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Exploration of crystal simulation potential by fluconazole isomorphism and its application in improvement of pharmaceutical properties

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ABSTRACT

Control of crystal morphology during crystallization is a paramount challenge in pharmaceutical processing. Hence, there is need to introduce computational methods for morphology prediction to manage production cost of drugs and improve related pharmaceutical and biopharmaceutical properties. Layer docking approach with molecular dynamics opens a new avenue for crystal habit prediction in presence of solvent. In the present study, attempts were made to correlate predicted and experimental crystal habits of fluconazole considering solvent interactions using layer docking approach. Simulated results from layer docking approach with methanol as solvent gave two dominant facets (0 1 1) and (1 0 1) with a surface area 22.43% and 19.82% respectively, which were in agreement with the experimental results. Experimentally grown modified crystal habit of fluconazole in methanol showed enhanced dissolution rate ($p < 0.05$) when compared to plain drug. This was attributed to the increased surface area on the specified facets caused by interactions with the solvent. Furthermore, Differential Scanning Calorimetry, Fourier Transform Infrared (FTIR) Spectroscopy and powder X-ray Diffraction of recrystallized samples confirmed only a habit change and absence of any polymorphs, hydrates or solvates. Flow and compressibility of fluconazole recrystallized in methanol was significantly improved when compared to plain drug. This study demonstrates a methodical approach using computational tools for prediction and modification of crystal habit, to enhance dissolution of poorly soluble drugs, for future pharmaceutical applications.

1. Introduction

Different crystal forms of drug possess different planes and thus differ not only in their specific surface, but also in their surface free energy thereby leading to differences in their physicochemical properties [1]. Variation in the solid-state properties of the crystallized material is of practical relevance in many industrial processes since, it affects solid–liquid separation characteristics, packaging, handling, drying, storage behavior and end-use properties of the crystallized material [2,3]. Similarly, use of different solvents and crystallization conditions may alter the polymorphic state and habit [4]. External morphology of a crystal is called the crystal habit or isomorphism. Crystal habit or isomorphs may or may not be altered with polymorphic transformation [5]. Iso-diametric (equant/cubic), plate, tabular, columnar, blade and acicular (needle) are some of the commonly found habits for pharmaceuticals. Iso-diametric crystal habit exhibits good flow and compressibility properties than other habits and hence is generally preferred for processing and manufacturing of solid dosage forms [5,6]. In many reported studies, crystal engineering strategies have been used to generate crystals of desired architecture with some degree of success [7,8]. In recent times, technological advancement in computational methodology has hastened research areas related to crystal engineering to design crystals of desired morphology [9].

BFDH (Bravais–Friedel–Donnay–Harker), growth morphology [10] and equilibrium morphology models are generally used to predict crystal morphology, however, the results obtained from these models are often not in full agreement with the experimental results [11] as these models do not consider the impact of solvents during crystallization process [12–14]. Schmidt and Ulrich used layer docking method to predict crystal habit in presence of solvent, and reported good agreement with experimental habit [15]. Tedesco et al., used a qualitative method to determine how solvents interact with different faces of crystal and modify the habit [16,17]. Molecular dynamics is a powerful tool to investigate the effect of solvent on crystal morphology based on the current findings of some authors who have reported successful crystal prediction for drugs, explosives and photoactive micro-crystals like alpha cyclodextrin hexahydrate [18], HMX [13], RDX [19], ginsenoside [20] and hydrocortisone methanol solvate [21].

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Fluconazole, a triazole anti-fungal drug is primarily indicated for candidiasis and cryptococcal meningitis [22]. It has poor dissolution rate owing to its limited solubility in water. Various formulation approaches to improve the dissolution rate of fluconazole includes solid dispersions [23] and microspheres [24]. Of all the methods, crystal habit modification is considered as a most simple, viable and economic option to improve the dissolution rate. Hence, due to its poor physico-chemical properties, fluconazole was selected as a model drug. The objective of the present study was to carry out simulation using layer docking approach and select an isometric crystal habit based on aspect ratio of simulated crystals for further crystallization studies. This approach saves time by reducing laboratory experiments and cost of crystallization of new products. In the reported study, molecular dynamics simulations on fluconazole were carried out with acetone, ethyl acetate and methanol to know the interactions between solvent and crystal faces. The solvent with aspect ratio close to one, i.e., methanol was chosen for experimental crystallization. The laboratory generated crystals were evaluated for various physico-chemical properties and compared with the plain drug.

2. Experimental methodology

2.1. Materials

Fluconazole was received as a gift sample from Chandra Life Sciences Pvt. Ltd. (Hyderabad, India). Acetone, methanol and ethyl acetate were purchased from SD Fine chemicals Ltd (Hyderabad, India). In-house ultrapure water from Millipore was used for all the experiments. All other chemicals used were of analytical grade.

2.2. Solubility studies

Solvents were selected in increasing order of polarity and dielectric constants. Preliminary trials were carried out to determine the solubility of drug in different solvents (supplementary Table 1). Fluconazole (50 mg) was taken in different screw capped glass vials and the selected solvents; dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), acetone, ethyl acetate (EA), methanol, chloroform, dichloromethane (DCM), isopropyl alcohol (IPA), petroleum ether and n-hexane were added in 0.1–0.5 mL increments. After each addition of the solvent, the mixture was vortexed for 5 min and visually checked for any undissolved parts of the sample. The total volume added to obtain a visually clear solution was noted as the saturation point [25]. The experiment was carried in triplicate to confirm the reproducibility of results.

2.3. Computer simulation details and theory

Crystal structure of Fluconazole anhydrate (IVUQOF) was taken from CSD (Cambridge Structural Database) as this is the only form used in pharmaceutical industry as reported by Caira et al. [26]. Crystal dimensions were defined in terms of length, height, and width as a, b, and c and angles between them as α, β, and γ. Fluconazole, triclinic P-1 crystal containing 2 molecules per unit cell with cell parameters as follows: a 7.4992 Å, b 7.7869 Å, c 11.9817 Å, α 84.947°, β 84.625°, and γ 75.894° (Fig. 1). All molecular dynamics and morphology predictions were performed using COMPASS (condensed phase optimized molecular potentials for atomistic simulation studies) force field. Geometry optimization was done by forcite algorithm with COMPASS force field. The general procedure for molecular dynamics was based on the literature available so far [27]. Material studio software package was used to run the calculations (Materials Studio 6.1., Accelrys Inc., San Diego, CA).

2.3.1. Methods for crystal morphology prediction in vacuum

Selection of appropriate force field and description of charge set is very essential in modeling of morphology. Initially, three models were used to predict crystal morphology in vacuum. First, BFDH model was used to list possible growth faces and their growth rates regardless of its low accuracy [20]. Second, attachment energy or growth morphology model was used to calculate attachment energy with the faces obtained from BFDH model [10]. Third, equilibrium morphology model was used to determine surface energies for all relevant crystal faces at absolute zero (or 0 K) temperature [28].

2.3.2. Crystal habit prediction with effect of solvent

Layer docking approach scrutinizes the effect of additives on the individual crystal faces, which are cleaved from a pure crystal. If the additive has inadequate interaction on specific face, then the growth rate of that face will be higher. This eventually results in smaller surface area or total disappearance of this face when compared to other faces [29–31]. From the crystallographic information file, initially, the unit cell was constructed and optimized. Smart minimizer was used to perform minimization on the unit cell. Crystal habit in vacuum was predicted by attachment energy model which gave information containing multiplicities, interplanar distances, facet areas and attachment energy. These morphologically important faces lattice parameters were used for amorphous cell construction and cleaved parallel to the ($h\,k\,l$) plane at a depth of four unit cell. Crystal structure layer was constructed as a periodic superstructure of 3×2 unit cells. Next, the crystal structure layer was optimized by molecular mechanics and dynamics [13]. Methanol, acetone and ethyl acetate with dielectric constant of 33, 20.7, 6.02 and density of 0.791, 0.791, 0.897 g/mL respectively were chosen as solvents for this simulation study. Subsequently, amorphous tool was used to construct solvent layer containing 300 methanol molecules by using lattice parameters of the faces obtained from attachment energy model. Amorphous cell was minimized by smart minimizer using Newton method at 10,000 iterations at medium quality. In the next step, NVE (N=constant number of particles, V=constant volume, E=constant energy), NPT (P=constant pressure, T=constant temperature) were performed for equilibration. This solvent layer was adsorbed onto the crystal surface layer with vacuum slab of 50 A° above the solvent layer to eliminate the effect of free boundaries. Constraints were fixed for crystal structure layer and were not allowed to relax during simulation, while solvent molecules were allowed to move. Molecular dynamic simulation was performed using Nose algorithm, and Andersen as temperature control method [32].

Energy minimization was carried out for the interfacial layer. In the next step, molecular dynamic simulation was carried out using NVT ensemble for 10 ps at a time step of 1 fs. Again, the layer was minimized and the potential energy (E_{total}) was obtained as a sum of crystal structure layer and solvent layer. Energy of the crystal structure layer and solvent layer was denoted as E_{surface} and $E_{\text{amorphous}}$, respectively. Similarly, simulations were also performed using 50 acetone and 190 ethyl acetate molecules separately. For the equilibration stage, the time step for the molecular dynamics simulation was 1 fs with a period of 60 ps. The Columbic and Vander Waals interactions were calculated by employing the standard Ewald summation [33]. After equilibration stage, production stage was performed. Modified attachment energy was then calculated by the formula which was used to correct the vacuum