# Recent advances in the identification and prediction of polymorphs

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## Abstract

An increased understanding of the phenomenon of polymorphism should enable pharmaceutical scientists to gain control over the crystallization process in order to selectively obtain the desired polymorph or suppress the growth of an undesired one. Phase changes during processing and scale-up are a problem, which may be avoided by carefully designed initial small-scale studies. The availability of detailed structural data, combined with strategic design of substrates and additives, has led to significant advances in the control over the polymorphs obtained in a particular crystallization. With all the information available from these initial studies, it should be possible to design and to select processing conditions which would give a desired polymorph and maintain the desired form throughout the various stages of drug processing and manufacture.

**Key words**: polymorphs, identification, prediction

## Introduction

Physical characterization of the active pharmaceutical ingredients is crucial for the successful development of the final drug product (1,2). It has long been known that pharmaceutical solids can exist in more than one solid form (crystal, amorphous). The different solid forms of a drug can display significantly different physical and chemical properties, including color, morphology, stability, dissolution, and bioavailability. Typically, the most thermodynamic stable form is chosen for development into the final dosage product, but more recently, metastable forms have been utilised due to enhanced dissolution or bioavailability profiles.

The common crystalline forms found for a given drug substance are polymorphs and solvates. Crystalline polymorphs have the same chemical composition but different internal crystal structures and, therefore, possess different physico-chemical properties. The different crystal structures in polymorphs arise when the drug substance crystallizes in different crystal packing arrangements and/or different conformations. The occurrence of polymorphism is quite common among organic molecules, and a large number of polymorphic drug compounds have been noted (2).

Solvates, also called pseudopolymorphs, are crystalline solid substances containing solvent molecules within the crystal structure. If the incorporated solvent is water, a solvate is termed a hydrate. Because different crystalline polymorphs and solvates differ in crystal packing, and/ or molecular conformation as well as in lattice energy and entropy, there are usually significant differences in their physical properties, such as density, hardness, compressibility, refractive index, melting point, enthalpy of fusion, vapour pressure, solubility, dissolution rate, other thermodynamic and kinetic properties and even colour (3).

Differences in physical properties of various solid forms have an important effect on the processing of drug substances into drug products, while differences in solubility may have implications on the absorption of the active drug from its dosage form, by affecting the dissolution rate and possibly the mass transport of the molecules (4).

These concerns have led to an increased regulatory interest in understanding the solid-state properties and behaviour of drug substances. For example, for approval of a new drug Food and Drug Administration (FDA) states that "appropriate" analytical procedures need to be used to detect polymorphs, hydrates and amorphous forms of the drug substance. It is also very important to control the crystal form of the drug substance during the various stages of product development (1), because any phase change due to polymorph interconversions, desolvation of solvates, formation of hydrates and change in the degree of crystallinity can alter the bioavailability of the drug. When going through a phase transition, a solid drug may undergo a change in its thermodynamic properties, with consequent changes in its dissolution and transport characteristics (5).

Processes such as lyophilization and spray drying may lead to the formation of the amorphous form of drug, which tends to be less stable and more hygroscopic than the crystalline product. Also, processing stresses, such as drying, grinding, milling, wet granulation, and compaction accelerate the phase transitions in pharmaceutical solids. Keeping these factors in mind, it is desirable to choose the most stable polymorphic form of the drug in the beginning and to control the crystal form and the distributions in size and shape of the drug crystals during the

entire process of development. The presence of a metastable form during processing or in the final dosage form often leads to instability of drug release as a result of phase transformation (6).

Crystallization plays a critical role in controlling the crystalline form and the distribution in size and shape of the drug (7). A crystalline phase is created as a consequence of molecular aggregation processes in solution that lead to the formation of nuclei, which achieve a certain size during the nucleation phase to enable growth into macroscopic crystals to take place during the growth phase. The factors affecting the rate and mechanisms by which crystals are formed are: solubility, supersaturation, rate at which supersaturation and desupersaturation occur, temperature, and the reactivity of surfaces towards nucleation.

The various forces are responsible for holding the organic crystalline solids together, such as nonbonded interactions and hydrogen bonding ( 8 ).

Various analytical methods are being currently used to characterize the crystalline form of the drug during the various steps of processing and development. With advances in analytical methods, the current focus of research in the solid-state area is to understand polymorphism and pseudopolymorphism at the molecular level. Knowledge of the crystal packing arrangements and the various intermolecular forces involved in the different packing arrangements will help in the prediction and preparation of the most stable polymorphs of a given compound.

Understanding of the physicochemical properties of polymorphs and solvates (hydrates) is of primary importance to the selection of a suitable crystalline form and development of a successful pharmaceutical product.

## Types of polymorphism

Polymorphs are classified, based on differences in the thermodynamic properties, as enantiotropes or monotropes, depending upon whether one form can transform reversibly to another or not.
In an enantiotropic system, a reversible transition between polymorphs is possible at a definite transition temperature below the melting point. In a monotropic system, no reversible transition is observed between the polymorphs below the melting point. Burger and Ramburger ( 9,10 ) have developed four rules to determine qualitatively the enantiotropic or monotropic nature of the relationship between polymorphs.

These rules are:

- the heat of transition rule,
- heat of fusion rule,
- infrared rule and
- density rule.

If it is established that the polymorphs of a particular drug are enantiotropic or monotropic, then the next goal is to define the thermodynamically stable (or metastable) domain of each crystalline phase of a substance as a function of temperature.

In recent years, the main focus of research has been the characterization of polymorphs arising from structural differences in the crystal lattice. It has been established for some time that organic molecules are capable of forming different crystal lattices through two different mechanisms. One of the mechanisms is termed packing polymorphism, and represents instances where conformationally relatively rigid molecules can be assembled into different three-dimensional structures through the invocation of different intermolecular mechanisms. The other mechanism is termed conformational polymorphism and arises when a nonconformationally rigid molecule can be folded into different arrangements, which subsequently can be packed into alternative crystal structures. The distinction between packing polymorphism and conformational polymorphism is somewhat artificial because different packing arrangements impose different conformations on the molecules, however slight, and different conformations will inevitably pack differently (11).

## Phase transformations in the solid state

Studies of phase transformations in the solid state are important, because the sudden appearance or disappearance of a crystalline form can threaten process development, and can lead to serious pharmaceutical consequences if the transformation occurs in the dosage forms. Hence, an understanding of the kinetics and mechanism of phase transformations is of practical importance. The rearrangement of molecules into a new structure during phase transformation mayor may not involve a solvent or vapor phase. To explain the mechanism of solid-solid physical transition, four steps have been proposed:

(a) molecular loosening in the initial phase;
(b) formation of an intermediate solid solution;
(c) nucleation of the new solid phase and
(d) growth of the new phase (11) .

In an interesting study, Skwierczynski (12) has proposed a two-environment model to describe the decomposition

reaction kinetics of a crystalline solid, aspartame. The decomposition reaction of aspartame is a simple unimolecular thermally-induced aminolysis and the reaction proceeds under anhydrous conditions, i.e., water is not a reactant (13). This model links the chemistry of the solid-state reaction with the molecular mobility of the reactant as the reaction proceeds. The advantage of this model is that it can be used to determine the shelf life of a product from kinetic data gathered at elevated temperatures. Apart from solid-solid physical transformations, solution-mediated physical transformations among polymorphs are also known to occur in processes, such as wet granulation and during dissolution testing.

The main challenge in managing the phenomenon of multiple solid forms of a drug is the inability to predict the number of forms that can be expected in a given case. This prediction would involve quantification of the myriad intermolecular forces within any proposed crystal structure as well as the ability to postulate the likely packing modes for a given molecule in all its configurations.

Accurate theoretical prediction of polymorphs from studies of molecular dynamics and crystal structure generation would be of outstanding importance in drug research (14).

More research is now being directed towards developing computational tools to understand the nature of polymorphism and to predict polymorphic forms at an early stage in the drug development process. The recent developments in computational chemistry allow the prediction of possible polymorphic forms based only on the molecular structure of the drug. The Polymorph Predictor, from Molecular Simulations, is currently the only commercial software package that can predict the possible polymorphs of an organic compound from its molecular structure (15).

The package developed by Karfunkel and co-workers (16) uses a Monte Carlo simulated annealing approach to generate thousands of possible crystal packing alternatives for a given molecule. Each of the unique crystal structures is then subjected to a lattice energy minimization to obtain the relative stability ranking of the various packing possibilities and the resulting lowest-energy structures are the potential polymorphs. This method has been successfully employed to generate known polymorphs of primidone and progesterone, starting from the molecular structures alone (17). The theoretical predictions of lattice energies, entropies, morphologies and polymorphs should stimulate experimental activities and vice versa. The current crystal-modeling efforts have the potential of producing more quantitative tools for bridging structures and properties, which could help in creating solid forms with desired properties (18).

There are many limitations in using computational methods for predicting polymorphs theoretically. The first limitation is that the ab initio screening is useful only for nonionic rigid molecules. For more complex systems, the method is very useful for generating plausible crystal structures, but it is not accurate enough to determine which of these possible structures can actually be crystallized (19).

In addition, the limitations in computer power can restrict the use of this method for predicting polymorphs of complex molecules. An issue of concern is that the existing methods only predict the lattice energies, which relate to internal energies or enthalpies of the crystals. However, the relative thermodynamic stability of polymorphs is determined by the Gibbs free energy, which is a linear function of both enthalpy and entropy. Prediction s of the relative stability of polymorphs will be more accurate when the entropies, as well as lattice energies, are considered. Application of molecular dynamics may enable the entropies to be calculated. Hence, no general method is currently available for the prediction or interpretation of the properties of complicated polymorphic or pseudopolymorphic systems.

## Conclusions

It is very important to choose the most suitable form of the crystalline drug in the initial stages of drug development. Systematic isolation and early characterization of the largest number of possible forms of a drug reduces the chances of surprises at the late production stage due to identification of a new crystalline form or phase change. With the development of more sophisticated computational tools, the main focus of many investigators is to be able to predict all the possible forms of a drug from its molecular structure. Understanding the origins of the multiple solid forms of a drug molecule, either due to differences in packing arrangement or conformation of the molecules, becomes the first step in prediction.

When crystal structures can be calculated with certainty, it will be possible to predict the various polymorphs of a compound and this information could be used to guide experimental studies. This goal may be difficult to achieve owing to the complex molecular structures of

new organic molecules and the presence of several molecules in each asymmetric unit, but the future development of improved force fields and increased computational speeds, may make it achievable.

It is important to make every effort to prepare and to identify the most stable polymorph in order to guide the selection of the optimal form for development. The emergence of sensitive methods and the use of combination techniques, facilitate the identification and the more accurate characterization of the various polymorphs of a drug molecule.

An increased understanding of the phenomenon of polymorphism should enable pharmaceutical scientists to gain control over the crystallization process in order to selectively obtain the desired polymorph or suppress the growth of an undesired one. Phase changes during processing and scale-up are a problem, which may be avoided by carefully designed initial small-scale studies. The availability of detailed structural data, combined with strategic design of substrates and additives, has led to significant advances in the control over the polymorphs obtained in a particular crystallization. With all the information available from these initial studies, it should be possible to design and to select processing conditions which would give a desired polymorph and maintain the desired form throughout the various stages of drug processing and manufacture.

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