1

Impact of the Polymorphic Form of Drugs/NCEs on Preformulation and Formulation Development

MHD Bashir Alsirawan and Anant Paradkar

Center for Pharmaceutical Engineering Sciences, University of Bradford, Richmond Road, Bradford BD7 1DP, UK

1.1 Introduction

Polymorphism is a well-established phenomenon which describes the ability of a solid-state molecular structure to be repetitively positioned in at least two different arrangements in three-dimensional space. These different arrangements can result in different sets of physicochemical properties of the same molecular structure, which can significantly affect material behavior during handling, processing, and storing. Hence, polymorphism is crucial for many applications, including the pharmaceutical industry. Most drugs, whether already produced or newly discovered candidates, and usually referred to as new chemical entities (NCEs), are found as solids under normal conditions of temperature and pressure. Eighty-five percent of active pharmaceutical ingredients (APIs) display pseudopolymorphism, including 50% having real polymorphism [1]. In addition, Cruz-Cabeza et al. have listed polymorphic incidence of single-component NCEs from the Cambridge Structure Database (CSD), European Pharmacopeia, and data from the extensive screening procedures performed in Roche and Lilly (Table 1.1) [2].

Consequently, polymorphism must be taken into consideration during every processing stage starting from early steps such as preformulation and formulation development, passing through processing, manufacturing, and storage, and eventually until consumption in humans.

1.1.1 Background

Polymorphism has been discussed and investigated by many reports [3–7]. Moreover, several definitions were made depending on the researcher or the field of research; McCrone (1965) defined polymorphism thus: "Polymorph is a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecule of that compound in the solid state." Buerger defined polymorphism of a crystal as "molecular arrangements having different properties." The definition by Purojit and Venugopalan states it is the "ability of a substance to exist as two or more crystalline phases that have different

Innovative Dosage Forms: Design and Development at Early Stage,
First Edition. Edited by Yogeshwar G. Bachhav.

Table 1.1 Polymorphism incidence for single-component NCE from several data source.

Source	Number of single NCEs	Polymorphism occurrence (%)
CSD	5941	37
European Pharmacopeia 2004	598	42
Roche	68	53
Lilly	68	66

arrangements or conformations of the molecules in the crystal lattice" [3]. IUPAC defined the phase transition between polymorphs as the "reversible transition of a solid crystalline phase at a certain temperature and pressure (the inversion point) to another phase of the same chemical composition with a different crystal structure" [8]. Other definitions were similar to those previously mentioned, such as different crystal arrangements for the same chemical composition [9], or crystal systems of same elemental structure but with unlike unit cells [4]. Desiraju has debated the experimentality of McCrone's definition depending on previous observations of polymorphism cases where coexistence of two polymorphs within the same crystal is found with no distinctive phase separation or, in other cases, where two structures are very similar with a barely identified difference (divergence). Desiraju has suggested setting criteria to differentiate whether two arrangements are genuine polymorphs or belong to the same solid phase [6].

The first reported polymorphism event was discovered with calcium carbonate in 1788 by Kalporoth. In 1832, benzamide was the first organic molecule the polymorphism of which was observed by Wöhler and Liebig [10]. The first crystal structure of polymorphic form determined by X-ray diffraction was for resorcinol in 1938 [11].

Although the term polymorphism seems specific, there is confusion around designating different structures as polymorphs. Moreover, reports follow different terminology rules depending on the fields of interest and background. To mitigate this confusion, other terms have arisen such as pseudopolymorphism or solvatomorphism. However, several reports do not encourage using these terms as it may create further confusion [7, 12].

1.1.2 Types of Polymorphism

If we stick to the pure definition of polymorphism and exclude chemically non-similar structures, there are two primary types of polymorphism, conformational and packing polymorphism.

1.1.2.1 Conformational Polymorphism

This type of polymorphism resulted in molecules having flexible moieties which, in turn, have rotatable bonding. The rotational movement of a single bond in the molecular structure leads to a symmetry change and produces a new

configuration, and, subsequently, a change in lattice packing [13]. A typical example of conformational polymorphism is ranitidine hydrochloride, which has two polymorphs, form 1 and form 2. Both phases are monoclinic, with the same space group but with only a difference in the conformation and disorder of nitroethenediamine moiety (Figure 1.1) [14]. Triamcinolone acetonide acetate, a drug commonly used for rheumatoid arthritis, exists in three polymorphic forms A, B, and C and a monohydrate; all these forms exhibit conformational variations (Figure 1.1) which result in different packing (Figure 1.2) [15].

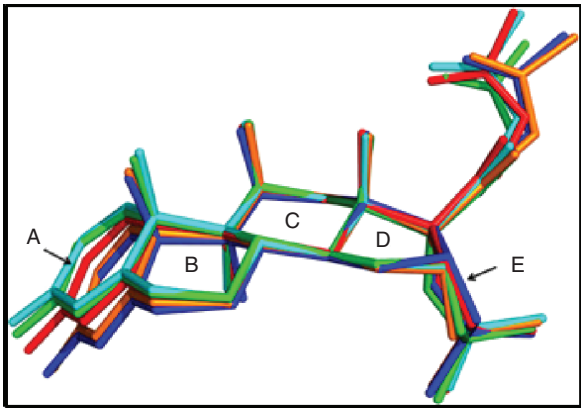

Figure 1.1 Molecular structure of triamcinolone polymorphs A (light blue), B (red and green), C (orange), and MH (blue). Source: Bučar et al. 2015 [14] and Wang et al. 2017 [15]. Adapted with permission of ACS.

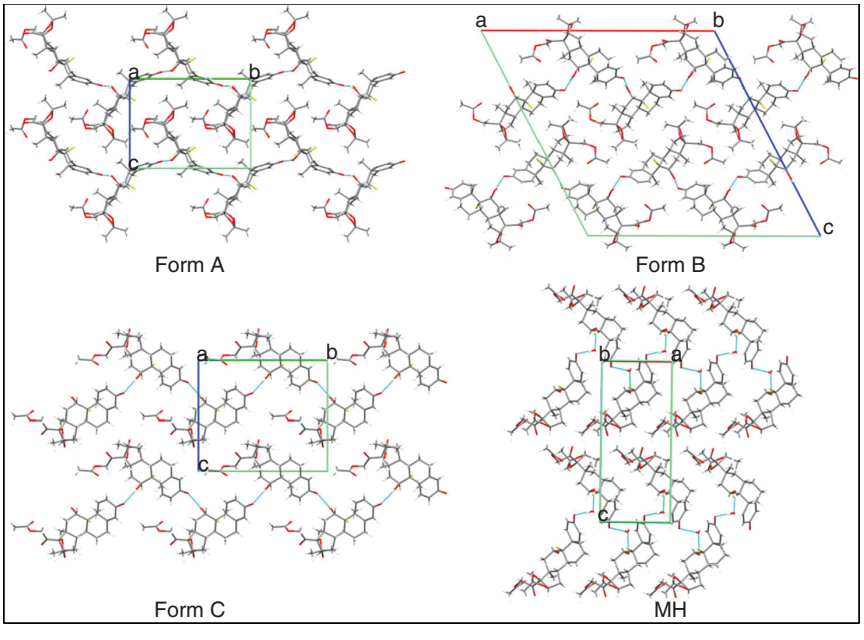

Figure 1.2 Lattice packing of triamcinolone acetonide acetate polymorphs. Source: Wang et al. 2017 [15]. Adapted with permission of ACS.

1.1.2.2 Packing Polymorphism

In this type, the configuration and bond orientation between two structures is identical, yet the arrangement and backing of this conformation in a three-dimensional structure is not similar. Most of the pharmaceutical materials have flexible moieties; thus, it is rare to observe packing polymorphism in the field. Donepezil, which is used in the palliative treatment of Alzheimer's disease, has two packing polymorphs, forms K and F. The conformation similarity of the two forms was investigated by superimposing their structure using Mercury 3.3, a 3D structure visualization and measurement program. Root-mean-square deviation (RMSD) was then calculated and found to be insignificant (0.0624 Å) supporting the identical confirmation (Figure 1.3) [16].

1.1.3 Thermodynamic-Based Classification of Polymorphism

Polymorphic interconversion is primarily governed by the thermodynamic state of the material, and as per thermodynamic rules, both temperature and pressure determine the thermodynamic stability of a certain polymorph. Polymorphism type depends on the nature of solid-phase transition with respect to temperature or pressure and can be divided into monotropic and enantiotropic (Figure 1.4). Understanding and identifying the transition nature of polymorphs is crucial for establishing optimum parameters for crystallization, screening [17], processing, and storage of active ingredients and excipients [18, 19].

1.1.3.1 Enantiotropic Polymorphism

In enantiotropic polymorphism, one polymorph (let us call it form I) is considered the most stable at a certain temperature and pressure, at which the other polymorph (form II) is not stable, usually called metastable. On the other hand, the metastable form II becomes stable when reaching different temperature or pressure zones or reaching transition temperature T_t or pressure P_t.

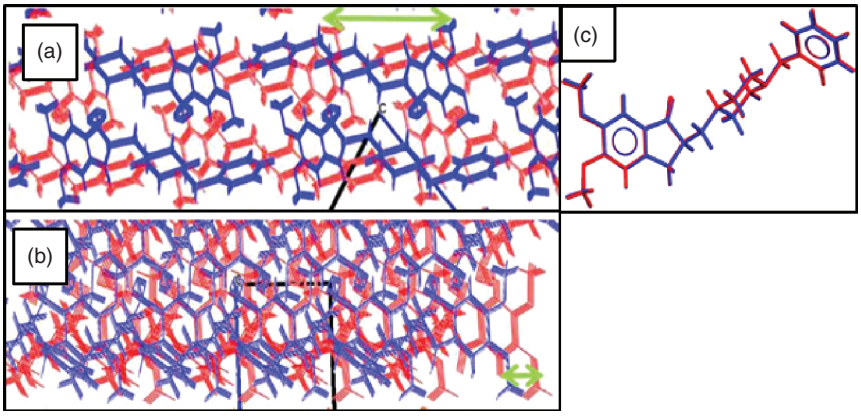

Figure 1.3 Superimposed view of donepezil form F (blue) and form K (red); (a) crystallographic A axis view, (b) 90° angle view where an axis is horizontally positioned, the packing of two polymorphs are translated (green double-headed arrows). However, (c) superimposed molecular structures show identical conformations, meaning that the two phases are packing polymorphs. Source: Part et al. 2016 [16]. Adapted with permission of American Chemical Society.

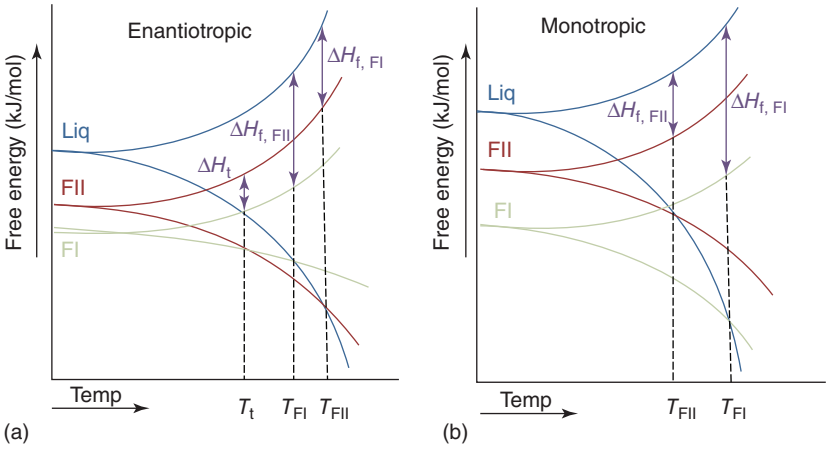

Figure 1.4 Phase energy versus temperature diagram for the (a) enantiotropic and (b) monotropic interconversion for two polymorphic phases FI and FII.

Simultaneously, the stable form I becomes metastable and a phase transition from form I to form II takes place. In some cases, a third polymorph (form III) is found and it has a third temperature or pressure zone, above specific transition temperature or pressure, where it becomes the most stable among others.

1.1.3.2 Monotropic Polymorphism

This type describes the case where one polymorph is considered the most stable in a wide range of temperatures reaching high transition levels, higher than the melting point of the other forms which are all considered to be metastable polymorphs under their melting point.

Two thermodynamic rules can be applied, which basically rely on thermal analysis to distinguish the type of polymorphism. These rules are heat of fusion and heat of transition, and may be referred to as Burger–Ramberger rules [20]. To describe these rules, let us propose two polymorphs form I and T_{FII} T_t form II, where form I is more stable under normal temperature or before heating. The heat of fusion rule states that if the polymorph with the higher melting point has lower fusion enthalpy compared to the other form, the relationship between the two polymorphs is enantiotropic. However, if the higher melting point form has higher enthalpy of fusion, the polymorphism is monotropic. In the case of the heat of transition rule, polymorphs I and II are monotropic if the transition from form II to I is exothermic; or enantiotropic if the transition from form I to II is endothermic. It should be noted that the interconversion is reversible in enantiotropic systems and irreversible in monotropic polymorphism [4].

Moreover, enantiotropic polymorphs have a defined transition temperature (Figure 1.3) and can be determined experimentally. Conversely, monotropic systems have no observable transition temperature, yet there is a theoretical transition point that can be calculated using the Bauer–Brandl equation (1.1):

$$T_{tr} = \frac{\Delta H^T_{m,I} - \Delta H^T_{m,II}}{\Delta H^T_{m,I}/T_{m,I} - \Delta H^T_{m,II}/T_{m,II}} \tag{1.1}$$

where $\Delta H^{T}_{m,\mathrm{I}}$ and $\Delta H^{T}_{m,\mathrm{II}}$ are the melting enthalpy of forms I and II, respectively, and $T_{m,\mathrm{I}}$ and $T_{m,\mathrm{II}}$ are the melting points of forms I and II, respectively.

1.1.4 Concomitant Polymorphism

Concomitant polymorphism describes the case where more than one solid phase displays simultaneous nucleation and crystal growth under the same conditions and within the same batch. The reason behind concomitant polymorphism is a struggle between kinetically and thermodynamically stable polymorphs [21]. In other words, the kinetic and thermodynamic phases have a slight free energy difference [22]. This event may occur momentarily as the kinetically stable phase could convert rapidly to the thermodynamically stable phase, and in most cases the event is temporary and not observed due to the polymorphic conversion with time, or after predisposition to water or solvent (recrystallization or dissolution) [21]. The appearance of concomitant polymorphism can depend on the nature of crystallization solvent, temperature, and solution concentration [23].

Concomitant polymorphism poses a challenge to preformulation scientists when controlling the formation of a specific and desired polymorph. Several cases of APIs which exhibit concomitant polymorphism have been reported. A concomitant polymorphism of methoxyflavone, a nonsteroidal anabolic flavone, was reported. Thermodynamically stable form A and kinetically form B have a negligible difference in lattice energies and appear simultaneously after crystallization (Figure 1.5). Form B can transform to form A under the influence of temperature [24]. The relative nucleation and crystal growth rate is a crucial factor in controlling polymorphic appearance; furthermore, higher growth rate will govern the presence of the phase at the end of crystallization. Two polymorphs of donepezil, forms I and II, can appear concomitantly. The nucleation rate of form I is slower than that of form II, yet crystal growth is

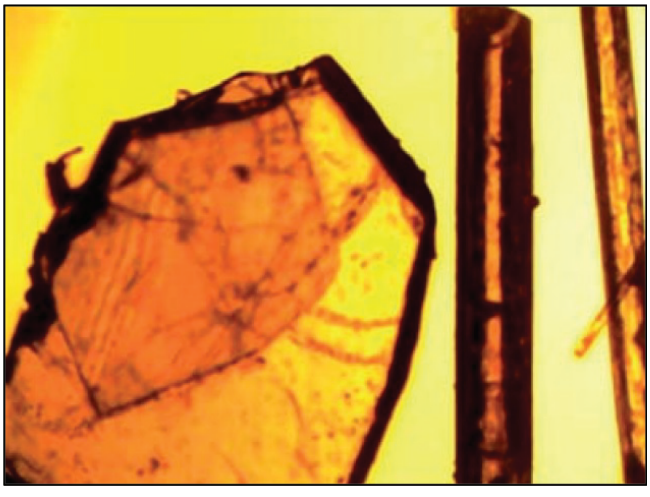

Figure 1.5 Concomitant polymorphism after crystallization of methoxyflavone form A (bulk shape) and form B (needle shape). Source: Gong et al. 2016 [24]. Adapted with permission of American Chemical Society.

higher in form I. As a result, form I appears at the beginning of the process followed by form II, which dominates its presence at the end of the process [16].

1.1.5 Debatable Polymorphism Cases

These types are considered by many researchers as imperfect or pseudopolymorphism. Unlike the known variations found in basic polymorphism, the structures under this category have variations within the chemical structure which results in a change in crystal confirmation of packing.

1.1.5.1 Tautomeric Polymorphism or Tautomerism

Tautomerism is a simultaneous interconversion of isomeric organic compounds resulting from proton transfer caused by the presence of strong electronegative atoms such as O or N. Tautomerism depends on the presence of weakly acidic functional groups such as amines, amides, ketones, and lactams. The transformations are classified as chemical reactions and primarily consist of interconverting pairs such as keto-enol, oxime-nitroso, amine-imine, amide-imidic acid, and lactam-lactim reaction (Figure 1.6).

Tautomerism transition occurs at solution or melt state, where the reaction is at equilibrium, while at solid state, the crystallization of different tautomers causes a unit cell structure producing polymorphs with tautomeric origin. Ranitidine hydrochloride form 2 is found to consist of a tautomeric mixture (50 : 50) of enamine and nitronic acid, which takes place in the nitroethenediamine group [26]. In addition, omeprazole tautomerism takes place in solution state with 5-methoxy–6-methoxy transition. However, in solid state, both tautomers exist continuously at the molecular level or as solid solution (Figure 1.7) [27].

1.1.5.2 Enantiomerism/Stereoisomerism

The concept describes structures having a similar composition of atoms and bonding; however, they differ in the three-dimensional arrangement or orientation of the atoms. This type of structural change is also considered a chemical reaction as it requires the deconstruction of a covalent bond to allow a new covalent bond to form, resulting in a configuration that is the mirror image of the first structure. Most organic molecules that comprise asymmetric or chiral carbon exhibit this phenomenon, and therefore are named chiral.

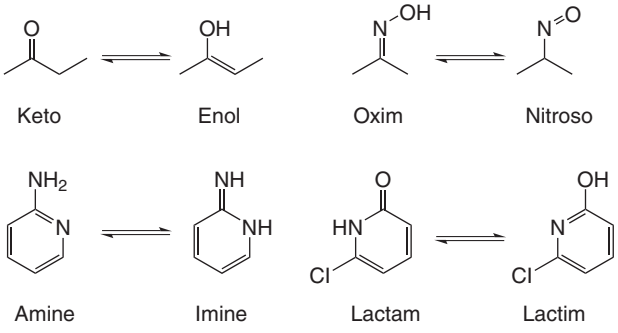

Figure 1.6 Examples of tautomeric reactions. Source: Braga et al. 2014 [25]. Adapted with permission of Bentham Science Publishers Ltd.

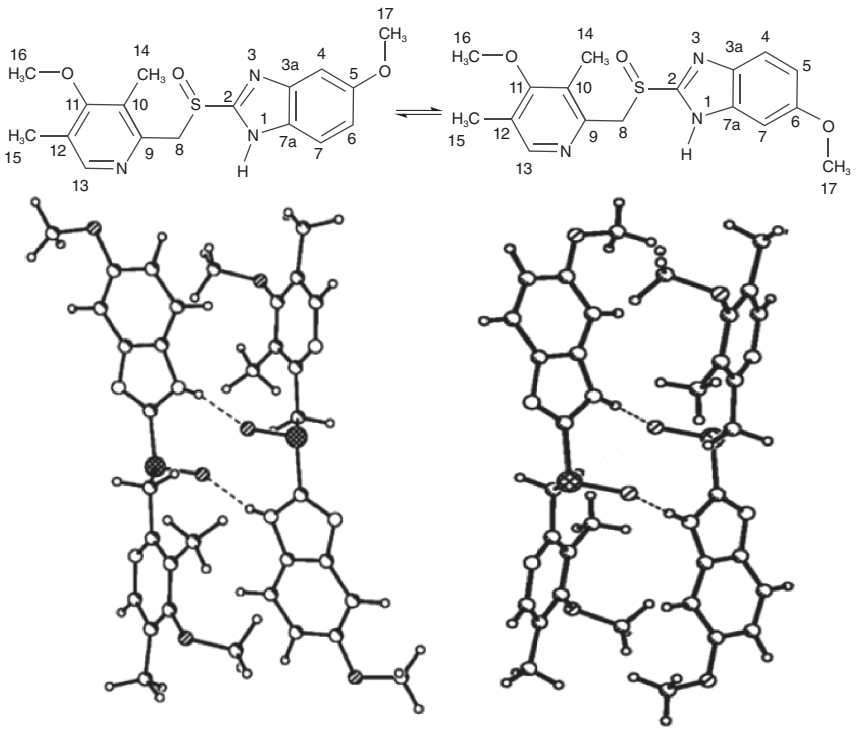

Figure 1.7 Tautomeric forms of omeprazole; 5-methoxy tautomer in form V (right), and 6-methoxy tautomer in form I (left). Source: Bhatt et al. 2007 [27]. Adapted with permission of Royal Society of Chemistry.

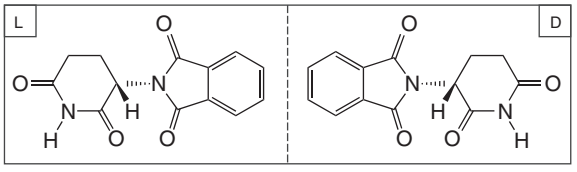

Figure 1.8 Enantiomerism of L-thalidomide and D-thalidomide.

Enantiomerism is a crucial property in the pharmaceutical and pharmacological fields, as nearly 50% of the drugs are chiral and 90% of them are marketed as racemate equimolar mixtures (containing both isomers). Moreover, different isomers exhibit different pharmacokinetic and pharmacodynamic properties. The advancement in chiral drug design has produced safer and more effective candidates [28]. One of the examples of chiral or enantiomeric drugs is thalidomide which displays two enantiomers, (*S*)-thalidomide and (*R*)-thalidomide (Figure 1.8). Thalidomide was used for motion sickness, but it turned out that L-isomer is teratogenic and the therapeutic activity comes from the D-isomer.

1.1.5.3 Pseudopolymorphism

The utilization of the term pseudopolymorphism supports part of the definition of polymorphism "having the same chemical composition" as it describes molecules with different crystal structures caused by the presence of a secondary

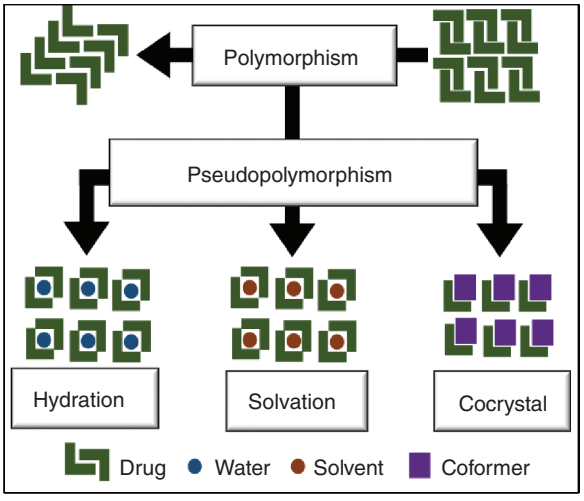

Figure 1.9 Representation of pseudopolymorphism events which involve the incorporation of a heterostructure within the crystal lattice compared to polymorphism.

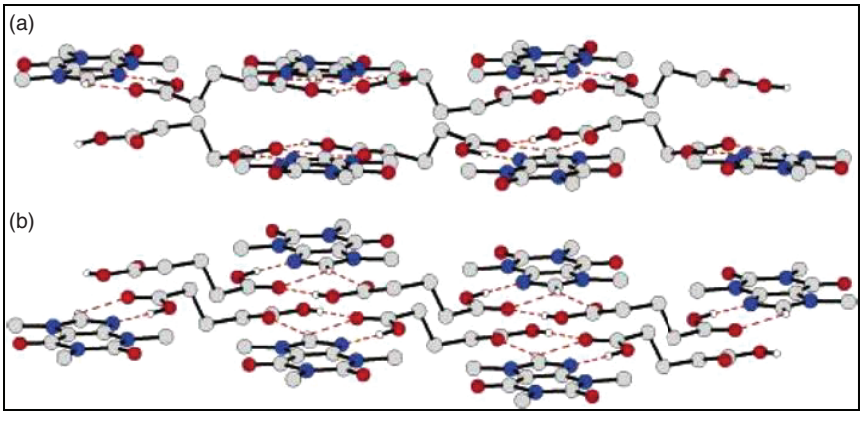

Figure 1.10 Packing polymorphism of caffeine: glutaric acid cocrystal, (a) FI and (b) FII. Source: Trask et al. 2005 [33]. Adapted with permission of American Chemical Society.

heterostructure within the crystal lattice (e.g. water, solvent, coformer, etc.) (Figure 1.9) [12]. However, the U.S. Food and Drug Administration (FDA) still consider hydrates, solvates, cocrystals, and amorphous phase as polymorphs [29–31].

However, some of these forms such as cocrystals tend to be polymorphic with their own structure [32]. For example, caffeine: glutaric acid cocrystal displays enantiotropic packing polymorphism; stable FII and metastable FI (Figure 1.10) [33, 34].

1.2 Polymorphism Impact on Drug/Excipient Properties

Different molecular conformation or packing for a compound provides specific characteristics and hence it necessitates formulation to utilize certain handling,

processing, or storage procedures. These characteristics can be categorized as physicochemical or mechanical properties, which are described in detail further.

1.2.1 Physicochemical Properties

Physicochemical properties are related to both physical and chemical features of molecular structure (e.g. presence of hydrophobic/hydrophilic groups, inter- and intramolecular bonding, crystal structure, etc.). Physicochemical properties include melting point, density, hygroscopicity, refractive index, surface activity, crystal habit, color, physical stability, and performance properties. Later involve solubility, dissolution rate, and bioavailability (which are interrelated). These properties are further described in detail due to their importance in pharmaceutical development (see Section 2.3). The difference in melting points originates from the variation in molecular interaction and lattice energy among polymorphs. Refractive index can be defined as the ratio of light speed in a vacuum to the speed of light within the crystal at a certain wavelength and temperature. Anisotropic crystals obtain multiple refractive index values, and hence are called birefringent, whereas isotropic crystals obtain a single refractive index, and thus are called non-birefringent. Refractive index is mainly determined by crystal structure and molecular arrangements; therefore, different polymorphs will exhibit different refractive index and birefringence. This property can be detected by polarized light microscopy, and it is used to identify different polymorphs or phase transitions

Crystal color and shape are primarily dependent on the molecular conformation or packing in the crystal lattice which results in different macroscopic orientation within the crystal structure. Crystal color can be determined depending on how the light is absorbed and reflected by the crystal lattice, which changes according to lattice conformation [35, 36]. Crystal morphology is dictated by the crystal growth mechanism of crystal nuclei faces. Therefore, the growth of crystal nuclei having different crystal packing results in morphological variations. Triamcinolone exhibits three polymorphs and a monohydrate having different crystal shapes (Figure 1.11) [15]

Hygroscopicity is the measure of moisture uptake, sorption, and retention from the atmosphere (humidity), neighboring liquids (mostly water), or solids in contact. Both thermodynamic and kinetic factors are involved in this process. Hygroscopicity is a crucial property in pharmaceutical development as it has a direct impact on other properties such as solubility, dissolution rate, and stability [37]. Dynamic vapor sorption is a very popular technique in assessing the hygroscopicity of materials; it measures the mass change as a function of relative humidity level (RH, %) at isothermal conditions, called sorption isotherms [38]. Different polymorphs can show varied moisture uptake behavior. This can be attributed to the variation in lattice structure, intermolecular interactions, and positioning of hydrophilic/hydrophobic molecular arrangement. Dynamic vapor sorption analysis of amisulpride forms I and II (Figure 1.12) shows that moisture uptake by form II is lower compared to that of form I [39].

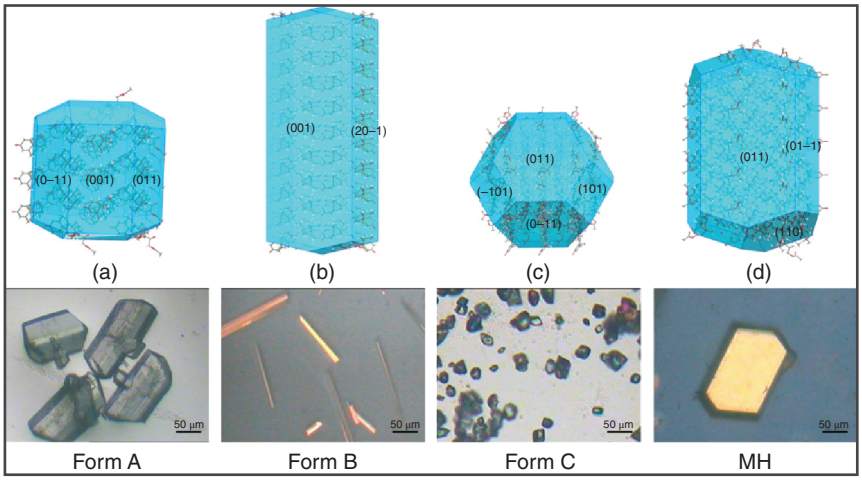

Figure 1.11 Predicted morphology and optical images of triamcinolone form A, B, C, and monohydrate (MH). Source: Wang et al. 2017 [15]. Adapted with permission of American Chemical Society.

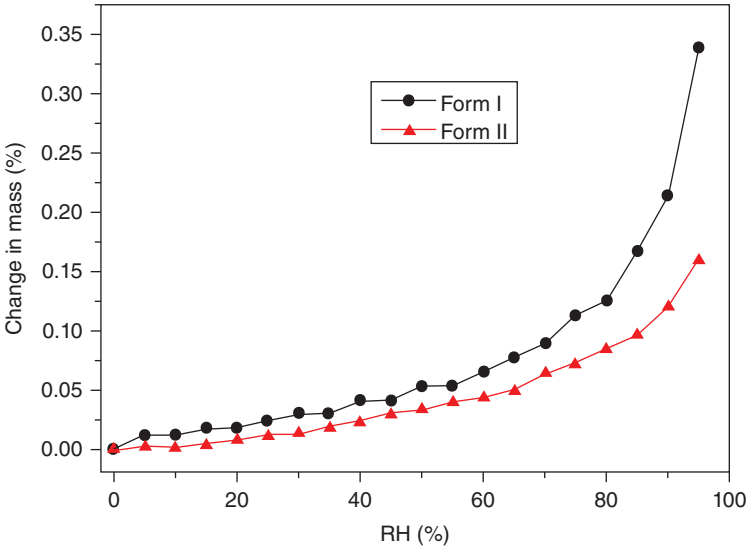

Figure 1.12 Dynamic vapor sorption isotherm of amisulpride forms I and II at 25 °C. Source: Zhang and Chen 2017 [39]. Adapted with permission of Elsevier.

1.2.2 Mechanical Properties

Mechanical properties are related to crystal behavior while subjected to mechanical stress such as compression or shear forces. These properties include plasticity, tensile strength, compressibility, or overall manufacturability. Different polymorphs that exhibit variations in terms of morphology, structural geometry, presence of defects or slip planes, density, or lattice strength mostly obtain different mechanical properties.

Morphology change caused by polymorphism can affect flowability and compressibility. However, the crystal shape can be changed while preserving the polymorph integrity using various crystal engineering approaches [40].

The presence of slip planes has been linked by many reports to superior compactability. Slip planes are comprised of crystallographic planes having the most vulnerable bonds attaching them to other planes. Slip planes accommodate compression force and use it to slide over neighboring planes, improving compressibility and deformation. However, active slip planes should be distinguished because the presence of weak hydrogen bonding across the plane can prevent plane sliding, thereby making it inactive. For example, ranitidine FI, although it contains slip planes within its crystal lattice, displays poor deformation which may be attributed to the presence of weak hydrogen bonding (Figure 1.13) [41]. The most popular example is the change in mechanical properties among paracetamol polymorphs. Metastable orthorhombic form II crystal structure is superior in compressibility compared to the monoclinic form I [42]. Therefore, polymorphic composition should be monitored and controlled before initiating direct compression of paracetamol. Form II obtains slip planes which enhance its deformation and plasticity, producing more coherent compacts [43]. Furthermore, sulfathiazole form III tablets were found to have the highest crushing force due to the presence of the slip plane in form III crystal structure which grants it excellent compressibility [44].

Variations in molecular density due to different crystal packing between polymorphs can also affect compressibility. It is proposed that stable polymorphs obtain denser packing and stronger intermolecular interactions which are more difficult to deform as in the case of metoprolol [45]. Other reports also found that true density negatively impacts compressibility but improves compactability, which results in higher tensile strength, as was the case with ranitidine polymorphs [46].

In addition, clopidogrel exhibits high true density in metastable form I, which results in low compressibility; yet it displays better properties for tableting compared to the less dense stable form II. It should be noted that form II structure involves stronger hydrogen bonding, which is reflected by the higher heat of fusion compared to form I.

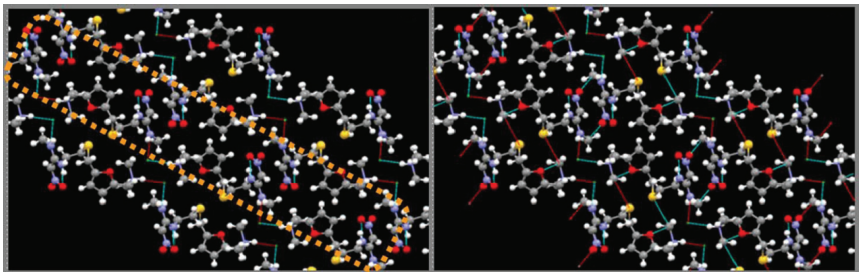

Figure 1.13 Crystal structure of ranitidine form I with (a) slip planes (yellow box) and (b) presence of weak hydrogen bonding (yellow dots). Source: Khomane and Bansal 2013 [41]. Adapted with permission of Elsevier.

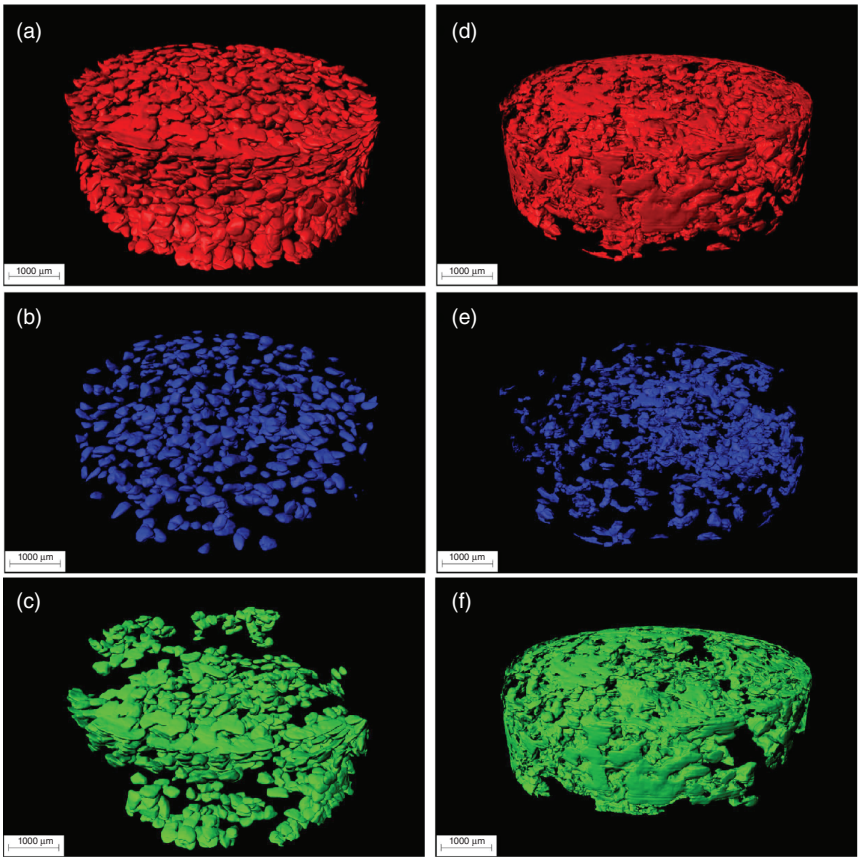

Figure 1.14 3D images of clopidogrel polymorphs after compression, (left) form I, and (right) form II, (a) and (d) are the overall particle content in tablets, (b) and (e) uncompressed or particles present in tablet core; (c, f) are compressed particles at the surface on the tablet. Source: Yin et al. 2016 [47]. https://creativecommons.org/licenses/by/4.0/(CC BY 4.0).

Further investigation was performed on clopidogrel compressibility using synchrotron radiation X-ray microtomography (SR-μ CT) and 3D reconstruction analysis. This revolutionary and nondestructive method enables the visualization and quantification of deformation after compression. Form II shows better deformation and compressibility compared to form I. Moreover, the distribution of particles within the tablet was different among the two polymorphs. Deformation was assessed on the basis of change of sphericity, volume, and ellipsoid parameters. Deformation of form I particles was found to be mediated by plastic–elastic mechanism, while form II exhibits brittle fracture mechanism [47]. SR-μ CT tomographic 3D images show how form I disc-shaped particles got flattened, while form II particles were crushed and lost their shape (Figure 1.14).

1.2.3 Impact of Polymorphism on *In Vivo* Performance

The development of drugs with appropriate *in vivo* performance and pharmacokinetics to satisfy the regulatory guidelines is paramount in the pharmaceutical industry. Furthermore, the selection of a specific polymorph of API for final

product manufacturing could have a significant impact on the *in vivo* profile of that drug product. Polymorphism can alter both solubility and chemical stability of the compound, which are great influencers of bioavailability.

1.2.3.1 Effect of Polymorphism on Solubility

Solubility, from the perspective of solid polymorphism, is a thermodynamic concept that describes the case where solid-state solute and liquid solvent coexist in equilibrium state. Equilibrium state indicates that the two phases have equal temperatures, pressures, and free energies. Solubility is an intensive property which is independent of the amount of solute but rather is affected by the nature of the solid phase.

Poorly soluble compounds are commonly divided into brick dust or grease ball materials. The brick dust materials have strong lattice energies which make it difficult to break the structure within the solvent. Grease ball materials are extremely hydrophobic and have low affinity to aqueous media including gastrointestinal fluids. The two effects could be concomitant in the case of NCEs with poor solubility, necessitating the application of further formulation techniques.

Intrinsic solubility is governed by the Gibbs free energy of solubilization (ΔG_{sol}), which should obtain a value less than 0 for the solubility reaction to take place. ΔG_{sol} can be mathematically obtained using the general Eq. (1.2).

$$\Delta G_{solu} = \Delta H_{solu} - T\Delta S_{solu} \tag{1.2}$$

where ΔH_{solu} is the solubility enthalpy, ΔS_{solu} is the entropy of solubilization, and T is the temperature in kelvin.

Solubilization enthalpy (ΔH_{solu}) can be defined as the amount of energy, or heat, absorbed or released to initiate the solubility reaction. ΔH_{solu} could have a positive or a negative value, if the reaction is endothermal or exothermal, respectively. ΔH_{solu} is mainly composed of two parts (Eq. (1.3)), crystal lattice enthalpy ΔH_{latt}, which is related to the cohesion energy within solute particles, and solvation enthalpy ΔH_{solv} which is related to solute–solvent interactions.

$$\Delta H_{solu} = -\Delta H_{latt} + \Delta H_{solv} \tag{1.3}$$

ΔH_{latt}, in the case of solid-state materials, where pressure and volume change can be neglected, is the energy required to form the lattice structure when gaseous phases bond together. Since bonding formation is an exothermic process, ΔH_{latt} always obtains a negative value; hence, $-\Delta H_{latt}$ is always positive. Equation (1.3) involves two competing forces at equilibrium state, the solute–solute bonding ΔH_{latt}, which is governed by the physical bonding within the crystal structure, and solute–solvent bonding ΔH_{solv} which is related to the solute–solvent chemical affinity or polarity (high affinity means ΔH_{solv} is highly negative, while low affinity means a low negative or a positive value). If solute–solvent affinity is high enough to overcome lattice energy, the negativity of H_{solv} overcomes the $-\Delta H_{latt}$ value. This will result in a negative value of ΔH_{solu}, meaning that overall solubilization is exothermal. Moreover, the solubilization will occur spontaneously as, according to Eq. (1.2), the ΔG_{solu} value will obtain a negative value.

On the other hand, if the lattice energy, or $-\Delta H_{latt}$ value, is high enough to overcome ΔH_{solv}, ΔH_{solu} will obtain a positive value. In this case, based on

Eq. (1.2) and depending on the entropy–temperature value $T\Delta S_{solu}$, two scenarios are possible. The first is that $T\Delta S_{solu}$ is high enough to overcome ΔH_{solu}, leading to a negative ΔG_{solu}, which means that solubilization is endothermic and can occur spontaneously provided enough energy is supplied to the reaction. The second scenario happens if $T\Delta S_{solu}$ cannot overcome ΔH_{solu}, resulting in a positive ΔG_{solu}, and thus solubility does not take place.

Therefore, ΔH_{solu} is crucial for the formulators, and it is targeted to enhance the solubility either by reducing lattice energy (decreasing $-\Delta H_{latt}$) or by increasing the affinity between the solute and solvent (decreasing ΔH_{solv}). Lowering lattice energy is performed by manipulating the solute physical structure, such as converting to amorphous form, solvate, salt, cocrystal, or the polymorph. Nevertheless, changing the solute–solvent interaction is associated with changing chemical composition, e.g. complexation, ionization, micellar solubilization, and prodrug formation.

Polymorphism, which results in different molecular conformation or packing, leads to a change in the lattice energy value and therefore a change in the solubility. The metastable form at a certain temperature has lower lattice energy than the stable form, and hence has higher solubility at the same temperature. In addition, the solubility differences between several polymorphs have been investigated and it was found that the solubility ratio between metastable and stable forms ranges from 1: 1–10 times [48]. Form C of phenylbutazone is 1.5 times more soluble than form A. Ritonavir, a protease inhibitor, has two polymorphs, the stable form II and metastable form I, which have significant solubility differences, approximately 4 : 1 in ethanol/water mixtures [49].

Conventional solubility determination has been discussed by many reviews and it involves preparing a saturated solution of the desired solute–solvent system using a shake-flask method. This is done by adding excess of solute to the solvent, agitation, or stirring for a certain time at a certain temperature and pressure, and subsequent filtration. If the solvent is aqueous, pH measurement or adjustment must be performed using a pH meter, and standard buffer systems, respectively. The next step is to determine the concentration of aliquots, which is measured using gravimetric, spectroscopic, or chromatographic techniques. Commonly, the solubility is investigated using the range of solvents (mostly water, buffers, and ethanol), temperatures, and pH level [50].

The process is exhaustive, stagnant, and requires a decent amount of sample, which is difficult to supply in the early stages of drug development. In addition, it requires expertise in the solid–liquid equilibria (SLE) field, including phase rule, phase diagrams, and thermodynamics. Moreover, solubility determination of metastable polymorphs is very tricky in terms of physical stability as metastable polymorphs tend to undergo solution-mediated phase transformation and convert to the stable form.

The solubility of polymorphic materials can be determined using thermal methods or be predicted using computational and mathematical models. Experimental thermal data can be utilized assuming that crystal lattice cohesion is the only controlling factor. In this case, solubility is referred to as ideal solubility (S_{ideal}). Lattice energy can be represented as the melting or fusion enthalpy, neglecting heat capacity change after melting, and used to calculate the

ideal solubility using the van 't Hoff equation (1.4). The equation is a deferential correlation between solubility/temperature change and enthalpy of fusion.

$$\frac{\mathrm{d}\ln S_{\mathrm{ideal}}}{\mathrm{d}T} = \frac{\Delta H_{\mathrm{fus}}}{RT^2} \tag{1.4}$$

where ln S is the natural logarithm of fractional solubility, T is the temperature in kelvin, R is the ideal gas constant, and ΔH_{fus} is the enthalpy of fusion, which can be also referred to as enthalpy of melting. Enthalpy of melting can be determined experimentally using differential scanning calorimetry (DSC). Moreover, the van 't Hoff equation is integrated to produce Eq. (1.5)

$$\ln S_{\mathrm{ideal}} = -\frac{\Delta H_{\mathrm{m}}}{R}\left(\frac{T_{\mathrm{m}} - T}{T T_{\mathrm{m}}}\right) \tag{1.5}$$

where ΔH_{m} is the melting enthalpy and T_{m} and T are the melting point and temperature, respectively. However, this method discards the contribution of the solvent–solute effect which is necessary to obtain realistic solubility (Eq. (1.6)).

$$\ln\ S_{\mathrm{realistic}} = \ln\ S_{\mathrm{ideal}} - \ln\ \gamma \tag{1.6}$$

where γ the activity coefficient of solute in the solvent.

The van 't Hoff equation (1.7) can be also employed to calculate the enthalpy of solubilization, depending on two solubility values at two distinct temperatures which are determined either experimentally or computed via prediction models. In this case, the solubility values are considered realistic, and thus the enthalpy value can be referred to as solubilization instead of melting enthalpy as the solvent contribution is present [51].

$$\Delta H_{\mathrm{solu}} = \frac{T_1 T_2}{T_1 - T_2} R \ln\left(\frac{S_1}{S_2}\right) \tag{1.7}$$

Solubility prediction of NCEs before conducting experimental measurement can save a lot of time and effort by avoiding to deal with extremely low-soluble candidates and focusing on the development of more suitable compounds. Quantum-mechanics-dependent computational methods such as lattice energy minimization algorithms combined with molecular dynamics (MD) can determine predicted solubility curves [51].

Moreover, mathematical models such as modified Apelblat equation, λh equation, van 't Hoff equation, ideal model, Wilson model, nonrandom two-liquid model (NRTL), and universal quasichemical model (UNIQUAC) are used to predict solubility curves as a function of temperature (kelvin). The calculated values are commonly used to correlate experimental data and to calculate solubilization enthalpy, entropy, and Gibbs free energy.

For example, experimental solubility of pioglitazone form II [52] in several solvents (Figure 1.15a) was calculated as a function of temperature and correlated to λh, van 't Hoff, and ideal model with good agreement. Furthermore, the van 't Hoff equation was applied to calculated solubilization enthalpy, entropy, and Gibbs free energy depending on the linear relationship between the natural logarithm of experimental solubilities and reciprocal of temperature (Figure 1.15b). Enthalpy

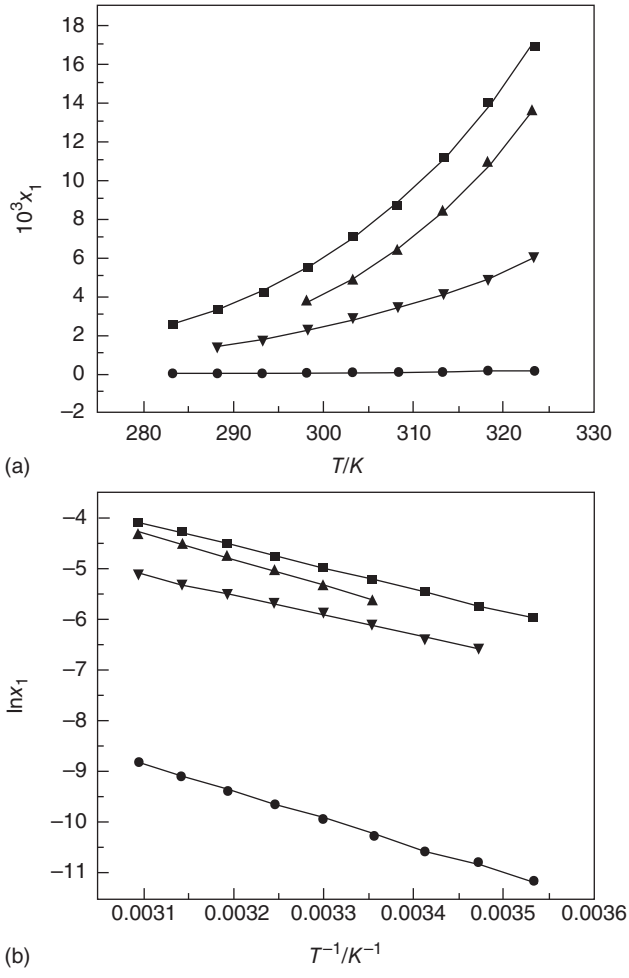

Figure 1.15 (a): Experimental solubility of pioglitazone form II in ■, *N*,*N*-dimethylacetamide; ●, methanol; ▲, dimethyl sulfoxide; ▼, acetic acid. Solid lines are predicted values using the van't Hoff model. (b) van't Hoff plot: natural logarithm of experimental mole fraction solubility vs reciprocal of temperature (K) of pioglitazone form II. Source: Tao et al. 2013 [52]. Adapted with permission of American Chemical Society.

of solubilization can be calculated from the slope of the van't Hoff plot. Similarly, the polymorphic solubilities of buspirone hydrochloride [53], mefenamic acid [54], and clopidogrel [55] in several solvents were investigated experimentally and correlated with the mathematical models.

1.2.3.2 Effect of Polymorphism on Dissolution Rate/Solubility Kinetics

Dissolution is the kinetic definition of solubility and is related to the mechanism or the way the solute dissolves in the solvent. Assessment of dissolution rates or kinetics is paramount during formulation development studies, especially for solid-state formulations.

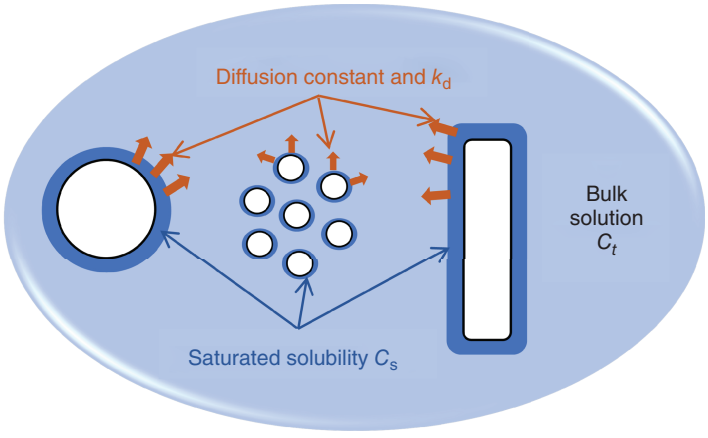

Figure 1.16 A representation of diffusion layer dissolution, solute particles (black shapes) obtain a diffusion layer (dark blue areas) within solvent (light blue). In addition, the effect of particle shape and size on the surface area is presented.

Dissolution rate can be represented mathematically as the change in solute mass with time (dm/dt). Moreover, for pharmaceutical proposes, dissolution is widely determined using the Noyes–Whitney equation (1.8) which is derived on the basis of the diffusion layer theory [56]. The theory (Figure 1.16) predicts the formation of a saturated solution layer over the solute's solid particles which acts as an intermediate phase through which the solute molecules are diffused to bind with the solvent molecules, and hence the name diffusion layer.

$$\frac{dm}{dt} = Ak_d(C_s - C_t) \tag{1.8}$$

where A is the solute surface area, k_d is the rate constant, and C_s is the saturated concentration or solubility of the drug in the solvent or biological fluid, and C_t is the drug concentration at time t. The equation states that the dissolution rate is proportional to the surface area, solubility, and to the concentration difference between the diffusion layer and solvent bulk. Surface area is basically related to particle size, shape, and surface; therefore, particles with elongated shapes, having a small particle size, or a rough surface, will obtain a relatively large surface area, and hence a large dissolution rate. Solubility is a major factor determining the dissolution rate, which is discussed in detail in Section 2.3.1. In addition, concentration difference and rate constant k_d control the extent and rate of diffusion from saturated layer to bulk solution. Rate constant is related to diffusion coefficient D and the thickness of diffusion layer (Eq. (1.9)):

$$k_d = D/h \tag{1.9}$$

Diffusion constant (unit: m^2/s) is the proportionality factor between molecular flux from the diffusion layer and the concentration difference between diffusion layer and bulk solution. Diffusion constant follows the Arrhenius equation as follows (Eq. (1.10)):

$$D = D_0 e^{-E_A/(\kappa T)} \tag{1.10}$$

where D_0 is the maximum diffusivity at infinite temperature, E_A is the diffusion activation energy (unit: J/atom), T is the temperature (kelvin), and κ is the Boltzmann constant. From the equation, it can be noticed that temperature is also a factor in determining the dissolution rate through the diffusion constant.

The dissolution test of pharmaceutical dosage forms is performed using four pharmacopeial apparatuses. Sink condition, which means dissolution medium volume, should be at least five times larger than the volume required to obtain a saturated solution, and is mandatory while performing dissolution testing. The purpose is to avoid reaching saturation levels in the bulk solution, which will significantly slow down the dissolution process [57]. Intrinsic dissolution rate (IDR) testing involves compressing the powder of the solute into flat disks which are held by rotating dies and through which a single surface with known area is exposed to the dissolution medium. This process eliminates the impact of particle size and shape and hence enables the formulator to compare the effect of crystal arrangement or lattice energy between different polymorphs.

Polymorphism can impact the dissolution rate of drugs by affecting solubility due to the change in lattice energy (see Section 2.3.1). In addition, polymorphism can affect crystal shape, thus affecting the particle surface area [15]. Examples in the literature with respect to the dissolution of polymorphic drugs such as carbamazepine [58], spironolactone [59], phenobarbital [60], triamcinolone (Figure 1.17), and mebendazole [61] reveal that metastable forms have a superior dissolution rate over stable forms. However, the metastable form of theophylline anhydrate was surprisingly found to have a significantly slower dissolution rate compared to the stable form. It was found that the metastable form rapidly converts to the monohydrate form in the medium which has a slow dissolution rate [62].

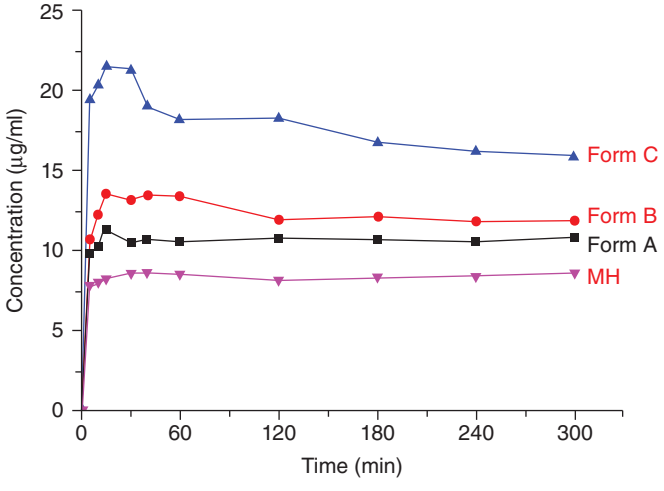

Figure 1.17 Dissolution profile of triamcinolone forms A, B, C, and monohydrate (MH). Source: Wang et al. 2017 [15]. Adapted with permission of American Chemical Society.

1.2.3.3 Effect of Polymorphism on Bioavailability

Bioavailability is represented as drug concentration levels in the blood versus time and is expressed as the area under the curve (AUC; concentration X time). Both solubility and dissolution rate are crucial for bioavailability. This is mostly emphasized in the Biopharmaceutical Classification System (BCS), which divides drugs into four classes based on solubility and permeability level (Table 1.2).

BCS class 2 (majority) and class 4 exhibit poor bioavailability and thereby reduced therapeutic response. Polymorphism modification, as discussed earlier, can improve bioavailability by enhancing both solubility and dissolution rate [63] as it influences both lattice energy and crystal habit (Figure 1.18).

Chloramphenicol palmitate form B shows a significantly higher blood level in humans compared to form A. Following the administration of a single oral dose using form B, mean blood serum concentration of 22 mcg/ml was observed compared to 3 mcg/ml in the case of from A [64]. Moreover, three mebendazole polymorphs (A, B, and C) were tested *in vivo* for pharmacokinetics, brain penetration in the case of glioblastoma, and medulloblastoma (central nervous system [CNS] cancers). Polymorphs were separately administered via oral route into the GL261 glioma mouse model to assess therapeutic and toxic effects; polymorph concentrations in plasma and brain were analyzed using liquid chromatography/mass spectroscopy LC/MS. Oral administration of pure forms B or C has improved

Table 1.2 Biopharmaceutical classification system.

Class	Solubility	Permeability
Class 1	High	High
Class 2	Low	High
Class 3	High	Low
Class 4	Low	Low

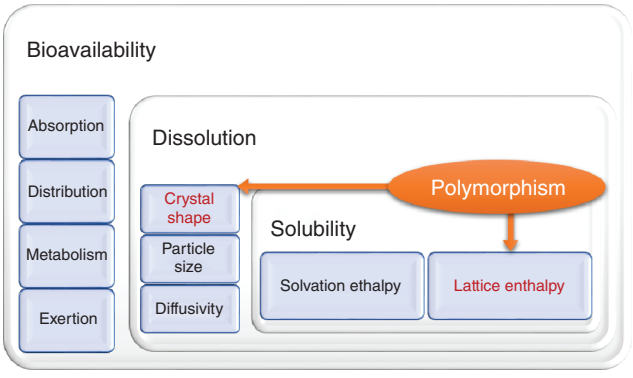

Figure 1.18 A schematic presentation showing different factors affecting solubility, dissolution, and bioavailability. Both solubility and dissolution rate are major integrated factors for bioavailability. Polymorphism has a dual impact on both lattice enthalpy and crystal shape affecting both solubility and dissolution.

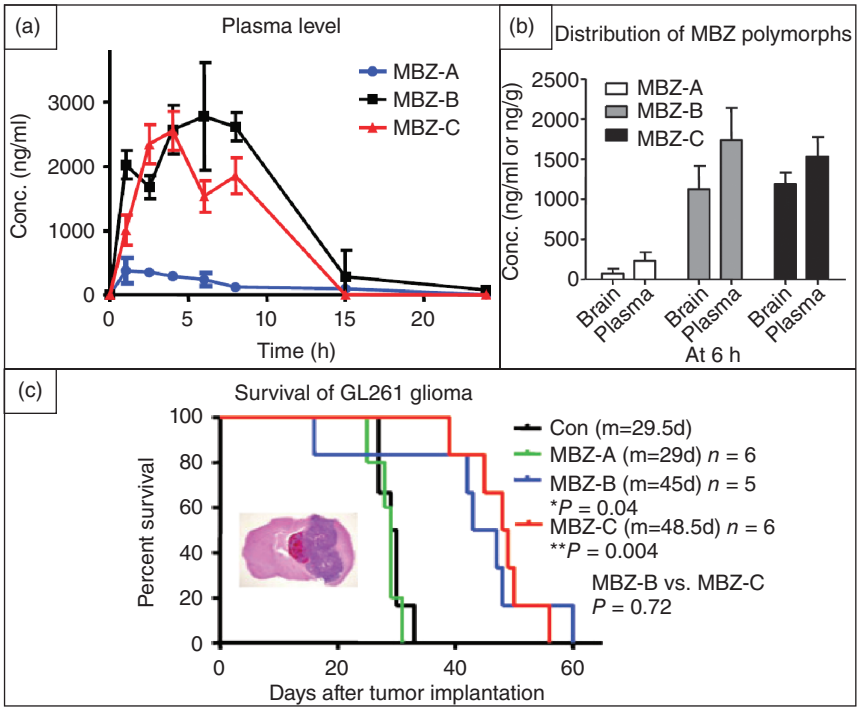

Figure 1.19 *In vivo* performance of mebendazole polymorphs (A, B, and C). (a): plasma concentrations of polymorphs, (b): distribution of polymorphs between plasma and brain tissues, and (c): therapeutic impact of polymorphs represented by GL261-uc glioma implanted mice survival percent vs time (Kaplan–Meier curves) after mebendazole administration compared to placebo control and P values of forms B and C versus control and form B vs C are mentioned. Median survival days (m) for each form are mentioned. Note: One mouse died after one-day administration of form B due to its toxicity; therefore, $n = 5$. Source: Adapted from [65] after permission and modification.

survival in mice compared to form A. While both forms reach high plasma levels (high AUC) effective concentration level (above IC_{50}) in brain tissues, form C is more efficient in crossing blood–brain barrier (BBB) than form B with higher brain-to-plasma ratio (B/P) of 0.82 (Figure 1.19). Nevertheless, form B displays high toxicity compared to other polymorphs [65].

It is highly implausible that polymorphs retain their crystal structure after dissolving in gastrointestinal liquids. However, the variation in pharmacokinetic and therapeutic effects substantially pertains to the *in vivo* performance of polymorphs. Moreover, mebendazole is a class II drug, meaning that solubility (dissolution) is the rate-limiting step in drug absorption. Indeed, the *in vitro* performance of mebendazole polymorphs [61] shows that the order of dissolution rate is C > B > A. This could help to explain polymorphic behavior *in vivo*; more specifically, the superior BBB penetration of form C could be due to the highest dissolution rate among other polymorphs.

Oral administration of methoxyflavone (a nonsteroidal anabolic isoflavone) in rats shows that the metastable form B has a faster absorption rate as it reached maximum concentration after 5 minutes compared to 29 minutes in stable form A (Figure 1.20). However, form A displays a higher AUC and C_{max} [24].

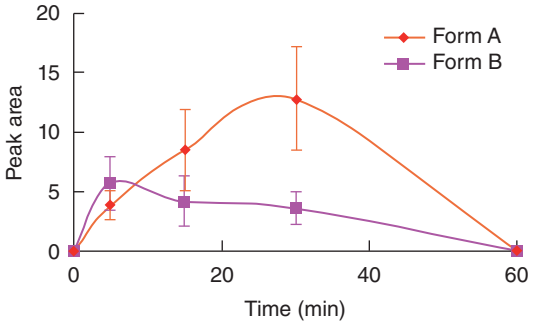

Figure 1.20 Plasma concentration–time curves of methoxyflavone polymorphs forms A and B. Source: Adapted from Gong et al. 2016 [24] after permission.

1.3 Critical Impact of Polymorphic Form of API on Processing and Formulation

Polymorphic forms of active ingredients can be obtained deliberately, or serendipitously; also, it can transform immediately or sluggishly at any stage of drug development or manufacturing. Polymorphic transition may be triggered using the simplest processing method, e.g. mixing, drying, milling, or even with time. In contrast, other polymorphic transformations require the existence of extremely specific conditions of temperature, or pressure such as the case of monotropic polymorphs of rotigotine [66, 67]. The main difficulty is that most of the polymorphic transition cases take place spontaneously and in an unexpected manner. This is mainly due to the lack of thermodynamic data for API, and less evidence of screening or equilibrium testing during the early stage of drug development, or API has a relatively stable (or stubborn) kinetic polymorph. The presence of a stubborn polymorph is mostly observed in monotropic polymorphs. The classical example to represent this case is of ritonavir, a drug first marketed by Abbott; the dosage form contained form I API. However, a thermodynamically more stable form II started to appear and replaced form I, which caused a regulatory catastrophe as batches failed the dissolution test owing to the poor solubility of form II compared to form I [49, 66]. Therefore, understanding of such behavior is crucial in process design and product development.

Two main mechanisms are involved in polymorphic transformation: reconstructive mechanism (nucleation and crystal growth) and topotactic/epitactic mechanism. The reconstructive mechanism is one of the most common for polymorphic transitions and it causes the breakdown of the original crystal structure. The topotactic/epitactic mechanism is responsible for the single-crystal-to-single crystal (SCSC) polymorphism where polymorphs have similar structures [68]. Epitaxy indicates that there is crystal lattice matching between the two interconverting phases, leading to buildup of the new form on the interface of the original, parent, lattice. For example, fingolimod hydrochloride under elevated temperature undergoes single crystal – single crystal form I to form II polymorphic transformation [69].

In either case, the transformation involves reaching an equilibrium state between two competing phases, and this is either driven thermodynamically or kinetically. Transformations are related to many factors which need to be taken

into consideration, such as number of polymorphs, enantiotropic/monotropic relation, degree of crystallinity, presence of an amorphous or a disordered phase, hygroscopicity, solubility, dissolution rate, nucleation and growth rates, or melting point, etc.

Since the late 1990s, process-induced transformation (PIT) has gained a lot of interest among researchers. To gain a comprehensive understanding about PIT, it is extremely valuable to cover both thermodynamic and kinetic aspects of polymorphic transition under process conditions [70]. PIT is based on the fact that any process can exert thermal or mechanical force on drug particles. This force can challenge the physical structure and bring it inward or outward equilibrium. This equilibrium can be influenced by the presence of other components, such as excipients, solvents, or humidity. At the end of the process, the force impact on the physical structure is withdrawn; however, the physical structure is either resistant to force which will return to its original equilibrium, and remain intact, or is vulnerable to force, bounded by the new equilibrium, and undergoes transformation. Five scenarios can take place during a PIT event, (Figure 1.21);

1. The metastable form is driven into equilibrium and after force dissipation it transforms to the more thermodynamic stable form.
2. The stable form is driven into equilibrium by force, and after dissipation, the stable form relaxes back to its original arrangement.
3. The system is brought into equilibrium region where the metastable becomes more thermodynamically favored, and after force dissipation, the form is trapped as the kinetic stable form.
4. Another type of force (e.g. pressure) could produce a new type of equilibrium, either forming a new component or the transition nature is changed (e.g. from enantiotropic to monotropic, resulting in an irreversible transition).
5. During the process, a heterogeneous component is added to the system which takes part in a new equilibrium, producing a multicomponent form or it acts as a reaction intermediate which facilitates the formation of a new form.

All these scenarios are primarily dependent on the following:

- *Nature of the molecule*: thermodynamic aspects, e.g. crystal structure, lattice energy, solubility, and kinetic aspects, e.g. nucleation rate, growth rate, and relaxation time;
- *Nature of processing*: e.g. thermal, mechanical, compressional, and process kinetics such as force application rate, force dissipation rate;
- *Presence of additives*: e.g. moisture, solvents, excipients which may cause a change in the composition of the system and is classified as the thermodynamic factor.

1.3.1 Process-induced Transformation Types

1.3.1.1 Grinding-induced Transitions

Grinding provides mechanical stress to the solid particles constituting the system. Moreover, thermal impact can rise during the process due to friction-force-mediated temperature. Grinding-induced transitions are mostly mediated by the formation of an amorphous or a disordered phase [71].

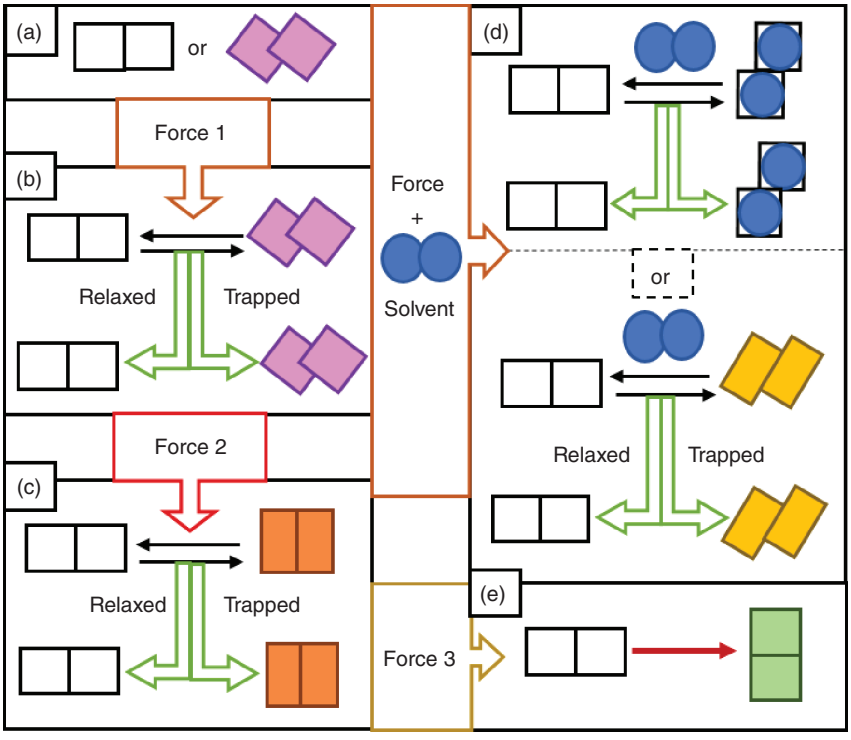

Figure 1.21 Chart summarizing all possible PIT mechanisms; (a): starting compound either metastable (purple) or stable (black). (b): applying force to (a) will result in equilibrium, and after force dissipation (green arrows) the system either will trap the force and result into kinetic stable form or it will relax into thermodynamic stable form. (c): Applying different force (force 2) could result in a new equilibrium having new component, in this illustration, a new metastable form exists. After force dissipation, the system will follow same steps as (b). (d): New equilibrium is formed due to the presence of a heterogeneous component (solvent, moisture, additive, etc.), which either participates as a discrete component or as an intermediate. Acting as an intermediate could result in producing a different equilibrium which enables forming a normally inaccessible phase, such as monotropic metastable forms. (e): Another type of force may transform the equilibrium into monotropic transition which is irreversible.

During grinding, mechanical force is injected into the crystal lattice which develops a local strain. As the force increases, the strain zone increases or a new strain zones appears. If the structural and energetic differences between the two phases are small, the lattice accommodates the energy and forms a new arrangement which obtains higher potential energy (metastable form). However, in most cases, the structural and energetic differences are large enough, so the developed strain overcomes lattice cohesion resulting in the crystal destruction and producing either deformed small crystals of the new phase, or an amorphous phase which, in later stages, recrystallizes to the new phase [70].

Ribavirin enantiotropic R-II stable form at room temperature (above T_g) transforms completely to the metastable form R-I after milling for 15 minutes (Figure 1.22), while no transformation was observed when unprocessed R-II was kept at above transition temperature, around 70 °C, for seven days.

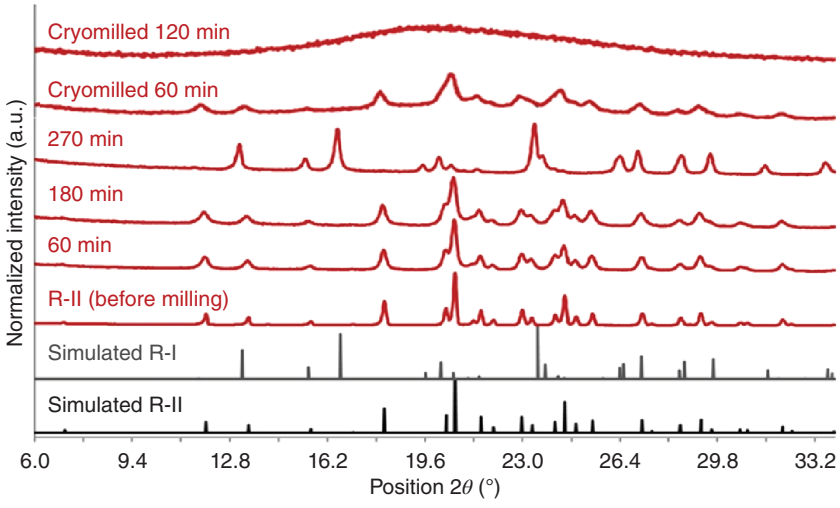

Figure 1.22 PXRD pattern showing phase transformation of ribavirin R-II to metastable R-I after 60, 180, and 270 minutes of milling; and amorphization of R-II after cryomilling for 120 minutes. Source: Vasa and Wildfong 2017 [72]. Adapted with permission of Elsevier.

This indicates that mechanical stress introduced by milling is necessary to overcome the energy barrier for the transition. However, cryomilling at −196 °C, below T_g to exclude temperature effect, of R-II resulted in an amorphous phase after two hours, suggesting a reduction in molecular mobility which prevented the recrystallization process (Figure 1.22). Moreover, this indicates that the milling-induced conversion is mediated by formation of the amorphous phase [72].

Excipients can influence polymorphic stability during co-milling. For instance, the effect of organic (starch and hydroxy propyl cellulose (HPC) and inorganic (silicone dioxide and calcium biphosphate) excipients on polymorphic transition of gabapentin was compared during milling with excipient free samples. The results show partial conversion of stable form II to metastable form III after milling only for the samples containing excipients. In addition, the transition level is dependent on excipient type, but there was no impact of type of excipient (organic vs inorganic) on the transition degree. The presence of $CaHPO_4$ and SiO_2 produced 39 ± 0.40, and 8.7 ± 0.12 mol% of FIII, respectively. Moreover, the presence of starch and HPC produced 21 ± 0.50 and 33 ± 0.31 mol% of FIII, respectively [73].

1.3.1.2 Granulation-induced Transitions

The granulation process is defined as agglomeration of powder into larger aggregates termed as granules. Methods used for granulation are dry, wet, and melt granulation; and it involves the use of mechanical and thermal forces. In addition, the presence of a solvent in wet granulation changes the thermodynamic composition of the system, leading to the evolution of solution-mediated transformation.

Wet Granulation Wet granulation can be performed in the pharmaceutical industry using several techniques and instruments; however, this chapter restricts the description to the most commonly used techniques. And these include high-shear granulation, twin-screw granulation, and fluid-bed granulation. These techniques are complex processes and generally constitute wetting the powder with binding liquid (granulation liquid) to form large agglomerates, then applying shear force (not in fluid-bed granulation) to break the agglomeration into granules, and applying thermal energy to dry the granules. Both high-shear and twin-screw granulation share similar wetting steps, but vary in the type of applied shearing force. The high-shear granulator, as indicated by the name, applies a high level of shear force using rapid rotating blades, called impellers, whereas the twin-screw granulator applies a lower shearing force using two oppositely revolving screws. Along the screw's axis, different configurations can be present to function as conveying, mixing, and shearing components. Fluid-bed granulation is performed by suspending the powder in a flowing air stream called a fluid bed, inside a vessel while granulation liquid is sprayed, which results in forming larger aggregates in a stage called spraying. Subsequently, the drying stage is performed by increasing inlet air temperature. Fluid-bed granulation has advantages in obtaining homogeneous granule size distribution compared to other methods. Each technique has key process parameters that affect physicochemical properties of API, including polymorphism (Table 1.3).

It is crucial to understand the impact of each parameter on triggering or preventing polymorphic change, and on the nature and amount of phase transition to enable the formulators to tune the parameters depending on the desired polymorphic outcome. This is achieved by correlating the parameters with thermodynamic and kinetic factors (Table 1.4) since they govern the polymorphism process.

In wet granulation, the solvent can interact with the active material either by incorporating in the crystal lattice forming a hydrate or solvate, or dissolving the material which may lead to the recrystallization of the drug into different phases (e.g. stable, metastable, and amorphous).

Metastable to stable phase conversion is very common [74] and is mainly caused by reaching saturation levels of stable form after metastable is dissolved in granulation liquid (the stable form is less soluble than the metastable form). Solubility of the metastable in the selected granulation liquid (at specific temperature) during wetting or drying is an important thermodynamic parameter.

Table 1.3 Key process parameters for each type of wet granulation.

High-shear granulation	Twin-screw granulation	Fluid-bed granulation
• Granulation liquid addition rate • Wetting time • Mixing speed • Impeller speed	• Granulation liquid addition method • Granulation liquid viscosity • Powder feed rate • Screw configuration • Screw speed	• Inlet air temperature • Air flow rate • Atomization pressure • Spraying nozzle position • Spraying rate of granulation liquid • Drying time

Table 1.4 Thermodynamic and kinetic factors that are related to process parameters and control polymorphism events.

Thermodynamic factors	Kinetic factors
• The solubility of drug or formulation components in the granulation liquid • Drying temperature • Amount or composition fraction of the components (i.e. dose or powder/granulation liquid ratio) • Quantity of the mechanical force	• Granulation, drying, sieving time • Dissolution rate of solids in the granulation liquid • Particle size • Nucleation and growth rates of involved phases • Relaxation time

Kinetically, granulation time, dissolution rate of the metastable phase, drying rate, and relaxation times (molecular mobility) of both phases determine the type of recrystallized phase. For example, mefenamic acid undergoes phase transformation from metastable form II to stable form I during the wetting step. The effect of granulation liquid type (ethanol or water) and temperature on transition rate was investigated [75]. As a result, form II conversion rate is proportional to temperature and it is faster in ethanol compared to water, which is attributed to the faster dissolution rate in ethanol [54]. The conversion rate followed the three-dimensional nuclei growth Avrami model (Figure 1.23).

If metastable is the desired phase, a granulation solvent having no or little solubilizing properties should be used. However, solvents used in granulation are limited (water and ethanol) due to toxicity issues. Alternatively, avoiding polymorphic conversion is attempted by trapping the phase kinetically and preventing the nucleation of the stable phase. Granulation time (which covers wetting, mixing, and shearing times) is set to minimize the dissolved amount (by slowing time of contact of metastable phase with granulation liquid). Moreover, drying time must be set below the relaxation time of the metastable phase so it does not have enough time to relax back to the stable form when crystallizing out of the granulation liquid. If kinetic control is not sufficient to control the

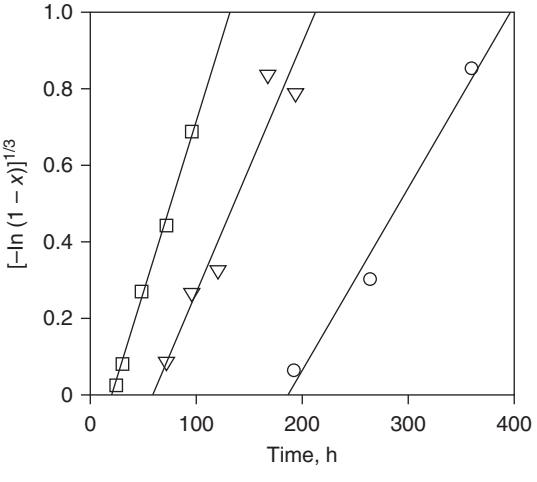

Figure 1.23 Transformation rates of mefenamic acid form II to form I following the Avrami model; squares, triangles, and circles represent temperatures 37, 33, and 28 °C respectively. Source: Otsuka 2004 [76]. Adapted with permission of Elsevier.

desired polymorphic form, other granulation techniques can be considered, such as dry granulation.

In contrast, stable to metastable transition during wet granulation is less common. However, it can take place if the stable form gets dissolved completely or partially in the granulation liquid. Subsequently, the metastable becomes the stable form (which is thermodynamically favored) either by reaching supersaturation levels or high temperatures (e.g. during drying) which promote the nucleation of the metastable form. Finally, the metastable phase is trapped kinetically, e.g. high drying rate, or nucleation and growth rate of the metastable phase is higher. This type of conversions can be prevented by slowing the drying process or limiting the amount of dissolved stable form. For example, the stable γ-glycine at room temperature converts to metastable α-glycine at high temperatures. D. Davis et al. monitored the phase transformation of glycine using NIR spectroscopy and powder X-ray diffraction (PXRD) during the drying step using a fluid-bed dryer during wet granulation. High drying rates overcome the slow rate of solution-mediated transformation from metastable to stable form and result in the formation of metastable α-glycine after drying [77].

As solvent is present during the process, the formation of solvate or, more commonly, hydrate should not be ruled out. In most of the cases, the hydrate is the stable form under wet conditions, which either remains stable after the process or it acts as an intermediate phase which transforms either into stable or metastable phase.

An example of stable – hydrate – metastable phase transformation is piracetam; it has five polymorphs and two hydrates (mono- and di-) and is highly soluble in water. Form III, the most stable, was subjected to varying amounts of water during the wetting stage. As the amount of water increases, more monohydrate formation is observed, even after the drying step. However, when monohydrate was left at ambient temperature (20 °C), metastable form II crystals were detected (Figure 1.24) [78]. In contrast, chlorpromazine hydrochloride shows the example of metastable – hydrate – stable. During wet granulation with water, metastable form II is subjected to phase conversion to form I hemihydrate which dehydrates under room temperature to stable form I [79].

Dry Granulation Dry granulation provides a solvent-free environment and is dedicated to improving the compressibility and flowability of materials that are unstable to solvent presence or to high levels of temperature during the drying process. The process is mainly performed by compressing the powder into large masses using roller compaction or slugging techniques using the dry binders. Subsequently, the large masses are shattered into smaller aggregates or granules [80]. Phase transformation during dry grinding is not common as the employed pressure is relatively low (8 MPa) [81] compared to the pressure used in tableting (200 MPa to 4 GPa), where most of the polymorphic transitions occur. For example, no polymorphic conversion was observed after roller compaction of theophylline [80], whereas theophylline monohydrate undergoes dehydration during tableting at 50–196 MPa and transforms to the metastable anhydrous form which it spontaneously converts to the stable form II phase. It was found that as compression pressure increases at fixed tablet thickness, the

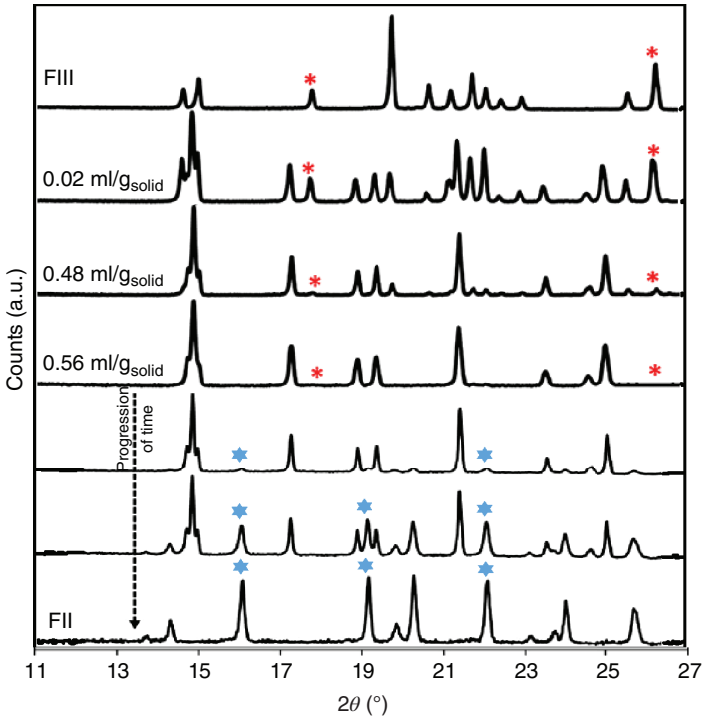

Figure 1.24 PXRD patterns of piracetam form III after wetting with increasing amount of water showing the formation of monohydrate phase once the water is added. The three patterns from the bottom show monohydrate transformation to metastable FII at ambient conditions. Source: Potter et al. 2017 [78]. Adapted after permission and modification of Elsevier.

mechanism changes from two-dimensional (at 50 MPa) to three-dimensional (at 98 MPa) [82].

Melt Granulation Melt granulation is performed by adding a meltable binder (polymer or wax) to the powder mixture followed by raising the temperature of the mixture to allow the liquidation of the binder, forming a pasty mass or large agglomerates which are subjected to shear force to break them into granules. This can be accomplished using a jacketed high-shear mixer or hot melt extrusion (HME). Process parameters include granulation temperature, powder feeding rate, and screw or impeller speed. Interestingly, the type, concentration of binder, and drug–binder interaction can have an impact on the degree of transition. For example, caffeine form II to form I transition is more pronounced using a high level of Soluplus®, according to DSC analysis (Figure 1.25) where no transition peak was observed [83].

Mechanical and thermal stresses contribute to the transformations during the process. The most common transformations are the enantiotropic thermal transitions where the metastable phase transforms into stable phase at high temperature, which subsequently either converts back or, in most cases, remains trapped after the process. Kulkarni et al. [84] suggested that the dry surrounding

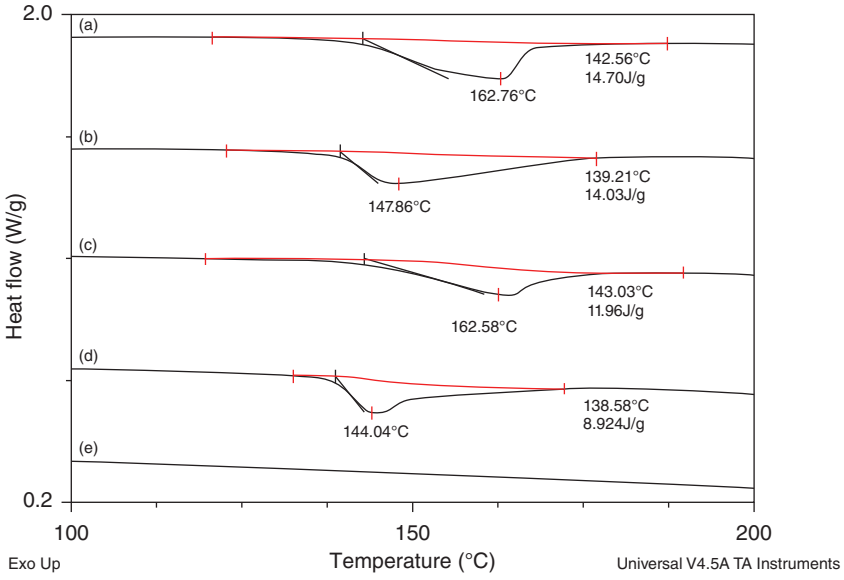

Figure 1.25 DSC thermograms of (a) transition endotherm of pure caffeine form II into form I, (b) granules of form II and low-level poly ethylene glycol (PEG), (c) form II and low-level Soluplus, (d) FII and high-level PEG, and (e) form II and high-level Soluplus where transition peak has disappeared, indicating that form II is completely transformed into form I after melt granulation. Source: Monteyne 2016 [83]. Adapted with permission of Elsevier.

conditions at metastable formation onset assist in preventing the transformation to the stable form. The researchers have investigated the polymorphic transformation of artemisinin orthorhombic polymorph to high-temperature stable triclinic polymorph using HME. This technique can produce a pure metastable form that resists solid-state conversion over a year, much greater than the metastable formed by regular solvent evaporation techniques. In addition, the HME process is easy to scale up and parameters such as temperature, screw speed, and configuration can be adjusted to control the produced polymorph. All these features make the HME technique an ideal option to be used in the development of resistant metastable polymorphs.

1.3.1.3 Tableting-induced Transition

Tableting-induced transition introduces pressure and thermal and mechanical forces into the system (tablet mass). Pressure influence may generate new transformation routes which produce solid phases that are not obtained during other processes (e.g. thermal) (Figure 1.26).

Phase transformation during compression is very common, and it can generate unexpected new phases. For example, caffeine [18, 85], chlorpropamide [86–88], paracetamol [89], and fluconazole [90] all are subjected to phase transformation under high pressure.

Factors that mostly control the transition are the crystal structure of the sample and the compression/decompression protocol. Thermodynamically, phases having lower molar volumes tend to be more stable at high pressure.

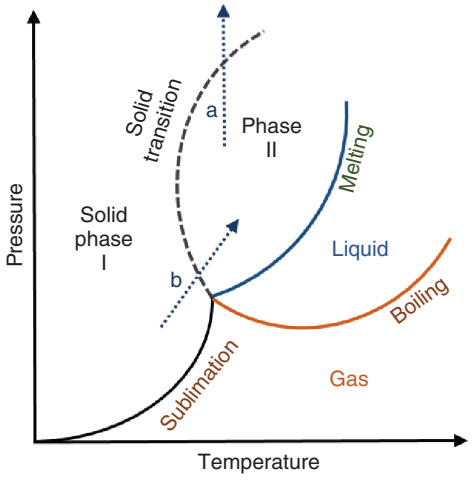

Figure 1.26 Pressure–temperature phase diagram of an enantiotropic polymorph compound under the influence of temperature and pressure. Dotted arrows show paths of solid phase transitions; (a) shows that solid phase II to I transition can be mediated by pressure only; (b) shows the transition of I to II path mediated by both temperature and pressure.

However, kinetic factors have a huge role in controlling phase transformation during compression. More specifically, nucleation of the new phase must take place to initiate the reaction. However, due to confined space generated by the increasing pressure, nucleation may be hindered leading to transition being prevented, i.e. the energy barrier cannot be overcome without nucleation. Therefore, high-pressure-induced transformation can take place in the presence of crystal seed [91], under melt (due to friction-mediated heating) [92], saturation conditions [93], or partial presence of amorphous phase [94], all of which grant flexibility in the molecular movements, thus facilitating the nucleation process. Otherwise, in the dry state, transition can occur under exceptional conditions of rapid pressure onset and slow pressure dissipation, which allows more time for molecular rearrangement. For example, paracetamol monoclinic form I to orthorhombic form II interconversion is thermodynamically favored under high pressure (c. 4 GPa) as the latter possesses lower molar volume (by 3.5%). However, it requires a large degree of crystal rearrangement and crushing of many hydrogen bonds which leads to inconsistent transformation results [89]. In addition, the transition kinetics are primarily controlled by nucleation rate.

The direct compression of caffeine form I, the metastable form at ambient conditions, resulted in a significant increase in transition to stable form II compared to uncompressed mixtures and regardless of the diluent type. However, the increase in compression force or velocity did not affect the transition degree [95]. Moreover, the transition takes place homogeneously at both tablet core and surface, meaning that distribution of compression force also does not affect the degree of transition. The polymorphic conversion keeps progressing for both powder and tablets, after compression, until reaching a plateau. However, the compression impact caused a significant increase in both degree and progressivity of the conversion [18].

Transition kinetics were assessed experimentally using DSC, and transformation rate curves were fitted in good agreement with the Johnson–Mehl Avrami (JMA) stretched exponential model, which expresses that transformation rate

is solely dictated by nucleation rate (excluding growth rate) due to constraint geometry conditions during compression (Eq. (1.11)):

$$X(t) = 1 - e^{\left[-\left(\frac{t}{\tau_N}\right)^n\right]} \tag{1.11}$$

where $X(t)$ is the transformed volume fraction, τ_N is the form II nucleation rate constant, t is the time, and n is the exponent which is either equal to or less than 1.

The study also investigated different types of diluents, microcrystalline cellulose (MCC) and dibasic calcium phosphate which deform plastically and are subjected to fragmentation under compression, respectively. Both diluents have less impact on the pressure-induced transition compared to direct pressure (Figure 1.27).

1.3.1.4 Freeze-drying-induced Transition

Freeze drying or lyophilization involves freezing of aqueous solutions of drugs and, subsequently, drying (in multiple steps) is performed by dropping pressure below vapor pressure of the solvent (water) to allow the ice to detach and sublimate away from the solute. Thermodynamically, the freezing process causes the formation of ice crystals, which form a highly concentrated solute state called freeze. On the other hand, the drying process can increase molecular mobility which can disturb the molecular interactions within the solute. The impact of freezing and drying processes on phase transformation is dependent on the type of solute, composition of the formula, solute concentration, solution pH, and

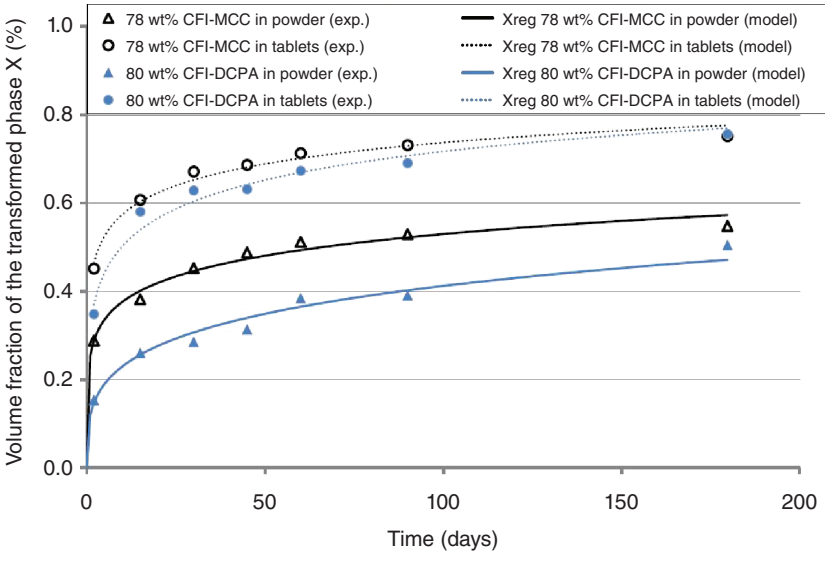

Figure 1.27 Volume fraction transformation as a function of time for caffeine form I (CFI) to form II in tablets and uncompressed powder mixed with two diluents, microcrystalline cellulose (MCC) and anhydrous dibasic calcium phosphate (DCPA) with content 78 and 80 wt% of CFI, respectively. Solid and dotted lines are the calculated values from stretched exponential equation for uncompressed powder and tablets, respectively. Source: Juban et al. 2016 [18]. Adapted with permission of Elsevier.

process parameters. During freezing, the solute either crystallizes with the ice, as in the case of mannitol [96] and glycine [97], or it get trapped as an amorphous phase, as in cephalosporins, sucrose, and peptides. However, the drying stage can induce crystallization of the amorphous phase. Kinetic factors have a huge role in controlling the solid-state phase during freeze drying. Cooling rate, drying rate, and nucleation and growth rates all contribute to the resulting phase. These factors and others such as onset of ice and solute nucleation, and end point of sublimation can be monitored using NIR and Raman spectroscopy [98]. Commonly, the final product of freeze drying tends to be the amorphous phase [99].

For instance, irrespective of initial solution concentration, pentamidine isethionate trihydrate is formed using a low freezing rate which dehydrates during the drying step into a partially crystalline metastable form B. On the other hand, using a high cooling rate, the amorphous phase is formed which transforms into stable form A after the drying step. Forms A and B are monotropically related, and form B transforms slowly to form A during storage [100]. The process was simulated and monitored using variant temperature – powder X-ray diffraction (VT-PXRD) (range −190–300 °C) which starts from 10% w/v drug solution and is cooled slowly, while trihydrate peaks started to appear followed by dehydration to partially crystalline form B after drying (Figure 1.28a), which may support the polymorphic transformation of form B into A. However, increasing pressure during primary drying from 100 to 500 mTorr (Figure 1.28b) prevented the dehydration process and produced the highly crystalline trihydrate form [101].

The interaction between different solutes in the multicomponent formulation can cause a preferential solid-state formation. For example, the presence of anticancer drug cyclophosphamide with mannitol during lyophilization led to the selective formation of pure metastable δ-mannitol, while lyophilization of mannitol alone produced a mixture of stable β-mannitol and minor amounts of the δ-form. This was attributed to cyclophosphamide's ability to inhibit the nucleation of β-mannitol during freeze drying, which is considered as the rate-limiting step in the solution-induced δ- to β-phase transition [102].

1.3.1.5 Spray-drying-induced Transitions

Spray drying shares an attribute similar to that of the freeze-drying process. It is performed by spraying a solution or dispersion of the active material at controlled temperature and under conditions which cause rapid removal of solvent and formation of spherical dry powder mostly with improved morphology, flowability, and dissolution properties. Critical process parameters include air flow rate, air humidity, inlet temperature, atomization type and flow, and feed rate, which are adjusted to control particle size, size distribution, porosity, moisture content, yield, and solid form [103].

Solid-phase transformation during spray drying is highly common and mostly generates physical structures having higher potential energy including amorphous [104, 105] and metastable phases. This is due to the rapid evaporation of solvent during atomization process and high temperature which thermodynamically favors the formation of high-energy phases. The most common example is the spray-dried amorphous lactose which has superior properties in terms of flowability and compressibility [106]. In addition, carbamazepine form IV can

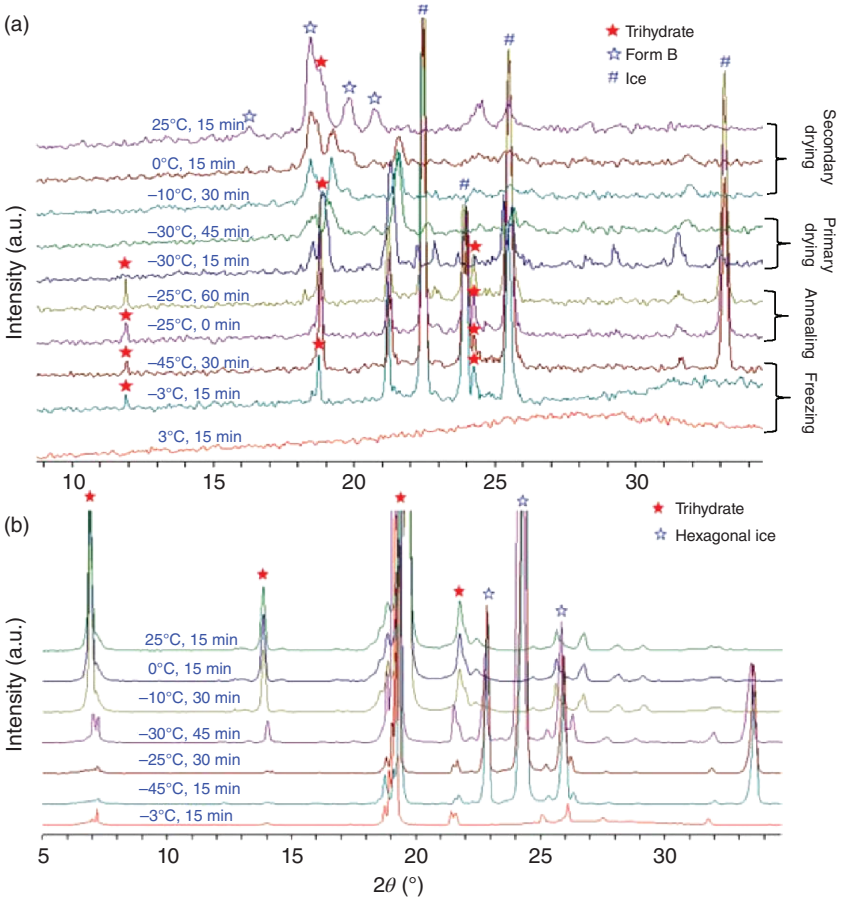

Figure 1.28 Variable temperature X-ray diffraction (VT-XRD) patterns of freeze-dried pentamidine solution. Freezing, annealing, primary, and secondary drying steps are indicated. Same conditions were applied in the case of (a) and (b), except that primary drying was performed under 100 mTorr in (a), while the primary drying in (b) was performed under 500 mTorr. Source: Sundaramurthi et al. 2012 [101]. Adapted with permission of Elsevier.

conventionally only be obtained using the polymers; however, the spray-drying process enables formation of this form using the drug solution in methanol [107]. The efficient control of process parameters can assist in producing the desired phase. For example, changing drying temperature during spray drying of phenylbutazone resulted in producing different polymorphic phases [108].

The effect of formulation additive on phase transformation has been investigated in spray drying. The presence of pH-adjusting buffers can affect the solid phase of glycine obtained after spray drying. Spray drying of glycine aqueous solution with no pH control (6.2) resulted in the formation of α-glycine, while γ-glycine is formed if pH is adjusted to below or above 6.2 with HCl and NaOH. The pH of the system affects the thermodynamic formation of α-glycine dimer [109]. Sulfamethoxazole polymorphism during spray drying is highly affected by

the presence of cellulose acetate phthalate (CAP) and talc. Spray drying of drug aqueous dispersion with CAP resulted in an amorphous phase, whereas drug dispersion with talc resulted in stable form I to metastable form II conversion. This was ascribed to the ability of these additives to form an interaction with the drug and disturb its structure during the process [110]. Pyrazinamide (PZA) metastable γ-form, produced by spray drying, undergoes transition to stable δ-form after 14 days. This transition can be prevented by adding 5% w/w 1,3-dimethylurea (DMU) during the spray-drying process and it helped obtain a stable γ-form over 12 months. It was found that 1,3-dimethylurea entraps the metastable phase, preventing any interaction at its surface (Figure 1.29). Furthermore, addition of polyvinyl pyrrolidone (PVP) instead of 1,3-dimethylurea during spray drying results in the formation of δ-form [111].

1.3.1.6 Supercritical-fluid-induced Transitions

Supercritical technology is a green, solvent-free, and single-step process that utilizes a gas after reaching the supercritical state, at a point which exceeds the critical temperature, and pressure values. At supercritical point, the border between gaseous and liquidus phases diminishes and is called supercritical fluid. This state combines a group of properties for both liquid and gas phases including density

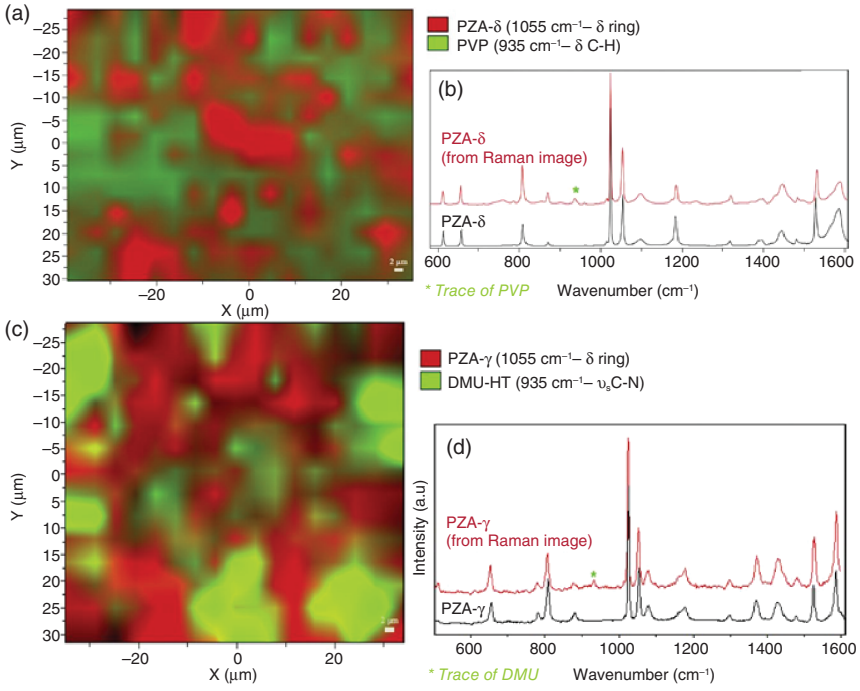

Figure 1.29 Raman mapping image of pyrazinamide (PZA) spray dried with polyvinyl pyrrolidone (PVP) (a) and extracted Raman spectrum compared to reference spectra of δ-form (b). Raman mapping image of PZA spray dried with dimethylurea (DMU) (c), and (d) extracted spectra compared to reference γ-form (d). Source: Baaklini et al. 2015 [111]. Adapted with permission of Elsevier.

of liquids and viscosity, and compressibility of gases. These properties enable the dense gas to dissolve the solid materials; simultaneously, like gases, its volume changes upon changing pressure which changes its density and thus its dissolving ability. This technology is used in separation, chemical synthesis, and powder technology. In pharmaceutical development, supercritical fluid is employed in particle design, micronization, and drying to obtain the desired physicochemical properties such as particle size, shape, dissolution, and stability [112, 113]. Moreover, one application that makes supercritical fluid a unique method is its ability to control and produce a pure polymorphic form in a short time and under moderate temperature and pressure values [114].

The use of supercritical CO_2 ($scCO_2$) as fluid constitutes 98% of pharmaceutical processing due to its economic, nontoxic, and ease of handling, plus achieving a CO_2 critical state is facile as critical temperature and pressure of CO_2 are 38 °C and 7.4 MPa, respectively [113]. Two types of $scCO_2$ processing are mainly used; in the first type, the drug is dissolved or liquefied in $scCO_2$ fluid. Subsequently, the solution is rapidly depressurized through atomization in a process called rapid expansion of the supercritical solution (RESS). This process reduces the drug solubility in $scCO_2$, leading to its precipitation as new solid particles having special properties [115]. Flufenamic acid metastable form I undergoes phase transition after RESS into stable form III. Key process parameters are extraction pressure, pre-expansion temperature, crystallization temperature, and capillary tube dimensions, where sc-CO_2 depressurization takes place before reaching the expansion chamber [116]. It is believed that this transformation is thermodynamically driven as the lower soluble form III starts to nucleate before form I.

However, RESS requires sufficient solubility of the drug in the sc-CO_2 (called ideal solute); however, not all drugs have this property. Therefore, the supercritical anti-solvent (SAS) was developed to enable the use of sc-CO_2 for drugs that are poorly soluble in sc-CO_2 (called nonideal). The method involves dissolving the drug in a suitable solvent, and then the $scCO_2$ is used as antisolvent for precipitating the drug. SAS techniques can have many variations, yet the most commonly used for polymorphic control [117] is *solution-enhanced dispersion by supercritical fluid (SEDS)*, which was invented by Hanna and York [118]. The process is performed by co-atomization of the drug solution and $scCO_2$ via a coaxial nozzle into a mixing chamber at a controlled temperature and pressure. This allows the $scCO_2$ to be transferred at high speed into a drug solution, forming small droplets and a rapid nucleation rate [119]. Theoretically, these conditions favor the formation of a metastable or an amorphous phase. PXRD analysis of baicalein powder after micronization using SEDS shows a reduction in crystallinity [120], which is a common observation also found for other drugs such as tretinoin and acetaminophen [121]. A novel minocycline β-form was produced using the ethanol–CO_2 system, which shows a higher melting point, 247 °C, compared to the commercial α-form, 187 °C [114]. Conventional supercritical antisolvent method SAS can trigger stable to metastable polymorphic transformation for indomethacin (triclinic γ- to monoclinic α-form) [122], carbamazepine (monoclinic FIII to trigonal FII), and theophylline (orthorhombic FII to polymorphic mixture) [123].

Process parameters of SEDS such as drug supersaturation, composition of solvent, flow rate, temperature, and pressure can contribute to polymorphism control. For example, acetaminophen polymorphism can be controlled by changing the type of solvent in the initial solution. Use of acetone resulted in the formation of orthorhombic form II, while ethanol favors the formation of monoclinic form I [124]. Etoposide stable form I was found to convert to metastable form II, which are monotropically related. Form II exhibits higher solubility and dissolution rate compared to FI [125, 126].

The effect of supercritical gas type on polymorphism has been investigated for carbamazepine, indomethacin, and theophylline [127, 128]. $scCO_2$ reactivity in comparison to inert supercritical nitrogen (scN_2) was investigated using solution-enhanced atomization (SEA) technique which, except for theophylline, produced the same results using both gases. Thus, this implies that transformation is mediated by the atomization process and the results can be reproduced using conventional spray drying. To investigate the difference obtained with theophylline, a new processing method was applied which utilizes a smaller sc-CO_2 volume (1 cm^3); and the sc-CO_2-solution mixing step takes place before atomization, producing a suspension. This method is called atomization of antisolvent-induced suspension (ASAIS) and it is used to investigate the impact of CO_2 before atomization. Parameters such as temperature, pressure, initial solution concentration, liquid flow, flow residence time, volume of mixing chamber, and nozzle orifice diameter are involved in the investigation. ASAIS using sc-CO_2 resulted in theophylline transformation [127], indicating the impact of sc fluid on crystal structure.

Polymorphs I, and III, and a dihydrate form of carbamazepine which is classified as BCS class 2 were thoroughly investigated in terms of *in vitro* and *in vivo* performance. Oral administration of the three phases at dose 40 mg resulted in similar AUC values. However, increasing the dose to 200 mg resulted in significant differences with AUC (unit: μg h/ml) values, form I (9.10) followed by form III (6.33), and then dehydrate (4.39). Moreover, it was found that form III transforms rapidly into dehydrate form in gastrointestinal fluid, which may explain the differences in the *in vitro* performance compared to the *in vivo* where form III obtained a higher rate compared to form I [58].

1.4 Conclusion

Polymorphism is a type of physical structure variation caused by the difference in conformational or packing arrangements, which involves a change in noncovalent bonding only. This event can be classified into several categories depending on type of structures and thermodynamic properties. Other types are being regarded as nonideal polymorphism due to the presence of chemical variations like a modification in covalent bonding, or the presence of a heterostructure within the crystal lattice. Polymorphism has a significant impact on the physicochemical and mechanical properties of API or excipients which in turn affect *in vivo* performance. On the other hand, extensive care is being

taken during the processing of formulation components that are prone to phase transition. These transitions can occur at any stage of formulation.

In order to achieve total control and to prevent any unwanted effect from polymorphic transformation during formulation, the following aspects should be considered:

1. NCEs or excipients must be subjected to sufficient preformulation testing and screening to explore all possible forms and to understand the relation and transition nature between these phases. At this step, two things must be assessed, whether the compound undergoes polymorphic transition within the range of temperature and pressure attained during processing. Secondly, if polymorphic transformation will result in a significant impact on the stability, handling, efficacy, and safety of the dosage form.
2. Selection of specific polymorphic phase with desired physicochemical and mechanical properties to be targeted in the final dosage form. Subsequently, thermodynamic and kinetic properties of targeted NCE or excipient phase should be identified.
3. Optimization of process thermodynamic and kinetic parameters with relevance to thermodynamic and kinetic properties of the selected polymorph. The optimization should aim to obtain the targeted phase at the end of the process.
4. The final dosage form should contain the targeted phase, which remains stable throughout storage and administration stages. No significant change should be observed for the *in vivo* performance or mechanical properties.

Despite the vast volume of literature reported regarding polymorphism, this phenomenon is still a subject of significant interest and requires enormous amount of investigation. Therefore, further investigation and reports in the future are expected to emerge whether it deals with existing issues, discovery of new polymorphic forms, or innovating new techniques to improve properties, processing, or stability.

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