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ENHANCING SOLUBILITY AND DISSOLUTION OF ITRACONAZOLE BY SPRAY DRYING USING PLURONIC F-68

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ABSTRACT

Itraconazole, an anti-fungal drug, exhibits poor water solubility, dissolution and flow properties. Thus, the aim of the present study was to improve the solubility and dissolution rate of itraconazole by preparing microspheres by spray drying technique. Microspheres containing different ratio of Itraconazole and Pluronic F-68 were produced by spray drying using dichloromethane as solvent to enhance solubility and dissolution rate. The prepared formulations containing different ratio of drug and polymer were evaluated for in vitro dissolution and solubility. The prepared formulations were characterized by scanning electron microscopy (SEM), differential scanning calorimeter (DSC), X-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FT-IR). Dissolution profile of the spray dried microspheres was compared with its physical mixture and pure sample. Spray dried microspheres exhibited decreased crystallinity and the solubility and dissolution of the microspheres containing different ratio of drug and pluronic F-68 were significant improved compared with its physical mixture and pure sample of Itraconazole. Dissolution of microspheres containing 8:2 w/w (SD 4) showed higher % release i.e. 98 % in 40 min compare to other prepared ratio formulation. Consequently, From the above result it can be conclude that spray dried microspheres of itraconazole is a useful technique to improve the solubility and dissolution of poorly water soluble drug like itraconazole.

KEYWORDS: Spray drying, Itraconazole, Pluronic F-68, microspheres, Solubility, dissolution.

INTRODUCTION

Itraconazole (ITZ) is a potent broad-spectrum triazole antifungal drug with activity against Cryptococcus, aspergillum, Candida, blast-mycosis, onychomycosis, and histoplasmosis organisms [1, 2]. The compound is insoluble in water (S ≈ 0.050 µg/ml at neutral pH and S = 1.2 µg/ml in 0.1mol/l HCl), and has an ionization constant of 3.7 and a very high n-octane/water partition coefficient (log P >5). According to the biopharmaceutical classification system (BCS), itraconazole is an extreme example of a class II compound meaning that its oral bioavailability is determined by its dissolution rate in the GI tract [3, 4]. Consideration of the modified Noyes-Whitney equation provides some hints as to how the dissolution rate of very poorly soluble compounds might be improved to minimize the limitations to their oral availability. There have been numerous efforts to improve drug dissolution rates. These include (a) reducing the particle size to increase the surface area; (b) using water-soluble carriers to form inclusion complexes; (c) solubilization in surfactant systems; (d) using pro-drugs and drug derivatization; and (e) manipulation of the solid state of drug substances to improve the drug dissolution i.e. by reducing the crystallinity of drug substances through formation of solid dispersions. However, there are practical limitations to these techniques [5]. Although particle size reduction is commonly used to increase the dissolution rate, there is a practical limit to the size reduction that can be achieved by such commonly used methods as controlled crystallization and grinding. The use of very fine powders in a dosage form may also be problematic because of handling difficulties and poor wet-ability. Salt formation is not feasible for neutral compounds and the synthesis of appropriate salt forms of drugs which are weakly acidic or weakly basic may often not be practical. Even when salts can be prepared, an increased dissolution rate in the gastrointestinal tract may not be achieved in many cases because of the reconversion of salts into aggregates of their respective acid or base forms. The solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and co solvents leads to liquid formation that is usually undesirable from the viewpoints of patient acceptability and marketing. Solid dispersions have been widely used to enhance the solubility, dissolution rate, and bioavailability of poorly soluble drugs [6, 7, 8]. There are different types solid dispersion systems categorized according to the physical states of the drug and the carrier in the systems. It may be a molecular solid solution, a dispersion of amorphous or crystalline drug particles in an amorphous carrier matrix, or a combination of a solution and dispersion of solids.

The enhancement in the dissolution rate is obtained by one or a combination of the following mechanisms: eutectic formation, increased surface area of the drug due to precipitation in the carrier, formation of true solid solution, improved wet-ability, and drug precipitation as a metastable crystalline form or a decrease in substance crystallinity. The type of solid dispersion formed depends on both the carrier-drug combination and the method of manufacture. Microwaves irradiation was used recently for the preparation of solvent-free solid dispersions and for enhancement of release of the poorly soluble drug, Spray drying is one such technique of preparing solid dispersion and is widely used as an alternative to milling to reduce particle size [9,10,11]. The large surface area of the resulting particle should result in an enhanced dissolution rate and, consequently, improved bioavailability. The aim of the present study was to improve the solubility and dissolution rate of itraconazole by spray drying technique using different ratio of Pluronic F-68.

METHOD AND MATERIAL

Materials

Itraconazole and Pluronic F-68 were obtained as a gift sample from IPCA Pharmaceutical, Mumbai, India. All chemicals and buffers used were of analytical grade.

Preparation of Microspheres of Itraconazole

The spray dried microspheres (SD) were prepared by spray-drying technique. The spray drying was performed by Mini Spray Dryer LSD -48; (Jay instrument & systems Pvt. Ltd. Mumbai). The different drug–polymer ratios used for various microsphere formulations were prepared described in Table 1. The polymer solution was prepared by adding given quantity of polymer to the dichloromethane as solvent. The given quantity of itraconazole was added to the polymer solution and the resulting mixture was spray-dried. The spray drying parameters are described in Table 2.

Table 1 Spray-Dried Microspheres Formulation

Numbers	Formulation numbers	Different ratio of polymer and drug (w/w)
1	SD 1	2:8
2	SD 2	4:6
3	SD 3	6:4
4	SD 4	8:2
5	PM 1	2:8
6	PM 2	4:6
7	PM 3	6:4
8	PM 4	8:2

Table 2 Spray-Drying Parameters

Inlet temperature (°C)	Feed pump speed %	Vacuum (mm Wc)	Aspirator level (kg/cm2)
38	15	-70	1.5

Preparation of Physical Mixtures of Itraconazole

Physical mixtures (PM) were prepared by mixing itraconazole and polymer (in the same ratio as used for spray dried) in a mortar for 5 min and sieving has been performed.

Evaluation of Microspheres

Determination of Percentage Yield and Drug Content

The percentage yield of each formulation was determined according to the total recoverable final weight of microspheres and the total original weight of itraconazole.

Microspheres (50 mg) were triturated with 10 ml of water. Allowed to stand for 10 min with occasional swirling and methanol was added to produce 100 ml. After suitable dilution, samples were measured at 260 nm. Drug content was determined from standard plot.

Differential Scanning Calorimeter (Dsc)

A DSC study was carried out to detect possible polymorphic transition during the crystallization process. DSC measurements were performed on a DSC DuPont 9900, differential scanning calorimeter with a thermal analyzer.

Fourier Transforms Infrared Spectroscopy (Ftir)

The FTIR spectral measurements were taken at ambient temperature using a Shimadzu, Model 8033 (USA). Samples were dispersed in KBr powder and the pellets were made by applying 5 ton pressure. FTIR spectra were obtained by powder diffuse reflectance on FTIR spectrophotometer.

Powder X-Ray Diffraction Analysis

X-Ray powder diffraction patterns were obtained at room temperature using a Philips X' Pert MPD diffract-meter, with Cu as anode material and graphite monochromatic, operated at a voltage of 40 *mA*, 45 kV. The process parameters used were set as scan step size of 0.0170 (2θ).

Scanning Electron Microscopy (Sem)

Scanning electron microscopic (Joel- LV-5600, USA, with magnification of 250x) photographs were obtained to identify and confirm spherical nature and Surface topography of the crystals.

Determination of Solubility

Drug solubility was determined by adding excess amounts of pure Itraconazole, its physical mixture and microspheres to water and pH 1.2 HCL buffer at 37 ± 0.5°C, respectively. The solutions formed were equilibrated under continuous agitation for 24 h and passed through a 0.8 µm membrane filter to obtain a clear solution. The absorption of then samples was measured using UV spectrophotometric method (UV 1601 A Shimadzu, Japan at 260 nm and the concentrations in µg/ml were determined. Each sample was determined in triplicate.

Dissolution Studies of Microspheres

The dissolution of itraconazole commercial sample, microspheres and recrystallized sample was determined by using USP dissolution apparatus XXIV-Type II (Electro Lab, Mumbai). Dissolution medium was 900 ml pH 1.2 HCL buffer. The amount of dissolved drug was determined using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 260 nm. Each sample was determined in triplicate.

Determination the Physical Stability

A Long term and accelerated stability study of prepared microspheres (SD 4) was carried out at 40 ^{0}C and 75% relative humidity for 6 month respectively according to the ICH guidelines [12]. The microspheres were packed in high density polyethylene (HDPE) container and placed in stability chamber. The samples were withdrawn at the interval of 0, 1, 3 and 6 and evaluated for appearance, characterization by FT-IR, XRD, drug content and *in vitro* release and compared with initials results.

RESULT AND DISSCUSION

The glass transition temperature (Tg) is the second-order phase change temperature at which a solid glass is transformed to a liquid-like rubber. As the temperature increases above, Tg various changes, such as increase of free volume, decrease of viscosity, increase of specific heat, and increase of thermal expansion, are noticed. During spray drying, if the drying temperature exceeds the Tg of the polymer, the powder becomes soft or sticky while still warm. This cause sticking of the powder to the side walls of drying chamber. The Tg of Pluronic F-68 as provided by the manufacturer is 56°C so dichloromethane was selected as solvent with boiling point 36°C, i.e., lower than the Tg of Pluronic F-68. The spray dried microspheres formulations collected and they were free-flowing and white in color. The percentage yield of spray dried microspheres of different ratio of Pluronic F-68 and Itraconazole was showed in Table 3. This small yield can be increase by adding of solid

substance or in large scale production as it was small scale preparation [13]. Drug content for the spray dried microspheres of different ratio of Pluronic F-68 and Itraconazole were showed in Table 3. DSC curves obtained for pure material, physical mixtures and microspheres are showed Fig. 1. In DSC curve, pure itraconazole had a sharp endothermic peak at 169°C that corresponded to the melting point of itraconazole. In the thermogram of Pluronic F-68, a sharp peak (56.1°C) was observed, which was associated with the endothermic melting of Pluronic F-68. In DSC study, as the amount of Pluronic F-68 increased in microspheres, the size of the itraconazole endothermic peak was reduced. In formulations number SD 1 & PM 1 small but shifted itraconazole endothermic peak was observed. Also, the two melting transitions in the system made up of Itraconazole and Pluronic F-68 indicated that both materials formed a separate phase. It was found that itraconazole was in a crystalline state in the microspheres. The position of the melting peak of Pluronic F-68 remained largely unchanged, while that of itraconazole shifted depending on the concentration. At formulation number SD 4, the endothermic peak of itraconazole was no longer observed. This could be because itraconazole was molecularly or amorphously dispersed in the phases, Suggesting absence of crystallinity and presence of amorphous state of the drug. On the other hand, the physical mixtures of itraconazole and Pluronic F68 showed an apparent endothermic peak for Itraconazole at 168.54°C ([3]). In the DSC curve of physical mixture number of PM 2, PM 3 and PM 4 did not showed endothermic peak of itraconazole.

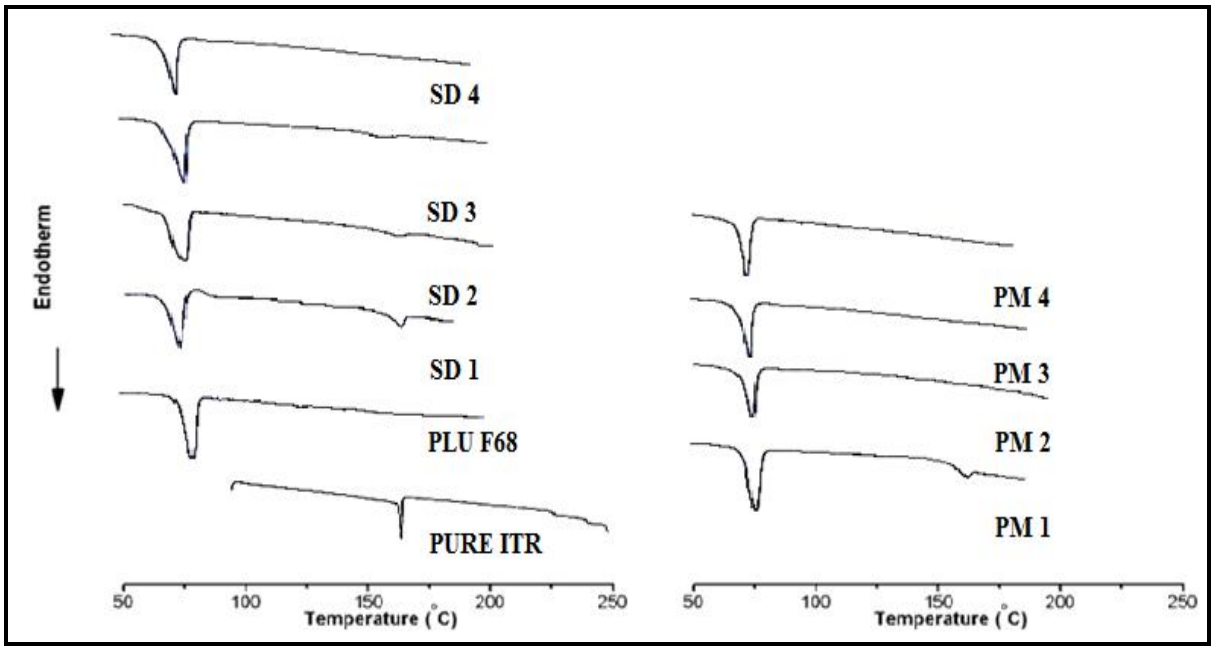

Fig 1. Shows DSC Spectrum of Pure Itraconazole, Pluronic F-68 & It's Different Ratio of Physical Mixture and Microspheres

The FTIR spectra of Itraconazole, Pluronic F-68 and their mixture and different ratio of microspheres show in Fig 2. 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. 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 [3, 4]. 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 Pluronic F-68 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. The prepared microspheres containing Itraconazole with Pluronic F-68 showed the characteristic peaks of the drug and the polymers. This suggests the absence of any interaction between the drug and the polymers.

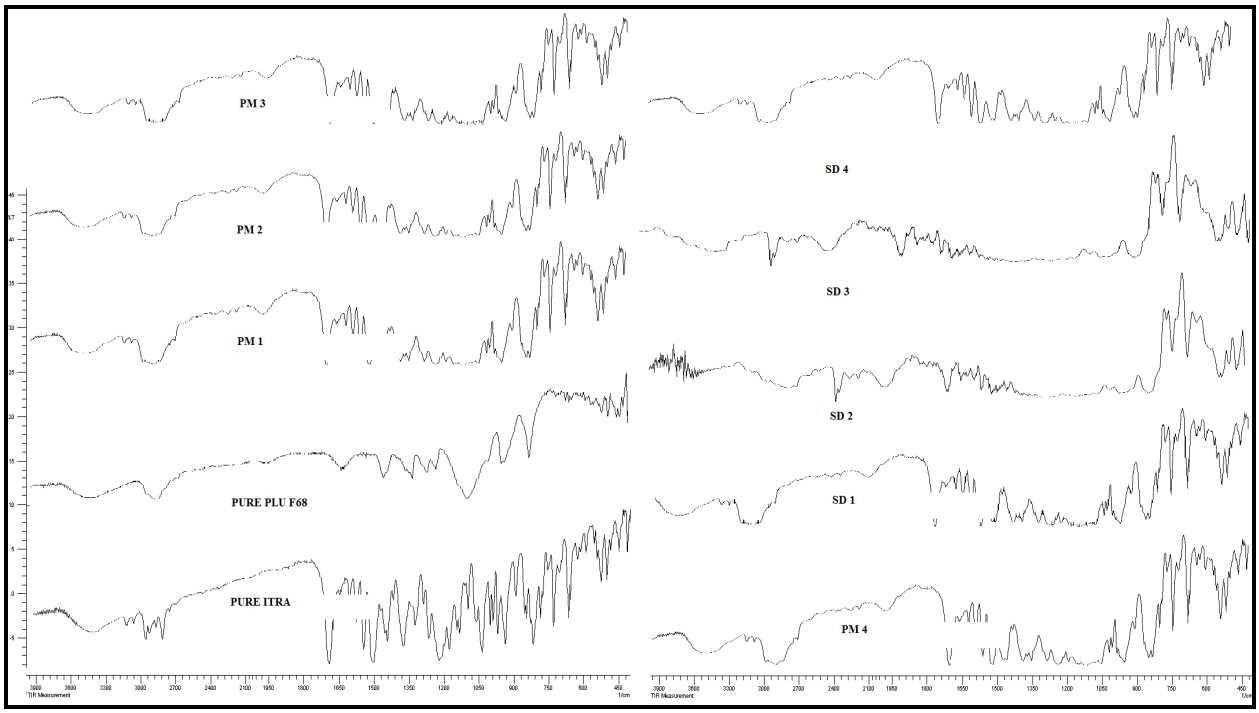

Fig 2 Shows FT-IR Spectrum of Pure Itraconazole, Pluronic F68 & Its Different Ratio of Physical Mixture and Microspheres

X-Ray diffraction was used to analyze potential changes in the inner structure of itraconazole nanocrystal during the formulation. The extent of such changes depends on the chemical nature and physical hardness of the active ingredient. The powder X-ray diffraction patterns of the unprocessed itraconazole and Pluronic F-68, their different physical mixture and microspheres formed by spray drying showed in Fig. 3. The characteristic peak of the itraconazole appeared in the 2θ range of $10–30^{0,}$ indicating that the unprocessed itraconazole was a crystalline material. In XRD thermograph of pure itraconazole powder, Pluronic F-68, their physical mixture and prepared microspheres showed that crystallinity of itraconazole in the formulations was not affected significantly ([3,4]). The x-ray diffraction pattern of the pure drug exhibit its characteristic diffraction peaks at various diffraction angles indicating the presence of crystallinity. The diffraction study of the different physical mixture of drug and Pluronic F-68 showed the peak corresponding to the crystalline drug molecules present in the mixture, although their intensity was lower than pure drug may be due to the high percentage of Pluronic F-68 & drug ratio employed. The diffraction pattern of the different spray dried microspheres of drug showed absence, broadening, and reduction of major itraconozole diffraction peaks indicating that mostly an amorphous form (disordered state) existed in the microspheres.

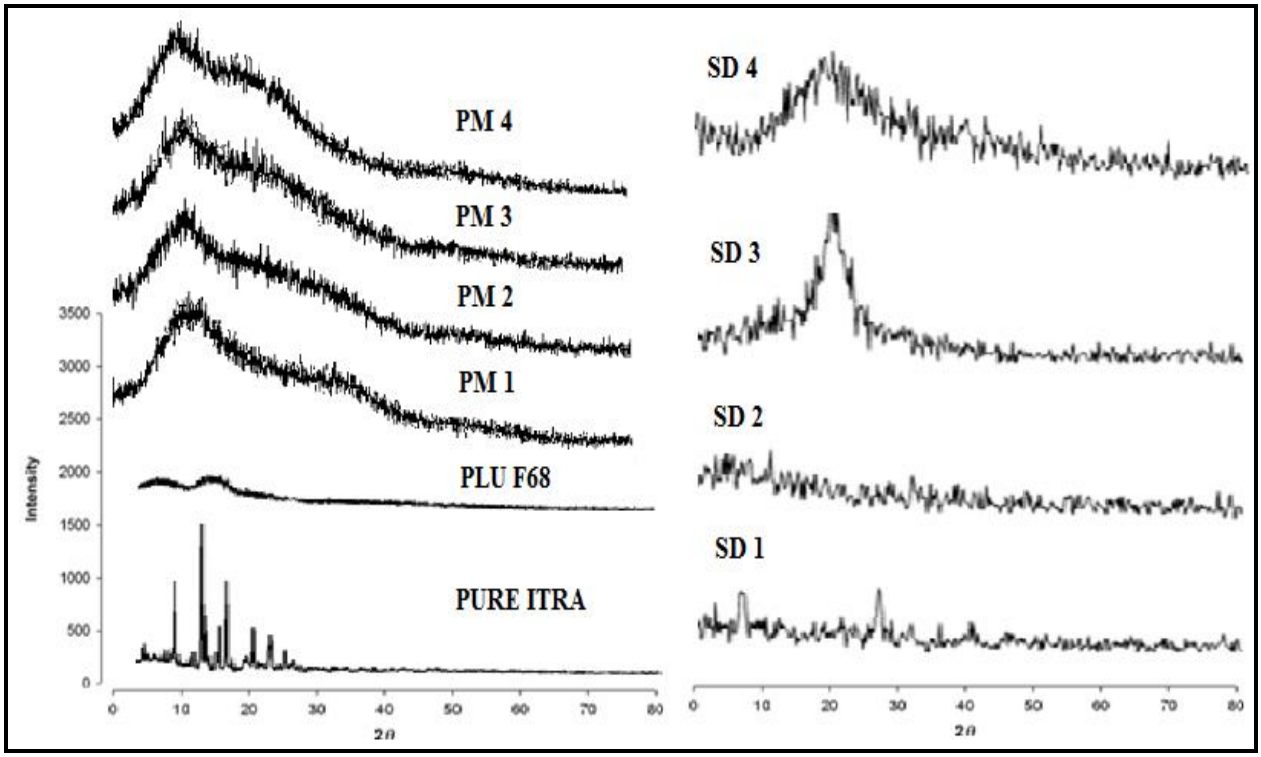

Fig 3. shows XRD Spectrum of pure Itraconazole, Pluronic F68 & its different ratio of physical mixture and microspheres.

The SEM image of the A) Itraconazole, B) Pluronic F-68, their C) physical mixture and D) microspheres are shown in Fig. 4. The itraconazole particles in the physical mixture were broken into much smaller ones, irregular size and result show that itraconozole particles could be seen in the physical mixture and on the other hand, the shape of microspheres were spherical in shape with small in size and micrograph of microspheres shows a matrix formation in which no crystals of itraconozole could be seen. The spherical shape of microspheres has advantage of not to form cake because of less point of contact during the time of storage compare to other shape [14].

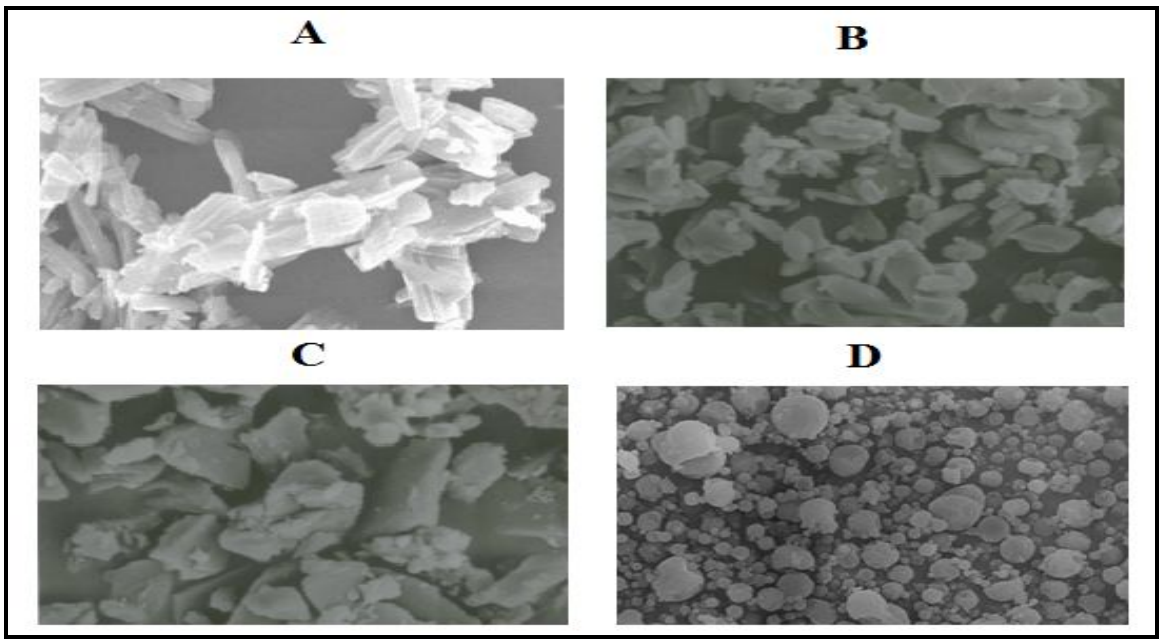

Fig 4 Shows SEM photographs of A) pure Itraconazole, B) Pluronic F68, C) Physical mixture D) Microspheres.

The solubility of Itraconazole, their physical mixture and microspheres in water and in pH 1.2HCl is shown in Table 3. The solubility of itraconazole at 37°C was found to be 0.050µg/ml and 1.2µg/ml in water & pH 1.2HCl buffer, respectively. These results show that the solubility of itraconazole increased on increasing the concentration of Pluronic F-68 in microspheres. The solubility of itraconazole from the microspheres was significantly higher than from it is physical mixture, when the microspheres and physical mixture contained the same weight ratio of itraconazole i.e. 8:2% (SD 4 & PM 4). It was found that the solubility of itraconazole from microspheres much higher than physical mixture of same % in pH 1.2 HCL as well as in water. The higher solubility of itraconazole from microspheres may be due to the increased in surface area, wet-ability of microspheres and solubilizing effect of the Pluronic F-68 as carrier to microspheres [15, 16].

Table 3 Physicochemical Properties of Itraconazole Microspheres

Different formulations containing polymer: Drug ratio(w/w)	Solubility Itraconazole microspheres in water (µg/ml) SD±3	Solubility of itraconazole microspheres in pH 1.2 HCl µg/ml SD±3	Percentage yield%	Drug content SD ±3
Pure drug	0.050	1.2		
SD 1	12.195	25.760	58.23	96.21±0.01
SD 2	17.875	29.864	59.80	95.39±0.04
SD 3	19.072	37.654	63.38	92.98±-0.01
SD 4	21.834	47.921	72.00	92.28±0.02
PM 1	5.983	8.286	-	96.29±0.02
PM 2	7.103	11.826	-	95.38±0.01
PM 3	8.675	16.148	-	97.37±0.03
PM 4	9.731	24.324	-	98.37±0.01

The dissolution curves of itraconazole in pH 1.2 buffer shown in Fig. 5. The dissolution rate profiles were plotted as the % release from the different microspheres, physical mixture and pure itraconazole versus time in minute. The rate of dissolution of pure itraconazole was slow Compared with itraconazole from its physical mixtures and different microspheres in 60 min. The % release of microspheres containing ratio of 8:2(SD 4) showed high release compare to other microspheres containing different ratio, its physical mixture and pure itraconazole. There was a significant difference in the drug release between the microspheres, physical mixture and pure sample. The increase in dissolution from the physical mixtures was probably due to the wetting and solubilizing effect of the Pluronic F68, which could reduce the interfacial tension between the itraconazole and the dissolution medium, thus leading to a higher dissolution rate. The large surface area of the resulting microspheres should result in an enhanced dissolution rate and thereby improve the bioavailability [17, 18].

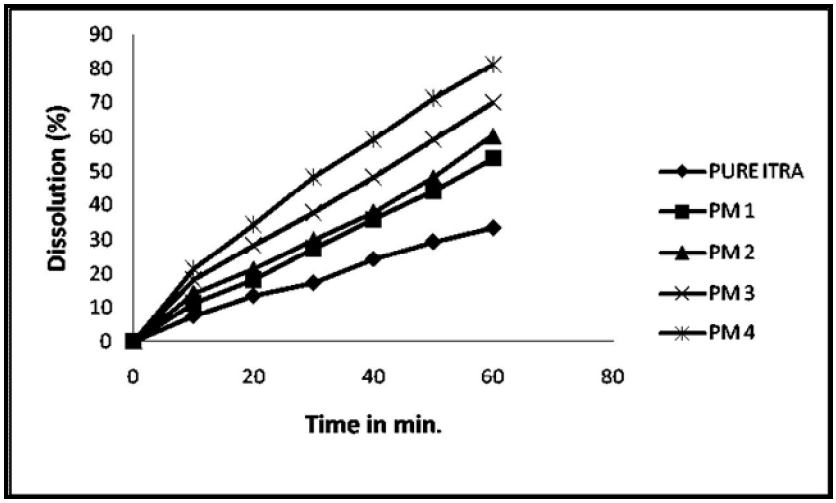

Figure 5 Shows Dissolution of Pure Itraconazole And Its Different Ratio of Physical Mixture.

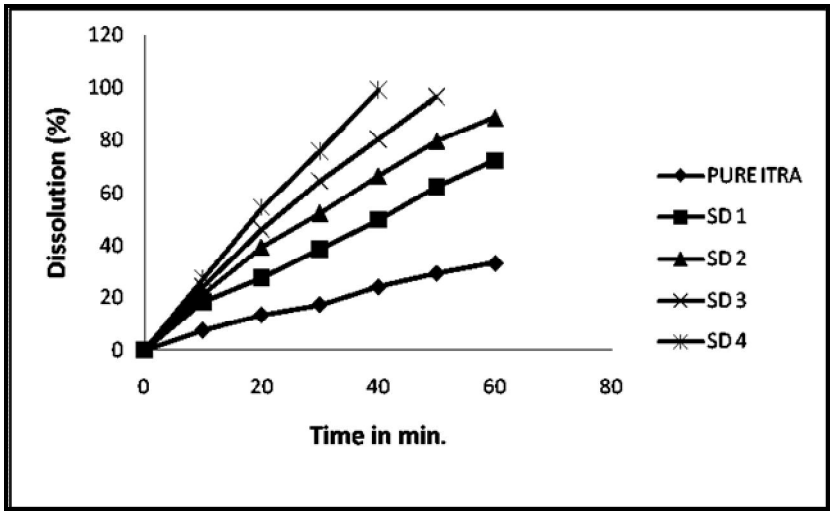

Figure 5 Shows Dissolution of Pure Itraconazole And Its Different Ratio of Microspheres

With respect to the influence of physical stability on prepared microspheres stored at 40 ^{0}C and 75% relative humidity for 6 month. The influence of physical stability on the prepared microspheres was investigated. Prepared microspheres were stable for 6 month and complied with all the selected properties when compared to initial result (Table-4) [12].

Table 4: Stability Study Data of Itraconazole Microspheres (Sd 4)

Testing interval	Appearance	FT-IR Study	XRD Study	Dissolution Study (±SD) after 40 min.
Sample name: Itraconazole microspheres Storage condition: 40^{0}C /75% RH				
Initial	White to Light yellowish powder	As Initial	As Initial	98.93±0.01
1 month	Complies	Complies	Complies	98.64±0.04
3 month	Complies	Complies	Complies	99.19±0.01
6 month	Complies	Complies	Complies	98.75±0.05

CONCLUSION

In this present study, an increased solubility and dissolution rate of itraconazole were achieved by spray dried microspheres using different ratio of Pluronic F-68. Spray dried microspheres exhibited decreased crystallinity compare to its physical mixture and pure itraconazole. DSC and XRD studies showed that there is no change in the crystal structure of itraconazole during the spray drying process i.e., polymorphism has not occurred. The solubility and dissolution of the spray dried microspheres was improved significantly compared with its physical mixture and pure sample. The drug dissolution rate from microspheres was highest at the polymer-drug ratio of 8:2 w/w (SD 4). Hence this spray

drying technique was very simple method & can be used for formulation of tablets of itraconazole by direct compression without further process like (mixing, granulation) with directly compressible tablet excipients.

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