CIRCE
Crystal Engineering

Virtual Polymorph Screening

Introduction

Active Pharmaceutical Ingredients (API) are nowadays mass-produced in the solid state in a variety of crystalline forms, or when this is not possible, as amorphous solids (1). In their crystalline form, their constituent atoms and molecules are arranged in long-range ordered structures along all spatial directions, while amorphous solids lack of such long-range order. Furthermore, different stoichiometric compositions are possible in crystals of API, Figure 1: pure compounds, co-crystals, solvates (hydrates) and salts. Making things even more complex, crystals of any of these stoichiometric compositions can be obtained with more than one long-range order. Each of them is one of the crystal polymorphs for such stoichiometric composition.

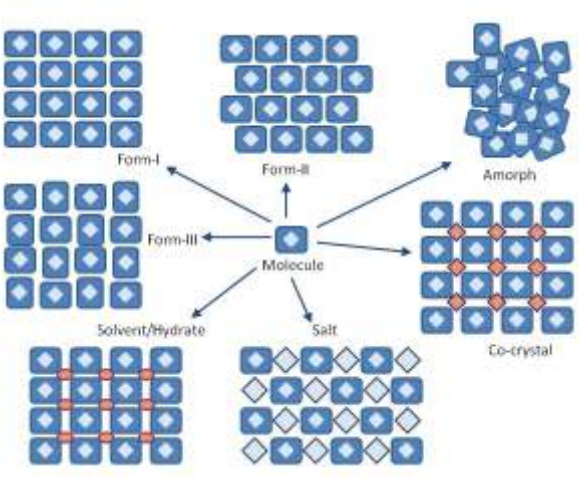

Figure 1. Structure of the different solid states.

At any given pressure and temperature, the most stable polymorph is the thermodynamically preferred one and all others (called metastable) should spontaneously convert into it. However, in some cases, some metastable polymorphs can be kinetically stable, (2) that is, the barrier towards the conversion into the thermodynamic most stable form is too high to be overcomed. In the later case, the metastable and the most stable forms can coexist, or even become the preferred crystalline form at the experimental crystallization conditions. Different polymorphs of the same crystalline composition sometimes present different physicochemical properties (solubility, dissolution rates, hygroscopicity, physical and chemical stability...), fact that can also affect their mechanical properties and bioavailability. This makes the discovery of new polymorphs a key topic in drug research and development. An early identification of the most appropriate polymorph and crystalline form of an API is fundamental in the development of a new drug candidate (1). Usually, the most important factor in such a quest is the solid solubility and bioavailability. Commonly, the thermodynamically most stable form is desired, as this guarantees the solid long-term stability. However, since metastable polymorphs show a better solubility profile (5) than the thermodynamically most stable polymorph, they can be better candidates, if they are kinetically stable. This fact, prompted the development of crystal-screening processes specifically aimed at obtaining metastable polymorphs that are kinetically-stable, see Table 1. A few of the most relevant are crystallization through solvent evaporations, anti-solvent crystallization, slow and fast cooling of saturated API solutions to induce precipitation, and slurrying of solid API for extended periods of time. These screenings require varying the solvent, temperature, and even pressure conditions. Consequently, exploring the existence of metastable polymorphs presenting improved physical properties and long-term stability are time-consuming studies (1).

Polymorph prediction methods can help to find proper candidates for kinetically-stable API polymorphs presenting the desired physi-

cal properties. As assessed in the so called "Blind Tests" carried out every two years by the Cambridge Crystallographic Data Centre, polymorph prediction methods have become a reliable tool to predict the most stable polymorph and the most stable of the metastable polymorphs with a reasonable accuracy (< 50% of success). The polymorph prediction methods that CIRCE uses in its predictions matches or improves that ratio of success, because it uses a new generation of intermolecular potentials, that does not use atom-atom potentials. Such method is known to properly reproduce the energy of a wide variety of molecular solids, their optimum geometry, and the energy landscape (relative stability of their metastable polymorphs) of various molecular crystals.

Composition type		Process variables[a]				
Polymorph/ solvates	Salts/ co-crystals	Thermal	Anti-solvent	Evaporation	Slurry conversion	Other variables
▪ Solvent/ solvent combinations	▪ Counter-ion type	▪ Heating rate	▪ Anti-solvent type	▪ Rate of evaporation	▪ Solvent type	▪ Mixing rate
▪ Degree of supersaturation	▪ Acid/base ratio	▪ Cooling rate	▪ Rate of anti-solvent addition	▪ Evaporation time	▪ Incubation temperature	▪ Impeller design
▪ Additive type	▪ Solvent/ solvent combinations	▪ Maximum temperature	▪ Temperature of anti-solvent addition	▪ Carrier gas	▪ Incubation time	▪ Crystallization vessel design (including capillaries, etc.)
▪ Additive concentration	▪ Degree of super-saturation ▪ Additive type and concentration ▪ pH ▪ Ionic strength	▪ Incubation temperature(s) ▪ Incubation time	▪ Time of anti-solvent addition	▪ Surface-volume ratio	▪ Thermal cycling and gradients	

[a] Applicable to all types of screens.

Table 1. Processing variables in screening studies, as a function of the type of polymorph being sampled (1).

Our approach to polymorph prediction

Most strategies nowadays employed in polymorph prediction are based on intermolecular atom-atom potentials where the crystal lattice energy (i.e. ΔH, whose experimental equivalent is the crystal formation enthalpy) is minimized. These approaches assume that the TΔS entropic contribution is not a structure-determining factor. Sometimes, these polymorph predictions are also carried out on crystals of similar molecules, in order to perform statistical studies that pinpoint similarities in their crystal structures.

Recently, the ΔH energy minimization techniques have been employed with GRACE potentials (6, 7), where the intermolecular energies are computed at the DFT (Density Functional Theory) level and used to fit analytical expressions. GRACE potentials obtained for a specific molecule are not extensible to other molecules. Although GRACE potentials properly reproduce the crystal structure of many crystals, they still fail in many salts and co-crystals. Furthermore, they are computationally very demanding.

Our polymorph prediction method, also a ΔH energy minimization technique, employs intermolecular energies computed using the semi-classical Pixel intermolecular potential (8-10). Such approach rigorously rooted in second-order expressions of the intermolecular interaction energy, describes the

interaction energy between two molecules as the sum of the exchange-repulsion, electrostatic induction, charge transfer and dispersion components. We have used this approach in a parallel computer code (PIXCRYPAR) that can predict the structure and energy of any molecular crystal, using as only starting point the geometry of the molecule. From such geometry, the electron density of the molecule, needed to evaluate the intermolecular potential in a fast and unbiased way, is computed. The most stable polymorphs are then computed for the most common crystalline groups.

Validation: Theoretical study of the Aspirin polymorphism

The quality of the PIXCRYPAR predictions can be demonstrated in the aspirin polymorph prediction, representative of the quality expected for APIs PIXCRYPAR polymorph predictions.

Acetylsalicylic acid, commonly called aspirin, was thought to have only one crystalline form, called form-I. In 2005, Zaworotko et al. (11) reported the existence of a new form of this compound, form-II, indicating that the new crystals were in good agreement with previous theoretical polymorph predictions, where the possible existence of a more stable polymorph of aspirin was suggested. However, Desiraju and Boese demonstrated in later works (12) that the form-II is not a conventional polymorph, but has mixed domains of the old form-I and the new form-II. Experimentally, form-II was shown to be almost isoenergetic with form-I, share the same space group, and have similar unit cell parameters to form-I. The later two authors also pointed out serious doubts about the patentability of form-II as an independent polymorph.

Using the Pixel potentials and PIXCRYPAR, the polymorphism prediction of aspirin was done for some of the most common crystallographic groups. The results obtained are presented in Figure 2 as an energy landscape map. The map indicates the presence of two structures with a similar energy to those obtained experimentally for form-I and form-II. An analysis of the theoretical structures concluded that the most stable predicted structure in Figure 2 is form-II. The good quality of the crystal predicted structure for form-II is visually demonstrated in Figure 3 (right). It can be numerically corroborated by

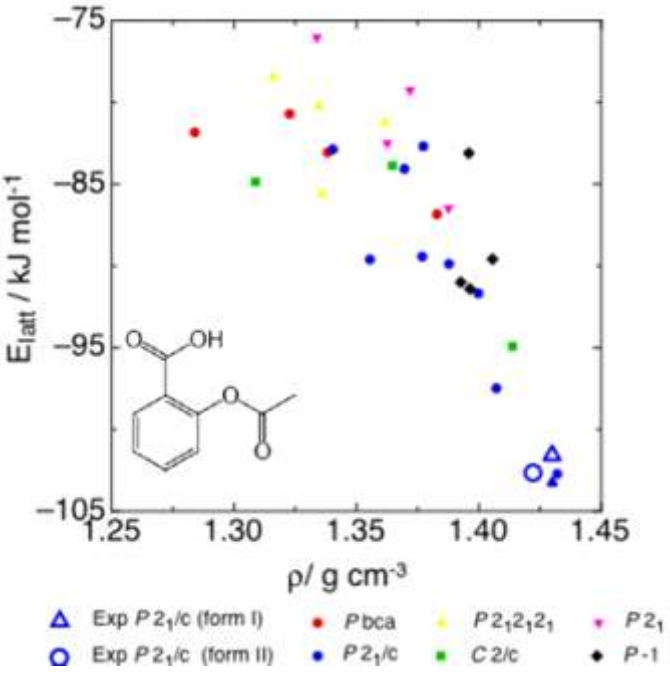

Figure 2. Energy-density distribution of all crystalline forms calculated in the pixel studies for aspirin. The two experimental polymorphs have also been included for comparison. Values for PIXCRYPAR structures form-I and form-II correspond to the points marked with a filled blue triangle and circle, respectively, and located close to the experimental form-I and form-II points (empty blue triangle and circle, respectively).

calculating the root-mean-square between the computed and experimental structures for a cluster of 15 molecules (RMSD15: the experimental and computed structures of form-II have a RMSD15 of only 0.112 Å). On top of this, form-I of aspirin also appears in the PIXCRYPAR calculation, with slightly lower energy and a density slightly higher than the form-II. Figure 3 (left) illustrates the good agreements between the predicted and experimental structures of form-I, which can be further numerically confirmed by calculating

the RMSD15 between the computed and experimental structures: 0.081 Å. However, as shown in Figure 4, form-I and form-II are different polymorphs. While the top two layers (linked by OH···O interactions that form a R22 supramolecular synthon) are identical, in the third layer (bonded to the second layer by CH···O interactions that also form a R22 supramolecular synthon) the relative orientation of the molecules varies between polymorphs. The ability to evaluate polymorphs that differ in such small difference demonstrates the performance of the PIRCRYPAR polymorph prediction program.

In special problems, we also have the software and hardware facilities that allow us to use the results of PIXCRYPAR studies as starting point on ΔH geometry optimizations using DFT and DFT+ (dispersion corrections) energies. The unit cell can also be fully optimized, when needed. On top of this, we can also perform Ab-initio Molecular Dynamic (AIMD) studies of crystals of special interest, where its properties are evaluated in the ΔG(T) potential energy surface. We have used the later two methodologies to study the kinetic stability of concomitant polymorphs and in the study of the parameters that define the dynamics of their phase transformation.

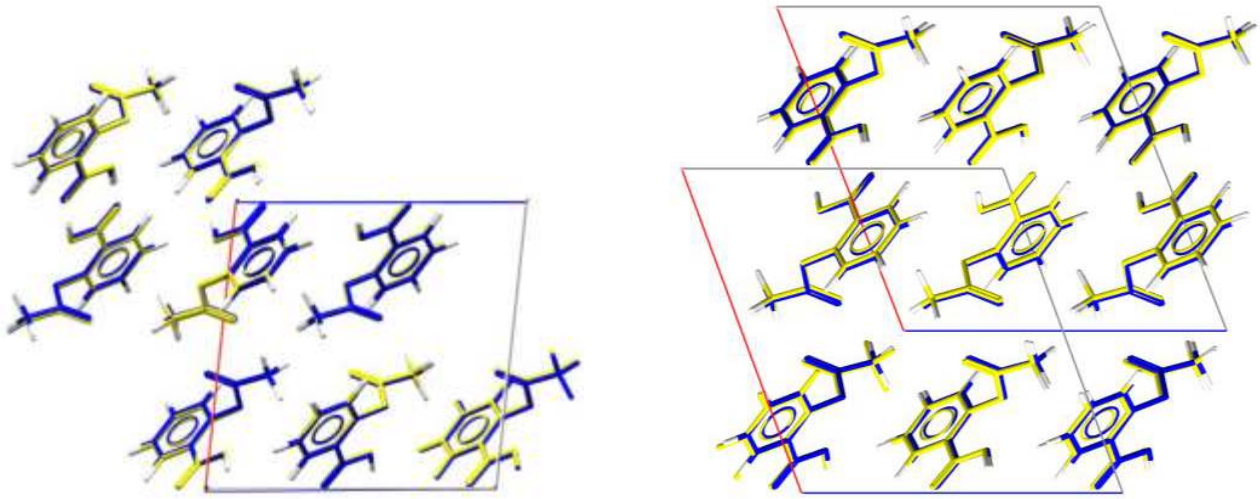

Figure 3. Superposition of the structure predicted by the experimental program PIXCRYPAR and aspirin: (left) form-I, (right) form-II.

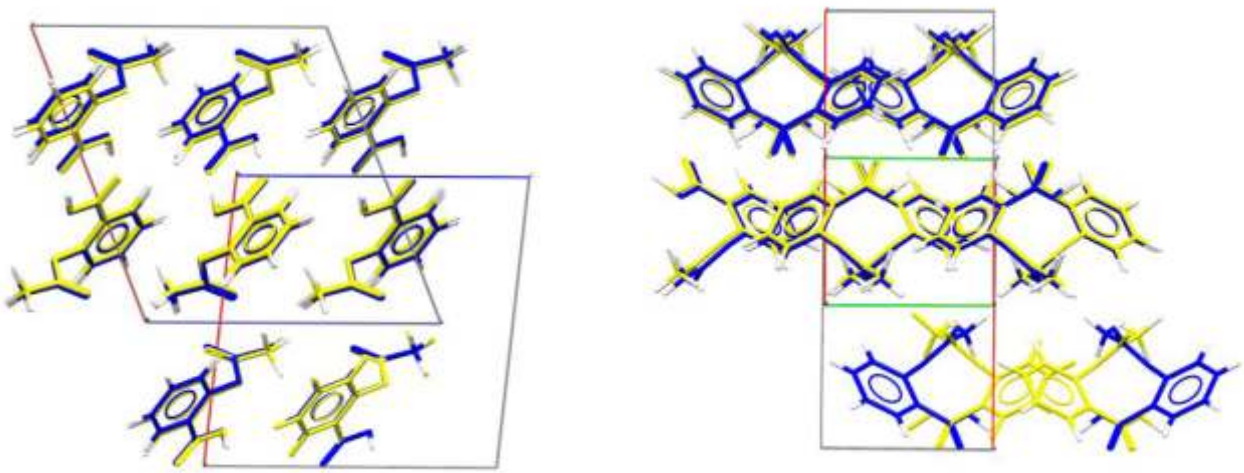

Figure 4. Superposition of aspirin form-I and form-II predicted by the PIXCRYPAR program: (left) viewed along the crystallographic b axis; (right) perpendicular to the previous view, c axis.

Closing remarks

The previously described theoretical tools have been developed in the Molecular Materials Structure Group (School of Chemistry, University of Barcelona), under the direction of Professor Juan J. Novoa. They result from years of research in the field of crystal packing analysis, computational polymorphic prediction, phase transformation dynamics, and prediction of the physical properties of crystals. Many of these tools and results are at the forefront of the state-of-the-art in the field, and can reproduce the available experimental results with enough accuracy.

Predicting the most likely structures and physical properties of a crystal polymorph can also serve as guide for a more efficient experimental work, by reducing the amount of time and costs of the experimental part of the research. For instance, the theoretical information about possible polymorphs having the desired physical properties could serve to focus the experimental research in their obtaining. Alternatively, the research on a molecule could even be discarded if no polymorphs presenting the desired properties are theoretically predicted. The synergy between the theoretical prediction and experimental analysis of a specific crystal can also be helpful in order to resolve doubtful crystalline structures originated from poor experimental data.

All the previous approaches allow a reduction in the costs and time needed to obtain new stable crystalline forms having the desired physicochemical properties. For companies working on drug discovery (or in developing functional molecular materials), such reduction gives them an extra inch that allows them to be more efficient, in today's highly competitive global market environment.

Bibliography

(1) Morissette S. et al. Advanced Drug Delivery Reviews. 2004 (56), 275– 300.

(2) Campeta AM. et al. Journal of Pharmaceutical Sciences. 2010, 99(9), 3874-86.

(3) U.S. Department of Health and Human Services - Food and Drug Administration - Center for Drug Evaluation and Research (CDER). Regulatory Classification of Pharmaceutical Co-Crystals. December 2011.

(4) D'Oria E. et al. Polimorfismo cristalino: fundamentos y aplicaciones en fármacos.

(5) Blagden N. et al. Advanced Drug Delivery Reviews 2007 (59), 617–630.

(6) Neumann, M. 2007. www.avmatsim.eu

(7) Neumann, M. A. Journal of Physical Chemistry B. 2008 (112), 9810-9829.

(8) Gavezzotti, A. CrystEngComm. 2003 (5), 429-438.

(9) Gavezzotti, A. CrystEngComm. 2003 (5), 439-446.

(10) Gavezzotti, A. Journal of Chemical Theory and Computation. 2005 (1), 834-840.

(11) Vishweshwar, P.; McMahon, J. A.; Oliveira, M.; Peterson, M. L.; Zaworotko, M. J. Journal of the American Chemical Society. 2005 (127), 16802-16803.

(12) Bond, A. D.; Boese, R.; Desiraju, G. R. Angewandte Chemie-International Edition. 2007, 46, 615-617.

Center for Intelligent Research in Crystal Engineering (CIRCE)

ParcBit - Technological Park - c/Isaac Newton, s/n. Edif. Disset, Local A-5. 07121. Palma de Mallorca, Spain
Tel. +34 871 946 047

Edif. FEUGA local 12 - c/Lope Gómez de Marzoa s/n. 15075. Santiago de Compostela, Spain
Tel. +34 981 521 594