American Journal of
Drug Discovery and Development

Characterization and Stability Testing of Itraconazole Solid Dispersions Containing Crystallization Inhibitors

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ABSTRACT

The aim of the present study was to enhance the dissolution rate of Itraconazole (ITZ) by a simple solid dispersion method (melt method). Binary and ternary ITZ systems were prepared using different polymers including crystallization inhibiting polymers (Pluronic F68, Pluronic F127, Eudragit EPO and polyvinyl pyyrolidone K25) at different ratios. The prepared solid dispersions of itraconazole were characterized by differential scanning calorimetry, X-Ray diffraction and infrared spectroscopy. All of the prepared systems showed faster and higher dissolution rates compared to raw and glassy ITZ. Stability studies of selected systems demonstrated that the itraconazole/Pluronic F127/Eduragit EPO (1:1:0.5), T6 ternary system was chemically (absence of degradation products) and physically stable (stable dissolution rate and negligible change in drug crystallinity) after three months of storage under different conditions.

Key words: Itraconazole, solid dispersion, ternary solid dispersion, stability study

INTRODUCTION

Itraconazole is a well tolerated and highly effective synthetic triazole antifungal with a broad spectrum of activity against many fungal species such as candidiasis and aspergillosis (Willems *et al.*, 2001; Jain and Sehgal, 2001; Odds *et al.*, 2000). ITZ is a poorly soluble weak base with a calculated log P of 6.2. Its aqueous solubility is estimated at approximately 1 ng mL^{-1} at neutral pH and approximately 4 μg mL^{-1} at pH 1. Given the high log P value, ITZ is classified as a class II drug according to the Biopharmaceutical Classification System (Peeters *et al.*, 2002).

Class II drugs are poorly water soluble drugs but once they are dissolved, they absorbed over the gastro-intestinal membrane (Lobenberg and Amidon, 2000). The dissolution rate of these poorly water soluble drugs often becomes a rate-limiting step in their absorption from the gastro-intestinal tract (Yu *et al.*, 2002).

There have been numerous efforts to improve drug dissolution rate. These include, (a) formation of emulsion (Okochi and Nakano, 2000), (b) solubilization in surfactant systems (Gharaei-Fathabad, 2011), (c) formation of water-soluble complexes using cyclodextrins (Khan *et al.*, 2001; Hisham Abou-Auda *et al.*, 2006), (d) use of pro-drug and drug derivatization such as a strong electrolyte salt forms that usually have higher rate of dissolution (Trapani *et al.*, 1998; Lokhande *et al.*, 2006) and (e) formation of liposomes (Salem and Duzgunes, 2003). However, the need for high levels of excipients in formulations a, b, c and e often limits the drug loading in the final product to well below 50% (drug weight/total weight).

Solid dispersions are one of the most promising strategies to improve the oral bioavailability of poorly water soluble drugs. By reducing drug particle size to the absolute minimum, improving drug wettability and hence dissolution and bioavailability may be significantly improved. They are usually presented as amorphous products, obtained by different methods, for example, melting (Verreck *et al.*, 2005; Six *et al.*, 2003) and solvent evaporation (Wang *et al.*, 2005; Seedher and Sharma, 2007). Recently, surfactants have been included to stabilize the formulations, thus avoiding drug recrystallization and potentiating their solubility (Vasconcelos *et al.*, 2007).

The aim of the present study was to enhance the dissolution rate of ITZ by a simple solid dispersion method using different polymers including crystallization inhibitors and to assess physical and chemical stability of selected formula (e).

MATERIALS AND METHODS

Materials: Crystalline itraconazole was kindly supplied by Adwia Pharma (ITZ, Cairo, Egypt). Pluronic F127 and Pluronic F68 (Sigma-Aldrich, Germany). Polyvinyl pyrrolidone K25 (PVP K25, BASF, Aktiengesellschaft, Germany). Eudragit® EPO (Röhm pharma, GmbH, Darmstadt, Germany). Acetonitrile high performance liquid chromatography (HPLC) grade (Merk Co, USA).Other chemicals and solvents were of analytical grade. This research article was a part of work conducted at Faculty of Pharmacy, Cairo University, Egypt; starting at Oct 2008 till Dec 2010.

Samples preparation

Preparation of glassy ITZ: Glassy ITZ was prepared by melting ITZ at 170°C, followed by rapid cooling to room temperature. The solidified mass was pulverized using a mortar and pestle. The pulverized mass was sifted through 500 μm sieve and stored in amber-colored glass bottles at room temperature.

Preparation of ITZ solid dispersions: Binary and ternary ITZ systems were prepared according to the composition shown in Table 1. Binary systems were prepared by heating physical mixtures of the drug and one of two hydrophilic carriers (Pluronic F68 or Pluronic F127) in porcelain dish at a temperature of 150°C using thermostatically controlled magnetic stirrer. The melted mass was cooled with stirring to room temperature, then the solidified mass was pulverized using a mortar and pestle. The pulverized mass was sifted through 500 μm sieve, transferred to plastic test tubes and stored in a desiccator. Ternary systems were prepared by mixing melted drug-Pluronic mass with pH-dependent (Eudragit EPO) or pH-independent (PVP K25) polymers, the rest of procedures were followed as mentioned above.

Characterization of ITZ solid dispersions

Drug content: Exactly weighed amounts of ITZ solid dispersions corresponding to 10 mg ITZ were dissolved in methanol and were sonicated for 10 min. The drug content was assayed spectrophotometrically at γ_{max} 262 nm after proper dilution using methanol as a blank. All experiments were run in duplicate.

Differential Scanning Calorimetry (DSC): Thermal characteristics of raw ITZ, various polymers and the solid dispersions were determined by a differential scanning calorimeter (Shimadzu, Japan, DSC-60). Samples equivalent to approximately 5 mg ITZ were placed in aluminum pans and DSC analysis were carried out at a nitrogen flow rate of 20 mL min^{-1} and a heating rate of 10°C min^{-1} from 20 to 200°C.

Table 1: Composition and drug content of the prepared ITZ binary and ternary systems

Formulation	ITZ	Pluronic F68	Pluronic F127	Eudragit EPO	PVP K25	ITZ content (wt%)
Binary systems						
B1	1	1				89.76±0.65
B2	1	3				92.47±0.66
B3	1		1			109.00±2.33
B4	1		3			101.13±1.94
Ternary systems						
T1	1	1		0.25		89.10±0.59
T2	1	1		0.5		106.05±0.22
T3	1	3		0.25		95.75±0.13
T4	1	3		0.5		96.62±1.25
T5	1		1	0.25		104.76±4.08
T6	1		1	0.5		105.00±0.12
T7	1		3	0.25		103.15±1.38
T8	1		3	0.5		105.78±5.46
T9	1	1			0.25	107.42±1.02
T10	1	1			0.5	92.94±1.19
T11	1	3			0.25	99.32±2.22
T12	1	3			0.5	100.79±1.004
T13	1		1		0.25	96.85±5.34
T14	1		1		0.5	103.13±0.89
T15	1		3		0.25	100.18±0.08
T16	1		3		0.5	99.98±0.01

X-Ray diffraction (XRD): The XRD was obtained using Scintag XGEN-4000 X-ray diffractometer (Advanced Diffraction system, Scintag Inc., USA). The samples were exposed to Cu-Ka radiation (40 kV×30 mA) at a scan rate of $2°$ min^{-1} over the $2\ \theta$ range of 4-50°, the output is given as intensity versus $2\ \theta$. The relative degree of drug crystallinity (RDC) was calculated according to the following relationship:

$$RDC = I_{sam}/I_{drug}$$

where, I_{sam} is the peak height of the sample under investigation and I_{drug} is the peak height at the same angle for the drug (Ryan, 1986).

Fourier transform infrared spectroscopy (FTIR): The Fourier transform infrared (FTIR) spectra of raw ITZ, polymers and solid dispersions (B4, T6 and T9) were recorded using FTIR spectrophotometer (FTIR-8400S, Shimadzu, Kyoto, Japan). Samples were mixed with potassium bromide (spectroscopic grade) and compressed into disks using hydraulic press before scanning from 4000 to 500 cm^{-1}.

Dissolution testing: Dissolution profiles of raw ITZ, glassy ITZ and ITZ solid dispersions were determined at 37±5°C at a stirring rate of 100 rpm using the USPXXX dissolution apparatus II. The dissolution medium was 900 mL of enzyme-free simulated gastric fluid with 0.5% sodium lauryl sulfate (pH 1.2) (Sinswat *et al.*, 2005). In each dissolution test, a weighed quantity of samples corresponding to 50 mg itraconazole was placed into the dissolution medium. Aliquots (5 mL each) were withdrawn at 2.5, 5, 10, 15, 20, 30, 45 and 60 min and replaced by equal volumes of the fresh

dissolution medium. Test samples were filtered, suitably diluted and measured spectrophotometrically at λ max 263 nm. All experiments were run in triplicate.

Stability testing: To assess the chemical (test for degradation products using HPLC analysis and drug content) and physical (test for drug recrystallization and dissolution testing) stability of the solid dispersions, a stability study was conducted for 3 months under different storage conditions. The sample was packed wrapped in aluminum foil inside screw capped glass bottles and stored at ambient room temperature in desiccator over anhydrous $CaCl_2$, 25±2°C/60% Relative Humidity (RH) and 40±2°C/75% RH. B4, T6 and T9 were selected for the stability study.

HPLC analysis: Degradation of drug substance was assessed using HPLC Apparatus, Lachrom Elite, L-2400 VWR, (Hitachi Ltd, Japan). The column was BDS-C18 (4.6 x 250mm, USA). The mobile phase consisted of 0.01 M tetrabutyl ammonium hydrogen sulphate in water and acetonitrile at a flow rate of 1.5 mL min^{-1}. The detection was conducted at a wavelength of 250 nm (Verreck *et al.*, 2003).

RESULTS

Drug content: The content of ITZ in solid dispersions prepared with various ratios of polymers ranged from 89.10 to 109.00% of the theoretical values (Table 1). Therefore, the melt method used in this study appears applicable to the preparation of ITZ solid dispersions with high content uniformity.

Solid state characterization: DSC curves obtained for raw ITZ, various polymers and the fresh solid dispersions are shown in Fig. 1. Raw ITZ showed a melting endotherm at 166.22°C. Pluronic F68 and pluronic F127 exhibited a single sharp melting endotherm at 53.82 and 56.68°C, respectively, PVP K25 showed a very broad melting endotherm at 81.06°C (corresponding to loss of water of hydration). Eudragit EPO (Eud) showed no endothermic peak.

B1 consisting of drug and pluronic F68 (1:1) exhibited two melting endotherms, a sharp one at 53.90°C corresponding to the melting peak of pluronic F68 and a reduced broad one at 164.21°C corresponding to ITZ melting peak. B3 has been found to behave similarly showing endothermic peak at 163.29°C. The presence of the broad peak may be attributed to melting of undissolved crystalline drug in the carrier during DSC heating. B2 and B4 showed weak and shifted endotherms at 153.06°C and 156.83°C respectively. It can be observed that reduction of peak increased on increasing the amount of pluronic F68 (B2) or pluronic F127 (B4).

T1 and T2 (1:1:0.25 and 1:1:0.5, ITZ:pluronic F68:Eud) showed small broad endotherms at 163.74 and 164.15°C respectively. Increasing amount of Eudragit in T2 was of minor effect in terms of drug molecular dispersion, increasing amount of pluronic F68 in T3 and T4 (1:3:0.25 and 1:3:0.5, ITZ:pluronic F68:Eud) produced weak and shifted endotherms at 152.08 and 151.88°C, respectively.

The ternary solid dispersion of ITZ, pluronic F127 and eudragit EPO at the ratio of 1:1:0.25 (T5) and 1:1:0.5 (T6) showed reduced broad endothermic peaks at 162.8 and 163.97°C, respectively. T7 and T8 (1:3:0.25 and 1:3:0.5, ITZ:pluronic F127:Eud) had been found to behave similarly as T3 and T4 showing endothermic peaks at 154.86 and 154.17°C, respectively.

T9 and T10 (1:1:0.25 and 1:1:0.5, ITZ: pluronic F68:PVP K25) showed small broad endotherms at 162.48°C and 162.74°C, respectively. T10 has been found to behave similarly as T2 where
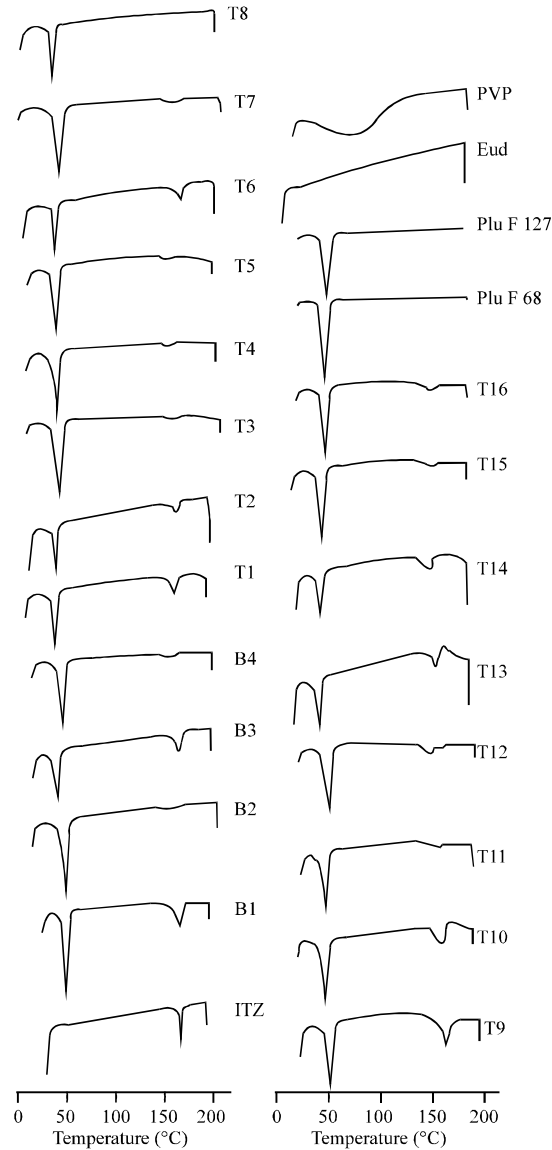
Fig. 1: Differential scanning calorimetry of different ITZ solid dispersion systems. Plu, pluronic, Eud, eudragit

increasing amount of PVP in T10 was of minor effect in terms of molecular dispersion of drug. T11 and T12 (1:3:0.25 and 1:3:0.5, ITZ:pluronic F68:PVP K25) showed weak slightly shifted endotherms at 160.23°C and 160.76°C, respectively.

The thermograms of T13 and T14 (1:1:0.25 and 1:1:0.5, ITZ:pluronic F127:PVP K25) showed small broad endotherms at 162.49 and 155.48°C, respectively. T15 showed small endothermic transition at 159.19°C while that of T16 showed small shifted endothermic peak at 151.53°C.

It can be deduced from the DSC results that ITZ presents partially as crystalline and partially as amorphous/dissolved after cooling and solidification of the melted mixture.

X-ray powder analysis was performed to confirm the results of DSC study. Representative X-ray diffractographs of ITZ solid dispersions are shown in Fig. 2. XRD patterns of raw ITZ showed
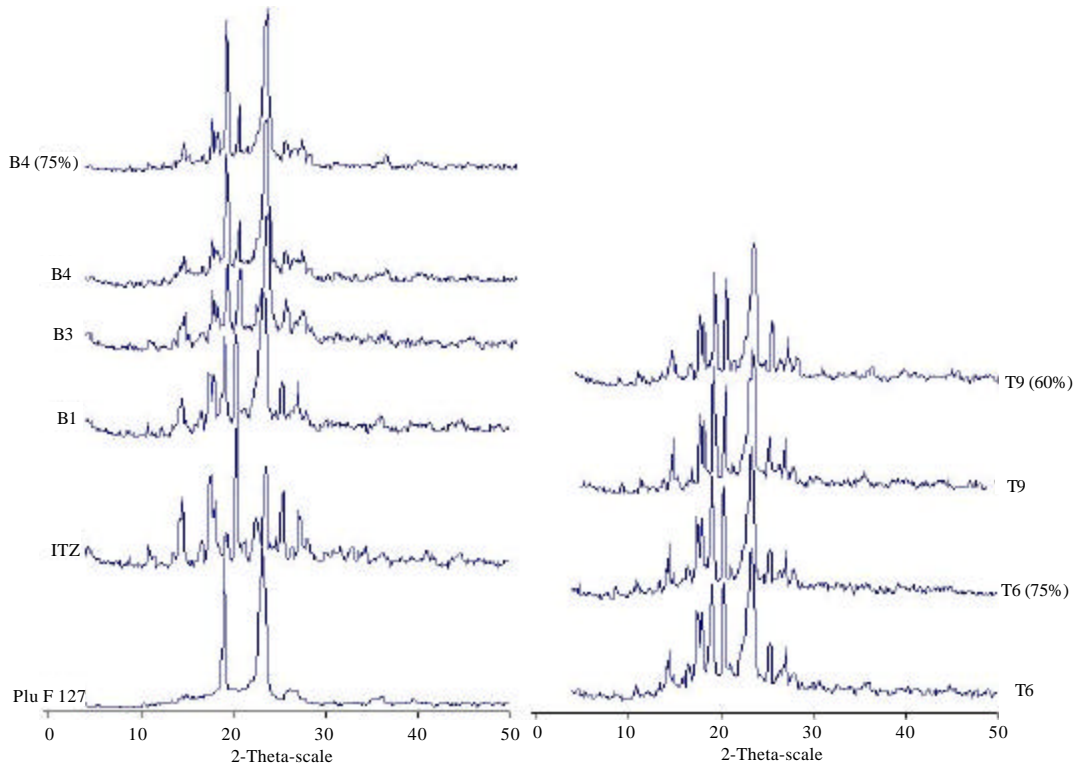
Fig. 2: Representative X-ray diffractographs of ITZ solid dispersions. Plu, pluronic

numerous distinctive peaks at 14.631, 17.689, 20.528, 23.648, 25.499 and 27.291° 2 θ indicating its crystalline nature. XRD patterns of ITZ solid dispersions showed the disappearance of some peaks and reduction in the intensity of the remaining detectable ITZ characteristic peaks indicating that ITZ is present as partially crystalline in the solid dispersion systems. Drug peak at 20.528° 2θ was used for calculating the relative degree of crystallinity.

XRD analysis showed that the degree of ITZ crystallinity in solid dispersions prepared with pluronic F127 (RDC was in the range of ≈0.5-0.64) was smaller compared to those prepared using pluronic F68 (RDC was in the range of ≈0.74-0.84). Also, XRD revealed that the degree of drug crystallinity in the solid dispersion is not significantly affected by the pluronic proportion.

Fourier transform infrared spectroscopy (FTIR): The IR spectra of raw ITZ, B4, T6 and T9 solid dispersions are shown in Fig. 3. The principal peaks of ITZ were observed at wave numbers 3126, 3069, 2969, 2822, 1698, 1511 and 1452 cm^{-1}. The absorption bands between 2800 cm^{-1} and 3200 cm^{-1} was attributed to the alkane, aromatic CH and amine groups (Shim *et al.*, 2006). The wave numbers observed at 1609 and 1425 cm^{-1} may be assigned to the C = N and C-N bonds, respectively and the sharp peak occurred at 1699 cm^{-1} is due to C = O of the drug. This is in agreement with the previously recorded spectra of the pure drug (Nesseem, 2001). The IR region from 1400 to 600 cm^{-1} which is termed the fingerprint region, usually contains large number of unassigned vibrations.

The IR spectra of solid dispersions (B4, T6 and T9) showed the characteristic peaks of ITZ and this suggested the absence of any interaction between the drug and the additives.
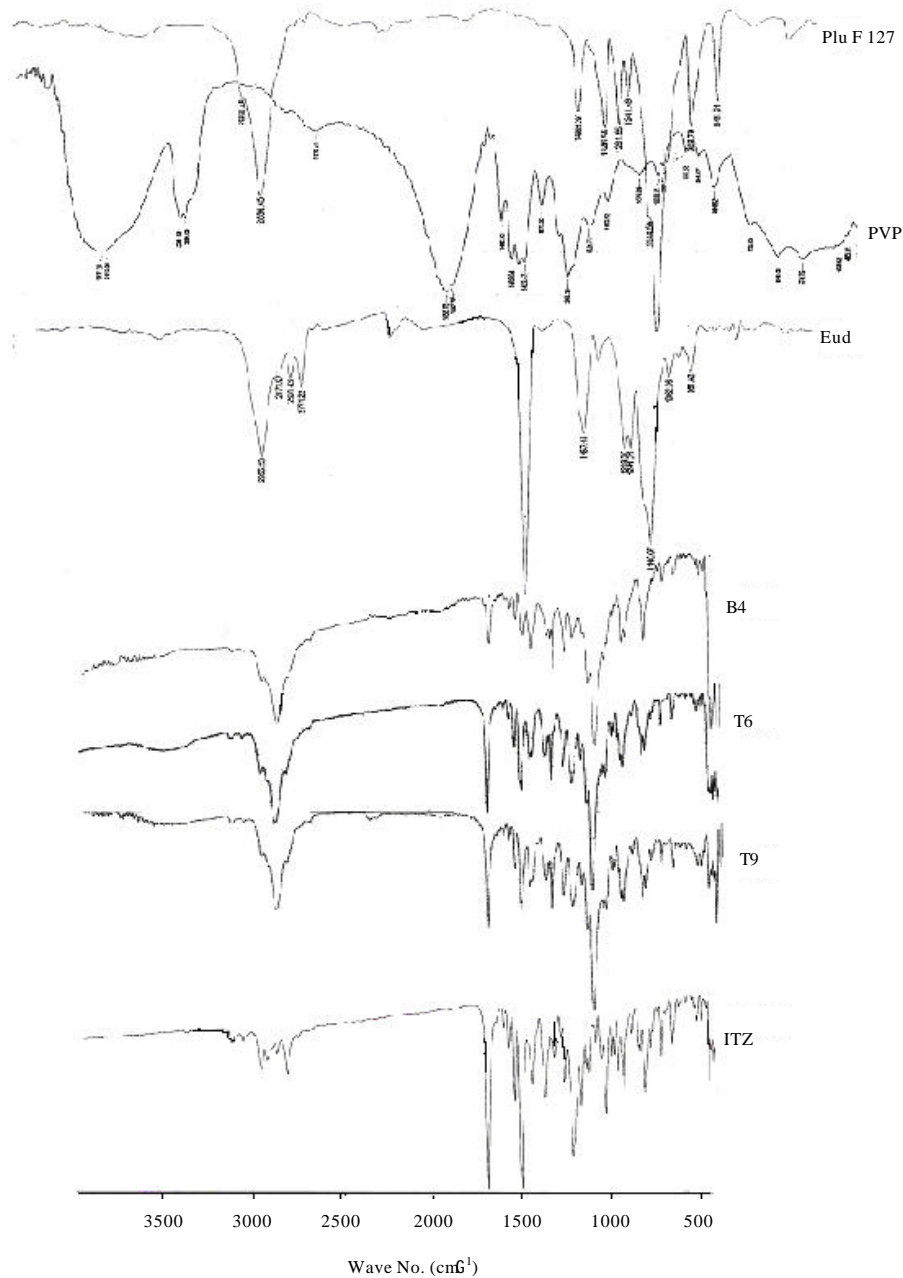
Fig. 3: IR spectroscopy of raw ITZ, B4, T6 and T9 formulae

Dissolution testing: Dissolution profiles of raw ITZ, glassy ITZ and binary ITZ solid dispersions are shown in Fig. 4. The amount dissolved of ITZ at 10 min was 52.26 and 59.48% for raw and glassy ITZ, respectively.

All prepared solid dispersions of ITZ showed significantly faster dissolution rate than raw and glassy ITZ. Increase in the amount of pluronic F68 was associated with enhancement in ITZ dissolution rate; increase in the amount of pluronic F127 relative to ITZ enhanced the dissolution

profile of ITZ although enhancement was minor. Solid dispersions prepared with pluronic F127 exhibited higher dissolution rate compared to those prepared with pluronic F68 which may be attributed to higher molecular weight of pluronic F127 (12600) and hence better molecular dispersion of the drug compared to that of pluronic F68 (8400) and also may be due to higher viscosity of pluronic F127 solution upon hydration which may helped in preventing drug recrystallization.

Adsorption of ITZ binary solid dispersion prepared with different pluronics at the two different ratios onto different polymeric crystal growth inhibitors synergistically improved dissolution profiles of ITZ compared to binary solid dispersions. For formulae T1-T8 prepared with Eudragit EPO (powder form of Eudragit E 100), the increase in Eudragit amount (from 0.25 to 0.5) relative to ITZ concentration was accompanied by enhancement in ITZ dissolution profile (Fig. 5), however the enhancement in dissolution profile for solid dispersions prepared at 1:3 drug to carrier ratio was minor. For formulae T9-T12 prepared with pluronic F68 as hydrophilic carrier and PVP K25 (Fig. 6), the increase in the amount of PVP K25 was accompanied by a decrease in the drug dissolution rate which could be attributed to the increase in the viscosity and hence thickness of diffusion layer that represents a barrier for the drug to diffuse prior to release into dissolution medium. This dissolution retarding effect of higher PVP K25 concentration was not obvious with T13-T16 prepared using pluronic F127 as hydrophilic carrier which may be due to greater dissolution rate enhancing effect of pluronic F127 which may oppose PVP K25 high concentration effect.
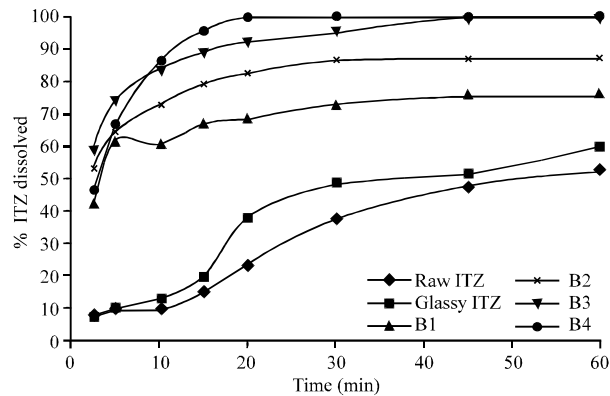

Fig. 4: Dissolution Profiles of ITZ binary solid dispersions in comparison to raw and glassy ITZ
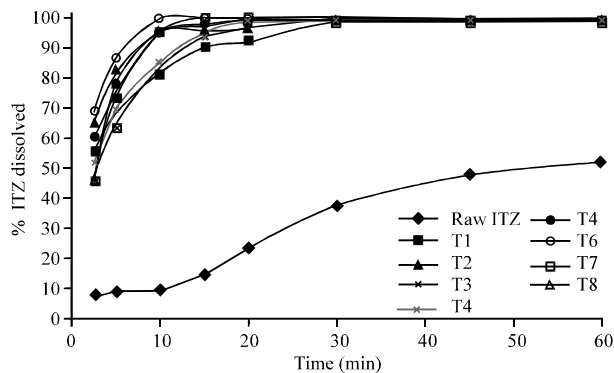

Fig. 5: Dissolution profiles of ITZ ternary solid dispersions prepared with Eudragit EPO in comparison to raw ITZ
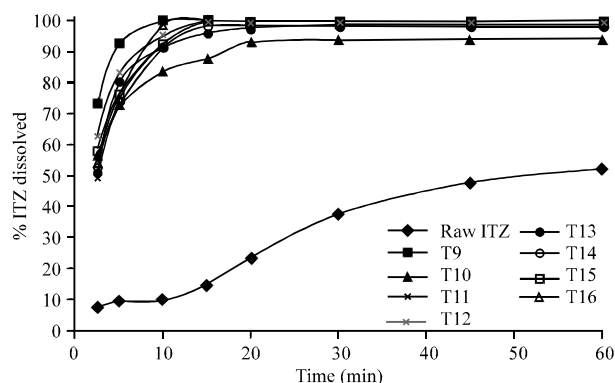
Fig. 6: Dissolution profiles of ITZ ternary solid dispersions prepared with PVP K25 in comparison to raw ITZ

The enhancement in ITZ dissolution rate caused by the presence of crystallization inhibitors allowed preparation of ITZ solid dispersions showing the required high dissolution rate (even higher than that of binary solid dispersion) and containing lower pluronic proportion (1:1 ITZ:pluronic) compared to binary systems (1:3 ITZ:pluronic).

Stability testing
Visual evaluation: After three months of storage under different conditions (ambient room temperature, 25±2°C/60% RH and 40±2°C/75% RH), no change in appearance or color of the stored B4 (1:3, ITZ: pluronic F127) and T6 (1:1:0.5, ITZ: pluronic F127: Eud) samples were observed. Raw drug showed slight aggregation after three months of storage at 40±2°C/75% RH. After 2 months of storage at 40±2°C/75% RH, T9 (1:1:0.25, ITZ:pluronic F68:PVP K25) acquired a sticky rubbery appearance so that the collection of samples for further evaluation was difficult; therefore T9 stored at 40±2°C/75% RH was excluded from further evaluation. It is worthy to mention that liquification of T9 stored at 40±2°C/75% RH was observed at the end of the storage period.

Drug content: There was no significant change in %ITZ potency after three months of storage under different conditions. At zero time, potency of ITZ was 100.16, 96.88 and 99.73% for B4, T6 and T9, respectively. While the corresponding values after three months at ambient temperature were 96.77, 94.81, 93.32% for B4, T6 and T9, respectively. The same observations were found for all stored formulae at 25±2°C/60% RH (95.37, 99.63, 98.5% for B4, T6 and T9, respectively) and at 40±2°C/75% RH (94.02, 94.68% for B4 and T6, respectively) for a period of three months.

Solid state characterization: Figure 7 illustrates thermograms of B4, T6 and T9 at zero time and after three months of storage under different storage conditions. At zero time, thermogram of B4 showed weak, broad and shifted endothermic drug peak at 156.83°C. After one month of storage, weak peaks were seen at 154.60, 153.95 and 153.78°C at ambient room temperature, 25±2°C/60% RH and 40±2°C/75% RH, respectively. After three months of storage, B4 showed endothermic transitions at 155.33, 154.78 and 160.51°C at ambient room temperature, 25±2°C/60% RH and 40±2°C/75% RH, respectively.

In the case of T6, at zero time, thermogram of T6 showed endothermic transition at 164.43°C. No significant change in the position or the intensity of the peak was seen and endothermic
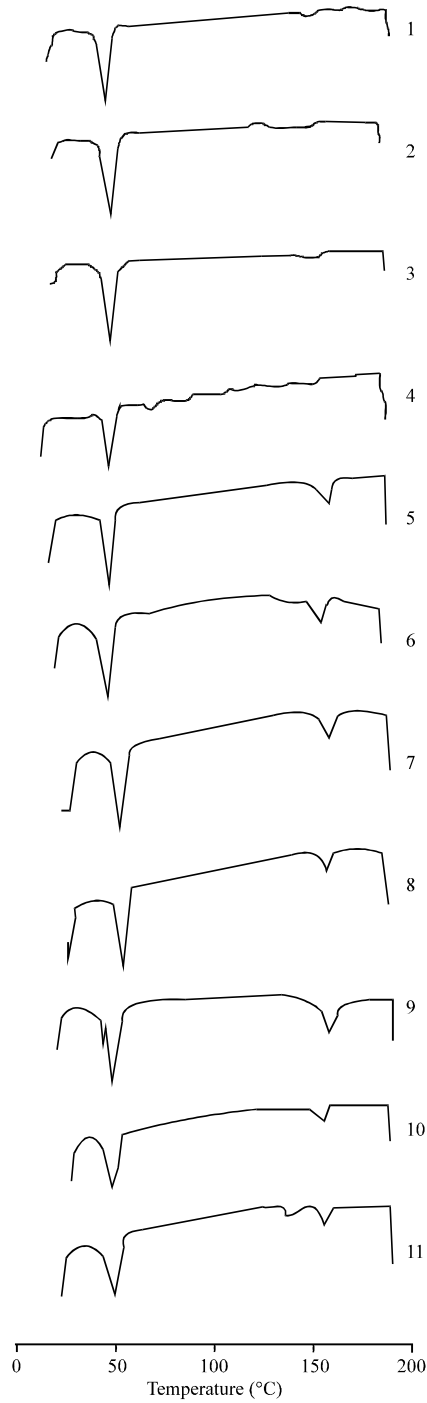
Fig. 7: Differential Scanning Calorimetry of (1) B4 (zero time), (2) B4 (ambient temperature), (3) B4 (60% RH), (4) B4 (75% RH), (5)T6 (zero time), (6) T6 (ambient temperature), (7) T6 (60% RH), (8) T6 (75% RH), (9)T9 (zero time), (10) T9 (ambient temperature), (11) T9 (60% RH), after 3 months of storage

transitions ranged between 162.27-163.20°C, 163.82-165.23°C and 163.54-164.42°C at ambient room temperature, 25±2°C/60% RH and 40±2°C/75% RH, respectively over storage period.
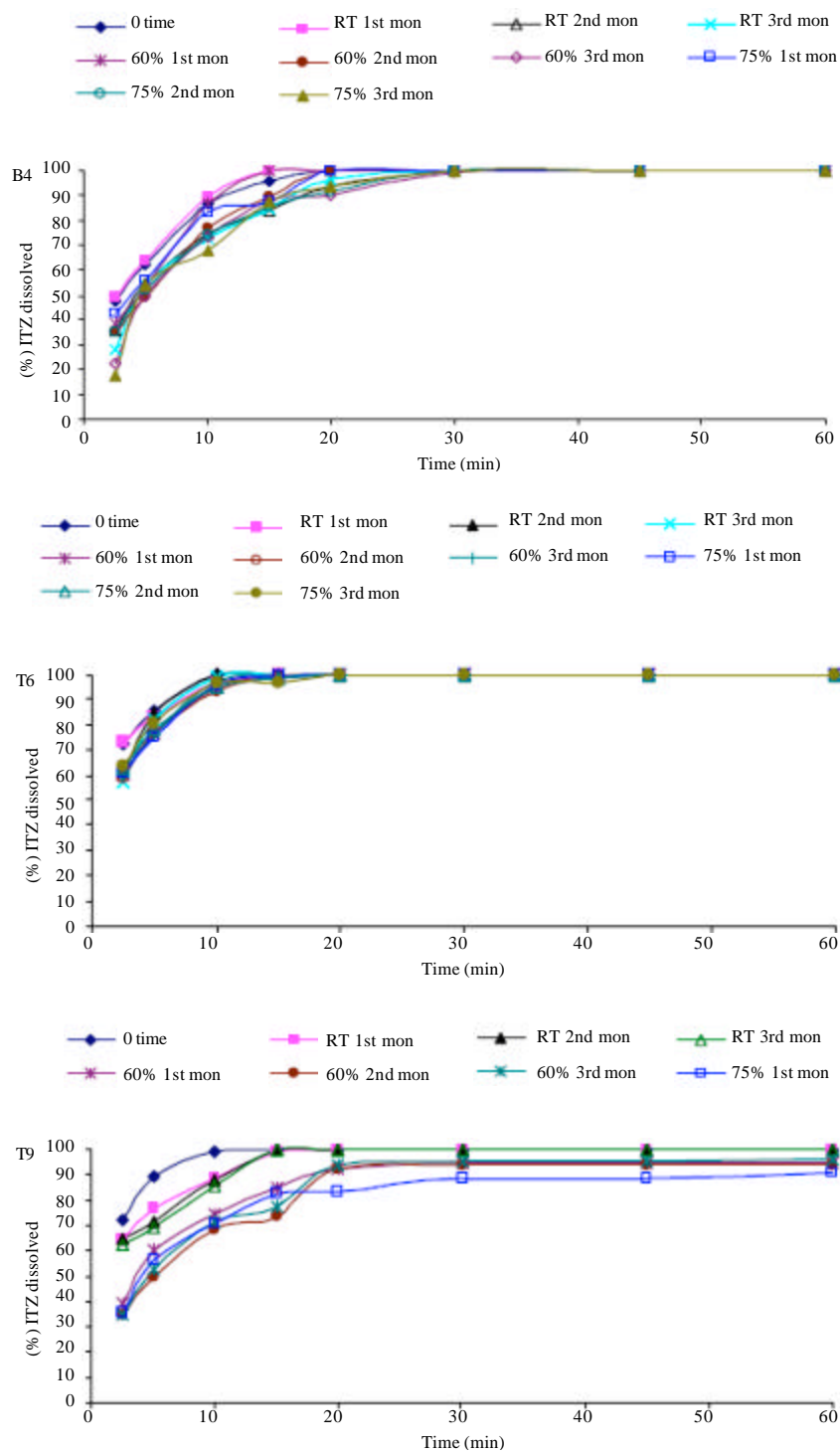
Fig. 8: Dissolution profiles of B4, T6 and T9 at zero time and over 3 months of storage period at different storage conditions. RT; ambient room temperature
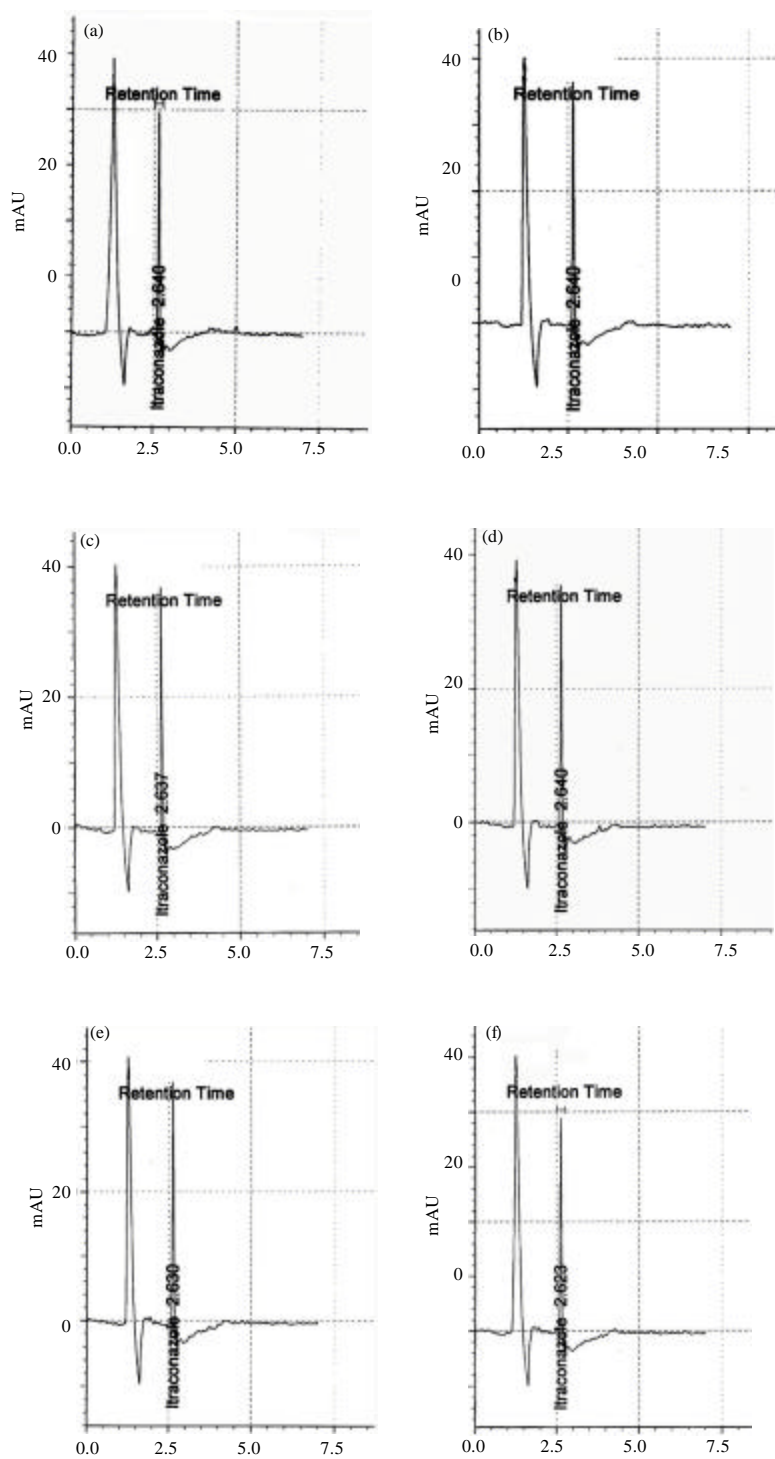
Fig. 9 (a-f):   HPLC Chromatograms of: (a) ITZ, (b) B4 (60% RH), (c) B4 (75% RH), (d) T6 (60% RH), (e) T6 (75% RH) and (f) T9 (60%RH), after 3 months of storage

At zero time, thermogram of T9 showed endothermic transition at 161.58°C. Over the storage period, T9 thermograms showed endothermic transitions ranged between 159.60-162.48°C and 161.92-162.47°C at ambient room temperature and 25±2°C/60% RH, respectively.

XRD (Fig. 2) revealed no significant increase in the number or intensities of the peaks corresponding to crystalline ITZ suggesting that there is no significant increase in the degree of the drug crystallinity over storage period which was in agreement with the results of DSC study.

Dissolution testing: The dissolution behavior of freshly chosen prepared solid dispersions were compared with those stored at ambient room temperature, 25±2°C/60% RH and 40±2°C/75% RH over a storage period of 3 months (Fig. 8). The dissolution profiles of T6 remained stable over the storage period under different storage conditions.

The dissolution rate of the drug from B4 and T9 stored at different storage conditions decreased as a function of storage time and relative humidity conditions (RH). However, the dissolution profiles of the stored samples remained higher than that of the raw drug.

HPLC analysis: HPLC analysis of the fresh samples showed that no degradation products were formed indicating thermal stability of ITZ under temperature used for solid dispersion preparation. The chromatograms of the stored samples obtained were compared with the chromatogram of drug alone and peaks other than the solvent peak and the main drug peak were considered as degradation products (Fig. 9). No degradation products was found for all samples stored at ambient room temperature, 25±2°C/60% RH or 40±2°C/75% RH after three months of storage.

DISCUSSION

Solid state characterization: ITZ solid dispersions were prepared by co-melting ITZ-carrier mixtures followed by cooling. Upon cooling, the drug could either remain dissolved in the carrier matrix to form a solid solution, or convert to amorphous form, or precipitate in crystalline form.

ITZ exists at concentration higher than its solubility in the polymeric carrier, so that a part of ITZ exists in the amorphous or molecularly dispersed state while the rest remains in the crystalline state (Okonogi and Puttipipatkhachorn, 2006).

The greater reduction in the intensity of ITZ endothermic peak upon increasing pluronics concentration could be attributed to further reduction in drug crystallinity and/or progressive and complete dissolution of remaining crystalline ITZ in the carrier at a temperature below its melting point during DSC heating run (Vippagunta *et al.*, 2002; Craig, 1990). It was confirmed using XRD that solid dispersions containing low and high pluronic proportion possess comparable degree of drug crystallinity.

The shift in the position of the endotherm to a lower temperature than melting point of ITZ could be explained on the basis of forming eutectic mixture between the drug and pluronic F68 or pluronic F127. Similar explanation was reported after preparation of binary solid dispersions of the lipophilic compound, ABT-963 with pluronic F68 (Chen *et al.*, 2004).

Dissolution testing: The absence of aggregation, reduction in the particle size of the drug, an increase in the solubility of the drug in the presence of hydrophilic excipients (Vippagunta *et al.*, 2002) and possibly reduced drug crystallinity may all contribute to enhancement of ITZ dissolution rate. Binary ITZ solid dispersions exhibited initial fast drug dissolution followed by slower drug dissolution which may be attributed to micro-environmental supersaturation, followed by drug

recrystallization and to the fast dissolution of water soluble carriers in the medium leaving a high concentration of ITZ leading to saturation of the dissolution medium with respect to ITZ (Vippagunta *et al.*, 2002). The aforementioned reason could be responsible for increase in ITZ dissolution rate associated with increase in the concentration of pluronic F68.

The ability of Eudragit (Kotiyan and Vavia, 2001) and PVP to inhibit drug re-crystallization upon contact with the dissolution medium is most probably a contributing factor for the higher dissolved percent of the drug obtained from ternary systems compared to binary ones.

Also, Eudragit E100 is hydrophilic polymer solubilized at pH<5 in a pH dependent manner; it has been previously reported as pH dependent hydrophilic carrier for increasing solubility of drugs that are ionized at low gastric pH as in the case of ITZ (Hamaguchi *et al.*, 1995).

Stability study: The change in the physical state of T9 over storage period could be explained on the basis of moisture sorption by the hygroscopic PVP and hence depression of PVP glass transition temperature (Tg). PVP changed from a dry powder to a sticky rubbery mass and then to a liquid when the Tg of PVP was depressed to a temperature below that of the storage one (40°C).

The ability of PVP to maintain its physical state until 60% RH is due to its high initial Tg, so that the plasticizing effect of sorbed water was insufficient to depress Tg of PVP to below 25°C (storage temperature) (Konno and Taylor, 2008; Fitzpatrick *et al.*, 2002).

The stable dissolution rate observed with T6 over storage period under different conditions could be explained on the basis that, Eudragit EPO (Eud) is a slowly dissolving polymer with pH dependent solubility. The small tendency of Eud to uptake water (water acts as a plasticizer) maintains glass transition temperature (Tg, 56°C) of Eud and hence that of the system high enough to impede drug mobility within solid dispersion which is the driving force for drug recrystallization, both in the solid state and upon coming into contact with the dissolution medium.

The slowing in the dissolution rate of B4 and T9 could be attributed to: physical change in the polymers caused by water uptake resulting in formation of aggregates that contributed to slowing down of the drug dissolution (Damian *et al.*, 2002). Dordunoo *et al.* (1997) reported that the particle size of triamterene or temazepam dispersed in PEGs increased during storage; and to the higher mobility of the drug within solid dispersions resulting into higher recrystallization tendency upon contact with the dissolution medium (sorbed water acts as plasticizer which counteracts the anti-plasticizing effect of the polymer).

When stored at ambient room temperature, the slowing of the dissolution rate observed with T9 was smaller compared to that of B4. This may be due to the high initial Tg of PVP polymer.

On the other side, the dissolution rate of T9 solid dispersion stored under humid conditions was more reduced when compared to that of B4 stored under the same conditions. This could be explained on the basis of PVP polymer hygroscopic nature while the pluronic is only hygroscopic under RH>80% (Vippagunta *et al.*, 2002).

CONCLUSION

Hot melt method is suitable for the preparation of different ITZ solid dispersions regarding chemical stability of the drug (during preparation of the solid dispersions) as revealed by absence of degradation products, drug content within acceptance limits and significantly improved dissolution rate compared to raw and glassy ITZ. Stability study revealed physical and chemical stability of T6 ternary system prepared at 1:1:0.5 ITZ:pluronic F127:eudragit EPO ratio.

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