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DEVELOPMENT AND CHARACTERIZATION OF ITRACONAZOLE-B-CYCLODEXTRIN COMPLEX FOR IMPROVED DRUG DELIVERY

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ABSTRACT

Itraconazole, a poorly water soluble antimycotic agent, is promising agent for various diseases. To improve the solubility of itraconazole, the inclusion compound of Itraconazole with β-cyclodextrin was prepared by spray drying, solvent evaporation, kneading, lyophilization, physical mixture method and characterized by solubility, scanning electron microscopy, differential scanning calorimetry, FTIR and dissolution study. DSC and FTIR confirmed the formation of complex. The solubility of the prepared complex was found to be improved. Itraconazole complex by spray drying method and Itraconazole showed 95.65 % and 80.55% of drug release at the end of 48 h in dissolution study. It was concluded that the complex of itraconazole may be of potential use for improving the solubility of itraconazole and hence its bioavaibility.

Keywords: Itraconazole, β cyclodextrin, inclusion compound, Antimycotic.

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INTRODUCTION

Itraconazole, a lipophilic, imidazole derivative, is an antimycotic agent with broad spectrum. Mainly Used in the treatment of various fungal Infections like blast mycosis, Histoplasmosis and onychomycosis. Itraconazole when administered orally, exhibits large difference in bioavailability due to its low aqueous solubility (0.42%).[1]

Cyclodextrin complexation has been extensively applied to enhance the solubility, dissolution rate and bioavailability of slightly water-soluble drugs.[2, 3, 4] The cyclodextrin complexes with slightly water-soluble drugs have been prepared using co-precipitation, kneading, lyophilization, kneading, spray drying and freeze drying method .[2,3,5,6] Among them, spray drying has been extensively applied to prepare the inclusion complexes, since it has many advantages of a good yield in a short operating and suitability for extension to manufacturing scale.[4]

Thus, in this study, to enhance the oral bioavailability of Itraconazole, the inclusion complex of itraconazole with β-cyclodextrin was prepared by spray drying method. The phase solubility and dissolution of inclusion complex were carried out.

MATERIAL AND METHODS

Itraconazole and β-Cyclodextrin were provided by Torrent Research centre, Gandhinagar. HP β-Cyclodextrin was provided by Roquette Frères, France. Methanol and Dichloromethane were obtained from Baroda chemical industrial ltd. All other chemicals were of reagent grade and used without further purification.

Preparation and Physicochemical Properties of Inclusion Complex

Table 1 formulation of itraconazole-β-cyclodextrin inclusion complex.

Ingredient	Quantity
Itraconazole	0.2 g
Dichloromethane	100 ml
β-cyclodextrin	1.6 g
Water	100 ml

Preparation

A Buchi 190 nozzle type mini spray dryer (Flawil, Switzerland) was used for the preparation of itraconazole-β-cyclodextrin inclusion complex. In brief, 0.2 g of itraconazole and 1.6 g of β-cyclodextrin (molar ratio, 1:2) were dissolved in 100 ml dichloromethane and 100 ml water, respectively, and then mixed. The resulting clear solution was delivered to the nozzle at a flow rate of 5 ml/min using a peristaltic pump and thereafter spray-dried at 120^{o}C inlet temperatures

with a flow rate of 10 ml/min. The residue, itraconazole-β-cyclodextrin inclusion complex was collected.[7, 8]

On the other hand, the physical mixture of itraconazole and β-cyclodextrin (molar ratio 1:2) was prepared by gentle mixing 0.2 g of itraconazole and 1.6 g of β-cyclodextrin in a mortar.

Complex by kneading method was prepared by geometric mixing of powders, Itraconazole with β-CD and then kneaded with 1:1 mixture of dichloromethane – water to obtain a mass with a pasty consistency, which was dried in hot air oven at 45 to 50°C. The dried mass was sieved through 100 #.

For complex by solvent evaporation method, dichloromethane and water were used as solvents. The required quantity of Itraconazole with β-CD was dissolved in dichloromethane and water respectively. Both the solutions were mixed and solvents were evaporated by controlled heating at 45 - 50°C. The resultant solid was pulverized and then sieved through 100 #.

Solution of drug and β-CD has previously been frozen to be dried under a vacuum in lyophilisation method, drug and β-CD was dissolved in dichloromethane and water. The product was prepared in three steps, freezing, drying (sublimation) and secondary drying.

DSC curve

The formation of inclusion complex was confirmed by DSC (Shimadzu 60 with TDA trend line software, Japan.) at a heating rate of 10/min over a 25-250 temperature range. A nitrogen purge, 20 cm^3/min was maintained throughout runs and base line optimization was performed before each run.[7]

Solubility

To determine the change in solubility due to complexation, solubility of itraconazole and itraconazole-β-cyclodextrin complex was determined in pH 1.2 HCl buffer and *n*-octanol by the shake-flask method. Itraconazole (100 mg) (and 100 mg equivalent in case of complex) was placed in a 100-mL conical flask. HCl buffer pH 1.2 (100 ml) was added and then stirred for 15 minutes. The suspension was then transferred to a 250 ml separating funnel with 100 ml *n*-octanol and was shaken well for 30 minutes. Then the separating funnel was kept still for about

Table 2 Solubility study of Itraconazole -β-cyclodextrin complex

Drug	Solubility in aqueous layer(in µg/ml)*
Itraconazole	4.2 ± 0.52
Itraconazole-β-cyclodextrin complex	27.31± 1.98

*Data expressed as mean values and standard deviations (±SD); n=3.

30 minutes. Concentration of the drug was determined from the aqueous layer spectrophotometrically at 258 nm and shows four times increase in solubility.

Scanning electron microscopy (SEM)

The surface morphology of raw materials (itraconazole, Hp-ßcd) and binary systems was examined by means of a scanning electron microscope (Jeol, JSM 5310, Tokyo, Japan). The samples were fixed on a brass stub using double-sided tape and then made electrically conductive by coating in a vacuum with thin layer of copper. The photographs were taken with a Pentax (model MZ-10) camera atan excitation voltage of 10 kV and magnification factors of 200 and 3500.

Infrared Spectroscopic Analysis

FTIR spectra for the various powders were obtained on a FTIR spectrometer (FTIR – 8400S model, Shimadzu, Japan) in transmission mode with the wave number 4,000-500 cm^{-1}. KBr pellets were prepared by gently mixing 1 mg sample powder with 100 mg KBr.

Dissolution

Itraconazole powder (50 mg) and inclusion complex (0.45 g) (equivalent to 50 mg itraconazole) were packed in semi permeable membrane and placed in a dissolution tester (Veego UDA-8D USP standard), respectively. Dissolution test was performed at 36.5^{o}C using the paddle method at 50 rpm with 500 ml of phosphate buffer (pH 7.4) as a dissolution medium. At appropriate time intervals, 5 ml aliquots of solution were withdrawn, filtered immediately through a membrane filter and analyzed directly by UV/visible spectrophotometer at 258 nm.[2, 11, 12]

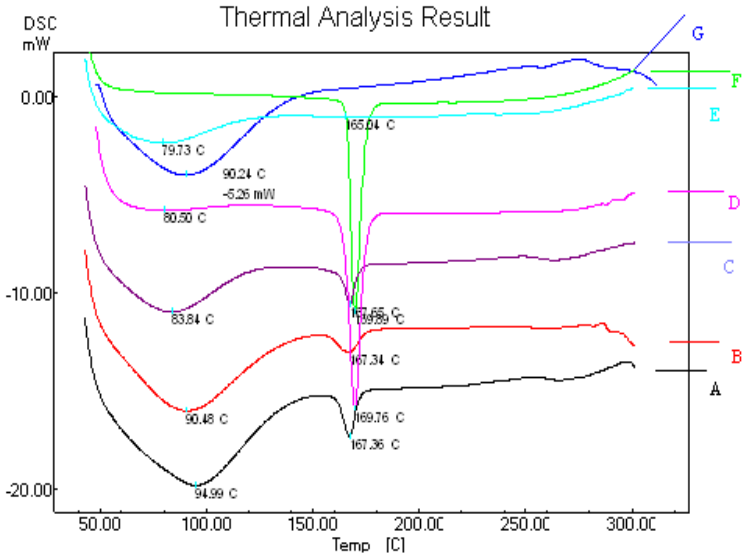

Figure 1 DSC Spectra of Physical mixer (A) Kneading product (B) Lyophilized (C) Solvent evaporated (D) Spray dried (E) Itraconazole (F) ß-CD (G).

RESULTS AND DISCUSSION:

The Itraconazole -β-cyclodextrin (1:2) inclusion complex was prepared easily by spray-drying 0.2 g itraconazole and 1.6 g β-cyclodextrin. Figure 1 illustrates DSC thermal curves of itraconazole, β-cyclodextrin and inclusion complex (1:2, molar ratio).

The DSC curve of itraconazole shows one characteristic sharp endothermic peak at around 169.89^{o}C indicating the melting point of the drug. DSC curve showed that the sharp endothermic peak at around 169.89^{o}C, which was observed for itraconazole, decreased in the inclusion complex (1:2). Furthermore, the wide peak at 90.24^{o}C, which was observed for β-cyclodextrin, shifted to 79.73^{o}C in the inclusion complex, indicating that the inclusion complex did not contain a much residue of itraconazole or β- cyclodextrin and thus suggesting that the drug is well dispersed in the β-cyclodextrin cavity.[9.10, 14]

Water solubility of itraconazole from itraconazole-β-cyclodextrin complex was found to be much higher than that of itraconazole. Table 2 provides the solubility data. This data illustrates that the apparent solubility of itraconazole-β-cyclodextrin complex (27.31± 1.98) is six fold higher than that of itraconazole drug (4.2 ± 0.52). These findings suggested that the formation of the soluble itraconazole-β-cyclodextrin inclusion complex with 1:2 stoichiometric according to Highuchi and Connors (1965).[13]

Scanning electron micrographs of the complex are shown in Figure 2(A to F) itraconazole-β cyclodextrin complexes were found to be irregular or disc shaped with rough surface morphology. The complex was found to involve free flowing particles.

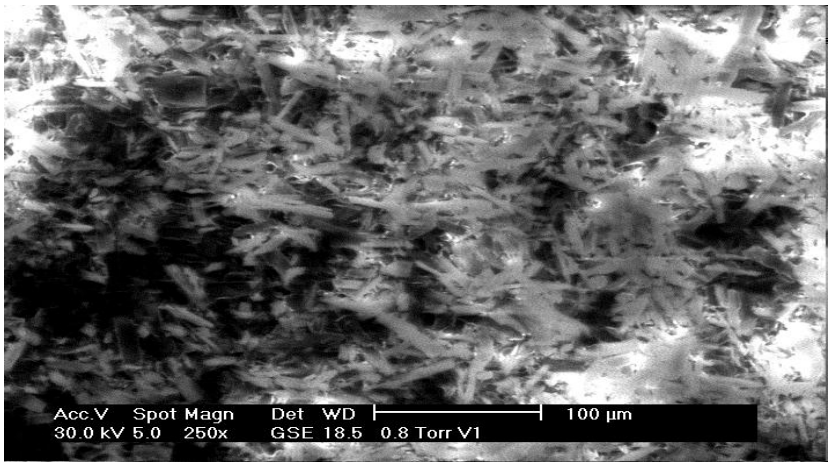

Figure 2(A): SEM of standard drug Itraconazole

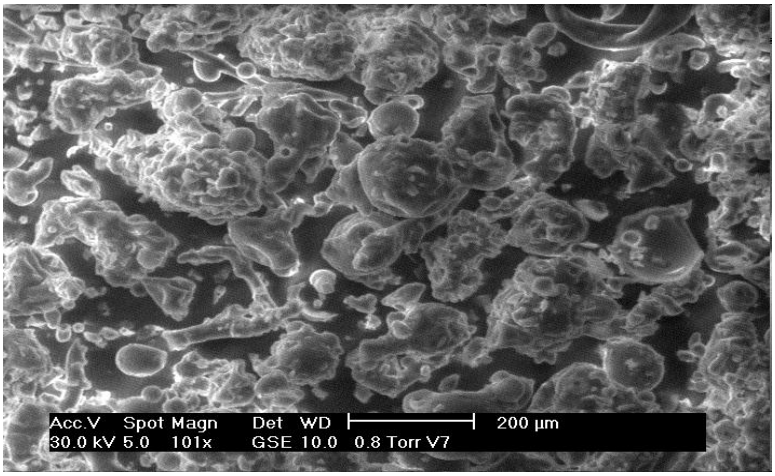

Figure 2(B): SEM of polymer β-CD

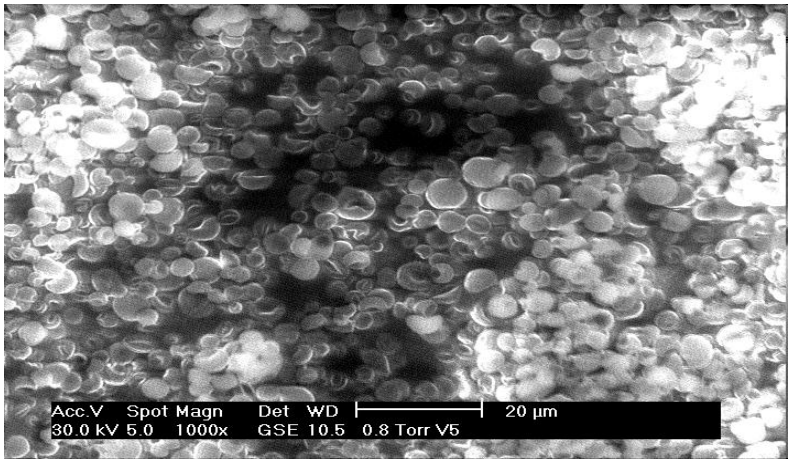

Figure 2(C): SEM of Itraconazole- β-CD complex by spray drying technique.

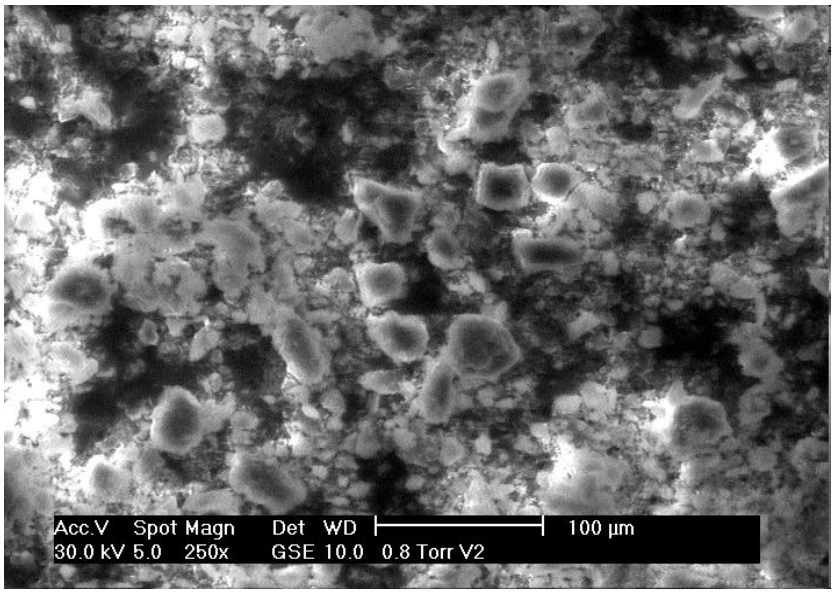

Figure 2(D): SEM of Itraconazole- β-CD complex by solvent evaporation technique.

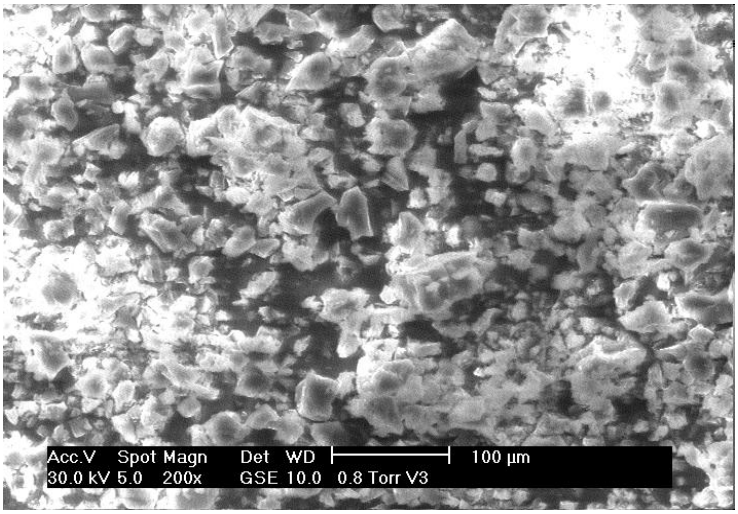

Figure 2(D): SEM of Itraconazole- β-CD complex by lyophilisation technique.

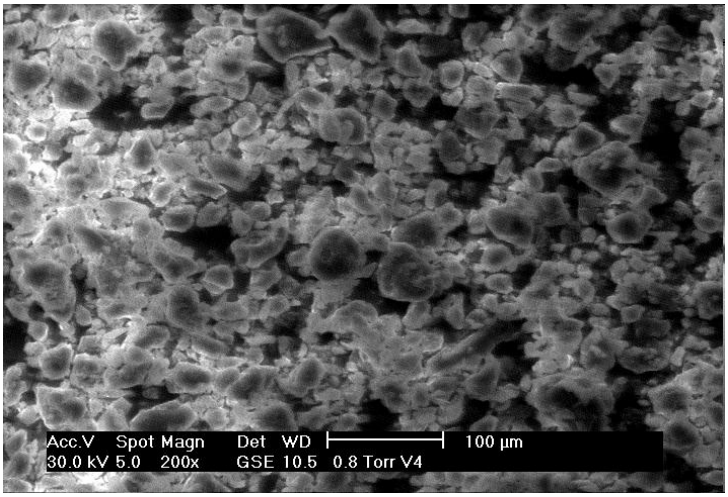

Figure 2(E): SEM of Itraconazole- β-CD complex by physical mixture method.

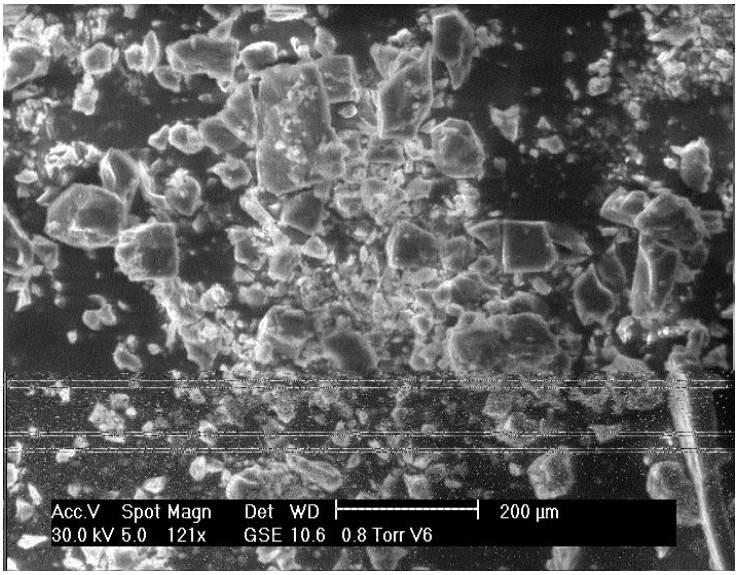

Figure 2(F): SEM of Itraconazole- β-CD complex by kneading method.

FTIR techniques have been used here to study the physical and chemical interaction between drug and polymer used. Infrared (IR) spectra of Itraconazole, -ß-CD, spray dried product of itraconazole & ß-CD are shown in figure. Infrared absorption spectroscopy (IR) itraconazole showed sharp band at 1679.41,1511.28, and 1226.77 cm^{-1} due to stretching vibration bands of C=O, N-O, C-O respectively. From the figure it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymer, which show there were no physicochemical interaction between drug and polymer because of some bond formation between drug and polymers.

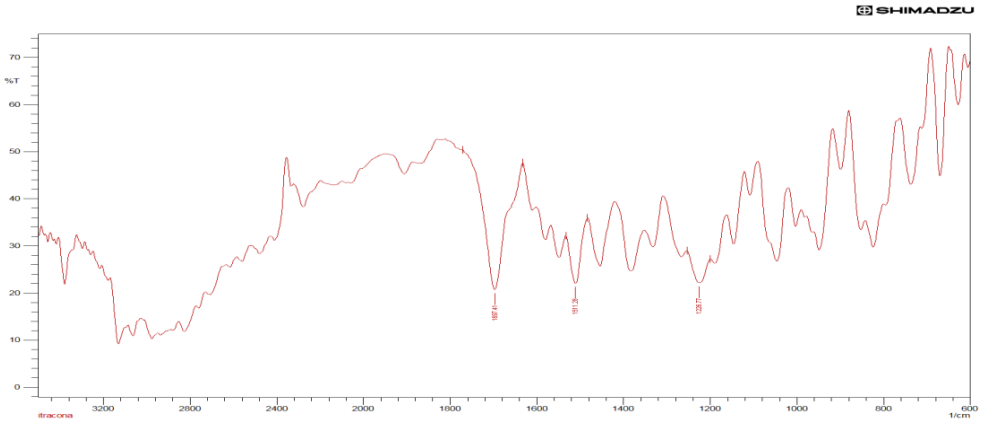

Figure 3(A): FTIR Spectra of Standard drug Itraconazole

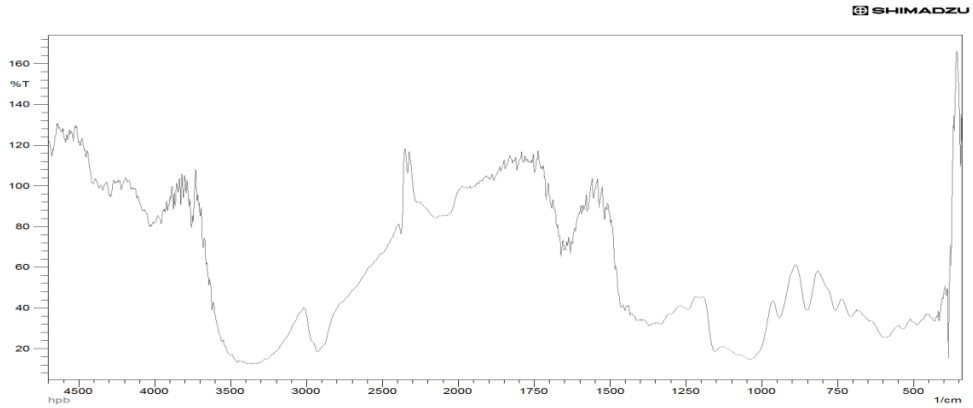

Figure 3(B): FTIR Spectra of ß-CD

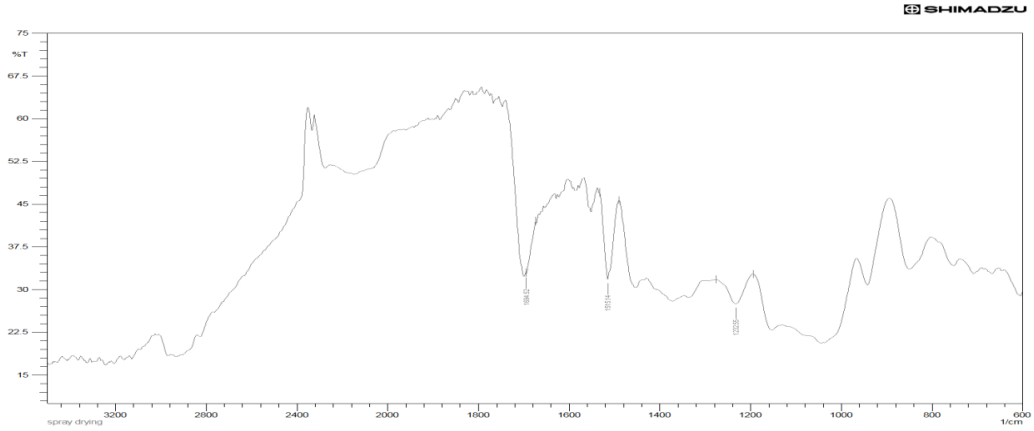

Figure 3(C): FTIR Spectra of Spray dried product.

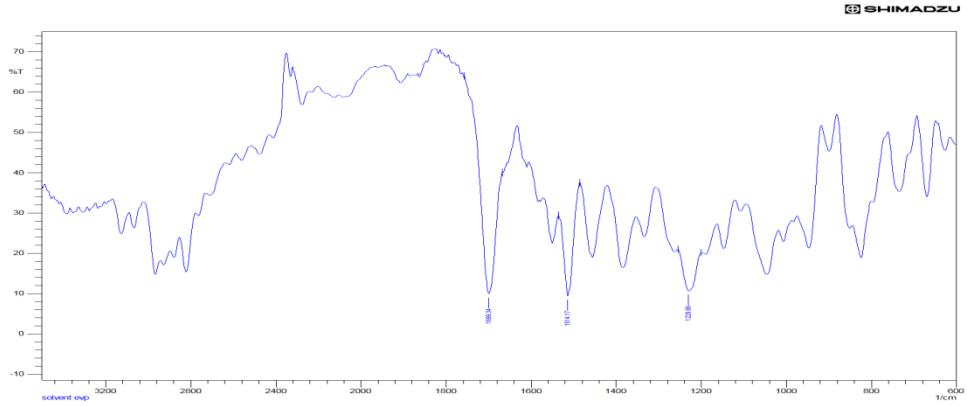

Figure 3(D): FTIR Spectra of Solvent evaporation product.

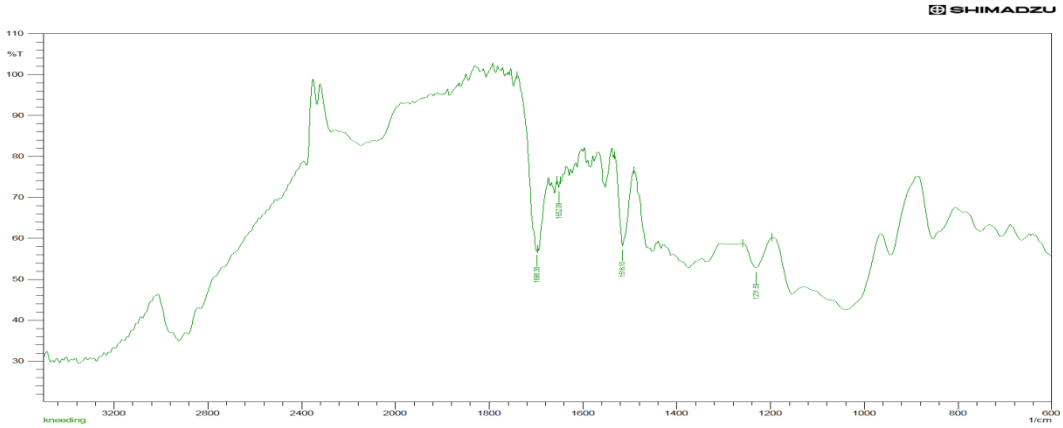

Figure 3(E): FTIR Spectra of kneading method product.

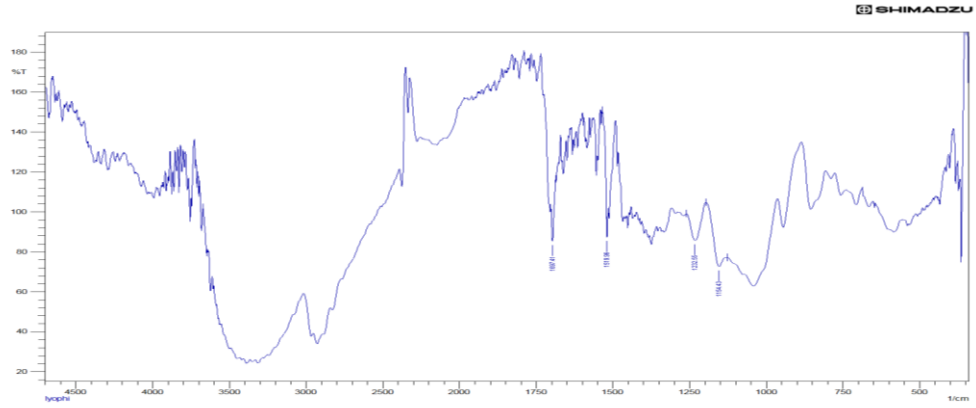

Figure 3(E): FTIR Spectra of lyophilized method product.

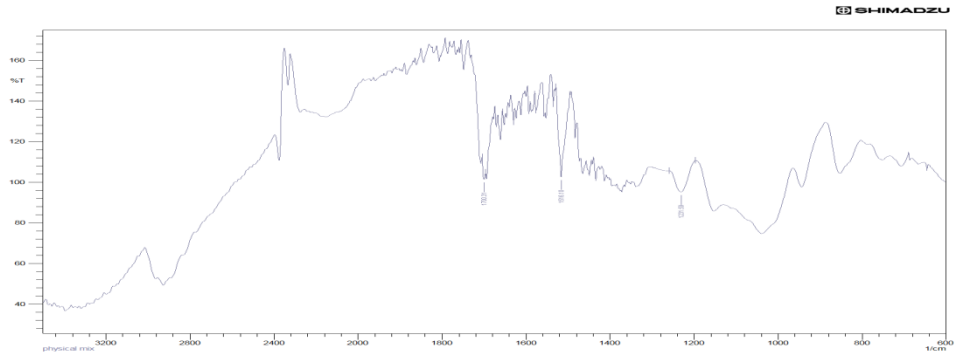

Figure 3(F): FTIR Spectra of physical mixture method product.

To evaluate whether inclusion compound affected the dissolution rate of itraconazole, the dissolution studies were performed for itraconazole powder, B-cyclodextrin and inclusion compound (1:2). The dissolution profiles of itraconazole from the itraconazole loaded preparations are illustrated in Figure 4 the dissolution rate of itraconazole in the inclusion compound increased greatly compared to itraconazole powder in pH 1.2 HCl buffer solution. The amounts of itraconazole dissolved from inclusion complex in pH 1.2 HCl buffer solution for 48 h increased about compared to itraconazole powder (80.55±1.6 vs. 95.65±5.7%). The significant enhancement in the dissolution rate of itraconazole from the inclusion complex could be explained from the increased solubility wettability of the drug by the inclusion complexation.[11,12] Furthermore, the increased dissolution rate of itraconazole in physical mixture might be possibly attributable to the wetting effect of the β-cyclodextrin at the initial stage of the dissolution process.[15,16] Thus, the inclusion complexation was useful for improving the dissolution rate of poorly water-soluble itraconazole.

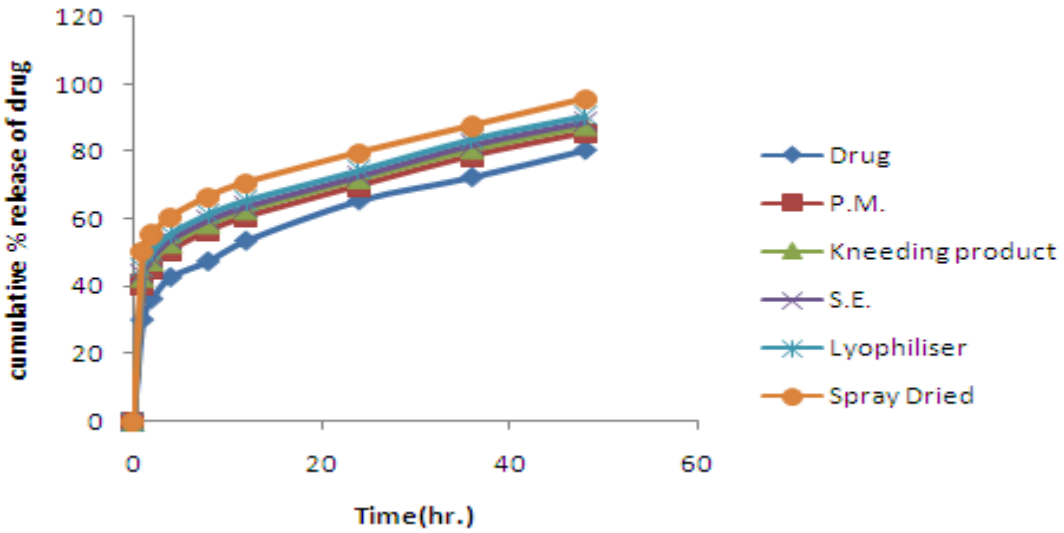

Figure 4 Dissolution study of itraconazole from the β-cyclodextrin complex.

CONCLUSION:

In the present study, an itraconazole - β-cyclodextrin complex was prepared by a spray drying method and evaluated for various physicochemical parameters. Physicochemical investigations showed that itraconazole formed a stoichiometric complex with β-cyclodextrin with improved solubility and dissolution profile. DSC and FTIR studies confirmed the formation of the complex. Thus it can be concluded that the complex of itraconazole may be of potential use for improving dissolution.

ACKNOWLEDGEMENTS

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REFERENCES

1. Rang HP, Dale MM, Ritter JM, Flower RJ. RANG & DALE's Pharmacology. Churchill Livingstone Elsevier publication, Sixth Edition 2008.
2. Bekers O, Uijtendaal EV, Beijnen JH, Bult A, Underberg WJM. Cyclodextrins in the pharmaceutical field. Drug Dev Ind Pharm 1991; 17:1503-1549.
3. Jarvinen T, Jarvinen K, Schwarting N, Stella VJ. β- Cyclodextrin derivatives, SBE4-β-CD and HP-β-CD, increase the oral bioavailability of cinnarizine in beagle dogs. J Pharm Sci 1985; 84: 295-299.

4. Nakai Y, Yamamoto K, Terada K, Akimoto K. The dispersed states of medicinal molecules in ground mixtures with α- or β-cyclodextrin. Chem Pharm Bull 1984; 32: 685-691.
5. Abosehmah-Albidy AZ, York PWV, Losowsky MS, Chrystyn H. Improved bioavailability and clinical response in patients with chronic liver disease following the administration of a spironolactone: β-cyclodextrin complex. Brit J Clin Pharmacol 1997; 44: 35-39.
6. Ammar HO, Ghorab M, El-nahhas SA, Omar, SM and Ghorab MM. Improvement of some pharmaceutical properties of drugs by cyclodextrin complexation, part 5. Theophylline, Pharmazie 1996; 54: 42-46.
7. Choi HG, Lee BJ, Yong CS, Rhee JD, Han JH, Lee MK, Park KM, Kim CK. Terfenadine-â-cyclodextrin inclusion complex with the anti-histaminic activity enhancement. Drug Dev Ind Pharm 2001; 27: 857-862.
8. Lee SW, Kim MH and Kim CK. Encapsulation of ethanol by spray drying technique: effects of sodium lauryl sulfate. Int J Pharm 1999; 187: 193-198.
9. Ahmed MO, El-Gibaly I, Ahmed SM. Effects of cyclodextrins on the physicochemical properties and antimycotic activity of clotrimazole. Int J Pharm 1998; 171: 111-121.
10. Davis NM, Wang G, Tucker IG. Evaluation of a hydrocortisone/ hydroxypropyl-β-cyclodextrin solution for ocular drug delivery. Int J Pharm 1997; 156: 201-209.
11. Gandhi RB, Karara AH. Characterization, Dissolution and Diffusion Properties of Tolbutamide-β-cyclodextrin Complex System. Drug Dev Ind Pharm 1988; 14: 657-682.
12. Hassan MA, Suleiman MS, Najib NM. Improvement of the in vitro Dissolution Characteristics of Famotidine by Inclusion in β-Cyclodextrins. Int J Pharm 1990; 58: 19-24.
13. Higuchi T, Conners KA. Phase-solubility Techniques. Adv Anal Chem Instrument 1965; 117-212.
14. Linares M, de Bertorello MM and Longhi M. Solubilization of Naphthoquinones by Complexation with Hydroxypropyl-β-cyclodextrin. Int J Pharm 1997; 159: 13-18.
15. Ozkan Y, Atay T, Dikmen N, Isimer A and Aboul-Enein HY. Improvement of water solubility and in vitro dissolution rate of gliclazide by complexation with β-cyclodextrin. Pharmaceutica. Acta Helvetiae 2000; 74: 365-370.
16. Stella VJ, Rajewski RA. Cyclodextrins and their future in drug formulation and delivery. Pharm Res 1997; 14: 556-567.