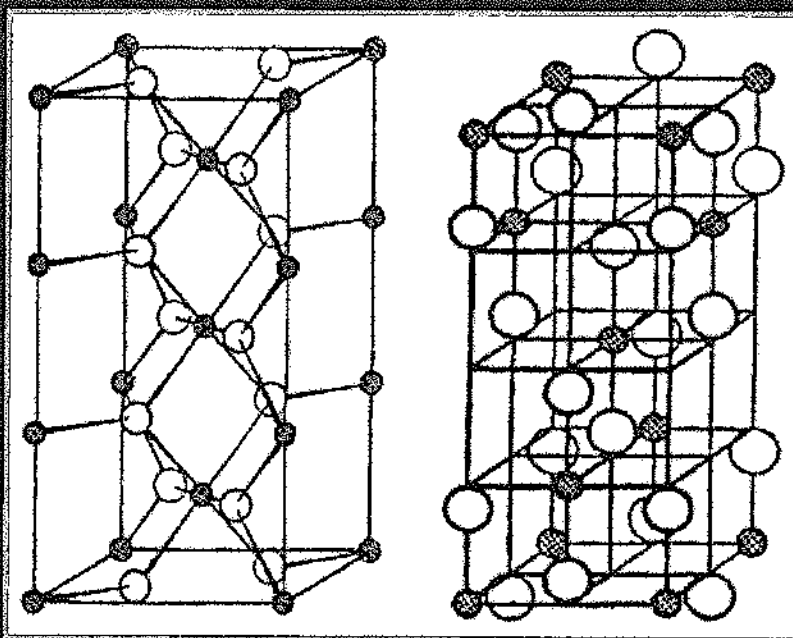


DRUGS AND THE PHARMACEUTICAL SCIENCES

VOLUME 192

SECOND EDITION

Polymorphism in Pharmaceutical Solids



edited by
Harry G. Brittain

informa
healthcare

prevent random nucleation, and its success is indicated by a unimodal size distribution (58,59). If insufficient seed is added, a bimodal distribution is obtained, because part of the product derives from the growth of seeds and the remainder arises as smaller particles from random nucleation and the growth of these nuclei. Conventionally, the surface area of the seeds is believed the critical parameter in determining the effectiveness of seeding (60), but some investigations contradict (58) this in showing that seeds above a certain critical size are more effective. It is also common practice to wash seed material with a slightly undersaturated solution of the substance being crystallized, which both dissolves out fine material and activates the surfaces by removing adsorbed impurities and other passivating effects.

In crystallizing polymorphic substances, seeding can also influence the solid form obtained by templating a particular polymorph at the expense of others. Because the seed nucleates the crystallization into its own crystalline form, with crystal growth as the dominant mechanism, it should be possible, in principle, to direct the crystallization to the required product by a judicious choice of seed material. In practice, this works on some occasions but not on others, and there are many cases where seeding with one polymorph leads to crystallization that gives an alternative form as the dominant product. This is because seeding is never perfect in that it can completely replace the nucleation step, and nucleation of other polymorphs can occur as in an unseeded process. Also, solvent-mediated transformation (see the section "Slurrying") is a very common mechanism by which less stable forms transform to more stable ones, and a crystallizing solution is a very effective medium for such transformations. Seeding with an unstable polymorph can thus give rise to a more stable product form at the point of isolation.

Seeding also underlies cases of "disappearing polymorphs" (10), whereby the crystallization of a new form in a process, either serendipitously or by design, has effectively prevented the form previously obtained from being produced again in the same equipment and process. Usually, the new form is more stable than the form previously obtained, and the reason postulated for its repeated formation is that plant and equipment remains contaminated with small quantities of seed of the new form that cannot be removed by cleaning procedures. There are also reports of different forms occurring at different laboratories and locations using nominally identical processes and procedures. The credibility of these seeding theories depends on the fact that most crystal nucleation is believed to occur heterogeneously, which is supported by the observations that crystallizations carried out in clean environments, such as sterile pharmaceutical areas, are often reluctant to nucleate. The presence of small traces of dirt and impurities are therefore believed to be important in initiating crystallizations, and the presence of residual material from previous batches may well exert a significant effect on crystallization and form selectivity.

The application of seeding to polymorph control also presupposes that a small quantity of seed material is available as a starting point at the beginning of the development. This is often obtainable from a set of polymorph screening experiments, but if these have been carried out at very small scale ($\sim\mu\text{g}$), there may have to be two or three scale-up stages before gram quantities of material can be prepared. Seed crystals generally have to be of good quality in terms of their size, shape, and morphological integrity. Hence, the preparation of suitable seed material is very often at a premium, and can be a major area of difficulty.

The principles of seeding also underlie the preparation of single crystals by growing a small, well-formed crystal from a moderately supersaturated solution.

Effects of Polymorphism and Solid-State Solvation on Solubility and Dissolution Rate

Harry G. Brittain

Center for Pharmaceutical Physics, Milford, New Jersey, U.S.A.

David J. R. Grant

College of Pharmacy, University of Minnesota, Minneapolis, Minnesota, U.S.A.

Paul B. Myrdal

College of Pharmacy, University of Arizona, Tucson, Arizona, U.S.A.

INTRODUCTION

It has now been amply demonstrated that the different lattice energies (and entropies) associated with different polymorphs or solvates give rise to measurable differences in the physical properties (density, color, hardness, refractive index, conductivity, melting point, enthalpy of fusion, vapor pressure, etc.). Even the explosive power of cyclotetramethylene-tetranitramine depends on which of its four polymorphs is being used (1). We have seen in previous chapters that the different lattice energies of polymorphs or solvates give rise to different solubilities and dissolution rates. If the solubilities of the various solid forms are sufficiently different, they can be very important during the processing of drug substances into drug products (2), and may have implications for the adsorption of the active drug from its dosage form (3). These concerns have led to an increased regulatory interest in the solid-state physics of drug substances, and in their characterization (4–10).

That the crystal structure can have a direct effect on the solubility of a solid can be understood using a simple model. For a solid to dissolve, the forces of attraction between solute and solvent molecules must overcome the attractive forces holding the solid intact and the solvent aggregates together. In other words, the solvation free energy released upon dissolution must exceed the lattice free energy of the solid plus the free energy of cavity formation in the solvent for the process to proceed spontaneously. The balance of the attractive and disruptive forces will determine the equilibrium solubility of the solid in question (which is an exponential function of the free energy change of the system). The enthalpy change and the increase in disorder of the system (i.e., the entropy change) determine the Ostwald free energy change. Because different lattice energies (and enthalpies) characterize different crystal structures, the solubility of different crystal polymorphs (or solvate species) must differ as well. Finally, the act of dissolution may be endothermic or exothermic in nature, so that measurements of solution calorimetry can be used to provide important information on the substance under study. The most common solvent media used in the characterization of polymorphs or solvates are liquids or liquid mixtures that give rise to liquid solutions of the solute (11) and that constitute the focus of this chapter.

The effect of polymorphism becomes especially critical on solubility because the rate of compound dissolution must also be dictated by the balance of attractive and

and alterations resulting from processing or storage conditions could affect the way the excipient interacts with the drug substance.

In another work, the multi-disciplinary application of atomic force microscopy, dynamic vapor sorption, and near infrared spectroscopy was used to investigate the outer-layer and bulk kinetics of the dehydration of trehalose dihydrate under conditions of ambient temperature and low humidity (36). Use of the microscopic technique enabled the determination of the dehydration kinetics of the outer layers both directly and from bulk data, and it was reported that no significant differences between the outer layer dehydration kinetics could be gleaned using these methods. The microscopic method also permitted the analysis of bulk-only kinetics from the vapor sorption and spectroscopic data, suggesting that the combination of atomic force microscopy and bulk characterization techniques should facilitate the acquisition of a more complete understanding of the kinetics of certain solid-state reactions.

X-ray powder diffraction was used to study the progressive conversion of raffinose pentahydrate to its amorphous form by heating at 60°C over a period of 72 hours (37). The presence of defects in the crystalline structure and any amorphous content was determined using a total diffraction method where both the coherent long-range crystalline order and the incoherent short-range disorder components were modeled as a single system. The long-range crystal structure of the initial pentahydrate phase remained intact in residual crystalline material, although the c-axis of the unit cell underwent an abrupt change after two hours of drying with the loss of one to two water molecules. The remaining crystal structure gradually disappeared over the two- to eight-hour time period, with the diffuse scattering containing both amorphous and defect contributions. It was concluded that removal of the first two waters of hydration created defects, and that these defects aided in subsequent conversion to the amorphous state.

PHASE TRANSFORMATIONS CAUSED BY THE ACTION OF A SECOND PHASE

When a solid consisting of a single component interacts with another phase consisting of a different component, the number of variables required by the Phase Rule to specify the system increases. Besides the usual variables of temperature and pressure, a concentration factor must also be specified in order to simplify the phase diagram. For a solvent interacting with a solid, the additional factor will be the solubility of the solute in the solvent at a given temperature and pressure, and the magnitude of this solubility will strongly affect the kinetics and outcome of the phase conversion process. For a solid interacting with a vapor, the partial pressure of the interacting component in the vapor will generally be the dominant factor in determining the kinetics and type of product formed by sorption of that interacting component.

Solution-Mediated Phase Transformation

Because it is not likely that a solution-mediated phase transformation could be adequately described by equilibrium theory, one must consider the process more from a kinetic viewpoint than from a thermodynamic viewpoint. For instance, during investigational work designed to determine the polymorphic and solvato-morphic space for a compound, one typically first crystallizes the substance out of

a variety of solvents and under a variety of conditions. Very often, if conditions are appropriate for the nucleation of a metastable crystal form, one can then obtain bulk quantities of that polymorph through continued crystal growth as long as no other phase transformation reactions take place. The identity of the isolated crystal form frequently depends on the properties of the crystallization solvent, as well as on the mechanism whereby the supersaturation of the solute in the crystallizing solution is discharged (38).

Owing to its inherent range of chemical and physical properties, the crystallizing solvent often exerts a strong influence over the nature of packing or conformation polymorphism that can exist for a given compound. Solvents have been classified on the basis of their proton donating, proton accepting, and dipole interaction abilities (39), and also divided into classes according to their high-performance liquid chromatography (HPLC)-related properties (40). Additional information about solvent classifications is available in the compilation of Riddick and Bunger (41). Given the additional variability introduced into the phase diagram of a compound, there certainly exists a substantial probability that a kinetically controlled, non-thermodynamic, process could dominate in a system formed by a solid substance and its saturated solution.

It has been recognized since the earliest studies of Ostwald (42) that the phase diagram for solubility is more complicated than is most commonly envisioned. At a specified temperature and pressure, a supersaturated solution will not necessarily spontaneously adjust to the equilibrium condition required by the phase rule (i.e., the equilibrium solubility) unless the degree of supersaturation exceeds a certain critical value. The concentration region where supersaturation can be obtained without the spontaneous formation of crystal nuclei is termed the metastable zone, whereas the concentration region where the formation of crystal nuclei cannot be stopped is termed the labile zone.

Ostwald made a number of important observations regarding the relative stability of crystal forms, one of which is that the polymorph having the least stability tends to crystallize first, and another is that metastable crystal forms tend to convert into more stable crystal forms during the time they were suspended in solution. As he stated, "When a given chemical system is left in an unstable state, it tends to change not into the most stable form, but into the form the stability of which most nearly resembles its own; that is, into that transient stable modification whose formation from the original state is accomplished by the smallest loss of free energy" (14). The practical implication of the Rule of Stages is that if investigators want to isolate a metastable polymorph formed during a rapid discharge of supersaturation, they must quickly remove the precipitated solids from the crystallizing solution before it has a chance to transform into a new crystal form.

That kinetics plays the essential role in the course of solution-mediated phase transformations has been known for quite some time, and non-equilibrium thermodynamic approaches have been used to develop a theory to explain the phenomenon. The most notable of these is the work of Davey, who deduced that the kinetic theory suggested the existence of very different profiles for discharge of supersaturation for the extremes of growth-controlled and dissolution-controlled transformations (43,44). Davey used examples taken from the dyestuff and agrochemical fields to confirm that both types of process could occur under suitable circumstances. Around the same time, van Santen used an irreversible thermodynamic approach to show that the step rule of Ostwald served to minimize entropy production (45).

transformation was adequately characterized by first-order reaction kinetics and an activation energy of 11.2 kcal/mol (47.4 cal/gram) for the phase conversion.

X-ray powder diffraction has been used to quantify the kinetics of the solution-mediated phase transformation of the metastable form of an active pharmaceutical ingredient to one of its more stable forms, and it was reported that the transformation rate could be influenced by the presence of structurally related, tailor-made, impurities (54). Modified attachment energy calculations were found to represent an effective indicator as to how likely a given impurity molecule would be incorporated in the growing crystal. In this work, it was proposed that the energetic calculations could facilitate the design of suitable molecules that would inhibit the crystallization of the stable form and therefore stabilize the metastable crystal form.

The kinetics associated with the phase conversion of mefenamic acid Form-II to Form-I was studied in three solvent systems and under high humidity conditions (55). As might be expected, the transformation was accelerated with increasing temperature, with the addition of seed crystals of the product phase, and with the degree of solubility in the suspending solvent system. The effect of a number of parameters on the solution-mediated Form-II to Form-I phase transformation of buspirone hydrochloride was studied with the aim of developing a response surface analysis in order to identify the more important factors affecting the polymorphic interconversion (56). The phase transformation of clopidogrel hydrogen sulfate Form-I into Form-II has been studied using *in situ* measurements of ultrasonic velocity, with the technique being able to provide information on the induction times and transformation rates for formation of the two polymorphs as well as effects of temperature and solvent composition (57).

Solution-mediated phase transformation reactions can play havoc with dissolution profile studies if they take place during the lifetime of the study, and any dissolution study of a metastable crystal form must take this possibility into account. Such phase transformations were studied for theophylline and nitrofurantoin using a channel flow intrinsic dissolution system, where the polymorphic form of the dissolving solid was continually monitored using Raman spectroscopy (58). It was concluded that knowing both the drug concentrations in the dissolution medium and the solid-state characterization provided a route to a deeper understanding of the phase transitions accompanying the dissolution. In a subsequent work, the solution-mediated phase transformation of theophylline anhydrate into the monohydrate were studied in rotating disc and channel flow cell dissolution devices with a particular aim of characterizing the kinetics of reactions taking place in both systems (59).

A rate enhancement effect due to secondary nucleation has been identified in the solution-mediated transformation of the α -phase of (*L*)-glutamic acid to its β -phase (60). In this study, the kinetics of the polymorphic transition were studied using optical microscopy combined with Fourier transform infrared, Raman, and ultraviolet absorption spectroscopies. In another work, four different *in situ* analytical techniques have been used to study the solvent-mediated $\alpha \rightarrow \beta$ phase transformation of (*L*)-glutamic acid, combined with a mathematical model based on population balance equations of equations describing the kinetics of nucleation and growth (61). This approach facilitated estimation of the nucleation and growth rates of the two polymorphs, profiling of the dissolution process, and a validation of the population balance model. On-line X-ray powder diffractometry has been