RESEARCH ARTICLE

Rational Coformer or Solvent Selection for Pharmaceutical Cocrystallization or Desolvation

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Received 29 February 2012; revised 2 May 2012; accepted 16 May 2012

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23227

ABSTRACT: It is demonstrated that the fluid-phase thermodynamics theory conductor-like screening model for real solvents (COSMO-RS) as implemented in the COSMO*therm* software can be used for accurate and efficient screening of coformers for active pharmaceutical ingredient (API) cocrystallization. The excess enthalpy, H_{ex}, between an API–coformer mixture relative to the pure components reflects the tendency of those two compounds to cocrystallize. Thus, predictive calculations may be performed with decent effort on a large set of molecular data in order to identify potentially new cocrystal systems. In addition, it is demonstrated that COSMO-RS theory allows reasonable ranking of coformers for API solubility improvement. As a result, experiments may be focused on those coformers, which have an increased probability of cocrystallization, leading to the largest improvement of the API solubility. In a similar way as potential coformers are identified for cocrystallization, solvents that do not tend to form solvates may be determined based on the highest H_{ex}s with the API. The approach was successfully tested on tyrosine kinase inhibitor axitinib, which has a propensity to form relatively stable solvated structures with the majority of common solvents, as well as on thiophanate-methyl and thiophanate-ethyl benzimidazole fungicides, which form channel solvates. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: cocrystals; solvates; desolvation; crystallization; *in silico* modeling; crystal engineering; solubility; COSMO-RS; excess enthalpy

INTRODUCTION

Cocrystals can be defined as homogeneous solid phases containing two or more neutral compounds in a crystal lattice with defined stoichiometry, which are solids in their pure form at ambient conditions.[1] The transformation of active pharmaceutical ingredients (APIs) from their pure crystalline form into cocrystals has experienced increasing interest recently. A cocrystal of the API and an additional compound may show modified properties (such as solubility, dissolution rate, and physical and chemical stability) as compared with the pure compounds.[2,3] The possibility to improve the bioavailability[4,5] of the API and to create patentable intellectual property[6,7] constitutes a new and highly attractive route for drug development.

Various experimental methodologies are currently employed for cocrystallization including grinding,[8,9] crystallization from melt,[10] traditional solution crystallization approaches, such as solvent evaporation,[11] cooling, or antisolvent addition, and slurry crystallization.[12] These experimental techniques are typically time consuming and expensive. Therefore, the ability to predict the propensity of different coformers to form a cocrystal with the given API is important.

From general consideration, a likelihood of cocrystal formation is related to the miscibility of API and coformer in the solid state. For a crystalline material, miscibility should be defined by the cocrystal lattice energy. In fact, it was demonstrated previously

Additional Supporting Information may be found in the online version of this article. Supporting Information

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Journal of Pharmaceutical Sciences

that rationalization of cocrystal formation in certain cases may be achieved by crystal structure prediction techniques.[13–16] However, these methods are time consuming and cannot be applied for virtual coformer screening. The effectiveness of the current crystal structure prediction methods quickly decreases with an increase in system complexity (number of molecules in the asymmetric unit and their conformational flexibility). Therefore, the majority of the current computational approaches to virtual coformer screening neglect stabilizing long-order packing contributions to the coformers miscibility.

In practice, rationalization of cocrystal formation is typically based on consideration of only dominant contributions to the miscibility. Intermolecular hydrogen (H)-bonding interaction is the most common focus because of its high strength and directionality. For example, the rational design of cocrystallization is typically performed by a crystal engineering approach, which is based on a hierarchy of H-bonded supramolecular synthons.[17–19] A theoretical model was recently proposed for virtual screening based on H-bonding propensities of cocrystal formers derived from molecular electrostatic potential surface calculations.[20] Alternatively, statistical analysis of Cambridge Structural Database (CSD)[21] was performed and a model of molecular complementary in cocrystals was suggested for virtual coformer screening, which was based predominantly on shape and polarity of cocrystal formers.[22] H-bond donor and acceptor counts showed no obvious statistical relationship. A potential drawback of the model is that it was trained on cocrystal observations in the CSD database, ignoring potential failures in realistic cocrystal screenings. Babu et al.[23] have calculated H-bond energies of amide and N-oxide synthons at the HF/6-31G* level in order to compute cocrystal formation. In addition, Hansen solubility parameters were recently applied to describe miscibility of API and coformer to predict cocrystal formation to guide cocrystal screening.[24]

In the current study, we demonstrate how conductor-like screening model for real solvents (COSMO-RS)[25] fluid-phase thermodynamics computations describing miscibility of cocrystal formers in a supercooled liquid (melt) phase can be applied to virtual coformer screening. It is assumed that the supercooled liquid phase mimics the cocrystal solid state, neglecting long-order packing contributions (an amorphous solid state). An extensive testing of the approach on multiple experimental screening observations, including pharmaceutical APIs paracetamol, bicalutamide, itraconazole, nicotinamide, meloxicam, carbamazepine, and indomethacine, is reported. Concerning the predictivity of the approach, it should be taken into account that a negative experimental result of cocrystallization of an API with a coformer does not completely exclude the possibility that such cocrystal exists. There are many reasons why it just may not have been observed in the specific experimental setup.

In a similar way as potential coformers are identified, solvents that do not tend to form solid solvates (sometimes called pseudopolymorphs) with the API may be found by COSMO-RS fluid-phase thermodynamics computations. The main difference between solvates and cocrystals is the physical state of the isolated pure components: if one component is a liquid at room temperature, the crystals are designated as solvates. Although cocrystal formulation can bring advantages by increasing dissolution rate and bioavailability of the API, solvate formation is typically undesirable. Solvates might be subsequently desolvated in a final drying step of the formulation process. In such a situation, the final polymorph could be metastable and undergo solid–solid transition during its shelf life. In addition, residual solvent levels in the API must be compatible with International Conference on Harmonisation guidelines (http://www.ich.org) in case of incomplete desolvation. Therefore, selection of the solvent system for crystallization which has the lowest probability of forming solvates with the API is important. Such solvent systems in general may be used directly for slurry crystallization of the stable form or for desolvation of the solvated forms by reslurry experiments to facilitate solvent-mediated transformation and conversion to a stable anhydrous nonsolvated form.

In the current study, we demonstrated how fluid-phase thermodynamics calculations allow selecting solvents, which do not form solvates with a tyrosine kinase inhibitor axitinib (trade name Inlyta), and with fungicides thiophanate-methyl (TM) and thiophanate-ethyl (TE).

Previously, such an idea was suggested[26] but never attempted for the solvent selection using the Fábián[22] model.

APPROACH AND METHODS

Approach

COSMO-RS (COnductor-like Screening MOdel for Real Solvents) is a universal theory to predict the thermodynamic equilibrium properties of liquids, which was originally developed by Andreas Klamt.[25,27] COSMO-RS thermodynamics is based on the statistical physics of interacting molecular surface segments. The polar and H-bond interaction energies are quantified based on the surface screening charge densities, which result from a quantum chemical continuum solvation calculation. Because of its ability to treat mixtures at variable temperatures and to compute accurate solvation energies based on first