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Synergistic Enhancement of Itraconazole Dissolution by Ternary System Formation with Pluronic F68 and Hydroxypropylmethylcellulose

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Abstract

Pluronic F68 is a surfactant which can inhibit CYP3A4, an enzyme responsible for hepatic metabolism of many drugs including itraconazole. This study investigated the effect of incorporation of Pluronic F68 as a ternary component in solid dispersions of itraconazole with hydroxypropyl-methylcellulose (HPMC) on the dissolution rate of itraconazole. Binary solid dispersions with HPMC, reduced the drug crystallinity, increased the equilibrium solubility but showed slow dissolution. Binary dispersions with Pluronic produced eutectic systems but the increase in solubility and dissolution was lower than that of HPMC systems. Ternary system comprising optimum proportions of drug with Pluronic and HPMC enhanced the dissolution rate showing dissolution efficiency comparable to that obtained with the marketed product of itraconazole. The study thus presented a system capable of increasing the dissolution rate of itraconazole with a potential for increased oral bioavailability by inhibiting its pre-systemic metabolism as well.

Keywords

Itraconazole dissolution • Ternary solid dispersion • HPMC • Pluronic F68

Introduction

Itraconazole is a potent broad-spectrum triazole antifungal drug with activity against histoplasmosis, blastomycosis and onychomycosis [1, 2]. It is a weakly basic compound ($pK_a=3.7$) which can only be ionized at low pH such as in gastric juice with a very poor aqueous solubility. It is also very lipophilic with an octanol/water log partition coefficient of 5.66 at a pH of 8.1. The drug has a pH dependent dissolution resulting in low and variable oral absorption [3–5]. Based on the biopharmaceuticals classification system, itraconazole is thus an extreme example of class II compounds meaning that its oral bioavailability is determined by dissolution rate in the GI tract [6]. In addition, the drug undergoes extensive hepatic metabolism [1]. The factors resulted in a low and variable oral bioavailability. Alternative techniques have been used to improve such bioavailability. The drug is marketed in the form of pellets in which the drug is layered onto sugar beads. This was achieved by dissolving the drug and hydroxypropylmethylcellulose (HPMC) in an organic solvent of dichloromethane and ethanol. This solution was used to coat the sugar particles with controlled drying, producing a dispersion of drug in HPMC on the pellets. This should dissolve quickly upon reaching the stomach [7]. To increase the bioavailability researchers formulated binary mixtures with various polymers creating either solid dispersions or solid solutions with enhanced dissolution rate [5, 8–9]. Solid dispersions containing ternary systems of the drug with polymers were also evaluated with successful increase in the dissolution of itraconazole [10–12]. Itraconazole dissolution was also enhanced by complexation with cyclodextrin derivatives or even by adsorption on ordered mesoporous silica [13–5]. All these techniques depended on increasing the dissolution rate of the drug as a tool to increase the oral bioavailability, with no consideration to the hepatic first pass metabolism. Other researchers employed the self-emulsifying drug delivery systems (SEDDS) with efficient solubilization of drug, easy dispersibility and higher lymphatic transport, bypassing the hepatic metabolism with the result of increased in vivo bioavailability [16, 17]. However, the tested itraconazole SEDDS formulations were either liquid or semisolid which require encapsulation into soft gelatin capsule to prepare solid oral dosage form.

Pluronic F68, a solid hydrophilic block copolymer was shown to inhibit the hepatic CYP3A4 which is the hepatic metabolizing enzyme of itraconazole [18]. Accordingly, the aim of this study was to investigate the effect of incorporation of Pluronic F68 as a component of the ternary system with HPMC and itraconazole on the solubility and dissolution rate of itraconazole. The study thus employed the simple solid dispersion technique and incorporated an excipient which can increase the bioavailability of itraconazole directly by enhancing the dissolution rate of the drug and indirectly by reducing its hepatic metabolism.

Results and discussion

Solid state characterization of the binary and ternary systems

Differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR) were used for solid state characterization of binary and ternary systems. Fig. 1 shows examples of the DSC traces of itraconazole and HPMC alone or as binary combinations. The calculated parameters of the melting transition of the drug are presented in Tables 1. Pure itraconazole produced a single sharp endothermic peak at

166.9 °C (Fig. 1). This is in good agreement with previous findings on the thermal analysis of itraconazole [9, 19]. Pure HPMC showed a broad endothermic peak with an onset of 36.5 °C and endset of 77.5 °C (Fig. 1). This endotherm was attributed to the release of the adsorbed moisture [20]. Appearance of this endotherm in coevaporates of HPMC with the drug can be attributed to evaporation of water and/or the solvent.

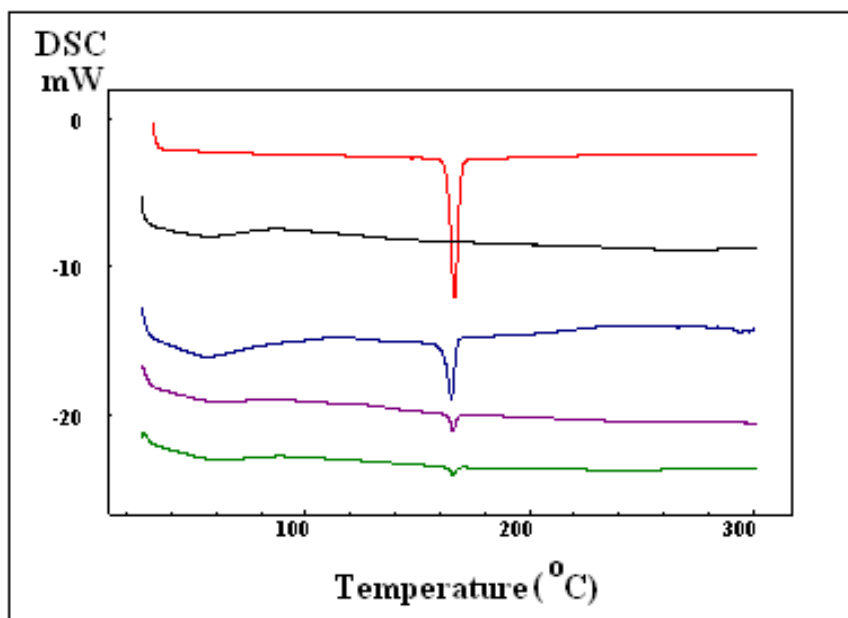


Fig. 1. Examples of the DSC traces of itraconazole – HPMC coevaporates. The traces from top to bottom are pure drug, pure HPMC, drug-HPMC (1:0.5), drug-HPMC (1:1) and drug-HPMC (1:1.5), respectively.

The itraconazole/HPMC binary solid dispersions produced only a trend of reduced T_m of the characteristic endothermic peak of the drug, with the endotherm retaining its sharpness but the enthalpy of the peak was significantly reduced compared to the endotherm of pure itraconazole. The reduction of the enthalpy increased on increasing the proportion of the HPMC in the solid dispersion (Fig. 1 and Table 1). This behaviour suggests a reduction in the crystallinity of the drug. Preparing the corresponding physical mixtures of itraconazole/HPMC, there was no significant effect on the endotherm of the drug with respect to the T_m or the enthalpy, compared with the pure drug (Table 2). Reduced crystallinity of itraconazole was also recorded after preparation of solid dispersion with HPMC and/or PEG 6000 [21]. The presence of the small endothermic peak of itraconazole in solid dispersion containing the highest concentration of HPMC indicates that small proportion of the drug remains in the crystalline form with the rest being in the amorphous state.

Tab. 1. The melting transition parameters, the equilibrium solubility at 37 °C and the dissolution efficiency of itraconazole binary and ternary coevaporates.

Formulation	T _m (°C)	Enthalpy (J/g)	Solubility (µg/ml)	Dissolution efficiency (%)
Pure drug	166.9 (0.8)	91.0 (8.8)	12.4 (0.7)	7.2 (0.2)
B1	165.5 (0.5)	43.4 (8.5)	ND	49.2 (0.8)
B2	165.8 (0.4)	12.9 (2.1)	100 (7.3)	47.1 (1.9)
B3	166.0 (0.4)	8.8 (3.7)	100.3 (3.8)	51.6 (2.1)
B4	163.7 (0.4)	62.0 (7.2)	ND	15.7 (0.2)
B5	161.6 (0.2)	61.9 (2.9)	20.5 (0.5)	12.2 (0.1)
B6	159.1 (0.1)	61.3 (3.2)	26.9 (1.0)	13.8 (0.2)
T1	163.1 (0.1)	59.1 (4.0)	81.6 (4.4)	47.3 (1.1)
T2	163.1 (0.2)	61.0 (3.1)	91.6 (4.4)	79.2 (1.1)
T3	161.9 (0.1)	65.7 (3.0)	28.6 (2.7)	21.2 (0.6)
T4	159.8 (0.4)	52.6 (5.1)	90.7 (3.9)	76.8 (1.4)
Sporanox	ND	ND	ND	82.2 (1.3)

Values between brackets are S.D. (n = 3). ND means not determined.

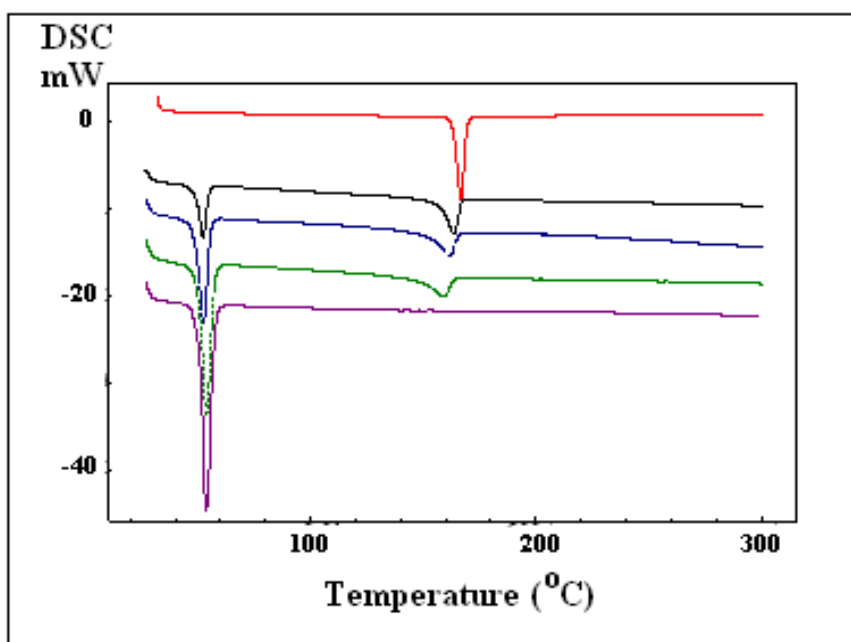
Fig. 2 shows examples of the DSC traces of itraconazole and Pluronic F68 alone or as binary combinations. Pure Pluronic F68 produced a sharp endothermic peak at 53.9 °C (Fig. 2) which agrees with previous finding recorded on thermal analysis of the Pluronic F68 [22]. Formulation of itraconazole as binary coevaporate with Pluronic F68 significantly reduced the T_m of its endothermic peak with the peaks becoming broader compared to the pure itraconazole. The reduction in the T_m and the broadness of the endotherm was increased with increasing the concentration of the polymer. These binary systems were also characterized by reduction in the enthalpy but this reduction was not to the same extent recorded with binary mixtures with HPMC (Fig. 2 and Table 1). This behaviour can be explained on the basis of forming eutectic mixture between the drug and Pluronic F68. Similar explanation was reported after preparation of binary solid dispersions of the lipophilic compound, ABT-963 with Pluronic F68 [22]. The corresponding binary physical mixtures of the drug with Pluronic F68 showed some reduction in the T_m and the enthalpy of the endothermic peak of the drug compared to that of the pure state but the reduction in the T_m was not as large as that obtained with solid dispersions (Table 2). This effect suggests that on heating the physical mixture in DSC, the drug progressively interacts with the Pluronic which melts at lower temperature. Similar suggestion was recorded for the interaction of nifedipine with Pluronic and/or Gelucire [23].

Fig. 3 shows examples of the DSC traces of itraconazole, HPMC and Pluronic F68 ternary systems. The ternary solid dispersion produced broad endothermic peak with T_m and the enthalpy being reduced with increasing the content of Pluronic in the ternary system (Table 1 and Fig. 3). Fig. 3 compares the thermograms of binary mixtures containing drug/polymer at 1:1 weight ratio with that of the ternary system containing drug, HPMC and Pluronic at 1:1:1 weight ratio.

Tab. 2. The melting transition parameters and the dissolution efficiency of itraconazole binary and ternary physical mixtures.

Formulation	T _m (°C)	Enthalpy (J/g)	Dissolution efficiency (%)
Pure drug	166.9 (0.8)	91.0 (8.8)	7.2 (0.2)
B1	166.5 (0.1)	96.3 (5.3)	6.6 (0.2)
B2	166.8 (0.8)	85.7 (7.1)	4.2 (0.1)
B3	166.9 (0.7)	86.4 (6.8)	4.9 (0.1)
B4	165 (0.3)	77 (17)	9.4 (0.1)
B5	165.6 (0.1)	50.6 (13)	11.0 (0.2)
B6	164.1 (2.1)	44.9 (7.3)	11.9 (0.03)
T1	164.6 (0.2)	74.8 (6.3)	7.3 (0.4)
T2	165.8 (0.8)	71 (25)	6.4 (0.5)
T3	164.6 (0.1)	63.5 (13.4)	7.7 (0.3)
T4	164.6 (0.9)	45.8 (0.3)	6.7 (0.1)

Values between brackets are SD.

**Fig. 2.** Examples of the DSC traces of itraconazole – Pluronic F68 (PL) coevaporates. The traces from top to bottom are pure drug, drug-PL (1:0.5), drug-PL (1:1), drug-PL (1:1.5) and pure PL, respectively.

These thermograms revealed the disappearance of the sharp endothermic peak and appearance of the broad endotherm in case of ternary system. This sharp endotherm was clear in case of drug/HPMC binary system and was attributed to the melting of the remaining crystalline drug. This behaviour indicates that Pluronic formed eutectic mixture with any remaining crystalline drug in the system. The ternary physical mixtures showed

thermotropic phase behaviour similar to that obtained in case of the binary physical mixtures with Pluronic (Table 2). This can be explained on the bases of interaction of the drug with Pluronic upon progressive heating in the DSC.

No evidence of the presence of a separate glassy itraconazole phase could be detected in any of the tested binary or ternary mixtures. This was indicated by the absence of both the glass transition of the glassy itraconazole (at 59 °C) and its typical endotherms (at 70.3 and 90 °C) which result from the formation of mesophase [24]. This suggests that the drug is molecularly dispersed in the carriers or present in a separate crystalline form. Similar conclusion was reported for the solid dispersions of itraconazole with HPMC and/or PEG 6000 [21]. The DSC trace of the binary solid dispersion of Pluronic F68 with HPMC showed a small base fleck at 142 °C which corresponds to the glass transition of the HPMC (Fig 3). This T_g is at lower value compared to the minor fleck obtained at 172 °C in case of pure HPMC (Fig 1), suggesting a possible plasticizing effect for the surfactant. However, detailed investigations are necessary at slower heating rate to determine the effect of Pluronic on the T_g of HPMC. The presence of HPMC resulted in a reduction in the T_m of the endothermic peak of Pluronic with the endotherm becoming broader compared to that of pure Pluronic (Fig 3). Similar effects were recoded in presence of the drug with the effect becoming significant in the ternary system (Fig 3).

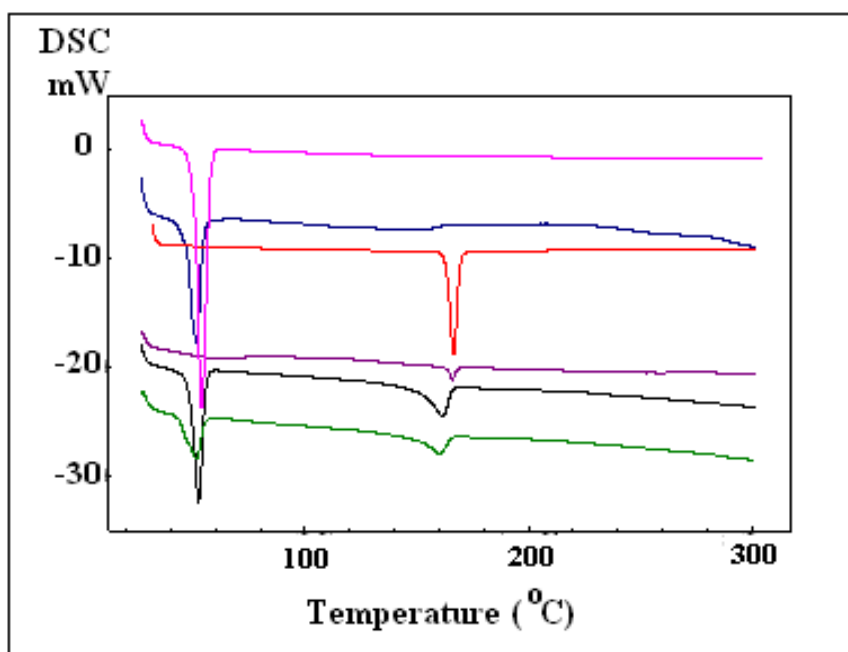


Fig. 3. Examples of the DSC traces of itraconazole – HPMC - pluronic F68 (PL) coevaporates. The traces from top to bottom are pure PL, HPMC – PL (1:1), pure drug, drug – HPMC (1:1), drug – PL (1:1) and drug – HPMC – PL (1:1:1), respectively.

The FTIR spectra of Itraconazole, HPMC, Pluronic F68 and their binary and ternary solid dispersions are shown in Figs 4-6. The FTIR spectrum of pure itraconazole was identical for the unprocessed powder and for the powder obtained after drying drug solution in the organic solvent used to prepare the solid dispersion. These spectra showed the

characteristic peaks of itraconazole which occurred at 3126, 3069, 2962, 2821, 1699, 1510, 1450, and 418 cm^{-1} (Fig. 4). The absorption bands between 2800 and 3200 cm^{-1} was attributed to the alkane, aromatic CH and amine groups [25]. The wave numbers observed at 1609 and 1425 may be assigned to the C=N and C-N bonds, respectively and the sharp peak occurred at 1699 is due to C=O of the drug. This is in agreement with the previously recorded spectra of the pure drug [19]. The IR region from 1400 to 600 cm^{-1} which is termed the fingerprint region, usually contains large number of unassigned vibrations.

The FTIR spectrum of pure HPMC showed the characteristic absorption band at 3100–3600 cm^{-1} which corresponds to the OH stretching vibrations (Fig. 4). The FTIR spectrum of pure Pluronic F68 showed the characteristic absorption bands at 3503, 2884 and 1114 cm^{-1} which corresponds to the stretching vibrations of OH, CH and C-O groups, respectively (Fig. 5). This spectrum correlates with previously recorded one [26].

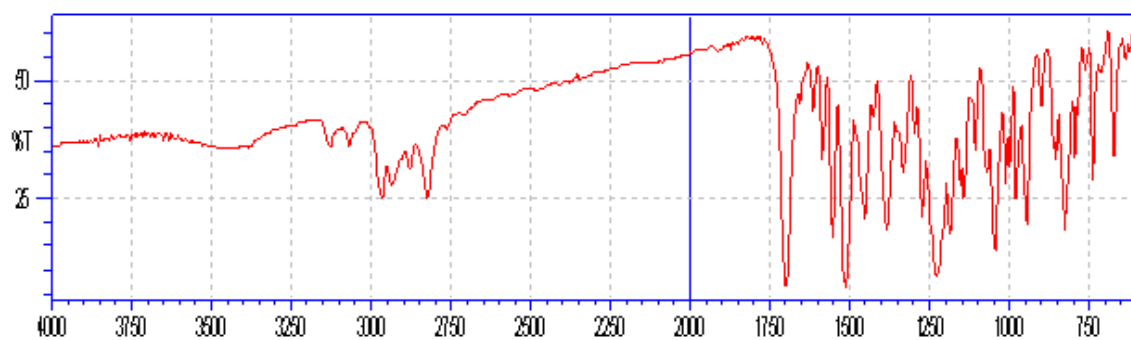
The binary and ternary solid dispersions containing itraconazole with HPMC and or Pluronic showed the characteristic peaks of the drug and the polymers (Figs 4–6). This suggests the absence of any interaction between the drug and the polymers.

Drug content and equilibrium solubility

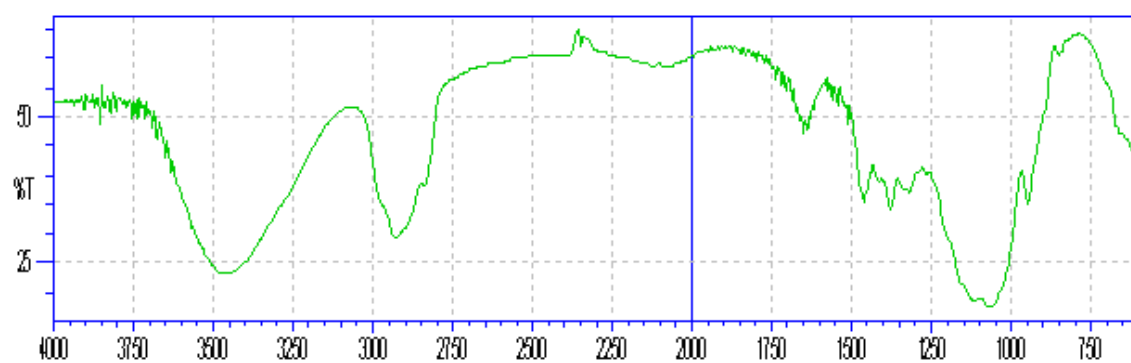
The drug content was determined to evaluate the homogeneity of distribution of the drug in the binary and ternary solid dispersion. The results revealed drug content values in the range of 95.8 to 104 % w/w indicating homogenous distribution of the drug in the prepared mixtures.

The equilibrium solubility of itraconazole was determined in 0.1 N HCl (pH 1.2) at 37°C. The results are presented in Table 1. The aqueous solubility of itraconazole at ambient temperature and neutral pH was recoded to be around 1 ng/ml. The solubility was found to undergo significant increase in acidic solution reaching 4 $\mu\text{g/ml}$ in 0.1 N HCl at 25°C [27]. The data in Table 1 revealed an equilibrium solubility value of 12.4 $\mu\text{g/ml}$ when determined in 0.1 N HCl, at 37°C (Table 1). This increase in solubility is expected and can be attributed the higher temperature (37°C) compared to that recorded at room temperature (25°C). Incorporation of Itraconazole in a binary solid dispersion with HPMC resulted in a significant increase in the solubility to reach values of 100.3 $\mu\text{g/ml}$ (Table 1). Higher solubility values were recorded for itraconazole after incorporation of the drug in a spray dried binary solid dispersion with HPMC [5]. The difference can be attributed to the difference in the preparation technique. The binary solid dispersion of the drug with Pluronic F68 revealed significantly higher solubility values compared to that of the pure drug, but the extent in increase in solubility was lower than that obtained with HPMC solid dispersion. Combining the Pluronic with HPMC provided ternary systems with itraconazole, but the presence of Pluronic did not augment the solubility compared to binary systems with HPMC.

Itraconazole



HPMC



Itra – HPMC (1:1)

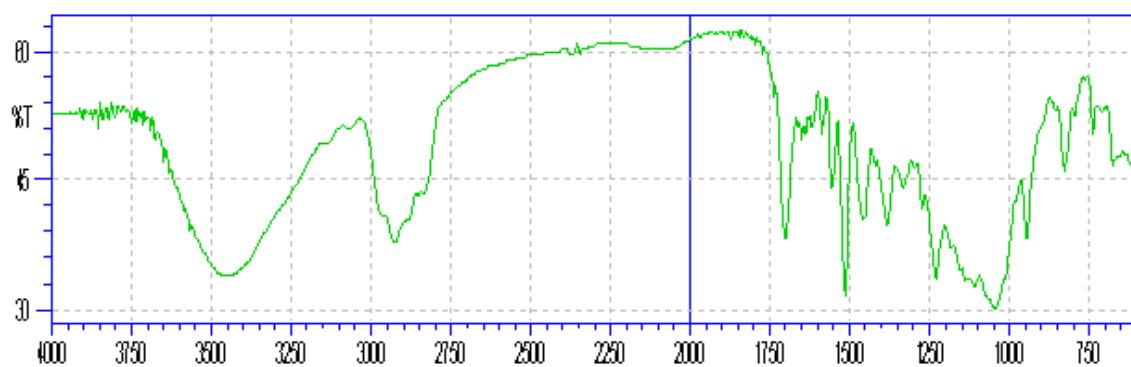
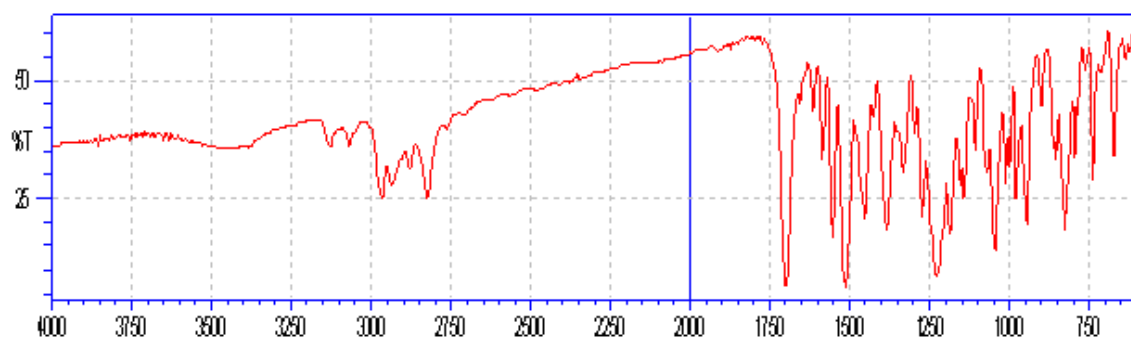
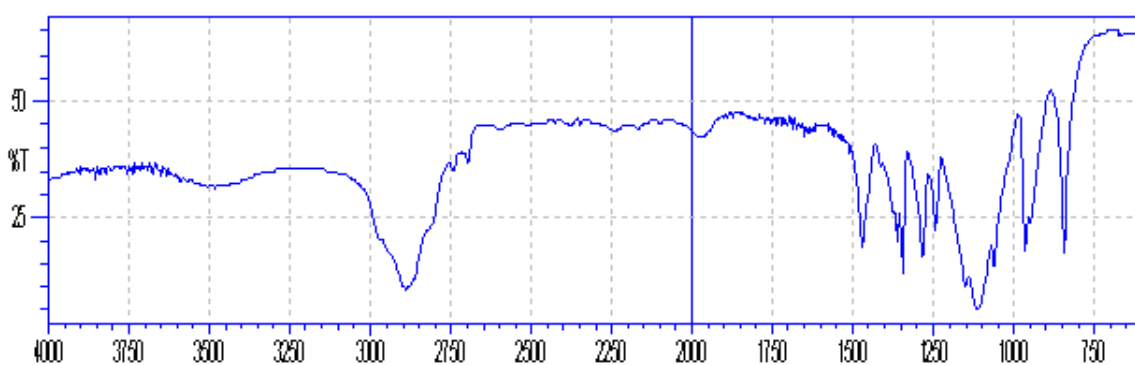


Fig. 4. FTIR spectra of itraconazole, HPMC and their binary solid dispersion.

Itraconazole



Pluronic F68



Itra – Pl (1:1)

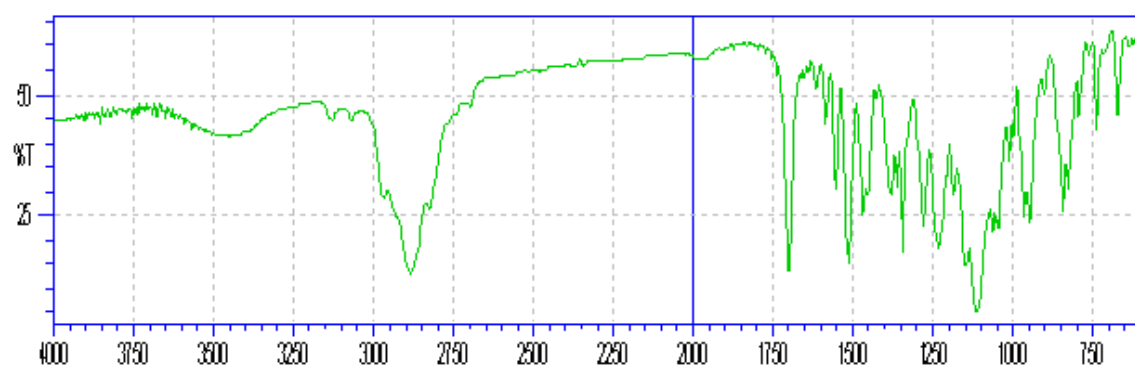
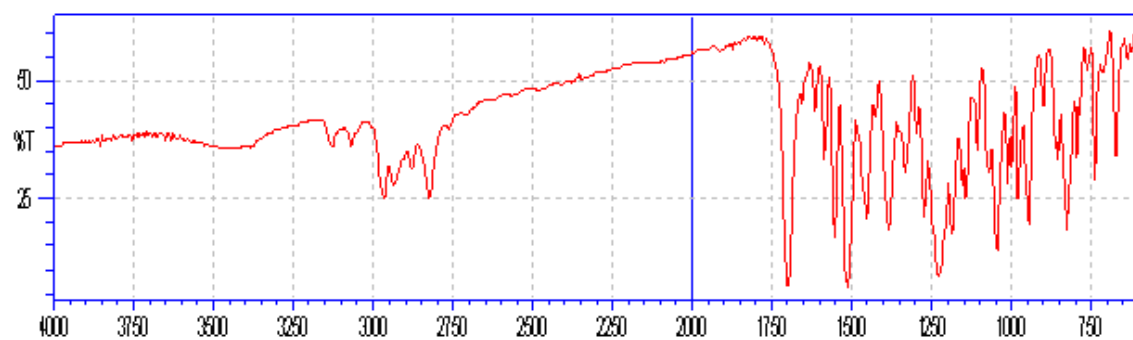
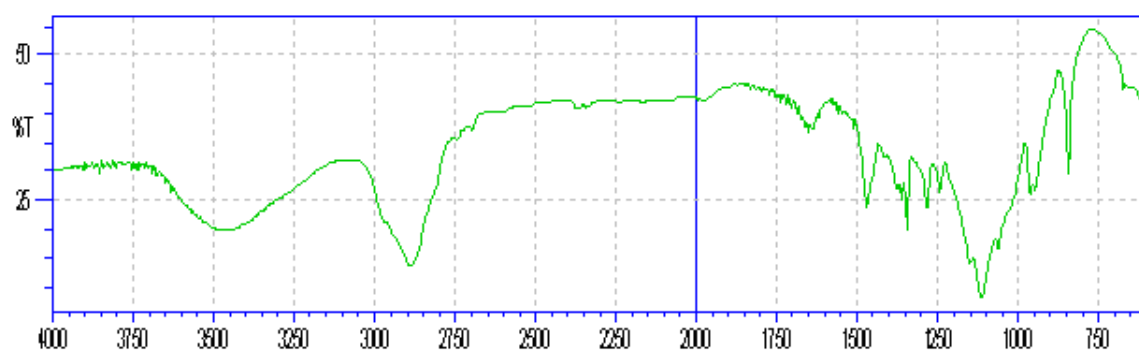


Fig. 5. FTIR spectra of itraconazole, Pluronic F68 and their binary solid dispersion.

Itraconazole



HPMC – PL (1:1)



Itra – HPMC – PI (1:1:1)

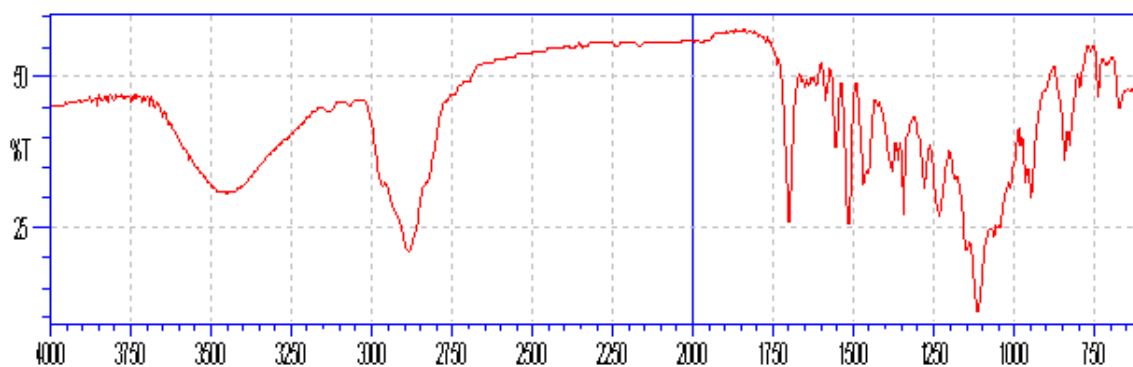


Fig. 6. FTIR spectra of itraconazole, HPMC/Pluoronic F68 binary solid dispersion and their ternary solid dispersion.

Dissolution studies

Fig. 7 shows the dissolution profile of itraconazole in pure state or in binary or ternary solid dispersions. The dissolution efficiency values are presented in Tables 1 and 2. The results revealed poor and slow dissolution of pure drug producing very small dissolution efficiency (Fig. 7a and Table 1). Preparation of the drug as binary solid dispersion with HPMC resulted in significant increase in drug dissolution. This is evidenced by the significant increase in the dissolution efficiency compared to the pure drug (Table 1). However, the dissolution profile of these solid dispersions showed slow release with drug dissolution reaching 72% after 2 hours in the best case (Fig. 7a).

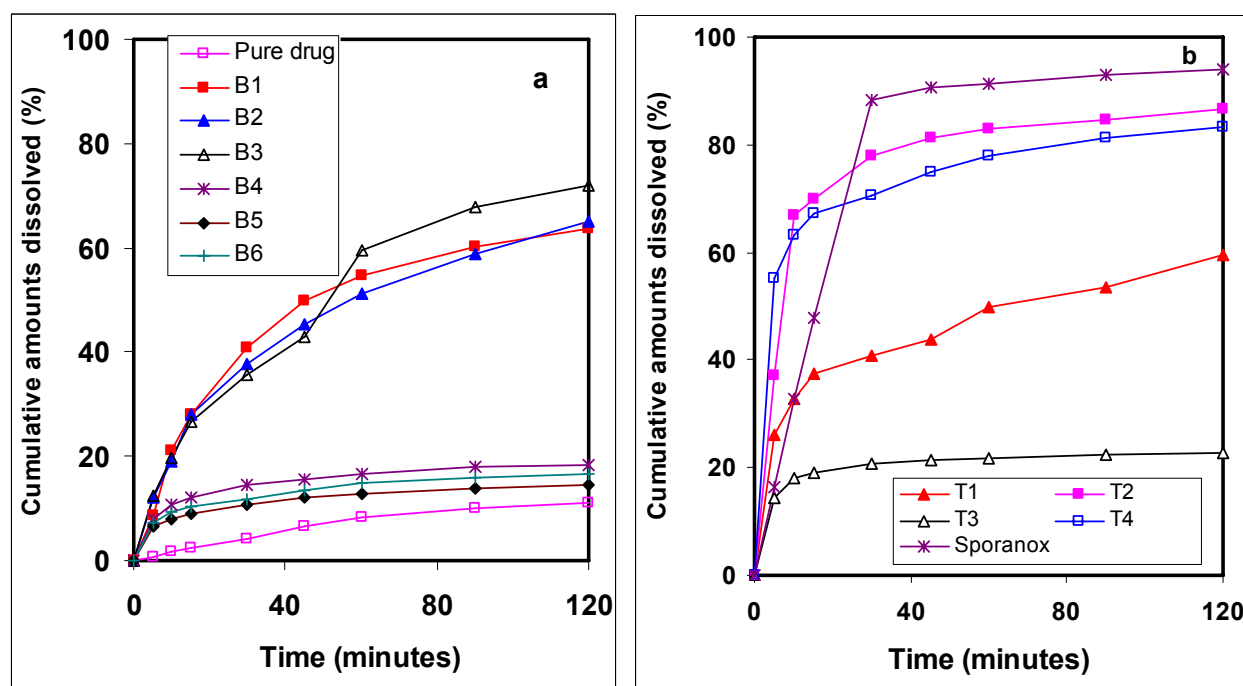


Fig. 7. Dissolution profiles of itraconazole binary (left) and ternary (right) solid dispersions (error bars were omitted for clarity, formulation details are presented in Tab 3).

The values of dissolution efficiency of the drug in binary or ternary physical mixtures are presented in Table 2. The binary physical mixtures of itraconazole with HPMC failed to increase the drug dissolution as indicated from the lower dissolution efficiency values (Table 2). Similar findings were recorded for the physical mixtures of the drug with HPMC, with the corresponding mixture prepared by melt extrusion producing significant increase in drug dissolution [28]. The lack of dissolution enhancing effect of binary physical mixtures with HPMC can be explained on the bases that HPMC does not act as simple solubilizer but the drug crystallinity is significantly reduced after preparation of solid dispersion with HPMC. The binary solid dispersions with Pluronic F68 increased the drug dissolution compared to the pure drug but the increase was not to the same extent obtained in case of HPMC (Fig 7a and Table 1). Unlike the case of HPMC binary systems the binary physical mixtures with pluronic F68 showed some increase in the drug dissolution (Table 2). The increase in drug dissolution in case of physical mixture with Pluronic F68 can be attributed to the solubilizing effect of the surfactant.

Incorporation of itraconazole in ternary solid dispersion with HPMC and Pluronic F68 produced synergistic effect in drug dissolution which depended on the relative amounts of each polymer. The greatest synergism was obtained in ternary system containing the drug with HPMC and Pluronic at a ratio of 1:1:0.5 (Fig. 7b, Formulation T2). This ternary system released more than 65% of the drug in the first 10 minutes with the percent of drug released exceeding 80% after 45 minutes. Comparing this ternary system with the marketed dosage form (Sporanox capsules), the dissolution profiles were comparable with the ternary system showing initial rapid release compared with the marketed product (Fig. 7b). Increasing the proportion of Pluronic F68 in the ternary system reduced the dissolution efficiency gradually compared to the previously discussed ternary system (Fig. 7b, T1), with the reduction becoming significant on using a system containing HPMC and Pluronic at a ratio of 0.5:1 (Fig. 7b, T3). The results also suggested that the proportion of HPMC in the ternary system must not be lower than 1:1 drug to HPMC. The synergistic effect of Pluronic F68 can be attributed to the possibility that the surfactant can increase the chain mobility of HPMC with the result that drug release is facilitated. This explanation can be supported if we consider the solubility data (Table 1) which revealed the greatest solubility from binary solid dispersion with HPMC. This increase in equilibrium solubility was not translated in the release profiles from the same binary systems with the drug release from the solid polymer matrix being slow. Addition of Pluronic F68 as the third component did not augment the solubility compared to that obtained from binary dispersions containing the drug with HPMC (Table 1) but this ternary combination (at optimum composition) showed synergistic effect on the dissolution profile. This effect can support our explanation. As for the binary systems the physical mixtures of the ternary systems failed to produce any significant increase in drug dissolution compared to the control suggesting that the net effect of the ternary system is not just a solubilizing effect and the system has to be formulated in a solid dispersion form. Surfactants were previously employed as plasticizers in preparing solid dispersions of poorly soluble drugs with water soluble polymers and the study showed similar effects to that suggested here [29]. Synergistic effect on the dissolution of itraconazole was obtained after addition of polyethylene glycol 600 to itraconazole/HPMC solid dispersion to form ternary system [21].

In conclusion, the study presented a surfactant containing ternary system which showed synergistic effect on the dissolution of itraconazole with a potential of improving the bioavailability of the drug by enhancing its dissolution with a possible reduction in the presystemic disposition. The highlighted the importance of using optimum composition in ternary system.

Experimental

Materials

Itraconazole was purchased from Betapharma (China). Hydroxypropylmethylcellulose (low viscosity HPMC with a 2% w/v aqueous solution having a viscosity of 100 cp at 25 °C) and Pluronic F68 were obtained from Sigma Chemical Co. (St. Louis, MO, USA). Other chemicals and reagents were of analytical grade.

Preparation of physical mixtures

Physical mixtures containing binary and ternary systems were prepared according to the composition presented in Table 3. The preparation involved mixing itraconazole and the

polymers with mortar and pestle according to the geometrical dilution method, followed by sieving (355 μ m sieve) [30].

Preparation of solid dispersions

Solid dispersions containing binary and ternary systems were prepared according to the composition presented in Table 3. The drug and the polymer(s) were dissolved in methylene chloride/ethanol (8:2). The organic solvent was removed at ambient temperature, under reduced pressure. The resulting powder was passed through a 355 μ m sieve.

Differential scanning calorimetry

Thermograms of the samples (itraconazole, excipients, binary and ternary physical mixtures and solid dispersions) were recorded using a differential scanning calorimetry (DSC) (DSC-60, Shimadzu, Japan). Samples equivalent to approximately 2.4 mg of the drug were loaded into aluminum pans and the lids were crimped using a Shimadzu crimper. The thermal behavior of each sample was investigated under nitrogen at a heating rate of 10 °C/min, covering temperature ranges of 25–300 °C. The instrument was calibrated with an indium standard. Data analysis was conducted using the TA-60WS thermal analysis software.

The following parameters were calculated:

T_m = transition med point.

Enthalpy (ΔH) = the area under the transition peak normalized to the sample weight.

Tab. 3. The composition of the prepared binary and ternary systems

Formulation	Itraconazole	HPMC	Pluronic F68
<u>Binary systems</u>			
B1	1	0.5	0
B2	1	1	0
B3	1	1.5	0
B4	1	0	0.5
B5	1	0	1
B6	1	0	1.5
<u>Ternary systems</u>			
T1	1	0.5	0.5
T2	1	1	0.5
T3	1	0.5	1
T4	1	1	1

Fourier Transform Infrared Spectroscopy

The Fourier transform infrared (FTIR) spectra of itraconazole, Pluronic F68, HPMC and their binary and ternary solid dispersions 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 600 cm^{-1} . The data were analyzed using IRSolution software (version 1.10).

Determination of drug content

Samples of the solid dispersions and physical mixtures were dissolved in a mixture of ethanol and 0.1N HCl (1:1). The drug concentration was determined by UV spectrophotometry at 257 nm after appropriate dilution, using the solvent as blank.

Solubility studies

The solubility of the drug was determined in 0.1 N HCl (pH 1.2) at 37 °C. Samples containing excess drug were transferred to flasks before adding 0.1 N HCl. The mixtures were bath sonicated for 15 minutes before incubation in a shaking water bath maintained at 37 °C for 7 days. The samples were filtered through 0.45 μm filter and assayed by UV spectrophotometry after suitable dilution.

Determination of drug dissolution

Dissolution experiments were conducted on the binary and ternary dispersions and the corresponding physical mixtures. The tests employed the USP XXIV method 2 (paddle method) dissolution apparatus (Electrolab TDT-06P, India). The dissolution medium was 0.1 N HCl (pH 1.2) maintained at a temperature of 37 °C with a paddle speed of 100 rpm. The powdered samples (sieved through a 355 μm sieve) of pure drug, physical mixtures or solid dispersion mixtures equivalent to 100 mg of Itraconazole were added to the dissolution vessels while stirring. Samples (5 ml) were taken and immediately replaced with fresh dissolution medium at 0, 5, 10, 15, 30, 45, 60, 90, 120, and 180 min. These samples were immediately filtered through 0.45 μm filters. The first 2 ml of the filtrate were discarded and the samples were assayed for drug content after appropriate dilution with the dissolution medium. The cumulative amounts of the drug dissolved (expressed as % of the total drug added) were plotted as a function of time to produce the dissolution profiles. The dissolution efficiency (DE) was calculated from the area under the dissolution curve at time t (determined using the nonlinear trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time [31]. The results were compared to the dissolution data of the marketed formulation (Sporanox capsule), where the dissolution data of the product were obtained after adding the contents of the capsule to the dissolution vessels while stirring as before.

Authors' Statement

Competing Interests

The authors declare no conflict of interest.

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