Research Paper

SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUG USING SPRAY DRYING TECHNIQUE

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ABSTRACT

Role of spray drying method was studied for solubility enhancement of poorly aqueous soluble model drug, Tinidazole, using solid dispersion approach. Diverse water soluble carriers *viz* Polyethylene glycols (PEG 4000), Hydroxypropyl Methyl cellulose (HPMC 5cps), and β-cyclodextrin were used for this purpose. Phase solubility studies revealed a linear increase in drug solubility with carrier concentration. All the carriers showed dissolution improvement *vis-à-vis* pure drug to varing degrees. Solid state characterization of various solid dispersions using XRD, FTIR, DSC and SEM techniques revealed distinct loss of drug crystallinity in the formulation, ostensibly accounting in dissolution rate.

KEYWORDS: BCS Class II; Bioavailability; Dissolution; Polyethylene glycol; Hydroxypropyl Methyl cellulose; β-cyclodextrin

1. INTRODUCTION

Poorly water soluble drugs are associated with slow drug absorption leading eventually to inadequate and variable bioavailability [1,2]. And nearly 40%of the new chemical entities currently being discovered are poorly water-soluble drugs [3]. Based upon their permeability characteristics, the biopharmaceutics classification system (BCS) classifies such drugs in two major classes, i.e., Class II and IV [5]. The BCS class II drugs are poorly water-soluble entities with high permeability [1,2,3]. Most formulation strategies for such drugs are targeted at enhancing their fine dispersion at absorption level [2,6,7].

Tinidazole (TZ), chosen in the current studies, is a poorly water-soluble drug known to demonstrate dissolution or solubility limited absorption [4]. Although the mean bioavailability of the drug is low, yet its rate of absorption is quite inconsistent and delayed with time. Based upon its aqueous solubility and various dissolution parameters, the drug bioavailability can unambiguously be regarded as limited solely to dissolution. A few attempts to enhance the solubility or dissolution of TZ have appeared in the literature using diverse like Polyethylene glycols (PEG 4000), Hydroxypropyl Methyl cellulose (HPMC 5cps), and β-cyclodextrin.

Beside investigating the role of diverse method in improvement of solubility or dissolution of TZ, the current studies aim at exploring different water-soluble carriers to improve solubility or dissolution using Spray drying as a method.

2. MATERIAL AND METHODS

2.1. Materials

Tinidazole (TZ) was procured from Unichem Ltd., Mumbai, India. Polyethylene glycols (PEG 4000), Hydroxypropyl Methyl cellulose (HPMC 5cps), and β-cyclodextrin were laboratory grade. All other chemicals used were of analytical grade.

2.2. Preparation of solid dispersions and corresponding Pure drug

The Tinidazole drug and the carriers (PEG 4000, HPMC 5cps, and β-cyclodextrin) were weight accurately in different ratios and then dissolved in appropriate quantity of acetone and water respectively. Finally both the solutions were mix well using glass rod to obtain a clear solution. Spray drying of this solution were performed using laboratory-scale spray dryer (LABULTIMA, Diamond Industrial Estate, Mumbai, 400068 India) under the following set of conditions: Inlet temperature, 140°C; Outlet temperature, 100°C; Feed pump rate, 5% (100% mean 1000ml/hour); Atomization air pressure, 2.5 kg/cm² and aspiration 45 m Bar. Each solid dispersion batch was prepared in duplicates employing each carriers in variable proportions, i.e., 1:1, 1:2, 1:3, 1:5, 1:7, 1:9 w/w. The dispersions were subsequently desiccated under vacuum for 48 hrs.

2.3. Phase-solubility studies

Solubility measurements were performed in triplicate. An excess quantity of the Tinidazole and solid dispersions were dissolved in 10ml of distilled water. The flasks were capped tightly and sonicate for 2 hours and left a side for overnight. After that the solutions were filtered by 0.45µm filter paper and analyzed by UV spectrophotometer (Elico) at 310nm.

2.4. In-vitro dissolution studies

Drug release studies were performed in triplicate on USP type II apparatus () for 2 hours in distilled water at 100rpm. The temperature was maintained at 37±1°C, solid dispersions equivalent to 50mg of Tinidazole were taken. The aliquots were taken at the particular interval of time and analyzed for absorbance using UV-spectrophotometer () at 310nm. 50 mg of pure drug was also treated in the same manner and the results of pure drug and solid dispersions were compared.

2.5. Powder X-ray diffraction studies

Powder X-ray diffraction (PXRD) patterns were traced employing X-ray diffractometer (Siemens D-5000 Germany)for samples, using Ni filtered Cu-k (α) radiation. The samples were analyzed over 2θ range of 5° to 50° value.

2.6. Differential scanning calorimetric studies

Differential scanning calorimetric (DSC) analysis were carried out using DSC TA 60 (Shimadzu Japan) for drug, carriers, solid dispersion formulations. Sample were heated in the aluminum disc over the range of 50°- 300°C at the rate of 10°C per minute under nitrogen atmosphere. DSC spectra were

recorded using TA 60 W software. The obtained spectra were then studied for the interaction between drug and the carrier in the solid dispersion.

2.7. Fourier transform infra red spectroscopy

Fourier transform infrared (FT-IR) spectroscopy was carry for all the solid dispersions using FTIR spectrophotometer (Shimadzu Japan) for drug and the carriers interaction. The 10mg sample was mixed with equal amount of KBr and scanned over a frequency range 4000-500 $cm^{-1.}$

2.8. Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) analyzed with 1 mg or 2 mg of sample of pure drug and the solid dispersion formulations were mounted on to the stubs using double sided adhesive tape and then coated with gold palladium alloy using fine coat ion sputter (Jeol, fine coat ion sputter, JFC1100). The samples were subsequently analyzed under the scanning electron microscope (JSM6100, Jeol, Japan) for external morphology.

3. RESULTS AND DISCUSSION

3.1. Phase-solubility studies

Phase-solubility studies show a linear increase in drug solubility with increased carrier level. Hydrophilic carriers are known to interact with drug molecules mainly by electrostatic forces and occasionally by other types of forces like hydrogen bonds.

The order of solubility enhancement of TZ using various carriers in water, i.e., β-cyclodextrin > HPMC 5cps > PEG 4000. Relative high drug solubility observed with β-cyclodextrin due to formation of inclusion complex. There observed 3 fold increases in the solubility of TZ with β-cyclodextrin (Shown in Table 1).

Table 1

Formulations	Concentration (µg/ml)
Tinidazole Drug	13.48
HPMC 5cps (1:1)	21.42
HPMC 5cps (1:3)	24.53
HPMC 5cps (1:5)	26.75
HPMC 5cps (1:7)	32.52
HPMC 5cps (1:9)	44.47
PEG 4000 (1:1)	23.21
PEG 4000 (1:3)	26.74
PEG 4000 (1:5)	28.41
PEG 4000 (1:7)	30.71
PEG 4000 (1:9)	38.03
β-Cyclodextrine (1:1)	28.60
β-Cyclodextrine (1:2)	43.15

3.2. In-vitro dissolution studies

The current dissolution studies on TZ and the TZ-carrier systems were carried out in dissolution medium, i.e., distilled water. Table 2 enlists the dissolution perameters of TZ solid dispersions with various carriers (PEG 4000, HPMC 5cps, and β-cyclodextrin) in different concentrations of each carrier. As is evident from the table, the dissolution rate of pure TZ is low after dissolution span of 2 hrs. Solid dispersions formulated with all the carriers exhibited significant improvement in the dissolution parameters of TZ. The order of dissolution enhancement with various binary systems was found to be β-cyclodextrin > HPMC 5cps > PEG 4000.

Table 2

Time (Min)	Cumulative Dissolution (%)			
	TZ	β-Cyclodextrin	HPMC 5cps	PEG 4000
5	3.54	11.02	10.88	8.94
15	16.37	29.87	27.20	22.35
30	24.99	49.09	44.29	36.41
60	33.21	68.49	63.95	54.69
90	41.21	88.01	83.95	74.41
120	51.12	99.06	98.37	96.25

However the dissolution profiles of TZ and various solid dispersions with carriers were plotted with % cumulative dissolution of the TZ (Fig-1).

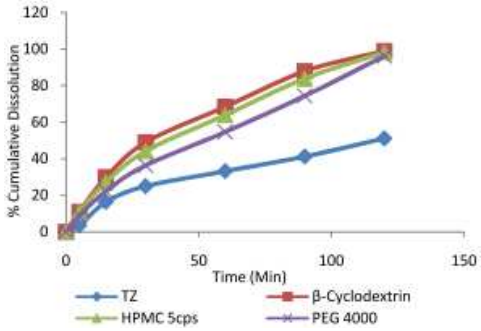
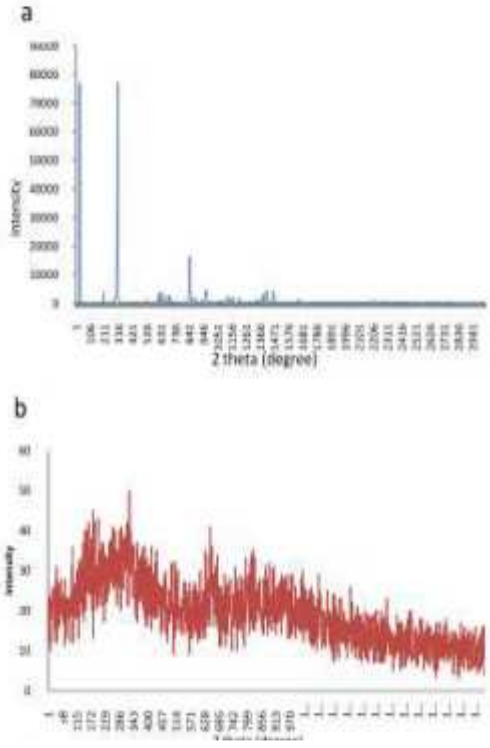


Fig-1 Dissolution Pattern of TZ and solid dispersions

3.3. Powder X-ray diffraction spectroscopy

Fig 2 shows the diffraction pattern of TZ and different solid dispersions. Powder X-ray diffraction analysis indicates the changes produced in the drug crystal structure. The change in crystallinity was obtained by Siemens D-5000 X-ray diffractometer, Germany.

The diffraction pattern of pure drug showed high degree of crystallinity for the drug as evidenced by few peaks of high intensity and in case solid dispersions the formation of different crystal habits or amorphous form of the TZ was found as a result low intensity peaks were observed. (Fig 2).



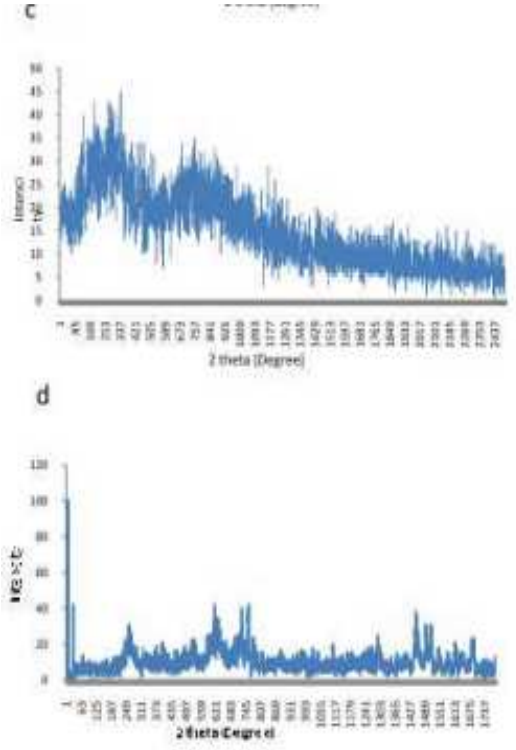
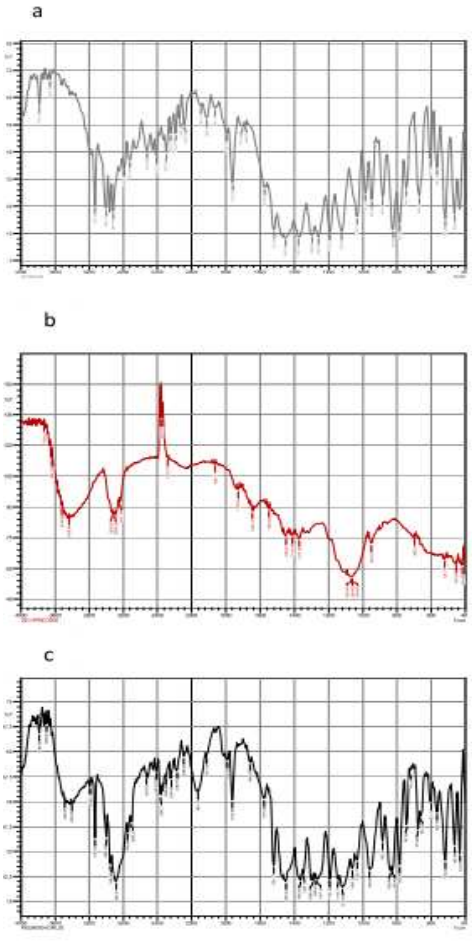


Fig. 2. X-ray diffraction patterns of (a) TZ; (b) 1:2 TZ: β-cyclodextrin solid dispersion; (c) 1:9 TZ: HPMC 5cps; (d) 1:9 TZ: PEG 4000

3.3.1. Fourier transform infrared spectroscopy

Fig. 3 shows the FTIR spectra of the drug, carriers was no significant change in the spectrum of solid dispersions, as incorporation of TZ into the carriers did not modify the position of its functional groups.



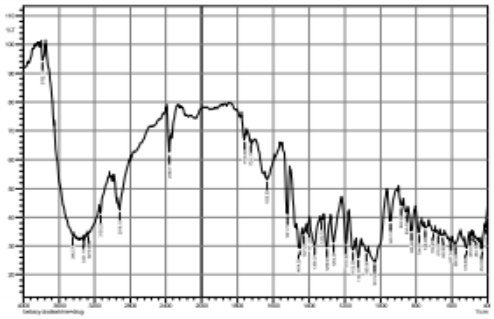
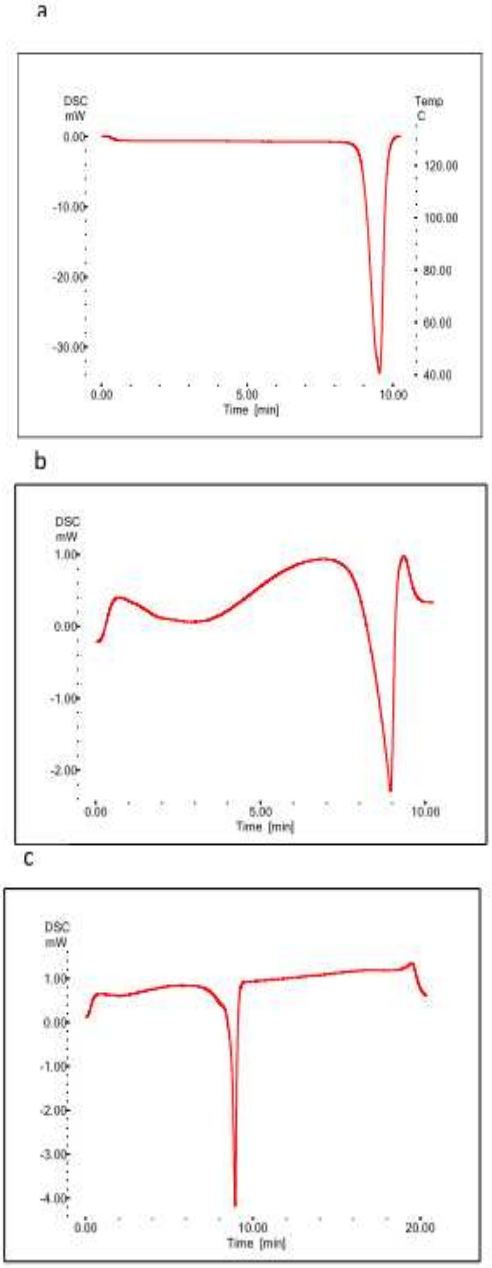


Fig. 3. FTIR spectra of (a) TZ; (b) TZ PEG 4000; (c) TZ HPMC 5cps; (d)TZ β-cyclodextrin

3.3.2. Differential scanning calorimetry studies

Fig 4 shows the DCS thermo grams of TZ, carriers and the solid dispersions. In case of drug TZ the melting point was 128°C and in case of PEG 4000, β-cyclodextrin and HPMC 5cps solid dispersions the melting points of drug were found to be 125.58°C, 126.68°C, and 125.75°C respectively in above solid dispersions indicating no any change in there melting points.



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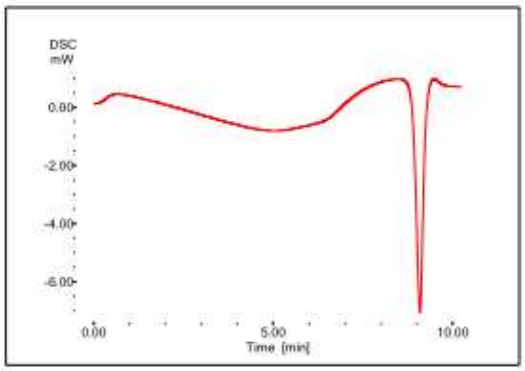


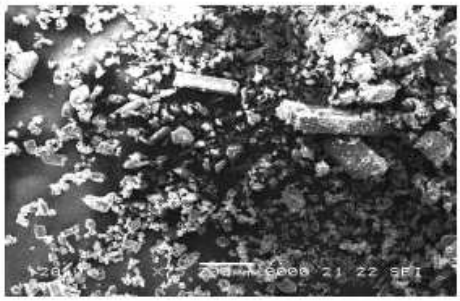
Fig.4. DSC thermograms of (a) TZ; (b) TZ PEG 4000; (c) TZ HPMC 5cps; (d)TZ β-cyclodextrin

3.3.3. Scanning electron microscopy

Fig. 5. Shows that pure drug TZ in irregular crystalline shapes. The solid dispersion of TZ and the carriers photomicrograph shows the topological changes produced in the carriers particles. The surface seems to be more porous in nature.

Solid state characterization studies reveled particle loss of drug crystallinity which can bring about significant change in the drug dissolution rate. However, other factors like reduced particle size, increased surface area, and closer contact between the hydrophilic carrier and the drug may also be influential in enhancing drug solubility and/or dissolution rate observed with the solid dispersion particles.

a



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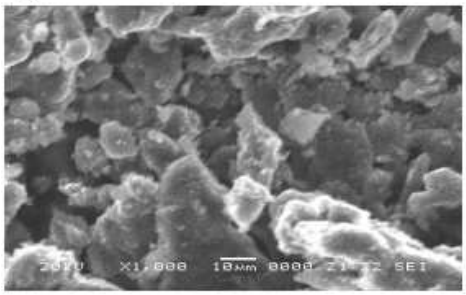

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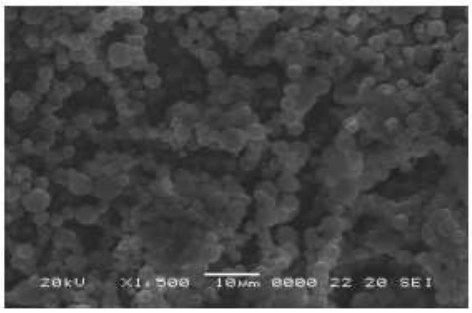

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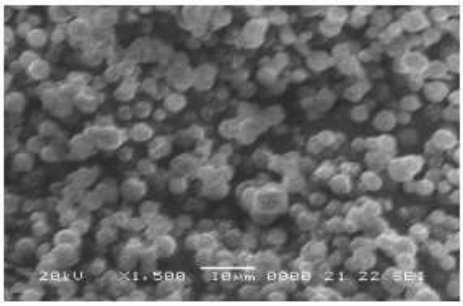

Fig. 5. Scanning electron microphotographs of (a) TZ; (b) TZ PEG 4000; (c) TZ HPMC 5cps; (d)TZ β-cyclodextrin

4. CONCLUSIONS

From the study it was investigated that spray drying technique is effective method for solubility enhancement. Solid dispersion of TZ with different water soluble carriers in different proportions were prepared. The different carriers were PEG 4000, β-cyclodextrin and HPMC 5 cps. A higher solubility profile was obtained may be due to effective particle size reduction in the TZ and was found to be approximately 3 times more. That is, enhancement in the solubility of Tinidazole solid dispersion was observed.

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