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COMPARISON OF CRYSTALLINE AND AMORPHOUS CARRIERS TO IMPROVE THE DISSOLUTION PROFILE OF WATER INSOLUBLE DRUG ITRACONAZOLE

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ABSTRACT

The present study investigates the effect of crystalline and amorphous carriers for the improvement of dissolution profile of broad spectrum antifungal agent Itraconazole. A comparative study was performed to estimate the ability of Poloxamer-407 (crystalline carrier) and modified Gum Karaya (amorphous carries) for enhancing the dissolution profile of Itraconazole (BCS class II). Solid dispersions prepared (using Poloxamer-407) by hot melt method, exhibited 92% drug release at the end of 2 hrs with good percent yield and percent drug content. While solid dispersions prepared (using modified gum karaya) by solvent evaporation method, exhibited 86% drug release at the end of 2 hrs but it possessed low drug content and low drug yield. Thus, complete amorphous state and absence of crystalline peaks of Itraconazole were observed with Poloxamer-407 while presence of small number of crystalline peaks with much reduced intensity (of Itraconazole) shifting towards lower melting endotherm were observed in case of modified gum karaya.

KEYWORDS: Dissolution, solid dispersion, amorphous carrier, modified gum karaya, poloxamer-407.

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INTRODUCTION

Out of newly discovered drugs more than 40 % drugs are lipophilic and out of which up to 40 % of pharmacologically active new molecules failed to reach to market only due to little or no water solubility; a serious challenge for the successful development and commercialization of new drugs in the pharmaceutical industry[1]. Poorly water soluble drugs are associated with slow drug absorption leading eventually to inadequate and variable bioavailability[2]. The enhancement of oral bioavailability of such poorly water soluble drugs remains one of the most challenging aspects of drug development[3]. The dissolution rate directly affects the onset of action, duration of and intensity of action[4]. Therefore demand for increasing the dissolution rate of such insoluble compounds is increasing. Antifungal drugs are used to treat infections caused by fungi and to prevent the development of fungal infections in patients with weakened immune systems. The model drug Itraconazole selected for present study is a synthetic broad-spectrum azole antifungal agent which is active against various strains of the fungi like dermatophytes (*Trichophyton spp, Microsporum spp, Epidermophyton floccosum),* yeasts (*Cryptococcus neoformans, Candida* spp), Aspergillus spp, *Histoplasma* spp, *Paracoccidioides brasiliensis, Sporothrix schenckii* etc[5]. Itraconazole is poorly water soluble (less than 1µg/mL of aqueous solution). Because of its very low aqueous solubility and poor dissolution rate, Itraconazole shows a large inter-individual difference in the bioavailability after oral administration[6]. Itraconazole belongs to BCS Class II with 3.7 pKa value[7]. Numerous reports are available to enhance the dissolution profile of Itraconazole in literature by using HPMC[8], Kollicoat IR[9], Kollidon[10], Poloxamer-188[11], beta cyclodextrins[12], Laponite based systems[13], Ternary solid dispersions using HPMC And Pluronic F-68[14], PVPVA 64 and Myrj 54 self emulsyfying systems[15]. All the techniques used so far are either sophisticated or are industrially feasible. An attempt has been done in this study to use simplest laboratory feasible methods i.e. hot- melt and solvent evaporation to prepare solid dispersion systems and to reduce the cost of production as well.

MATERIALS AND METHODS

Itraconazole was purchased from Metrochem Asia Private Limited (Hyderabad, India). Poloxamer -407 was obtained as a gift sample from Signet labs Mumbai, India). Gum karaya (Grade 1) was obtained as gift sample from Girijan Cooperative Corporation Ltd. (Visakhapatnam, India). All the other chemicals and reagents used in the study were of analytical grade.

1) Preformulation studies

A. Solubility

The solubility of Itraconzole was estimated in Water, 0.1 N HCl, 0.1N HCl + 0.5 % SLS and pH 6.8 phosphate buffer. For this a saturated solution of Itraconazole was prepared in a 10 mL of each of the solvent. To facilitate maximum solubilization of the drug in the solvent at room temperature it was kept in water bath incubator shaker for 24 h at 25 °C to achieve equilibrium. The solution was then observed for a clear transparent solution. If the solution was not transparent, it was filtered through 0.45 µm membrane filter. The amount of Itraconazole present in the solvent was then estimated using UV visible spectrophotometer after appropriate dilutions.

B. *Phase solubility studies*

Phase solubility study was performed according to the Higuchi and Connors method[16]. Excess amount of Itraconazole was added to aqueous solutions containing Poloxamer-407 in the concentrations (0.5, 1, 2, 4, 6, 8 and 9%). The contents were stirred on the water bath shaker at 25^0C for 48 h. The contents were filtered and assayed spectrophotometrically at 253.6 nm. Phase solubility with modified gum karaya was

also conducted. However due to high swelling index of gum karaya, entire water was absorbed by it and readings could not be taken. The Gibbs free energy of transfer (ΔGtr°) of Itraconazole from water to aqueous solutions of carrier was calculated[17] using the following equation:

Eq1 $\Delta G_{tr}^{o} = -2.303\ RT \log (Sc/S_o)$

Where ΔG_{tr}° is Gibbs free energy of transfer, R (8.314 J/ ^{o}Cmol) is gas rate constant, T is temperature at which phase solubility studies were conducted and S_c/S_o is the ratio of molar solubility of Itraconazole in aqueous solution of carrier to that of water. The acquired values of ΔG_{tr}° indicate that whether the drug solubilization in the aqueous solution is favorable or not i.e. negative ΔG_{tr}° values indicate favorable conditions and as the values increases more negative means more favorable conditions.

C. Preparation of Modified gum karaya

Gum karaya is having very high viscosity and good swelling index but it is of limited value for the dissolution enhancement of a drug because it forms a thick viscous layer from which the drug release becomes slower[18]. So gum karaya was modified by the method discussed by Murali Mohan Babu, 2002[18,19]. The crude tears of gum were pulverized and passed through mesh no.100. Powdered gum was taken in china dish and subjected to heating using sand bath for different time periods at different temperatures.

D. Characterization of GK/MGK

a) Measurement of swelling index (SI)

About 1 gm of Gum karaya powder was weighed and transferred to a 100 mL stoppered measuring cylinder[19]. The initial height of the powder in the measuring cylinder was noticed. The volume was made 100 mL with distilled water. The cylinder was closed with lid and was shaken and set aside for 24 h. The same procedure was carried out for the Modified gum karaya. Swelling index was expressed as a percentage and calculated according to the following equation. Where X_o is the initial height of powder in the graduated cylinder and X_t denoted the height of swollen gum after 24 h.

$$SI = \frac{(X_t - X_o) \times 100}{X_o}$$

b) Determination of volatile acid number

About 1 gm of gum was weighed and transferred to 500 mL RBF. 100 mL of water and 5 mL of orthophosphoric acid were added and allowed to stand for 6 h until gum was completely swollen. Then it was boiled for 2 h under a reflux condenser and steam distilled until 80 mL of the distillate was obtained. The distillate was titrated with 0.1N NaOH using phenolphthalein as indicator. The procedure was repeated omitting the sample. The difference between two readings represented the amount of alkali required to neutralize the volatile acid. Each mL of 0.1N NaOH is equivalent to 0.006005 g of $C_2H_4O_2$.

c) Determination of pH

The pH of 1 % w/v solution of gum karaya and modified gum karaya was noted.

d) Determination of Viscosity

The viscosity of 1 % (w/v) GK/MGK solution was measured using Brookfield Viscometer at 37 °C

2) Preparation of solid dispersion

A. Hot-melt technique

Solid dispersions of Itraconazole with Poloxamer-407 were prepared by the hot melt method. Poloxamer-407 was first of all pulverized in mortar and passed through mesh # 100. Itraconazole was also passed through the same sieve. The physical mixture of itraconazole and poloxamer-407 in different proportions was heated to a liquid state. The mixtures were stirred for 15 minutes at this temperature for the solubilization of the drug in the carrier and the resulting homogeneous preparations were rapidly cooled on ice cool water, leading to rapid solidification[20].

Subsequently, the dispersions were pulverized, passed through sieve #100 and then stored in a vacuum desiccator at room temperature until use. The composition of Itraconazole-Poloxamer solid dispersions prepared by this method are shown in Table 1.

Table 1
Compositions of Itraconazole-Poloxamer solid dispersions prepared by Hot-melt technique

Formulation	Drug : Carrier
IP-1	1:1
IP-2	1:2
IP-3	1:4
IP-4	1:6
IP-5	1:8
IP-6	1:9

B. Solvent-evaporation method

Accurately weighed amount of Itraconazole was dissolved in 10 mL of dichloromethane to a clear solution. 25 mL of 70 % v/v ethanol was added to the clear solution of drug. The accurately weighed GK/MGK (passed through sieve #100) was then added to it and dispersed well with magnetic stirrer for 6 h. The wet mass obtained was dried at 60°C for 6 h in the vacuum oven. The dried mass was mixed well and sifted through 100 mesh and then stored in vacuum desiccators at room temperature until use. The Compositions of Itraconazole-GK/MGK solid dispersions prepared by this method are shown in Table 2 and Table 3.

Table 2
Compositions of Itraconazole-GK solid dispersions prepared by Solvent evaporation method

Formulation	Drug : Carrier
IGK-1	1:1
IGK-2	1:2
IGK-3	1:4
IGK-4	1:6

Table 3
Compositions of Itraconazole-MGK solid dispersions prepared by Solvent evaporation method

Formulation	Drug : Carrier
IMGK-1	1:1
IMGK-2	1:2
IMGK-3	1:4
IMGK-4	1:6

3) Preparation of Physical mixtures

A. Physical mixture preparation with Poloxamer-407

Physical mixture of the Itraconazole and Poloxamer-407 was also prepared by geometrical mixing of two components in a mortar for 5 minutes and then sieving through #100. The compositions of Itraconazole-Poloxamer physical mixture prepared are shown in Table 4.

Table 4
The compositions of Itraconazole-Poloxamer Physical mixtures prepared by geometrical mixing

Formulation	Drug : Carrier
IP-7	1:1
IP-8	1:6

B. Physical mixture preparation with Gum karaya and Modified gum karaya
Physical mixture of the Itraconazole and GK/MGK was also prepared by geometrical mixing of two components in a mortar for 5 minutes and then sieving through # 100. The compositions of Itraconazole- GK/MGK physical mixture prepared are shown in Table 5 and Table 6.

Table 5
The compositions of Itraconazole-Gum Karaya physical mixtures prepared by geometrical mixing

Formulation	Drug : Carrier
IGK-5	1:1
IGK-6	1:4

Table 6
The Compositions of Itraconazole-Modified gum karaya Physical mixtures prepared by geometrical mixing

Formulation	Drug : Carrier
IMGK-5	1:1
IMGK-6	1:4

4) Percentage drug content
Physical mixtures and solid dispersions equivalent to 20 mg of drug were dissolved in a mixture of ethanol and 0.1N HCl. The drug concentration was determined by UV-visible spectrophotometer after appropriate dilution, using 0.1N HCl as blank.

5) Percentage drug yield
Solid dispersions were calculated for the percentage drug yield[21]. The equation is as follows-

$$Y = \left(\frac{a}{b + c} \right) X\ 100$$

Where **a** is the weight of solid dispersion sifted through mesh no.100, **b** is the weight of Itraconazole taken and **c** is the weight of polymer (Poloxamer or GK/MGK) taken for solid dispersion/physical mixture preparation.

6) In vitro drug dissolution studies
Pure drug, physical mixtures and solid dispersions equivalent to 100 mg of the dose were filled in empty capsule shells and subjected to dissolution studies. The dissolution media (900 mL) consisted of 0.1N HCl + 0.5 % SLS[22]. To maintain sink conditions 0.5 % SLS was added to the dissolution media. Adding SLS to the dissolution media for the water insoluble drugs has a physiological significance as natural surfactants like bile salts are usually present in gastrointestinal tract[2]. Dissolution was assessed using a paddle rotating at 75 rpm and a temperature of 37± 1 ºC was maintained in each study (USP XXIV method 2). The release was followed for 2 h and samples were taken after 5, 10, 20, 30, 45, 60, 90, 120 minutes. An aliquot of 5 mL was drawn at each point and replaced the same with buffer. The sample was filtered through 0.45 µm filter and concentration of Itraconazole was quantified

with UV spectrophotometer at the maximum wavelength of 259.2 nm.The cumulative amounts of drug dissolved (expressed as % of the total drug added) were plotted as a function of time to produce the dissolution profiles.

7) FTIR Spectroscopy

Drug–carrier interactions in the solid dispersions and physical mixture were determined based on the FTIR spectra measured using Rkin-Elmer FT-IR spectrometer. Samples were mixed with potassium bromide (spectroscopic grade) and compressed into disks using hydraulic press. The IR spectra in absorbance mode were obtained in the spectral region 500-4000 cm^{-1} using a resolution of 2 cm^{-1} and 4 scans. The FTIR spectra of pure drug, physical mixture and solid dispersions were compared to check any interactions between the drug and polymer or change in the positions of the functional group of the drug.

8) X-ray diffraction studies

XRD were carried out to determine the physical state of the drug in the solid dispersion systems. The XRD of pure drug, carriers, physical mixtures and solid dispersion were recorded using X' Pert PRO instrument. The radiation used was generated by a Cu K*α* source fitted with a nickel filter at 0.154 nm wavelengths at 40 mA and 45 kV. Samples were scanned for 2θ values over a range from 5-45°, at a scan rate of 10°C/min. All XRD spectra were compared.

9) Differential Scanning Calorimetry

The thermal behavior of Itraconazole, Poloxamer-407, Gum karaya, Modified gum karaya, Physical mixtures and Solid dispersions were investigated using a Diamond DSC (Perkin, USA). Accurately weighed samples (3.13 mg) were placed in standard aluminium pans and covered with a pierced lid. Dry nitrogen was used as the purge gas, at a flow rate of 50 mL/min. The thermograms were obtained by heating the samples at a rate of 10°C/min from 30 °C temperature to 300 °C.

RESULTS

1) Preformulation studies

A. Solubility of Itraconazole

The solubility of Itraconazole was determined by shake flask method in various solvents and dissolution media. The results are shown in Table 7 and Table 8. The solubility of Itraconazole in various solvents meets the specifications as per COA (Certificate of Analysis) issued by the manufacturer.

Table 7
Solubility of Itraconazole in different media at 25 ºC

Dissolution media	Solubility	
	Qualitative	Quantitative (µg/mL)
0.1N HCl	+	4.08 ± 0.14
0.1N HCl + 0.5% SLS	+	19.64 ± 0.21
Water	+	0.81 ± 0.18
6.8 Phosphate buffer	+	3.51 ± 0.11

Data are represented as mean ± S.D (n=3)

Table 8
Solubility of Itraonazole in organic solvents at 25 ºC

Solvents	Solubility (Qualitative)
Dichloromethane	++++
Tetrahydrofuran	++
Ethanol	+++

Where: + Insoluble; ++ sparingly soluble; +++ very slightly soluble; ++++ freely soluble

B. Phase solubility studies

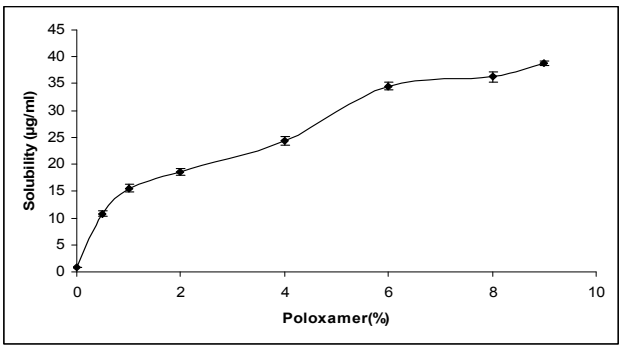

Figure 1
Phase solubility behavior of Itraconazole at 25 ºC in Poloxamer-407 solutions in distilled water (pH=5.8)

Phase solubility studies indicated that drug solubility was increased with increasing concentration of Poloxamer (Figure 1). At Poloxamer concentration of 6 % w/v there was a sharp increase in solubility. Although, the solubility was increased further by adding more poloxamer to the aqueous solution but a constant phase was observed thereafter. All the ΔGºtr values were negative at all the levels of the carriers, demonstrating spontaneity of the drug solubilization process (Table 9). The process of drug transfer from the dissolution media to the carrier solution is more favorable at higher carrier levels.

Table 9
Thermodynamic parameters for the solubilization process of Itraconazole in aqueous solution of Poloxamer-407

Poloxamer-407 concentration (% w/v)	0	0.5	1	2	4	6	8	9
$\Delta G_{tr}°$ (KJ/mol)	0	-0.533	-0.616	-0.649	-0.701	-0.780	-0.791	-0.802

2) Solid state characterization of physical mixtures and solid dispersions

A. Differential Scanning Calorimetry

Differential scanning Calorimetry (DSC), X-Ray diffraction spectroscopy and Fourier transform Infrared spectroscopy (FTIR) were used for solid state characterization of all the systems. Figure 2 shows examples of the DSC traces of the optimum compositions of solid dispersion and physical mixture of Itraconazole and Poloxamer-407. DSC of pure drug Itraconazole showed sharp melting endothermic peak (T_m) at 166.8 ºC. This is in the good agreement with the previous findings on the thermal analysis of Itraconazole[23]. Poloxamer-407 showed the endothermic peak (T_m) at 54.29 ºC. The Physical mixture of Itraconazole and poloxamer-407 (IP-8) showed two endothermic peaks (T_m) at 154.23 ºC and 52.60 ºC with reduction in the peak areas and melting endotherms (ΔH value). Solid dispersion on the other hand (IP-4) showed only one endothermic peak due to the poloxamer alone. No another peak was detected due to the drug, showing the loss of crystalline nature of the drug. The drug was converted to the complete amorphous state indicating the drug was molecularly dispersed within the carrier system.

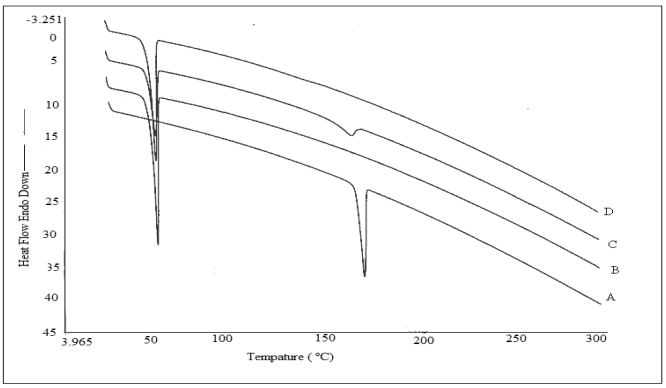

Figure 2

Examples of the DSC traces of Itraconazole – Poloxamer 407. A) Pure drug Itraconazole, B) Poloxamer - 407, C) Physical mixture of Itraconazole and Poloxamer-407 (IP-8), D) Solid dispersion of Itraconazole and Poloxamer 407 (IP-4)

In the case of physical mixture and solid dispersion of Itraconazole with Modified gum karaya (MGK), there was reduction in the crystalline nature of drug although drug was not completely converted to the amorphous form as shown in Figure 3. Physical mixture (IMGK-6) showed only a little shifting of melting endotherm of drug but solid dispersion (IMGK-3) showed more shifting towards lower melting endotherm. Also ΔH value, in case of solid dispersion was much reduced as compared to pure drug

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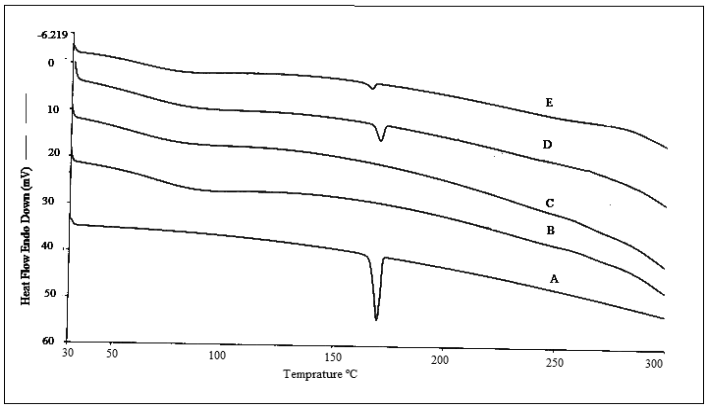

Figure 3

Examples of the DSC traces of Itraconazole – Poloxamer 407. A) Pure drug Itraconazole, B) um karaya, C) Modified gum karaya, D) Physical mixture of Itraconazole and Modified gum karaya (IMGK-6) D) Solid dispersion of Itraconazole and Modified gum karaya (IMGK-3).

B. X-ray diffraction study

X-ray diffraction of pure drug Itraconazole showed the intense diffraction peaks at 2θ values 14.5º, 17.5º, 18.01º, 19.3º, 20.3º, 23.5º, 25.3º, 25.5º and 27.1º. Poloxamer exhibited the intense diffraction peaks at 2θ values of 19.1º and 23.2º. This is in the agreement with the previous recorded X-ray powder diffraction of Poloxamer-407 [24]. The physical mixture (IP-8) possessed the diffraction peaks of both pure drug and carrier. One peak of drug at 19.3º and one peak of Poloxamer at 19.1º are present as a single peak at 19.2º. Similarly instead of drug peak at 25.3º and carrier peak at 23.2º there is single peak at 23.4º with reduced intensity indicating that some crystalline nature of drug has been reduced (Figure 4). In the diffraction pattern for the IP-4 (1:6) and IP-6 (1:9) solid

dispersions, crystalline peaks due to drug have disappeared indicating that there was complete conversion of crystalline drug to amorphous state (also confirmed by DSC analysis described above). There is no significant change in the diffraction patterns of IP-4 and IP-6.

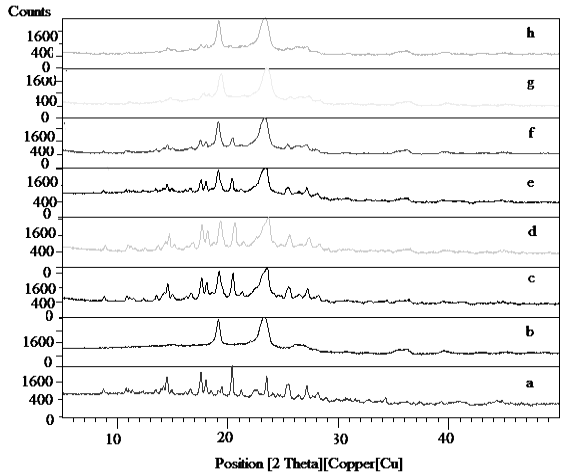

Figure 4
X-ray powder diffraction patterns of a) Itraconazole; b) Poloxamer - 407; c) Physical mixture (IP-8); d) Solid dispersions IP-1; e) IP-2; f) IP-3; g) IP-4; h) IP-6

The amorphous carrier Modified gum karaya, showed no diffraction peak (Figure 5).The physical mixture IMGK-6 (1:4) showed the diffraction peaks at 14.5º, 17.5º, 19.4º, 20.4º, 23.5º, 25.3º and 27.1º with reduced intensity indicating that some crystalline nature of the drug had reduced. The solid dispersion of the optimum ratio IMGK-6 (1:4) showed that the number of crystalline peaks due to drug had reduced in number and intensity of such diffraction peaks also reduced to a great extent.

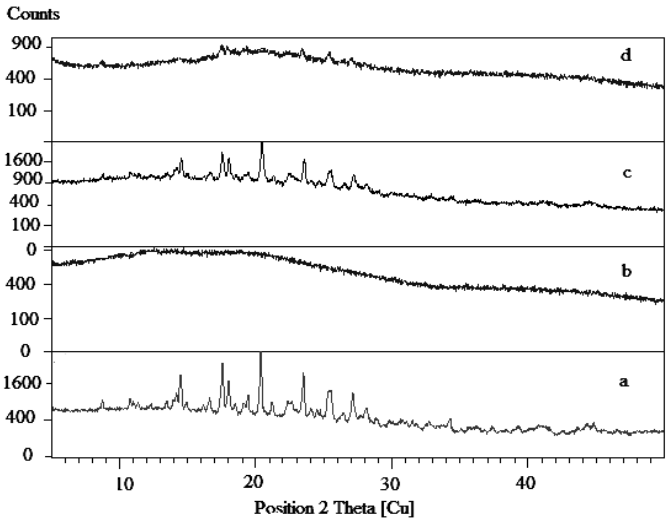

Figure 5
X-ray powder diffraction studies of a) Itraconazole; b) MGK; c) Physical mixture (IMGK-6); d) Solid dispersion (IMGK-3)

C. FTIR spectroscopy

The FTIR spectra of Itraconazole showed comparable principal absorption bands (Stretching) at 1698.6 cm^{-1} (C=0), 1512 cm^{-1} (CO-NH_2), 1453.2 cm^{-1} (C-N), 1612.3 cm^{-1} (C=N) and 945.3 cm^{-1} (C-Cl). The absorption bands between 2600 cm^{-1} and 3200 cm^{-1} were attributed to the alkane, aromatic (C-H) and amine groups. The FTIR spectra of Poloxamer-407 showed the principal absorption bands (Stretching) at 3460 cm^{-1} (O-H), 2885 cm^{-1} (C-H), 1112.5 cm^{-1} (C-O). It was also found to be comparable with the previous recorded FTIR spectra of Poloxamer-407[24]. There was no significant change in the absorption spectra of solid dispersion and physical mixture as incorporation of drug into Poloxamer did not modify the position of functional groups. The FTIR spectra of pure drug Itraconazole, Poloxamer-407, Physical mixture (IP-8) and Solid dispersion (IP-4) are shown in Figure 6.

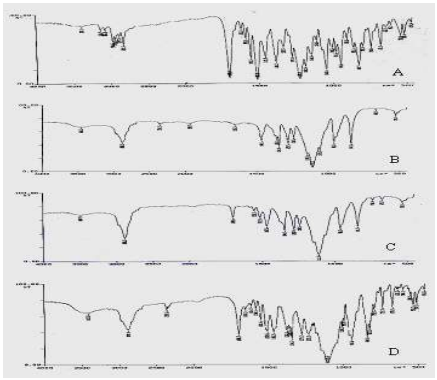

Figure 6
FTIR Spectra of A) Itraconazole; B) Poloxamer-407; C) Physical mixture (IP-8); D) Solid dispersion (IP-4).

The FTIR spectra of MGK/GK showed the absorption bands at 3390 (Free -OH), 2936 (-CH Alkane) and 1734.3 (C=0). Gum karaya also showed the same absorption bands showing that there was no chemical/structural change on modifying gum karaya. This is in the agreement with the previous recorded FTIR spectra of GK/MGK[19]. Solid dispersion and physical mixture showed all the characteristic bands both due to drug and modified gum karaya suggesting that there was no chemical interaction between them as shown in Figure 7.

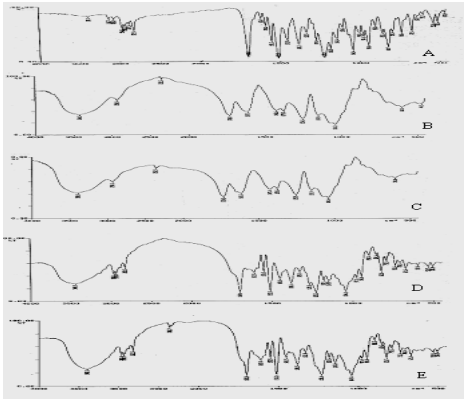

Figure 7
FTIR Spectra of A) Itraconazole; B) Gum karaya; C) Modified gum karaya; D) Physical mixture IMGK-6; E), Solid dispersion IMGK-4.

3) Percentage drug content and percentage drug yield

The drug content was determined to evaluate the homogeneity of distribution of drug in physical mixtures and solid dispersions and drug yield was determined to evaluate any loss of drug that occurred during the preparation of mixtures. The results revealed drug content values in the range of 98.7-100.02 % w/w indicating homogenous distribution of the drug in prepared mixtures in the case with Poloxamer-407 as the carrier. The results of % age drug content and % age drug yield are shown in Table 10.

Table 10.
Percent yield and Percent drug content of Itraconazole-Poloxamer-407 solid dispersions and physical mixtures prepared by Hot-Melt method

Formulation Number	% Yield	% Drug Content
IP-1	99.23	98.90 ± 0.123
IP-2	99.21	99.36 ± 0.245
IP-3	100.12	99.98 ± 0.312
IP-4	98.87	98.32 ± 0.187
IP-5	99.23	99.15 ± 0.183
IP-6	98.84	98.78 ± 0.201
IP-7	100.04	99.94 ± 0.304
IP-8	100.1	100.02 ± 0.164

Data are represented as mean ± S.D (n=3)

For GK/MGK solid dispersions and physical mixtures the percent drug content and percent yield were less. This was due to the adsorption of drug on the surface of carrier due to which there was some loss of drug. The results of % age drug content and % age drug yield are shown in Table 11

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Table 11
Percent yield and Percent drug content of Itraconazole-GK/MGK solid dispersions and physical mixtures prepared by Solvent evaporation method

Formulation Number	% Yield	% Drug Content
IGK-1	89.23	89.90 ± 0.123
IGK-2	89.21	87.36 ± 0.245
IMGK-1	89.23	89.15 ± 0.183
IMGK-2	87.84	88.78 ± 0.201
IMGK-3	89.04	89.94 ± 0.304
IMGK-4	86.74	90.02 ± 0.164

Data are represented as mean ± S.D (n=3)

4) In vitro drug dissolution studies

Figure 8 shows the dissolution profile of Itraconazole in pure state, physical mixture and solid dispersion. As compared to pure drug Itraconazole, which was 41 % released at the end of 2 h. Physical mixture having high proportion of carrier (IP-8) released 57 % of the drug at the end of 2 h. Solid dispersion of the optimized formulation released 92 % of drug. Also for the optimized solid dispersion more than 75 % of the drug was released in 45 mins, thus comply the official requirements.

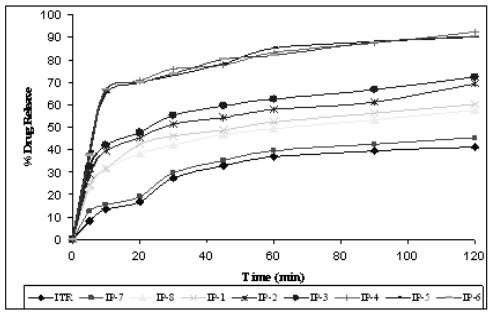

Figure 8
Dissolution profile of pure drug Itraconazole, Physical mixture and Solid dispersions with Poloxamer-407

Gum karaya, on the other hand was not a good carrier for the dissolution enhancement of drug. This was because of its high viscosity which forms gel layer on the hydrated surfaces[19]. Only 51 % drug was released at the end of 2 h at lower concentration of gum karaya (Figure 9). Higher proportions of gum karaya resulted in the retarded drug release.

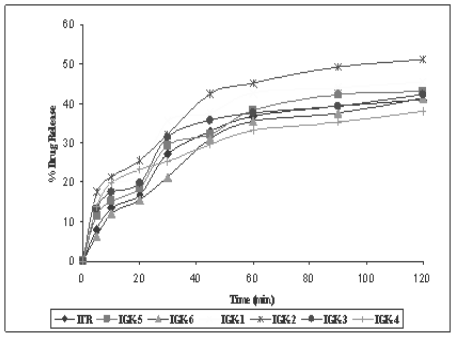

Figure 9
Dissolution profile of pure drug Itraconazole, Physical mixture and Solid dispersions with Gum karaya

In case of solid dispersion with MGK, the optimized formulation (IMGK-3) exhibited 86 % drug release (Figure 10) which was more than twice as compared to the pure drug. Also more than 75 % of the drug was released in 45 mins which complies with the official requirements.

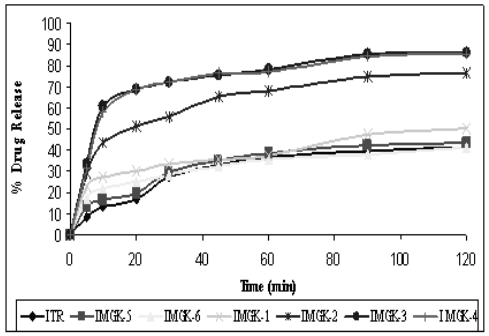

Figure 10
Dissolution profile of pure drug Itraconazole, Physical mixture and Solid dispersions with Modified gum karaya

DISCUSSION

Solid dispersions and physical mixtures of Itraconazole were prepared by using two carriers: Poloxamer-407 and Modified Gum Karaya. Poloxamer is crystalline and MGK is completely amorphous in nature. A comparison was done for their ability to increase the dissolution profile of water insoluble drug Itraconazole. Drug was evaluated for the compatibility study with Poloxamer-407 and Modified Gum Karaya for one month at 45ºC temperature and 65% RH. The phase solubility study of the drug was carried out in the different concentration of the Poloxamer (0.5, 1, 2, 4, 6, 8 and 9%). Itraconazole- Poloxamer (IP-1, IP-2, IP-3, IP-4, IP-5, IP-6, IP-7 and IP-8) systems were prepared by Hot melt method and Itraconazole-Modified gum karaya (IMGK-1, IMGK-2, IMGK-3, IMGK-4, IMGK-5 and IMGK-6) systems were prepared by Solvent evaporation method. Gum karaya is having a very high viscosity and good swelling index but it is of limited value for the dissolution enhancement of a drug because it forms a thick viscous layer from which the drug release becomes slower. So Gum karaya was modified. The crude tears of gum were pulverized and passed through mesh no.100. Powdered gum was taken in china dish and subjected to heating using sand bath for different time periods at different temperatures. It was concluded that heating gum karaya at 120ºC for 2 h reduced the viscosity of gum karaya with no significant effect on swelling index. Gum karaya is water insoluble so the drug was adsorbed to the surface of carrier. Solid dispersions and physical mixtures were evaluated for Percentage drug yield, Drug content, in vitro drug release studies, FTIR Spectroscopy, X-Ray Diffraction and Differential scanning calorimetry analysis. The results obtained showed that the rate of dissolution of the drug in the case of solid dispersions was much enhanced as compared to the pure drug and their physical mixtures. The polymorphic changes were studied with the XRD gave the idea that the solid dispersions were quite amorphous in nature as compared to the pure drug. In the diffraction pattern for the IP-4 (1:6) and IP-6 (1:9) solid dispersions, the number of crystalline peaks due to drug had disappeared. From the DSC it was also clear that polymorphic transition occurs. Solid dispersion (IP-4) shows only one endothermic peak due to the poloxamer alone. No another peak was detected due to the drug, showing the loss of crystalline nature of the drug. The drug was converted to the amorphous form. There was no significant change in the diffraction patterns of IP-4 and IP-6 (Figure 4). On the other hand, number of crystalline peaks due to drug had reduced in number and intensity of such diffraction peaks also reduced to a great extent (Figure 5) in case of solid dispersion with IMGK-6 (1:4). DSC showed that there was shifting in melting endotherm of drug in case of solid dispersion IMGK-6. Thus, in the case of modified gum karaya the drug was not completely converted to amorphous form but there was reduction in crystalline nature of drug. FTIR spectra showed that there was not any interaction or hydrogen bonding between the drug and polymers in solid dispersions as well as physical mixtures. From the XRD and DSC it was confirmed that the increase in the solubility and dissolution rate was due to polymorphic transition of crystalline to amorphous form.

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