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Original Article

PARTICLE DESIGN OF KETOCONAZOLE BY SPHERICAL CRYSTALLIZATION

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ABSTRACT

Objective: This research aimed to make ketoconazole spherical crystals to improve the micromeritic properties and the dissolution rate using the solvent change method.

Methods: The solvent that is used in the process of spherical crystallization consists of three types: ether (good solvent), distilled water (bad solvent), and n-hexane (bridging liquid), with a 20:70:10 ratio each. The agglomerates were characterized by differential scanning calorimetry (DSC, powder X-ray diffraction (XRPD), Fourier transform infrared (FTIR), and scanning electron microscopy (SEM).

Results: Based on PXRD, DSC, and FTIR spectrophotometer results, it was determined that there was no internal change of ketoconazole crystalline structure during the recrystallization process into spherical crystals, and SEM results revealed that the morphology of the crystal became spherical. Based on the micromeritic properties evaluation results, it was concluded that the ketoconazole spherical crystals have superior micromeritic properties than the conventional ketoconazole. The dissolution test results showed an enhancement in the dissolution rate of spherical crystals compared with the untreated ketoconazole.

Conclusion: Thus, spherical crystals of ketoconazole appear to be a viable approach for enhancing solubility characteristics and micromeritic properties, which would be highly advantageous for processing ketoconazole as a high-dose drug.

Keywords: Ketoconazole, Spherical crystallization, Particle design

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INTRODUCTION

Tablets are the most widely used and most popular solid oral dosage form. Tablets come in many varieties and shapes, sizes, weights, hardness, thickness, dissolution properties, and other aspects, depending on their intended use and method of manufacture [1]. One method of making tablets currently being developed is direct compression [2]. In addition, the procedure is simpler to verify and automate, resulting in nightly unmanned operations [3]. To achieve this, the drug particles must be extremely compact; otherwise, numerous powder binders such as microcrystalline cellulose, dicalcium phosphate dihydrate, and others must be included in the formulation, resulting in bigger tablets [4]. Therefore, particle design techniques were carried out to improve properties such as flowability, compressibility, solubility, particle size, and specific density to ensure that the powder was more stable so that it could be used for the manufacture of tablet dosage form by direct compression [5].

Spherical crystallization is an agglomeration process that may immediately transform the finest crystals formed during the crystallization process into spherical shapes [6]. This approach is a particle engineering technology in which crystallization and agglomeration may be performed concurrently in a single step to convert the crystal straight to a solid spherical shape [7]; it has been applied effectively to increase the compatibility of pharmaceutical crystals [8, 9].

Ketoconazole is a synthetic antifungal drug of the azole group that is an imidazole derivative used to treat or prevent fungal infections, particularly skin infections [10]. Ketoconazole is classified as a class II based on Biopharmaceutical Classification System (BCS) [11]. Due to the high permeability and low solubility of this compound, it is challenging to improve its solubility in water and rate of dissolution [12].

To increase the micromeritic characteristics and dissolution rate of ketoconazole, this study intends to develop spherical crystals of the drug utilizing the solvent change approach. Powder X-Ray Diffraction, Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy, Scanning Electron Microscopy (SEM), and further examination of micromeritic and dissolution assay were used to characterize the spherical crystal solids of ketoconazole.

MATERIALS AND METHODS

Materials

Ketoconazole was purchased from Interbat, Ltd., Sidoarjo, Indonesia. Ether and n-hexane were purchased from Merck KGaA (Darmstadt, Germany), and distilled water was obtained from Bratachem, Ltd, Tasikmalaya, Indonesia. All chemicals used were of analytical grade (Smart-Lab, Tangerang, Indonesia).

Preparation of spherical crystals

Precipitation from solution is the initial stage in spherical crystallization, and it can be done either thermally, physiochemically (addition of another solvent, salting), or chemically. Antisolvent crystallization was utilized in this study. A total of 400 mg of ketoconazole were dissolved in 20 ml of room-temperature ether. The solution combination was poured into 70 ml of 20 °C-temperature distilled water. While fine crystals of ketoconazole start to appear, add 10 ml of n-hexane and constantly mix at 250 rpm with a mechanical stirrer (C-MAG HS 7, IKA, Germany). The spherical crystals are further filtered and dried at 45 °C for 12 h.

Characterization of spherical ketoconazole

Powder x-ray diffraction (PXRD)

This analysis was carried out on standard ketoconazole and ketoconazole resulting from spherical crystallization. Tests were carried out using a diffractometer (Bruker D2 Phaser, Germany) with Cu as the anode and monochromatic graphite. The instrument is operated at a voltage of 40 kV, a current of 30 mA, and the analysis is carried out at 2θ in the 5°-50°.

Differential scanning calorimetry (DSC)

A small sample was placed into the DSC (DSC-60 Plus Shimadzu, Japan) and programmed in a temperature range of 30 °C to 300 °C with a heating rate of 10 °C/min. Purge gas used nitrogen gas with a flow rate of 20 ml/min.

Fourier transform infrared (FTIR)

KBr pellets were used to evaluate the sample powder using an infrared spectrophotometer (FTIR) Cary 630 Agilent (Germany).

Wavenumbers ranging from 4000-400 cm^{-1} were used to conduct the experiments.

Scanning electron microscopy (SEM)

Crystals of ketoconazole and spherical crystals of ketoconazole were analyzed for their surface shape and morphology using SEM (Phenom Prox, Thermo Fisher, USA). The sample was affixed to an aluminum sample holder and coated with 10 nm of gold, observed under various magnifications. The collected images determined the spherical crystal characteristics and surface morphology.

Evaluation of micromeritic properties

Micromeritic analysis was utilized to examine the flowability, angle of repose, bulk density, tap density, compressibility index, and Hausner ratio of spherical ketoconazole crystals.

Dissolution test

Ketoconazole passed a dissolution test (Electrolab, Mumbai, India) compared to its spherical crystal form. It used 0.1 N hydrochloric acid as the dissolution medium and up to 900 ml of type II apparatus (paddle type). Stirring was conducted at a temperature of 37±0.5 °C at 50 rpm. The appropriate quantity of samples was dispersed in 900 ml of the dissolution medium for sink conditions. During a dissolution test on a sample of 100 mg, 10 ml were obtained at intervals of 5, 10, 15, 20, 25, and 30 min and filtered through a 0.45 µm filter membrane. A UV-Vis spectrophotometer (Cary-60, Agilent, Germany) determines the absorbance at 268.5 nm. The average results and standard deviations were calculated for each dissolving experiment that was conducted in triplicate.

RESULTS

Pure and spherical ketoconazole crystals were subjected to PXRD analysis to assess their crystallographic transformations. Since each crystalline phase has its unique diffraction pattern, this method may examine alterations in the internal crystal structure [13]. Presented in fig. 1 are the PXRD images of pure ketoconazole and an upgraded batch of spherical agglomerates.

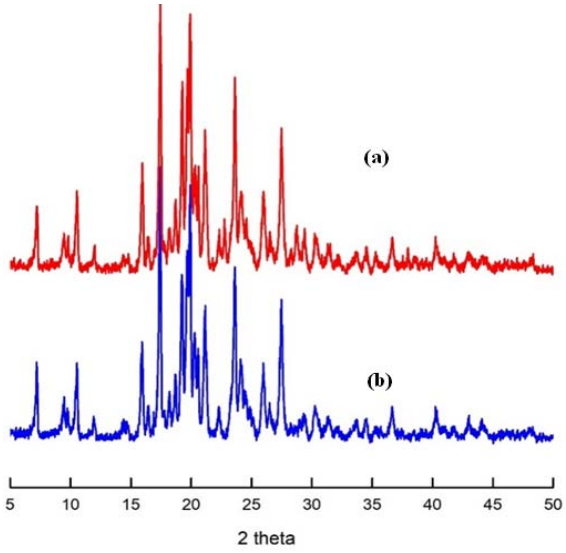


Fig. 1: PXRD Diffractogram (a) ketoconazole standard (b) spherical crystals of ketoconazole

DSC thermograms for ketoconazole agglomerated and unagglomerated particles make it possible to exclude polymorphic transitions during crystallization. This instrument produces a record of the change in enthalpy versus the melting temperature of the samples [15]. Fig. 2 shows the DSC thermograms of pure and aggregated ketoconazole.

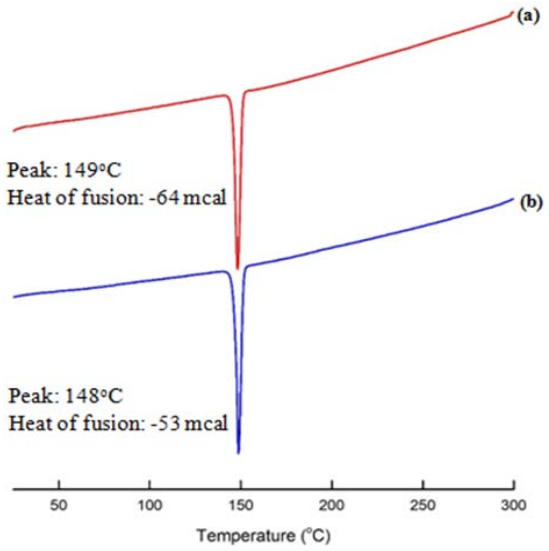


Fig. 2: DSC thermogram (a) ketoconazole standard, (b) spherical crystals of ketoconazole

FTIR spectrophotometric analysis was carried out to determine the changes in functional groups and chemical interactions during the spherical crystallization process. The possibility of chemical interactions in the sample can be detected by changes in the number of peaks, intensity, and wavenumber at each peak. Fig. 3 depicts the FTIR spectra of pure drugs and agglomerates.

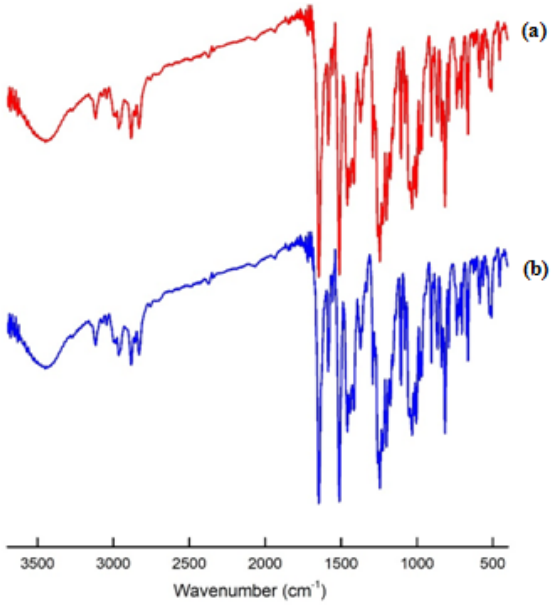
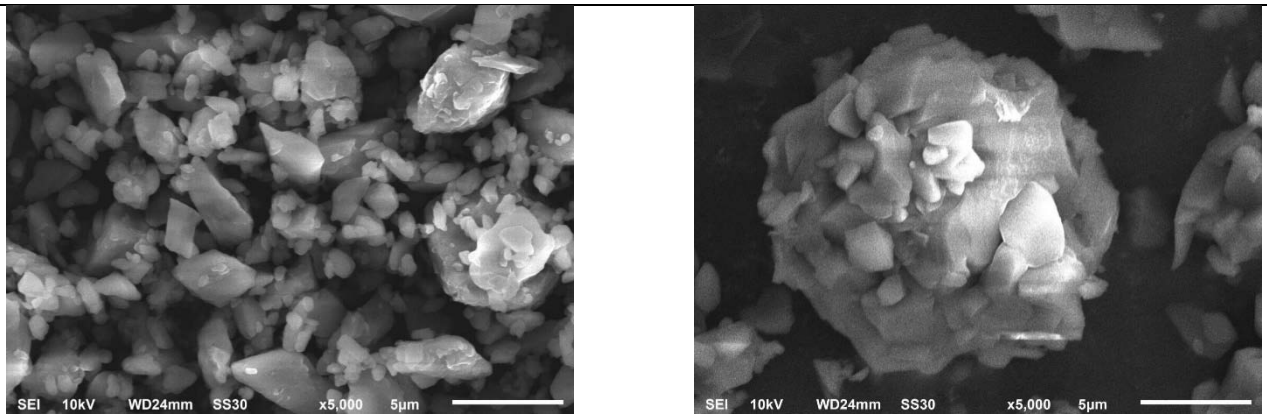


Fig. 3: FTIR Spectrum, (a) standard ketoconazole, (b) ketoconazole spherical crystalline

Fig. 4 shows an SEM image of standard ketoconazole and spherical crystal. SEM (Scanning Electron Microscopy) analysis was performed to observe the surface morphology of a standard ketoconazole solid and ketoconazole spherical crystals. This analysis was also carried out to determine the particle size of the samples.



(a) **(b)**

Fig. 4: SEM Image, (a) standard ketoconazole, (b) ketoconazole spherical crystal

Table 1 compares the micromeritic characteristics of conventional ketoconazole and spherical crystalline ketoconazole. Fig. 5 demonstrates that the spherical crystals of ketoconazole have a major increase in dissolution rate than the regular ketoconazole.

Table 1: Results of evaluation of micromeritic properties

Parameters	Untreated ketoconazole (n=3)	USP powder flow*	Spherical ketoconazole (n=3)	USP powder flow*
Angle of repost	-	no flow	27.34 °±0.64	25-30 (Excellent)
Bulk density	0.34 g/ml±0.006	-	0.35 g/ml±0.003	-
Tap density	0.51 g/ml±0.0069	-	0.42 g/ml±0.002	-
Compressibility index	32.70 %±2.648	32-37 (very poor)	16.84 %±0.879	16-20 (fair)
Hausner ratio	1.49±0.058	1.46-1.59 (very poor)	1.20±0.012	1.19-1.25 (fair)

*United States Pharmacopeial [19]

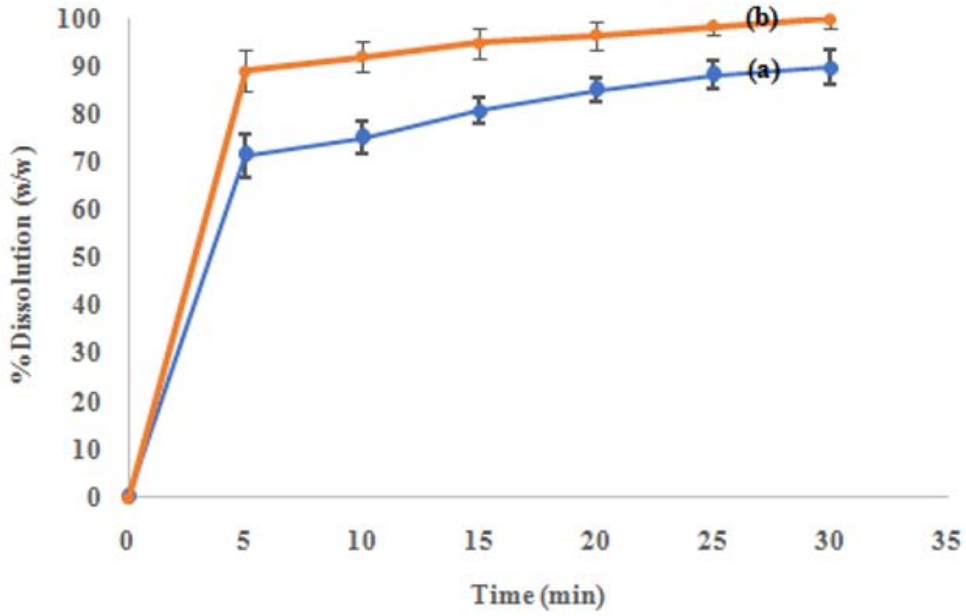


Fig. 5: Dissolution profile of standard ketoconazole (a) and ketoconazole spherical crystals (b). (The results are the mean±SD from three replicates)

DISCUSSION

The technique of making ketoconazole spherical crystals used is the solvent change method. In the process of making spherical crystals, three different solvents are used. The solvent used is ether, which acts as a good solvent; n-hexane as a bridging liquid; and distilled water as a poor solvent. The drug-containing ether dispersion was added directly to the aqueous dispersion, creating quasi-emulsion droplets of the drug solution. The drug then crystallizes from the outer surface of the droplet due to the back-diffusion of the two solvents across the interface of the emulsion droplet. In this investigation, the stirring duration was a crucial parameter since swirling the final mixed dispersion for more than 5 min did not increase in percent yield but also in the disruption of the generated agglomerates. However, 5 min of stirring is required following the addition of the drug to create an agglomerate. When the dispersion becomes a coarse suspension of agglomerates in a transparent continuous phase, essentially, the endpoint of the operation is readily visible.

The parent drug PXRD patterns showed strong peaks that implied crystallinity and no significant change in crystal structure compared with agglomerated. Reduced crystallinity was detected in agglomerated crystals by PXRD analysis, which revealed fewer intensity peaks as compared to those obtained from the pure drug. This might be due to differences in the particle size or crystallinity of the sample. Reports of similar findings have been made by Ravouru *et al.* [1], Maghsoodi *et al.* [14], and Patra *et al.* [2]. This means ketoconazole undergoes no polymorphic alterations during agglomeration.

In the thermogram, clear endothermic peaks were seen at 148.82 °C and 148.29 °C for pure and aggregated ketoconazole and were found in the drug melting point range (150 °C). Since no hydrates, solvates, no polymorphs were formed during the crystallization process, the baselines seen for both thermograms were flat. In the thermograms, there was a negligible difference in the enthalpy of fusion (Hfus) for unagglomerated and agglomerated ketoconazole (-63.91 mcal and-53.13 mcal, respectively), which may be the result of a minor reduction of the crystal lattice. The DSC data has been shown to have reduced crystallinity in agglomerates, which supports the XRPD results. Similar findings were reported by Kedia *et al.* [16] and Garala *et al.* [17].

An FTIR analysis was conducted to investigate molecular diversity in the agglomerated form of ketoconazole. Untreated ketoconazole spectrum exhibited characteristic spectral bands at 1645.28 cm^{-1} (C=O), 1033.85 cm^{-1} (C-O aliphatic ether), and 1247.94 cm^{-1} (C-O aliphatic ether, C-O cyclic ether). The FTIR bands of agglomerated ketoconazole did not exhibit significant shifts or decreases in intensity. Overlapping FTIR spectra of pure and agglomerated ketoconazole revealed no chemical structural change or polymorphism transition.

Based on the SEM results analysis, it can be seen in fig. 4 that the surface morphology of standard ketoconazole at 5000x magnification with a resolution of 5 µm shows an irregular shape. In contrast, the surface morphology of ketoconazole spherical crystals shows a regular and spherical shape. The manufacture of spherical crystals can increase the particle size of the solid, as seen from the analysis where the particle size of ketoconazole spherical crystals is more significant than that of standard ketoconazole.

Evaluation of micromeritic characteristics was conducted to provide information on the size and shape of the particles, size distribution, surface area, and the amount and mass of the particles in the sample [18]. The CI for agglomerates was determined to be less than that of the pure substance. This could be the result of agglomeration. Fine particles with high surface-to-mass ratios are more cohesive than coarse particles and, as a result, are more susceptible to gravitational force. Similar findings were obtained by Lamei *et al.* [20]. Regarding the suitability of agglomerates for direct tableting when CI values were low. The samples flow the angle of repose represented qualities. The angle of repose of the agglomerates was determined to be less than that of pure ketoconazole. Similar findings were obtained by Indra *et al.* [7] and Maghsoodi *et al.* [14]. This decreased value implies an improvement in flowability, i.e., the free flow of powder mass compared to pure drug. It was discovered that their flowability was enhanced when the powder formed agglomerates. Compared to pure ketoconazole, which has a feeble flow, the values of compressibility and angle of repose indicate that agglomerates have superior and good flow, respectively.

The dissolution test measures the amount of active ingredient dissolved in a known volume of the liquid medium at a specific time [21]. The dissolution test used a dissolution media containing 0.1 N hydrochloric acid. The absorbance was determined using UV-Vis spectrophotometry at a wavelength of 268.5 nm, and samples were collected every 5 min for 30 min.

In fig. 5, it can be observed that the % dissolution of conventional ketoconazole dissolution after 5 min was 71.92%, while the percentage of spherical ketoconazole crystals was 89.20%. The

increase in dissolution was maintained until the 30th min. The reason for the faster dissolution may be due to the excellent wettability of the agglomerates. Thus, it was quickly dissolved in the dissolution fluid, as reported by Ravouru *et al.* [1] and Maghsoodi *et al.* [9]. Based on this, it may be concluded that spherical crystals of ketoconazole can generate a superior dissolution profile than regular ketoconazole.

CONCLUSION

The solid characterization analysis using PXRD, DSC, and FTIR spectrophotometry instruments showed no internal change in the crystal structure between standard ketoconazole and spherical crystals. While the surface morphology examination using SEM showed a difference in the shape of the crystal to be more spherical, and the particle size enlarged in ketoconazole. The micromeritic evaluation showed that ketoconazole spherical crystals had better micromeritic properties than standard ketoconazole. The dissolution test results showed an increase in the dissolution rate of ketoconazole spherical crystals compared to standard ketoconazole. Thus, spherical crystals of ketoconazole appear to be a feasible technique for improving dissolution characteristics and, thus, bioavailability.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors have stated no conflict of interest.

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