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Crystallization as a Tool for Controlling and Designing Properties of Pharmaceutical Solids

by

Sabiruddin Mirza

ACADEMIC DISSERTATION

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To my parents, beloved wife
and sweet little daughter

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ABSTRACT

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The ability to deliver the drug to the patient in a safe, efficacious and cost-effective manner depends largely on the physicochemical properties of the active pharmaceutical ingredient (API) in the solid state. In this context, crystallization is of critical importance in pharmaceutical industry, as it defines physical and powder properties of crystalline APIs. An improved knowledge of the various aspects of crystallization process is therefore needed. The overall goal of this thesis was to gain better understanding of the relationships between crystallization, solid-state form and properties of pharmaceutical solids with a focus on a crystal engineering approach to design technological properties of APIs. Specifically, solid-state properties of the crystalline forms of the model APIs, erythromycin A and baclofen, and the influence of solvent on their crystallization behavior were investigated. In addition, the physical phenomena associated with wet granulation and hot-melting processing of the model APIs were examined at the molecular level. Finally, the effect of crystal habit modification of a model API on its tabletting properties was evaluated.

The thesis enabled the understanding of the relationship between the crystalline forms of the model APIs, which is of practical importance for solid-state control during processing and storage. Moreover, a new crystalline form, baclofen monohydrate, was discovered and characterized. Upon polymorph screening, erythromycin A demonstrated high solvate-forming propensity thus emphasizing the need for careful control of the solvent effects during formulation. The solvent compositions that yield the desirable crystalline form of erythromycin A were defined. Furthermore, new examples on solvent-mediated phase transformations taking place during wet granulation of baclofen and hot-melt processing of erythromycin A dihydrate with PEG 6000 are reported. Since solvent-mediated phase transformations involve the crystallization of a stable phase and hence affect the dissolution kinetics and possibly absorption of the API these transformations must be well documented. Finally, a controlled-crystallization method utilizing HPMC as a crystal habit modifier was developed for erythromycin A dihydrate. The crystals with modified habit were shown to posses improved compaction properties as compared with those of unmodified crystals. This result supports the idea of morphological crystal engineering as a tool for designing technological properties of APIs and is of utmost practical interest.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS ..... **i**

ABSTRACT ..... **iii**

ABBREVIATIONS AND ACRONYMS ..... **VI**

LIST OF ORIGINAL PUBLICATIONS ..... **VII**

1. INTRODUCTION **1**

2. THEORY AND LITERATURE REVIEW **3**

2.1 PHARMACEUTICALS AS MOLECULAR CRYSTALS 3

2.1.1 Classification *3*

2.1.2 General aspects of the formation of polymorphs and solvates *5*

2.1.3 Stability relationships between crystalline phases *6*

2.2. CRYSTALLIZATION FROM SOLUTION 10

2.2.1 The driving force for crystallization *10*

2.2.2 Nucleation processes *11*

2.2.3 Crystal growth *13*

2.2.5 Crystal habit *15*

2.3 CRYSTALLIZATION AND DESIGNING PROPERTIES OF PHARMACEUTICALS 16

2.3.1 Polymorph screening *17*

2.3.2 Directed crystallization of specific crystalline forms *19*

2.3.3 Solvent-mediated transformations *22*

2.3.4 Particle size control *23*

2.3.5 Morphological crystal engineering *25*

2.3.6 Improving solubility and dissolution rate *28*

2.3.7 Crystal morphology in relation to pharmaceutical processes and dosage form performance *29*

3. AIMS OF THE STUDY **31**

4. EXPERIMENTAL **32**

4.1. MATERIALS 32

4.1.1 Active substances *32*

4.1.2. Excipients *32*

4.1.3. Solvents *32*

4.2 CRYSTALLIZATION AND PROCESSING OF MATERIALS 33

4.2.1 Generation of anhydrous, hydrated, dehydrated and amorphous phases (I-IV) *33*

4.2.2 Polymorph screening (III) *33*

4.2.3 Additive-controlled crystallization of EM dihydrate (V) *33*

4.2.4 Preparation of physical mixtures and solid dispersions (IV) *34*

4.2.5 Wet massing (II) *34*

4.2.6 Preparation of powder compacts (V) *34*

4.3 PHYSICAL CHARACTERIZATION OF MATERIALS AND PHASE TRANSFORMATION MONITORING 35
4.3.1 X-ray Powder diffraction (XRPD)(I-V) *35*
4.3.2 Thermal analyses (I-V) *35*
4.3.3 Microscopy (II-V) *35*
4.3.4 Vibrational spectroscopy (I,II, IV) *36*
4.3.5 Water sorption/desorption analysis (II) *36*
4.4 MOLECULAR MODELLING (I,V) 37

5. RESULTS AND DISCUSSION 38

5.1 CHARACTERIZATION OF CRYSTALLINE FORMS OF MODEL APIS 38
5.1.1 Crystalline forms of erythromycin A (I, III, IV) *38*
5.1.2 Crystalline forms of baclofen (II) *39*
5.2 SOLVATOMORPHISM OF MODEL APIS 40
5.2.1 Effect of solvent composition on crystallization behaviour of erythromycin A (III) *40*
5.2.2 Desolvation behaviour of erythromycin A solvatomorphs (I, III) *41*
5.2.3 Impact of crystal structure on dehydration mechanism of EM dihydrate (I) *43*
5.2.4 Hydrate formation of baclofen (II) *44*
5.2.5 Dehydration behaviour of baclofen monohydrate (II) *44*
5.3 EFFECT OF PROCESSING ON CRYSTALLINE STATE OF MODEL APIS IN SOLID FORMULATIONS 45
5.3.1 Effect of PEG on phase behaviour of erythromycin A dihydrate during hot-melt processing (V) *45*
5.3.2 Factors affecting hydrate formation of baclofen during wet massing (II) *46*
5.4 ENHANCING COMPACTION PROPERTIES BY CRYSTAL HABIT MODIFICATION (V) 48
5.4.1 HPMC as a crystal habit modifier *48*
5.4.2 Mechanistic considerations of the additive effect on crystallization *49*
5.4.3 Impact of crystal habit on compaction behaviour *50*

6. CONCLUSIONS 52

REFERENCES 53

ABBREVIATIONS AND ACRONYMS

Ac	Acetone
API	Active pharmaceutical ingredient
BF	Baclofen
BFDH	Bravais-Friedel-Donnay-Harker theory
CSD	Cambridge Structural Database
DSC	Differential scanning calorimetry
EM	Erythromycin A
EtOH	Ethanol
FDA	Food and Drug Administration
GRAS	Generally regarded as safe
HPMC	Hydroxypropyl methylcellulose
HSM	Hot-stage microscopy
ICH	International Conference on Harmonization
IPR	Intellectual Property Rights
i-PrOH	Isopropanol
MeEtCO	Methylethylketone
MW	Molecular weight
NIR	Near-infrared spectroscopy
PEG	Polyethylene glycol
Ph. Eur.	European Pharmacopoeia
RH	Relative humidity
SCF	Supercritical fluid
SEM	Scanning electron microscopy
TGA	Thermogravimetric analysis
USP	United States Pharmacopoeia
VT-XRPD	Variable temperature x-ray powder diffraction
XRPD	X-ray powder diffraction

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their respective Roman numerals I V.

I Miroshnyk I, Khriachtchev L, Mirza S, Rantanen J, Heinämäki J, Yliruusi J. Insight into thermally induced phase transformations of erythromycin A dihydrate. *Crystal Growth & Design* 6 (2006) 369–374. DOI: 10.1021/cg050159t

II Mirza S, Miroshnyk I, Rantanen J, Aaltonen J, Harjula P, Kiljunen E, Heinämäki J, Yliruusi J. Solid-state properties and relationship between anhydrate and monohydrate of baclofen. *Journal of Pharmaceutical Sciences* 96 (2007) 2399–2408. DOI: 10.1002/jps.20894

III Mirza S, Miroshnyk I, Heinämäki J, Christiansen L, Karjalainen M, Yliruusi J. Influence of solvents on the variety of crystalline forms of erythromycin. *AAPS PharmSci*, 5 (2003), Article 12. DOI: 10.1208/ps050212

IV Mirza S, Heinämäki J, Miroshnyk I, Rantanen J, Christiansen L, Karjalainen M, Yliruusi J. Understanding processing-induced phase transformations in erythromycin-PEG 6000 solid dispersions. *Journal of Pharmaceutical Sciences* 95 (2006) 1723–1732. DOI: 10.1002/jps.20640

V Mirza S, Miroshnyk I, Heinämäki J, Rantanen J, Antikainen O, Vuorela P, Vuorela H, Yliruusi J. Hydroxypropyl Methylcellulose-Controlled Crystallization of Erythromycin A Dihydrate Crystals with Modified Morphology. *Crystal Growth & Design* 8 (2008) 3526-3531. DOI: 10.1021/cg7007599

1. INTRODUCTION

The vast majority of active pharmaceutical ingredients (APIs) are formulated as solid dosage forms due to their convenience and excellent patient compliance, with most marketed products containing API(s) and/or excipients in the crystalline state (Byrn, 1999). The bioavailability of a solid dosage form is strongly dependent on physical properties of the actual API to be formulated (crystalline form, morphology, particle size distribution). In addition, the processability (filtration, drying, milling, granulation, tableting) is determined by the physical properties of the material (*Table 1*).

Table 1 *Effect of solid-state properties defined by crystallization process on properties of an API and drug product (modified from Shekunov and York, 2000)*

Solid-state properties		Affected bulk and/or performance properties
Structural	Solid-state form, crystallinity, crystal defects	Physical and chemical stability; hygroscopicity; solubility, dissolution rate and bioavailability; all aspects of processing
Dimensional	Crystal size distribution, crystal habit, surface structure	Processing behaviour (agglomeration, flow properties, compaction); particle permeability (adsorption); bioavailability; consistency and uniformity of the dosage form
Chemical	Chemical purity, residual solvent, microbial purity, chiral purity	Toxicity; chemical, physical and enantiotropic stability
Electrical	Electrostatic charge distribution	Agglomeration and flow properties

Crystallization, particularly crystallization from solution, is the bottom-up unit operation in the production of pharmaceutical solids and is invariably used as a separation and purification procedure. In addition to purity (chemical and structural), physical properties of a material are originally determined when it is crystallized. Even minor changes in crystallization conditions can significantly alter the crystal and powder properties, namely particle size, shape, surface characteristics, purity and defect structure followed by thermodynamic and mechanical properties. These effects have been recognized as the major batch-to-batch and source variation problems leading to inconsistency of the final tablet properties (Shekunov and York, 2000). Nevertheless, the

significance of crystallization processes has been underestimated in the pharmaceutical industry. Overall, unfavourable and inadequately understood physical properties are often at the root of many of the problems that delay new drug approvals by regulatory agencies; and manufacturing issues, stock-outs and product recalls are costly consequences of poor control over materials properties (Gardner *et al.*, 2004; Yu *et al.*, 2004). Crystallization can therefore be regarded as the first step in formulation and must be properly designed to achieve adequate control of the required characteristics and the desired pharmaceutical performance. This concept is being increasingly recognised by the pharmaceutical industry and driven under new regulatory directives encouraging quality by design (FDA, 2004a; FDA, 2004b; ICH, 2005a; ICH, 2005b). In addition, a thorough understanding of solid-state properties of APIs, particularly phenomenology of *polymorphism*, is relevant for intellectual property rights (IPR) protection.

Crystallization at the molecular level is a supramolecular process (Davey, 2004). In this context, the properties of the solid state are dependent on molecular recognition (Doherty, 1996). Understanding of a solid structure allows the crystal designer to manipulate the crystal chemistry in order to optimise specific performance characteristics. Within the pharmaceutical industry, where bringing an innovative drug molecule to the market often exceeds US $800 million (DiMasi *et al.*, 2003), the crystal engineering approach (Desiraju, 2001) may offer the valuable tool for tailoring physicochemical properties of already marketed APIs. Pharmaceutical *co-crystals* (crystalline complexes of two or more noncovalently bound neutral molecular constituents) are an example on how crystal-engineering concept can be utilised to address physical and intellectual property issues in the context of drug development and delivery (Remenar *et al.*, 2003; Vishweshwar *et al.*, 2006; Blagden *et al.*, 2007). In future, crystal engineering may be applied to design a molecule that is guaranteed to crystallize in a particular polymorphic form under physiological conditions (Desiraju, 2001).

In-depth knowledge of crystallisation processes and solid-state properties of APIs is therefore clearly requested to ensure consistent quality of dosage forms and implement new and existing crystal engineering approaches to drug delivery system design.

2. THEORY AND LITERATURE REVIEW

2.1 Pharmaceuticals as molecular crystals

2.1.1 Classification

Solid materials can exist as *crystalline* or *amorphous phases*, depending on the presence or absence of long-range three-dimensional (3-D) order, respectively. Due to their high stability and ease of processing, most pharmaceuticals are produced as *molecular crystals* that are composed of molecules held together by weak attractive forces such as van der Waals forces or hydrogen-bonding (Byrn, 1999; Datta and Grant, 2004). Molecular crystals may exist as *single molecular entities* or as *molecular adducts* (multicomponent phases) (Haleblian, 1975) and may show *polymorphism* or *isomorphism*. Polymorphism is the ability of a substance to exist as two or more crystalline phases with different molecular arrangements and/or conformations (Bernstein, 2002), while isomorphism is the capability of different chemical species to form crystals with identical molecular arrangements (Myerson, 1999). A crystalline form that contains either stoichiometric or nonstoichiometric amounts of solvent, in addition to molecules of the major component, is termed *solvate*; if the incorporated solvent is water, a term *hydrate* is used. The major component and incorporated solvent are often termed the *host* and *guest*, respectively. The ability of a substance to form solvates is sometimes referred to as *pseudopolymorphism* (Byrn, 1999; Vippagunta *et al.*, 2001) or *solvatomorphism* (Brittain, 2007).

On the basis of the location of water in their structures, crystalline hydrates are classified into three categories (Morris and Rodríguez-Hornedo, 1993; Morris, 1999). (1) *Isolated site hydrates*, in which water molecules are separated from each other by host molecules, can usually be distinguished during non-isothermal dehydration by sharp DSC endotherms and a narrow TGA weight loss range. The dehydration of isolated site hydrates often leads to amorphous and unstable products. (2) A distinctive feature of *ion-associated hydrates* that contain ion coordinated water is dehydration at high temperatures due to the strong metal-water interaction. (3) In *channel hydrates* water molecules are localized in lattice channels and form hydrogen bonded chains. These hydrates are usually

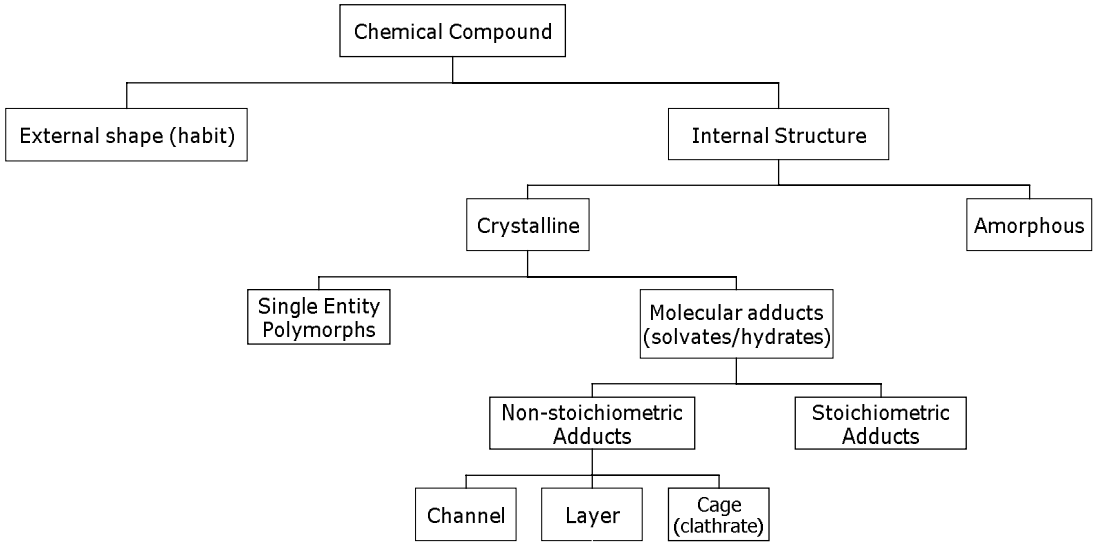


Figure 1 *General classification of possible solid phases of an organic chemical compound (adapted from Haleblian, 1975).*

discriminated by continuous dehydration beginning at relatively low temperatures during non-isothermal dehydration. *Clathrates* are a special type of molecular adducts in which the guest molecules occupy, fully or partially, cages in the crystal lattice of the host without specifically interacting with the host molecules. For instance, the ability of cyclodextrine to form clathrates is widely used for solubility enhacing of poorly water soluble APIs (Grattan, 1995). C*rystal habit* (morphology) describes the overall external shape of a particular crystal, differences in external crystal shape being not necessarily indicative of a change in the internal structure. General classification of possible solid phases of organic molecular solids is presented in *Fig. 1*.

The different crystal packing and lattice energies associated with different polymorphs and solvates give rise to measurable differences in physical properties (thermodynamic, spectroscopic, kinetic, surface, and mechanical) (Grant, 1999). For pharmaceutical industry, the impact polymorphism and solvatomorphism may ultimately have on therapeutic efficacy, toxicity, and bioavailability as well as processing (Haleblian and McCrone, 1969; Brittain and Fiese, 1999; Byrn *et al.*, 2001; Morris *et al.*, 2001) is of major concern. These concerns are reflected by an increased regulatory interest in thorough physico-chemical characterization of APIs (Grant and Byrn, 2004; Byrn *et al.*, 1995; ICH, 1999).

2.1.2 General aspects of the formation of polymorphs and solvates

Although the majority of organic crystals (~85%) tend to exist as single entities (Nangia and Desiraju, 1999), the prevalence of solvatomorphism among APIs has been documented more frequently – 29% of APIs are known to form hydrates and 10% form other solvates (Griesser, 2006). The ease of formation and subsequent stabilization of molecular solids can be explained by Kitaigorodskii's close packing theory (Kitaigorodskii, 1973), which states that the molecules within the crystal will attempt to pack so that the amount of unoccupied space is minimized and the number of close contacts with neighbouring molecules maximized. Hence, the desire to pack efficiently generally provides the driving force towards selected structural arrangements in molecular materials (Doherty, 1996), especially those that are dominated by van der Waals interactions. In some cases, however, energetically favourable hydrogen bonds compensate for the loss of spatial efficiency and thus stabilize the crystal structure with large voids (Bernstein, 2002).

Some classes of drugs (e.g., steroids, antibiotics, and sulfonamids) are particularly prone to forming solvates. This is probably due to cavities or large channels that often exist in the crystal structures of these compounds. The size and chemical environment of the cavity or channel determine the type of incorporated solvent molecule as well as kind of interaction between guest and host (Guillory, 1999). When the solvent molecules are trapped, as in clathrates, the solvate is more stable than when the solvent molecules are located along channels in the lattice.

Water represents the smallest guest molecule in solvates. Owing to this feature, it can easily fill structural voids. In addition, due to multidirectional hydrogen bonding capability the water molecule is ideal for linking a majority of drug molecules into stable crystal structures. Hydrates with one mole-equivalent water (monohydrates) are the most common form of hydrate in organic APIs (Morris, 1999).

Among organic solvents, methanol, benzene, dichloromethane, ethanol and acetone are the most common solvate-forming molecules. However, when a solvent usage correction is applied, dimethylformamide, dimethyl sulfoxide and dioxane are most commonly involved in solvate formation due to their ability to form multiple hydrogen bonds with organic molecules. As a result, the extrusion of the solvent during the aggregation and nucleation process becomes disadvantageous from an enthalpic viewpoint and the solvent

remains an integral part of the nucleating crystal. The fact that only a minority of organic compounds form solvates is attributed to the entropic gain in eliminating solvent molecules during nucleation (Nangia and Desiraju, 1999).

2.1.3 Stability relationships between crystalline phases

The thermodynamic relationship between different phases of a substance is governed by Gibbs' phase rule:

$$P + F = C + 2 \quad (1)$$

where C is the number of components, P is the number of phases that exist in equilibrium, and F is the number of degrees of freedom of the system. If two polymorphs of a single substance are in equilibrium (i.e. P = 2 and C = 1), the variance F equals unity, meaning that at a given pressure, usually atmospheric, the temperature of the system is fixed at the transition temperature, T_t. This dictates that only one phase can exist at any given temperature and pressure, except at the transition temperature, in which case two phases (e.g. polymorphs) exist in equilibrium.

Polymorphic systems

A *phase transition,* the process of transformation of one polymorph into another, may occur at a given pressure by changing the temperature. The ability of a system to undergo such spontaneous change is measured by the Gibbs free energy (*G)*, which is given by

$$G = H \quad TS \quad (2)$$

where *H* is the enthalpy, *T* is the absolute temperature and *S* is the entropy. A reduction in Gibbs free energy is the thermodynamic driving force for a phase transition. A reversible phase transition is characteristic of *enantiotropy* (*Fig. 2A*), whereas an irreversible phase transition is typical of *monotropy* (*Fig. 2B*). For enantiotropic systems, the transition temperature is less than the melting point of either polymorph; the energy of the transition

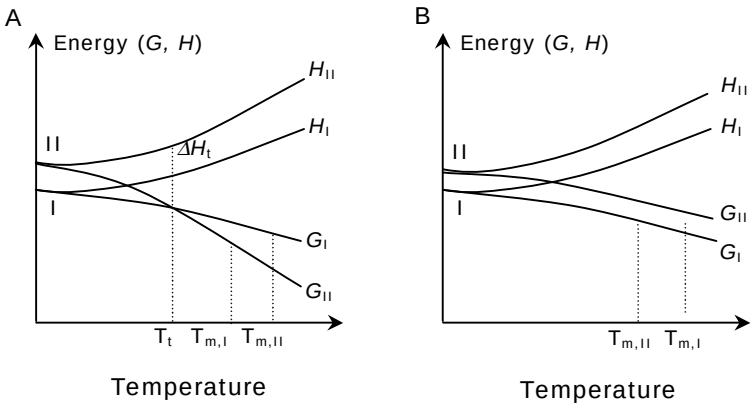


Figure 2 *Energy diagrams showing relationship between enantiotropes (A) and monotropes (B). Modified from Burger and Ramberger, 1979.*

on heating is endothermic; each enantiotrope has its own temperature range of stability; and the melting enthalpy and density of the higher-melting form are lower. Examples demonstrating such behaviour are carbamazepine and metochlorpramide (Burger and Ramberger, 1979; Giron, 1995). For monotropic systems, only one form is *stable* (i.e. has the lower free energy content) at all temperatures; the unstable to stable form transformation is exothermic; and the stable form is less soluble and has the higher melting point and density (Burger and Ramberger, 1979; Burger, 1982). An example of this type of system is chlorampehicol palmitate (Giron, 1995).

Solvated systems

The stability of solvates depends, in addition to pressure and temperature, on the partial pressure (*activity*) of the solvent of crystallization above the solid (Grant and Higuchi, 1990). Analogously to an energy diagram for polymorphic systems, the stability range of solvate and unsolvated form can be established using a van't Hoff plot (natural logarithm solubility versus reciprocal temperature plot) (Shefter and Higuchi, 1963). The relationship between free energy and an ideal solubility of a solid is given by:

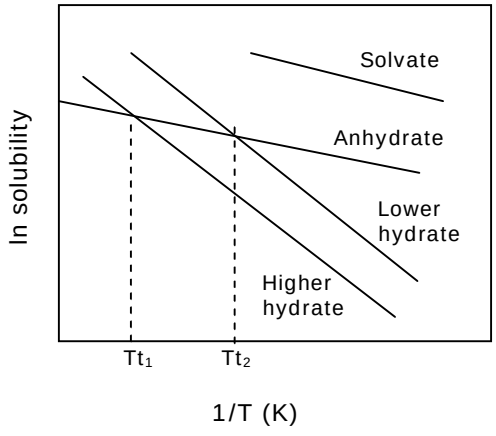


Figure 3 *Solubility diagram for a system of different solvates showing transition temperatures, Tt_1 and Tt_2, between the anhydrate and the hydrates. Modified from Shefter and Higuchi, 1963.*

$$\Delta G = RT \ln X \qquad (3)$$

or

$$\ln X = \frac{\Delta S_f}{R} - \frac{\Delta H_f}{R} \cdot \frac{1}{T} \qquad (4)$$

where ΔS_f and ΔH_f are the entropy and enthalpy of fusion respectively, and R is the gasconstant. A negative slope of a van't Hoff plot is equal to $\Delta H_f/R$, while an intercept yields $\Delta S_f/R$ for each phase. It is generally accepted that a solvate is the most stable and thus the least soluble form in its own solvent. Therefore, aqueous solubility (and hence stability) order for solvated systems is typically following: stable hydrate < metastable hydrate < anhydrate < solvate with organic solvent, as illustrated in *Fig. 3*.

Desolvated solvates

Desolvation of a solvate may result in one of three types of reaction product, specifically a crystalline anhydrate, amorphous solid or an isomorphic desolvate. An *isomorphic desolvate* (or *desolvated solvate*) forms when solvent is removed from a specific solvate but the crystal structure is essentially retained (Byrn *et al.*, 1994). By definition, an isomorphic desolvate can only be obtained via the isostructural solvate. Hence, it is of importance to refer to the parent solvated structure when naming the desolvated structure (Pfeiffer *et al.*, 1970). If there already exists an anhydrous crystalline form of the molecule, the desolvated solvate can also be regarded as a polymorph (Morris, 1999), although this is a matter of some debates in the literature (Griesser, 2006).

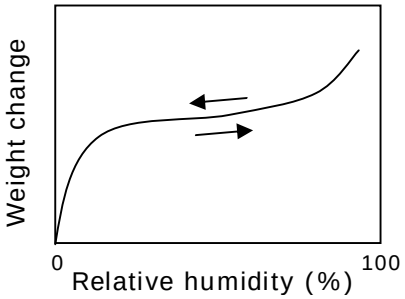


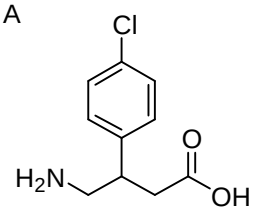
Figure 4 *An example of moisture sorption/desorption behaviour of an isomorphic desolvate system*

The resulting voids in the crystal lattice after solvent loss reduce packing efficiency of isomorphic desolvates leading to a higher energy (metastable) state. For this reason, the isomorphic desolvate is usually stable only at low partial pressure of an incorporated solvent or low humidity. The internal energy of the desolvate can be reduced by processes that increase packing efficiency, such as sorption of small guest molecules (resolvation) or structural relaxation (reducing the unit cell volume) (Stephenson *et al.*, 1998; Stephenson and Diseroad, 2000). Overall, the main consequences of the loose packing efficiency are reduced thermodynamic and chemical stability, and extreme hygroscopicity (*Fig. 4*) of the isomorphic desolvate.

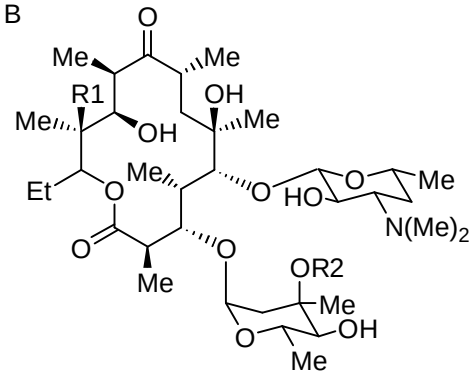
The model APIs applied in this thesis, baclofen and erythromycin, are structurally diverse, slightly water soluble, hydrate forming compounds. Baclofen (BF) (*Fig. 5A*) is a derivative of γ-aminobutyric acid and is a potent antispastic agent, while erythromycin (*Fig. 5B*) is a mixture of macrolide antibiotics produced by fermentation of strains of S*accharopolyspora erythrea*. Erythromycin A (EM) is the main component, but during fermentation several related substances such as erythromycins B, C, D, E, F, N-oxide and N-demethylerythromycin A are formed in small amounts (REF), with erythromycin A and B being isomorphous (Stephenson *et al.*, 1997). In addition, degradation products such as pseudoerythromycin A enol ether, formed in alkaline medium, and anhydroerythromycin A and erythromycin A enol ether, which are formed under mild acidic conditions, may also be present.

EM dihydrate is an example of isomorphic desolvate systems. While it exists as a stoichiometric hydrate when first isolated from the crystallization medium, under non-equilibrium conditions deficiency of the solvent of crystallization leads to nonstoichiometric characteristics (Cox *et al.*, 1971; Stephenson *et al.*, 1998; Chen *et al.*, 1999). This means that the degree of its dehydration is a function of the relative humidity or temperature and equilibration of the dehydrated dihydrate is rapid and reversible. Worth noting is that to date there are no specifications in any pharmacopoeias concerning this isomorphic transition of EM dihydrate and only its maximum

A



B



EM	Brutto Formula	MW	R1	R2	Content (%) Ph. Eur.	Content (%) USP
A	$C_{37}H_{67}NO_{13}$	734	OH	CH_3	93–102*	85–100.5*
B	$C_{37}H_{67}NO_{12}$	718	H	CH_3	max 5	max 12
C	$C_{37}H_{67}NO_{13}$	720	OH	H	max 5	max 5

*Sum of the percentages of erythromycin A, B and C

Figure 5 Structural formula of baclofen (A) and general structural formula and composition of commercial erythromycin (B).

water content is limited (6.5 and 10% according to Ph. Eur. and USP, respectively). Meanwhile, varying water activity throughout processing and the lifetime of the compound causes repeatable dehydration-hydration cycles, which are assumed to be a major source of batch-to-batch variations and batch failures of EM products (Bauer, 1999). This indicates that solid-state behaviour of this molecule is not adequately understood including the regulatory level.

2.2. Crystallization from solution

Crystallization is defined as a phase change that results in the formation of a crystalline solid (Myerson, 1999). The most common type of crystallization is crystallization from solution, in which a material that is a crystalline solid at a temperature of interest is dissolved in a solvent while crystallization is induced by changing the state of the system in some way that reduces the solubility of the solute. Classically, this kinetic process is described in terms of two distinct steps, nucleation and crystal growth. The properties of the crystals obtained are the result of the kinetic relationship between these two processes. The goal of this review is therefore to introduce basic concepts of nucleation and crystal growth from solution and impact of these processes on the properties of pharmaceutical materials.

2.2.1 The driving force for crystallization

Crystallization can take place over the concentration range limited by the equilibrium composition of the system at specified conditions (*Fig.6*). *Thermodynamic equilibrium* refers to the solutions *saturated* with respect to the solute (i.e., the concentration of the solution represents the solubility value for that solid phase); the rates of dissolution and crystallization are equal under these conditions. A solution with solute concentration below the saturation limit (shown by solid line) is

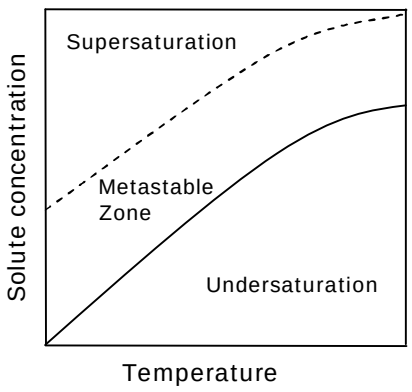


Figure 6 *Schematic solubility/ supersolubility diagram.*

termed *undersaturated* and existing crystals will dissolve. In order for crystallization to occur, the system must be brought into a non-equilibrium state where the concentration of the solute exceeds its equilibrium concentration (i.e., the solution is *supersaturated*). The driving force for crystallization is therefore the degree of supersaturation, expressed as the difference in concentration between the supersaturated and saturated solutions. The most common methods to create supersaturation in a solution include temperature change, solvent evaporation, chemical reaction, pH change, and alteration in solvent composition. The *metastable limit* (dashed line) defines the compositions at which spontaneous crystallization occurs and the region bounded by the solubility curve and the metastable limit is termed *metastable zone*. The metastable zone width depends on purity of the system, thermal history of solution and density of foreign particles present in the solution and is of practical importance since it defines the working area for designed crystallizations (Beckmann, 2000).

2.2.2 Nucleation processes

Crystal nucleation involves the aggregation of dissolved molecules in the supersaturated solution into organized clusters (embryos) thus developing a surface that separates them from the environment. This process can be split into two main categories (Zettlemoyer, 1969; Mullin, 2001): (1) *primary nucleation*, when no crystals are initially present in the solution, and (2*) secondary nucleation*, when crystals of the solute are already present or are deliberately added to the solution as seeds. Primary nucleation is further classified into *homogeneous nucleation*, which occurs spontaneously in bulk solutions, and *heterogeneous nucleation*, which occurs at interfaces or surfaces and may be induced by foreign particles. Homogeneous nucleation rarely occurs in large volumes (greater than 100 µl), as most solutions contain random impurities which may induce nucleation (Perepezko, 1994; Gunton, 1999). Although heterogeneous and/or secondary nucleations are commonly

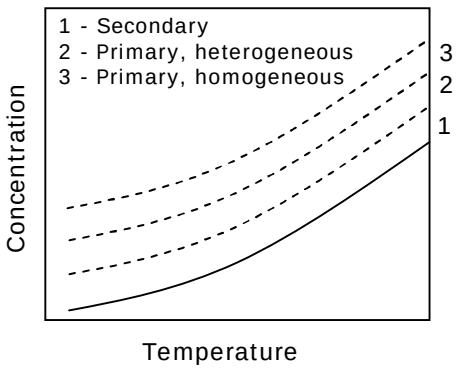


Figure 7 *Schematic diagram showing metastable zone width with respect to nucleation type.*

encountered in practice, homogeneous nucleation forms the basis for classical nucleation theory. Metastable zone widths with respect to nucleation type are schematically shown in *Fig. 7*.

Classical Nucleation Theory

The classical nucleation theory (Volmer, 1939; Gibbs, 1948; Nielsen, 1964) was originally derived for the condensation of vapor into liquid and has been extended to crystallization from solutions. According to this theory, the free energy change (ΔG_{total}) for a cluster undergoing a phase transition is given by

$$\Delta G_{total} = \Delta G_{surface} + \Delta G_{volume} \quad (5)$$

where ΔG_{volume} is a volume free energy term that proportional to the cube of the radius and favours aggregation of molecules and $\Delta G_{surface}$ is a surface free energy term that proportional to the square radius of the cluster and favours the dissolution of molecular clusters. Thus for a small radius, r, where the positive surface energy predominates, the nucleus is unstable and tend to dissolve. Eventually, the cluster attains the critical size ($r = r_c$) at which the surface term and volume term exactly balance. At this point the total free energy of the cluster attains a maximum, which corresponds to the activation free energy of nucleation (ΔG^*) (*Fig. 8*). Thus, supersaturation is required to overcome the free energy barrier to nucleation. After this stage, the cluster becomes viable and is termed a *nucleus*, which eventually grows into a crystal. For a polymorphic system, the polymorph that nucleates first is thought to come from the cluster that exhibits the fastest growth rate as a result of its lowest free energy barrier to nucleation. However, the nature of the polymorph that eventually crystallizes is determined by the combination of

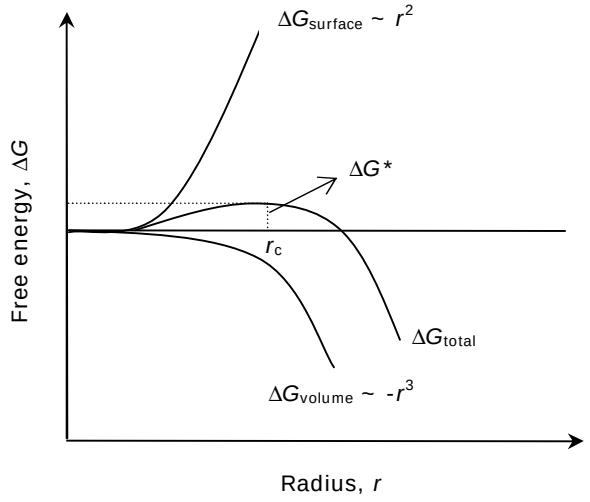


Figure 8 *Schematic plot of Gibbs free energy change of clusters during the process of molecular aggregation. Modified from Lohani and Grant, 2006.*

the relative nucleation rates and the relative crystal growth rates of the polymorphs (Bernstein *et al.*, 1999).

Recent theoretical and experimental evidence however suggests that the classical nucleation theory may not be qualitatively correct (Oxtoby, 1998; Davey *et al.*, 2002; Vekilov, 2004; Parveen *et al.*, 2005). The most critical limitation is that cluster size is the only criterion for whether concentration fluctuations become nuclei; thus this theory fails to recognized randomly oriented molecular aggregates that do not correspond to the solid crystals and organized clusters (Lee and Myerson, 2006). In addition, latest studies suggest that nucleation of solutes from solution is a two-step process (ten Wolde and Frenkel, 1997; Galkin and Vekilov, 2000; Vekilov, 2004; Chattopadhyay *et al.*, 2005): the creation of a droplet of a dense liquid, metastable with respect to the crystalline state, followed by ordering within this droplet to form a three-dimensional lattice structure.

In pharmaceutical industry, understanding and controlling nucleation is of importance, for example, when crystallizing specific crystalline forms or stabilizing supersaturated solutions (e.g. in transdermal formulations).

2.2.3 Crystal growth

Once formed, nuclei begin to grow larger through the addition of solute molecules to the crystal lattice, and this stage of crystallization process is known as *crystal growth*. Crystal growth is a multi-step process (Rodríguez-Hornedo and Murphy, 1999, Davey and Garside, 2000), which includes (1) transport of a *growth unit* (a single molecule, atom, ion, or cluster) from or through the bulk solution to an impingement site, which is not necessarily the final *growth site* (i.e. site of incorporation into the crystal); (2) adsorption of the growth unit at the impingement site, (3) diffusion of the growth units from the impingement site to a growth site, and (4) incorporation into the crystal lattice. Desolvation of the growth unit may take place anywhere in

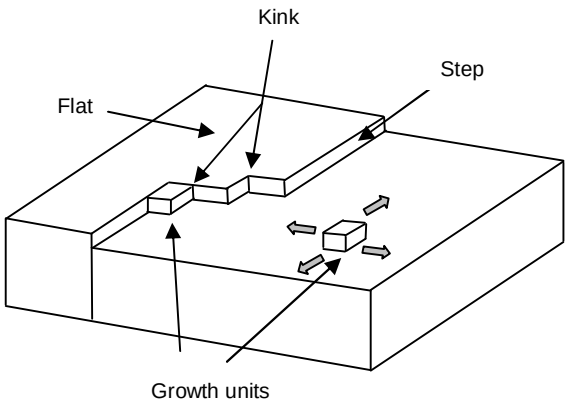


Figure 9 *A three-dimensional crystal surface showing three type of growth sites.*

steps 2–4 or the solvent may be adsorbed with the growth unit. The relative importance of each step depends on the surface structure of the crystals and the properties of the solution (Meenan *et al.*, 2002).

Based on their ability to capture arriving growth units, three types of crystal surfaces (and thus growth sites created by these surfaces) can be differentiated (Hartman and Perdock, 1955) (*Fig. 9*): kink, step and flat faces, which provide three, two and one surface bond(s), respectively. Assuming the linear relationship between a face growth rate and the total binding energy of a growth unit to the surface, the final shape of a crystal is defined by the slowest growing flat faces. Crystal growth theories are therefore concerned with the mechanisms by which these faces grow.

Crystal growth theories

The possible pathways by which a growth unit passes from solution to become integrated into the crystal lattice are known as *growth mechanisms*. Two mechanisms are considered to be of relevance to the actual process of growth on crystal faces – *two-dimensional (2-D) nucleation* and *screw dislocation* (Davey and Garside, 2000). Two-dimensional nucleation, also called the Birth and Spread (B+S) model, occurs when nuclei at the crystal surfaces act as sources of steps that allow for the further incorporation of growth units (Volmer, 1922). This mechanism has gained popularity, since it is simple yet based on firm thermodynamic and kinetic principles. However, it mainly accounts for the crystal growth observed at high supersaturations (Rodríguez-Hornedo *et al.*, 2006a).

An alternative mechanism suggested by Burton, Cabera and Frank (BCF) (Burton *et al.*, 1951) underlines the assumption that growth occurs by flow of steps across the surface. *Screw dislocation*, a common crystal defect formed when one region of the crystal is pushed up through one (or more) unit cells relative to another region, can be an infinitive source of these steps, onto which oncoming growth units can be incorporated. Since screw dislocations exist on crystal faces at low supersaturations level, the model suggest that the growth can take place under realistic conditions.

2.2.4 Crystal lattice imperfections

Industrially produced crystals are always *polycrystals* composed of a great number of small crystals whose lattices show numerous *imperfections*. There are four major types of lattice imperfections (Zhang and Grant, 1999; Mullin, 2001): (1) *zero-dimensional* or *point defects* (vacancies, interstitials, and substitutional), (2) *one-dimensional* or *line defects* (edge, slip, and screw dislocations); (3) *two-dimensional* or *surface defects* (grain, tilt, and twist boundaries), and (4) *three-dimensional* or *phase defects* (solid, liquid or gaseous inclusions).

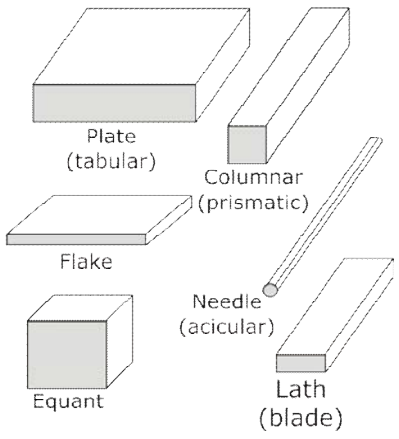
In addition to affecting crystal growth, these imperfections are known to influence the physicochemical (e.g. chemical reactivity, dissolution rate) and mechanical (e.g. elasticity, plactisity) properties of materials (Boldyrev *et al.*, 1979; Burt and Mitchell, 1981; Chow and Grant, 1989; Forbes *et al.*, 1992; Mullin, 2001). The nature and frequency of the crystal defects may change as a function of mechanical (e.g. grinding or milling) or thermal stress applied to the material. Milling, for example, can result in the formation of a large number of vacancies and dislocations (Fabbiani and Pulham, 2006), ulimately leading to the disappearance of long range order and crystallinity (amorphisation). Hence, crystal defects are thought to be an important source of batch-to-batch and lot-to-lot variations giving rise to processing problems and poor and inconsistent product performance (York, 1983; Shekunov and York, 2000). Quantitatively, crystal imperfections are commonly assessed in terms of crystallinity (York, 1992) or entropy changes (Grant and York, 1986a; Grant and York, 1986b).

2.2.5 Crystal habit

At equilibrium, the external shape of a crystal, also termed *habit*, *form* or *morphology*, is determined by its internal structural symmetry and this idealized equilibrium (minimum-energy) form is known as the *Wulff form*. Experimentally obtained crystals however exhibit a *growth habit* since the crystal growth is a nonequilibrium process. The equilibrium form can be achieved through an *aging process*, which involves solvent-mediated dissolution and regrowth of the crystal faces equilibrated in a saturated solution over time (Stranski and Honigmann, 1950; Saska and Myerson, 1987).

In crystallography, to relate a surface structure to the crystal structure a system of Miller Indices is used. These define the orientation of the surface in relation to the crystallographic unit cell, the smallest three-dimensional volume element from which the crystal can be constructed. Each face is designated with three integers, *h*, *k*, *l*, which are the inverse of intersections of that face with the crystallographic axes *a*, *b* and *c*; faces which are parallel to a crystal axis are given the Miller index of 0. In practice, crystal morphology is usually described in terms of length, width and thickness. Within the pharmaceutical industry the classifications of crystal shapes adopted by either British Standrad (BS 2955:1993) or the US Pharmacopoeia (monograph 776) (*Table 2)* are commonly used for routine microscopical examination of solid materials.

Table 2 *Classification of common crystal morphologies for pharmaceutical solids accepted by the US Pharmacopoeia*

Morphology	Description	Diagram
Equant	Crystal with similar length, width, and thickness	
Flakes	Thin, flat crystals of similar width and length	
Plates	Flat, tabular crystals with similar width and length but thicker than flakes	
Laths	Elongated, thin and blade-like crystals	
Needles	Acicular, thin and highly elongated crystals having similar width and breadth	
Columnar	Elongated, prismatic crystals with greater width and thickness than needles	

2.3 Crystallization and designing properties of pharmaceuticals

The quality of crystallization depends on a large number of factors that influence crystal nucleation and growth, including the composition of the crystallization medium and the process(es) used to generate supersaturation and promote crystallization. The crystallization of pharmaceutical solids should be designed to control the crystalline form, purity, yield, crystal size distribution, and crystal shape. Apart from yield, all these

qualitaties have a profound effect on stability, processability and/or bioavailability of the product (see *Table 1*). This section of the thesis is focused on general approaches used to generate and tailor properties of pharmaceutical solids.

2.3.1 Polymorph screening

Polymorph screening, which includes generation and characterization of different solid phases, is an obligatory procedure specified by the International Conference on Harmonization (ICH) guideline for new APIs (ICH, 1999). The ultimate goal of this procedure is to select a form with the appropriate balance of critical properties for development into the drug product (typically, the most thermodynamically stable). In addition, precise knowledge of the polymorphic behaviour of an API is needed for intellectual property protection and design of robust larger-scale crystallization processes.

Although several flow charts and decision trees have been suggested (Byrn *et al.*, 1995), there is no universally accepted guideline on how to perform polymorph screening. In general, the procedure must be tailored to the substance investigated and the actual product development phase (Huang and Tong, 2004; Hilfiker *et al.*, 2006). For example, a screening performed early in development simply aims to identify the thermodynamically stable form and hydrates, and thus slow crystallization experiments should be favoured over fast ones. Later product development phases require identification of all relevant solid forms.

Crystallization from solution (cooling or evaporative, as well as slurry conversion) and recrystallization from neat API (sublimation, thermal treatment, crystallization from the melt, grinding, and thermal desolvation) are most often employed in screening experiments (Guillory, 1999; Morissette, 2004). To increase the probability of discovering all relevant forms, the multiparameter space that contributes to solid form diversity (see *Table 3*) should be covered as broadly as possible. This is usually achieved by designing a rational set of the process variables (Huang and Tong, 2004; Hilfiker *et al.*, 2006). With respect to crystallization solvent, for example, such set typically encompasses (1) solvents with broad distribution of properties (Gu *et al.*, 2004), (2) potential solvents of synthesis, purification and processing, (3) potential solvents for formulation (e.g. polyethylene

glycols). In addition, crystallizations from water and water-solvent mixtures are usually included in the screens to generate hydrates.

Table 3 *Process variables affecting crystallization outcome. Modified from Morissette et al., 2004*

Crystallizing phases		Crystallization method			
Polymorphs/ solvates	Salts/ co-crystals	Cooling crystallization	Evaporation	Precipitation	Slurry conversion
Solvent composition	Counter-ion type	Heating rate	Evaporation rate	Anti-solvent type	Solvent type
Degree of supersaturation	Acid/base ratio	Cooling rate	Evaporation time	Rate of anti-solvent addition	Incubation temperature
Additive type	Solvent/Solvent combination	Maximum temperature	Carrier gas	Temperature of anti-solvent addition	Incubation time
Additive concentration	Degree of supersaturation	Incubation time	Surface-volume ratio	Time of anti-solvent addition	Thermal cycling and gradients
	Additive type	Incubation temperature			
	Additive concentration				
	pH				
	Ionic strength				

Recently developed high-throughput crystallization technologies (Peterson *et al.*, 2002; Hilfiker *et al.*, 2003) utilize a combination of robotic handling together with small volume crystallization reactors and allow for more rapid and comprehensive exploration of multivariate crystallization space. In addition, several innovative techniques have been reported, such as capillary crystallization (Childs *et al.*, 2004a), laser-induced crystallization (Myerson and Garetz, 2002) and sonocrystallization (Ruecroft *et al.*, 2005) that promote nucleation and hence discovery of alternate crystalline forms. Finally, a number of attempts to develop *ab initio* polymorph screening algorithms has been reported (Karfunkel and Gdanitz, 1992; Chaka *et al.*, 1996; Ferrari *et al.*, 2006). However, success using computing approach is limited (Gavezzotti, 1994) and thus theoretical prediction of crystal structures still remains an admirable long-term goal.

2.3.2 Directed crystallization of specific crystalline forms

Exploring Ostwald's law of stages

The key thermodynamic variables that affect the kinetics of crystal nucleation and growth are supersaturation and interfacial energy. This implies that resulting the crystalline form may vary with *degree of supersaturation* and *type of crystallizing solvent*. The effect of supersaturation on crystallization of polymorphs has been described by the empirical Ostwald's law of stages (Ostwald, 1896), which states that the most soluble and the least stable form crystallizes first. Theoretically, it can be justified by a higher nucleation rate of the least stable form arising from a smaller critical nuclei radius (Shekunov and Grant, 1997). Hence, fast crystallization or crystallization at high supersaturations will preferentially lead to a metastable form. However, Ostwald's law of stages is not universal because the appearance and evolution of solid phases are determined by the kinetics of nucleation and growth under specific experimental conditions (Cardew and Davey, 1985; Davey *et al.*, 1997). The above concept is also applicable for solvates and hydrates (Khankari and Grant, 1995).

Altering crystallizing solvent, temperature or pH

The selectivity of solvent on the formation of specific polymorphs is well recognized. This effect is largely kinetic (Khoshkhoo and Anwar, 1993) and depends on the nature and strength of solute-solvent interactions (Weissbuch *et al.*, 1999; Weissbuch *et al.*, 2005). More precisely, preferential solvent adsorption on the nuclei's surface alters the activation energy of nucleation for a particular polymorph (see *Fig. 7*) by decreasing the surface free energy and consequently total free energy of these nuclei (Gu *et* al, 2002). Hence, in one solvent one form might be obtained preferentially while the other one may crystallize in a second solvent under exactly the same crystallization conditions. The relative stability of polymorphs is not affected by the solvent as the latter can only interact with the surface and the surface contribution to the free energy of a crystal is generally negligible (Hilfiker *et al.*, 2006).

Overall, it has been demonstrated that the crystallization outcome is under thermodynamic control when the concentration and temperature of crystallization is

significantly above or below the transition temperature (*Fig. 10*), while near the transition temperature the resulting polymorph may be significantly influenced by the relative nucleation rates of the polymorphs and/or specific interaction between a given polymorph and the solvent (Threlfall, 2000). Therefore, interplay between kinetic and thermodynamic conditions is usually employed to produce the desired polymorph from different solvent or solvent systems (Berman *et al.*, 1968; Gu, 2001; Bernstein, 2002). For example, metastable crystalline solids can be obtained either by rapid crystallization in a monotropic system or by temperature change in an enantiotropic system. Clearly, the solvent is the decisive factor for the crystallization outcome if a solvate can be formed with that particular solvent. By changing the activity of water in both miscible and immiscible organic solvents the desired hydrate can be produced (Zhu *et al.*, 1996), with lower temperatures favouring formation of solvates of higher stoichiometry (Byrn, 1999).

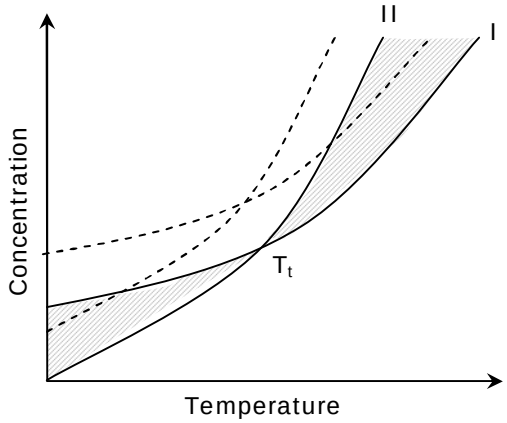


Figure 10 *Solubility curves (solid lines) and metastable zone limits (dashed lines) for two enantiotrops I and II. The regions of negligible solvent effect on the crystallization outcome are highlighted. Modified from Threlfall, 2000.*

The pH of the crystallizing solvent is of particular importance for crystallization of salts. In some cases, however, the pH or polarity of the solvent can be decisive factor for controlling the crystallization of polymorphs (Byrn *et al.*, 1994; Towler *et al.*, 2004).

Using Additives and Impurities

Impurities (unintentionally present components) and *additives* (intentionally added impurities) are also known to affect nucleation via the mechanism described for solvents (see the previous subsection). The examples of additives employed for controlling polymorphic outcome of pharmaceuticals include structurally related (tailor-made) organic molecules (Weissbuch *et al.*, 1991; Mukuta *et al.*, 2005; Lee *et al.*, 2006), polymers (Lang *et al.*, 2002b; Langevin, 2002) and surface-active agents (Garti and Zour, 1997; Rodríguez-Hornedo and Murphy, 2004). Polymers and surfactants can also act as crystallization or

phase transformation inhibitors in pharmaceutical formulations (Simonelli *et al.*, 1970; Katzhendler *et al.*, 1998; Airaksinen *et al.*, 2005; Klein *et al.*, 2005; Leveque *et al.*, 2006; Salameh and Taylor, 2006; Tian *et al.*, 2007). Furthermore, reaction by-products and other impurities have been recognized to direct polymorph appearance (Blagden *et al.*, 1998), and in some cases, a metastable one (Davey *et al.*, 1997; He *et al.*, 2001; Gu *et al.*, 2002). In addition, a variety of inorganic and organic crystal surfaces have been proposed to control polymorph crystallization (Hooks *et al.*, 2001; Mitchell *et al.*, 2001; Lee *et al.*, 2005). This approach is based on an epitaxial mechanism when the oriented growth of a substance on a surface occurs due to the alignment of their lattice parameters. Polymer heteronucleation is the first combinatorial approach to controlling polymorphism that directly targets nucleation (Lang *et al.*, 2002a). In this case, the polymer acts as an additional diversity element to affect the crystallization outcome. This provides the potential for controlling the formation of established forms as well as the discovery of unknown polymorphs without prior knowledge of crystal structure. For example, a fourth polymorph of carbamazepine was discovered (Lang *et al.*, 2002b) using this approach that, remarkably, proved more stable that the well-studied trigonal form (Grzesiak *et al.*, 2003).

Seeding

The addition of solid particles (seeds) of the desired phase to a crystallization medium is known as *seeding*. It is often only reliable way to obtain the desired form (Beckmann, 2000) and even if an API does not show polymorphism, seeding is frequently applied to control the crystallization process (Hilfiker *et al.*, 2006). Controlling crystallization outcomes via seeding relies on the potential of crystal surfaces to promote heterogeneous or secondary nucleation, while avoiding heterogeneous nucleation mediated by unknown contaminants (Mullin, 2001). The crystallization of ritonavir polymorphs (Bauer *et al.*, 2001) is an example of the vivid effects of accidental heterogeneous nucleation where an insoluble degradation product promoted the nucleation of a more stable polymorph. Seeding can also be employed for chiral resolution of enantiomers during crystallization (Collet *et al.*, 1980; Sheldon, 1990; Gu and Grant, 2000). The factors affecting the seeding effectiveness include seed addition timing and method, seed surface properties, and the rate of supersaturation generation (Paul *et al.*, 2005).

2.3.3 Solvent-mediated transformations

The stable crystalline modification is usually preferred to its metastable counterpart for formulation and processing. However, sometimes a metastable solid phase with greater thermodynamic activity is chosen due to its better biopharmaceutical performance. The drawback is that since any system strives to reach equilibrium, a metastable form present in the formulation is prone to a *solvent-mediated transformation* upon processing (e.g. wet granulation) and/or storage. Such transformation is driven by the solubility difference between the two phases when the metastable phase is in contact with the saturated solution and allows for the transition from a metastable to the stable phase. Based on this, solvent-mediated transformations are widely used to produce the most stable polymorph (Gu *et al.*, 2001).

A solvent-mediated transformation involves three consecutive steps (Cardew and Davey, 1985): (1) initial dissolution of the metastable phase into the solution to reach and exceed the solubility of the stable phase; (2) nucleation of the stable phase; (3) crystal growth of the stable phase coupled with the continuous dissolution of the metastable phase, with step (2) or (3) being usually the slowest one. When step (2) is rate-determining, the overall transformation is influenced by factors that affect nucleation (e.g. solubility and solubility differences between the phases, processing temperature, contact surfaces, agitation, and soluble excipients/impurities). When step (3) is the rate-controlling step, the kinetics of the conversion is determined by the solubility difference, solid/solvent ratio, agitation, processing temperature, particle size of the original phase, and soluble excipients/impurities (Zhang *et al.*, 2004).

This kind of transformation may also occur during solubility measurements, dissolution studies and accelerated stability tests in hydrated systems (Khankari *et al.*, 1998; Aaltonen *et al.*, 2006; Tian *et al.*, 2007). The rate of transformation may be influenced by retarding the rate of dissolution of the less stable species e.g., by introducing specific impurities that act as inhibitors. Finally, the effect of formulation on the phase transformations cannot be overlooked. For example, solid dispersions or high viscosity lipid-based formulations can be ideal environments for the formation of a more stable crystalline form (Martinez-Oharriz *et al.*, 1999; Huang and Tong, 2004). Potentially, solvent-mediated polymorphic transformations can be exploited for exclusive production

of a metastable form of an API by utilizing solvents in which the transformation is slow (Okamoto *et al.*, 2004).

2.3.4 Particle size control

Particle size is one of the physicochemical properties influencing the performance of the drug product and its manufacturability (http://www.ich.org) (see *Table 1*). Accordingly,

Table 4 *Particle size distribution of pharmaceuticals with respect to dosage form and route of administration (according to Shekunov et al., 2007)*

Dosage form or route of administration	Particle Size (μm)	
	min	max
Oral granules	200	1000
Oral depot	50	200
Intraperitoneal	10	50
Nasal	5	20
Aerosols	1	5
Ocular	0.1	2.5
Intravenous/intramuscular	0.2	2
Gene delivery	0.2	0.9
Transdermal	0.06	0.6
Long-circulating (brain, tumor)	0.06	0.2
Lymphatic	0.01	0.06

the design of particle size distribution with respect to dosage form and administration route (*Table 4*) as well as consistent particle size control during crystallization are required. In this context, production of micro- and nanosized particles represents the most challenging area (Chow *et al.*, 2007).

Supersaturation is the key factor affecting particle size as the number of molecules necessary to achieve an effective nucleating cluster is inversely proportional to the level of supersaturation (Rodríguez-Hornedo and Murphy, 1999). Therefore, the number of crystals produced increases with the supersaturation, whilst the size of crystals decreases. A number of crystallization techniques for generating micron- and submicron-sized particles – for example, impinging jet crystallization (Midler *et al.*, 1994) and solvent shifting (Horn and Rieger, 2001) - are based on fast nucleation under high supersaturation

conditions. Potential problems associated with such nucleation-driven processes include lack of control over the resulting solid form (e.g. amorphous material or an undesired polymorph), broad particle size distribution, high surface area, low bulk density, agglomeration and aggregation, the risk of large batch-to-batch variations, and solvent or impurity entrapment (Mullin, 2001; Paul *et al.*, 2005).

Other crystallization-based approaches to controlling crystal size include seeding (Bohlin and Rasmuson, 1992; Braatz *et al.*, 2006), precipitation in the presence of growth-retarding additives (Rasenack *et al.*, 2003; Mathiowitz *et al.*, 2004), sonocrystallization (Dennehy, 2003; Price and Kaerger, 2005; Bucar and MacGillivray, 2007), confined crystallization (Yano *et al.*, 2000; Lee *et al.*, 2005), and supercritical fluid crystallization (Hanna and York, 2006).

Supercritical Fluid Crystallization

Supercritical fluid (SCF) technologies enable single step crystallization of particulate pharmaceutical materials with precisely controlled characteristics such as solid-state form, particle size, shape and crystallinity (Loth and Hemgesber, 1986; Kordikowski *et al.*, 1999; Shekunov and York, 2000; Edwards *et al.*, 2001; Shekunov *et al.*, 2006). This control is achieved by utilising SCFs (gases and liquids at temperatures and pressures above their critical points) as solvents with tunable viscosity, density, and solvation strength (Tom and Debenedetti, 1991). For pharmaceutical applications, the most widely used SCF is carbon dioxide because of its low critical temperature (31.1 ^{o}C), attractiveness for heat sensitive materials including biomolecules, as well as being non-flammable, non-toxic, GRAS ('generally regarded as safe') status and inexpensive (York, 1999).

For pharmaceutical materials, the most commonly used modifications of SCFs processing have been precipitation from supercritical solutions composed of SCF and solute(s) and precipitation from saturated solutions using SCF as a non-solvent or antisolvent. The former process involves dissolving the solute in a SCF, followed by a rapid expansion of the SCF solution across an orifice to cause a supersaturation of the solute, homogeneous nucleation and thereby particle formation (Shekunov, 2004). The main weakness of this method is the poor solubility of most drugs in SCFs (Shah, 2006). The second approach utilizes a similar concept to the use of antisolvents in solvent-based crystallization processes and overcomes the solubility limitation by dissolving the drug in

a conventional solvent. In addition, it allows for the efficient separation (by decompression) of the antisolvent from both the solvent and solid products (Palakodaty and York, 1999; Kordikowski *et al.*, 2001).

Ostwald ripening

Theoretically, the particle size distribution should ultimately change towards that of a monosized dispersion when the solid remains in contact with its own saturated solution as larger crystals tend to grow (or ripen) at the expense of smaller ones. This process of crystal coarsening is known as "*Ostwald ripening*" (Ostwald, 1896) and is driving by the solubility difference between smaller and larger crystals; small crystals (>1 μm) have excess free energy (i.e. higher solubility compared with larger crystals) due to their high surface curvature and thus larger crystals are more energetically favoured. Ripening can take place, for instance, in suspension during crystallisation or wet granulation. Control of this process is important in cases where small particle size is needed (e.g aerosol products). In order to retard this process, additives (e.g. gelatin or carboxymethyl cellulose) are commonly used in industry (Mullin, 2001). In contrast, this process can be accelerated by the use of controlled temperature fluctuations (temperature cycling).

2.3.5 Morphological crystal engineering

The growth habit of a crystal is the result of the relative growth rates of its faces, with the morphological importance of a crystal's face being inversely proportional to its growth rate. The growth rates of the different crystal faces are determined by intermolecular interactions between molecules in the crystal as well as by a number of external parameters such as solvent, supersaturation, temperature, and impurities (Myerson, 1999). Changes in any of these may lead to significant modifications in crystal morphology. This gives rise to crystal habit diversity of a chemical entity grown under various crystallization conditions and provides the basis for morphological crystal engineering.

Varying degree of supersaturation and temperature

Owing to anisotropic growth rates of surfaces, the growth habit of a crystal reflects the supersaturation in which the crystal grows (Okutsu *et al.*, 2003). This effect can be expressed as:

$$y/x = k\Delta S^{n} \quad (6)$$

where y/x is the ratio of crystal length to width; k is a coefficient of proportionality depending on diffusion; ΔS is the degree of supersaturation (moles/1000 moles of solvent, at the moment of nuclei formation); and n is a number that depends on the crystallographic classification and chemical composition of the substance (Grzymek, 1937). Thus, a system at very high supersaturation may produce a vast quantity of small, elongated microcrystals over a very short timescale, whilst a low supersaturation solution is likely to produce larger, granular-shaped crystals over a longer period (Haleblian, 1975). The size and habit of many crystalline products are particularly sensitive to degree of supersaturation (Ristic *et al.*, 2001).

The effect of temperature on the crystal morphology can be described by Arrhenius equation dictating linear relationship between the crystal growth rate and temperature. Hence, crystals tend to be more isotropic in their shape when grown at higher temperatures (Davey and Garside, 2000).

Influence of solvent

Solvents may influence the rate of crystal growth through their effects on solution properties (e.g. density, viscosity, diffusivity), solubility of the crystallizing species and surface-solvent interactions. However, it is generally accepted that the underlying mechanism for the solvent action as crystal habit modifier is preferential adsorption at specific crystal faces which will inhibit their growth as removal of bound solvent possesses an additional energy barrier for continued growth (Weissbuch *et al.*, 1991). As a result, the crystallization from a solvent with high structural affinity to the crystallizing species may yield fine, symmetrical or elongated crystals due to the delayed growth of all or selected crystal faces, respectively (Tiwary, 2006).

Crystal habit modification by changing the solvent has been widely used (Haleblian, 1975; Davey *et al.*, 1982; Marshall and York, 1989; Marshall and York, 1991; Garekani *et al.*, 2001; Karunanithi *et al.*, 2006). However, this approach is limited by the solvent toxicity and cost, crystallization efficiency and the purity requirements of the final product. Hence, it is not always possible to find a suitable solvent that yields a desirable habit.

Employing additives

Similar to solvents, additives control crystal shapes by virtue of their structural relationships with the crystal surfaces in question and the decisive mechanism takes place when they are adsorbed on the crystals faces (Mersmann *et al.*, 2001). Additives can be classified into three categories based on their chemical nature (Rodríguez-Hornedo 1990).

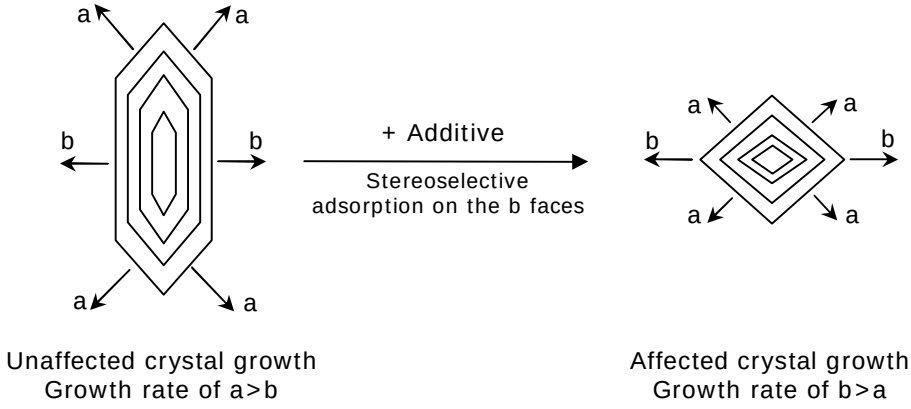


Figure 11 A *schematic showing changes in crystal morphology via selective adsorption of an additive/impurity/solvent onto specific crystal faces. Modified from Weissbuch et al., 1999.*

The first includes low-molecular-weight inorganic compounds that are active mainly in ionic systems. The second class is composed of low-molecular-weight organic substances (e.g. citric or succinic acids) or substances with similar structures to the crystallizing solute but possessing additional functional groups. These adsorbates are generally incorporated into the crystal at the surface, introducing lattice strains that markedly influence the apparent solubility of the developing faces. Polymeric materials and surface-active agents that are active for both ionic and non-ionic systems constitute the third group. Additives may adsorb generally upon all crystal faces, reducing the rate of

crystallization to zero, or, upon selective faces, leading to a change in morphology of the developing crystals. Because additives may affect the crystallization kinetics in low concentrations ($<10^{-3}$), this approach is frequently used to modify the crystal habit of pharmaceuticals (Michaels and Colville, 1960; Fairbrother and Grant, 1978; Chow *et al.*, 1985; Williams-Seton *et al.*, 2000; Garnier *et al.*, 2002; Shekunov *et al.*, 2003; Jarmer *et al.*, 2005; Kuldipkumar, 2006). A mechanism of morphological change due to preferential adsorption of an additive (or solvent) is illustrated in *Fig. 11*.

2.3.6 Improving solubility and dissolution rate

The dissolution rate can sometimes be enhanced by crystallizing poorly soluble APIs in aqueous solutions containing surfactants or water-soluble polymers as additives (Chiou *et.* al., 1976; Naggar *et al.*, 1980; El-Bary *et al.*, 1990). This effect has been attributed to improved wettability due to traces of adsorbed additive in the crystals. In addition, the deposition of additive molecules onto the crystal during crystal growth might produce a defect in the crystal structure making the crystal thermodynamically unstable and hence, faster dissolving (Chiou *et al.*, 1976). The same effect can be achieved by using structurally-related additives (Fairbrother and Grant, 1978). Alternatively, in situ micronization during crystallization (Rasenack and Müller, 2002b) and crystal habit modification (Haleblian, 1975; Blagden *et al.*, 2007) may improve the dissolution rate of poorly water-soluble APIs.

An emerging approach to enhancing the solubility of APIs is the formation of *cocrystals* (Vishweshwar *et al.*, 2006), where crystalline complexes of two or more neutral molecular constituents are bound together in the crystal lattice through noncovalent interactions (primarily hydrogen bonding). Cocrystallization can be performed by evaporation of a heteromeric solution, cogrinding the components, sublimation, growth from the melt, or slurry technique (Blagden *et al.*, 2007). Two main benefits associated with this approach are the theoretical capability of all types of molecules, including weakly ionisable and non-ionizable, to form cocrystals, and the existence of numerous potential counter-molecules for cocrystal synthesis (Vishweshwar *et al.*, 2006). Examples of the pharmaceutical cocrystals reported include caffeine (Trask *et al.*, 2005;

carbamazepine (Rodríguez-Hornedo *et al*., 2006a), fluoxetine hydrochloride (Childs *et al.*, 2004b), ibuprofen (Walsh *et al*., 2003), and itraconozole (Remenar *et al.*, 2003).

2.3.7 Crystal morphology in relation to pharmaceutical processes and dosage form performance

A number of formulation- and dosage form-related properties (e.g. bulk density, flowability, compressibility, filterability, suspension stability, wettability, dissolution rate) can vary with crystal habit (York, 1983; York, 1992; Rasenack and Müller, 2002a; Tiwary, 2006). Equidimensional crystals such as cubes or spheres are usually preferred in industry as they have better handling and processing characteristics. For instance, such crystals demonstrate better flow properties and minimum aggregation due to their loose packing and low bulk density (Bandyopadhyay and Grant, 2000; Carstensen, 2001; Sun and Grant, 2001). Crystals with a high-aspect-ratio, however, were shown to be advantageous for pulmonary drug delivery demonstrating a tendency to deposit more effectively into the deep lung (Chikhalia *et al.*, 2006). On the other hand, needle-like crystals are complicated to inject through a fine needle (Haleblian, 1975) and tend to clog the pores in the filter medium in filtration processes (Lee and Myerson, 2006). Therefore, morphological crystal engineering should be considered as a valuable tool to enable material with optimal physical properties for a specific formulation.

The effect of crystal habit on tabletting behaviour can be linked to the relative orientation of the crystallites during compression (Shell, 1963; Bandyopadhyay and Grant, 2002). Certain crystal habits (e.g. plates, rods or needles) tend to pack preferentially with their longer dimension(s) oriented normal to the compression axis forming a layered structure. Such a structure often exhibits low lateral stress transmission characteristics and results in a weak compacts (Windheuser, 1963; Bandyopadhyay and Grant, 2002). In contrast, more equidimensional crystals have a propensity to orient randomly and demonstrate overall reduced anisotropy during compression leading to better tabletting performance. The crystals habit of drugs to be administered in high doses (e.g. erythromycin A base) is of special concern since compression properties of the tabletting mass will be dominated by the API. Additive-induced crystal habit modification may also favour mechanical properties of the material by introducing lattice strain (Fairbrother and

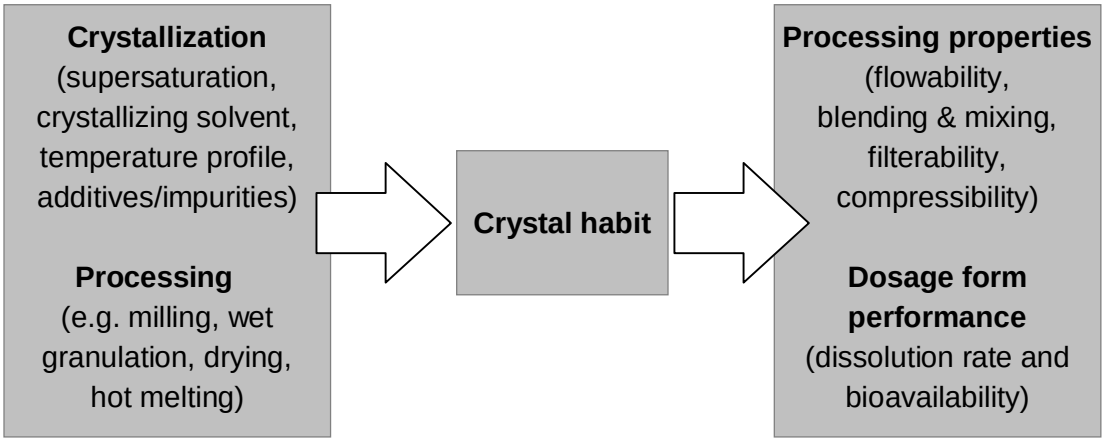


Figure 12 *Schematic representation of the relationship between crystal habit, processing and dosage form performance.*

Grant, 1978; Chow *et al.*, 1984; Byrn *et al*., 1994) and hence reducing the energy required for plastic deformation (Alderborn and Nyström, 1995; Feng and Grant, 2006). The latter underlines the fact that at fundamental molecular level mechanical properties of the material are primary defined by internal structure of the crystal (Roberts *et al*., 1995; Sun and Grant, 2001; Bandyopadhyay and Grant, 2002; Wildfong *et al*., 2007).

The dissolution rate can vary with the habit because differences in surface chemistry of the crystal faces give rise to differences in their surface free energy (Lee and Myerson, 2006). Thus modified crystal habit can be exploited to increase the dissolution rate of poorly-water soluble drugs.

Finally, it is worth mentioning that processing and formulation procedures may induce changes in the crystal morphology of an API and/or excipient(s) (York, 1992; Yoshinari *et al.*, 2002; Zhang *et al.*, 2004). For example, during drying or wet granulation supersaturated states are often created which may lead to the crystallization of an API or excipient(s). In the strictest sense, the excipient is an impurity with respect to the API (or vice versa) and may serve as a crystal habit modifier (Rodríguez-Hornedo *et al.*, 2006a). Consequently, the drug-excipient (or excipient-excipient) interactions could have a tremendous impact on the morphology with an adverse effect on further processing and/or drug delivery. The similar effect can be observed if an API or excipient is able to undergo a processing-induced phase transformation resulting in a crystalline form with different crystal habit. The relationships between crystal habit, processing and dosage form performance are schematically present in *Fig. 12*.

3. AIMS OF THE STUDY

The overall goal of this thesis was to gain better understanding of relationships among crystallization, solid-state nature, and properties of pharmaceutical solids. In addition, an objective was to employ a crystal-engineering approach for designing technological properties of APIs.

The specific aims were:

1) To study solid-state properties of crystalline forms of the model APIs, erythromycin A dihydrate and baclofen anhydrate, and to ascertain interconversion pathways between these forms (*Papers I, II, III*)

2) To investigate influence of the solvent system on crystallization behaviour of erythromycin A dihydrate (*Paper III*)

3) To get an insight into hydrate formation and dehydration phenomena of the model APIs (*Papers I and II*)

4) To understand the physical phenomena associated with aqueous wet granulation of baclofen and solid dispersion formation of erythromycin A with PEG 6000 (*Papers II and IV*)

5) To probe HPMC as a crystal habit modifier for erythromycin A dihydrate in relation to compaction properties (*Paper V*).

4. EXPERIMENTAL

Complete experimental details can be found in the original publications (*I-V*).

4.1. Materials

4.1.1 Active substances

The model APIs investigated in this study were erythromycin A base (EM) (USP) and baclofen (BF) (Ph. Eur.). EM dihydrate from Sandoz (Italy) (I, V) and EM dihydrate from Pharmacia & Upjohn (Kalamazoo, MI) (III, IV) and BF anhydrate from PCAS (Finland) (II) were used as received.

4.1.2. Excipients

Polyethylene glycol (PEG) (PEG 6000; Fluka Chemie AG, Buchs, Switzerland) was selected as a carrier polymer for solid dispersions (IV). In the crystallization experiments hydroxypropyl methylcellulose (HPMC) (Methocel E 4000, Dow Chemical Company, USA) was used as a polymeric additive (V).

4.1.3. Solvents

Purified water (Ph. Eur.) (I–V) and the following analytical-grade organic solvents were used in the crystallization experiments: methanol (MeOH) (III), ethanol (EtOH) (III, V), isopropanol (*i*-PrOH) (III), acetone (Ac) (III) and methylethylketone (MeEtCO) (III).

4.2 Crystallization and processing of materials

4.2.1 Generation of anhydrous, hydrated, dehydrated and amorphous phases (I–IV)

EM anhydrate (I, IV) was obtained by slurry conversion from an EM dihydrate aqueous suspension at ~100 ºC. EM dehydrate (I, IV) was obtained by dehydration of the dihydrate at 40 ºC. Amorphous EM (IV) was prepared by quench cooling of the melt in liquid nitrogen. BF monohydrate (II) was crystallized from water.

4.2.2 Polymorph screening (III)

Screening crystallization was performed using an automated 24-slotted reaction block crystallizer (Variomag 24.4-1, H+P Labortechnik GmbH, Munich, Germany) equipped with a PC-controlled cryostat (Huber, Offenburg, Germany). EM dihydrate was recrystallized from solutions (50 ml) in the abovementioned organic solvents or in 1:9, 2:1, and 5:5 (v/v) water-organic solvent mixtures. The crystals harvested were vacuum-filtered, dried in a vacuum oven at 40 °C for 12 hours, and stored in a desiccator at room temperature (21 ± 1°C).

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4.2.3 Additive-controlled crystallization of EM dihydrate (V)

The crystallizations (n=3) were carried out by precipitation technique at ambient temperature. A saturated solution of the drug in ethanol was slowly poured into an aqueous solution of HPMC of varying concentrations under constant stirring and the experiments were completed at solvent/antisolvent ratio of 1:9 (v/v). The final additive concentrations in the crystallization medium studied were 0 (hereafter referred to as *reference*), 0.1, 0.5 or 1 g/L (V, Table 1).

4.2.4 Preparation of physical mixtures and solid dispersions (IV)

Physical mixtures were prepared by gently mixing the drug (EM dihydrate) with a carrier polymer (PEG 6000), using a mortar and pestle at various weight ratios (10:90, 30:70, 50:50, 70:30, and 90:10) and were subsequently used for *in situ* monitoring of the solid dispersion formation.

Solid dispersions were prepared by melting the corresponding physical mixtures of the drug and polymer with constant stirring in a metallic mortar heated in a water bath and subsequent quench cooling with liquid nitrogen.

4.2.5 Wet massing (II)

Wet massing was carried out using a varying amount of purified water as granulating liquid (II, Table 1). The wet massing was performed with a mortar and pestle to simulate the early stages of preformulation, when the amount of a new API is relatively small. The wetted mass was stirred thoroughly and packed in sealed glass vials. The samples were analyzed by XRPD and Raman spectroscopy immediately after water addition as well as after 24 h of storage at room temperature.

4.2.6 Preparation of powder compacts (V)

Powder compaction behavior was evaluated with an instrumented eccentric tablet machine (Korsch EK0, Erweka Apparatebau, Germany). For each experiment, the powder (250±10 mg) was manually poured into a die and compacted at various compression pressures using flat-faced punches with a diameter of 9 mm. Thereafter crushing strength of the tablets was measured using a tablet hardness tester (Erweka, Germany). The results are represented as the mean and standard deviations of three determinations.

4.3 Physical characterization of materials and phase transformation monitoring

4.3.1 X-ray Powder diffraction (XRPD)(I–V)

X-ray powder diffraction (XRPD) patterns were measured using a theta-theta diffractometer (D8 Advance, Bruker AXS GmbH, Karlsruhe, Germany) (I–V). The experiments were performed in symmetrical reflection mode using a CuKα radiation source (λ=1.54 Å) with Göbel mirror bent gradient multilayer optics. Variable-temperature X-ray powder diffraction (VT-XRPD) was used to detect temperature-induced phase transformations (I–III) and in situ monitoring of solid dispersion formation (IV).

4.3.2 Thermal analyses (I–V)

The differential scanning calorimetry (DSC) curves were obtained with a DuPont instrument (Model 910S, TA Instruments Inc., New Castle, DE) connected to a data station (Thermal analyst 2000, TA Instruments Inc., New Castle, DE) (I–V).

Thermogravimetric analysis (TGA) was performed on a Mettler Toledo TA8000 system (Mettler-Toledo, Greifensee, Switzerland) equipped with a TGA850 thermobalance (I–III, V).

A hot stage (FP900, Mettler-Toledo GmbH, Greifensee, Switzerland) mounted on the optical microscope (Leica Microscopie und Systeme GmbH, Wetzlar, Germany) was used for visual examinations of temperature induced phase transformations (I, IV).

4.3.3 Microscopy (II–V)

The morphology of the crystals (II, III) and hydrate formation (II) were examined with an optical microscope (DAS Mikroskop, Leica Microscopie und Systeme GmbH, Wetzlar, Germany) equipped with a 3-CCD color camera (Sony XC-003P, K-Vision B.V., Huizen, Netherlands). The snapshots were captured using WinTV 2000 software (Hauppauge, London, UK).

Scanning electron microscopy (SEM) was used for detailed examination of the crystal morphology (II, V). SEM micrographs were recorded with a Zeiss DSM-820 (Carl Zeiss, Oberkochen, Germany) scanning electron microscope at an acceleration voltage of 10 kV.

4.3.4 Vibrational spectroscopy (I,II, IV)

Mid-infrared (mid-IR) spectra (IV) were recorded with a Vertex 70 Fourier-transform IR spectrometer (Bruker optics GmbH, Ettlingen, Germany).

The near infrared (NIR) spectra (II) were measured with a NIR spectrometer (Control Development Inc., South Bend, IN, USA) with a thermoelectrically cooled InGaAs diode array detector, tungsten light source and a fiber optic probe.

Raman spectra were collected using two different instruments. In paper I a Kaiser Holoprobe RXN1/785 Raman module (Kaiser Optical Systems, Inc., Ann Arbor, MI, USA) coupled via a mono-mode optical fiber to a Leica DMLP microscope (Leica Microscopie und Systeme GmbH, Wetzlar, Germany) was used, while in Paper II the spectra were recorded with a process-type Raman spectrometer (Control Development Inc., South Bend, IN, USA) equipped with a thermoelectrically cooled CCD detector and a fiber optic probe (RamanProbe, InPhotonics, Norwood, MA). A 500 mW laser source at 785 nm was used (Starbright 785S, Torsana Laser Technologies, Skodsborg, Denmark). Both NIR and Raman spectral intensities reported herein were normalized by standard normal variate (SNV) transformation.

4.3.5 Water sorption/desorption analysis (II)

Samples of BF anhydrate were dried in the oven (Heraeus Vacutherm, Heraeus, Germany) at 40 °C and 70 mbar for 3 h. The water sorption profile of the powder was determined gravimetrically after storage at 22 °C at different relative humidities (RHs) (0–95%). These RH conditions were achieved in vacuum desiccators by using saturated salt solutions. The sample weight (n=3) was monitored over time until no further weight change was observed. For the desorption study, samples of the monohydrate were stored at 0% RH.

4.4 Molecular modelling (I,V)

The single crystal X-ray diffraction data for EM dihydrate (Stephenson *et al.*, 1997) were retrieved from Cambridge Structural Database (CSD). The theoretical powder X-ray diffraction pattern of EM dihydrate (CSD refcode: NAVTAF) was calculated, and the Miller index of each diffraction peak was assigned using the Property Prediction Module of Cerius2. The theoretical growth form was computed by using molecular simulation software (Mercury, Cambridge Crystallographic Data Center, Cambridge, UK, v. 1.2.1) according to the Bravais-Friedel-Donnay-Harker (BFDH) theory. The same software was used for crystal structure visualization.

5. RESULTS AND DISCUSSION

5.1 Characterization of crystalline forms of model APIs

In this section, the crystalline forms of two APIs, erythromycin A (EM) and baclofen (BF), have been studied. There has been some confusion in the literature about the solid-state properties of EM crystalline forms (Bauer *et al.*, 1985; Murthy *et al.*, 1986), since none of the crystal structures has been solved until recently. In this study, an attempt has been made to bring physical characterization of unsolvated and several solvated forms of EM in line with the published crystal structure of EM dihydrate. In addition, the solid-state properties of the crystalline forms of another drug, BF, are reported for the first time.

5.1.1 Crystalline forms of erythromycin A (I, III, IV)

EM base (see *Fig. 5B*) can exist in several, with respect to water content, crystalline forms – the dihydrate, dehydrate, and anhydrate (Fukumori *et al.*, 1983; Laine *et al.*, 1987, Stephenson *et al.*, 1997) – with the dihydrate being the thermodynamically stable form at ambient conditions (Fukumori *et al.*, 1983). The experimental X-ray powder diffraction (XRPD) patterns for the crystalline forms of EM are shown in *Fig. 13*. Obviously that reflections associated with EM dihydrate (III, Table 1) are sufficiently distinguished from those of EM dihydrate. Meawhile, EM dehydrate – a stable form between 60 and 130 °C or RH<15% and 23 °C (Stephenson *et al.*, 1997) – is isomorphic to EM dihydrate and thus yields an XRPD pattern similar to EM dihydrate.

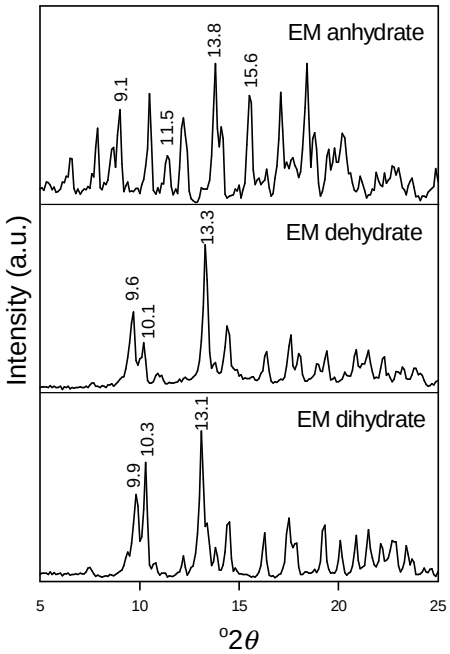

Figure 13 *XRPD patterns of the three crystalline forms of erythromycin A (EM). The values (°2θ) of the characteristic diffraction peaks are indicated. Modified from Paper I.*

EM dihydrate and EM anhydrate were also readily discriminated by their mid-IR spectra, especially in the C=O stretching region between 1740 and 1700 cm^{-1} (*IV, Fig. 2B*).

Raman spectra of the three crystalline forms of EM differed clearly in the spectral regions around 3100–2800 and 1750–1650 cm^{-1} (*I, Fig.* 2C), which correspond to the C-H and C=O stretching modes (Lin-Vien, 1991), respectively (*I*, Table 1).

5.1.2 Crystalline forms of baclofen (II)

Baclofen (see *Fig. 5A*) was found to exist in two crystalline forms, the anhydrate and monohydrate, as confirmed by multiple analytical techniques. There were distinct differences in the diffraction profiles of the anhydrate and monohydrate (*Fig.14*), indicating that these two solid forms have unique crystal structures. The most intense diffraction peaks were observed at 5.8, 17.5, 23.4 and 29.4° 2θ for the anhydrate and at 10.7, 16.1 and 21.5° 2θ for the monohydrate.

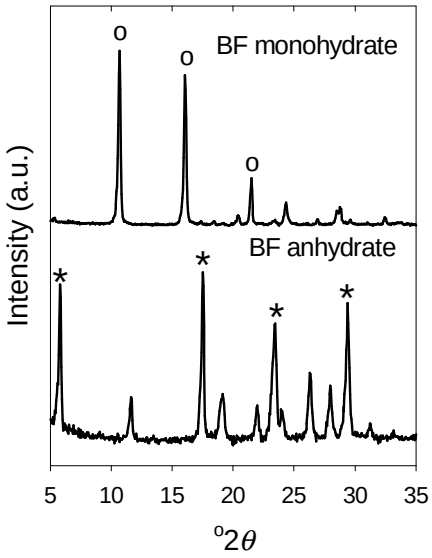

Figure 14 *XRPD patterns of the crystalline forms of baclofen reported with the characteristic diffraction peaks of the anhydrate and monohydrate indicated by (*) and (o). Modified from Paper II.*

The mid-IR spectrum of the monohydrate (*II; Fig. 2B*) shows a broad band at 3337 cm^{-1} that is absent in the anhydrous phase. This band corresponds to O–H stretch vibrations of water of crystallization, confirming its presence in the crystal structure of the monohydrate. The NIR (*II, Fig. 2C*;) spectrum of the monohydrate showed a distinct water absorbance maximum (due to combination of OH stretching and bending vibrations (Buijs and Choppin, 1963)) at around 1990 nm, while the anhydrate demonstrated no absorption bands in this spectral region. The principal differences in the Raman spectra of the two forms of BF occur between 700–1600 cm^{-1} and are shown in *Fig. 2D* (*II*).

In summary, it was shown that the two crystalline forms of BF are readily distinguished by XRPD and vibrational spectroscopy.

5.2 Solvatomorphism of model APIs

A number of common unit operations (e.g., wet granulation, spray-drying, lyophilisation, film-coating) in pharmaceutical industry expose APIs and excipients to solvents or solvent vapors, thus providing a possibility for a solvent to be incorporated into the crystal lattice. Since solvate formation is inevitably linked to a significant change in the material properties, this phenomenon should be systematically studied.

5.2.1 Effect of solvent composition on crystallization behaviour of erythromycin A (III)

Screening crystallization of EM dihydrate resulted in five crystalline solvates, as verified by XRPD, DSC and TGA – plate-like crystals of EM dihydrate (*III*, *Fig.* 6A) and EM ethanolate (EM·EtOH) (*III*, *Fig.* 6D), and needle-shaped crystals of EM acetonate (EM·Ac), EM methylethylketonate (EM·MeEtCO) (*III*, *Fig.* 6B) and EM isopropanolate (EM·*i*-PrOH) (*III*, *Fig.* 6C). When EM dihydrate was crystallized from a non-aqueous organic solvent, or from 1:9 or 1:1 water–organic solvent mixtures, a corresponding solvate was formed. Recrystallization from 2:1 water–organic solvent mixture resulted in plate-like EM dihydrate crystals with the exception of the water–MeEtCO solvent system, which yielded only crystals solvated with MeEtCO. Note that none of the solvent systems yielded EM anhydrate, indicating a high solvate-forming propensity of EM.

The crystals of EM·EtOH and EM·i-PrOH produced unique XRPD patterns, while the diffractograms of EM·Ac and EM·MeEtCO were very similar (*III*, *Fig.2*), suggesting that the latter two crystalline phases are isomorphous. Given the close relationship between the molecular structures of Ac and MeEtCO, the relatively small range of their molecular masses (58.1 and 72.1 g mol^{-1}, respectively) and the same hydrogen bonding capacity, isomorphism of EM·Ac and EM·MeEtCO is easily explainable. Dirithromycin, a

semisynthetic macrolide antibiotic, is also known to form isomorphic solvates (Stephenson *et* at, 1994). The quantitative characteristics of the XRPD patterns of EM solvatomorphs are presented in Table 1 (*III*). In summary, the relationships between all the crystalline forms of EM studied is schematically presented in *Fig. 15*.

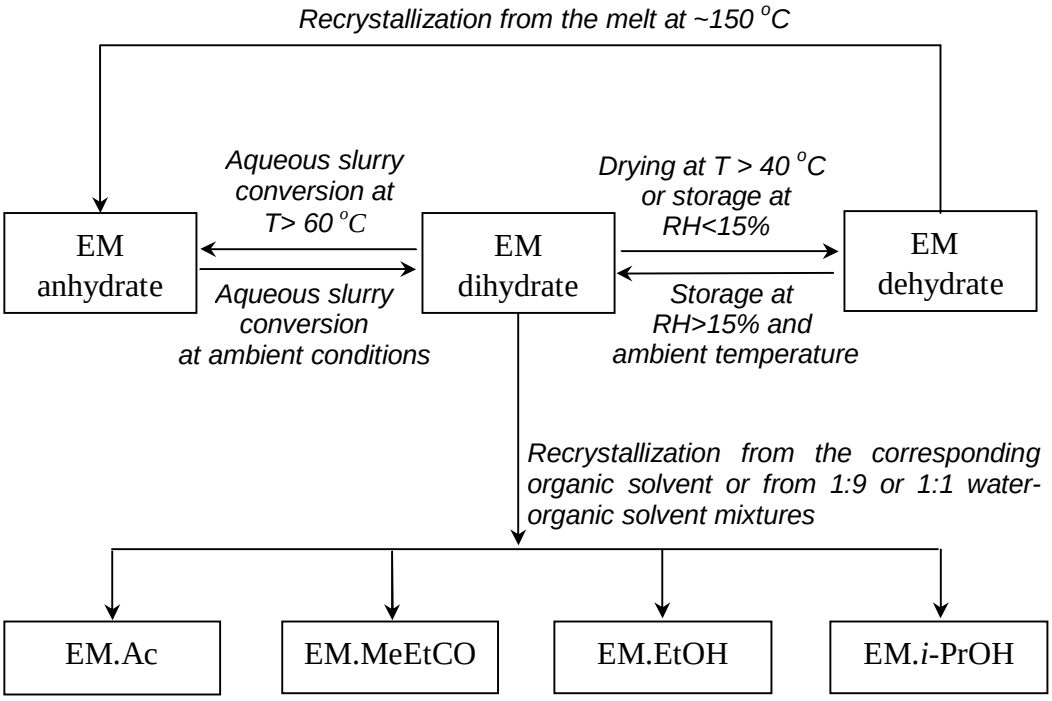

Figure 15 *Phase transformations between the reported crystalline forms of erythromycin A.*

5.2.2 Desolvation behaviour of erythromycin A solvatomorphs (I, III)

The desolvation behaviour of the solvatomorphs of EM was studied by thermogravimetric analysis (TGA), differential scanning calorimetry (DSC) and variable temperature XRPD (VT-XRPD). Since the single crystal data for the EM solvates and BF monohydrate are not available, this information allows for the general features of the solvent association to be deduced.

The desolvation characteristics for the EM solvatomorphs are summarized in *Table 5*. All the solvatomorphs demonstrated one-step desolvation, with the exception of EM·EtOH (*I*, *Fig.* 2B and *III*, *Fig.* 4). In the latter case, desolvation was a two-step process. Dehydration behaviour of EM dihydrate was in accordance with that of channel-type hydrates (Morris, 1999). In particular, smooth dehydration with the early onset was observed over a wide temperature range (40–100 °C). This result is in a good agreement with the EM dihydrate crystal structure (Stephenson *et al.*, 1997) indicating water molecules reside in the lattice channels (*I*, *Fig.* 5B). It is this structural feature of EM dihydrate that allows for an isomorphous dehydrate to be formed upon dehydration, as was revealed by VT-XRPD (*I*, *Fig.* 2A).

Table 5 *Desolvation characteristics of erythromycin A solvatomorphs*

Incorporated solvent	MW (g mol^{-1})	Onset of desolvation (^oC)	Enthalpy change J g^{-1}	TGA weight loss (%)	Number of solvent molecules/mol of drug
Acetone	58.1	56.5± 1.4	59 ± 1	7.6	1
Ethanol	46.1	54 ± 1.3 75 ± 2.6	68 ± 1 29 ± 1	19.0	3
Isopropanol	60.1	90.8 ± 1.2	143 ± 5	16.0	2
Methylethylketone	72.1	72.3 ± 1.9	68 ± 1	11.6	1
Water	18.0	50.7 ± 1.9	157 ± 3	4.6	2

The desolvation of Em·EtOH was observed under ambient conditions, as indicated by the formation of the opaque crystals. This phenomenon was attributed to the location of the guest molecules in the intersecting solvent tunnels running within the crystal lattice (Byrn, 1999). The DSC data also supported this assumption. The complete loss of the solvent of crystallization resulted in the collapse of the host crystal lattice.

The DSC desolvation endotherms of EM·Ac, EM·MeEtCO and EM·*i*-PrOH were relatively narrow, with the onset temperatures of the process observed near the boiling points of the corresponding solvents of crystallization (T_{onset} = 57, 59 and 91 ^oC, respectively) (*III*, *Fig.* 3). Such desolvation behaviour clearly differs from that of EM dihydrate and suggests different topology (e.g. isolated sites) of solvent inclusion (Morris,

1999). Desolvation of these solvates resulted in the formation of amorphous phase, as revealed by VT-XRPD (*III*, *Fig. 5B and 5C*).

5.2.3 Impact of crystal structure on dehydration mechanism of EM dihydrate (I)

The packing diagram of EM dihydrate (space group $P2_12_12_1$) (*I*, *Fig.5B*) shows that the water molecules are located in the lattice channels parallel to the *a*-axis. The presence of large enough channels (*I, Fig. 5C*), which have an approximately circular cross-section with a radius about 4 Å (Stephenson *et al.*, 1998), allows easy passage of water molecules with minimum energy expenditure and minimum disruption of the packing arrangement. Thus, it is hypothesized that the release of water from the EM dihydrate crystal occurs along these structural channels, as was demonstrated for a number of channel hydrates (Byrn, 1999).

The unified model for the dehydration mechanism of molecular crystals proposed by Petit and Coquerel (1996) classifies the process of water departure as: (1) cooperative, (2) destructive, or (3) possibly reconstructive. If the product phase retains structural information of the reactant (as in the case of EM dehydrate), the release of water molecules must occur by a cooperative process through lattice channels of sufficient size (≥3.5Å). The data obtained by TGA, where continuous dehydration and a low onset temperature were observed, are in agreement with this concept. Furthermore, the cooperative departure of water molecules presumes that the process is anisotropic, and again our results fit well with this concept. As observed by VT-XRPD, the (015) reflection plane shows the greatest reduction in interplanar spacing when the crystal is dehydrated. This effect can be caused by lattice contraction of either the *b*-axis or the *c*-axis. In the *b* direction, the crystal structure is stabilized against deformation by an intermolecular host–host hydrogen bond (*I, Fig. 5A*), while in the *c* direction several host molecules are separated by water (*I, Fig. 5B*). Thus, the *c*-axis is likely to experience the greatest degree of contraction upon water loss, providing anisotropic shrinkage of the lattice. Based on the information presented above, it can be concluded that the dehydration of EM dihydrate follows II topotactic mechanism (Petit and Coquerel, 1996), where no reorganization of

the dehydrated phase is required since the whole process is limited to the cooperative departure of water molecules through the water channels (one-step dehydration).

5.2.4 Hydrate formation of baclofen (II)

The phenomenon of hydrate formation of baclofen was probed using optical microscopy. Snapshots of the crystals periodically taken during the recrystallization of baclofen anhydrate from water are shown in *Fig.* 5 (*II*). As the dissolution of the acicular crystals of the anhydrate proceeds (*II*, *Fig. 5A*), the growth of whisker-like crystals takes place (*II*, *Fig. 5B*), suggesting that the anhydrous phase acts as a nucleation site for the monohydrate. Thereafter, fast dissolution of these whisker crystals was observed, and a few plate-like crystals of the monohydrate appeared in these crystallization conditions (*II*, *Fig. 5C*). During the cooling phase the monohydrate was the only form present (*II*, *Fig. 5D*).

It is generally accepted that anhydrous to hydrate phase transformations may occur by one of two processes when the solid is in contact with water: (i) a solid-solid transformation in which water molecules are incorporated into the crystal lattice while remaining in the solid state or (ii) a solvent-mediated process where the anhydrous solid dissolves and creates the necessary supersaturation for the nucleation and growth of a hydrate (Cardew and Davey, 1985). Our observations indicate that baclofen anhydrate to baclofen monohydrate transformation occurs via the second, i.e. solvent-mediated, route.

5.2.5 Dehydration behaviour of baclofen monohydrate (II)

The TGA trace for baclofen monohydrate (*II, Fig. 3A*) yielded a 7.5% weight loss (theoretical 8.4 %) in the temperature range of 40–80 ºC, confirming a stoichiometric drug–water ratio 1:1. Like in the case with the EM solvatomorphs, the low onset of dehydration suggests that the water molecules are located in the crystallographic channels.

The DSC curve of the monohydrate, superimposed in *Fig. 3A (II)*, is characterized by two endothermic events. Apart from a dehydration endotherm with the peak maximum at 67.1 ºC, the DSC trace yielded an endotherm at 211.8 ºC. The latter thermal effect

corresponds to the melting of the anhydrate (T_{max} = 213.3 ºC). This suggests that the dehydration of the monohydrate leads to the crystalline anhydrate. To verify this assumption, the dehydration of the monohydrate was also investigated by VT-XRPD over a temperature range of 25–100 ºC (*II*, *Fig. 3B*). The patterns of the sample generated below 50 ºC compare well with those of the monohydrate. At about 60 °C, the diffraction profile significantly changes resulting in the pattern similar to that of the anhydrate. Thus, on the basis of the data obtained by TGA, DSC and VT-XRPD it is deduced that baclofen monohydrate is a channel hydrate (Morris, 1999), which dehydrates at around 60 ºC with the formation of the anhydrate. Note that in contrast to EM dihydrate that was observed to form a metastable form upon dehydration (*I*, *III*), no intermediate crystalline or amorphous form was detected during dehydration of BF monohydrate.

5.3 Effect of processing on crystalline state of model APIs in the solid formulations

The existence of several solid forms of an API implies that interconversion among these forms during processing can occur. In this chapter, the physical phenomena taking place during two simulated processes, solid dispersion formulation by hot-melting (EM) and wet granulation (BF) are discussed.

5.3.1 Effect of PEG on phase behaviour of erythromycin A dihydrate during hot-melt processing (IV)

EM dihydrate – PEG 6000 (PEG) solid dispersions produced by hot-melting were used as model formulations, while the process was simulated in VT-XRPD, DSC, and HSM experiments in order to monitor in situ physical changes in the system. Upon heating from 25 to 135 ºC pure EM dihydrate was shown to undergo a single phase transformation – dehydration to isomorphic EM dehydrate at about 60 ºC (*III*, *Fig. 5A* and *IV*, *Fig.* 3). Thermal treatment of the drug with PEG caused multiple phase transformations (EM dihydrate → EM dehydrate → EM anhydrate) in the same temperature range, as was

detected by VT-XRPD (*IV, Fig. 3*) and visually observed by HSM (*IV, Fig. 5*). The onset temperature of the additional, EM dehydrate → EM anhydrate, transition, was seen between 80–130 ^{o}C and was found to depend on the drug-polymer ratio. Specifically, with increased polymer fraction, the onset temperature of the phase transition decreased.

Physical phase transformations are generally classified as solid-state transformations and solvent-–mediated transformations (Morris *et al.*, 2001). Because EM dehydrate did not convert to EM anhydrate in the solid state, the alteration in phase behaviour of EM was attributed to the ability of PEG in promoting nucleation and crystal growth of EM anhydrate via a solution-mediated route. The mechanism for solution-mediated transformations includes three steps: (i) dissolution of the less stable phase, (ii) nucleation of the more stable phase, and (iii) growth of the more stable phase (Cardew and Davey, 1985). Due to low melting point of PEG (~60 ^{o}C) (*IV, Fig. 4*, trace (h)), it can act as a solvent (Verheyen *et al.*, 2001) for a higher melting API, thus providing a medium for a solvent-mediated transformation. Further, at the melting temperature of the polymer, dehydration of EM dihydrate takes place (*IV, Fig. 4*, trace (a)) and EM dehydrate (m.p. ~ 137 ^{o}C) becomes the stable form relative to EM dihydrate. Meanwhile, EM dehydrate is less stable (and therefore more soluble) relative to EM anhydrate above 60 ^{o}C. This suggests fast dissolution of EM dehydrate in the molten carrier and creation of a supersaturated solution. The latter provides a thermodynamic driving force for nucleation and growth of the EM·AH crystals (the least soluble and therefore more stable form above 60 ^{o}C). Hence, three subsequent processes – dissolution, nucleation and crystal growth – are inferred to take place during EM dihydrate and PEG hot-melting, supporting the assumption that the EM dehydrate → EM anhydrate transformation is governed by the solvent-mediated route.

5.3.2 Factors affecting hydrate formation of baclofen during wet massing (II)

The wetting phase of aqueous wet granulation with BF as a hydrate-forming model API was studied using wet masses with a wide range of moisture content (*II, Table 1*). The hydrate formation was detected off-line using qualitative XRPD and Raman spectroscopy.

According to the XRPD and Raman results, the rate and extent of hydrate formation of BF during the wetting process depended on both the amount of water added and contact time with the granulating liquid. In particular, the onset of hydrate formation was detected when 0.25 g of water/g of anhydrous BF (i.e. 3 mol of water/mol of BF) was used for the wet massing, while the conversion to the monohydrate was completed at a moisture level of 0.63 g/g of anhydrous BF (7 mol of water/mol of BF) (*II, Fig. 8A* and *8B*). In addition, it was observed that less moisture was needed for the complete transformation when wet masses were allowed to equilibrate for 24 hours at ambient conditions; in this case, 0.25 g of water/g of anhydrous BF was sufficient for the anhydrate to entirely convert into the monohydrate (*II, Fig.* 8C). Overall, our results showed that relatively high moisture content (at least 3 mol of water/mol of anhydrous BF) was needed for BF to start converting into the monohydrate during the wetting process. For comparison, anhydrous theophylline was shown to convert to the monohydrate with addition of approximately one mole/mole of water (Jørgensen *et al.*, 2002).

The hydrate formation of BF is a solvent-mediated transformation, as discussed in the Section 5.2.4. In accordance with the mechanism of such transformations, the factors affecting the extent of phase conversion include solubility of a metastable phase in a given solvent and the amount of the solvent available for dissolving this phase. In terms of wet granulation, it means that the extent of hydrate formation will be proportional to the solubility of the anhydrate and the volume of the granulating liquid used (Davis *et*. al., 2004).

In agreement with this concept, the degree of anhydrate to monohydrate conversion increased with more granulating liquid in the present study. In addition, the concept suggests that, under the identical conditions, a less soluble material will require more solvent in order to reach the same degree of conversion compared to a more soluble one. The solubility of BF anhydrate in water was estimated to be approximately 2 mg/ml at room temperature, while the solubility of theophylline anhydrate is approximately 12 mg/ml at 25 ^{o}C (Wikström *et al.*, 2005). Therefore, the larger amount of water needed for the hydrate formation of BF, compared to that of theophylline, can be partly attributed to its poor solubility.

Furthermore, BF anhydrate was assumed to possess poor wettability since no phase transition was observed at high RHs (*II, Fig. 6*) (theophylline anhydrate, for example,

converts to the monohydrate at 75% RH (Salameh and Taylor, 2006)). Because material wetting is a factor governing hydrate formation kinetics (Otsuka *et al.*, 2002), it is clear that the APIs with poor wettability will require the excessive amount of moisture and/or prolonged contact with granulating liquid for the hydrate to form. Finally, BF monohydrate is inferred to be a channel hydrate (see Section 5.2.5) with a dehydration onset as low as 40 ^{o}C (vs. ~60 ^{o}C for theophylline (Aaltonen *et al.*, 2007)), assuming low activation energy for the dehydration. The latter suggests that the dehydration proceeds in the crystallographic direction with the least resistance to water molecules migration, which corresponds to the direction of water channels (Morris, 1999). In some cases, as with caffeine monohydrate (Byrn, 1999), such dehydration pathway allows for efflorescence and rapid dehydration to take place at room temperature and relative humidities greater than 50%. Hence, it is possible that BF monohydrate dehydrates during the wet massing, resulting in a shift of the equilibrium to the initial solid phase.

5.4 Enhancing compaction properties by crystal habit modification (V)

In pharmaceutical industry, a large number of batch failures are attributed to poor compaction characteristics of APIs arising from their undesirable crystal habit (York, 1992). For high dose APIs such as EM dihydrate this issue is of special interest since the most advantageous technique to produce tablets with these APIs is direct compression. In this study, an attempt was made to enhance the compactibility of EM dihydrate crystals via morphological crystal engineering.

5.4.1 HPMC as a crystal habit modifier

The scanning electron microscopy (SEM) photographs of EM dihydrate recrystallized in the absence and in the presence of the additive (hydroxylpropylmethylcellulose, HPMC) (*V, Fig.* 2) clearly show a concentration-dependent effect of HPMC on the crystal habit. In particular, the shape of the crystals grown at a relatively low additive concentration (0.45

wt%) was similar to the reference sample (*V, Fig. 2A*) and was rather irregular. Upon further increase in the additive concentration to 2.25 and 4.5 wt% the plate-shaped (*V, Fig. 2B*) and elongated plate-shaped (*V, Fig. 2C*) crystals were produced, respectively. This result suggests that HPMC affects the growth rates of the EM dihydrate crystal faces differently.

5.4.2 Mechanistic considerations of the additive effect on crystallization

Based on the Bravais-Friedel-Donnay-Harker (BFDH) theory, the shape of EM dihydrate is plate-like, slightly elongated along the *b* direction, and bounded by faces (002), (011) and (101) (*Fig. 16*). The comparison of this model with the observed morphology of the reference crystals (i.e., grown in the absence of the additive) was complicated due to rather irregular shape of the latter crystals. In contrast, it was striking to observe that the morphology of the crystals grown in the presence of 2.25 wt% of HPMC (*V, Fig. 3B*) was in a reasonable agreement with the model, suggesting that the crystals achieved a dynamic equilibrium with the solution.

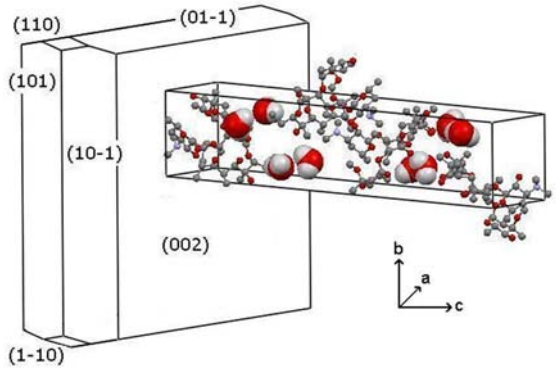

Figure 16 *BFDH model along with the unit cell of erythromycin A dihydrate crystal. Modified from Paper V.*

Considering the general effect of the additives on crystallization kinetics, it can be assumed that with addition of HPMC to the crystallization medium the mean growth rate is suppressed and altered growth rates of individual crystal faces results in crystal habit modification. Theoretically, EM dihydrate should demonstrate the fastest growth along the *b*-axis, because this direction has the strongest drug-drug intermolecular interactions (Miroshnyk *et al*., 2001) and the shortest unit cell dimensions. The growth rate along the *a*-axis should be of the same magnitude, since this direction bears water channels and the drug molecules H-bonded through the water. While the morphology of the crystals grown in the presence of 2.25

wt% of the additive almost reassembles the BFDH model, an increase in the additive concentration results in more elongated crystals, apparently with decreased growth rate along the *b*-axis. This change in morphology suggests specific interactions between the polymer and the functional groups on the {011} faces of the crystal.

The well-defined arrangement of molecules on crystal surfaces offers a means to probe molecular recognition events taking place at interfaces during crystallization. Due to anisotropy of the EM dihydrate crystal structure, the terminating surfaces of the crystal differ substantially (*V, Table 3* and *V, Fig. 6*). In particular, the largest (002) face of the crystal is the most hydrophobic one, while the (011) face is the most hydrophilic, with the two water molecules being exposed to this face. HPMC has been previously shown to be capable of interacting with the drug molecules via H-bonds (Katzhendler *et al.*,1998; Wen *et al.,* 2005; Tian *et al.,* 2006). It is therefore assumed that the polymer reversibly interacts with the ED crystal surfaces, especially with (011) and (101), during crystallization thus suppressing overall crystal growth. At relatively low concentrations of the additive, this effect is hindered due to an insufficient number of polymer molecules. With increased additive concentration, more polymer molecules are available and the probability of the drug-polymer interactions is higher. The preferred adsorbtion of HPMC at the {011} crystal faces leads to retarded crystal growth in the *b* direction and this effect is macroscopically evident as elongated EM dihydrate crystals.

5.4.3 Impact of crystal habit on compaction behaviour

Mechanical properties of the powdered material can roughly be assessed in terms of compact strength as a function of applied compaction stress (Riippi *et al.,* 2000). In order to estimate the consequences of the crystal habit modification on the compactibility of EM dihydrate, powder compacts were prepared and evaluated by plotting their crushing strength versus compaction pressure (*V, Fig. 7*). The commercial sample, reference crystals and the crystals grown in the presence of 0.45 wt% of HPMC all produced weak compacts with a high capping tendency, regardless of the compaction pressure applied. For the crystals obtained in the presence of 4.5 wt% of HPMC, a linear relationship between the crushing strength of the compacts and the compaction force was observed at

lower compaction forces (<8 kN); upon further increase in the compaction force the relationship was inverse. The crushing strength of the compacts loaded with the crystals grown in the presence of 2.25 wt% of HPMC constantly increased with increasing compaction force.

Compression cycles can be considered as a sequence of three steps: (1) rearrangement and packing of powder in the die, (2) fragmentation and/or plastic deformation of the particles, and (3) elastic recovery of the compact (Jetzer *et al.*, 1983). Overall, behaviour of the material during these steps is defined by internal structure of the crystal (Roberts *et al.* 1995; Sun and Grant, 2001; Feng and Grant, 2006). Meanwhile, crystal habit may influence the compaction profile through its effect on the initial particle rearrangement. More specifically, the relative orientation of the crystallites during compression and hence the contact area between them are influenced by the crystal habit (Bandyopadhyay and Grant, 2002). More rounded or more equidimensional crystals (such as crystals obtained in the presence of 2.25 wt% of HPMC) are likely to orient randomly, while less equidimensional crystals (obtained in the presence of 4.5 wt% of the polymer) tend to pack preferentially with their longer dimension(s) oriented normally to the compression axis. Owing to differences in surface free energy and thus in physicomechanical properties of crystal faces arising from the differences in their surface chemistry (Lee and Myerson, 2006), it is assumed that the crystals grown in the presence of 2.25 wt% of HPMC with random orientation during compression possess improved mechanical properties, as compared to those of the crystals precipitated in the presence of 4.5 wt% of HPMC. In addition, the adsorbed polymer may increase lattice strain, reducing the energy required for plastic deformation and thus leading to improved tableting performance.

In conclusion, this study reports a practical approach, based on additive-induced crystal habit modification, to enhancing compaction behaviour of APIs. Future studies should employ crystal chemistry analysis and various prediction models (Plumb *et al.*, 2005; Shao *et al.*, 2007) to provide insight into the relationship between the modified crystal habit and tabletting performance of the model API.

6. CONCLUSIONS

Solid state properties and interconversion pathways among the different crystalline forms of EM (dihydrate, dehydrate, and anhydrate) and BF (anhydrate and monohydrate) are reported. This study highlights structural and analytical aspects of the isomorphic dehydrate of EM that has long been a source of a large number of inconsistencies and misinterpretations in the literature. BF monohydrate is described for the first time. Overall, this information enables improved understanding and control of the solid-state of these APIs during processing and storage.

Upon polymorph screening, a high solvate-forming propensity of EM was observed. Moreover, the formation of isomorphic solvates with structurally related solvents such as acetone and methylethyl ketone was discovered. The solid-state properties of the EM solvates are reported and the solvent compositions that yield the thermodynamically stable dihydrate form are defined.

The mechanisms of dehydration of EM dihydrate and hydrate formation of BF anhydrate were elucidated. Dehydration of EM dihydrate is a solid-state reaction that follows a topotactic mechanism and results in an isomorphic dehydrate. Hydrate formation of BF takes place via a solvent-mediated route and thus this phase transformation can occur during water-based processes (e.g. recrystallization, wet granulation, film-coating). An understanding of the mechanisms involved in these phase transformations provides a scientific basis for designing the manufacturing processes.

Hot-melt processing of high melting crystalline APIs or excipients with PEG 6000 can induce a solvent-mediated transformation, with the polymer acting as a solvent. This knowledge can be extremely beneficial in predicting the performance and stability of the final dosage form as well as in the design of the process.

Morphological crystal engineering provides an effective tool for tailoring technological properties of pharmaceuticals solids. By using pharmaceutically accepted excipients as crystal habit modifiers toxicity and/or environmental concerns can be overcome. This also supports the concept of crystallization as the very first formulation step.

REFERENCES

Aaltonen J, Heinänen P, Peltonen L, Kortejärvi H, Tanninen VP, Christiansen L, Hirvonen J, Yliruusi J, Rantanen J (2006) In-situ measurement of solvent-mediated phase transformations during dissolution testing. J Pharm Sci 95:2730–2737.

Aaltonen J, Kogerman K, Strachan CJ, Rantanen J (2007) In-line monitoring of solid-state transitions during fluidization. Chem Eng Sci 62:408–415.

Airaksinen S, Karjalainen M, Kivikero N, Westermarck S, Shevchenko A, Rantanen J, Yliruusi J (2005) Excipient selection can significantly affect solid-state phase transformation in formulation during wet granulation. AAPS PharmSciTech 6:311–322.

Alderborn G, Nyström C (1995) Pharmaceutical powder compaction technology, 1st ed., New York: Marcel Dekker. 377 pp.

Bandyopadhyay R, Grant DJ (2000) Influence of crystal habit on the surface free energy and interparticulate bonding of L-lysine monohydrochloride dihydrate. Pharm Dev Technol 5: 27–37.

Bandyopadhyay R, Grant DJ (2002) Plasticity and slip system of plate-shaped crystals of L-lysine monohydrochloride dihydrate. Pharm Res 19:491–496.

Bauer J, Quick J, Oheim R (1985) Alternate interpretation of the role of water in the erythromycin structure. J Pharm Sci 74:899–900.

Bauer J, Spanton S, Henry R, Quick J, Dziki W, Porter W, Morris J (2001) Ritonavir: an extraordinary example of conformational polymorphism. Pharm Res 18:859–866.

Bauer JF, Dziki W, Quick JE (1999). Role of an isomorphic desolvate in dissolution failures of an erythromycin tablet formulation. J Pharm Sci 88:1222–1227.

Beckmann W (2000) Seeding the desired polymorph: background, possibilities, limitations, and case studies. Org Process Res Dev 4:372–383.

Berman HM, Jeffrey GA, Rosenstein RD (1968) The crystal structures of the alpha and beta forms of D-mannitol. Acta Crystallogr B 24:442–449.

Bernstein J, Davey RJ, Henck JO (1999) Concomitant Polymorphs. Angew Chem Int Ed Engl 38:3441–3461.

Bernstein J (2002) Polymorphism in Molecular Crystals. Oxford: Clarendon Press. pp. 297–307.

Blagden N, Davey RJ, Rowe R, Roberts RJ, Rowe RC (1998) Disappearing polymorphs and the role of reaction by-products: the case of sulphathiazole. Int J Pharm 172:169–177.

Blagden N, de Matas M, Gavan PT, York P (2007) Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Adv Drug Deliv Rev 59:617–630.

Bohlin M, Rasmuson AC (1992) Application of controlled cooling and seeding in batch crystallization. Can J Chem Eng 70:120–126.

Boldyrev VV, Bulens M, Delmon B (1979) Studies in surface science and catalysis, Vol. 2: The control of the reactivity of solids, Amsterdam: Elsevier. 226 pp.

Braatz RD, Fujiwara M, Wubben TJ, Rusli E (2006) Crystallization: particle size control. In: Swarbrick J, editor. Encyclopedia of pharmaceutical technology, 3rd ed, New York: Informa Healthcare USA, Inc. pp. 858–871.

Brittain HG, Fiese EF (1999) Effects of pharmaceutical processing on drug polymorphs and solvates. In: Brittain HG, editor. Polymorphism in pharmaceutical solids, New York: Marcel Dekker, Inc. pp. 331–361.

Brittain HG (2007) Polymorphism and solvatomorphism 2005. J Pharm Sci 96:705–728.

Bucar D-K, MacGillivray LR (2007) Preparation and reactivity of nanocrystalline cocrystals formed via sonocrystallization. J Am Chem Soc 129:32–33.

Buijs K, Choppin GR (1963) Near-infrared studies of the structure of water. I. Pure Water. J Chem Phys 39:2035–2041.

Burger A (1982) Differential thermal analysis and differential scanning calorimetry: basis, methods and use. Pharm Unserer Zeit 11:177–189.

Burger A, Ramberger R (1979) On the polymorphism of pharmaceuticals and other molecular crystals I. Theory of thermodynamic rules. Mikrochim Acta [Wein] II:259–271.

Burt HM, Mitchell AG (1981) Crystal defects and dissolution. Int J Pharm 9:137–152.

Burton WK, Cabrera N, Frank FC (1951) The growth of crystals and the equilibrium structure of their surfaces. Phil Trans R Soc, Lond. A243:299–358.

Byrn SR, Pfeiffer RR, Stephenson G, Grant DJW, Gleason WB (1994) Solid-state pharmaceutical chemistry. Chem Mater 6:1148–1158.

Byrn SR, Pfeiffer RR, Stowell JG. (1999) Solid-State Chemistry of Drugs. 2nd ed, West Lafayette; SSCI, Inc. pp. 233–258.

Byrn SR, Pfeiffer RR, Ganey M, Hoiberg C, Poochikian G (1995) Pharmaceutical solids: a strategic approach to regulatory considerations. Pharm Res 12:945–954.

Byrn SR, Xu W, Newman AW (2001) Chemical reactivity in solid-state pharmaceuticals: formulation implications. Adv Drug Deliv Rev 48:115–136.

Cardew PT, Davey RJ (1985) The kinetics of solvent-mediated phase transformations. Proceedings of the Royal Society of London. Series A Mathematical and Physical Sciences 398:415–428.

Carstensen JT (2001) Advanced pharmaceutical solids. New York: Marcel Dekker, Inc. 518 pp.

Chaka AM, Zaniewski R, Youngs W, Tessier C, Klopman G (1996) Predicting the crystal structure of organic molecular materials. Acta Cryst B52:165–183.

Chattopadhyay S, Erdemir D, Evans JMB, Ilavsky J, Amenitsch H, Segre CU, Myerson AS (2005) SAXS study of the nucleation of glycine crystals from a supersaturated solution. Cryst Growth Des 5:523 – 527.

Chen LR, Young VGJr, Lechuga-Ballesteros D, Grant DJ (1999) Solid-state behavior of cromolyn sodium hydrates. J Pharm Sci 88:1191–1200.

Chikhalia V, Forbes RT, Storey RA, Ticehurst M (2006) The effect of crystal morphology and mill type on milling induced crystal disorder. Eur J Pharm Sci 27: 19–26.

Childs SL, Chyall LJ, Dunlap JT, Coates DA, Stahly BC, Stahly GP (2004a) A metastable polymorph of metformin hydrochloride: isolation and characterization using capillary crystallization and thermal microscopy techniques. Cryst Growth Des 4:441–449.

Childs SL, Chyall LJ, Dunlap JT, Smolenskaya VN, Stahly BC, Stahly GP (2004b) Crystal engineering approach to forming cocrystals of amine hydrochlorides with organic acids. Molecular complexes of fluoxetine hydrochloride with benzoic succinic and fumaric acids. J Am Chem Soc 126:13335–13342.

Chiou WL, Chen SJ, Athanikar N (1976) Enhancement of dissolution rates of poorly water-soluble drugs by crystallization in aqueous surfactant solutions I: Sulfathiazole prednisone and chloramphenicol. J Pharm Sci 65:1702–1704.

Chow AH, Tong HH, Chattopadhyay P, Shekunov BY (2007) Particle engineering for pulmonary drug delivery. Pharm Res 24:411–437.

Chow AHL, Grant DJW (1989) Physical factors influencing the aqueous dissolution rate of acetaminophen crystals doped with p-acetoxyacetanilide: evaluation by multiple linear regression. Int J Pharm 51:129–135.

Chow AHL, Chow PKK, Zhongshan W, Grant DJW (1985) Modification of acetaminophen crystals: influence of growth in aqueous solutions containing p-acetoxyacetanilide on crystal properties. Int J Pharm 24:239–258.

Chow KY, Go J, Mehhdizadeh M, Grant DJW (1984) Modification of adipic acid crystals: Influence of growth in the presence of fatty acid additives on crystal properties. Int J Pharm 20:3–24.

Collet A, Brienne MJ, Jacques J (1980) Optical resolution by direct crystallization of enantiomer mixtures. Chem Rev 80:215.

Cox JS, Woodard GD, McCrone WC (1971) Solid-state chemistry of cromolyn sodium (disodium cromoglycate). J Pharm Sci 60:1458–1465.

Datta S, Grant DJ (2004) Crystal structures of drugs: advances in determination prediction and engineering. Nat Rev Drug Discov 3:42–57.

Davey RJ, Mullin JW, Whiting MJL (1982) Habit modification of succinic acid crystals grown from different solvents. J Cryst Growth 58:304–312.

Davey R, Garside J (2000) From molecules to crystallizers: an introduction to crystallization. Oxford: Oxford University Press.

Davey RJ, Allen K, Blagden N, Cross WI, Lieberman HF, Quayle MJ, Righini S, Seton L, Tiddy GJT (2002) Crystal engineering – nucleation the key step. CrystEngComm 4:257–264.

Davey RJ (2004) Crystallization: How come you look so good? Nature 428:374–375.

Davey RJ, Blagden N, Potts GD, Docherty R (1997) Polymorphism in molecular crystals: stabilization of a metastable form by conformational mimicry. J Am Chem Soc 119:1767–1772.

Davis TD, Peck GE, Stowell JG, Morris KR, Byrn SR (2004) Modeling and monitoring of polymorphic transformations during the drying phase of wet granulation. Pharm Res 21:860–866.

Dennehy RD (2003) Particle Engineering Using Power Ultrasound. Org Process Res Dev 7:1002–1006.

Desiraju GR (2001) Chemistry beyond the molecule. Nature 412:397–400.

DiMasi JA, Hansen RW, Grabowski HG (2003) the price of innovation: new estimates of drug development costs. J Health Econom 22:151–185.

Doherty R (1996) The application of computational chemistry to the study of molecular materials. In: Myerson AS, Green D, Meenan P, editors. Crystal Growth of Organic Materials, Washington DC: American Chemical Society. pp 2–14.

Edwards AD, Shekunov BY, Kordikowski A, Forbes RT, York P (2001) Crystallization of pure anhydrous polymorphs of carbamazepine by solution enhanced dispersion with supercritical fluids (SEDS). J Pharm Sci 90:1115–1124.

El-Bary AA, Kassem MA, Foda N, Tayel S, Badawi SS (1990) Controlled crystallization of chlorpropamide from surfactant and polymer solutions. Drug Dev Ind Pharm 16:1649–1660.

European Pharmacopoeia (2000) 5th ed, Strasbourg France: Council of Europe. pp. 1050–1051.

Fabbiani FPA, Pulham CR (2006) High-pressure studies of pharmaceutical compounds and energetic materials. Chem Soc Rev 35:932–942.

Fairbrother JE, Grant DJW (1978) The crystal habit modification of a tablet lubricant adipic acid. J Pharm Pharmacol 30:S19.

FDA (2004a) Pharmaceutical cGMPs for the 21st century – a risk based approach. U.S. Food and Drug Administration.

FDA (2004b) Process Analytical Technology (PAT) – a framework for innovative pharmaceutical development manufacturing and quality assurance. U.S. Food and Drug Administration.

Feng Y, Grant DJ (2006) Influence of crystal structure on the compaction properties of n-alkyl 4-hydroxybenzoate esters (parabens). Pharm Res 23:1608–1616.

Ferrari ES, Burton RC, Davey RJ, Gavezzotti A (2006) Simulation of phase separation in alcohol/water mixtures using two-body force field and standard molecular dynamics. J Comput Chem 27:1211–1219.

Forbes RT, York P, Fawcett V, Shields L (1992) Physicochemical properties of salts of p-aminosalicylic acid. I. Correlation of crystal structure and hydrate stability. Pharm Res 9:1428–1435.

Fukumori Y, Fukuda T, Yamamoto Y, Shigitani Y, Hanyu Y, Takeuchi Y, Sato N (1983) Physical characterization of erythromycin dihydrate anhydrate and amorphous solid and their dissolution properties. Chem Pharm Bull 31:4029–4039.

Galkin O, Vekilov PG (2000) Are nucleation kinetics of protein crystals similar to those of liquid droplets? J Am Chem Soc 122:156–163.

Gardner CR, Walsh CT, Almarsson O (2004) Drugs as materials: valuing physical form in drug discovery. Nat Rev Drug Discov 3:926–934.

Garekani HA, Sadeghi F, Badiee A, Mostafa SA, Rajabi-Siahboomi AR (2001) Crystal habit modifications of ibuprofen and their physicomechanical characteristics. Drug Dev Ind Pharm 27:803–809.

Garnier S, Petit S, Coquerel G (2002) Influence of supersaturation and structurally related additives on the crystal growth of alpha-lactose monohydrate. J Cryst Growth 234:201–219

Garti N, Zour H (1997) The effect of surfactants on the crystallization and polymorphic transformation of glutamic acid. J Crystal Growth 172:486–498.

Gavezzotti A (1994) Are crystal structures predictable? Acc Chem Res 27:309–314.

Gibbs JW (1948) Collected works, Vol. I: Thermodynamics. New Haven: Yale University Press.

Giron D (1995) Thermal analysis and calorimetric methods in the characterization of polymorphs and solvates. Thermochim Acta 248:1–59.

Grant DJW, Higuchi (1990) Solubility behaviour of organic compounds. In: Saunders WH, editor. Techniques of chemistry, Vol. 21. New York: John Wiley & Sons, Inc. 600 pp.

Grant DJW, York P (1986a) A disruption index for quantifying the solid state disorder induced by additives or impurities. II. Evaluation from heat of solution. Int J Pharm 28:103–112.

Grant DJW, York P (1986b) Entropy of processing: a new quantity for comparing the solid state disorder of pharmaceutical materials. Int J Pharm 30:161–180.

Grant DJ, Byrn SR (2004) A timely re-examination of drug polymorphism in pharmaceutical development and regulation. Adv Drug Deliv Rev 56:237–239.

Grant DWJ (1999) Theory and origin of polymorphism In: Brittain HG, editor. Polymorphism in pharmaceutical solids. New York: Marcel Dekker, Inc. pp 1-34.

Grattan TJ (1995) Pharmaceutical composition containing a drug/β-cyclodextrin complex in combination with an acid-base couple. World patent WO/1995/004528.

Griesser (2006) The importance of solvates. In: Hilfiker R, editor. Polymorphism in the Pharmaceutical Industry, Weinheim: WILEY-VCH Verlag GmbH. pp 211–234.

Grzesiak AL, Lang M, Kim K, Matzger AJ (2003) Comparison of the four anhydrous polymorphs of carbamazepine and the crystal structure of form I. J Pharm Sci 92:2260–2271.

Grzymek J (1937) Control of the exterior form of crystals during crystallization. J Przemysl Chem 21:279–280.

Gu CH, Chatterjee K, Young JrV, Grant DJW (2002) Stabilization of a metastable polymorph of sulfamerazine by structurally related additives. Cryst Growth 235:471–481.

Gu CH, Grant DJ (2000) Effects of crystallization in the presence of the diastereomer on the crystal properties of (SS)-(+)-pseudoephedrine hydrochloride. Enantiomer 5:271–280.

Gu C-H, Li H, Gandhi RB, Raghavan K (2004) Grouping solvents by statistical analysis of solvent property parameters: implication to polymorph screening. Int J Pharm 283:117–125.

Gu CH, Young VJr, Grant DJ (2001) Polymorph screening: influence of solvents on the rate of solvent-mediated polymorphic transformation. J Pharm Sci 90:1878–1890.

Gu C-H (2001) Influence of solvent and impurity on the crystallization and properties of crystallized products. PhD thesis: University of Minnesota.

Guillory JK (1999) Generation of polymorphs hydrates solvates and amorphous solids. In: Brittain HG, editor. Polymorphism in pharmaceutical solids. New York: Marcel Dekker, Inc. pp. 183–226.

Gunton JD (1999) Homogeneous nucleation. J Stat Phys 95:903–923.

Haleblian J, McCrone W (1969) Pharmaceutical applications of polymorphism. J Pharm Sci 58: 911–929.

Haleblian JK (1975) Characterization of habits and crystalline modification of solids and their pharmaceutical applications. J Pharm Sci 64:1269–1288.

Hanna MH, York P (2006) Method of particle formation. US patent: 7150766.

Hartman P, Perdock WG (1955) On the relations between structure and morphology of crystals. I. Acta Cryst 8:49–52.

He X, Stowell J, Morris K, Pfeiffer R, Li H, Stahly P, Byrn S (2001) Stabilization of a metastable polymorph of 4-methyl-2-nitroacetamide by isomorphic additives. Cryst Growth Des 1:305–312.

Hilfiker R, Berghausen J, Blatter F, Burkhard A, De Paul SM, Freiermuth B, Geoffroy A, Hofmeier U, Marcolli C, Siebenhaar B, Szelagiewicz M, Vit A, von Raumer M (2003) Polymorphism – integrated approach from high-throughput screening to crystallization optimization. J Therm Anal Cal 73:429–440.

Hilfiker R, Blatter F, von Raumer M (2006) Relevance of solid-state properties for pharmaceutical products. In: Hilfiker R, editor. Polymorphism in the pharmaceutical industry. Weinheim: WILEY-VCH Verlag GmbH. pp. 1–19.

Hooks DE, Fritz T, Ward MD (2001) Epitaxy and molecular organization on solid substrates. Adv Mater 13:227–241.

Huang L-F, Tong W-Q (2004) Impact of solid state properties on developability assessment of drug candidates. Adv Drug Deliv Rev 56:321–334.

ICH Q6A (1999) Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances. International Conference on Harmonisation.

ICH Q8 (2005a) Pharmaceutical Development. International Conference on Harmonization.

ICH Q9 (2005b) Quality risk management. International Conference on Harmonization.

Jarmer DJ, Lengsfeld CS, Anseth KS, Randolph TW (2005) Supercritical fluid crystallization of griseofulvin: crystal habit modification with a selective growth inhibitor. J Pharm Sci 94:2688–2702.

Jetzer W, Leuenberger H, Sucker H (1983) The compressibility and compactibility of pharmaceutical powders. Pharm Tech 4:33–39.

Jørgensen A, Rantanen J, Karjalainen M, Khriachtchev L, Räsänen E, Yliruusi J (2002) Hydrate formation during wet granulation studied by spectroscopic methods and multivariate analysis. Pharm Res 19:1285–1291.

Karfunkel R, Gdanitz RJ (1992) Ab initio prediction of possible crystal structures for general organic molecules. J Comp Chem 13:1171–1183.

Karunanithi AT, Acquah C, Achenie LEK, Sithambaram S, Suib SL, Gani R (2006) A computer-aided molecular design framework for crystallization solvent design. Chem Eng Sci 61:1247–1260.

Katzhendler I, Azoury R, Friedman M (1998) Crystalline properties of carbamazepine in sustained release hydrophilic matrix tablet based on hydroxypropyl methylcellulose. J Control Release 54: 69–85.

Khankari RK, Grant DJW (1995) Pharmaceutical hydrates. Thermochim Acta 248:61–79.

Khankari R, Chen L, Grant DJ (1998) Physical characterization of nedocromil sodium hydrates. J Pharm Sci 87:1052–1061.

Khoshkhoo S, Anwar J (1993) Crystallization of polymorphs: the effect of solvent. J Phys D: Appl Phys 26:90–93.

Kitaigorodskii AI (1973) Physical chemistry, Vol. 29: Molecular crystals and molecules. New York: Academic Press. 572 pp.

Klein R, Meconi R, Müller W (2005) Transdermal therapeutic system containing hormones and crystallization inhibitors. US Patent: 6899894.

Kordikowski A, Shekunov B, York P (2001) Polymorph control of sulfathiazole in supercritical CO2. Pharm Res 18:682–688.

Kordikowski A, York P, Latham D (1999) Resolution of ephedrine in supercritical CO(2): A novel technique for the separation of chiral drugs. J Pharm Sci 88:786–791.

Kuldipkumar AK (2006) Amphiphilic block copolymers as crystal habit modifiers. PhD Thesis: University of Wisconsin-Madison.

Laine E, Kahela P, Rajala R, Heikkilä T, Saarnivaara K, Piippo I (1987) Crystal forms and bioavailability of erythromycin. Int J Pharm 38:33–38.

Lang M, Gzesiak AL, Matzger AJ (2002a) The use of polymer heteronuclei for crystalline polymorph selection. J Am Chem Soc 124:14834– 14835.

Lang M, Kampf JW, Matzger AJ (2002b) Form IV of carbamazepine. J Pharm Sci 91:1186–1190.

Langevin BC (2002) The effect of polymers on the crystallization of carbamazepine and indomethacin polymorphs from aqueous and organic solutions. PhD thesis: University of Michigan.

Lee AY, Myerson AS (2006) Particle engineering: fundamentals of particle formation and crystal growth. MRS Bulletin 31:881–886.

Lee AY, Lee IS, Dette SS, Boerner J, Myerson AS (2005) Crystallization on confined engineered surfaces: a method to control crystal size and generate different polymorphs. J Am Chem Soc 127:14982–14983.

Lee EH, Byrn SR, Carvajal MT (2006) Additive-induced metastable single crystal of mefenamic

acid. Pharm Res 23:2375–2380.

Leveque N, Raghavan SL, Lane ME, Hadgraft J (2006) Use of a molecular form technique for the penetration of supersaturated solutions of salicylic acid across silicone membranes and human skin in vitro. Int J Pharm 318:49–54.

Lin-Vien D (1991) Handbook of infrared and raman characteristic frequencies of organic molecules. Boston: Academic Press.

Lohani S, Grant DJW (2006) Thermodynamics of polymorphs. In: Hilfiker R, editor. Polymorphism in the pharmaceutical industry. Weinheim: WILEY-VCH Verlag GmbH. pp. 21–42.

Loth H, Hemgesber E (1986) Properties and dissolution of drugs micronized by crystallization from supercritical gases. Int J Pharm 32:265–276.

Marshall PV, York P (1991) The compaction properties of nitrofurantoin samples crystallised from different solvents. Int J Pharm 67:59–65.

Marshall PV, York P (1989) Crystallization solvent induced solid-state and particulate modifications of nitrofurantoin. Int J Pharm 55:257–263.

Martinez-Oharriz MC, Martin C, Goni MM, Rodriguez-Espinosa C, Tros-Ilarduya MC, Zornoza A (1999) Influence of polyethylene glycol 4000 on the polymorphic forms of diflunisal. Eur J Pharm Sci 8:127–132.

Mathiowitz E, Thanos C, Liu Z (2004) Methods for micronization of hydrophobic drugs. US Patent: 6824791.

Meenan PA, Anderson SR, Klug DL (2002) The influence of impurities and solvents on crystallization. In: Myerson AS, editor. Handbook of industrial crystallization. Boston: Butter-Worth-Heinemann. pp. 67–97.

Mersmann A (2001) Physical and chemical properties of crystalline systems. In: Mersmann A, editor. Crystallization Technology Handbook, 2nd ed. New York: Marcel Dekker, Inc. pp. 1–44.

Mersmann A, Eble A, Heyer C (2001) Crystal Growth. In: Mersmann A, editor. Crystallization Technology Handbook, 2nd ed, New York: Marcel Dekker, Inc. pp. 81–144.

Michaels AS, Colville AR (1960) The effect of surface active agents on crystal growth rate and crystal habit. J Phys Chem 63:13–19.

Miroshnyk I, Mirza S, Zorkii PM, Obodovskaya AE, Heinämäki J, Yliruusi J (2001) Interpretation of pharmacokinetic properties of erythromycin and its derivatives on the basis of calculation of intermolecular interaction energy in crystals. AAPSPharmSci 3(3).

Mitchell CA, Yu L, Ward MD (2001) Selective nucleation and discovery of organic polymorphs through epitaxy with single crystal substrates. J Am Chem Soc 123:10830–10839.

Morissette SL, Almarsson O, Peterson ML, Remenar JF, Read MJ, Lemmo AV, Ellis S, Cima MJ, Gardner CR (2004) High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids. Adv Drug Delivery Rev 56:275– 300.

Morris K, Rodríguez-Hornedo N (1993) Hydrates. In: Swarbrick J, Boylan JC, editors. Encyclopedia of pharmaceutical technology, Vol. 7. New York: Marcel Dekker, Inc. pp. 393–440.

Morris KR, Griesser UJ, Eckhardt CJ, Stowell JG (2001) Theoretical approaches to physical transformations of active pharmaceutical ingredients during manufacturing processes. Adv Drug Deliv Rev 48:91–114.

Morris KR (1999) Structural aspects of hydrates and solvates. In: Brittain HG, editor.

Polymorphism in pharmaceutical solids. New York: Marcel Dekker, Inc. pp 125–181.

Mukuta T, Lee AY, Kawakami T, Myerson AS (2005) Influence of impurities on the solution-mediated phase transformation of an active pharmaceutical ingredient. Cryst Growth Des 5:1429–1436.

Mullin JW (2001) Industrial techniques and equipment in crystallization. Oxford: Butterworth Heinemann. pp. 315–402.

Murthy KS, Turner NA, Nesbitt RU, Fawzi MB (1986) Characterization of commercial lots of erythromycin base. Drug Dev Ind Pharm12:665–690.

Myerson AS, Garetz BA (2002) Method for using laser light to control crystal form. US patent: 6426406B1.

Myerson AS (1999) Crystallization basics. In: Myerson AS, editor. Molecular modeling applications in crystallization. New York: Cambridge University Press. pp. 55–105.

Naggar VFB, El-Gamal S, Shams-Elden MA (1980) Physicochemical studies of phenylbutazone recrystallized from polysorbate 80. Sci Pharm 48: 335–343.

Nangia A, Desiraju GR (1999) Pseudopolymorphism: occurrences of hydrogen bonding organic solvents in molecular crystals. Chem Commun 7: 605–606.

Nielsen AE (1964) Kinetics of precipitation. New York: Macmillan. 153 pp.

Okamoto M, Hamano M, Ooshima H (2004) Utilization of solvent-mediated transformation for exclusive production of metastable polymorph crystals of AEI-923. J Chem Eng Jap 37:95–101.

Okutsu T, Nakamura K, Haneda H, Hiratsuka H (2004) Laser-induced crystal growth and morphology control of benzopinacol produced from benzophenone in ethanol/water mixed solution. Cryst Growth Des 4:113–115.

Ostwald W (1896) Studien über die Bildnung und Umwandlung fester Körper. Zeitschrift für Physicalische Chemie 22:289–330.

Otsuka M, Ishii M, Matsuda Y (2002) Effect of surface-modification on hydration kinetics of nitrofurantoin anhydrate. Colloid Surf B 23:73–82.

Oxtoby DW (1998) Nucleation of first-order phase transitions. Acc Chem Res 31:91.

Palakodaty S, York P (1999) Phase behavioral effects on particle formation processes using supercritical fluids. Pharm Res 16:976–985.

Parveen S, Davey RJ, Dent G, Pritchard RG (2005) Linking solution chemistry to crystal nucleation: the case of tetrolic acid. Chem Commun (Camb) 12:1531–1533.

Paul EL, Tung H-H, Midler M (2005) Organic crystallization processes. Powder Tech 150:133–143.

Perepezko JH (1994) Nucleation reactions in undercooled liquids. Mater Sci Eng A 178:105–111.

Peterson ML, Morissette SL, McNulty C, Goldsweig A, Shaw P, LeQuesne M, Monagle J, Encina N, Marchionna J, Johnson A, Gonzalez-Zugasti J, Lemmo AV, Ellis SJ, Cima MJ, Almarsson O (2002) Iterative high-throughput polymorphism studies on acetaminophen and an experimentally derived structure for form III. J Am Chem Soc 124:10958–10959.

Petit S, Coquerel G (1996) Mechanism of several solid-solid transformations between dihydrated and anhydraous copper(II) 8-hydroxyquinolinates. Proposition for a unified model for the dehydrarion of molecular crystals. Chem Mater 8:2247–2258.

Plumb AP, Rowe RC, York P, Brown M (2005) Optimisation of the predictive ability of artificial neural network (ANN) models: a comparison of three ANN programs and four classes of training algorithm Eur J Pharm Sci 25:395–405.

Pfeiffer RR, Yang KS, Tucker MA (1970) Crystal pseudopolymorphism of cephaloglycin and cephalexin. J Pharm Sci 59:1809–1812.

Price R, Kaerger JS (2005) Process for the production of particles.World Patent WO 05/073827.

Rasenack N, Müller BW (2002a) Crystal habit and tableting behaviour. Int J Pharm 244:45–57.

Rasenack N, Müller BW (2002b) Dissolution rate enhancement by in situ micronization of poorly water-soluble drugs. Pharm Res 19:1894–1900.

Rasenack N, Steckel H, Muller BW (2003) Micronization of anti-inflammatory drugs for pulmonary delivery by a controlled crystallization process. J Pharm Sci 92:35–44.

Remenar JF, Morissette SL, Peterson ML, Moulton B, MacPhee JM, Guzman HR, Almarsson O (2003) Crystal engineering of novel cocrystals of a triazole drug with 14-dicarboxylic acids. J Am Chem Soc 125:8456–8457.

Riippi M, Tanninen V, Yliruusi J (2000) Effect of compression force on the crystal properties of erythromycin acistrate tablets. Eur J Pharm Biopharm 50:365–371.

Ristic RI, Finnie S, Sheen DB, Sherwood JN (2001) Macro- and micromorphology of monoclinic paracetamol grown from pure aqueous solution. J Phys Chem B 105:9057–9066.

Roberts RJ, Rowe RC, York P (1995) The relationship between the fracture properties, tensile strength, and critical stress intensity factor of organic solids and their molecular structure. Int J Pharm 125:157–162.

Rodríguez-Hornedo N (1990) Crystallization and the properties of crystals. In: Swarbrick J, Boylan JC, editors. Encyclopedia of pharmaceutical technology, Vol. 3. New York: Marcel Dekker, Inc. pp. 399–434.

Rodríguez-Hornedo N, Kelly RC, Sinclair BD, Miller JM (2006a) Crystallization: general principles and significance on product development. In: Swarbrick J, editor. Encyclopedia of pharmaceutical technology, 3rd ed. New York: Informa Healthcare USA, Inc. pp. 834–857.

Rodríguez-Hornedo N, Nehm SJ, Seefeldt KF, Pagan-Torres Y, Falkiewicz CJ (2006b) Reaction crystallization of pharmaceutical molecular complexes. Mol Pharm 3:362–367.

Rodríguez-Hornedo N, Murphy D (1999) Significance of controlling crystallization mechanisms and kinetics in pharmaceutical systems. J Pharm Sci 88:651–660.

Rodríguez-Hornedo N, Murphy D (2004) Surfactant-facilitated crystallization of dihydrate carbamazepine during dissolution of anhydrous polymorph. J Pharm Sci 93:449–460.

Ruecroft G, Hipkiss D, Ly T, Maxted N, Cains PW (2005) Sonocrystallization: the use of ultrasound for improved industrial crystallization. Org Process Res Dev 9:923−932.

Salameh AK, Taylor LS (2006) Physical stability of crystal hydrates and their anhydrates in the presence of excipients. J Pharm Sci 95:446–461.

Saska M, Myerson AS (1987) Crystal aging and crystal habit of terephthalic acid. AIChE Journal 33:848.

Shah P (2006) Use of nanotechnologies for drug delivery. MRS Buletin 31:894–899.

Shao Q, Rowe RC, York P (2007) Comparison of neurofuzzy logic and decision trees in discovering knowledge from experimental data of an immediate release tablet formulation. Eur J Pharm Sci 31:129–136.

Shefter E, Higuchi T (1963) Dissolution behaviour of crystalline solvated and nonsolvated forms of some pharmaceuticals. J Pharm Sci 52:781–791.

Shekunov BY (2004) Production of powders for respiratory drug delivery. In: York P, Kompella

UB, Shekunov BY, editors. Supercritical fluid technology for drug product development. New York: Marcel Dekker, Inc. pp 247–283.

Shekunov BY, Bristow S, Chow AHL, Cranswick L, Grant DJW, York P (2003) Formation of composite crystals presipitation in supercritical CO_2.Cryst Growth Des 3:603–610.

Shekunov BY, Chattopadhyay P, Seitzinger J, Huff R (2006) Nanoparticles of poorly water-soluble drugs prepared by supercritical fluid extraction of emulsions. Pharm Res 23:196–204.

Shekunov BY, Chattopadhyay P, Tong HH, Chow AH (2007) Particle size analysis in pharmaceutics: principles methods and applications. Pharm Res 24:203–227.

Shekunov BY, Grant DJW (1997) J Phys Chem 101:3973.

Shekunov BY, York P (2000) Crystallization processes in pharmaceutical technology and drug delivery design. J Cryst Growth 211:122–136.

Sheldon R (1990) Industrial synthesis of optically active compounds. Chem Ind 7: 212–219.

Shell JW (1963) X-ray and crystallographic applications in pharmaceutical research. III. Crystal habit quantitation. J Pharm Sci 52:100–101.

Simonelli AP, Mehta SC, Higuchi WI (1970) Inhibition of sulfathiazole crystal growth by polyvinylpyrrolidone. J Pharm Sci 59:633–638.

Stephenson GA, Diseroad BA (2000) Structural relationship and desolvation behavior of cromolyn cefazolin and fenoprofen sodium hydrates. Int J Pharm 198:167–177.

Stephenson GA, Groleau EG, Kleemann RL, Xu W, Rigsbee DR (1998) Formation of isomorphic desolvates: creating a molecular vacuum. J Pharm Sci 87:536–542.

Stephenson GA, Stowell JG, Toma PH, Dorman DE, Greene JR, Byrn SR (1994) Solid-state analysis of polymorphic, isomorphic, and solvated forms of dirithromycin. J Am Chem Soc 116: 5766–5773.

Stephenson GA, Stowell JG, Toma PH, Pfeiffer RR, Byrn SR (1997) Solid-state investigations of erythromycin A dihydrate: structure NMR spectroscopy and hygroscopicity. J Pharm Sci 86:1239–1244.

Stranski IN, Honigmann B (1950) The spontaneous appearance of equilibrium forms in crystals of hexamethylenetetramine. Z Phys Chem 194:180–198.

Sun C, Grant DJ (2001) Influence of crystal shape on the tableting performance of L-lysine monohydrochloride dihydrate. J Pharm Sci 90:569–579.

ten Wolde PR, Frenkel D (1997) Enhancement of protein crystal nucleation by critical density fluctuations. Science 277:1975–1978.

Threlfall TL (2000) Crystallisation of polymorphs: thermodynamic insight into the role of solvent. Org Procsess Res Dev 4:384–390.

Tian F, Sandler N, Aaltonen J, Lang C, Saville D, Gordon K, Strachan C, Rantanen J, Rades T (2007) Influence of polymorphic form, morphology, and excipient interactions on the dissolution of carbamazepine compacts. J Pharm Sci 96:584–594.

Tian F, Sandler N, Gordon KC, McGoverin CM, Reay A, Strachan CJ, Saville DJ, Rades T (2006) Visualizing the conversion of carbamazepine in aqueous suspension with and without the presence of excipients: A single crystal study using SEM and Raman microscopy. Eur J Pharm Biopharm 64:326–335.

Tiwary AK (2006) Crystal habit changes and dosage from performance. In: Swarbrick J, editor. Encyclopedia of pharmaceutical technology, 3rd ed. New York: Informa Healthcare USA, Inc. pp. 820–833.

Tom JW and Debenedetti PG (1991) Particle formation with supercritical fluids – a review. J Aerosol Sci 22:555–584.

Towler CS, Davey RJ, Lancaster RW, Price CJ (2004) Impact of molecular speciation on crystal nucleation in polymorphic systems: the conundrum of gamma glycine and molecular 'self poisoning'. J Am Chem Soc 126:13347–13353.

Trask AV, Motherwell WDS, Jones W (2005) Pharmaceutcial cocrystallization: engineering a remedy for caffeine hydration. Cryst Growth & Des 5:1013–1021.

USP, The United States Pharmacopeia (1995) XXIII Revision, United States Pharmacopeial Convention, Rockville, Md.

Vekilov PG (2004) Dense liquid precursor for the nucleation of ordered solid phases from solution. Cryst Growth Des 4:671–685.

Verheyen S, Augustijns P, Kinget R, van den Mooter G (2001) Melting behavior of pure polyethylene glycol 6000 and polyethylene glycol 6000 in solid dispersions containing diazepam or temazepam: a DSC study. Thermochim Acta 380: 153–164.

Vippagunta SR, Brittain HG, Grant DJ (2001) Crystalline solids. Adv Drug Deliv Rev 48:3–26.

Vishweshwar P, McMahon JA, Bis JA, Zaworotko MJ (2006) Pharmaceutical co-crystals. J Pharm Sci 95:499–516.

Volmer M (1939) Die chemische reaktion. Bd. IV. Kinetik der phasenbildung. Leipzig: Steinkopf. 220 pp.

Volmer M (1922) Ordered crystal growth. Z Phys 9:193–196.

Walsh RDB, Bradner MW, Fleischman S, Morales LA, Moulton N, Rodríguez-Hornedo N, Zaworotko M (2003) Crystal engineering of the composition of pharmaceutical phases. Chem Commun 2:186–187.

Weissbuch I, Addadi L, Leiserowitz L (1991) Molecular recognition at crystal interfaces. Science 253:637–645.

Weissbuch I, Lahav M, Leiserowitz (1999) Towards an understanding and control of nucleation, growth, habit, dissolution and structure of crystals using ‘tailor-made’ auxiliaries. In: Myerson AS, editor. Molecular Modelling Applications in Crystallization, New York: Cambridge University Press. pp 166–227.

Weissbuch I, Torbeev V Yu, Leiserowitz L, Lahav M (2005) Solvent effect on crystal polymorphism: why addition of methanol or ethanol to aqueous solutions induces the precipitation of the least stable form of glycine? Angew Chem 117:3290–3293.

Wen H, Morris KR, Park KJ (2005) Hydrogen bonding interactions between adsorbed polymer molecules and crystal surface of acetaminophen. J Colloid Interface Sci 290:325–335.

Wikström H, Marsac PJ, Taylor LS (2005) In-line monitoring of hydrate formation during wet granulation using Raman spectroscopy. J Pharm Sci 94:209–219.

Wildfong PLD, Morris KR, Anderson CA, Short SM (2007) Demonstration of a shear-based solid-state phase transformation in a small molecular organic system: chlorpropamide. J Pharm Sci 96:1100–1113.

Williams-Seton L, Davey RJ, Lieberman HF, Pritchard RG (2000) Disorder and twinning in molecular crystals: impurity-induced effects in adipic acid. J Pharm Sci 89:346–354.

Windheuser JJ, Misra J, Eriksen SP, Higuchi T (1963) Physics of tablet compression. XIII. Development of die-wall pressure during compression of various materials. J Pharm Sci 52:767–772.

Yano J, Furedi-Milhofer H, Wachtel E, Garti N (2000) Crystallization of organic compounds in

reversed micelles. I. Solubilization of amino acids in water-isooctane-AOT microemulsions. Langmuir 16: 9996–10004.

York P (1983) Solid-state properties of powders in the formulation and processing of solid dosage forms. Int J Pharm 14:1–28.

York P (1992) Crystal engineering and particle design for the powder compaction process. Drug Dev Ind Pharm 18:677–721.

York P (1999) Strategies for particle design using supercritical fluid technologies. Pharm Sci Technol Today 2:430–440.

Yoshinari T, Forbes RT, York P, Kawashima Y (2002) Moisture induced polymorphic transition of mannitol and its morphological transformation. Int J Pharm 247:69–77.

Yu LX, Lionberger RA, Raw AS, D'Costa R, Wu H, Hussain AS (2004) Applications of process analytical technology to crystallization processes. Adv Drug Deliv Rev 56: 349–369.

Zettlemoyer AC (1969) Nucleation. New York:Marcel Dekker. 606 pp.

Zhang GG, Grant DJ (1999) Incorporation mechanism of guest molecules in crystals: solid solution or inclusion? Int J Pharm 181:61–70.

Zhang GGZ, Law D, Schmitt EA, Qiu Y (2004) Phase transformation consideration during process development and manufacture of solid oral dosage forms. Adv Drug Deliv Rev 56:371–390.

Zhu H, Yuen C, Grant DJW (1996) Influence of water activity in organic solvent + water mixtures on the nature of the crystallizing drug phase. Int J Pharm 135:151–160.