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Design and development of solid dispersions of satranidazole for enhancing the solubility

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Abstract

Solubility and dissolution behaviour of a drug are the key determinants of its oral bioavailability. Different approaches have been attempted to increase the solubility of poorly soluble drugs. Satranidazole an antibacterial and antiprotozoal drug is poorly soluble in water .In the present work an attempt has been made to enhance its dissolution by preparing solid dispersions using hydrophilic polymers such as PVP K30, mannitol, PEG 4000 and PEG 6000 in various ratios (1:1 and 1:2).All the solid dispersions showed considerably higher dissolution rate than corresponding physical mixtures and pure drug. Dissolution studies showed that formulation containing PEG 6000 in 1:1 ratio showed higher dissolution rate after 1 hr and was selected as the optimized formulation .Pure drug, physical mixture and solid dispersion were subjected todifferent studies such as Differential scanning Calorimetry, Fourier transform infrared (FT – IR) studies, X-ray powder diffractometry studies and Scanning electron microscopic studies.

Keywords: Solid dispersion, Satranidazole, Water soluble carriers, Solubility enhancement.

1. INTRODUCTION

Satranidazole is an antibacterial and antiprotozoal drug. It belongs to nitroimidazole group of drugs. It is chemically 1(1-methyl -5-nitroimidazol-2-yl) -3 methylsulfonylimidazolidin -2 - one. The drug has been classified as classII drug as per BSC [1,2]. Owing to its low aqueous solubility, the dissolution rate also is low. The solubility and dissolution rate might be increased using solid dispersion technology [3].

The incorporation of drugs into hydrophilic carriers has frequently been reported to increase the dissolution rate of poorly water soluble drugs, leading to improved drug bioavailability. Solid dispersions when exposed to aqueous media, the carrier is dissolved and the drug gets released as very fine particles. This enhanced surface area may lead to improved solubility and dissolution rate of the drug. [4 - 20]

The present work aims to evaluate the potential of solid dispersion for the enhancement of solubility and dissolution rate of poorly water soluble drug – Satranidazole, using different carriers such as PVP K30,mannitol, PEG 4000 and PEG 6000.

2. MATERIALS AND METHODS

2.1. Materials

Drug satranidazole was obtained from Alkem pharmaceuticals, Mumbai. All the carriers used were of analytical grade.

2.2. Methods

2.2.1. Preparation of solid dispersion

Solid dispersions of satranidazole were prepared by using polymers mannitol, PVP K30, PEG 4000 and PEG 6000 in ratios 1:1 and 1:2.

2.2.1.1. Fusion method

Dispersions of drug with mannitol, PEG 4000 and PEG 6000 were prepared by this method. Accurately weighed amount of polymers were melted in porcelain dish by keeping in a sand

bath. To this required amount of drug was added and thoroughly mixed. Once the dispersion was formed the mixture was quickly cooled. The dried mass was pulverized and passed through #44.The powder was stored in desiccator for further studies.

2.2.1.2. Solvent evaporation method

This method was adopted for polymer PVPK30.Drug and carrier in required proportions were dissolved in minimum volume of organic solvent methanol and the solvent was evaporated by keeping on a hot plate.The dried mass was pulverized and passed through #44.The powder was stored in desiccator for further studies.

2.2.2. Preparation of physical mixture

Physical mixtures were prepared by triturating the required amounts of drug and carriers.The resultant powder mixture was passed through #44.The powder was stored in desiccator for further studies.

Composition and formulation code of different solid dispersions and physical mixtures are given in table 1.

Table - 1: Composition of different solid dispersions and physical mixtures.

Carrier mixture	Drug: Carrier	Formulation code	
		Solid dispersion	Physical
Mannitol	1:1	F1	P1
	1.2	F2	P2
PEG 4000	1:1	F3	P3
	1.2	F4	P4
PEG 6000	1:1	F5	P5
	1.2	F6	P6
PVP K 30	1:1	F7	P7
	1.2	F8	P8

2.2.3. Evaluation of solid dispersions and physical mixtures

2.2.3.1. Drug content estimation

Drug content of each formulation was determined by taking physical mixtures and solid dispersions equivalent to 100mg of drug and transferring it to 100ml volumetric flask. Each sample was dissolved in minimum amount of methanol and further diluted with phosphate buffer of pH 6.8. The drug content was determined spectrophotometrically at 319nm using Schimadzu UV Visible spectrophotometer. Three readings were taken and then the mean and standard deviation were calculated.

2.2.3.2. *In Vitro* dissolution studies

In Vitro dissolution studies were performed by USP XXIII apparatus II (Electrolab TDT-06T). Dissolution medium was 900 ml phosphate buffer with a pH of 6.8 kept at 37±1℃. satranidazole 100mg, equivalent amounts of solid dispersion and physical mixtures were added to each flask. Rotation speed of paddle was set at 50 r.p.m. Samples of 5ml were withdrawn for a period of 1hour at regular intervals. After appropriate dilution the samples were analysed for satranidazole using UV spectrophotometer at 319 nm. The study was conducted in triplicate.

2.2.3.3. Differential scanning calorimetry (DSC) studies

Differential Scanning Calorimetry (DSC) studies of pure drug, carrier, solid dispersion and physical mixtures were carried out using DSC instrument Mettler Toledo DSC 822e.

2.2.3.4. Fourier transform infrared (FT – IR) studies

FT – IR spectra of pure drug, carrier and solid dispersion were taken using instrument Shimadzu FTIR Spectrophotometer- FTIR 8400 S

2.2.3.5. X-ray powder diffractometry studies

X-ray powder diffractometry studies of pure drug, carrier and solid dispersion were carried out using the diffractometer Bruker AXS D8 Advance.

2.2.3.6. Scanning electron microscope

Electron micrographs of pure drug, carrier, solid dispersion and physical mixtures were obtained using JEOL Model JSM - 6390LV operating at 20kV. Micrographs at different magnifications (10 μm, 5 μm and 2μm) were obtained.

3. RESULTS AND DISCUSSION

3.1. Drug content estimation

Drug content for all the formulations were in the range of 98.35 – 99.86% with low standard deviation (Table 2). The results revealed that the methods used for the preparation of solid dispersion were reproducible.

3.2. *In vitro* dissolution studies

The dissolution data of pure drug, physical mixtures and solid dispersions are shown in Table-1.It was shown that the pure drug has the slowest dissolution rate and only 47.45% of drug was dissolved after 60 minutes, while in case of physical mixtures and solid dispersions with different carriers with different ratios, the dissolution increased profoundly. When compared with physical mixtures, solid dispersions showed increased dissolution rate. The amount of drug

Table - 2: Drug content and dissolution study data

Formulation code	Drug content (%)	Drug dissolved in 60 mins (%)	Formulation code	Drug content (%)	Drug dissolved in 60 mins. (%)
F2	98.92	69.56	P2	99.21	60.23
F3	99.2 3	80.43	P3	98.71	70.55
F4	98.94	82.91	P4	98.78	68.34
F5	99.25	98.72	P5	98.66	78.43
F6	98.86	90.58	P6	99.13	67.69
F7	99.44	78.12	P7	99.68	66.67
F8	99.86	76.32	P8	99.2	67.51
Satranidazole		47.45			

dissolved in 60 minutes for different formulations was in the following order PEG 6000> PEG 4000> PVP K 13>mannitol. The fastest dissolution rate was obtained forthe formulation F5with the Drug and carrier (PEG 6000) ratio of 1:1(98.72% .The fast and rapid dissolution rate of satranidazole in solid dispersion may be due tothe presence of drug in amorphous form which is revealed by the results of different studies mentioned below. The increased dissolution rate might also be due to factors like reduction in particle size and increase in surface area when converted to solid dispersion. The dissolution profiles of pure drug, physical mixtures (P5) and solid dispersion (F5) are shown in figure 1.

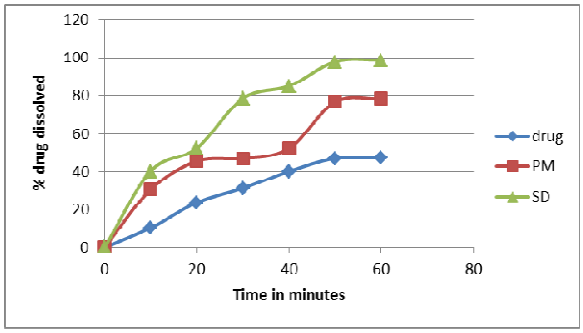
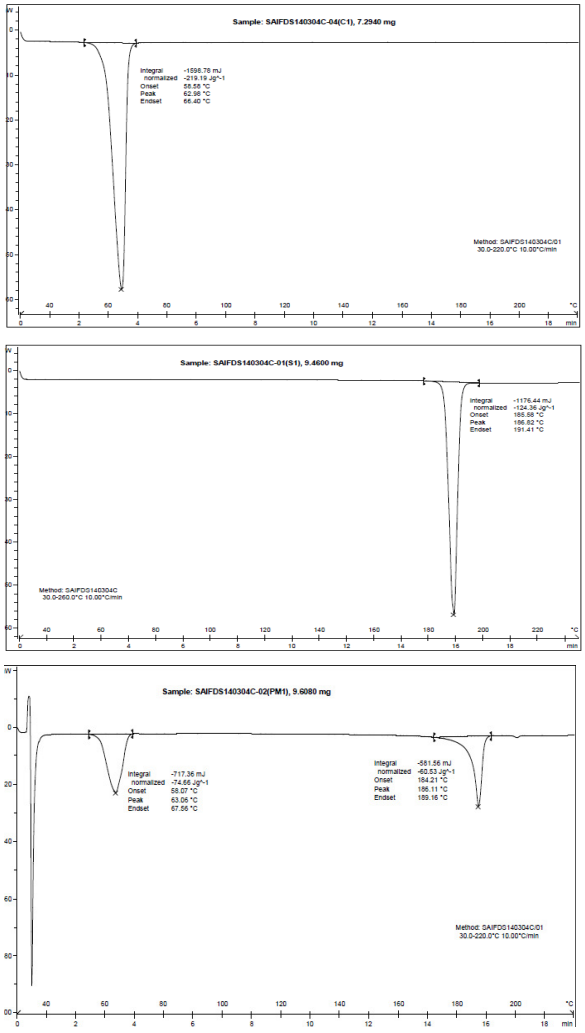


Fig - 1: The dissolution profiles of pure drug, physical mixture(P5) and solid dispersion(F5).

3.3 Differential scanning calorimetry (DSC) studies

Differential scanning calorimetric (DSC) studies of pure satranidazole, carrier, their physical mixtures and solid dispersions were conducted to investigate the crystallinity and drug – carrier interaction. The DSC thermogram of the solid dispersion showed endothermic peaks around 185.99ºC and 61.19ºC, corresponding to the melting point of satranidazole and PEG 6000, respectively**.** The endothermic peak of satranidazole is of very high intensity, showing the crystalline form of the drug. The DSC thermograms of drug, carrier, physical mixture and solid dispersions showed both the endothermic peaks (Figure 2) with some changes in the characteristics of the peaks shown by individual components. The endothermic peaks of physical mixture and solid dispersions lost its sharpness and distinctive appearance. It showed that no possible interaction was found between drug andcarrier but the loss of peaks sharpness may be due to conversion from crystalline form toamorphous form of the drug.



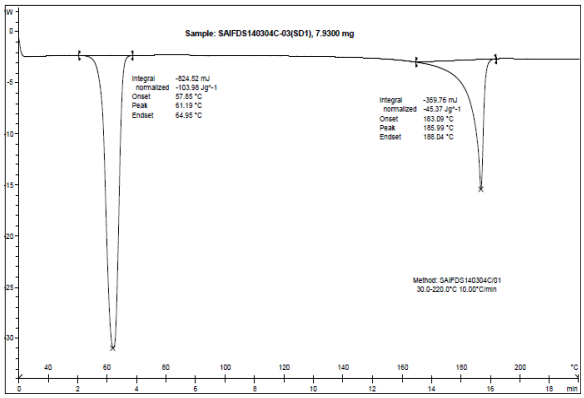


Figure - 2: The DSC thermograms of carrier(C1), satranidazole (S1), Physical mixture (PM1), and solid dispersion (SD1).

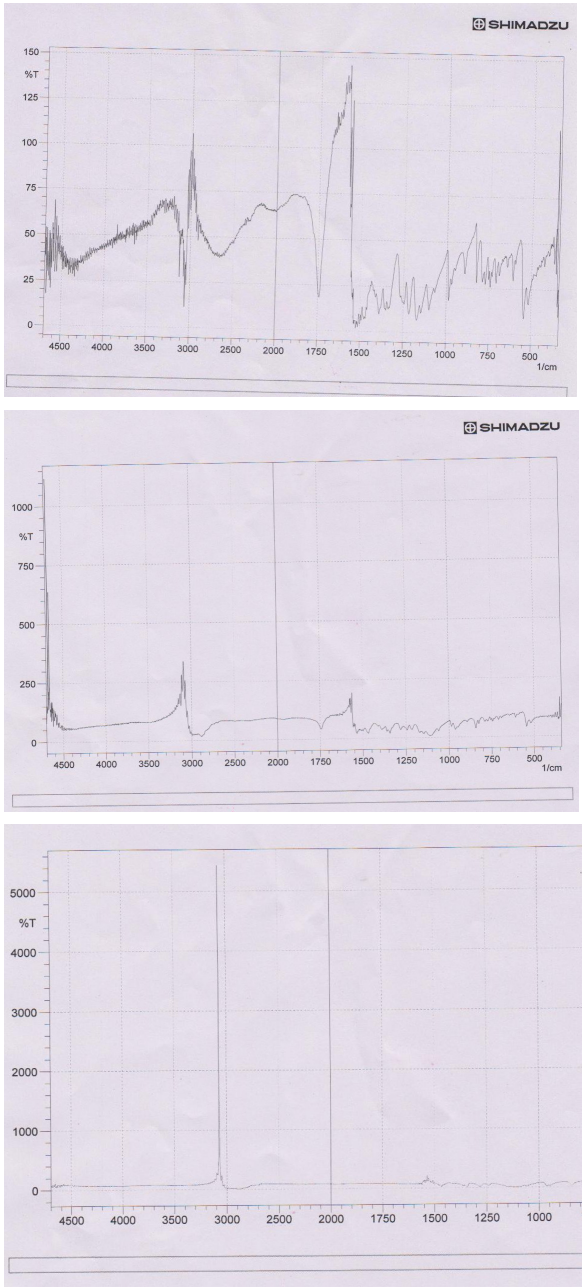


Figure - 3: IR spectra of pure drug, solid dispersion and carrier.

3.4 Fourier transform infrared (FT-IR) Studies

The IR spectra of SD, showed that there was no shifting of the band indicating that there is no interaction between satranidazole and carrier (PEG 6000) by fusion method (Figure 3).

3.5. X-ray diffractometry Studies

Fig.ure 4 shows the diffractograms of pure satranidazole, physical mixture and solid dispersion.

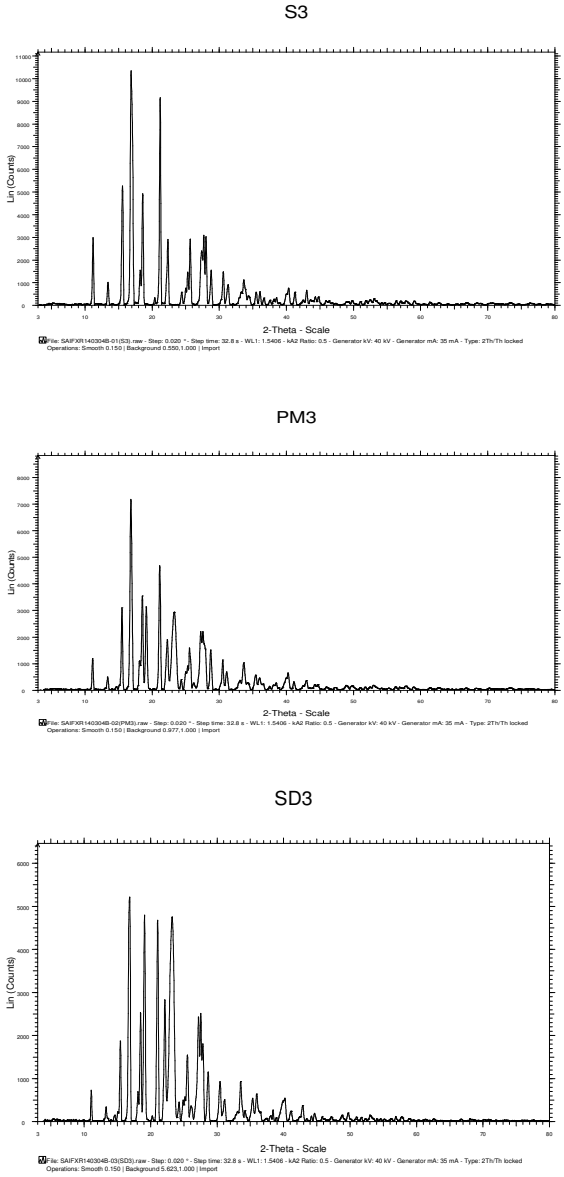


Figure - 4: X-ray diffractograms of (a) pure satranidazole; (b) Physical mixture; and (c) Solid dispersions.

The diffractograms of pure satranidazole with numerous distinctive peaks showed that the drug is highly crystalline in nature. Peaks with high intensity were present in the diffractogram at around 15.5°, 16.8°, 21.1° and 22.3° along with

some other peaks of lower intensity. The same peaks were present in the diffractogram of solid dispersion, but with lower intensity. This indicates that crystallinity of the drug has been diminished. As compared to pure satranidazole and physical mixture, the peaks in the diffractogram of solid dispersions were of much reduced intensities, indicating the amorphous nature of the drug.

3.6. Scanning Electron Microscope Analysis

Figure 5 shows the scanning electron micrographs of carrier, physical mixture, pure drug and solid dispersion. After analysis, the scanning electron microscopy (SEM) revealed that pure satranidazole has smooth surfaced crystalline shape. But in case of solid dispersions the crystals of satranidazole are in smallest size and they have irregular shapes. The dissolution rate of satranidazole in solid dispersions was rapid and more as compared to pure satranidazole and physical mixture because the particle shape irregularity and small particle size, increased the specific surface area and enhanced the dissolution rate .

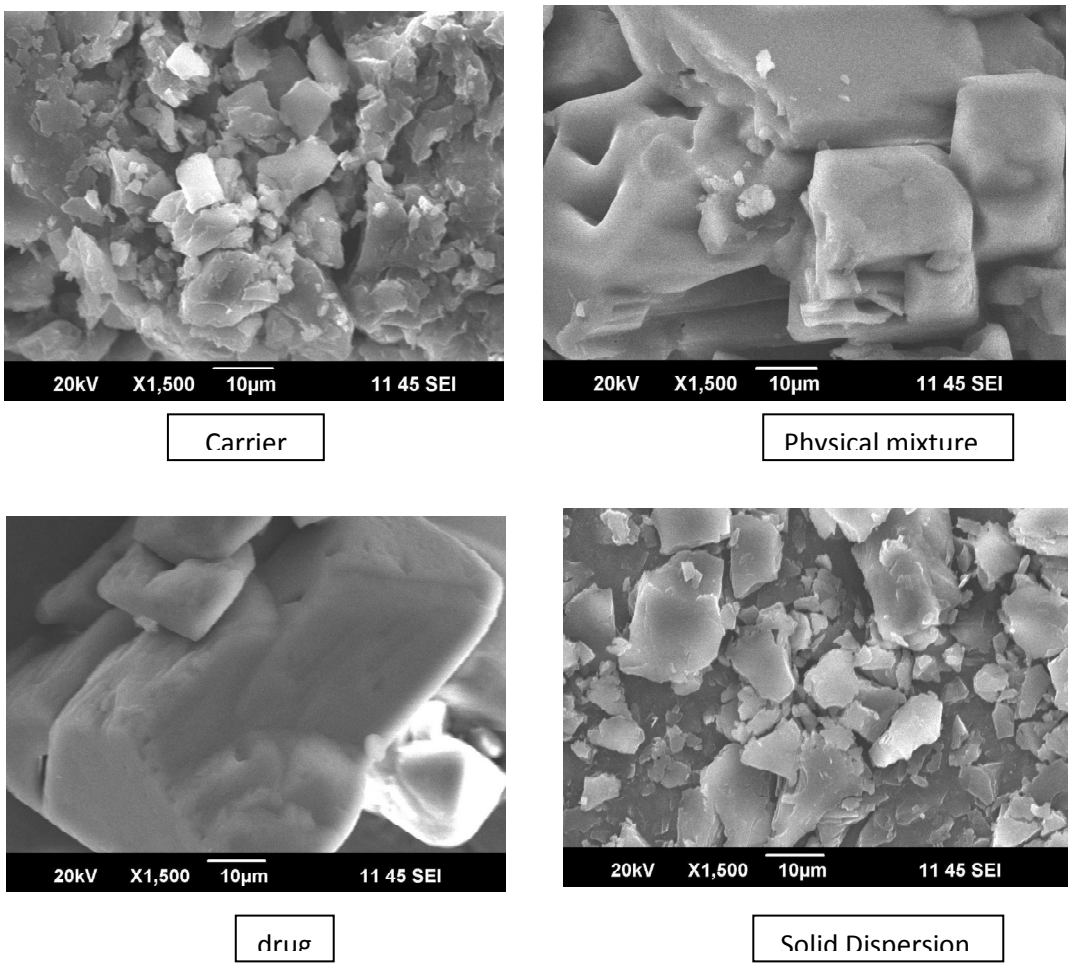


Figure - 5: Scanning electron micrographs of carrier, physical mixture, pure drug and solid dispersion.

4. CONCLUSION

The study shows that the dissolution rate and solubility of poorly soluble drug satranidazole can be improved and enhanced to great extent by solid dispersion technique, using hydrophilic polymers. Among the different polymers used, highest dissolution rate was achieved using PEG 6000 as carrier using fusion method.

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