1

1.1 INTRODUCTION

Traditionally, pharmaceutical industry is focusing on discovery and manufacturing of small-molecule drug compounds. Pharmaceutical industry workflow is characterized by two somewhat overlapping stages—Drug Discovery and Drug Development. At the first stage, a new chemical entity (drug candidate molecule for clinical development) is being discovered and tested on animals. At the end of this stage it is important to make sure that the selected molecule passes preclinical testing such as *in vivo* biological activity in animal models, *in vitro* metabolism, pharmacokinetic profiling in animals, and animal toxicology studies. The drug candidate progresses into an early development stage to pass proof of concept (POC), which refers to early clinical studies on human divided into Phase I and Phase Ila. At this step the candidate molecule becomes an active pharmaceutical ingredient (API) of drug product and is typically formulated in a solid form. The subsequent Drug Development process is focused on drug product and process development to ensure reliable performance, manufacturing, and storage.

Along the pharmaceutical industry workflow path, a drug substance undergoes a significant physical transformation (Fig. 1.1). It starts in early Drug Discovery as a single molecule (ligand) binding to a receptor in order to activate or inhibit...
the receptor’s associated biochemical pathway. Then the drug molecule becomes a biologically active component of a typically solid-state (e.g., crystalline or amorphous) formulation in early Drug Development. Finally, the drug molecule acts as an API of the solid particles of the drug product at the later stages of Drug Development. This transformational pathway reflects the complex nature of the drug design workflow and dictates a diversity of experimental and especially computational methods, which are applied to support Drug Discovery and Drug Development.

The pharmaceutical industry as a whole has faced many challenges in recent years in addition to patent expirations of blockbuster drugs. In particular, the Drug Development branch faces challenges of accelerated development under a high regulatory pressure. An ability to rationalize and guide Drug Development process has become crucial [1]. Computational chemistry methods have become deeply integrated into Drug Discovery over the past 30 years [2, 3]. However, the computational support of Drug Development has emerged only in recent years and is now tasked with the whole spectrum of Drug Development fields including drug formulation and product design, process chemistry, chemical engineering and analytical research and development. This chapter provides a high-level overview of pharmaceutical solid-state landscape and introduces a field of computational modeling in Drug Development, hereinafter called computational pharmaceutical solid-state chemistry (CPSSC).

1.2 PHARMACEUTICAL SOLID-STATE LANDSCAPE

1.2.1 Some Definitions

Approximately 70% of the drug products marketed worldwide are formulated in oral solid dosage forms [4]. The pharmaceutical solid state may be characterized by molecular arrangement displaying long-range order in all directions (crystalline), long-range order in one or two directions (liquid crystals), or only close-range order (amorphous). An overall pharmaceutical solid-state landscape is presented in Figure 1.2. The advantage of formulation of drug substances in crystalline form is
dictated by more desirable manufacturing properties: superior stability, purity, and manufacturability relative to amorphous and liquid form formulations. All solid drugs can be subclassified as single- (anhydrous) and multicomponent compounds. Multicomponent substances can be crystalline solvates (including solid hydrates) [5, 6], cocrystals (or co-crystals) [7], and salts [8]. Solid solvates (also named pseudopolymorphs or solvatomorphs) represent crystal structures in which solvent molecules are integrated into the crystal lattice. Solid hydrates are the most common pharmaceutical pseudopolymorphs. Pharmaceutical cocrystals are defined as stoichiometric multicomponent crystals formed by an API (or an intermediate compound) with at least one cocrystal former (coformer), which is solid at ambient temperature. Within the family of solvates, hydrates, and cocrystals, the components are neutral. Pharmaceutical salts are multicomponent materials in which components are ionized via proton transfer and are involved in ionic interactions with each other.

Different crystalline structures of one substance (single- or multicomponent) are named polymorphs [9, 10]. Polymorphism, which exists as a result of different crystal packing of rigid molecules, is called a packing polymorphism. Conformational polymorphism is a more common phenomenon for typically flexible drug-like molecules and results from crystallization of different conformers of the same molecule. At a given environmental conditions (temperature, humidity, pressure, etc.) only one solid form is thermodynamically stable (lowest free energy), while all other forms are considered metastable.

The solid-state complexity of a typical distribution of pharmaceutical solid forms was reflected in a recent analysis of 245 polymorph screens performed at Solid State Chemical Information (SSCI) (http://www.ssci-inc.com) [11]. It was demonstrated
that about 90% of the compounds screened exhibited multiple crystalline and noncrystalline forms. About half of the compounds screened were polymorphic, and about a third of the compounds exist in hydrated and solvated forms. In cases where cocrystals were attempted for a particular API, 61% of these were able to form cocrystals.

1.2.2 Impact of Solid-State Form on API and Product Properties

Variations of pharmaceutical solid form can result in alternations of physicochemical properties of drug product, which may affect drug performance, safety, and processing [12]. Therefore, solid form selection is strongly regulated by the Food and Drug Administration according to guidelines outlined in an International Conference on Harmonisation (ICH; http://www.ich.org) [13] as well as by other regulatory agencies around the world. Table 1.1 summarizes major properties that may be affected by crystal form change, a selection of these properties are discussed in more detail later.

Solubility and dissolution rate are the key properties of drug product, which are directly related to bioavailability and are often vital for the drug performance. These two properties display a strong dependence on the solid form selected. The largest difference in solubility is observed between crystalline and amorphous pharmaceutical materials and may be as high as several hundred times [14, 15]. Solid crystalline hydrates are known to drop the solubility of the drug relative to its anhydrous form up to 10 times [16]. On the contrary, solid solvates formed from water-miscible solvents are typically more soluble in water than the corresponding nonsolvated form. Generally, dissolution rate is increased significantly in salt and cocrystal solid formulations predominantly due to favorable hydration free energies of counter ion and cocrystal former, respectively [17, 18]. Therefore, salt or cocrystal formulations are the most popular strategies for improving the solubility (dissolution) of poorly soluble drugs [19].

Thermodynamic solubility of a crystalline compound decreases with increased stability (lower free energy) of its polymorphic form. It has been reported that there is a 95% probability that a thermodynamic solubility ratio between a pair of polymorphs is less than twofold [20], although in certain cases it may reach much higher values. At first glance an impact of change of polymorphic form on the solubility and dissolution rate may seem to be less problematic in comparison with amorphous to crystalline or anhydrous to a solid hydrate form transformation. However, in cases where drug absorption is not limited by permeability (BCS classes I and II [21]), depending on the drug dose even 1.5- or 2-fold decrease of solubility due to a switch to a more stable form may have a profound effect on bioavailability of the API (see Section 1.2.3 for discussion of polymorph impact on drug performance). In order to avoid an unexpected interconversion into a less soluble form (with generally different solid-state properties) during manufacturing or shelf life of the drug product, it is a common practice in pharmaceutical industry to perform a stable form screening prior to the selection of a commercial solid form.

Another key property of the drug product, which can be impacted by the solid form, is chemical stability [22]. Drug degradation in solid dosage forms is mostly
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<tr>
<th>Chemical stability/reactivity</th>
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<th>Mechanical</th>
<th>Surface</th>
<th>Thermodynamic</th>
<th>Kinetic</th>
</tr>
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<tr>
<td>Chemical stability/reactivity</td>
<td>Stability</td>
<td>Compactability</td>
<td>Surface free energy</td>
<td>Solubility</td>
<td>Dissolution rate</td>
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<td>Hygroscopicity</td>
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<td>Stickiness</td>
<td>Free energy of fusion</td>
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<td>Morphology</td>
<td>Powder flow</td>
<td>Interfacial tensions</td>
<td>Melting point</td>
<td>Solid-state reaction rate</td>
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<td>Color</td>
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determined by the surface characteristics of both the API and the excipient particles. Most pharmaceutical reaction rates are typically the greatest in the amorphous rather than crystalline states due to a higher surface area and molecular mobility. Additionally, amorphous substances show a higher surface energy and may be more hygroscopic, which may be coupled with chemical stability problems [23]. Therefore, an amorphous formulation is generally less preferable than the crystalline one. Chemical reactivity in the solid state may also correlate with the nature of the crystalline form (polymorphic or pseudopolymorphic) and related crystalline morphology [24]. Generally, a stable solid form is more chemically stable than metastable forms.

A change in the solid form may lead to a different crystal morphology, which may have an impact on processibility of the drug product due to the different mechanical and flow properties [25]. For example, needle-shaped crystals are generally undesirable for pharmaceutical applications since they are difficult to process [26].

### 1.2.3 Challenges of Pharmaceutical Industry Related to Solid Form Selection

A likely dependence of drug performance, processing, and safety on the solid form selection imposes a series of challenges on the pharmaceutical industry. Here three challenges are outlined—solubility improvement, physical stability, and unfavorable solvates and hydrates.

An increasing trend toward low solubility is a major issue for Drug Development as the formulation of poorly soluble compounds can be quite problematic [27]. Aqueous thermodynamic solubility of solid pharmaceutical compound may be defined by two contributions—molecular hydration free energy and lattice (or sublimation) free energy [28]. Consequently, strategies to enhance solubility and drug delivery include molecular modification (lowering hydration free energy) or solid form optimization (crystal packing destabilization or/and lowering hydration free energy). It is only the latter strategy that is applicable at the Drug Development stage. Solid form optimization would typically include counter ion or coformer screening for salt or cocrystal formulation, respectively, of the API with improved dissolution properties. Additionally, amorphous API formulation could be possible via, for example, spray-dried dispersion (SDD) technique [29].

Physical instability of pharmaceutical solids is related to interconversion into a new form in the course of handling, manufacturing, processing, or storage, which may have a profound effect on the drug performance and process development. The conversion from one form to another is thermodynamically driven and may take place when a solid form is metastable relative to a more stable form within specific environmental conditions. The most common cases of physical instability are transformation into a stable polymorphic form, desolvation, hydration/dehydration, crystallization of amorphous form or amorphization of a crystalline one. A timeline of events involving physical stability over the past 30 years is presented in Figure 1.3 [9]. In most of the cases, the products were recalled as a result of poor performance. Perhaps, the most famous example of polymorph-induced impact is related to the marketed drug Norvir® (ritonavir). Abbott Laboratories had to stop sales of Norvir in
1988–Clinical failure of Tegretol (carbamazepine) tablets, possibly due to phase conversion of anhydrate form to dihydrate.

1990–Product withdrawal of Norvir (ritonavir) due to dissolution failure of oral capsules as a result of the appearance of a more thermodynamically stable form.

1994–Open letter in the South African Medical Journal asking that regulatory or quality control authorities ensure that analytical tests are performed to confirm the intended polymorphic form (Form C) of Vermox (anthelmintic mebendazole) raw material and tablets. Solid-state evidence revealed that imported raw material contained an inactive or less efficacious polymorph (Form A) or mixtures of undesired solid phases (Forms A and B).

1998–Clinical failure of Tegretol (carbamazepine) tablets, possibly due to phase conversion of anhydrate form to dihydrate.

2006–Recall of 1.5 million tablets of the popular blood thinner Coumadin (warfarin sodium 2-propanol solvate), due to concerns with variability in the 2-propanol levels, which in turn might affect the crystallinity of warfarin sodium. Complete loss of 2-propanol content would result in amorphous formation.

2008–Batch recall of Neupro (transdermal rotigotine) patches due to the crystallization of a new polymorph that resembled snowflake-like crystals.

2010–Drug product recall of 60 million tablets of the blood pressure medication Avalide, a combination of two anti-hypertensives, hydrochlorothiazide and irbesartan. Concerns were over possible variability in the amounts of the less soluble polymorph of irbesartan, which may result in slower dissolution.

FIGURE 1.3 A timeline of events concerning solid-state issue with polymorphism of pharmaceutical drugs over past 30 years. Adapted from Lee et al. [9]. Reproduced with permission of Annual Reviews.
1998 due to a failure in a dissolution test, which was caused by the precipitation of a more stable and less soluble form II of the compound [30]. Some APIs may display a high propensity for forming stable solvates [31]. Though there are marketed drug products that contain solvates such as Prezista®, Crixivan®, and Coumadin®, formulation of a drug product in solvated form is typically undesirable. Solvates (including hydrates) might be subsequently desolvated in a final drying step of the formulation process. In such a situation, the final form could be metastable and may undergo a solid–solid transition during its shelf life. In addition, residual solvent levels in the API must be compatible with ICH guidelines. As a result hydrates and solvates are generally avoided for the reasons mentioned earlier. Therefore, selection of the solvent system for crystallization, which has the lowest probability of forming solvates/hydrates with the API, is a good practice.

1.3 PHARMACEUTICAL COMPUTATIONAL SOLID-STATE CHEMISTRY

Given the complexity of the pharmaceutical solid-state landscape and challenges facing the pharmaceutical industry, an accelerated Drug Development greatly benefits from guidance provided by computational methods. The emerging field of the CPSSC covers the whole spectrum of state-of-the-art computational approaches, which are used to support all steps related to the development of solid-state pharmaceuticals. An outline of these steps in Drug Discovery and Drug Development is presented in Figure 1.4. According to the provided broad definition of the field, the CPSSC covers more than just solid-state calculations. In fact, the CPSSC represents a true multiscale modeling from quantum mechanical studies of molecules (subnanometer scale) to discrete or finite element modeling of solid particles (micron scale) (Fig. 1.5).

Typical CPSSC approaches may be broadly classified into two major categories—those that are used to guide properties and process optimization (engineering) and those that are used for analysis and interpretation of the experimental results. The former category includes all kind of virtual screening approaches—solvent selection for crystallization and desolvation [34, 35], solvent selection for polymorph screening

**FIGURE 1.4** An outline of stages of solid form development in pharmaceutical industry. RSM is a regulatory starting material.
1Å

API molecule
QM, MM, statistical

Solid form—crystalline, amorphous, liquid crystal
QM, MM, MD, MC, statistical

Drug product—Solid form and excipients
MM, MD, MC, statistical

Solid particles
DEM, FEM

FIGURE 1.5 Multiscale modeling in computational pharmaceutical solid-state chemistry. Here DEM and FEM are discrete and finite element methods; MC, Monte Carlo simulation; MD, molecular dynamics; MM, molecular mechanics; QM, quantum mechanics, respectively; statistical approaches include knowledge-based models based on database analysis (e.g., Cambridge Structure Database [32]) and quantitative structure property relationships (e.g., group contributions models [33a]).

[31b, 36], solvent selection for impurity purge via recrystallization [37], cocrystal former and counterion selection for crystallization and solubility improvement [35, 38, 39] as well as for improved relative humidity stability [40], virtual polymorph screening via crystal structure prediction (CSP) to explore lattice energy landscape [41], solvent selection for optimization of size and shape distribution of the crystalline product [25, 42], etc. In addition, physical (solubility [43], $T_g$ [44], $T_m$ [33], surface energy [45], etc.) and mechanical [46, 47] properties prediction of solid materials; prediction of excipient effect on API chemical degradation [48]; in silico modeling of drug–polymer interaction for amorphous pharmaceutical formulations [49]; and simulations of unit operations in solid dose manufacturing [50] can be also assigned to this category. The second category includes all methods used to support solid form selection via risk analysis of physical stability of a commercial solid form [51], in silico prediction of pharmaceutical stress (forced) degradation pathways [52], prediction of structure and dynamics in pharmaceutical solids based on analytical methods alternative to single crystal diffraction (SSNMR [53] and PXRD [54]), analysis of source of poor solubility of the drug substance [28], etc. Approaches from the second category are typically used to provide recommendations for a potential experimental follow-up.

As could be expected, challenges facing the pharmaceutical industry contribute to the advancement of the computational solid-state chemistry. For example, some of the virtual screening and other CPSSC methods were developed specifically to help address issues of the pharmaceutical industry. Significant progress has been made recently in many traditional applications (e.g., solubility prediction [55], CSP [56], and morphology prediction [25, 57, 58]) in order to accommodate predictions for complex pharmaceutical systems (solid and liquid multicomponent phases of relatively large and flexible molecules).

1.4 CONCLUSIONS

A complex nature of the pharmaceutical solid-state landscape imposes a series of challenges on the pharmaceutical industry. Computational modeling enables better understanding of the fundamentals of solid-state chemistry and allows an enriched selection of solid form with desired physicochemical and processing properties.
Though the CPSSC is an emerging field, many of the approaches have proved their importance for the industry and are already embedded in the workflows of various pharmaceutical companies. Moreover, though it is currently impossible to build a reliable statistics regarding the use of CPSSC over the whole industry, it is known that some of the methods (like computational support of solid form selection) have already been successfully used to support New Drug Applications (NDAs) of some of the recently approved drugs.

A future outlook of the CPSSC field envisions a wide acceptance of CPSSC support of NDA submissions by all regulatory agencies. Moreover, it is feasible that in addition to guidance of the experimental work, future improvements of the CPSSC field once validated may lead to replacement of some of the experimental studies by accurate predictions.

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REFERENCES


COMPUTATIONAL PHARMACEUTICAL SOLID-STATE CHEMISTRY


