



Journal of Pharmacy and Allied Health Sciences

ISSN 2224-2503

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Modification of Crystallization Behaviour of Sertaconazole by Preparing its Solid Dispersions

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ABSTRACT

Sertaconazole is one of the most effective fungicidal and fungistatic agents. But its practical use is limited due to its extremely low aqueous solubility and therefore, search for an adequate delivery system is still a challenging issue. So, the aim of present study was to modify the crystalline behaviour of sertaconazole by preparing its solid dispersions so as to increase the solubility of sertaconazole. Some methods have been reported in literature but these methods require high amount of carrier which can be toxic in such amount. In the present study, melting method was used to prepare the solid dispersions and these solid dispersions were characterized by various techniques in solid as well as in solution state. Solution state studies showed a profound increase in the solubility and dissolution rate of sertaconazole with nicotinamide in presence of surfactant and fatty acid and solid state studies showed an absence of chemical interaction between sertaconazole and nicotinamide. It is concluded that oleic acid and tween 80 when combined with sertaconazole and nicotinamide in the solid dispersions results in profound increase in solubility. So, these dispersions can be used for oral delivery of sertaconazole and can be considered as better choice for the treatment of dermatological and gynaecological infections.

Key words: Nicotinamide, solid dispersion, crystallinity, dissolution, oleic acid

INTRODUCTION

One of the simplest and easiest ways to administer a drug is by oral drug delivery system (Anguiano-Igea *et al.*, 1995). Comparing different oral dosage forms, solid dosage forms have many advantages over other dosage forms like easy to formulate, greater stability and accurate dosage etc. Therefore, main focus during the development of New Chemical Entities (NCE) in these days is to develop their solid dosage (Serajuddin, 1999; Craig, 2002). But, many of these NCE are poorly water soluble resulting in less absorption after oral administration (Chiou and Riegelman, 1971; Matsumoto and Zografi, 1999). Low drug solubility also results in decreased bioavailability, increased chance of food effect, incomplete release from the dosage form and higher inter-patient variability. These poorly soluble drugs are also associated with complex dissolution testing with poor correlation to *in vivo* absorption. Their poor solubility and *in vivo/in vitro* correlations leads to difficulties in the development on many newly synthesized compounds. Therefore, to overcome these difficulties, various strategies have been adopted to improve the water solubility of drugs (Tanaka *et al.*, 2006). Solid Dispersions (SDs) are one of the most successful

strategies to improve drug release of poorly soluble drugs but very few marketed products are available based on the solid dispersion strategy. The main reasons for this are poor physical stability, reproducibility of physicochemical characteristics, cost of production, difficulty in incorporating into formulation of dosage forms and requirement of large amount of carrier to achieve the desired dissolution (Dhirendra *et al.*, 2009).

To overcome these problems, one useful approach is to use surfactant as additional additive along with hydrophilic carrier for preparing solid dispersions. However, solid dispersions containing this combination are also very less in market due to high amount of carrier and surfactant required and toxicity of surfactants in high concentration.

To overcome these disadvantages, one of the useful methods is to combine one more excipient (oleic acid) to these solid dispersions so as to decrease the required amount of carrier and surfactant and having enhanced solubility and dissolution rate. These solid dispersions can be developed into different solid dosage forms for oral and parenteral administrations (Tang *et al.*, 2008). Many advantages are associated with these solid dispersions like improved solubility and dissolution rate, improved stability, decrease in production cost and better patient compliance.

The development of antimycotic agents is very essential due to the increased morbidity and mortality caused by fungal infections in recent years (Ortiz, 1992). Sertaconazole (SER) is one of the effective fungicidal and fungistatic agents and has a broad-spectrum activity against dermatophytes, opportunistic filamentous fungi and also gram positive bacteria (Agut *et al.*, 1992; Carrillo-Munoz *et al.*, 2008). It has a good profile of security, high cutaneous permanence and low systemic absorption while using for the treatment of dermatologic and gynaecological infections (Palacin *et al.*, 2000). Despite these valuable features, one main problem associated with SER is its extremely low aqueous solubility (<0.01% w/v) which strongly limits its practical use (Albet *et al.*, 1992) and therefore, the search for an adequate delivery system is still a challenging issue. Inclusion complexes of SER with cyclodextrins (Perdomo-Lopez *et al.*, 2002; Rodriguez-Perez *et al.*, 2006) are reported but such system needed more than 70% of cyclodextrins which can be toxic in such amount (Gould and Scott, 2005).

Therefore, in the present work, solid dispersions of sertaconazole nitrate were prepared containing Nicotinamide (NIC) along with low content of surfactant (tween 80) and fatty acid (oleic acid), with the aim to improve the solubility and dissolution rate of sertaconazole nitrate. The novelty of the present study lies in the fact that solid dispersions of sertaconazole nitrate with low concentration of excipients have not been reported previously. The drug-carrier interactions in the liquid and solid-state were studied by phase solubility studies, saturation solubility analysis, dissolution studies, Powder X-ray Diffraction (PXRD), Fourier Transform Infrared spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC).

MATERIALS AND METHODS

Materials: Sertaconazole nitrate was obtained as gift sample from Glenmark Pharmaceutical Ltd. (Mumbai, India). Nicotinamide was purchased from Loba chemie Pvt. Ltd. (Mumbai, India). Tween 80 and oleic acid were purchased from S.D. Fine Chem. Ltd. (Mumbai, India). All other reagents and solvents used were of analytical grade. Triple-distilled water was used throughout the experiments.

Methods

Preparation of physical mixtures: Physical mixtures of sertaconazole with nicotinamide in the weight ratios of 90:10 (PMS1), 80:20 (PMS2), 65:35 (PMS3), 50:50 (PMS4), 30:70 (PMS5) and

10:90 (PMS6) were obtained by geometric mixing and pulverizing accurately weighed amounts of SER and NIC in a glass mortar. The pulverized mass was then sifted through 100 mesh sieve and stored in a desiccator till further studies.

Preparation of solid dispersions: Binary solid dispersions containing SER and NIC in the weight ratios 90:10 (SDS1), 80:20 (SDS2), 65:35 (SDS3), 50:50 (SDS4), 30:70 (SDS5) and 10:90 (SDS6) were prepared by the fusion method. This method included the melting of NIC in a porcelain dish over a calibrated hot plate at 145-150°C and addition of drug to the molten carrier to prepare binary solid dispersions. The fused mass was then placed immediately in a freezing mixture of ice and salt for solidification. The mass was then placed in a vacuum desiccator for at least 48 h till complete drying. The dried mass was pulverized and sifted through 100 mesh sieve and stored in a desiccator till further studies.

Ternary solid dispersions containing SER, NIC and tween 80 in weight ratios 50:50:5 (SDS7) and 65:35:5 (SDS8) were prepared by the same procedure as discussed above. The only difference is that the drug was mixed in tween 80 and then added to molten carrier.

Similarly, solid dispersions containing SER, NIC, tween 80 and oleic acid in the weight ratios 50:50:5:5 (SDS9) and 65:35:5:5 (SDS10) were prepared by mixing drug with tween 80 and oleic acid and then added to molten carrier. Rest of the procedure is same as mentioned in the preparation of binary solid dispersions.

Content uniformity analysis: Drug content in all the Solid Dispersions (SDs) and Physical mixtures (Pms) were evaluated in methanol Using Ultraviolet (UV) spectrophotometer (Perkin Elmer, Bangalore, India) at 302 nm. The absorbance was recorded at 302 nm against a blank solution containing equivalent amount of nicotinamide in methanol to overcome the absorbance of nicotinamide.

Saturation solubility studies: Weighed amounts of each sample (SER, solid dispersions and physical mixtures) equivalent to 100 mg of drug, were separately introduced into 25 mL stoppered conical flasks containing 10 mL of distilled water. All the flasks were shaken on a water bath shaker for 72 h at 37°C and equilibrated for 2 days. Aliquots were passed through 0.2 micron filter (Millipore, Bangalore, India) and the filtrates were suitably diluted with methanol and analyzed on a UV spectrophotometer. The samples were studied in triplicate for saturation solubility.

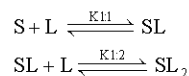
Phase solubility studies: The phase solubility studies were conducted as per the method reported by Higuchi and Connors (1965). Excess drug was added into 25 mL stoppered conical flasks containing 10 mL of aqueous solution (0-1% w/v) of NIC. The flasks were shaken on a water bath shaker at 37°C, for 72 h and equilibrated for 2 days. Preliminary experiments have been carried out which showed that this time period was sufficient to assure saturation. After attaining the equilibrium, all the saturated solutions were filtered through a membrane filter (0.2 micron) and the filtrates were suitably diluted and analyzed at 302 nm against the blank having same concentration of NIC as that of sample. All the data were the average of three determinations.

Similarly, phase solubility studies of SER were carried out in NIC solutions in presence of 1% w/v tween 80 alone and in combination with 1% w/v oleic acid.

Calculation of complexation constants from the phase solubility studies: The aqueous solubility of pure SER was found to be 16.69 $\mu\text{g mL}^{-1}$. The solubility increased in a non-linear

fashion in presence of NIC suggesting the formation of higher order complexes. So, the interaction between the drug and NIC was studied by assuming that both 1:1 and 1:2 complexes were formed. The complexation constants and fit parameters multiple R^2 and F-values were calculated as determined by Aggarwal and Jain (2011) and the method is given below. The closer R^2 approaches 1 and the higher the F-value, the better the fit.

Complexation for a system in which 1:1 and 1:2 complexes of a substrate S with a ligand L are formed is represented by Scheme 1:



And

$$K_{11} = \frac{[SL]}{S_0 [L]} \quad (1)$$

$$K_{12} = \frac{[SL_2]}{[SL][L]} \quad (2)$$

In Eq. 1 and 2, where, S_0 is the equilibrium solubility of the substrate, $[L]$ is the concentration of free ligand, $[SL]$ is the concentration of the 1:1 complex, $[SL_2]$ is the concentration of the 1:2 complex and $K_{1,1}$ and $K_{1,2}$ are the 1:1 and 1:2 complexation constants, respectively.

Phase solubility profile of SER in aqueous solution of NIC was shown in four different ways which corresponds to four different conditions as:

- Linear fit assuming $[L] \sim [L_t]$
- Linear exact fit
- Parabolic fit assuming $[L] \sim [L_t]$
- Exact parabolic fit

where, $[L_t]$ is total ligand concentration.

***In vitro* dissolution studies:** Dissolution tests of the pure drug, SDs and PMs (equivalent to 0.1 g drug) were performed *in vitro* using the dissolution apparatus type II paddle method at $37 \pm 0.5^\circ\text{C}$ for 4 h, with a stirring rate of 50 rpm, in 900 mL of a dissolution medium of enzyme-free simulated intestinal fluid (pH 7.4 ± 0.1). Samples were collected at different time intervals with replacement of an equal volume of temperature equilibrated dissolution medium. The samples were filtered through a $0.2 \mu\text{m}$ membrane filter and the concentration of the drug was determined by UV spectrophotometry. Blank experiments with nicotinamide were also performed at the same wavelength for correction. All samples were analyzed in triplicate.

Fourier transform infrared (FTIR) spectroscopy: FTIR spectroscopy can be used to study the extent of interactions between drug and NIC by detecting the variation in the energy distribution of the interactions between drug and NIC.

To collect the spectra using FTIR spectrophotometer (Type Spectrum RX 1, California, USA), small amount of each material (pure drug, NIC, PMs and SDs) was compressed in KBr pellets. All the samples were dried overnight in a desiccator to avoid the effect of moisture. The IR spectra were obtained in the spectral region of 4000-500 cm^{-1} using a resolution of 2 cm^{-1} and 4 scans.

Powder X-ray diffraction (PXRD): The crystallinity of the pure drug, NIC, all PMs and SDs were determined using X-ray diffractometer (XPERT-PRO, Mumbai, India). Samples were scanned in a 2θ range from 5-50°.

Differential Scanning Calorimetry (DSC): The thermal behavior of pure drug, NIC, PMs and SDs were investigated using a differential scanning calorimeter (NETZSCH-204F1 Phoenix, AZ, USA) in the range of 25-600°C (heating rate 5°C min^{-1}).

RESULTS

Content uniformity analysis: All the solid dispersions exhibited good content uniformity. The content of SER (data not shown) in PMs and all the SDs were found to vary from 98.22 to 101.9%.

Phase solubility study: The solubility of SER was enhanced significantly by NIC in a nonlinear fashion as a function of NIC concentration (Fig. 1c, 2c, 3c) indicating an A_p type of phase solubility diagram (Higuchi and Connors, 1965). So, at lower concentrations of NIC, 1:1 complexation occurred between drug and NIC while at higher concentrations 1:2 complexation occurred. A representation of the data with the fitted parabola and the linear fit are shown in Fig. 1-3. The apparent stability constants ($K_{1,1}$ and $K_{1,2}$) were calculated along with the fit parameters from the phase solubility data and are given in Table 1.

An indication of the process of transfer of SER from pure drug to aqueous solution of NIC was obtained from the values of Gibbs free energy change (ΔG_{tr}°) (Patel *et al.*, 2008) and was calculated using the following equation and given in Table 2:

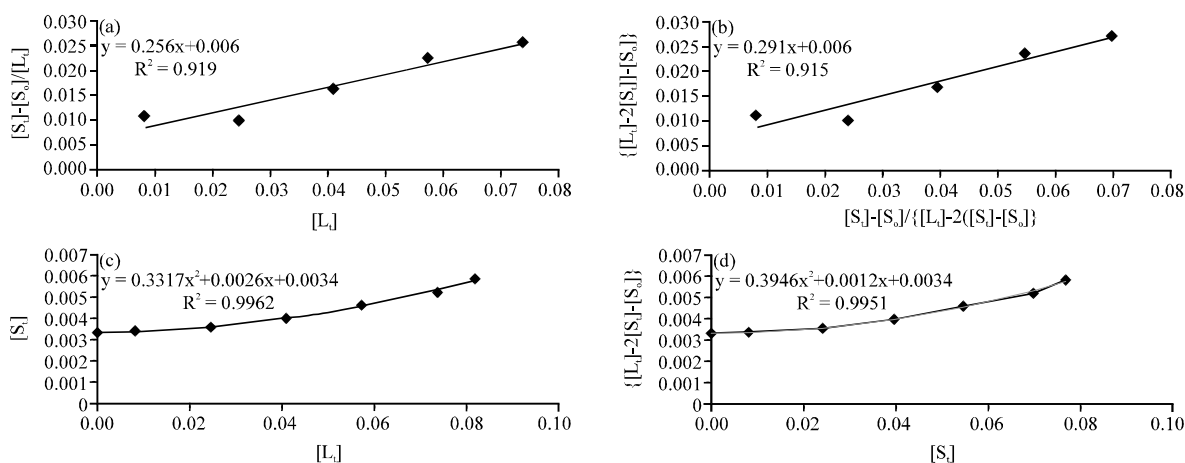


Fig. 1(a-d): Phase solubility profile of SER in aqueous solution of nicotinamide, (a) Linear fit assuming $[L_t] \sim [L_t]$, (b) Linear exact fit, (c) Parabolic fit assuming $[L_t] \sim [L_t]$ and (d) Exact parabolic fit, where, $[L]$ is concentration of free ligand, $[L_t]$ is total ligand concentration, S_0 is the equilibrium solubility of the substrate, S_t is total substrate concentration

Table 1: Apparent stability constants along with fit parameters for the interaction between sertaconazole and nicotinamide

Solutions	Model	Assumption	Linear solution		Linear fit parameters		Parabolic solution		Parabolic fit parameter	
			K _{1:1} (M ⁻¹)	K _{1:2} (M ⁻¹)	R ²	F	K _{1:1} (M ⁻¹)	K _{1:2} (M ⁻¹)	R ²	F
NIC	Approx.	[L]~[L _t]	1.8	42.7	0.919	31.470	1.40	58.5	0.996	812.0
	Exact	None	1.8	48.1	0.915	32.300	1.20	83.0	0.995	718.0
NIC+1% w/v Tween 80	Approx.	[L]~[L _t]	27.1	23.3	0.958	22.890	46.00	10.0	0.998	2050.0
NIC+1% w/v Tween 80+% w/v oleic acid	Exact	None	10.6	314.3	0.973	107.970	3.00	1435.0	0.994	672.0
NIC	Approx.	[L]~[L _t]	32.6	21.3	0.803	16.220	53.30	8.6	0.986	373.0
NIC	Exact	None	19.3	224.5	0.641	7.144	38.20	99.4	0.911	51.4

K1:1: Apparent stability constant for 1:1 complexation between drug and NIC, K1:2: Apparent stability constant for 1:2 complexation between drug and NIC, R2: Goodness-of-fit correlation coefficient, F: Ratio of the regression mean square to the residual mean square, M: Molar, [L]: Concentration of free ligand, [L_t]: Total ligand concentration

Table 2: ΔG_{tr}^o values for the transfer of SER from water to aqueous solutions of NIC

% NIC (w/v)	ΔG _{tr} ^o (kJ mole ⁻¹)		
	NIC solutions	NIC solutions containing 1% w/v tween 80	NIC solutions containing 1% w/v tween 80 and 1% w/v oleic acid
0.1	-6.092	-7.468	-7.507
0.3	-6.368	-10.770	-12.205
0.5	-7.114	-19.772	-25.707
0.7	-8.215	-29.835	-31.093
0.9	-9.276	-38.031	-40.507
1.0	-10.370	-43.278	-48.939

kJ: Kilojoules, Δg_{tr}^o: Gibbs free energy change

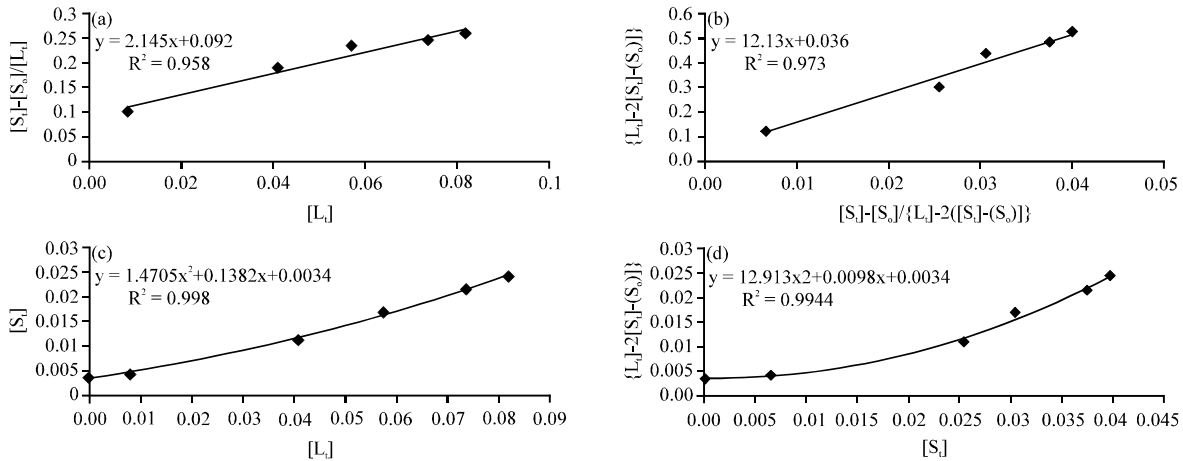


Fig. 2(a-d): Phase solubility profile of SER in aqueous solution of nicotinamide containing 1% w/v tween 80 by, (a) Linear fit assuming [L]~[L_t], (b) Linear exact fit, (c) Parabolic fit assuming [L]~[L_t] and (d) Exact parabolic fit, where, [L] is concentration of free ligand, [L_t] is total ligand concentration, S_o is the equilibrium solubility of the substrate, S_t is total substrate concentration

$$\Delta g_{tr}^o = -2.303RT \log (S_t/S_o)$$

where, S_e/S_o is the ratio of molar solubility of SER in aqueous solution of NIC containing 1% tween 80 alone or in combination with 1% oleic acid to that in pure water.

Saturation solubility studies: The solubility of physical mixtures and the solid dispersions are given in Table 3. Substantial improvement of 9.9 fold increase in solubility was obtained in case

Table 3: Saturation solubility of SER from physical mixtures and solid dispersions

Composition	Solubility ($\mu\text{g mL}^{-1}$) Mean \pm SD
Pure SER	16.69 \pm 1.210
PMS1	29.50 \pm 10.600
PMS2	38.22 \pm 0.130
PMS3	40.72 \pm 0.160
PMS4	55.94 \pm 0.200
PMS5	78.72 \pm 0.180
PMS6	129.94 \pm 0.11
SDS1	35.50 \pm 00.130
SDS2	49.83 \pm 0.120
SDS3	64.94 \pm 0.300
SDS4	86.88 \pm 0.100
SDS5	136.66 \pm 0.023
SDS6	165.33 \pm 0.26
SDS7	333.30 \pm 0.047
SDS8	522.20 \pm 0.420
SDS9	2780 \pm 2.0004100
SDS10	4171 \pm 0.0004000

SD: Standard deviation

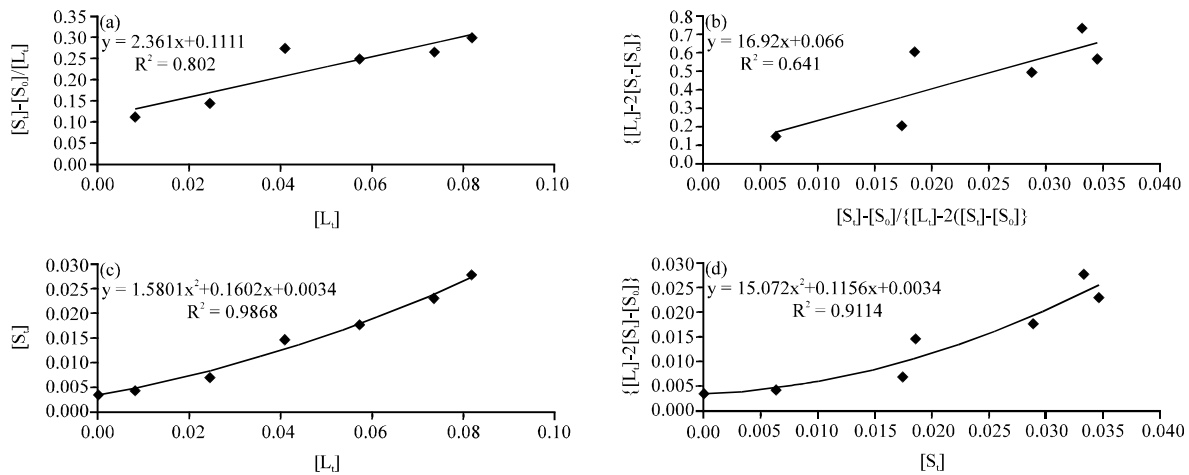


Fig. 3(a-d): Phase solubility profile of SER in aqueous solution of nicotinamide containing 1% w/v tween 80 and 1% w/v oleic acid by, (a) Linear fit assuming $[L] \sim [L_t]$, (b) Linear exact fit, (c) Parabolic fit assuming $[L] \sim [L_t]$ and (d) Exact parabolic fit, where, $[L]$ is concentration of free ligand, $[L_t]$ is total ligand concentration, S_o is the equilibrium solubility of the substrate, S_e is total substrate concentration

Table 4: Summary of wave numbers of different functional groups for SER, NIC, physical mixtures and solid dispersions

Wave No. (cm ⁻¹)	Product									
	Pure drug	NIC	PMS3	PMS4	PMS5	SDS3	SDS4	SDS5	SDS8	SDS10
N-H str.	-	3365	3366	3367	3366	3366	3366	3366	3367	3368
C-H str. Ar.	-	3160	3157	3150	3163	3162	3155	3157	3164	3158
C-O-C str. (ether)	1308	-	1303	1312	1310	1312	1313	1310	1310	1308
C = O str.	-	1679	1680	1680	1680	1678	1679	1680	1681	1675
C = C Ar. str.	1461	-	1458	1461	1461	1460	1460	1458	1459	1461
C = N Ar. str.	1637	-	1639	1639	1639	1639	1638	1638	1638	1642
C-N Ar. str.	1385	-	1386	1385	1385	1387	1381	1390	1384	1387
C-Cl str.	793	-	792	792	791	790	788	788	795	790

of solid dispersion (SDS6) whereas 31.3 fold was obtained in solid dispersion SDS8 and 249.9 fold in SDS10. A remarkably improved solubility of drug was also seen in the ternary SDs and oleic acid based SDs as compared to the binary systems.

In vitro dissolution studies: The dissolution behavior of SER from PMs and SDs is shown in Fig. 4. It can be seen from these figures that the dissolution rates of pure SER were very low with less than 7% drug dissolved after 4 h. It is also demonstrated that NIC enhanced the drug dissolution rate in binary SDs as compared to PMs. It can also be seen that dissolution rate was increased further in ternary solid dispersions and in oleic acid based solid dispersions.

Fourier transform infrared (FTIR) spectroscopy: SER showed IR bands at (cm⁻¹) 1308 (C-O-C ether stretch), 1461 (C = C aromatic stretch), 1637 (C = N aromatic stretch), 1385 (C-N aromatic stretch), 793 (C-Cl stretch) and NIC displayed important bands at (cm⁻¹) 3365 and 3160 (N-H stretch) and 1679 (C = O stretch) (Table 4). Table 4 also showed the various IR bands in different physical mixtures and solid dispersions.

Differential Scanning Calorimetry (DSC): DSC scans of SER, NIC, their PMs and SDs are shown in Fig. 5. The DSC scan of SER and NIC showed melting peaks at 156.6 and 136.9°C, respectively with an enthalpy of fusion 83.23 and 194.63 J g⁻¹.

Powder X-ray diffraction (PXRD): PXRD pattern of SER, NIC, their PMs and SDs are shown in Fig. 6. The powder X-ray diffractogram of SER showed 2θ values at 15.5, 17.11, 18.86, 20.94, 23.19, 24.62 and 28.09 indicating a high crystallinity. NIC also exhibited crystallinity as indicated by distinctive peaks at 2θ values of 11.40, 14.86, 19.56 and 22.28.

DISCUSSION

Phase solubility study: The nonlinear solubility behavior of SER in the presence of NIC might be due to the aromaticity (π-system) of the pyridine ring in NIC (Aggarwal and Jain, 2011; Rasool *et al.*, 1991).

Comparison of the values of R² and F statistical fit parameters shows clearly that the data were best represented by the parabolic regression method with approximate fit in all the systems.

The negative values of Gibbs free energy change are indicative of the spontaneity of reaction between SER and NIC. From Table 2, a decrease in Gibbs free energy change was observed with

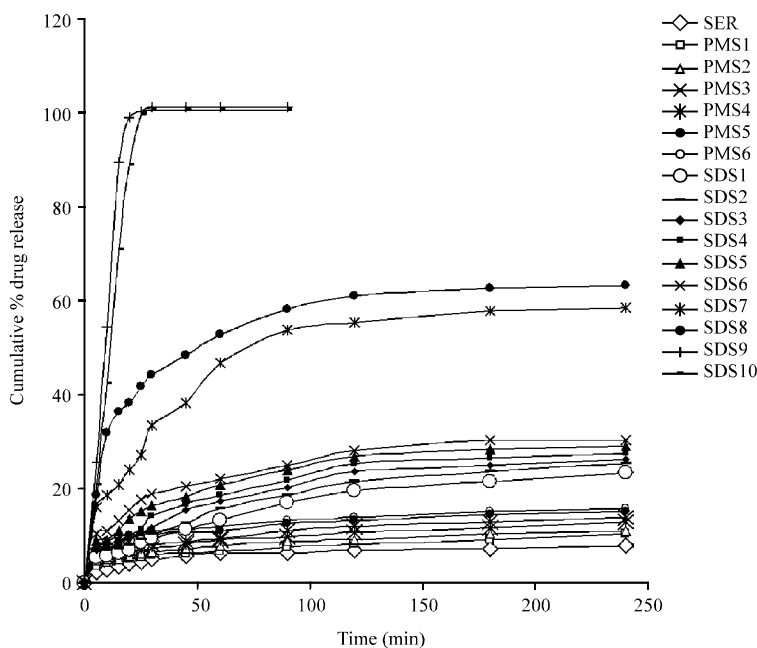


Fig. 4: Dissolution profile of physical mixtures (PMS1, PMS2, PMS3, PMS4, PMS5, PMS6), binary solid dispersions (SDS1, SDS2, SDS3, SDS4, SDS5, SDS6), ternary solid dispersions (SDS7, SDS8) and self emulsifying solid dispersions (SDS9, SDS10) of sertaconazole

increase in carrier concentration indicating that reaction became more favorable with increase in concentration of nicotinamide. The values of Gibbs free energy change decreased further when 1% w/v tween 80 was added to the NIC solutions indicating that the reaction was more favorable in presence of tween 80. The values further decreased when both 1% w/v tween 80 and 1% w/v oleic acid were added to the NIC solutions indicating that spontaneity further increased in presence of both tween 80 and oleic acid.

Saturation solubility studies: The solubility enhancement of SER from the PMs might be due to the solubilization effect of nicotinamide. Whereas, the solubility enhancement of SER from binary SDs might be due to decrease in crystallinity of the drug and also due to a highly dispersed state of the drug in the SDs resulting in its higher wettability (Marin *et al.*, 2002) as shown by XRD and DSC results.

In ternary SDs, tween 80 might improve the wettability and solubilize the non-molecularly dispersed or crystalline fraction of SER (Okonogi and Puttipatkhachorn, 2006). On the other hand, the enhancement in aqueous solubility of SER from oleic acid based SDs might be due to the microemulsifying effect of oleic acid when coming in contact with water along with the solubilizing effect of tween 80 (Heo *et al.*, 2005).

In vitro dissolution studies: There might be several factors for the enhancement of dissolution of SER from binary systems which includes increased wettability and dispersibility, lack of crystallinity and particle size reduction (Chaulang *et al.*, 2008; Ford, 1986; Martinez-Oharriz *et al.*, 2002). In PMs, dry mixing of drug with a hydrophilic carrier probably resulted in reduction of the electrostatic charges which tend to keep drug particles united together.

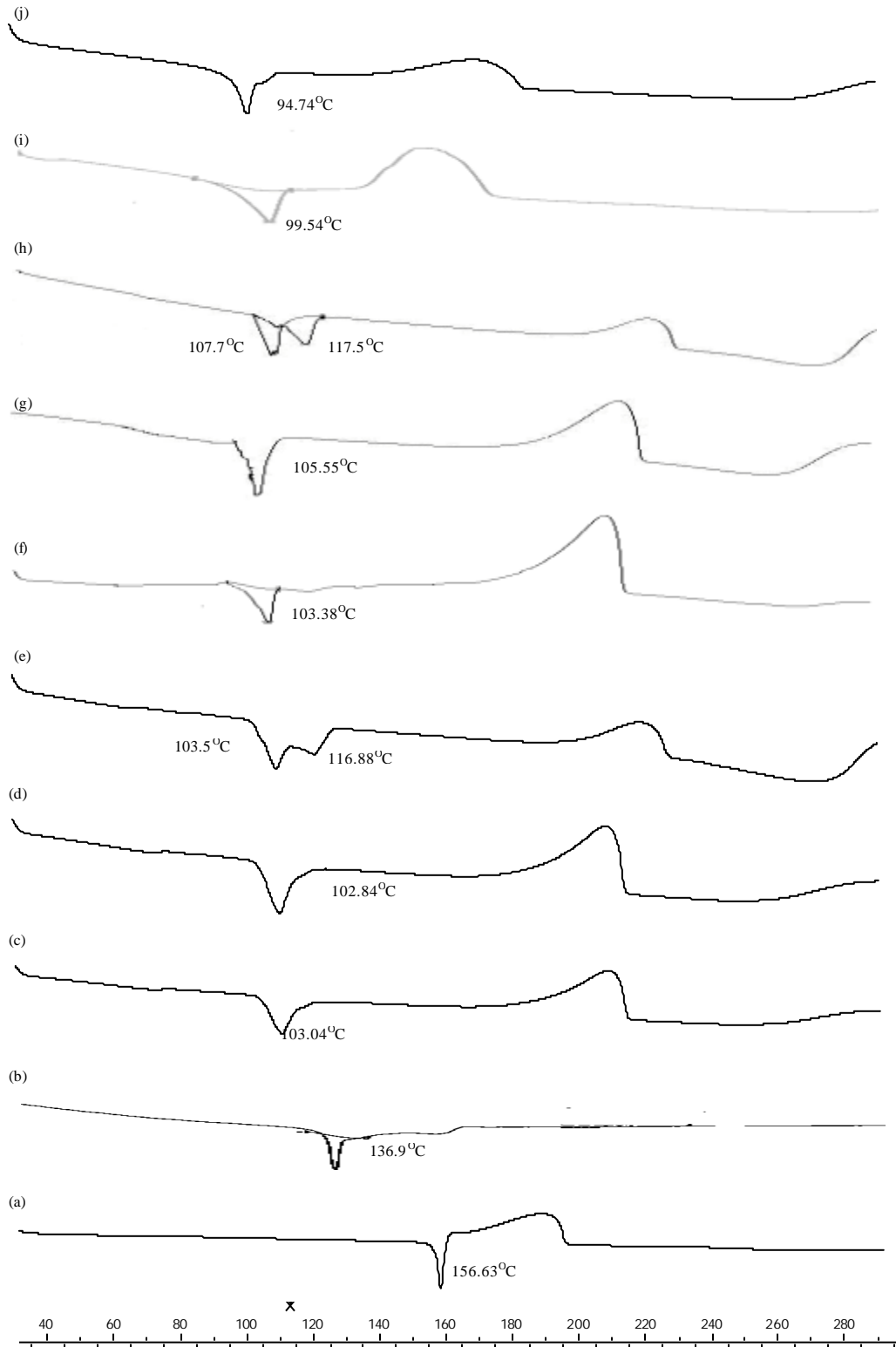


Fig. 5(a-j): DSC thermograms of, (a) SER, (b) NIC, (c) PMS3, (d) PMS4, (e) PMS5, (f) SDS3, (g) SDS4, (h) SDS5, (i) SDS8 and (j) SDS10

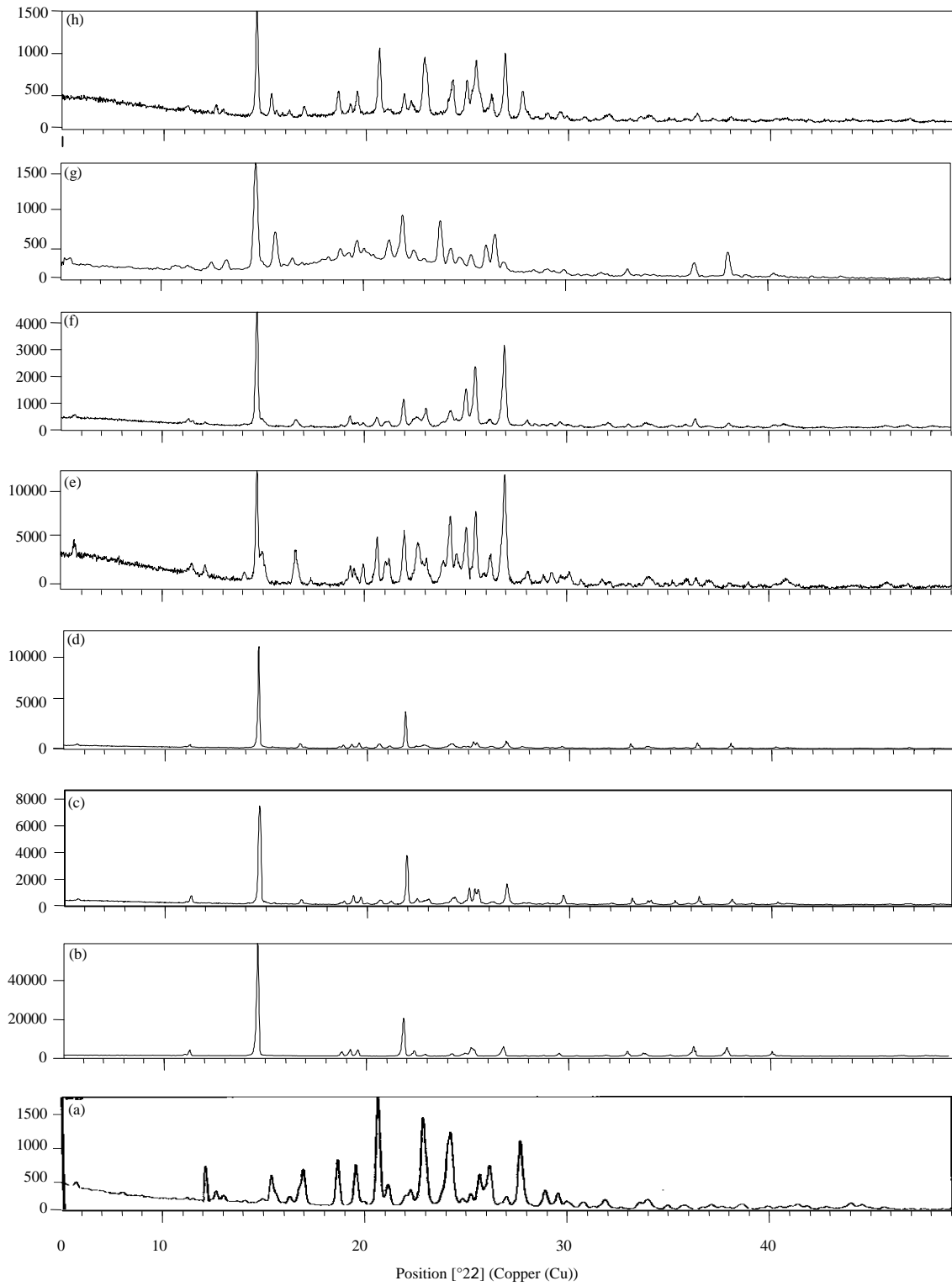


Fig. 6(a-h): PXRD pattern of, (a) SER, (b) NIC, (c) PMS3, (d) PMS5, (e) SDS3, (f) SDS5, (g) SDS8 and (h) SDS10

Whereas, in binary SDs, drug was dissolved in the melted NIC during the preparation of the system and fast cooling yielded a very fine dispersion of SER particles into the NIC matrix (Ahuja *et al.*, 2007).

In ternary SDs, it was supposed that tween 80 decreased the surface tension of the drug. This led to very high interaction of drug to tween 80 and increased drug wettability (Okonogi and Puttipipatkachorn, 2006). Synergistic effect on drug dissolution was shown when tween 80 and oleic acid were combined and incorporated into NIC-based SDs. It could be due to the formation of fine, submicronized emulsion trapping poorly water-soluble drug as very fine particles or dispersions when exposed to gastrointestinal fluid (Heo *et al.*, 2005).

Fourier transform infrared (FTIR) spectroscopy: The IR spectra of binary systems were the addition spectra of both drug and NIC and hence, proved the absence of any chemical incompatibility between NIC with SER. Addition of tween 80 alone and oleic acid did not appear to affect the solid state characteristics of SER significantly (Ahuja *et al.*, 2007; Newa *et al.*, 2008).

Differential Scanning Calorimetry (DSC): Binary systems PMS3 and SDS3 (SER:NIC ratio 65:35) showed sharp peaks at 103.04 and 103.38°C with an enthalpy of fusion 91.84 and 41.65 J g⁻¹, respectively. In binary systems PMS4 and SDS4 having more carrier, the DSC scan even showed only one but slightly broad endothermic peak corresponding to the melting of carrier at 102.84 and 105.55°C with enthalpy of fusion 106.81 and 33.31 J g⁻¹, respectively. With further increase in carrier (30:70) in case of PMS5 and SDS5, the DSC scan showed the endotherms of both the drug and the carrier at 116.8 and 103.5°C with enthalpy of fusion 17.33 and 35.29 J g⁻¹ for physical mixture and 117.5 and 107.7°C with enthalpy of fusion 49.04 and 27.75 J g⁻¹ for solid dispersion. Therefore, SER was shown to form eutectics with NIC at around 65% w/w concentration of drug in the mixture.

Almost same thermal behavior as that of binary systems was shown by ternary solid dispersion (SDS8) and oleic acid based dispersion (SDS10) which further proves the facts shown by FTIR studies. Only difference is that the incorporation of tween 80 alone and both tween 80 and oleic acid into drug-NIC system resulted in more shift in the peak temperature (T_m) of the endotherms displayed by the carrier as compared to that in the case of binary systems indicating that the presence of the drug affected the lattice energy of the crystalline NIC even more in ternary SDs and oleic acid based SDs than in the binary systems. Similar effect was seen in the solid dispersions of naproxen and polyethylene glycol containing surfactant (Mura *et al.*, 1999).

Powder X-ray diffraction (PXRD): The PXRD patterns of the binary systems (Fig. 6) showed the characteristic peaks of both NIC and drug but the height of the characteristic peaks of the drug decreased extensively in all the binary systems. Some peaks were even absent in the binary systems. There was only some physical interaction but no chemical interaction between drug and the carrier which was suggested by relative reduction of diffraction intensity and absence of some peaks in binary SDs and further no new peaks were observed. Similar behaviour was shown by solid dispersions of nifedipine in Pluronic F68 and Gelucire 50/13 in 1:1 ratio, UC-781 in PEG (polyethylene glycol) 6000 and etoricoxib in PEG (Vippagunta *et al.*, 2002; Damian *et al.*, 2002; Suhagia *et al.*, 2006).

PXRD spectra of ternary SDs and oleic acid based SDs (Fig. 6) further confirmed the study of FTIR and DSC as similar patterns were obtained in these systems as that of binary systems

(Okonogi and Puttipipatkachorn, 2006; Mura *et al.*, 1999). These SDs only caused a further decrease in intensity of the peaks as compared to binary systems indicating an increase in the amorphous content of drug in these SDs.

CONCLUSION

A significantly high dissolution rate was achieved by ternary solid dispersions and oleic acid based dispersions containing high drug content. Solid state studies showed that high solubility and dissolution rate from these solid dispersions might be due to decrease in the crystallization of drug. Solution state studies showed a profound increase in the interaction between sertaconazole and nicotinamide in the presence of tween 80 and oleic acid as shown by very high solubility and dissolution rates in presence of these excipients. So, these oleic acid based solid dispersions could be considered as better choice of treatment in dermatological and gynaecological infections with fast release and achieving good patient compliance.

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