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Processing factors in development of solid solution formulation of itraconazole for enhancement of drug dissolution and bioavailability

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Abstract

This study investigated solid solutions of itraconazole, a water insoluble antifungal, for improved dissolution and improved bioavailability. Influence of processing factors on drug and carrier properties in solid solution and subsequently on drug dissolution behavior was also studied. An optimized solid solution formulation was compared with marketed product in healthy human subjects under fasted and fed conditions for bioequivalency. Polyethylene glycol (PEG) and drug were made into a solid solution at 120 °C. The cooled, solid solution was then ground into granules of different sizes. Solid solutions of lower drug concentration dissolved at a faster rate, and drug dissolution improved considerably with increasing molecular weight of PEG. Initial treatment of itraconazole with the wetting agent/cosolvent glycerol prior to making itraconazole into a solid solution improved drug dissolution, and also reduced the PEG amount required to dissolve drug to form solid solution. Addition of a polymer such as HPMC to the solid solution eliminated precipitation of drug following dissolution. As the granule size of the solid solution was reduced, precipitation of drug during dissolution became prominent. Equivalence of two formulations could not be shown for pharmacokinetic parameters C_{max} and AUC, under both fasting and fed conditions. © 2001 Published by Elsevier Science B.V.

Keywords: Itraconazole; Solid solution; PEG 20000; Bioavailability; Granule size

1. Introduction

Development of solid dosage forms for water-insoluble drugs has been a major challenge for pharmaceutical scientists for decades. It is well known that drug efficacy can be severely limited by poor aqueous solubility because the driving force for absorption of most drugs across biological membranes is concentration of drug in solution. Dosage forms that enter the stomach and travel down the gastrointestinal tract must release the drug in solution to achieve good drug bioavailability. Consequences of poor solubility include low bioavailability, large inter and intra-

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subject variation, and large variations in blood drug concentrations under fed versus fasted conditions.

There have been numerous efforts to improve drug dissolution rates. These include, (a) reducing particle size to increase surface area, thus increasing dissolution rate of drug (Kubo et al., 1996); (b) solubilization in surfactant systems (Martis et al., 1972; Rees and Collett, 1974); (c) formation of water-soluble complexes (Cassella et al., 1998); (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); and (e) manipulation of solid state of drug substance to improve drug dissolution i.e. by decreasing crystallinity of drug substance through formation of solid solutions/amorphous solids.

Sekiguchi and co-workers (Sekiguchi and Obi, 1961; Sekiguchi et al., 1964) have reported the use of eutectic mixtures (formed by fusion) capable of enhancing dissolution and absorption rates of certain drugs. Subsequent studies (Goldberg et al., 1966a,b; Chiou and Riegelman, 1971) have shown that the magnitude of increase in dissolution rates was a function of the ratio of carrier to drug in the eutectic.

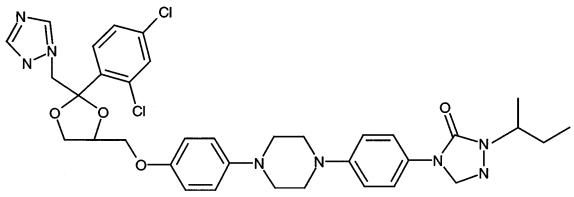
The term 'solid dispersion' is applied to those systems in which drug particles are homogeneously distributed throughout a solid matrix. Solid dispersions are prepared either by fusion, solvent or solvent-fusion method. This system provides the possibility of reducing the particle size of drugs to nearly molecular level, to transform the drug from the crystalline to partially amorphous. Where as in solid solution the drug is completely molecularly dispersed and drug has no crystal structure in the solid solution.

Solid solutions can be classified as either continuous or discontinuous solid solutions based on their miscibility. They can also be classified as substitutional, interstitial and amorphous solid solutions based on the way in which the solvate molecules are distributed in solvendum (Leuner and Dressman, 2000). In continuous solid solution, the components are miscible in all proportions, where as in discontinuous solid solution the components solubility in each is limited. That is, in discontinuous solid solution, one of the solid components is completely dissolved only in a certain region of the phase diagram (Leuner and Dressman, 2000).

Various techniques have been used to differentiate solid solutions from solid dispersions. These include thermoanalytical (MDSC/DSC), XRD, IR and drug dissolution rate from the formulation. Absence of crystallinity of drug or complete absence of drug peak (either in DSC or XRD) indicates formulation to be a solid solution (Damian et al., 2000).

Itraconazole (**1**) is a synthetic anti-fungal drug consisting of a 1:1:1:1 racemic mixture of four diastereomers (two enantiomeric pairs) each possessing three chiral centers. It has a molecular formula $C_{35}H_{38}Cl_2N_8O_4$ and molecular weight of 705.64, and is poorly soluble in aqueous media (less than 100 mcg/100 ml in aqueous solutions ranging in pH from 1–12.7). Itraconazole is a weak base ($pK_a = 3.7$) and has a log partition coefficient in octanol/water of more than 5 at pH 6. It is highly lipophilic and has very rapid oral absorption, if it is in solution. Itraconazole has extensive tissue distribution and is found at higher concentrations in tissues (including brain) than in plasma (Heykants et al., 1987). It binds to plasma proteins extensively. The drug has a half-life of approximately 20 h. The mechanism of action of this drug is similar to all other azole antifungals. It inhibits cytochrome P450 of the fungi and thus interferes in sterol biosynthesis in cell membrane, leading to cell death. The drug has a lesser effect on mammalian cytochrome P450 (Heykants et al., 1987).

Currently, itraconazole is marketed as Sporanox® capsules by Janssen Pharmaceutica. Sporanox® capsules contain itraconazole coated on sugar spheres. Drug was layered onto the sugar beads by dissolving the drug and HPMC in an organic solvent of dichloromethane and ethanol. This solution upon coating (cosolvent evaporation) and controlled drying of coated beads produced a particulate dispersion of drug in HPMC that produces quickly dissolved drug upon reaching the stomach (FOI, 1990).



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The aim of this study was to formulate solid solutions of itraconazole to improve rate of dissolution, and to carry out evaluation of an optimized formulation for bioavailability in healthy human subjects. More specific objectives were then to examine the influence of processing factors on drug and carrier properties in solid solutions, and subsequently on drug dissolution behavior. Factors studied were concentration of drug, incorporation of crystal growth inhibitor, addition of a wetting agent, and effect of granule size of final formulation on drug dissolution.

2. Materials and methods

2.1. Materials

All chemicals used in the present study were purchased from standard sources. The following compounds were obtained from the companies mentioned in parentheses. Itraconazole, Polyethylene glycol 3500, 8000 (Union Carbide Co) and 20000 (branched, PEG Compound, Sigma Chemical Co, St. Louis, MO), PEG 20000 linear, Glycerol (Sigma Chemicals Co, St. Louis, MO), Hydroxypropyl methylcellulose (Methocel K15M, Dow Chemical Co Midland, MI), Sodium starch glycolate (Explotab, Edward Mendell Co), Acetonitrile (Fisher Chemicals, Lawn, NJ), methanol (EM Sciences, Gibbstown, NJ), *n*-heptane, *iso*-amyl alcohol (Spectrum quality products, NewBrunswick, NJ), diethylamine, soldium carbonate, sodium bicarbonate, sodium citrate (Mallinckrodt Inc, Paris, KY) and glacial acetic acid (JT Baker, Phillisburg, NJ).

2.2. Method of preparation

Polyethylene glycol (PEG) and drug were made into a solid solution at 120 °C. Initially, PEG was melted at 60–70 °C in a beaker and then temperature was raised to 120 °C. Itraconazole was added in small quantities until it dissolved with the formation of a clear solution. This hot solution was then rapidly cooled by dipping the beaker in ice-cold water, leading to rapid solidification of PEG, producing a solid solution as shown by DSC (see later data). This solid solution was then reduced into granules of different sizes with the help of a blender, and sieving through different sizes of mesh screens. Unless otherwise mentioned, PEG 20000 refers to branched PEG 20000.

Solid solutions were also prepared by initially wetting itraconazole with glycerol, prior to adding itraconazole to molten PEG.

Addition of sodium starch glycolate (Explotab®) or hydroxypropyl methylcellulose (HPMC) was to the melted PEG–drug solution at 120 °C.

2.3. Dissolution testing of the formulation

Dissolution profiles of drug release from formulations were determined using the US Pharmacopoeia (USP) apparatus II, paddle stirring method (VK 7000®, Vankel Industries, Inc, Edison, NJ). Dissolution media (degassed and maintained at 37 °C) included 900 ml of enzyme-free simulated gastric fluid (pH 1.4 ± 0.1). Other parameters include paddle speed of 100 rpm, 37.5 °C. Dissolution samples were analyzed by direct UV measure at 226 nm (HP diode array spectrophotometer).

Dissolution samples were collected at 10, 20, 30, 45 and 60 min through 5 μm filters (Acrodisc Versapor® from Gelman Sciences, medium: acrylic polymer, hydrophilic and bidirectional). Standard was prepared by dissolving itraconazole in 10 ml acetonitrile and diluting with simulated gastric fluid (SGF) to obtain 0.11 mg/ml. In all the dissolution studies discussed in this paper, formulation equivalent 100 mg of itraconazole was used. Particle size range of the formulation granules used for dissolution studies was between US standard mesh size 12 and 20 (i.e. 1700 microns to 850 microns), unless otherwise specified.

2.4. Differential scanning calorimetry (DSC) analysis

Samples (4–8 mg) were examined using a

Perkin-Elmer DSC instrument. A heating rate of 10 °C per min was used with the samples placed in closed aluminum pans. Indium was used as a standard.

2.5. Bioavailability studies

Bioavailability comparison of an optimized solid solution with marketed product Sporanox® was done in 12 healthy human volunteers. Six subjects each under fed conditions and fasting conditions, in a crossover manner. Blood samples were collected at 1, 2, 3, 4, 5, 6, 8, 10, 24, 32, 48 and 72 h. Pharmacokinetic parameters including Cmax and AUC for itraconazole under the conditions of fasting and fed, were compared using two one-sided *t*-tests (FDA, 1997).

2.5.1. Drug assay method

Concentrations of itraconazole after extraction from plasma were detected by HPLC using ketoconazole as an internal standard. The mobile phase modified from Compas et al., was 60:40 acetonitrile: water containing 0.05% diethylamine and adjusted to have a final pH of 8.0 with 30% acetic acid. Mobile phase was filtered under vacuum and degassed before use. The HPLC column was a Microsorb-MV® C18 5 μm 110 Å 25 cm (Rainin Instrument Company, Inc, Woburn, MA). The flow rate was 1.2 ml/min. The UV absorbance was detected at 254 nm (Waters model 444, fixed wavelength UV detector).

Carbonate buffer pH 10 was prepared by adding 53.4 ml of 1 M sodium carbonate to 46.6 ml of 1 M sodium bi-carbonate. Itraconazole standard stock solution (1 mg/ml) was prepared by dissolving in methanol. Standard solutions containing 400, 200, 100, 80, 60, 40, 20 and 10 ng/ml containing itraconazole were prepared by serial dilution from stock solution. Ketoconazole stock solution at a concentration of 1 mg/ml was prepared by dissolving in methanol. A solution of 0.2 μg/ml ketoconazole was prepared by diluting the stock solution.

2.5.2. Sample preparation

Liquid–liquid extraction method used for extraction of drug from plasma was modified from two different methods described separately by Compas et al., 1996; Woestenborghs et al., 1987 2.0 ml of plasma was transferred into a centrifuge tube. About 100 μl of (10 μg/ml) ketoconazole was added to the same tube and vortex-mixed and to this 200 μl of 1 M carbonate buffer was added. Samples were vortex-mixed for 3 s. For the extraction, 8 ml of heptane-isoamyl alcohol (90:10 v/v) was added and the mixture was vortex-mixed for 2 min. After centrifugation (5 min, $2000 \times g$) the organic layer was collected and evaporated to dryness under vacuum at 40 °C. The residue was dissolved in 125 μl of mobile phase and 60 μl was injected into the HPLC column.

3. Results and discussion

Dispersion of itraconazole in melted PEG was found not to improve drug dissolution unless there was a formation of a solid solution of itraconazole in molten PEG. This solid solution was formed at specific temperature of 120 °C and at certain minimum ratio of PEG to drug.

Other excipients such as sodium starch glycolate and HPMC, when added to the solid solution to optimize the formulation, do not completely dissolve in the solid solution. Thus, the overall system is now a solid dispersion of excipients in a solid solution of the drug in PEG. Since the nature of itraconazole in PEG and drug dissolution behaviour is of the main interest, and solid solution is primarily responsible for improved drug dissolution, the final formulation will be referred to here in as a solid solution, while recognizing that some excipients are insoluble.

3.1. Differential scanning calorimetry (DSC) analysis

DSC studies were carried out to characterize the solid solutions. Fig. 1a shows DSC for itraconazole with a sharp endothermic event at 166 °C that corresponds to the melting point of itraconazole. DSC of solid solution showed only one peak at 53 °C, corresponding to melting point of PEG and complete absence of drug peak (Fig. 1b). This complete absence of itraconazole

peak indicates that itraconazole is present as amorphous or as a solid solution inside the PEG matrix. However, an XRD study would be needed to confirm this. A systematic change in cell dimensions or a gradual shift in the positions of the diffraction lines of the carrier with changes in composition is considered as an indication of solid solution formation (Sjokvist et al., 1989). DSC of Sporanox® showed two peaks, one at 55 °C and the other at 186 °C corresponding to melting points of PEG and itraconazole respectively (Fig. 1c). In Sporanox®, PEG is coated as a protective layer onto itraconazole layered beads.

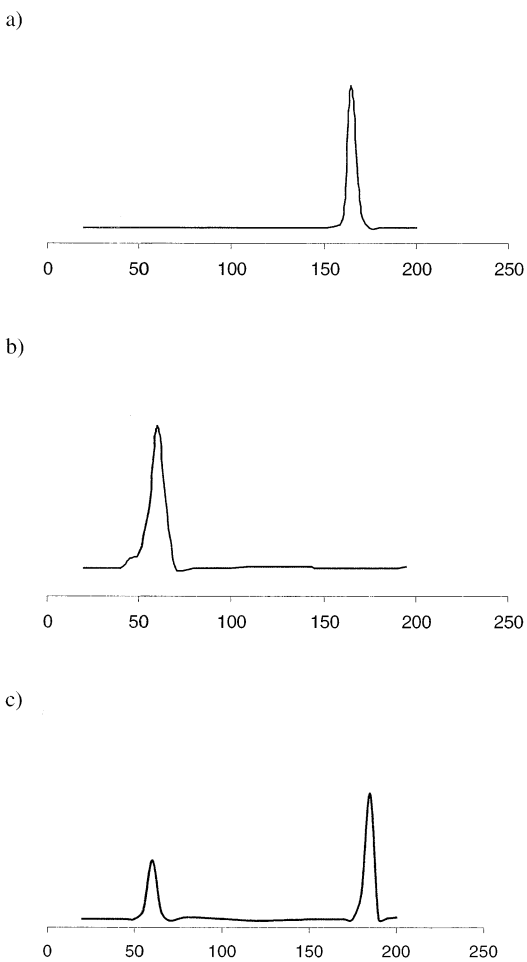

Fig. 1. DSC curves for (a) itraconazole, (b) solid solution formulation and (c) Sporanox®.

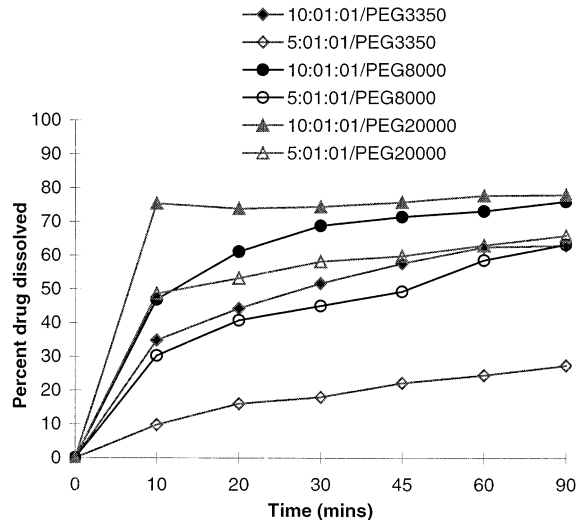

Fig. 2. Effect of type and amount of PEG on drug dissolution from a solid solution. Legend indicates ratio as PEG: itraconazole:Explotab®, respectively, along with the type of PEG used in the formulation.

This results show that itraconazole in Sporanox® is not a solid solution in HPMC, but is finely divided particles of drug dispersed in a HPMC film.

3.2. Influence of a disintegrating agent in the solid solutions

A simple eutectic mixture formulation with PEG did not dramatically improve the drug dissolution rate. Addition of a disintegrating agent such as croscarmellose sodium to a hot melt of mycophenolate mofetil has been reported to improve drug dissolution (Samuels et al., 1996). Sodium starch glycolate (Explotab®) was added to the PEG/itraconazole melt. Addition of this disintegrant improved the drug dissolution. PEG 3350, 8000 and 20000 were compared at varying ratios with drug such as 10:1, 5:1, 2.5:1. All these preparations contained 1 part of Explotab® with respect to drug and drug dissolution profiles are shown in Fig. 2. It follows from the dissolution profiles that solid solutions of the lower drug concentrations gave faster dissolution, and drug dissolution improved considerably with increasing molecular weight of PEG. PEG 20000 gave maximum drug dissolution at a ratio of 10:1 whereas other PEGs

of lower molecular weight, and at lower PEG–drug ratios, resulted in slower drug dissolution.

3.3. Influence of glycerol

It can be hypothesized that increase in drug dissolution rate with increase in molecular weight of PEG can be related to an increase in number of oxyethylene molecules. With increasing number of oxyethylene molecules, there is more interspatial space for the drug to be trapped. In the case of increased itraconazole concentration, it was thought that wetting of drug substance could be a rate-retarding step in dissolution of drug substance in PEG/gastric fluid/drug bead interface. Wetting agents or solubility enhancers (cosolvents) have been used to improve wettability of hydrophobic drug substances, and thereby increase dissolution rate of drugs. Glycerol, a well-known wetting agent/suspending agent/cosolvent, was used in the solid–solution preparations to enhance the wettability of drug. Itraconazole was wetted with glycerol by mixing the drug with glycerol, before adding it to molten PEG to produce solid solution. Drug dissolution rate increased considerably from a solid solution prepared with glycerol-treated itraconazole. That is, glycerol enhanced dissolution of drug in PEG during processing, and then enhanced the wetting of PEG and thus wetting of PEG/drug solid solution in gastric fluid. Effect of glycerol in enhancing drug dissolution rate is evident in Fig. 3. Various formulations were made with incorporation of glycerol and dissolution profiles are shown in Fig. 4. It is clear from this figure that there was no benefit in increasing the glycerol amount to twice the drug, and PEG to drug ratio was effectively reduced to 3 by addition of glycerol without affecting drug dissolution. However, any further reduction in ratio affected drug dissolution rate adversely.

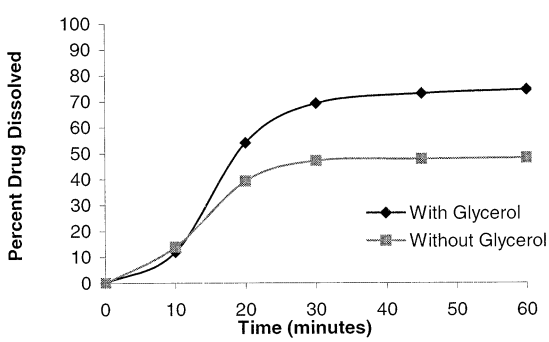

Fig. 3. Effect of glycerol on drug dissolution. Formulation contained PEG 20000:itraconazole:Explotab® at 3:1:1 ratio. Glycerol is present as 1 part in one formulation.

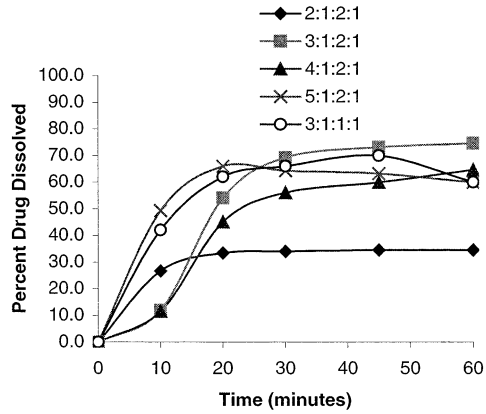

Fig. 4. Effect of reduced PEG to drug ratio on drug dissolution from solid solutions containing glycerol. Ratios represent PEG 20000:itraconazole:glycerol:Explotab®, respectively.

3.4. Influence of hydrophilic polymer HPMC

An interesting aspect observed during dissolution of solid solution formulations, mainly in finely ground formulations, was rapid initial dissolution followed by precipitation of drug. There could be many explanations for this phenomenon of drug precipitation. Grinding/milling is known to cause physical changes such as phase conversion or nucleation of drug substance. As the particle size of formulation is reduced, drug dissolves at a much faster rate and can form a supersaturated solution, followed by precipitation. Crystalline growth occurs after the nucleation in the precipitation process. Hydrophilic polymers such as PVP, PVP–hexacedene are known to inhibit nucleation of compounds in supersaturated solution (Ma et al., 1996). To prevent effects of nucleation, an antinulceation agent or phase retardant agent hydroxypropyl methylcellulose (HPMC) was incorporated in the formulation.

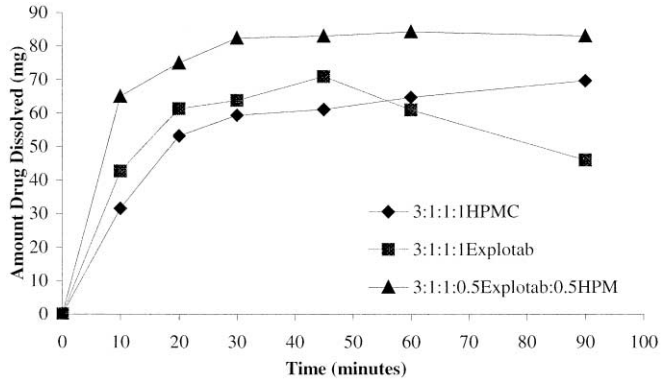

Fig. 5. Effect of addition of HPMC on drug dissolution. HPMC prevented precipitation of dissolved drug during dissolution. Ratios represent PEG 20000:itraconazole:glycerol:HPMC and/or Explotab®, respectively.

Dissolution profiles for formulations containing Explotab® and HPMC are shown in the Fig. 5. The formulation containing Explotab® showed rapid drug dissolution followed by precipitation of drug, whereas the formulation containing HPMC showed slower drug dissolution but no precipitation of drug. When both of these excipients were used at equal proportions in the formulation, the dissolution profile was not only fast, but also there was no precipitation of drug (Fig. 5). It follows from this that HPMC prevented precipitation of drug during dissolution and addition of Explotab® to the formulation containing HPMC enhanced rate of drug dissolution.

3.5. Influence of 'formulation granule' size

A 'formulation granule' size is defined as particle size of final solid solution formulation. A solid solution formulation containing PEG 20000, itraconazole, glycerol, Explotab® and HPMC at 3:1:1:0.5:0.5 (50:16.7:16.7:8.3:8.3%) was made into different size granules, viz., 240–380 μm (mesh size 60), 381–590 μm (mesh size 40), 591–480 μm (mesh size 30), 841–1180 μm (mesh size 20) and 1180–1400 μm (mesh size 16). In this range, dissolution from larger granule sizes is better, and without precipitation of drug. As the particle size of granules is reduced, precipitation became prominent resulting in poor overall drug dissolution (Fig. 6). These findings are counter-intuitive in terms of known particle size versus dissolution relationships.

It may be that very rapid dissolution produces a localized saturated solution and the drug then precipitates. Another possible explanation for this phenomenon is that the solvent microenvironment around the drug molecules changes rapidly during dissolution. The finer the granule size, the faster will be the rate at which solubilized molecule loses its glycerin/PEG dominated environment through exposure of high concentrations of dissolved drug to mostly aqueous environment and due to which precipitation of drug occurs.

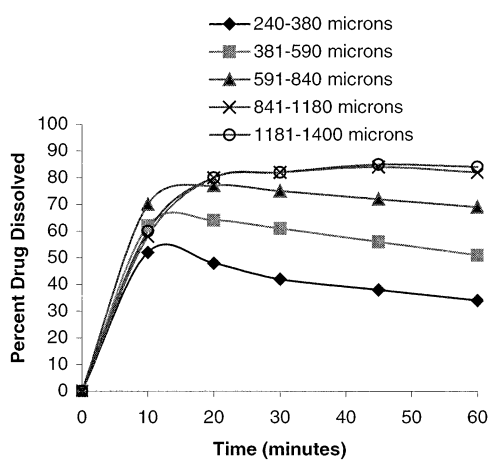

Fig. 6. Effect of granule size of solid solution formulation on drug dissolution. Formulation contains PEG20000:itraconazole:glycerol:Explotab®:HPMC at 3:1:1:0.5:0.5 ratios, respectively.

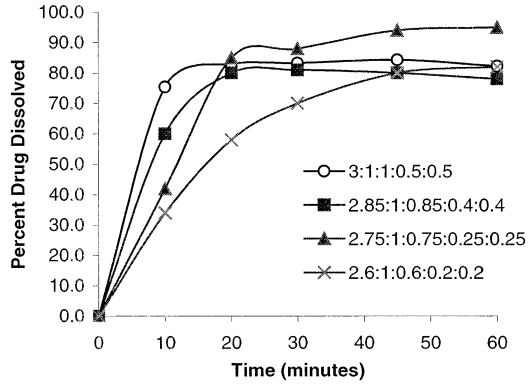

Fig. 7. Dissolution of drug from various solid solution formulations at different ratios of PEG 20000:itraconazole:glycerol:Explotab®:HPMC.

3.6. Optimization of formulation

Various formulations were prepared by varying each ingredient in the formulation and dissolution profiles are shown in Fig. 7. A formulation containing PEG 20000, drug, glycerol, Explotab® and HPMC at 2.75:1:0.75:0.25:0.25 respectively, was found to be an optimum formulation. A formulation that can be easily placed into a single zero capsule i.e. a 500 mg of total formulation equivalent to 100 mg of itraconazole. Dissolution comparison of this formulation with Sporanox® is shown in Fig. 8. The initial dissolution rate for solid solution formulation is faster than for Sporanox®. This formulation was administered to human subjects for bioequivalency comparison with Sporanox®.

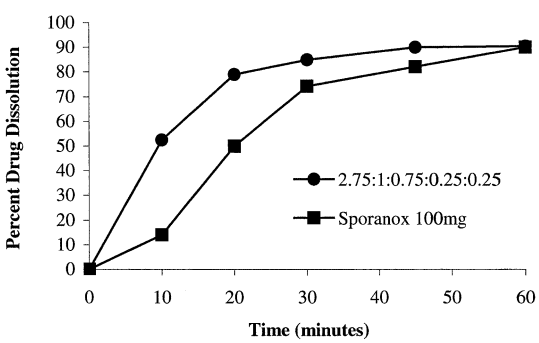

Fig. 8. Dissolution comparison of optimized solid solution formulation with marketed product Sporanox®. Ratios indicate PEG20000:itraconazole:glycerol:HPMC:Explotab®, respectively.

3.7. Effect of blends of various PEGs

Blends of PEG 20000 and PEG 8000 at ratios such as 60:40, 50:50 and 40:60 were used to prepare solid solution of drug using ingredients at the same ratio as in the optimized formulation. Dissolution results are as shown in Fig. 9. As the ratio of PEG 8000 increased in the blend, there was a decrease in the dissolution rate of itraconazole. This supports initial studies that indicated decrease in drug dissolution with decreasing molecular weight of PEG. Lower molecular weight PEGs are linear chains of ethylene glycols, where as PEG 20000 is a branched complex containing linear PEGs linked through a spacer. Is there a complexation formed between drug and PEG 20000 due to branched nature of PEG 20000 or is it just a higher molecular weight of PEG that is responsible for increased drug dissolution? This was investigated by making solid solutions using linear chain PEG 20000.

3.8. Influence of type of PEG 20000

Branched PEG 20000 consists of 2 moles of polyethylene glycol (mol.wt. 7000–9000) joined internally through a homobifunctional aromatic spacer (UC, 1997). Linear PEG 20000, as indicated by the name, is linear in nature. Itraconazole dissolution rate from formulations containing linear PEG 20000 was found to be very poor and never reached completion (Fig. 10). However, dissolution from granules was better than from powdered formulation similar to that observed for all previously described formulations (not shown in the figure).

The reason for poorer dissolution rate from linear PEG relative to branched chain PEG is unknown. DSC results clearly show that a solid-in-solid solution is formed for itraconazole in all PEG preparations, including both branched and linear chain PEG 20000. There may be slower dissolution of the linear PEG–drug complex in gastric fluid (although linear PEG 20000 alone, by itself, dissolved similarly as branched PEG 20000

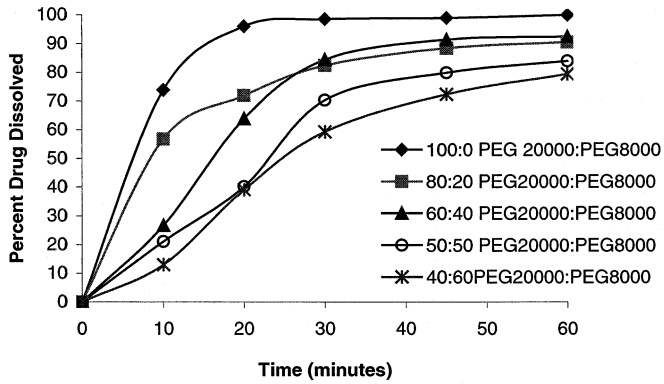

Fig. 9. Effect of ratio of PEG 20000:PEG 8000 in drug dissolution from solid solution formulations. All the formulations contained PEG, drug, glycerol, HPMC and Explotab® at 2.75:1:0.75:0.25:0.25 respectively.

in gastric fluid) or some unknown difference in the eutectic nature of the formulation complex. This needs further evaluation.

3.9. Biostudy in human volunteers

Tables 1 and 2 give comparison of bioavailability parameters such as the mean ($\pm$ S.D.) time to reach maximum plasma concentration (T_{max}), maximum plasma concentration (C_{max}), elimination rate constant, plasma half-life ($t_{1/2}$) and area under the curve (AUC) for both the new solid solution formulation and marketed product (Sporanox®) under fasting and fed conditions respectively. The mean plasma concentration versus time curves obtained for both formulations under fasted and fed conditions are plotted in Figs. 11 and 12. Average curves for both formulations look similar under both the conditions of testing. However, average of individual C_{max} for solid solution formulation is higher than that seen for Sporanox®. The two formulations were found to be not bioequivalent, since pharmacokinetic parameters were not within 80–125% when analyzed by two one-sided t-tests on log-transformed data.

4. Conclusions

Successful solubilization of itraconazole was achieved using solid solution techniques. Solid solutions of lower drug concentrations gave faster dissolution rate, and drug dissolution improved considerably with an increase in molecular weight of PEG. Initial treatment of itraconazole with the wetting agent glycerol, prior to making itraconazole into solid solution, reduced the amount of PEG required to produce a solid solution. Addition of HPMC in the solid solution eliminated precipitation of drug during dissolution. As granule size of the solid solution was reduced, precipitation of drug during dissolution became prominent. The type of PEG also influenced drug dissolution rate from solid solution. Higher molecular weight PEG resulted in complete drug

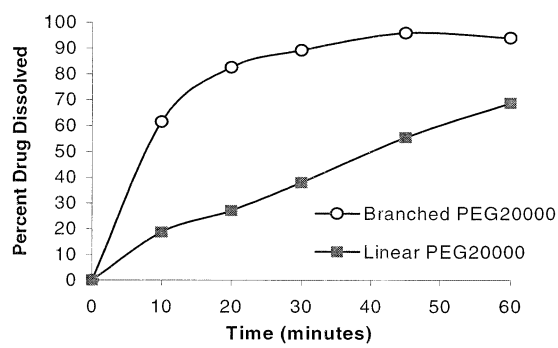

Fig. 10. Effect of type of PEG 20000 on drug dissolution. Dissolution of drug from linear PEG 20000 complex was slower and incomplete when compared with branched PEG 20000 complex. Both the formulations contained PEG, drug, glycerol, HPMC and Explotab® at 2.75:1:0.75:0.25:0.25 respectively.

Table 1
Average of individual pharmacokinetic parameters under fasting conditions

Parameter	Test formulation (mean ± S.D.)	Sporanox® (mean ± S.D.)
T_{max} (h)	2.33 ± 0.52	2.83 ± 0.75
C_{max} (ng/ml)	47.1 ± 27.4	32.13 ± 8.6
β (1/h)	0.03476 ± 0.007	0.0387 ± 0.013
$t_{1/2}$ (h)	20.63 ± 4.32	19.96 ± 7.66
$AUC_{0\rightarrow t}$ (ng h/ml)	406.55 ± 213.35	429.6 ± 252.8
Subjects (n)	5	6

Table 2
Average of individual pharmacokinetic parameters under the conditions of fed

Parameter	Test formulation (mean ± S.D.)	Sporanox® (mean ± S.D.)
T_{max} (h)	5.5 ± 1.52	3.75 ± 1.7
C_{max} (ng/ml)	63.95 ± 21.0	58.37 ± 13.65
β (1/h)	0.03678 ± 0.0078	0.041 ± 0.01
$t_{1/2}$ (hr)	19.55 ± 4.1	18.155 ± 5.6
$AUC_{0\rightarrow t}$ (ng h/ml)	946.24 ± 453.22	772.4 ± 470.0
Subjects (n)	6	4

dissolution. Branched PEG 20000 resulted in a faster drug dissolution rate than from linear PEG 20000. Bioavailability comparison of solid solution formulation with marketed product in human volunteers showed these two products to be not bioequivalent.

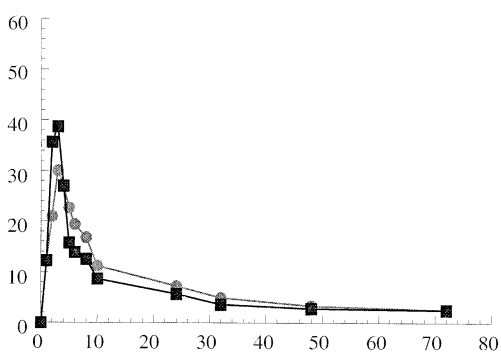

Fig. 11. Average plasma concentration for two formulations under conditions of fasting. (●-Sporanox, ■-Test formulation). X-axis: Time (h), Y-axis: Plasma Drug Conc (ng/ml).

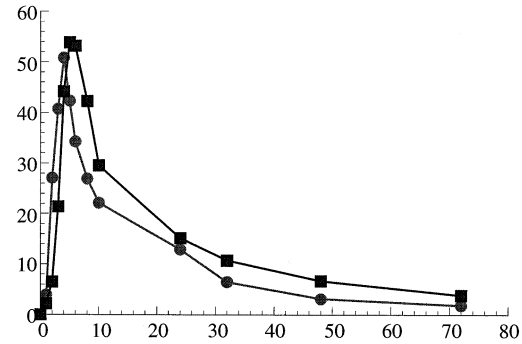

Fig. 12. Average plasma concentration for two formulations under fed conditions (●-Sporanox, ■-Test formulation). X-axis: Time (h), Y-axis:Plasma Drug Concentration (ng/ml).

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