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*Research Article*

*Theme: Advanced Technologies for Oral Controlled Release*
*Guest Editors: Michael Repka, Joseph Reo, Linda Felton, and Stephen Howard*

# Formulation and Stability Testing of Itraconazole Crystalline Nanoparticles

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***Abstract.*** Itraconazole (ITZ) crystalline nanoparticles were prepared using relatively simple, low-cost sonoprecipitation technique, in which both the solvent and antisolvent were organic in nature. The effect of stabilizer type (hydroxypropyl methylcellulose, hydroxypropyl cellulose, Inutec SP1®, and pluronic F127), drying method (oven and freeze drying) and matrix former used (Avicel PH101, and Aerosil®200) on the dissolution performance as a key characteristic of nanocrystals was evaluated. In 10 min, all of the prepared nanocrystals showed 3.77−8.59 times improvement in percent drug dissolved compared to pure ITZ. Concerning the effect of stabilizer type, the following rank order can be given: pluronic F127≥ hydroxypropyl cellulose≥hydroxypropyl methylcellulose (HPMC)>inutec SP1. Freeze-dried ITZ nanocrystals containing Avicel PH 101 showed better dissolution rate compared to other nanocrystals. The chemical structure of itraconazole nanocrystals was not changed as revealed by Fourier transform infrared. Stability study of selected nanocrystals (F5, F7, and F8) revealed physical and chemical stability of F7 and F8, while a decrease in dissolution rate of F5 was observed (although being chemically stable) when stored under high relative humidity conditions. Although inutec is less potent than pluronic F127 and HPMC regarding their effect on dissolution rate enhancement, it is equipotent to pluronic F127 in preserving the rapid drug dissolution.

**KEY WORDS:** itraconazole; nanocrystals; nanoparticles; stability study.

## INTRODUCTION

Oral drug delivery is the preferred way of drug administration (1). Designing an oral dosage form with adequate bioavailability is becoming challenging by the fact that a large number of newly discovered compounds have poor solubility and/or dissolution rate (2). The rapidly emerging field of nanoscience, which concerns with formulation of drugs as drug nanoparticles having a size below 1 μm, has been proven effective to enhance the bioavailability of poorly soluble compounds (3–5). Also, nanoparticles have an advantage for oral drug delivery as they can be formulated as solid dosage form for the general population or as suspension for pediatrics and geriatrics (6).

Fungal infection can be a serious medical problem, particularly as a complicating factor in serious illnesses and immunocompromised conditions (7).

Itraconazole (ITZ), a broad-spectrum antimycotic triazole has been used for both prophylaxis and treatment of invasive fungal diseases, such as candidiasis and aspergillosis for the last two decades (8). ITZ is classified as a class II drug according to the Biopharmaceutical Classification System (9). It has an extremely low aqueous solubility ($S$<1 μg/ml) and poor dissolution rate in the gastrointestinal tract and hence low and variable bioavailability.

There have been many attempts to produce submicron particles of ITZ by high pressure homogenization (need high energy, time-consuming, and show some disadvantages in practice such as electrostatic effects (10)), evaporative precipitation into aqueous solution (require specially designed equipments), and supercritical fluid-based technologies (expensive, difficult to control, and scale up (11))

The main objectives of this work are to prepare ITZ crystalline nanoparticles using bottom-up technique (antisolvent sonoprecipitation technique) to assess the effect of drying method (oven drying and freeze drying), stabilizer type, and matrix former used on the performance of the prepared crystalline nanoparticles, and finally to evaluate the stability of selected crystalline nanoparticles formulae under different storage conditions. According to our knowledge, the stability of itraconazole crystalline nanoparticles has not been investigated before. The antisolvent sonoprecipitation technique was chosen as it has the advantages of using relatively simple, low cost equipments and relatively easy scale up (12).

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**Table I.** Composition of Different Prepared Itraconazole Crystalline Nanoparticles

| | Type and concentration of stabilizers (% *w/w*) | | | | | Drying method | |
|---|---|---|---|---|---|---|---|
| | | | | | | FD | |
| Formulae | HPMC 1% | HPC 1.33% | Plu F127 2% | Inutec 2% | OD | Avicel PH101 | Aerosil®200 |
| F1 | √ | | | | √ | | |
| F2 | | √ | | | √ | | |
| F3 | | | √ | | √ | | |
| F4 | | | | √ | √ | | |
| F5 | √ | | | | | √ | |
| F6 | | √ | | | | √ | |
| F7 | | | √ | | | √ | |
| F8 | | | | √ | | √ | |
| F9 | √ | | | | | | √ |
| F10 | | √ | | | | | √ |
| F11 | | | √ | | | | √ |
| F12 | | | | √ | | | √ |

Drug concentration was kept constant in all formulae at 15% (*w/w*) in the solvent phase
*OD* oven dried, *FD* freeze dried

## MATERIALS AND METHODS

### Materials

Itraconazole was kindly supplied by Adwia Pharma, Egypt. Hydroxypropyl methylcellulose K15M (HPMC) by Colorcon, England. Hydroxypropyl cellulose low viscosity EF pharma (HPC) was kindly supplied by EPICO Pharmaceutical Company, Egypt. Inutec SP1® was kindly supplied by Beneo Biobased Chemicals, Belgium. Pluronic F127 by Sigma-Aldrich, Inc., Germany. Tween 80®, methylene chloride, ethyl alcohol 95% *V/V*, sodium lauryl sulfate, and hydrochloric acid 30% by El-Nasr Co for Pharmaceutical Industries, Cairo, Egypt. Microcrystalline cellulose (Avicel PH101) by FMC Co, Pennsylvania, USA. Colloidal silicon dioxide (Aerosil®200) by Degussa, USA. High-performance liquid chromatography (HPLC) grade acetonitrile and tetrabutyl ammonium hydrogen sulfate by Merk Co, Hohenbrunn, Germany. All other reagents and chemicals were of analytical grade.

### Preparation of Itraconazole Nanocrystals

Twelve ITZ nanocrystals formulae were prepared by antisolvent sonoprecipitation technique. The composition of the prepared formulae is shown in Table I. ITZ and one of four different stabilizers (pluronic F127, HPC, HPMC, or inutec SP1) were dissolved in methylene chloride (solvent phase). Tween 80 as stabilizer was dissolved in ethyl alcohol (antisolvent phase) and the solution was cooled to 4°C. Solvent to antisolvent ratio was kept at 2:1.

The solvent phase was poured into precooled alcoholic phase and irradiated with 50% output amplitude of ultrasonic energy for 5 min (Ultrasonicator, Model GE 130 SN 35886E Sartorius, USA). Then, the formed suspension was centrifuged (Megafuge 1.0 R, Heraeus, Germany) at 18,000 rpm at 4°C for 30 min (11). The supernatant was removed, the collected nanocrystals were either oven dried at 40°C overnight or they were redispersed in 10 ml of distilled water, then either microcrystalline cellulose or aerosil®200 were added as matrix former in amount of 100% relative to the weight of ITZ. The nanosuspension was sonicated, frozen in freezer for 24 h, and subsequently freeze dried at −40°C for 24 h (Freeze dryer, SNL 216 V, Sanvant Instruments, Inc, Holbrook, NY, USA). Dried powders were kept in desiccator for complete removal of moisture and until further evaluation.

### Characterization of Itraconazole Nanocrystals

#### *Determination of Drug Content*

Drug content of the dried powders was determined by dissolving 10 mg of each sample in 10 ml methanol. Samples were assayed spectrophotometrically at $\lambda_{max}$ 262 nm after proper dilution using methanol as a blank.

#### *Particle Size Measurement*

The samples were redispersed in pure water to obtain weak obscuration and then the particle size was measured

**Table II.** Particle Size and Drug Content of Itraconazole Crystalline Nanoparticles

| | Particle size (μm) | | |
|---|---|---|---|
| | Mean | D90 | Drug content (wt.%) |
| F1 | 0.38±0.219 | 0.78 | 104.01±0.29 |
| F2 | 0.3±0.109 | 0.46 | 90.60±0.02 |
| F3 | 0.33±0.140 | 0.56 | 100.00±0.26 |
| F4 | 0.36±0.144 | 0.57 | 98.03±0.89 |
| F5 | 0.25±0.080 | 0.36 | 85.77±0.20 |
| F6 | 0.17±0.045 | 0.23 | 84.73±0.25 |
| F7 | 0.28±0.083 | 0.39 | 91.51±0.11 |
| F8 | 0.23±0.062 | 0.31 | 91.54±0.22 |
| F9 | 0.26±0.102 | 0.43 | 79.58±0.25 |
| F10 | 0.25±0.098 | 0.41 | 80.50±0.41 |
| F11 | 0.26±0.100 | 0.42 | 83.97±0.14 |
| F12 | 0.26±0.120 | 0.45 | 92.89±0.35 |

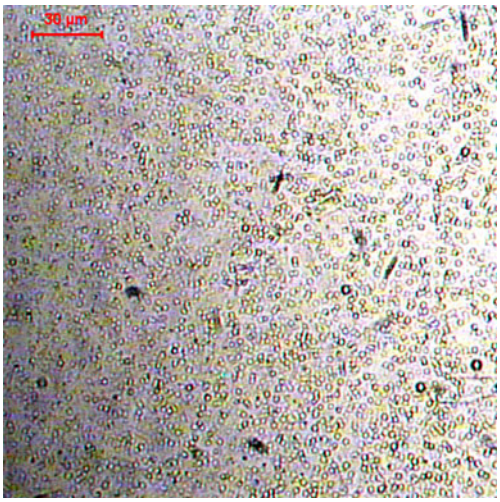


**Fig. 1.** Optical microscopy of ITZ nanoparticles stabilized using HPMC

using laser diffraction particle size analyzer (Mastersizer, XVER 219 Malvern Instruments Ltd, Worcestershire, UK). From the resulting volume distribution, the diameters 50% (D50) and 90% (D90) were calculated.

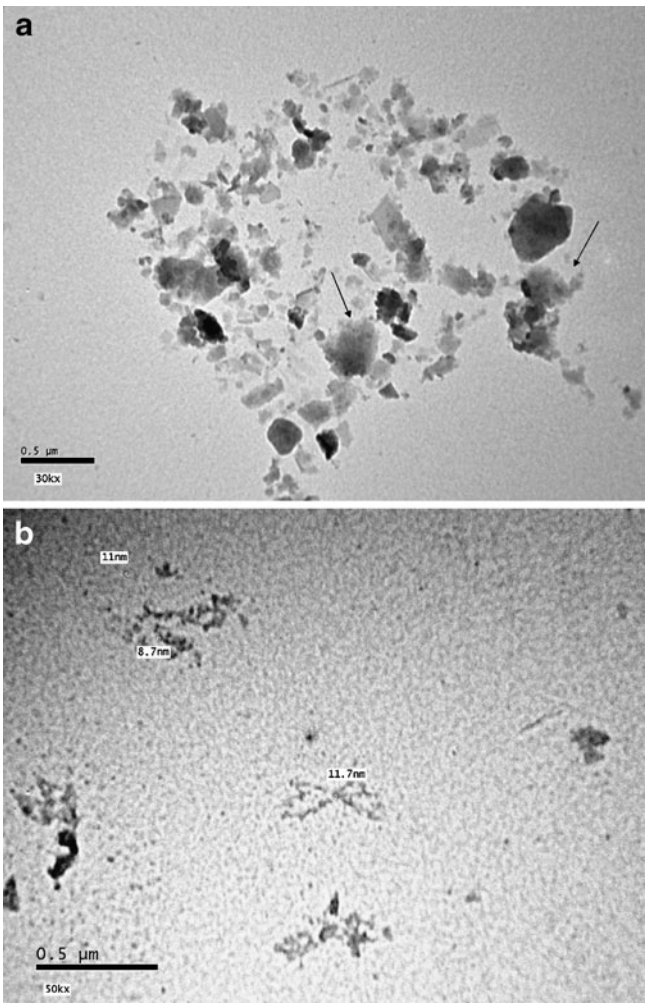


**Fig. 2.** Transmission electron micrographs of **a** F3 (oven dried) and **b** F7 (freeze dried) ITZ nanoparticles

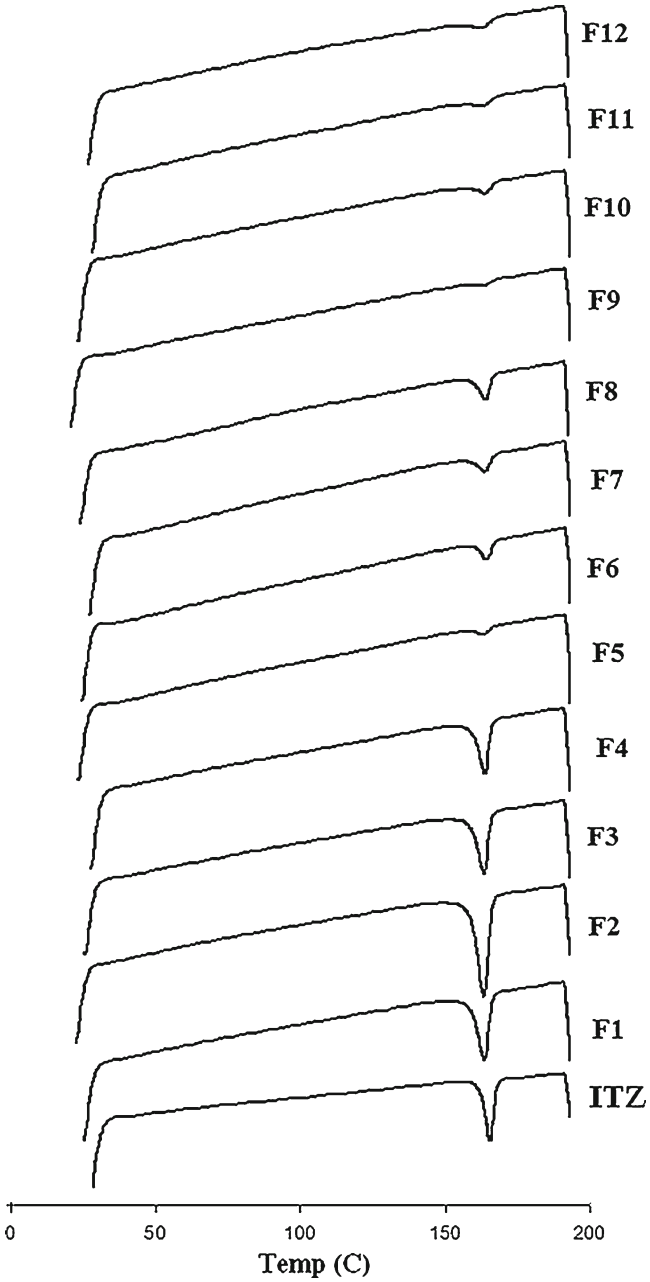


**Fig. 3.** DSC thermograms of pure and nanosized ITZ formulae

*Particle Morphology*

The morphological examination of drug nanosuspensions and drug nanoparticles was performed using both image analyzer (LEICA Quin Image Analyser, Model Q5501W) equipped with Leica DMLB microscope (Cambridge, England, UK) and by transmission electron microscope (TEM: Jeol JEM 1230, Japan) respectively. For TEM, the dry powders were redispersed in water and placed on a Cu grid and then the grid was inserted into the TEM column for examination.

*Differential Scanning Calorimetery*

Samples of 4 mg were hermetically sealed in a flat bottomed aluminum pans and heated in the differential

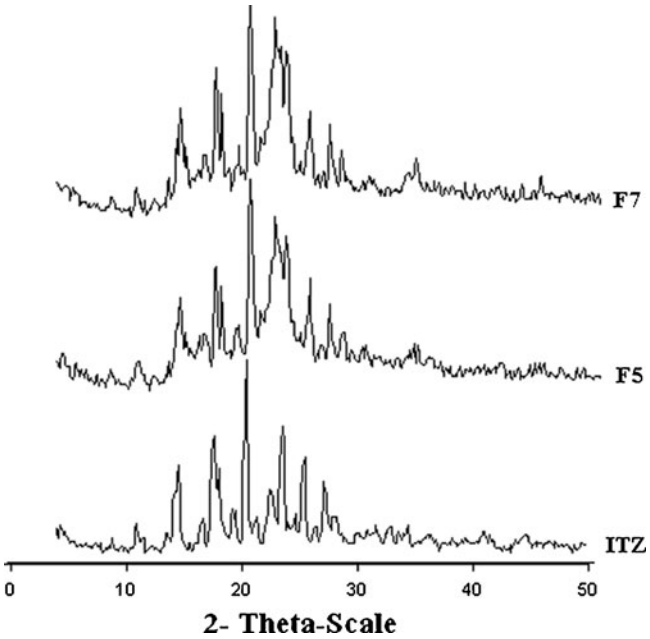


**Fig. 4.** X-ray diffraction patterns of pure and nanosized ITZ

scanning calorimetery (DSC) instrument (Shimadzu, Japan, DSC–60) in an atmosphere of nitrogen at a flow rate of 20 ml/min. A temperature range of 20–200°C was used and the heating rate was 10°C/min.

*X-Ray Diffraction*

The X-ray diffraction (XRD) was obtained using Scintag XGEN-4000 X-ray diffractometer (Advanced Diffraction system, Scintag Inc., USA). The samples were exposed to Cu–Ka radiation (40 kV×30 mA) at a scan rate of 2°/min over the 2 θ range of 4–50°, the output is given as intensity *versus* 2θ.

*Fourier Transform Infrared Spectroscopy*

The Fourier transform infrared (FTIR) spectra were recorded using FTIR spectrophotometer (FTIR-8400S, Shimadzu, Kyoto, Japan) in the range of 4,000–500 $cm^{-1}$. Samples were mixed with potassium bromide (spectroscopic grade) and compressed into disks using hydraulic press before scanning.

*In Vitro Dissolution Studies*

The dissolution of ITZ nanocrystals was studied using USPXXX dissolution tester, apparatus (II). An amount of nanocrystals equivalent to 50 mg of ITZ was placed into 900 ml 0.1NHCL containing 0.5% sodium lauryl sulfate (SLS) as dissolution medium maintained at 37±0.5°C. The paddle was made to rotate at 100 rpm. At the predetermined time intervals of 5, 10, 20, 40, 60, 90, and 120 min, aliquots equivalent to 5 ml of the dissolution medium were withdrawn, filtered, and analyzed for ITZ content after proper dilution by measuring the absorbance at $\lambda_{max}$ 263 nm using 0.1NHCl containing 0.5% SLS as a blank. The withdrawn samples were replaced by equal volumes of fresh dissolution medium.

**Stability Study of Selected Itraconazole Nanocrystals**

F5, F7, and F8 were chosen for the stability study. Selected formulae were packed in aluminum foil inside tightly sealed glass bottles and stored at ambient room temperature in desiccators over anhydrous $CaCl_2$, 25±2°C/60% relative humidity (RH) or 40±2°C/75% relative humidity for 3 months. The chosen formulae were evaluated for change in physical state (DSC), particle size change, dissolution rate, and for chemical stability (drug content). The relative humidity of approximately 60% RH and 75% RH were initiated and maintained in desiccators using saturated solution of ammonium nitrate and saturated solution of sodium chloride respectively.

**HPLC Analysis**

Degradation of drug substance was assessed using HPLC Apparatus, Lachrom Elite, L-2400 VWR, (Hitachi Ltd, Japan). The column was BDS-C18 (4.6×250 mm, USA). The mobile phase consisted of 0.01 M tetrabutyl ammonium hydrogen sulfate in water and acetonitrile at a flow rate of 1.5 ml/min. The detection was conducted at a wavelength of 250 nm (13).

**Preparation of Itraconazole Capsules**

Depending on the results of stability study, both F7 and F8 containing pluronic F127 and inutec SP1 respectively as stabilizers were chosen for preparation of ITZ capsules. An amount of F7 and F8 equivalent to 100 mg of ITZ was filled into capsules size (00).

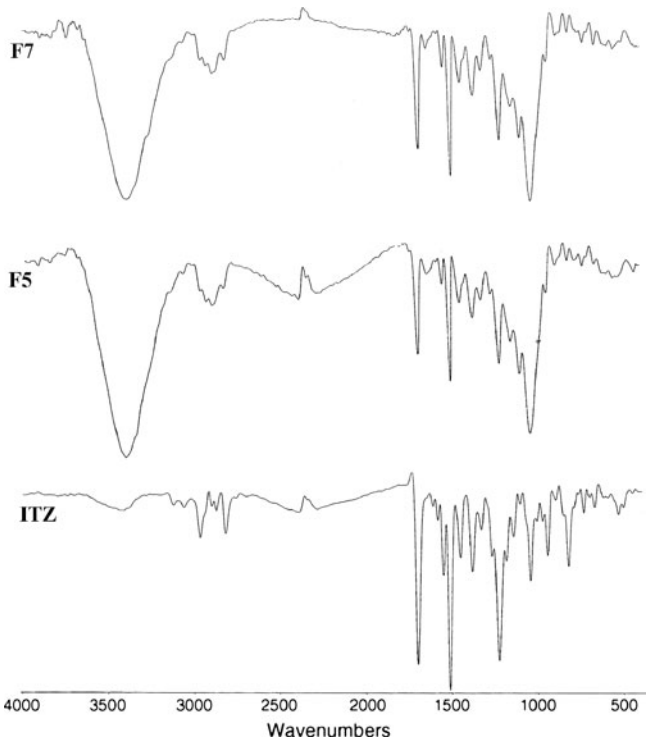


**Fig. 5.** FTIR spectra of pure and nanosized ITZ

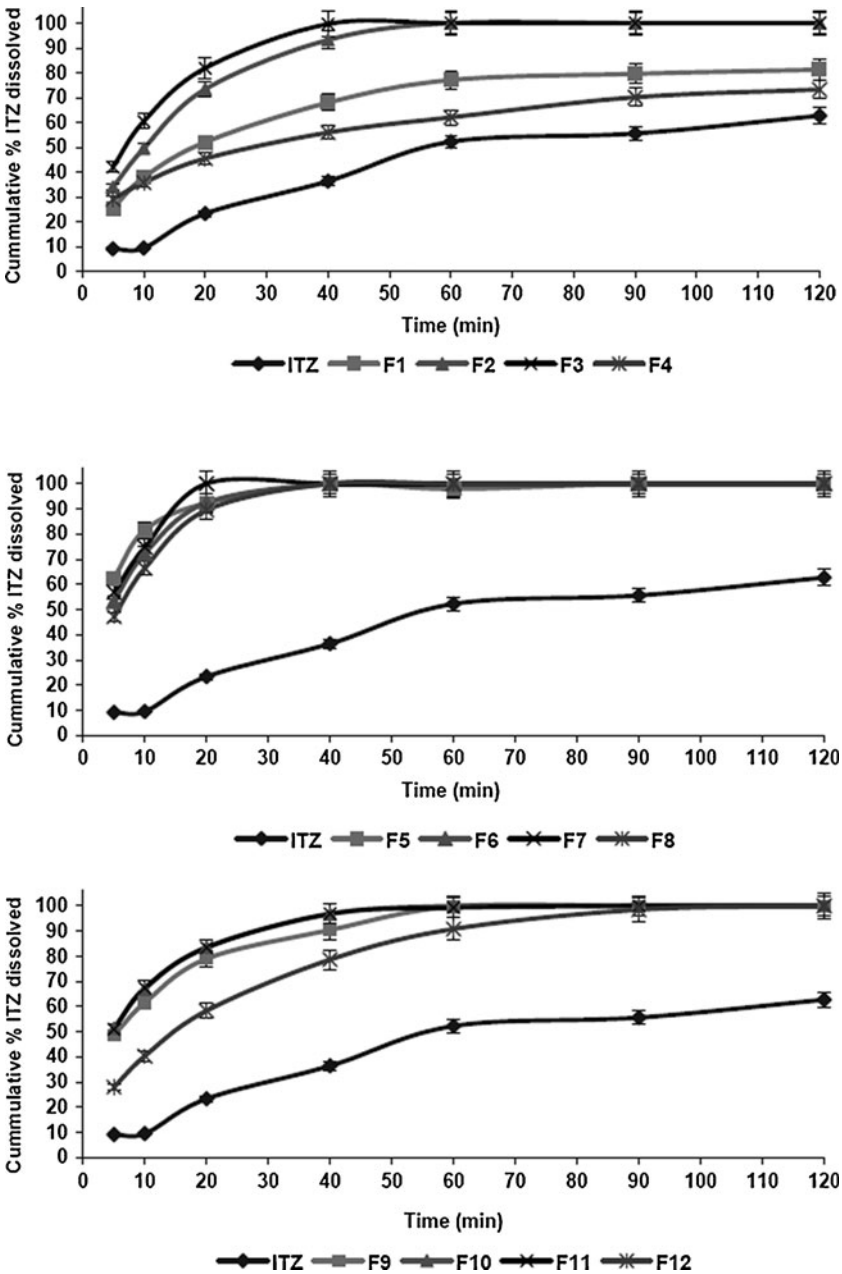


**Fig. 6.** Dissolution profiles of nanosized ITZ formulae in comparison to pure ITZ

### *In Vitro* Dissolution of Capsules Filled with F7 and F8 Itraconazole Nanocrystals

The dissolution of ITZ from its capsules filled with nanocrystals in comparison to marketed product was studied using USPXXX dissolution tester, apparatus (I). The same procedures were followed as mentioned under *in vitro* dissolution studies except that the sampling time intervals were at 5, 10, 15, 20, 30, 45, and 60 min.

## RESULTS AND DISCUSSION

### Determination of Drug Content

Drug content of the dried powders is summarized in Table II. ITZ content of the oven-dried powders (F1–F4) was greater than 90%, the high potencies result from the removal of a large amount of non-adsorbed stabilizer in the supernatant (14). The drug content of the freeze-dried powders (F5–F12) was slightly lower than oven-dried ones (which may be attributed to presence of matrix formers). Percent drug content in the range of 39–52% *w*/*w* was previously reported for different drugs nanoparticles prepared with matrix formers in comparison to percent drug content ≥70% *w*/*w* for the same nanoparticles without matrix formers (15).

### Particle Size Analysis

Table II lists particle size (D50 and D90) of the different prepared ITZ nanoparticles. The results confirm that all of the prepared particles were in the submicron range with the freeze-dried particles showing smaller size compared to oven-

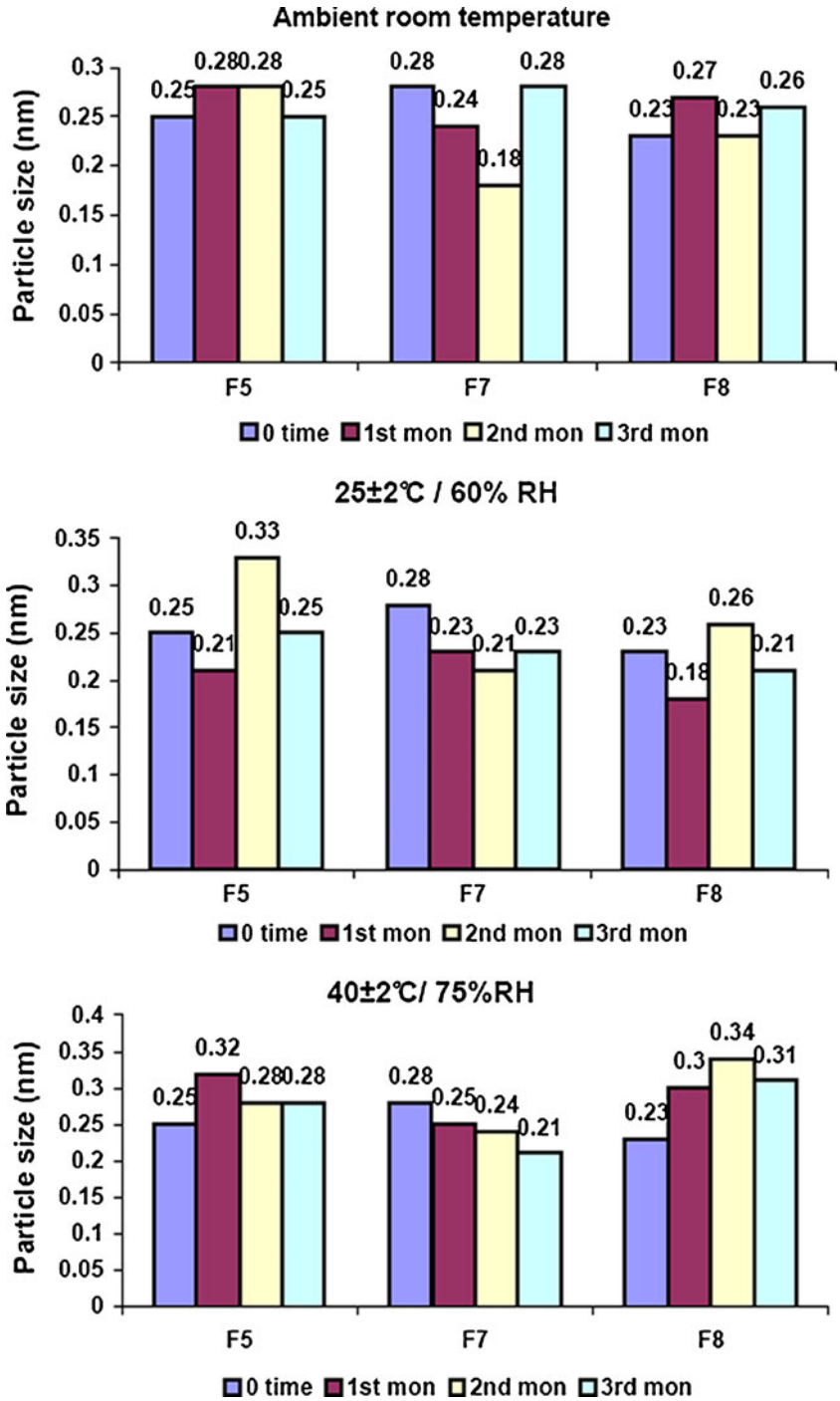


**Fig. 7.** Mean particle diameters of selected ITZ nanoparticles over 3 months of storage period under different conditions

dried ones. These larger particles may be due to agglomeration of particles during oven drying process (16). The D90 of all of the prepared particles was less than 1 μm, which indicates a narrow size distribution (17).

### Particle Morphology

Optical microscopy of itraconazole nanosuspensions revealed that the particles were regular with no aggregations (Fig. 1).

Transmission electron microscopy showed that the oven-dried nanoparticles were slightly aggregated compared to freeze-dried ones. The freeze-dried nanoparticles were of smaller particle size compared to oven-dried ones which confirms results of particle size analysis (Fig. 2).

### DSC and XRD

DSC thermograms of pure ITZ and different prepared ITZ nanoparticles are shown in Fig. 3. Pure ITZ exhibited a

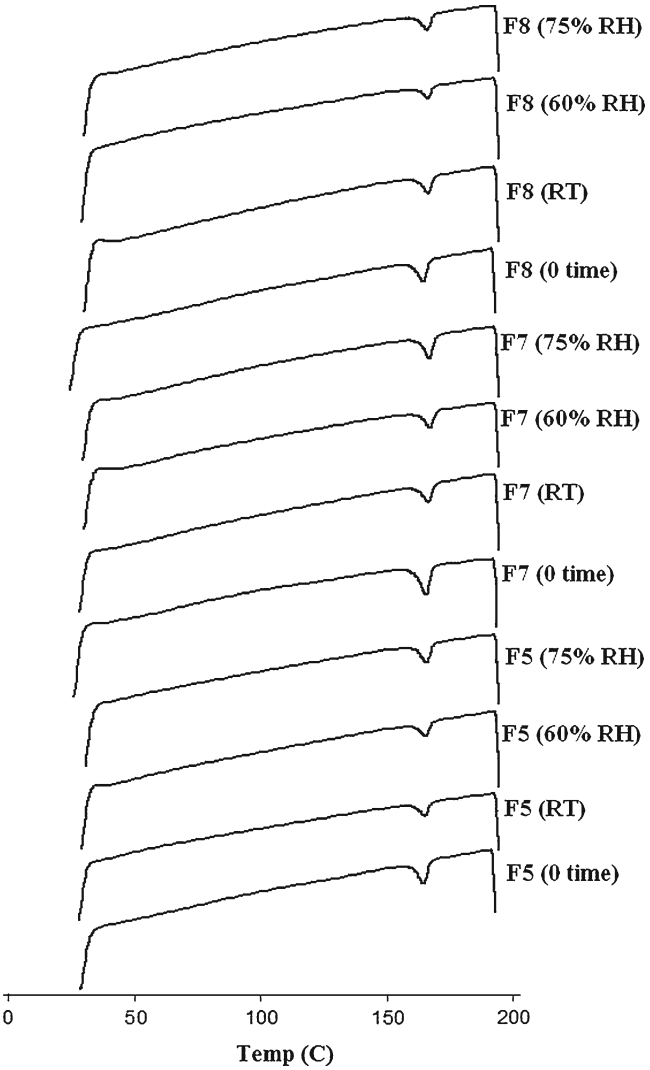


**Fig. 8.** DSC thermograms of selected ITZ nanoparticles after 3 months of storage under different conditions. *RT* ambient room temperature

sharp endothermic melting peak at 166.22°C. Oven-dried nanoparticles showed melting peaks at 164.59°C, 164.44°C, 160.74°C, and 164.77°C for F1, F2, F3, and F4, respectively.

Freeze-dried formulae with avicel PH101, F5, F6, F7, and F8 showed endothermic peaks at 164.10°C, 165.38°C, 164.71°C, and 164.63°C, respectively. While that with aerosil®200, F9, F10, F11 and F12 showed endothermic peaks at 163.22°C, 164.69°C, 163.11°C, and 162.20°C, respectively. The presence of the small endothermic peak of ITZ with some broadening may be due to smaller particle size (18) and also may be due to good dispersion of drug in the matrix former. The shift in the ITZ peak to a lower temperature in the nanosized product compared to pure drug might be due to smaller ITZ crystals (19).

The presence of endothermic peak of ITZ in all of the prepared formulae indicates that the drug is in the crystalline form which is good in the terms of physical stability.

XRD analysis (Fig. 4) confirmed the crystalline nature of both pure and nanosized ITZ. Nanosized ITZ showed broadening in some crystallinity peaks compared to pure ITZ that can arise from smaller crystal sizes (18). The results of XRD analysis are in agreement with DSC results.

## FTIR

The FTIR spectra of pure and nanosized ITZ are shown in Fig. 5. The similarity between FTIR spectra of the pure and nanosized ITZ suggested that there were no change in the ITZ chemical structure during processing.

## *In Vitro* Dissolution Studies

Dissolution profiles of the prepared nanosized ITZ in comparison to pure ITZ are shown in Fig. 6. The dissolution rate of all formulations is significantly greater than that compared to pure ITZ. The dissolution rate was correlated to stabilizer type, drying method, and matrix former used.

Concerning the effect of stabilizer type on ITZ nanocrystals dissolution rate, the following rank order can be given: at first 10 min, pluronic F127≥HPC≥HPMC>inutec SP1.

During the first 10 min, freeze-dried nanosized ITZ gave higher dissolution rates (81.53%, 72.20%, 74.73%, 66.37%, 61.49%, 66.90%, 67.42%, and 40.29% for F5, F6, F7, F8, F9, F10, F11, and F12, respectively) compared to oven-dried ones (37.88%, 49.53%, 60.44%, and 35.76% for F1, F2, F3, and F4, respectively) which may be due to agglomeration of nanocrystals during oven drying while presence of water-insoluble matrix formers formed a permanent barrier against nanocrystals agglomeration during freeze drying (18).

Burst dissolution is observed at 5 min for all freeze-dried formulae which could be explained on the basis of individual nanocrystals dissolution, followed by slower dissolution of the remaining product which may be related to dissolution of agglomerated fraction of nanocrystals (18, 20, 21).

Both avicel PH101 and aerosil®200 are potential matrix formers for ITZ with avicel PH101 showing better performance compared to aerosil®200. The % ITZ dissolved after 20 min is 92.23%, 92.41%, 100.00%, and 89.48% for F5, F6, F7, and F8 made with avicel PH101, respectively, compared to 78.94%, 83.57%, 83.31% and 58.31% for F9, F10, F11, and F12 made with aerosil®200 respectively.

## Stability Study of Selected Itraconazole Nanocrystals

### *Visual Evaluation*

After 3 months of storage at ambient room temperature, 25±2°C/60% RH, and 40±2°C/75% RH, no change was observed in the appearance or color of all selected stored formulae (F5, F7, and F8). Pure drug showed a slight aggregation after 3 months of storage at 40±2°C/75% RH.

### *Determination of Drug Content*

There was no significant change in the content of ITZ (83.93%, 91.23%, and 94.13% for F5, F7, and F8 respectively, at zero time) after 3 months of storage at different conditions. At ambient temperature, content of ITZ was 83.82%±0.18, 93.52%±0.84, and 93.28%±1.24 after 3 months of storage for F5, F7, and F8, respectively. While the corresponding values at 40±2°C/75% RH were 84.28%±0.33, 91.84%±1.20, and 90.87%±0.04 for F5, F7, and F8, respectively. The same observations were found for all formulae at 25±2°C/60% RH

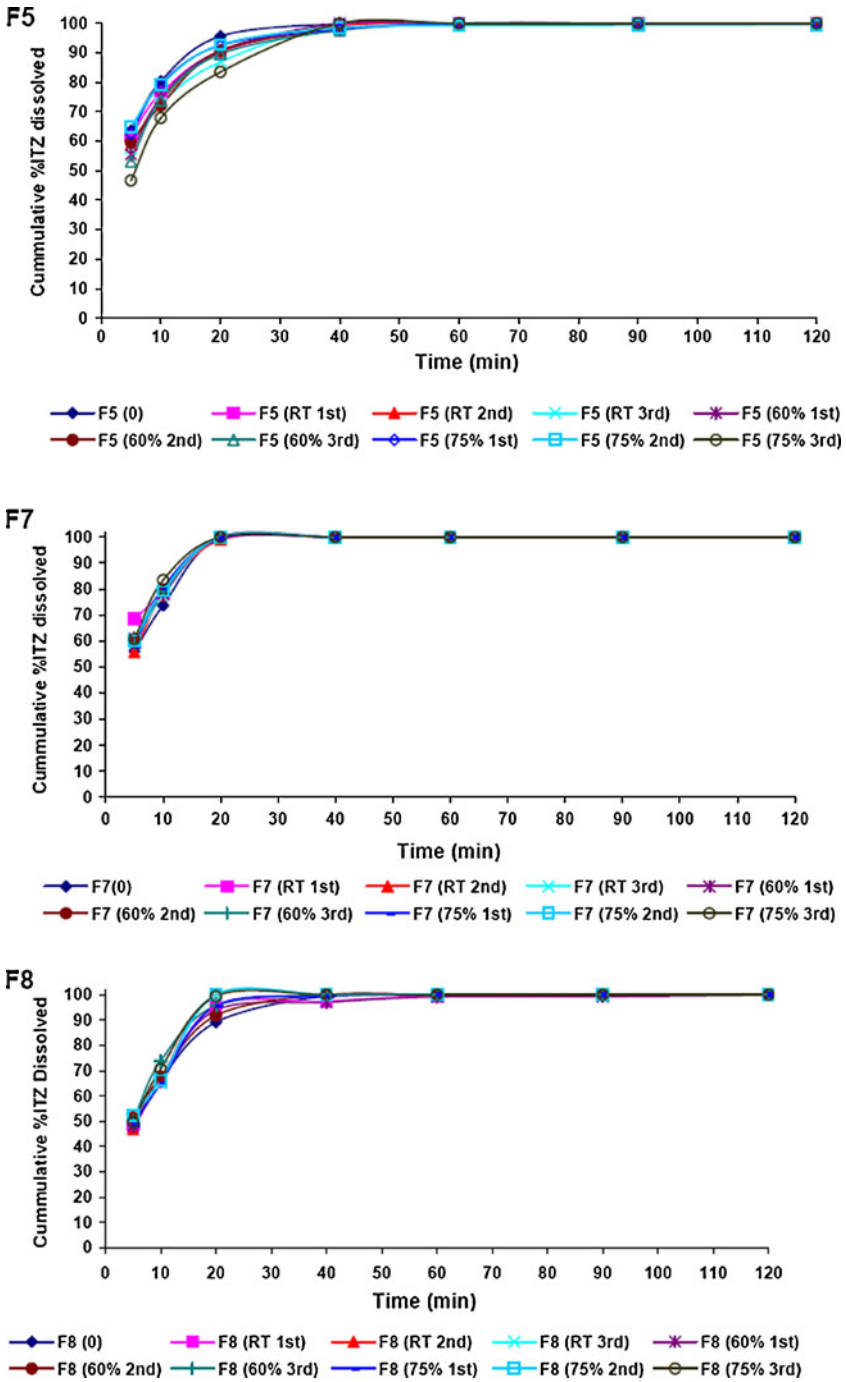


**Fig. 9.** Dissolution profiles of selected ITZ nanoparticles at zero time and over 3 months of storage period at different storage conditions; *0*, at zero time; *1st*, first month; *2nd*, second month; *3rd*, third month; *RT*, ambient room temperature; *60%*, 25±2°C/60% RH, and *75%*, 40±2°C/75% RH. Error bars were omitted for clarity purposes

(85.35% ±0.99, 94.97% ±0.64, and 93.28% ±0.85 for F5, F7, and F8, respectively) after 3 months of storage.

*Particle Size Analysis*

Figure 7 shows mean particle sizes of F5, F7, and F8 at different storage conditions. F7 containing pluronic F127 as stabilizer showed no significant change in mean particle size at different conditions during 3 months of storage period. The mean particle size of F5 and F8 was slightly affected throughout storage period especially at 40±2°C/75% RH. However, the mean particle size of F5 and F8 ranged from 0.23 to 0.34 μm which is in an acceptable range (22).

*DSC*

Figure 8 illustrates thermograms of F5, F7, and F8 at zero time and after 3 months of storage at different storage

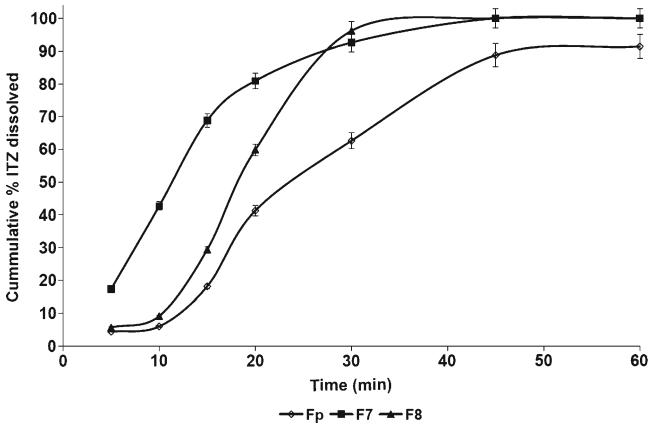


**Fig. 10.** Dissolution profiles of nanosized ITZ from its capsules containing F7 and F8 in comparison to the marketed product (Fp)

conditions. At zero time, the thermogram of F5 showed endothermic transition at 164.97°C. No change in intensity of the peak was seen and endothermic transitions were in the range of 165.32–165.97°C, 165.09–166.55°C, and 165.51–166.01°C at ambient room temperature, 25±2°C/60% RH and 40±2°C/75% RH, respectively throughout storage period.

At zero time, the thermogram of F7 showed endothermic transition at 166.10°C. After 3 months of storage, thermograms showed endothermic transitions in the range of 166.27–166.61°C, 166.60–167.23°C, and 166.35–167.02°C at ambient room temperature, 25±2°C/60% RH and 40±2°C/75% RH, respectively.

At zero time, the thermogram of F8 showed endothermic transition at 164.63°C. After 3 months of storage thermograms showed endothermic transitions ranged between 165.32°C and 166.63°C, 165.08°C and 166.35°C, and 165.45°C and166.53°C at ambient room temperature, 25±2°C/60% RH and 40±2°C/75% RH, respectively. It can be concluded that no appreciable change in the ITZ physical state was observed throughout the storage period.

### *In Vitro Dissolution Studies*

Figure 9 displays the *in vitro* dissolution profiles of selected ITZ nanocrystals over 3 months of storage at different conditions.

No obvious differences were detected in the rate of dissolution of F5 and F7 after 3 months of storage at ambient room temperature and at 25±2°C/60% RH.

Storage at high relative humidity (40±2°C/75% RH) affected dissolution rates of pure drug and F5. After 10 min, the percent of ITZ dissolved at zero time was 9.49% and 81.53% for pure drug and F5, respectively. The corresponding values after 3 months of storage at 40±2°C/75% RH were 3.45% and 67.85%.

F7 containing pluronic F127 showed no significant change in the rate of dissolution at 40±2°C/75% RH after 3 months of storage. A slight improvement in the dissolution rate of F8 was observed throughout storage period at different conditions.

It can be concluded that inutec was equipotent to pluronic F127 in maintaining the ease of redispersibility (disintegration) of drug nanoparticles when reconstituted in water (coming in contact with dissolution medium).

### HPLC Analysis (Chemical Stability)

The chromatograms of the stored samples obtained were compared with the chromatogram of pure drug and peaks other than the solvent peaks and the main drug peak were considered as degradation products. No degradation was found for all samples stored at ambient room temperature, 25±2°C/60% RH and 40±2°C/75% RH after 3 months of storage.

### *In Vitro* Dissolution of Capsules Filled with F7 and F8 Itraconazole Nanocrystals

Figure 10 shows the dissolution results of the prepared capsule formulae in comparison to marketed product (Fp). The percent ITZ dissolved after 20 min is 41.28%, 80.91%, and 59.87% for Fp, F7, and F8, respectively.

It is obvious that F7-filled capsules dissolved a greater amount of ITZ within first 20 min compared to that dissolved from F8-filled capsules. The finding is consistent with the *in vitro* dissolution study of nanocrystals which revealed that pluronic F127 is a better stabilizer for the preparation of ITZ nanocrystals compared to inutec SP1.

## CONCLUSION

Antisolvent sonoprecipitation appeared to be applicable to formulate ITZ which is poorly soluble drug in both aqueous and most organic media as particles in the nanometer range for enhancing its dissolution rate. The method used for drying of ITZ nanosuspension-influenced particle size and dissolution rate of itraconazole nanocrystals. Freeze-dried nanocrystals showed smaller mean particle diameters and faster dissolution rates compared to oven dried ones. Both inutec SP1® and pluronic F127 were effective in preserving the rapid drug dissolution after 3 months of storage under different conditions.

## ACKNOWLEDGMENT

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