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Can vacuum morphologies predict solubility and intrinsic dissolution rate? A case study with felodipine polymorph form IV

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ABSTRACT

The impact of felodipine (Fel) polymorphism on vacuum morphology was studied and correlated with the structural properties like solubility and intrinsic dissolution rate (IDR). A correlation was established between solubility and IDR of three Fel polymorphs with their BFDH aspect ratio, growth morphology aspect ratio and polar/non polar ratio. The predicted solubility and IDR values for form IV by three methods were in agreement, however, morphology growth aspect ratio model showed better prediction capability due to its higher coefficient of determination. The solubility for form IV was 0.0154 mol l^{-1} while the IDR was 0.246 mg min^{-1} cm^{-2} for growth morphology aspect ratio.

1. Introduction

Different polymorphs of any given API (active pharmaceutical ingredient) can have different physicochemical properties, such as melting point, solubility, dissolution rate, and oral bioavailability; which in turn may affect their adequacy in drug formulations [1,2]. Prediction of crystal structures on the basis of molecular information [3–5] and use of a variety of theoretical methods to generate possible crystal structures [6] has thus resulted in increased interest of pharmaceutical industries toward the crystal morphology prediction. This may be due to the fact that crystal habits, especially the preferred equi-dimensional habit, tend to show considerable impact on the pharmaceutical and biopharmaceutical properties of API [7,8].

Queries on growth mechanism and growth rate of crystals and simultaneous research work related to different crystal morphologies in various environments are increasing day by day. A detailed information on the growth mechanism of crystals usually aids in controlling purity, cost of manufacture and end-use [9,10]. Crystal habit simulations have advanced to a state where habit prediction for drug molecules is relatively straightforward [11]. With the help of molecular simulation tools, the crystal habit prediction along with solvent and additive interactions has become feasible [11,12]. Bravais-Friedel-Donnay-Harker (BFDH), morphology growth (MG) and equilibrium morphology (EM) models are widely employed for comparing the morphologies [13–16].

In order to determine the surface chemistry of a specific crystal facet, information on crystal structure and the miller indices of that particular crystal face is required [17–19]. Thus, in an effort to demonstrate the computational efficiency for optimizing the crystal morphology, various reported morphology models were analyzed for different polymorphs of a single drug molecule, felodipine (Fel). Fel is a calcium channel inhibitor, which is widely recommended for treatment of hypertension and prevention of angina pectoris. Fel belongs to class II of BCS (biopharmaceutical classification system) scheme and is practically insoluble in aqueous medium [20]. The structure, pharmaceutical and biopharmaceutical profiles of three polymorphs of Fel (forms I–III) are established and reported in literature [2]. The crystal structure of Fel form I (marketed product) is well described and is reported to be the most stable form by R. Fossheim [21]. Form II was first discussed by Srcic et al., in 1992 [22] and its structure was reported by Lou and velaga in 2009 [23]. Surov et al., 2012 have reported form III and IV along with their crystal structures. Additionally, Surov et al., have also reported the solubility and IDR (Intrinsic dissolution rate) for forms I–III but were unable to calculate the solubility and IDR of form IV due to limited amount of crystals available [2]. Hence, the study was further extended to predict important pharmaceutical properties like solubility and IDR for form IV. Aspect ratio of crystal habit and distribution of functional groups exposed to the most relevant crystal faces was calculated from vacuum

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morphology models for three polymorphs of Fel and a correlation was established between surface structural parameters and their solubility/IDR. On basis of these correlations, the solubility and IDR of form IV was predicted.

2. Methods for computer simulation

Crystal structures of Fel polymorphs were obtained from CSD (Cambridge Structural Database). Crystal dimensions were defined in terms of length, height, width as a, b, c and angles between them as α, β and γ, respectively. Fel form I crystallographic information file (DONTIJ) was reported by R. Fossheim [21] with the following cell parameters: symmetry: monoclinic $P2_1/c$, a: 12.086 Å, b: 12.077 Å, c: 13.425 Å, α: 90, β: 116.13, γ: 90. Fel form II crystallographic information file (DONTIJ01) was reported by Lou and velaga in 2009 [23] with the following cell parameters: symmetry: monoclinic C2/c, a: 32.392 Å, b: 18.717 Å, c: 23.771 Å, α: 90, β: 91, γ: 90. Fel form III crystallographic information file (864026) was reported by Surov et al., in 2012 [2] with the following cell parameters: symmetry: monoclinic $P2_1/n$, a: 15.1255 Å, b: 7.2302 Å, c: 17.2796 Å, α: 90, β: 110.198, γ: 90., Fel form IV crystallographic information file (864027) was also reported by Surov et al., in 2012 [2] with the following cell parameters: symmetry: monoclinic $P2_1/n$, a: 11.1129 Å, b: 12.5688 Å, c: 13.4969 Å, α: 90, β: 107.009, γ: 90. The crystal morphology modeling procedure was developed on basis of the reported literature [24]. Prediction and study of possible crystal morphologies was performed using a preliminary equilibration protocol, by means of the Morphology package included in the Material Studio 6.1 package of Accelrys, adopting the molecular mechanics approximation and the COMPASS (condensed phase optimized molecular potentials for atomistic simulation studies) force field. Geometry optimization was done with forcite algorithm with COMPASS force field. Face list was generated using morphology calculation which gave *hkl* values of important faces with d_{hkl} (center to plane distance) values.

The morphology prediction tools consist of three different computational approaches: BFDH, MG, and EM methods. The first vacuum model used was BFDH, which generated a list of possible growth faces [19]. The second vacuum morphology model used was the attachment energy also known as MG method. The MG method assumes that the growth rate of a crystal face is proportional to its attachment energy, i.e., faces with the lowest attachment energies are the slowest growing and, therefore, have the morphological importance [25–27]. The third prediction model for vacuum morphology used was surface free energy model, which is also known as EM method. The surface energy at a temperature of 0 K, was calculated by EM model [25]. In this study, the reported solubility and IDR of polymorphs were correlated with their various structure and morphology related factors like aspect ratio, polar/non-polar, surface/volume (S/V) ratio, attachment energy and surface energy. Simple linear regression equations were obtained using three reported polymorphs data. From the obtained equations, values were plugged in to estimate the solubility and IDR of Fel polymorph IV.

Hirshfeld surface analysis of intermolecular interactions for each polymorph was performed using Crystal Explorer (Version 3.0). This alternative way was employed to assess the differences among polymorphs, by comparing the intermolecular interactions a molecule makes with its neighbors. Felodipine polymorphs were comparing taking into account the molecular conformation differences among the polymorphs, and the absence of strong hydrogen bonding that limits the utility of topological descriptions [28]. The Hirshfeld surface defines each independent molecule's environment within a crystal. This information was used to describe the dissolution potential of a particular crystal structure.

3. Results and discussions

3.1. Form I

Crystal structure of Fel form I is shown in Fig 1a. Vacuum morphology of form I was generated by BFDH model (Fig. 1b), which gave 6 important facets along with their planes (*hkl*), center to plane distance (d_{hkl}) and % surface area. The BFDH method is an approximation and does not account for the any kind of energetics of the system [25]. The accuracy of method reduces inversely with the bonding strength of system [26]. Thus, the only benefit of this method was to identify important faces in the growth process [26,29]. Table 1 lists the inter-planar spacings of various low index faces of the crystal habit of form I based on the BFDH calculation.

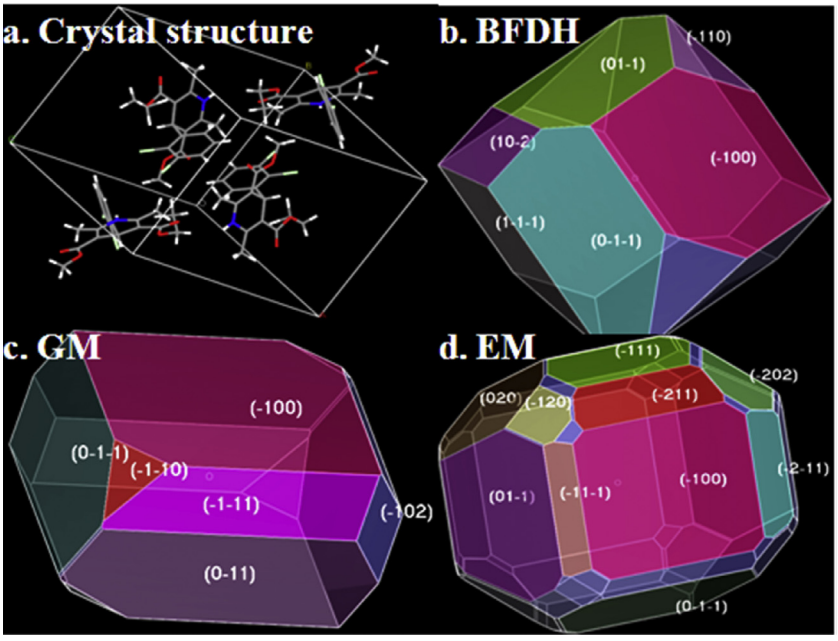

Fig. 1. Vacuum morphology of Polymorph I (a) crystal structure, (b) BFDH, (c) morphology growth and (d) equilibrium morphology.