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Innovative Dosage Forms

Design and Development at Early Stage

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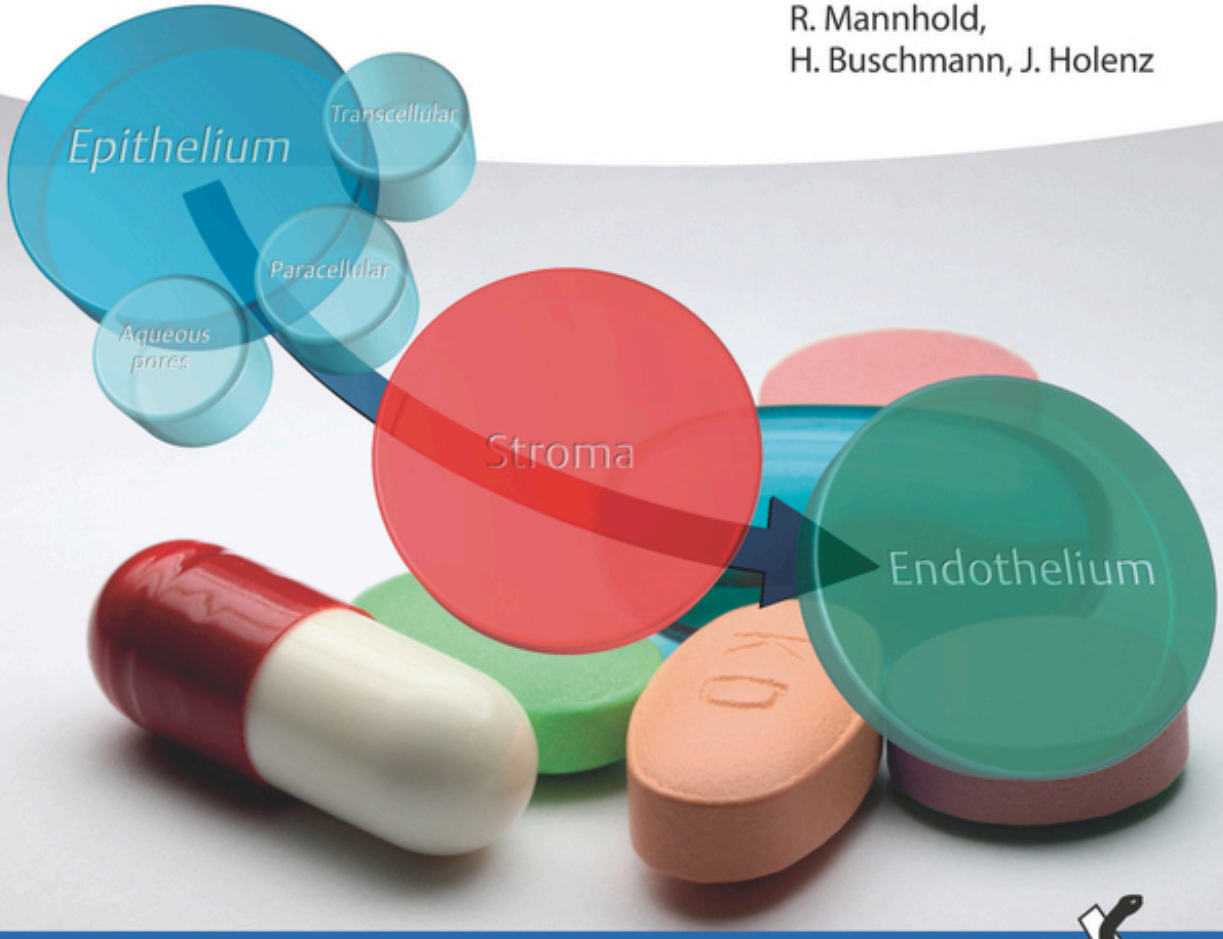

Methods and Principles in Medicinal Chemistry

Innovative Dosage Forms

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Edited by R. Mannhold, H. Buschmann, Jörg Holenz
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Contents

Preface

Drug discovery and development is an outstandingly complex task. Technological innovations in biology, chemistry, and medicine have provided the pharmaceutical industry with a wealth of targets and molecules, with the potential to treat diseases formerly assumed intractable to drug therapy.

The consequential increase in complexity, both in terms of the molecules and their biological targets, combined with the increasing need to work in an efficient and cost-constrained environment has necessitated an evolution in the role of pharmaceutical sciences in discovery support.

Because more and more drug candidates in the pipeline pose constraints such as poor solubility and stability, the development of an overall formulation strategy to support *in vivo* studies should be considered carefully as it can reduce cycle time and resources.

The *in vivo* studies performed in the preclinical setting can broadly be classified as pharmacology, pharmacokinetic, and toxicology studies. The goals and challenges of these studies are diverse.

Therefore, drug developers must consider many aspects when positioning a preclinical drug candidate to succeed in first-in-human clinical trials.

Besides many other factors, a biopharmaceutical assessment of drug substances is crucial for different phases of the development process. In an early phase, pharmaceutical profiling should help to rate candidate molecules in terms of their "drug-like" properties.

The first step for a new molecule moving out of the discovery phase is the preformulation studies, or developability assessment. Indeed, preformulation work lays the foundation for choosing the right salt and polymorph, delivery technology, and formulation strategies.

Formulation approaches to deliver molecules in the preclinical setting include, besides many other innovative forms, the more traditional ones like suspensions, solutions, and amorphous dispersions administered as solids or in aqueous vehicles. Nowadays, advanced systems such as nanosuspensions and silica particles are also explored for this purpose.

The goals of preformulation studies are to choose the correct form of the drug substance, evaluate its physical and chemical properties, and generate a thorough understanding of the material's stability under the conditions that will lead to the development of a practical drug delivery system. Preformulation is a science that

serves as a big umbrella for the fingerprinting of a drug substance or product both at the early and later stages of development in pharmaceutical manufacturing.

Traditionally, pharmaceutical scientists participated in the discovery teams only in the later phases of lead development or in the lead optimization phase, and their role was largely to assess the development risks (developability) of the molecule advancing to clinical dosing.

These activities, while important, have been augmented to include early discovery formulation support related to building a basic understanding of biology through *in vivo* target validation and demonstration of proof of mechanism.

The book in hand, edited by a very experienced pharmaceutical scientist with many years of experience in this preformulation field, has pointed out with the selected chapters a comprehensive view of actual research filed in this area. In particular, the following chapters are enclosed:

- Impact of the polymorphic form of the drugs/NCEs on the preformulation and formulation development
- Regulatory aspects for formulation design – with focus on the solid state
- Effect of residual reactive impurities in excipients on the stability of pharmaceutical products
- Assessing pharmacokinetics of various dosage forms at early stage
- Preclinical safety assessment for excipients; oral, IV, and topical routes
- Preclinical formulation assessment of NCEs
- Strategies for the formulation development of poorly soluble drugs via oral route
- Physical characterization techniques to access amorphous nature
- Design and development of ocular formulations for preclinical and clinical trials
- Insights into innovative applications of parenteral formulations
- Transdermal medical devices: formulation aspects
- Formulation of therapeutic proteins: strategies for developing oral protein formulations

The series editors are confident that this book and the highly actual topics will provide valuable benefits to interdisciplinary drug discovery teams working in industry and academia. Last but not least, we thank Yogeshwar Bachhav for excellently editing this volume as well as Frank Weinreich and Stefanie Volk from Wiley-VCH for their valuable contributions to this project.

September 2018
Düsseldorf, FRG — *Raimund Mannhold*
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1

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

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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

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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].

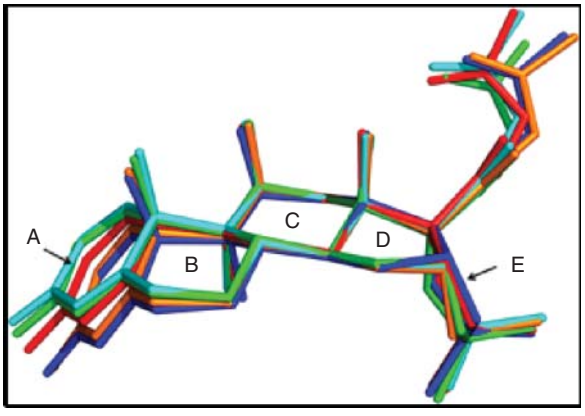

Figure 1.1 Molecular structure of triamcinolone polymorphs A (light blue), B (red and green), C (orange), and MH (blue). Source: Bučar et al. 2015 [14] and Wang et al. 2017 [15]. Adapted with permission of ACS.

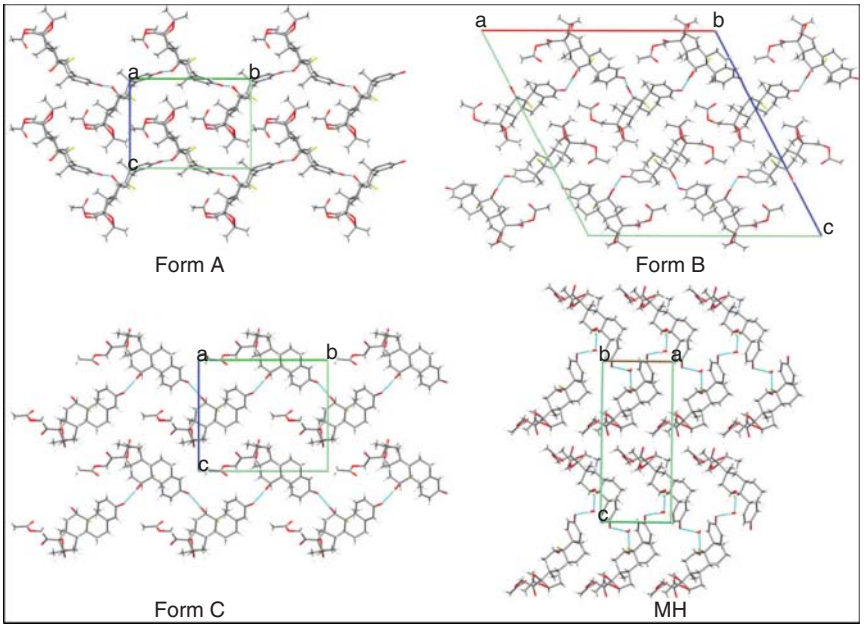

Figure 1.2 Lattice packing of triamcinolone acetonide acetate polymorphs. Source: Wang et al. 2017 [15]. Adapted with permission of ACS.

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.

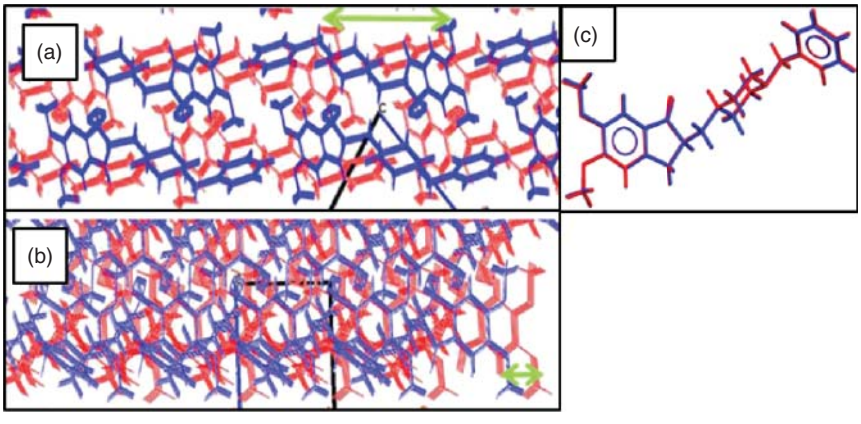

Figure 1.3 Superimposed view of donepezil form F (blue) and form K (red); (a) crystallographic A axis view, (b) 90° angle view where an axis is horizontally positioned, the packing of two polymorphs are translated (green double-headed arrows). However, (c) superimposed molecular structures show identical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

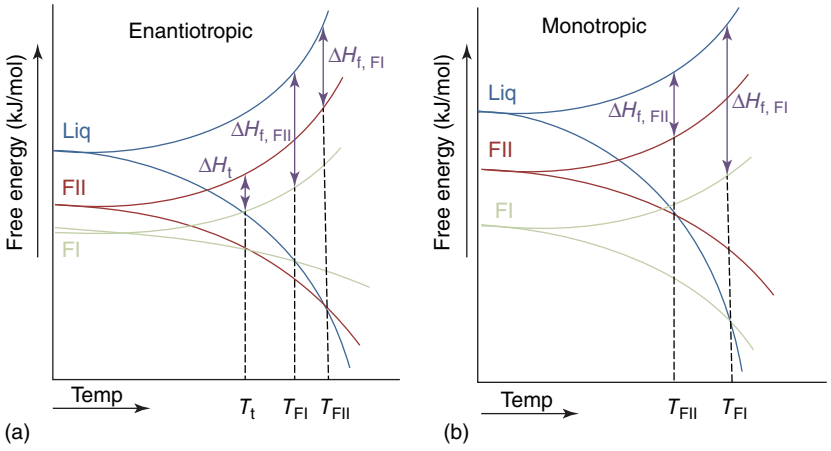

Figure 1.4 Phase energy versus temperature diagram for the (a) enantiotropic and (b) monotropic interconversion for two polymorphic phases FI and FII.

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

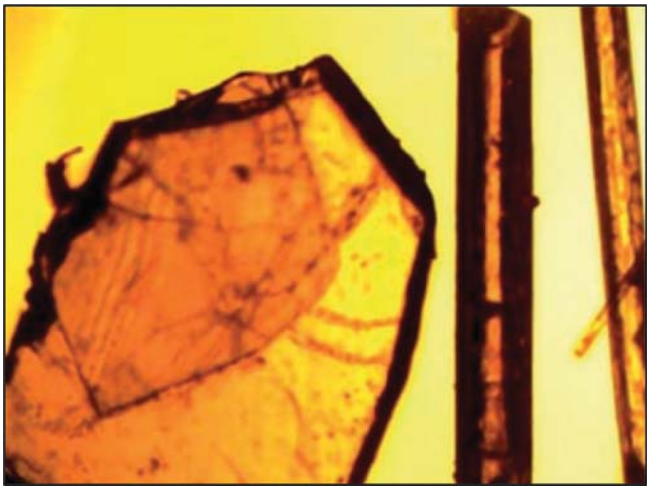

Figure 1.5 Concomitant polymorphism after crystallization of methoxyflavone form A (bulk shape) and form B (needle shape). Source: Gong et al. 2016 [24]. Adapted with permission of American Chemical Society.

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.

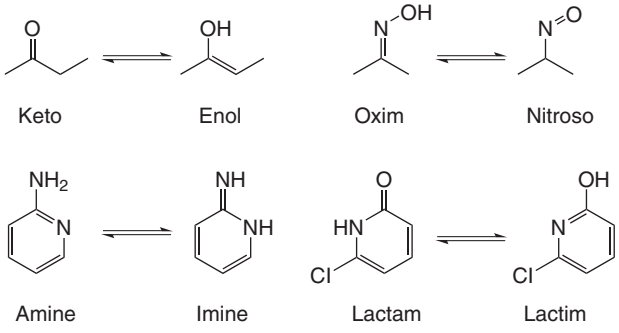

Figure 1.6 Examples of tautomeric reactions. Source: Braga et al. 2014 [25]. Adapted with permission of Bentham Science Publishers Ltd.

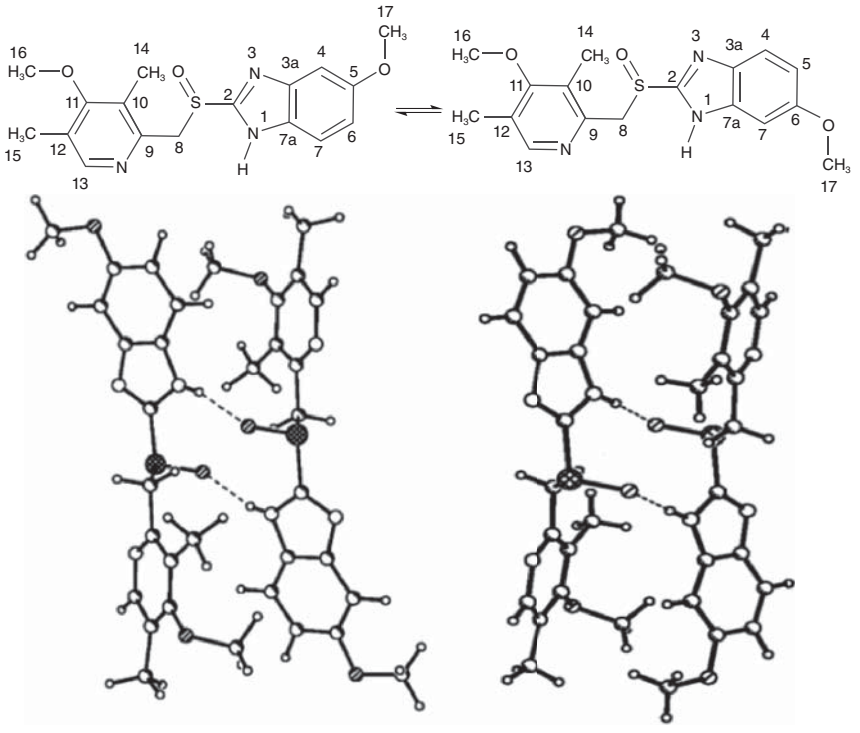

Figure 1.7 Tautomeric forms of omeprazole; 5-methoxy tautomer in form V (right), and 6-methoxy tautomer in form I (left). Source: Bhatt et al. 2007 [27]. Adapted with permission of Royal Society of Chemistry.

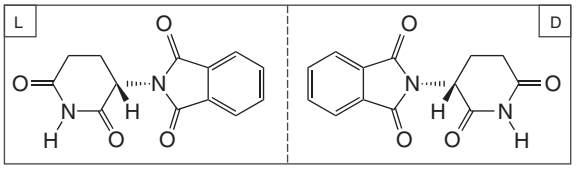

Figure 1.8 Enantiomerism of L-thalidomide and D-thalidomide.

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

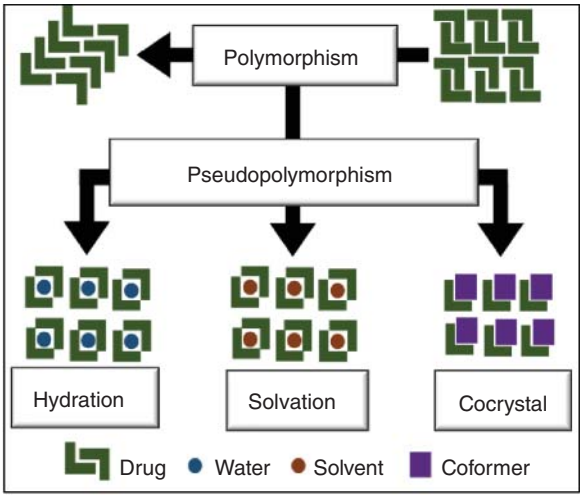

Figure 1.9 Representation of pseudopolymorphism events which involve the incorporation of a heterostructure within the crystal lattice compared to polymorphism.

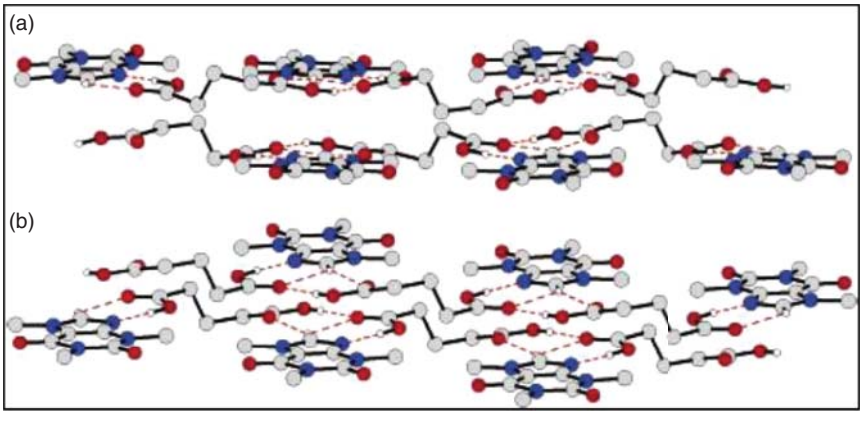

Figure 1.10 Packing polymorphism of caffeine: glutaric acid cocrystal, (a) FI and (b) FII. Source: Trask et al. 2005 [33]. Adapted with permission of American Chemical Society.

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].