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DISSOLUTION RATE ENHANCEMENT OF KETOCONAZOLE BY SPHERICAL AGGLOMERATION

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ABSTRACT

The purpose of this study was to enhance the dissolution rate of poorly water soluble drug of Ketoconazole by preparing spherical agglomerates by Quassi emulsion solvent diffusion technique using chloroform, water, and methanol as bridging liquid and to illustrate the effect of different polymers on the solubility and dissolution rate of Ketoconazole. Polyvinyl Pyrrolidone (PVP K30) was used in spherical agglomeration process. The formulation was done by 3^2-full factorial design. Stirring speed and the concentration of PVP K30 were used as the variable factors in the applied design. Fourier Transform Infra-Red spectroscopy was used to examine the drug-excipient compatibility. Prepared formulations were evaluated for micromeretic properties and dissolution rate. The spherical agglomerates have lower micrometric properties compared to pure drug. The agglomerates exhibited good compressibility and packability characteristics. The spherical agglomerates with different polymers exhibited increasing in the saturation solubility and dissolution rate.

KEYWORDS

Ketoconazole, Agglomerates, Dissolution and Polyvinyl Pyrrolidone (PVP K30).

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INTRODUCTION

There are many types of fungal germs (fungi) live mainly in the soil, on food, on our skin and in other places in the environment. However, some types of fungi can grow vigorously on the surface of the body, to cause infection of the skin, nails, mouth or vagina. General mechanism of action of ketoconazole is that, they inhibit C-14α-demethylase, thus blocking the demethylation of lanosterol to ergosterol. This inhibition disrupts membrane structure and function and therefore

inhibits fungal cell growth. There are several different antifungal preparations that are used to treat various fungal infections. They are as creams, shampoos, tablets, injections and pesaries. Ketoconazole is developed for the first-choice treatment of human mycotic infections. It is poorly soluble in water; it is administered either topically or by mouth. Ketoconazole (KTZ) [(±)-cis-1-acetyl-4-(4-{[2-(2, 4-dichlorophenyl-2(1H-imdazol-1-ylmethyl)-1, 3-dioxolan-4-yl] methoxy} phenyl) piperazine], is an imidazole derivative with a wide antifungal spectrum and posses some antibacterial activity. It is reported to be active in the treatment of systemic blastomycosis, candidiasis, cocioidimycosis, histoplasmosis, paracocidioidomycosis and tinea of skin and nails. Ketoconazole is classified in the class II of the Biopharmaceutic Classification System (BCS) as decreased stomach acid levels will lower the drug absorption. It is very lipophilic and tends to accumulate in fatty tissues[1].

Literature review reveals that the attempts have been made by many researchers by various techniques to improve the dissolution rate of the drug. There are various techniques are available to increase the solubility of poorly water-soluble Ketoconazole i.e. solid dispersion[2-3], nano-emulsion[4], liquisolid[5], salt and co-crystal formation[6-7], nano crystallization[8], self-emulsifying drug delivery[9], spherical crystallization[10] and co-solvency. Among the various approaches, spherical crystallization techniques successfully improve the dissolution and bioavailability of poorly soluble, active Pharmaceutical ingredients because it is simple, economical and advantageous.

MATERIAL AND METHODS

Ketoconazole was received as gift sample from Ajanta Pharma Ltd, Aurangabad India. Polyvinyl Pyrrolidone PVP K30 was purchased from New Modern Chemical Corporation, Mumbai. All other chemicals were used as AR grade.

Preparation of spherically agglomerates of Ketoconazole

Spherical agglomerates were obtained by the quasi emulsion solvent diffusion method. Spherical agglomerates were prepared with and without stabilizers by spherical crystallization Technique as described in Table No.1. Ketoconazole (2 gm) was dissolved in good solvent chloroform. The bridging liquid methanol was added to it. The resulting solution was then poured drop-wise into the poor solvent distilled water containing stabilizer like Poly vinyl pyrolidone K-30 with a stirring rate of 1000 rpm using magnetic stirrer (Remi Motors Ltd., Mumbai, India) at room temperature. After agitating for 30 min, the prepared agglomerates were collected by filtration through Whatman filter paper, washed with distilled water and dried by desiccation at room temperature.

Evaluation of Spherical Agglomerates

Drug Content

Drug content in the spherical agglomerates were evaluated by the UV-spectrophotometry. The samples were dissolved in chloroform to extract the drug in the formulation. Drug content was determined out by UV-spectrophotometry at 224 nm.

Particle size by Optical Microscopy

The prepared crystals were subjected to the Optical microscopy equipped with Saglo Particle size analyzer. The samples were taken on three glass slides and distributed uniformly as a thin layer on the slides. Particle size and morphology as observed.

Micrometric properties

The bulk density and tapped bulk density test were performed by tapped density apparatus. Carr's index and Hauser's ratio were calculated using bulk density and tapped bulk density values. The angle of repose was accessed by funnel method.

Intrinsic Solubility

The intrinsic solubility of the drug was determined by Higuchi-Connor's method[12]. The excess of the drug sample was added to the solvent in a screw capped glass vials. The vials were shaken for 48 hr in a thermostatically controlled water bath shaker at 37±0.5°C The equilibration period of 24 hr was provided. The samples were filtered through using 0.45µm Whatmann filter and saturation solubility study was determined out by UV-spectrophotometry.

In vitro dissolution studies

In vitro dissolution studies were carried out using USP 2 dissolution Testing apparatus (Electrolab, India). The dissolution medium used was 900 ml of 0.1N HCl. The dissolution medium was kept at in a thermostatically controlled water bath at 37±0.5 °C. The agglomerates and pure drug containing 10 mg of Ketoconazole were weighed and introduced into the dissolution medium. The medium was stirred at 100 rpm using paddle. At predetermined time intervals 5 ml of samples were withdrawn maintaining sink condition. The aliquots were analyzed spectrometrically at 224 nm after suitable dilutions.

RESULTS AND DICUSSIONS

Calibration curve

The absorbance for the different concentration (2-10µg/ml) was recorded at 224 nm. The regression coefficient was found to be 0.9989 and regression equation of the calibration curve was found to be y = 0.0522x + 0.0127.

Intrinsic solubility

The intrinsic solubility of the drug in distilled water was found to be 24.288±1.47µg/ml which shows that the drug is poorly soluble in water and there is a strong need to improve the solubilization and drug dissolution rate for enhancing the absorption *in vivo*.

FTIR studies

The possible interaction between drug and stabilizer used was studied in Fourier Transform Infrared Spectroscopy. The FTIR spectrum of Ketoconazole and stabilizer and the spherical agglomerates of Ketoconazole are depicted in Figure No.2-5. It can be observed that the characteristic peaks of the drug are unaffected in the physical mixture and the prepared batches which is the evidence for the compatibility between the drug and polymer.

Morphology /Description

The prepared batches were morphologically described means of color, shape and odour which represented in (Table) indicates the pure drug was Crystalline while the formulations were irregular, partial and spherical.

% Yield

Due to the variability in the formulation, the yield of the spherical crystals was found to be ranging from 20.16 to 61.76%. The results of the yield are tabulated in Table No.2.

Micromeritic properties

The micromeretic evaluation indicates that the agglomerates exhibited Carr's Index ranging from 19.23 to 25.37 while Hausner's ratio ranging from 1.28 to 1.34. It can be concluded from the observations that the flow ability and compressibility of the crystals appear to fair to good due to the characteristic spherical shape. The spherical crystals with the 1000 rpm rate of agitation showed comparatively better results owing to the formation of spherical crystals which can be correlated to the optimum speed of the agitation. The micromeretic evaluation is presented in Table No.2. As the yields of batches at higher content of PVP K30 were very less, the batches were excluded from the evaluation.

***In vitro* dissolution rate**

The results and comparison of dissolution profiles of untreated ketoconazole and its spherical agglomerates with PVP K30 are depicted in Figure No.6. The dissolution profile of KTZ shows that after 90 minutes, only 13.98% of drug was dissolved. On the other hand, the cumulative drug release from all the spherical agglomerates show enhanced dissolution rate. It can be observed from the comparison between the prepared batches that batch B6 was able to deliver approximately entire dose within the period of 90 minutes, while few batches although showed enhanced release in comparison with KTZ, failed to release 100% dose. The enhanced release can be attributed to the co-solvency effect by the polymer as well as enhanced effective surface area available for the dissolution due to controlled crystallization.

Table No.1: Composition of spherically agglomerates of Ketoconazole

S.No	Ingredients	B1	B2	B3	B4	B5	B6	B7	B8	B9
1	Ketoconazole(gm)	2	2	2	2	2	2	2	2	2
2	Chloroform (ml)	5	5	5	5	5	5	5	5	5
3	Methanol (ml)	2	2	2	2	2	2	2	2	2
4	PVP K30	0.75	0.75	0.75	1.125	1.125	1.125	2.250	2.250	2.250
5	RPM	750	1000	1250	750	1000	1250	750	1000	1250
6	Distilled Water (ml)	150	150	150	150	150	150	150	150	150

Table No.2: Micromeritic, solubility data for spherical agglomerates

S.No	Batches	% Yield	Carr's Index	Hausner's Ratio	Angle of repose
1	B1	34.94	21.8	1.28	28.07
2	B2	59.27	23.07	1.3	17.78
3	B3	36.8	25.37	1.34	39.45
4	B4	20.16	19.23	1.23	31.03
5	B5	61.76	23.52	1.3	30.96
6	B6	32	25.33	1.34	40.14

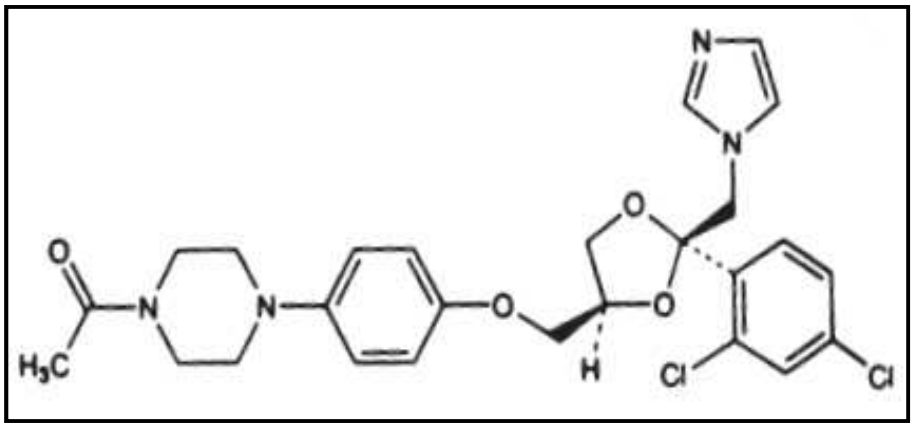

Figure No.1: Chemical Structure of Ketoconazole

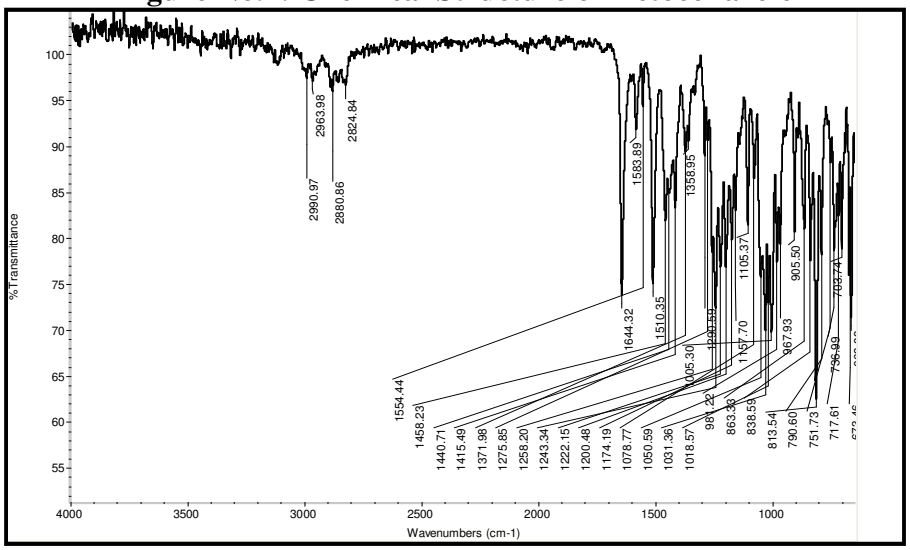

Figure No.2: FTIR Spectra of Ketoconazole

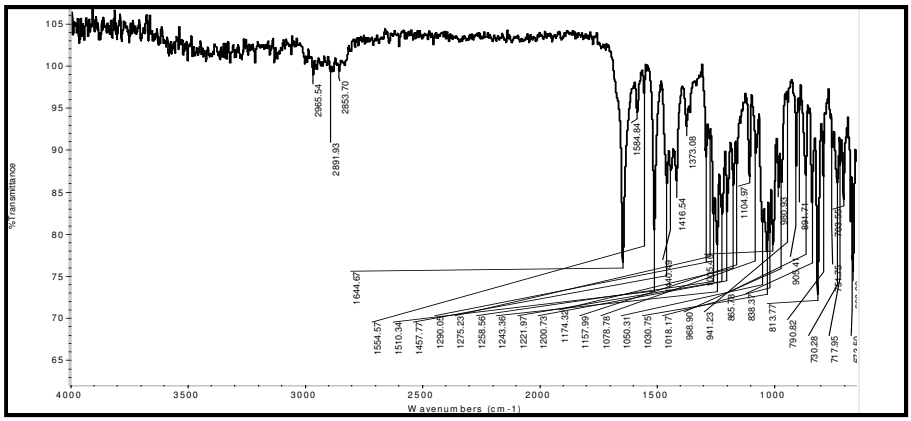

Figure No.3: FTIR Spectra of Physical Mixture of Ketoconazole and PVP K 30

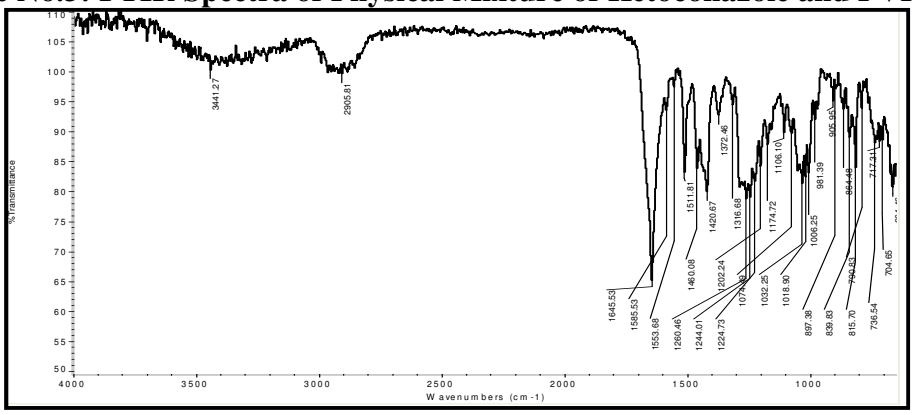

Figure No.4: FTIR Spectra of PVP K 30

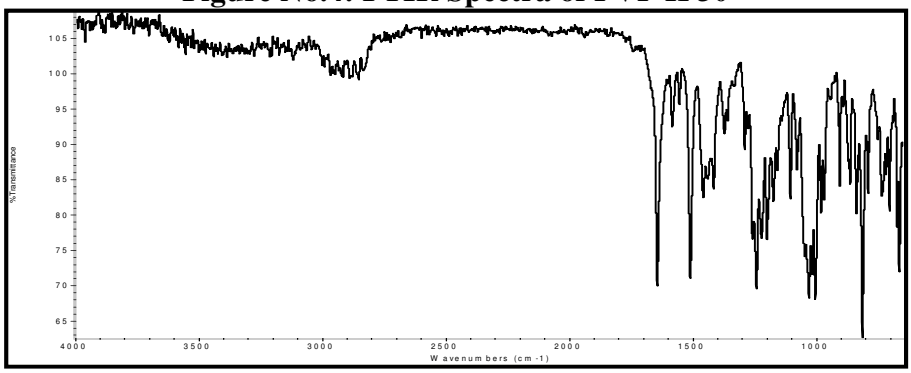

Figure No.5: FTIR Spectra of Spherical Agglomerates (Batch 6)

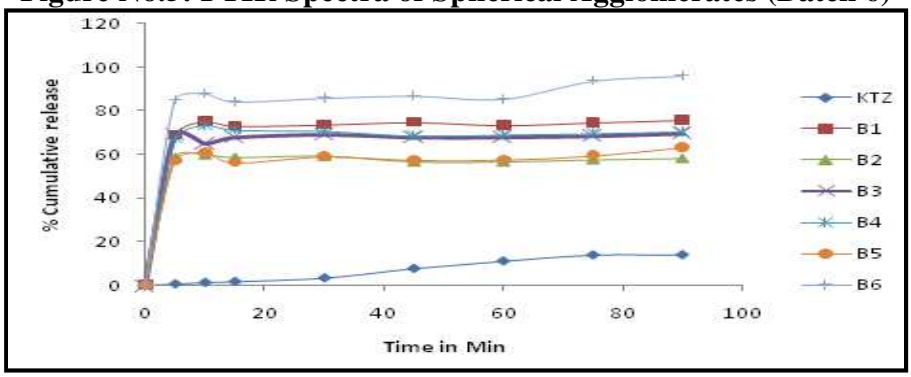

Figure No.6: Dissolution profile of KTZ and spherical agglomerates

CONCLUSION

The present research shows that the spherical agglomerates of Ketoconazole was prepared by using different polymers like PVP K30 shows an excellent improvement in dissolution rate also to improving micromeritics properties. This technique may be applicable for producing oral solid dosage form of Ketoconazole with improving dissolution rate, bioavailability and physiochemical properties.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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