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ORIGINAL ARTICLE

Formulation of betacyclodextrin based nanosponges of itraconazole

Shankar Swaminathan · P. R. Vavia · Francesco Trotta · Satyen Torne

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Abstract Nanosponges are betacyclodextrins cross-linked with carbonate bonds. The polymer formed is nanoparticulate in nature. Itraconazole is a BCS Class II drug that has a dissolution rate limited poor bioavailability. Rationale of the work was to enhance the solubility of Itraconazole so that the bioavailability problems are solved. Solid dispersion technique has been used for drug incorporation. The effect of a ternary component copolyvidonum on solubility of itraconazole has been studied. Phase solubility studies has been carried out with a rationale of comparing the solubilization efficiency of nanosponges, copolyvidonum and combination. The dispersions were characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and photon correlation spectroscopy (PCS). It was found that the solubility of itraconazole was enhanced more than 50-folds with a ternary solid dispersion system. Using copolyvidonum in conjunction with nanosponges helps to increase the solubilization efficiency of nanosponges as evident from the phase solubility studies.

Keywords Betacyclodextrins · Nanosponges · Itraconazole

S. Swaminathan · P. R. Vavia (✉) · S. Torne
Pharmaceutical Division, Mumbai University Institute of Chemical Technology, Matunga, Mumbai 400019, India
e-mail: vaviapradeep@yahoo.com

F. Trotta
Departimento di Chemica IFM, Universita degli studi di Torino, Via Pietro Giuria 7, Torino 10125, Italy

Introduction

Betacyclodextrins (β CDs) have been the most widely used of all the cyclodextrins [1–3] (Fig. 1). It is also reported that of all the potentially useful polymers in drug delivery systems naturally occurring polysaccharides appear as attractive alternative due to low cost, high biodegradability and biocompatibility [4]. Nanosponges are β CDs cross linked with carbonate bonds prepared as per procedure (Fig. 2) [5]. Itraconazole is a broad-spectrum triazole antifungal agent (Fig. 3). Physicochemically it can be characterized as a very poorly water soluble and weak base. The aqueous solubility of the compound is estimated ~1 ng/ml at neutral pH and ~10 μg/ml in 0.1 N HCl [6]. It is classified as a BCS class II drug. It has been reported to have poor oral bioavailability due to poor aqueous solubility [7].

The objective of the work was enhancement of solubility of itraconazole by using synthesized nanosponges of β CD and additionally studying the effect of a ternary component copolyvidonum on the solubility of itraconazole. Because itraconazole is effectively solubilized, it is immediately available, and the phase-to-phase transition which limits bioavailability is eliminated [6]. Hydrophilic polymers have been used in the recent past for enhancing the complexation efficiency of β CDs [8–10]. With a similar rationale we have used copolyvidonum to enhance the complexation efficiency of nanosponges. Solid dispersion technique has been used to incorporate drug in nanosponges. The binary system of drug nanosponges, drug copolyvidonum and the ternary system of drug–nanosponges–copolyvidonum were formulated.

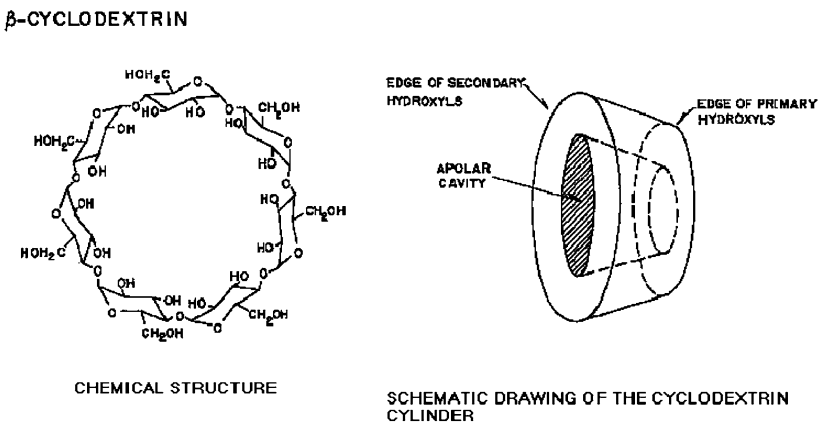


Fig. 1 The chemical shape and the molecular shape of β CD

Experimental

Materials

Itraconazole was obtained as a sample from Hetero drugs Ltd. India. β CD was obtained from SA Pharmchem., India. Copolyvidonum was obtained from ISP Technologies Inc., NJ, USA. All other reagents and solvents were of analytical grade.

Methods

Phase solubility studies

Phase solubility equilibrium plots were obtained for both binary and ternary systems at 25 °C in 0.1 N HCl. The studies were performed as per the procedure of Higuchi and Connors [11]. Studies for binary system were carried out by adding excess amount of the drug to 10 ml of 0.1 N HCl containing increasing amounts of nanosponges (0–2% w/v) or copolyvidonum (0–2% w/v). Studies for ternary systems were carried out by keeping the amount of copolyvidonum constant (1% w/v) and increasing the amount of nanosponges from 0–2% w/v. The so formed series of suspensions were equilibrated on a mechanical shaker for 48 h. The equilibrated suspensions were then filtered through a membrane filter (0.45 μm) and assayed for drug content.

Solution state interaction studies

Ultraviolet spectroscopy was used as a tool. Increasing concentrations of nanosponge solutions (1–80 ppm) were added to fixed concentrations of drug 10 ppm. The samples were then kept overnight for interaction. Finally the samples were scanned for λ_{max} and absorbance were measured. The parameter studied was spectral shift.

Drug incorporation

Itraconazole was dissolved in dichloromethane to form a solution. To this solution nanosponges were added along with copolyvidonum and triturated until the solvent evaporates. The drug, nanosponges, copolyvidonum were added in a ratio of 1:1:1 by weight. The obtained solid dispersion was dried in an oven overnight (at 50 °C at atmospheric pressure) to remove any traces of dichloromethane. The obtained powder was sieved through 60 mesh and used for further work.

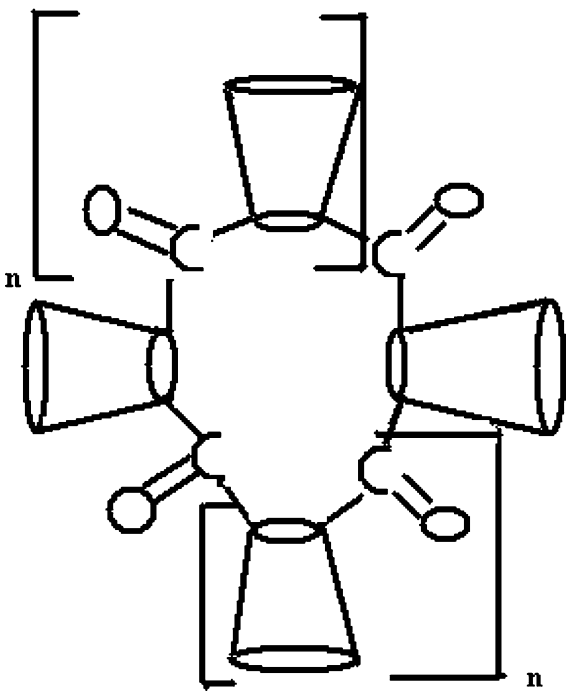
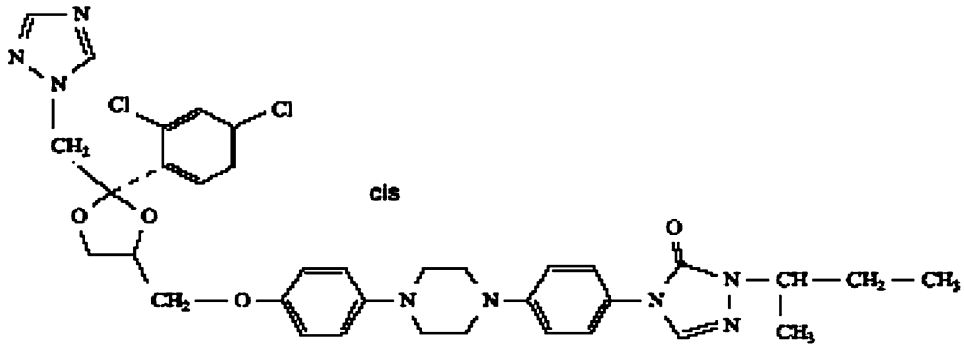


Fig. 2 Proposed structure of nanosponges of β CD. The structure showed is a cyclic structure, the structure could also be of a linear conformation

Fig. 3 Structure of itraconazole



Saturation solubility studies

Excess drug/binary complexes or ternary complex were added to 25 ml of 0.1 N HCl and were equilibrated on a mechanical shaker. The equilibrated suspensions were filtered through membrane filter (0.45 μm) and assayed for drug content. The studies were performed in triplicate.

In vitro dissolution studies

Dissolution studies of the formulations were performed in triplicate in 900 ml of 0.5% sodium lauryl sulphate in 0.1 N HCl using USP XXVII dissolution apparatus 2. Samples were withdrawn at predetermined intervals and analysed spectrophotometrically at 260 nm (UV spectrophotometer UV-1650 PC, shimadzu).

Differential scanning calorimetry (DSC) studies

The samples were subjected to DSC studies using Perkin Elmer pyris 4 series. Samples were sealed in a 40 μl aluminium pans. An identical empty pan was used as a reference. The samples were scanned at 10 °C/min with a 20 ml/min nitrogen purge.

Powder X-ray diffraction (PXRD) studies

PXRD studies were carried out using Rigaku Geiger flex instrument with JADE software.

Particle size analysis

The samples were dispersed in filtered glass distilled water and sonicated in an ultrasonicator for 15 min. The obtained dispersion was then diluted suitably with filtered glass distilled water and particle size was measured using N4 plus Beckmann submicron coulter counter.

Results and discussion

Phase solubility studies

It was carried out with a rationale of comparing the solubilization efficiency of nanosponges, copolyvidonum and their combination. The plots are shown in Fig. 4. The plots are of A_L type. It was found from the studies that as the concentration of nanosponges or copolyvidonum was increased, the drug solubilization also increased proportionately. The solubilization at 1.8% w/v of nanosponges, 1.8% w/v copolyvidonum and combination (1% w/v copolyvidonum and 1.8% w/v nanosponges) were extrapolated from the Fig. 4. The amount of drug solubilized by the ternary system was found to be 3.4 mmol/l, by nanosponges was found to be 2.444 mmol/l and that by copolyvidonum was found to be 0.138 mmol/l From the results it can be said that the ternary system solubilizes the drug to the maximum extent i.e. 1.39 times more than nanosponges and 24.6 times more than copolyvidonum. The increase in solubilization in case of ternary system could be attributed to the adjuvant effect of a hydrophilic polymer

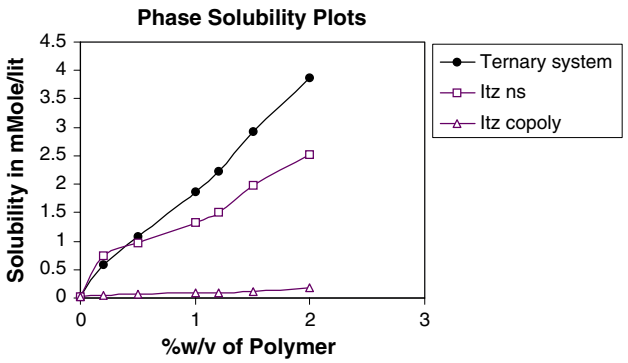


Fig. 4 Phase solubility plots of itraconazole with nanosponges, copolyvidonum and combination. Itz ns—plot of itraconazole in presence of nanosponges; Itz colpoly—plot of itraconazole in presence of copolyvidonum

along with nanosponges. On the other hand nanosponges solubilizes drug by possibly masking the hydrophobic groups of itraconazole, by increasing the wetting of the drug, and/or by decreasing the crystallinity of the drug.

Solution state interaction studies

The drug was found to absorb ultraviolet light at 260 and 222.4 nm (Fig. 5). As the concentration of nanosponges increases, the shift in the wavelength also increases. At 10 ppm of Nanosponge concentration, the peak in standard drug at 222.4 nm was masked (Fig. 5). This could be attributed to the weak interactions between nanosponges and itraconazole or possibly a hydrophobic group in itraconazole is masked, which may also be responsible for the enhanced solubilization of itraconazole by nanosponges.

Saturation solubility studies

The solubility was maximum in case of ternary complex followed by binary systems of nanosponges drug and copolyvidonum drug (Table 1). The enhancement factors were also calculated for the same (Table 1). The solubility was enhanced over 55-folds in case of ternary complex and over 27-folds in case of binary complex with nanosponges.

Nanosponges possibly forms a combination of inclusion and non-inclusion complex with itraconazole as seen in DSC studies also (Fig. 7). Thus the solubility of itraconazole is enhanced and copolyvidonum, a hydrophilic polymer when used with nanosponges tends to increase the complexation efficiency of nanosponges. It possibly improves the interaction between nanosponges and itraconazole. It can be further postulated that the enhanced solubility of itraconazole in case of ternary complex is due to the following mechanisms: reduction of crystallinity of itraconazole, reduced particle size, improved wetting, surfactant action of copolyvidonum, masking of hydrophobic groups of itraconazole by nanosponges.

Evaluation of the dispersions

Dissolution studies were performed in dilute surfactant solutions so as to maintain the sink conditions (Fig. 6). It was found that the dissolution was fastest in case of ternary complex with a dissolution efficiency in 10 min (DE 10 min) of 71.5 as compared to binary complexes of nanosponge drug: 5.833 and copolyvidonum drug: 3.240. The DE 10 min of the marketed formulation was found to be a mere 0.25. Particle size analysis showed that the average particle size reduced to 645–675 nm in case of ternary system as compared to 1,300–1,400 nm in case of Nanosponge system. The polydispersibility index which symbolizes the distribution of the particles in the solution was reduced to 0.675 in case of ternary system as compared to 0.907 in case of itraconazole nanosponge complex.

The particle size of the plain nanosponges were found to be 275–300 nm with a polydispersibility of 0.421 and that of copolyvidonum was found to be 150–250 μm. Reduced particle size and polydispersibility could be attributed to the stabilization of the colloidal system and reduction of agglomeration due to copolyvidonum in case of ternary system. The DSC endotherms are illustrated in Fig. 7. The endotherm in

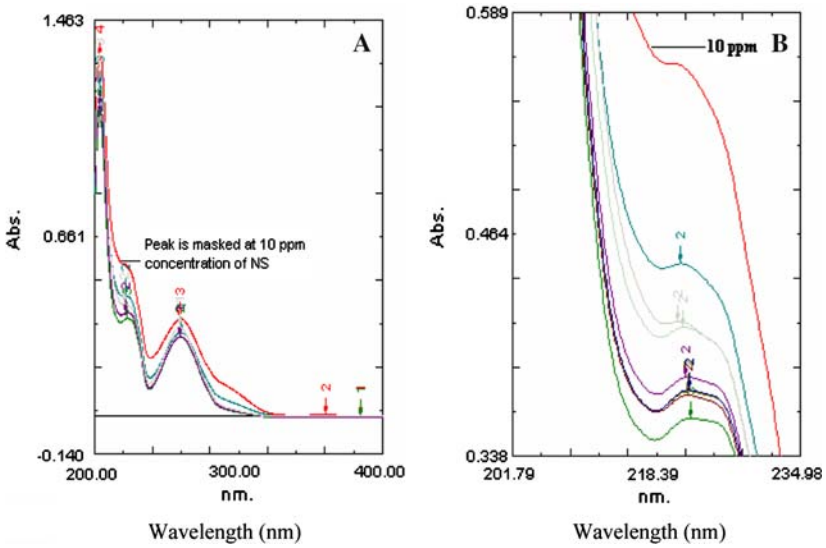


Fig. 5 Solution state interaction studies. (**A**) Spectra of itraconazole in presence of increasing concentrations of nanosponges; (**B**) magnified view of the spectra at 222.4 nm showing a substantially masked peak at 10 ppm nanosponge concentration

Table 1 Saturation solubility studies of formulations with their enhancement factors

Type	Solubility (μg/ml) ± RSD	Enhancement factor
Itz	10.35 ± 0.56	–
Itz ns sd	285.4 ± 0.58	27.57
Itz copoly sd	56.10 ± 0.69	5.42
Ternary sd	571.33 ± 0.98	55.2

Itz—Itraconazole; Itz ns sd—itraconazole nanosponge solid dispersion; Itz copoly sd—itraconazole copolyvidonum solid dispersion; Ternary sd—ternary solid dispersion

Enhancement factor = solubility of formulation/solubility of drug. RSD—relative standard deviation

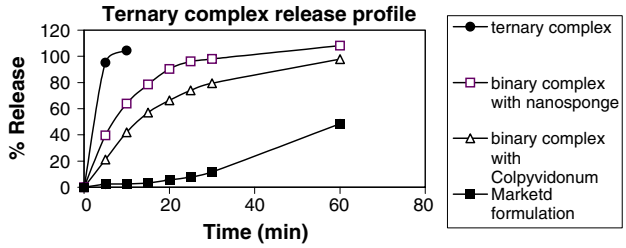


Fig. 6 Dissolution profiles of formulations

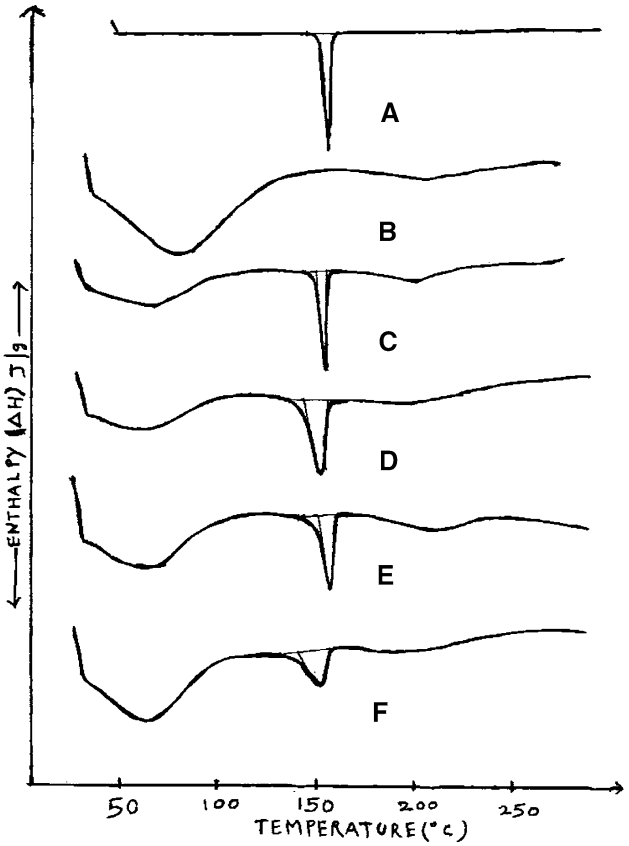


Fig. 7 DSC endotherms of formulations. A—itraconazole; B—nanosponges of β CD; C—itraconazole nanosponge physical mixture; D—itraconazole nanosponge solid dispersion; E—ternary physical mixture of itraconazole nanosponge and copolyvidonum; F—ternary nanosponge complex of itraconazole with colpolyvidonum

case of ternary complex showed a shift of 10.74 °C as compared to plain drug, that of binary complex of nanosponges showed a shift of 6.48 °C, that of itraconazole nanosponge physical mixture showed a shift of a mere 0.5 °C and that of ternary physical mixture shows a shift of 2.3 °C. Thus it indicates complexation in case of nanosponges and even more so in case of ternary complex. Additionally the enthalpy and endotherm areas were reduced in case of ternary complex as compared to binary complexes. The results are shown in Table 2. From the table it is seen that the area and the enthalpies of the drug progressively decreased in the following order: Plain drug, drug nanosponge physical mixture, drug nanosponge solid dispersion, ternary physical mixture and ternary solid dispersion. These could be due to change in the state of the drug form crystalline to amorphous. Thus the energy required to melt the drug is reduced i.e. enthalpy is reduced. In case of ternary complex the drug shows maximum amorphousness as evident form the area values and enthalpy values, which are minimum and also it can be confirmed form the PXRD studies (Fig. 8 and Table 3) which revealed formation of a new state in case of ternary system that is amorphous in nature. It can also be seen from the reduced number of peaks and reduced peak areas in case of ternary complex. The results of the PXRD studies are shown in Fig. 8 and the interpretation is shown in Table 3. Thus it can

Table 2 DSC interpretation of all formulations

Type	Area (mJ)	ΔH (J/g)	Temperature onset (X)	ΔX
Itz	436.999	82.452	169.01	–
Itz ns pm	300.612	38.052	168.51	0.5
Itz ns sd	249.917	31.239	162.53	6.48
Ter pm	182.237	22.779	166.71	2.3
Ter sd	100.789	17.377	158.27	10.74

Itz—Itraconazole; Itz ns pm—itraconazole nanosponge physical mixture; Itz ns sd—itraconazole nanosponge solid dispersion; ternary pm—ternary physical mixture; Ternary sd—ternary solid dispersion. ΔH—Enthalpy change, ΔX—difference in temperature onset

Table 3 PXRD interpretation of all formulations

2θ	Itz	Itz ns pm		Itz ns sd		Ter pm		Ter sd	
		Area	RDC	Area	RDC	Area	RDC	Area	RDC
20.30	8,063	2,238	0.7	1,131	0.1	4,241	0.5	1,498	0.1
17.42	6,209	2,959	0.4	2,201	0.3	3,994	0.6	1,625	0.2
17.88	6,042	3,562	0.5	5,449	0.9	4,249	0.7	4,181	0.6
23.4	2,893	618	0.21	1,176	0.4	1,432	0.4	1,380	0.4
10.7	3,147	966	0.3	2,644	0.8	1,995	0.6	2,444	0.7

Itz—Itraconazole; Itz ns pm—itraconazole nanosponge physical mixture; Itz ns sd—itraconazole nanosponge solid dispersion; ternary pm—ternary physical mixture; Ternary sd—ternary solid dispersion

RDC = relative degree of crystallinity = area of formulation at a specific 2θ/area of drug at that value of 2θ

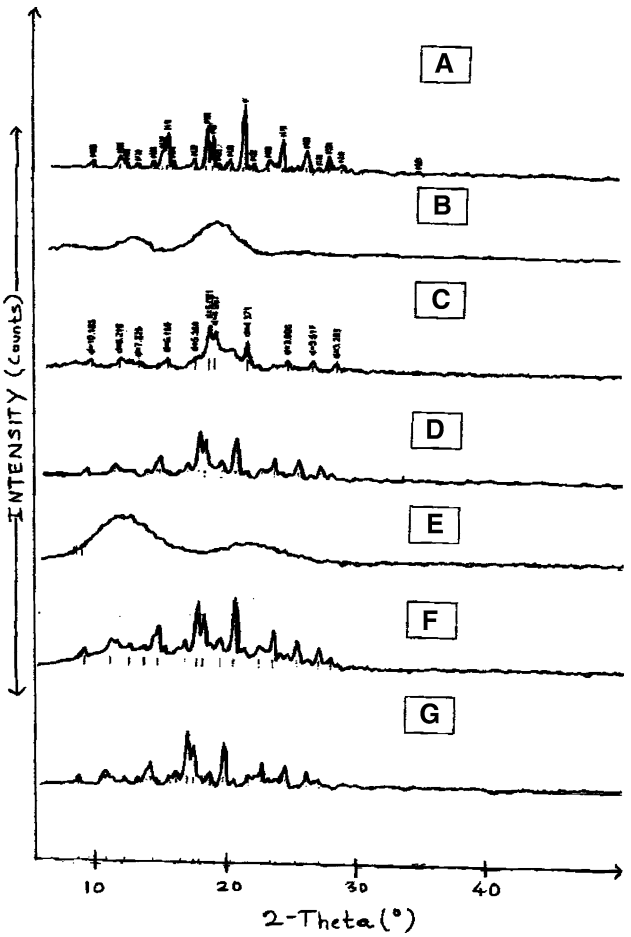


Fig. 8 PXRD Analysis of formulations. A—itraconazole; B—nanosponges of β CD; C—itraconazole nanosponge physical mixture; D—itraconazole nanosponge solid dispersion; E—copolyvidonum; F—ternary physical mixture of itraconazole nanosponge and copolyvidonum; G—ternary nanosponge complex of itraconazole with copolyvidonum

be predicted that the enhanced dissolution and solubility of itraconazole in case of ternary complex is due to the following mechanisms: reduction of crystallinity of itraconazole, reduced particle size, improved wetting, surfactant action of coplyvidonum, masking of hydrophobic groups of itraconazole by nanosponges.

Conclusions

Our study proved that nanosponges of β CD improved the solubility of itraconazole many folds and addition of an auxiliary component copolyvidonum enhanced the solubility further. Due to more solubilization, the bioavailability of itraconazole can be expected to be more as compared to plain drug. Thus the objective of the work was achieved using a ternary system of nanosponges and copolyvidonum.

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