablets of elvitegravir solid dispersions. The enhancement of oral bioavailability of poorly water soluble drugs like Elvitegravir could be improved by enhancing aqueous solubility. Among numerous ways of enhancing drug dissolution, solid dispersions and inclusion complexation are promising techniques to enhance the dissolution of poorly water soluble drugs. The calibration curve of Elvitegravir was obtained in the range of 2-10 µg/mL at the wavelength of 313 nm. It has shown good linearity with a regression coefficient of 0.999 (r^2 value). This result exhibit a direct relationship between concentration of polymers and drug release. Among the various formulations tablets of batch E2 prepared with 40mg Guar gum showed complete release of drug within 24 hrs.

Keywords: Elvitegravir, solid dispersions, Sustained release tablets, Guar gum

INTRODUCTION

Solubility of active pharmaceutical ingredients (API) has always been a concern for formulators, since inadequate aqueous solubility may lead to development of parenteral products and limit use of oral products. Solubility plays an important role in drug disposition, since the maximum rate of passive drug

transport across a biological membrane, is the product of permeability and solubility. Poor solubility has been identified as the cause of numerous drug development failures. For drugs that have very poor aqueous solubility, the rate at which the drug dissolves (dissolution) is often the slowest step and therefore exhibits a rate limiting effect on drug bioavailability. Therefore, one of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs. Consequently, great efforts have been made to improve oral bioavailability of poorly water soluble drug by increasing their dissolution rate through various techniques. The formulation of hydrophobic drugs as solid dispersions is a significant area of research

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aimed at improving the dissolution and bioavailability of hydrophobic drugs. 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. In recent years, in association with progress and innovation in the field of pharmaceutical technology, there has been an increasing effort to develop prolonged release dosage forms for many drugs. Correspondingly, a growing number of new prolonged release dosage forms have been submitted for regulatory approval. Prolonged release dosage forms have many advantages in safety and efficacy over immediate release drug products in that the frequency of dosing can be reduced, drug efficacy can be prolonged and the incidence and/or intensity of adverse effects can be decreased. Sustained-release dosage forms either as capsules or tablets provide a constant therapeutic plasma level of the drug, with less frequent administration and hence, improved patient compliance during medication. Such prolonged action dosage forms are particularly useful in the management of chronic illnesses such as hypertension, diabetes and schizophrenia.

MATERIALS AND METHODS

Drug & excipient compatibility: Prior to the development of the dosage forms the pre-formulation study was carried out. Hence infrared spectra of pure drug and the physical mixture of drug and polymers were taken. Infra red spectra matching approach was used for the detection of any possible chemical reaction between the drug and the excipients. A physical mixture (1:1) of drug and polymer was prepared and mixed with suitable quantity of potassium bromide. About 100mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 10 tons pressure. It was scanned from 4000 to 150 cm^{-1} in a shimadzu FT-IR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and excipients and matching was done to detect any appearance or disappearance of peaks.

SOLID DISPERSION OF WITH POLYETHYLENE GLYCOL 6000, UREA AND MANNITOL

Methods of Preparation of Solid Dispersion

Solid dispersions were prepared by different methods like solvent evaporation and fusion method.

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. Solid dispersions were prepared using compositions as given in Table 1,2.

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 6.8 pH Phosphate buffer. The content of Elvitegravir was determined spectrophotometrically at 313 nm against suitable blank using UV-visible spectrophotometer (1601, Shimadzu, Kyoto, Japan).

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 312 nm against suitable blank using UV-visible spectrophotometer (1601, Shimadzu, Kyoto, Japan).

Preparation of sustained release tablets of solid dispersion by direct compression method

Solid dispersion of PEG-6000 (1:3 ratio) equivalent to 150mg of drug prepared by fusion method were taken and mixed with directly compressible diluent, superdisintegrants and other excipients in a plastic container. Table gives composition of the tablet formulation. Powder blend were directly compressed using 8mm, round-shaped flat punch in a multi station tablet compression machine (Cadmach, Ahmedabad, India).

POST COMPRESSION PARAMETERS

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various

pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters.

Physical Appearance: The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, colour, presence or absence of odour, taste etc.

Size & Shape: It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.

Weight variation test: Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Thickness and diameter: The thickness and diameter of 10 tablets were recorded during the process of compression using vernier calipers.

Friability: The percentage friability was determined by the formula:

% Friability = $(W_1-W_2) / W_1 X 100$

W_1 = Weight of tablets before test

W_2 = Weight of tablets after test

In vitro dissolution studies: In-vitro dissolution study was performed by using USP dissolution testing apparatus 2 (Paddle method). Weighed tablets from different batches were kept in a flask of the dissolution apparatus containing 900 ml of 6.8pH Phosphate buffer dissolution medium maintained at 37 ± 0.5ºC and at a speed of 50 rpm. Aliquot of dissolution medium (5 ml) was withdrawn at specific time intervals and the samples were replaced with fresh dissolution medium. Aliquot were analyzed spectrophotometrically at 313 nm against Suitable blank using UV-visible spectrophotometer (1601, Shimadzu, Kyoto, Japan).

RESULTS AND DISCUSSION

Drug and Excipients compatibility studies: FTIR studies were performed to understand the compatibilities between the drug with different excipients. The figures above illustrate that the functional groups like O-H Stretching with the observation range of 3550-3200 has peaks at 3283.32 in pure drug and 3284.25 in optimized formulation. Similarly the functional group C ═O Stretching has a peak range of 1710-1680 has peaks at 1685.78 in pure drug and 1686.17 in optimized formulation. Similarly the functional group C-F Stretching has a peak range of 1400-1000 has peaks at 1134.39 in pure drug and 1134.59 in optimized formulation. The functional groups in both the pure drug and optimized formulation are found. Hence it can be concluded that the pure drug is compatible with the excipients used in the study.

Invitro drug release of solid dispersion: Analysing the release profile it was found **FSDPN3** formulation with API and PEG 6000 with ratio 1:3 has shown maximum release compared with others.

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.

Invitro drug release of sustain release tablets: Tablets were evaluated for *in vitro* dissolution studies in simulated gastric fluid and the results were shown in the Table. Formulations E1 showed 94.8% of drug release with 20mg of Guar gum, E2 showed 97% of drug release with 40mg of Guar gum, E3 which contain 20mg 0f HPMC K4M showed 78.6% of drug release within 15 min, E4 showed 88.3% of drug release with 40mg of HPMC K4M, E5 showed 98.3% of drug release with 20mg of EC and finally E6 showed 90.2% of drug release with 40mg of EC. This result exhibit a direct relationship between concentration of polymers and drug release. Among the various formulations tablets of batch E2 prepared with 40mg Guar gum showed complete release of drug within 12 hrs.

CONCLUSION

Among the various solid dispersions prepared, the formulation i.e., the solid dispersion of Elvitegravir with PEG 6000 prepared by fusion method shows faster dissolution rate it was decided to use formulations FSDPN3 to formulate sustained release tablets using polymers like Guar gum, HPMCK4M, E.C by direct compression Method. The powder blend was subject to various physical characteristics tests such as bulk density, tapped density, Hausners ratio, compressibility index. The powder was compressed and the core tablets were evaluated for weight variation, hardness, thickness, disintegration time and the results were within specification. In the formulation the best results showed was with Guar gum10% in formulation with MCC.

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

Table 3 : Formulation Table of sustain release tablets

Ingredients (mg)	E1	E2	E3	E4	E5	E6
Elvitegravir SD	150	150	150	150	150	150
Guar gum	20	40	-	-	-	-
HPMC K4M	-	-	20	40	-	-
EC	-	-	-	-	20	40
MCC	QS	QS	QS	QS	QS	QS
Magnesium Stearate	10	10	10	10	10	10
Talc	10	10	10	10	10	10
Total weight	400	400	400	400	400	400

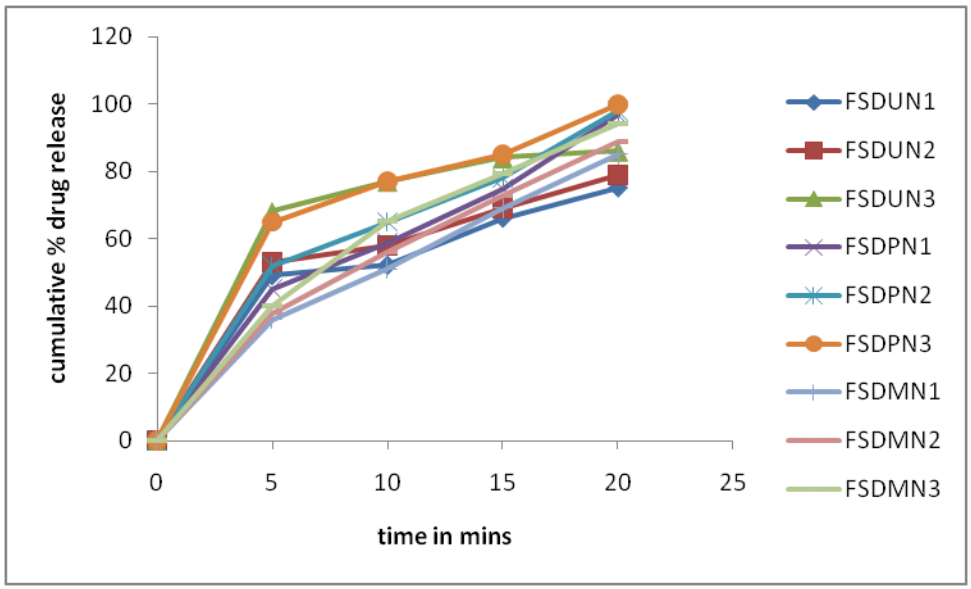

Figure 1: Drug release profile for solid dispersions of Elvitegravir

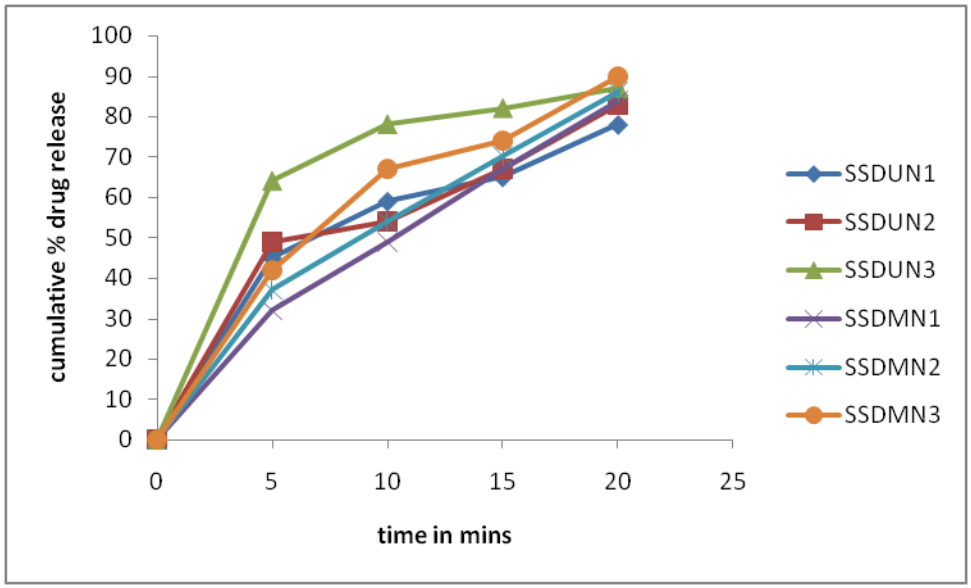

Figure 2: Drug release profile for solid dispersions of Elvitegravir

Table 4: Evaluation of Tablets for formulations (F1 – F6)

Formulation	Hardness (kg/cm^2)	Friability (%)	Weight Variation (mg)	Thickness (mm)
E1	3.2	0.35	401	2.20
E2	3.0	0.32	400	2.21
E3	3.4	0.36	400	2.16
E4	3.6	0.34	401	2.11
E5	3.2	0.38	399	2.19
E6	3.5	0.40	398	2.13

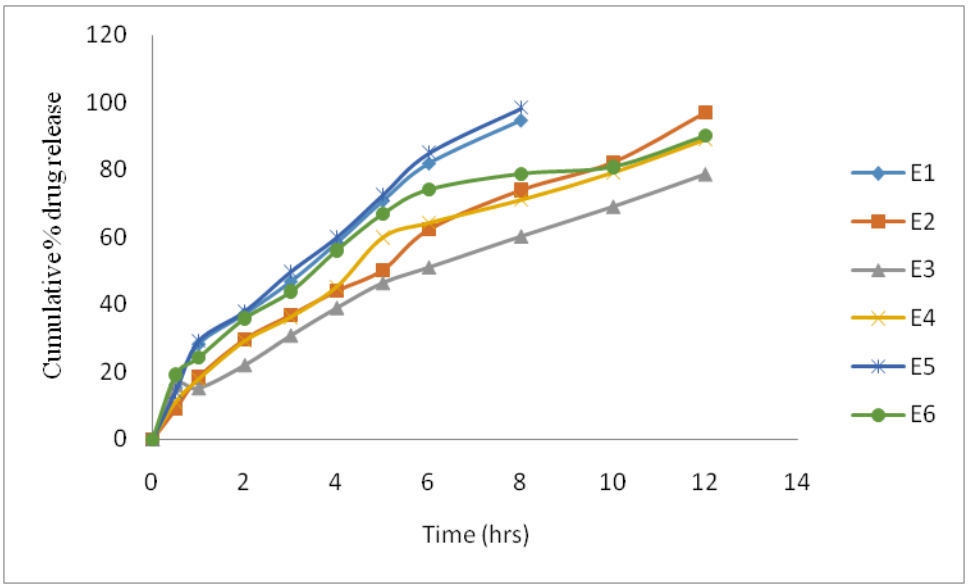

Figure 3: Dissolution graph for SD to sustained release formulations E1-E6

REFERENCES

1. Vasconcelos TF, Sarmento B and Costa P. Solid dispersions as strategies to improve the oral bioavailability of poorly water soluble drugs. Drug discovery today.2007;12:23-24.
2. Sheu MT, Yeh CM, Sokoloski TD. Characterization and dissolution of fenofibrate solid dispersion systems. Int J Pharm. 1994;103:137-146.
3. Sastry S, Nyshdham J, Fix J. Recent technological advances in oral drug delivery: A review. AAPS PharmSciTech. 2000;13:138-44.
4. Prasad Tandale, Dipti Joshi , R. S. Gaud Formulation and Evaluation of Extended Release Solid Dispersions Conatining Simvastatin
5. Anusha Pagadala, Madhuri Asiniparthi and Vaidehi Donti Formulation and Evaluation of Solid Dispersion of Glimepiride in to Sustained Release A sustained release tablet containing Glimepiride was formulated by using solid dispersion technique.
6. Modi A, Tayade P. Enhancement of dissolution profile by solid dispersion (kneading) technique. AAPS Pharm Sci Tech. 2006;7(3):68.
7. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm. 2000;50:47-60.
8. Prasad Tandale, Dipti Joshi , R. S. Gaud Formulation and Evaluation of Extended Release Solid Dispersions Conatining Simvastatin
9. Khayyam Shaikh, Patwekar Shailesh, Santosh Payghan, John Disouza formulation and evaluation of sustained release tablets from solid dispersions of lovastatin.