1.1.8.2 Crystallization and Precipitation

Precipitation (i.e. rapid, uncontrolled solidification) and crystallization are not the same. To get a hand on the material, synthetic chemists often crash out (precipitate) the solid form and believe they have crystallized. However, common understanding of crystallization is that crystallization is a controlled process step, whereas precipitation is mostly uncontrolled and can lead to amorphous products, too (which are not crystalline).

Crystallization and precipitation processes both have their justification and application. Thorough investigation of the underlying process parameters and knowing the intended product profile is essential for successful development, implementation, and integration of such processes.

1.1.8.3 Understanding the Phase Diagram – Analytical Characterization of the Solid–Liquid and Solid–Solid Systems

Besides microscopy, X-ray diffraction, and thermal techniques, there is a variety of additional analytical techniques more or less suitable to investigate and characterize the solid state. There are ssNMR spectroscopy, vibrational spectroscopy like Raman, infrared spectroscopy (IR) and terahertz spectroscopy, dynamic vapor sorption (DVS) methods, electron microscopy (scanning and transmission techniques), and electron diffraction crystallography, to name the most commonly used. With a particular focus on industrial applications, other chapters of this edition describe in further detail some of the techniques mentioned along with examples for application.

In addition, investigating the liquid phase that is in contact, under equilibrium or nonequilibrium conditions, with the solid phase are relevant to foster understanding the complete picture leading to formation or stability of one or the other solid phase. Knowing the composition of the liquid phase as well, e.g. supersaturation, impurity profile, solvent composition, in particular water activity, is important. Appropriate means to determine concentration profiles are spectroscopic methods like Raman and IR, titration (e.g. Karl Fischer), and chromatography and coupled methods (high-performance liquid chromatography [HPLC]; liquid chromatography coupled with mass spectroscopy [LC–MS]).

Collecting and putting together information gathered about the liquid and solid phase under various conditions (like temperature, composition, pressure) constitutes a phase diagram that eventually indicates regions of stability and potential transformation pathways between solid phases. Phase diagrams are, for example, treated in detail in the chapter “Thermodynamics of Polymorphs and Solvates” written by Coquerel in [22], the construction of phase diagrams by means of DSC is described [49] and the utility of phase diagrams is discussed also in context with cocrystals [50–52]. The concept of phase diagram investigation is extendable to the exploration of polymorphic landscapes by computational methods. For example, to predict thermodynamic stability regions for crystal structures along with subsequent attempts to prepare those polymorphic forms, by application of high-pressure experiments [53].

1.1.8.4 Polymorphism

Polymorphic per se means multiple morphic forms. It stems from the ancient greek πολύς (polús, “many, much”) [54] and μορφή (morphḗ, “form, shape”) [55].

The morphology, in terms of shape and outer form, of a crystal corresponds not necessarily one-to-one to the crystal structure, meaning the construction of the inner matter as constituted by the internal arrangement of atoms or molecules.

Unfortunately, this can lead to confusion. Especially, the frequently used term “crystal form” does not inherently clarify if it addresses the inner form of a crystal. If not specified, crystal form can refer to the inner form, the crystal structure, or the outer form, the morphology or shape. For further clarification, the chapter “Form vs. habit” in [24] is recommended reading.

In the context of solid-state development of inorganic or organic compounds, the terms polymorphism and polymorphic forms are undoubtedly connected with the inner form of the matter.

Scientific literature extensively dealing with polymorphism as well as consideration on the regulatory treatment of polymorphism and solid-state-related topics are available [31]. Various scientific definitions for polymorphism can be understood as covering the spatial arrangement in a crystal of a single molecule or a single entity formed by atoms as well as that of a substance that consists of two or more molecules or other constituents. Sharma states “the term ‘polymorphs’ has in-fact all-encompassing through its application to different crystalline forms of an element or a compound with different atomic arrangements.” [56]

The European regulatory perspective considers polymorphism as “the ability of a compound in the solid state to exist in different crystalline forms having the same chemical composition” and that it may be exhibited in the solid state by all types of compounds “single as well as multiple entities, such as salts, hydrates, cocrystals, etc.” It is acknowledged that “different forms may possess different physico-chemical properties” [57].

Other terms in this context are

- *Allotropic forms*. “The phenomenon that a substance exists in various solid states, depending on the conditions (temperature, pressure), is found not only in sulfur, but also in many other substances [...]. This is called ‘allotropy’ in the case of elements, and ‘polymorphism’ in the case of compounds.” Translated from: [58]. A discussion of the use of the terms allotropes and polymorphs is provided in [56] that concludes with the recognition that the terms have taken on the same meaning.
- *Modification*. Typically, the term modification is used synonymously with polymorph or polymorphic form. In English, the word “modification” has several meanings like change, alteration, limitation, deviation, and also deformation [59], which explains the synonymous use.

  However, a statement found in a reference from 1966 [60] indicates that there formerly might have been some differentiation in meaning of the terms. The reference states

> “*Wann liegt eine Modifikation vor? Der klassische Polymorphiebegriff und seine Definition der Modifikationen erscheint eindeutig, wenn man etwa an den Schwefel oder den Phosphor denkt. Er verliert jedoch an Klarheit, wenn nahe verwandte Strukturen vorliegen, zwischen denen noch Übergänge möglich sind.”* which translates to
> *“When is there a modification? The classic concept of polymorphism and its definition of modifications seems clear when one thinks of sulfur or phosphorus. However, it [the concept] loses clarity when there are closely related structures between which transitions are still possible.”*

In particular, “*concept of polymorphism and its definition of modifications*” suggest a difference in meaning. Unfortunately, no further description of what the authors meant could yet be found. One understanding could be that” a modification exist only under thermodynamic conditions” (R. Glaum [2019]. What is a modifiation? personal communication). This would mean that enantiotropic polymorphs are (both) also a modification because there are conditions under which either polymorph is thermodynamically stable. Whereas in the case of monotropically related polymorphs, only the thermodynamically stable one is a modification of the compound.

- *Morphic form*. The term “morphic form” is used, e.g. by Saal (see Chapter 10), to express the singular of polymorphic form. Saal understands the term as a synonym by stating “polymorphic forms – also called morphic forms”. Therefore, the term in that chapter refers clearly to the inner structure.

Critical may be the use of “polymorphic” if a crystalline form is denominated as such if no different crystal structures, i.e. polymorphic forms, exist (or are known) from that compound. Since the term “poly” means more than just one, it is assumed that more than just crystalline form exists, which is contrary to the belief that only one crystalline form exists. This may justify the use of “morphic form”. In reality simplicity wins, therefore using “polymorphic” may be acceptable in daily use for such cases, too. However, the term “morphology” is typically used to describe the outer shape of materials. Therefore, it is recommended to think twice what is expressed with the term “morphic form” when read or written.

1.1.8.5 Multi-component Compounds – Salt, Cocrystal, Solvate, and Hydrate

An overview about various definitions for multi-component compounds and alternatively used terms was collected by Stahly [61]. His broad definition of a cocrystal is “a crystalline structure with unique properties that is made up of two or more components. A component may be an atom, ionic compound, or molecule”. By stating that the component “may be ionic,” this cocrystal definition also comprises salts. Solvates and hydrates are included as a subset of cocrystals. In the case of solvates, the molecule is a compound that is also known or used as solvent. In case the solvent is water, the solvate is called hydrate.

The term clathrate describes multi-component compounds where one component is contained in spaces within the crystal structure of the second component.

Other terms may be synonymously used for cocrystal. So expressions like co-crystal, molecular complex, or multi-component molecular crystal can also be found in literature and may have a subtle different meaning.

Various discussions about definitions when a solvent is a solvent and the wording are published [30, 61, 62].

One definition about when a multi-component compound can be considered a salt and when a cocrystal is based on the difference in pKa values of the particular components shall contribute to the extent of the proton transfer between two components in the crystal structure. The situation has been discussed as the salt–cocrystal continuum [63, 64] with the conclusion that the crystal environment and other factors like temperature are decisive for the extent of proton transfer and not a definition (pK_a) based on equilibrium in aqueous environment. Sometimes the decision about the position of the proton cannot be easily made [65] or answering the question takes time [66]. Discussion of these definitions may seem to be of academic nature; the terms mentioned are used in regulatory documents. This means potential commercial impact. Therefore, meaning, understanding, and interpretation of words, data, and experiments can make an important and decisive difference. For example, the perspective of the European Medicines Agency (EMA) on the topic is that "solvates including hydrates can be considered as a subgroup of cocrystals. The solvent, or the water, acts as a co-former in the same way as other co-formers" [57]. The EMA acknowledges that there is no strict borderline between complete and no proton transfer at all. As a criterion of relevance, salts and cocrystals are considered to have defined stoichiometries. EMA considers the properties that determine the suitability for the intended objective and application as decisive: "Ultimately, the resulting material properties are the critical factors that determine the suitability of a developed solid-state form for the designated purpose, regardless of the molecular bonding involved" [57].

Consideration of regulatory implications may alter as time goes by. Nevertheless, the current perspective of regulatory aspects is important for registering and marketing DPs (Chapter 10, [31, 67], or [68]).

One important conclusion is that classification is desirable but "researchers do not always agree on what does or does not belong in a particular category or what the definition of each category is" [64].

1.1.8.6 Solvates, Hydrates, Non-solvated Forms, or Ansolvates

A crystalline compound that does not contain a solvate is called an ansolvate or non-solvated form. If a solid phase, e.g. a crystal, is in proximity of a liquid phase, e.g. a solvent, the solid can attract the solvent. If the liquid phase remains at the surface of the solid, the liquid is adsorbed. If it penetrates through the surface, it becomes absorbed. If the liquid is eventually incorporated into the crystal structure, a solvate or solvated form is formed. In case the liquid is water, the solvate is called a hydrate. In analogy, there are names for solvates formed by the various organic solvents (Table 1.3). If an ansolvate is formed from a previously solvated form that lost the liquid, the resulting polymorphic form may be called a desolvate or desolvated form. In the case of water, the form is called dehydrated form or anhydrate. There is

Table 1.3 Naming of common solvate forms.

Solvent	Name of the solvate
Water	Hydrate
Methanol	Methanolate
Ethanol	Ethanolate
Propanol	Propanolate
Alcohol	Alcoholate

a specific nomenclature indicating the amount of water per mol parent compound (see Table 1.4 and Figure 1.10).

Cave! In organic chemistry, some compounds are called hydrates (e.g. carbohydrates, diols, aldehyde hydrates), which actually do not contain any molecular water. The name stems from water added by a chemical addition reaction (see Figure 1.11). These types of compounds must not be mixed up with those containing water in the crystal lattice.

"Hygroscopicity" names the tendency of a compound to attract water. Deliquescence describes beginning dissolution of a compound in water that it has attracted from the surrounding atmosphere. Characterization of the degree of hygroscopicity (or attractiveness to water) of a compound as a function of humidity and temperature is possible by DVS experiments [69]. These kinds of investigation provide information on the kinetics of adsorption and desorption as well as the determination of threshold values for humidity levels where sorption and desorption happen. A rather simple setup is storing the compound in an exsiccator or glass

Table 1.4 Nomenclature for compounds with crystal water.

Amount of crystal water	Name of the hydrate
0	Anhydrate
0.5	Hemihydrate
1	Monohydrate
1.5	Sesquihydrate
2	Dihydrate
3	Trihydrate
4	Tetrahydrate
5	Pentahydrate
…	…
12	Dodecahydrate
Uneven amount	Non-stoichiometric hydrate
Variable amount	Variable hydrate

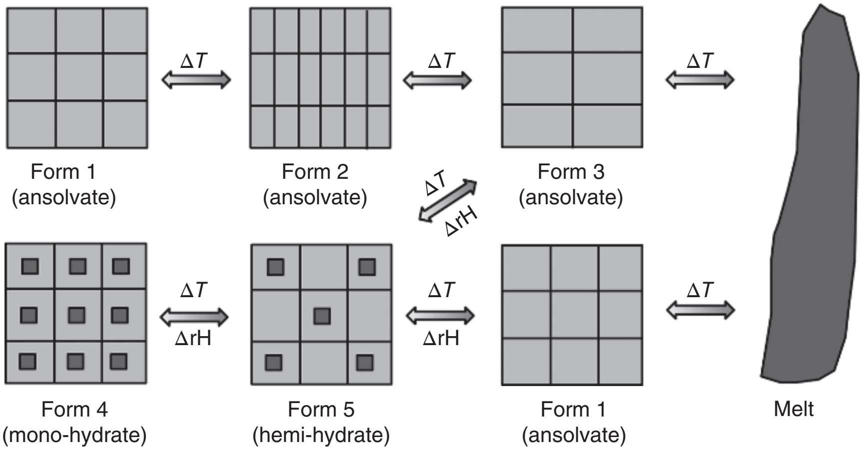

Figure 1.10 Schematic representation of potential interconversions between polymorphic and hydrated forms and melt upon changing temperature (Δ*T*) and/or relative humidity (ΔrH). Pathways depend on conditions.

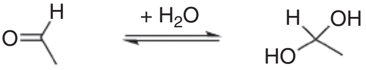

Figure 1.11 Acetaldehyde, a geminal diol – an organic compound "containing" water.

vial exposed to saturated salt solutions [70]. This setup enables quantification of water take-up (sorption) or loss (desorption) by gravimetry of larger (100 mg to g) quantities of material. Analytical characterization of the physico-chemical nature by solid-state analytical techniques such as XRPD, DSC, TGA, and the like as well as by chemical analytical methods such as HPLC prior and after storage is recommended. Hygroscopicity classification schemes are reported in [69]. The scheme of the European Pharmacopeia classifies percent (w/w) water uptake at 25 °C and 80% relative humidity (RH)

- 0–0.12% (w/w) as non-hygroscopic
- 0.2–2% (w/w) as slightly hygroscopic
- 2–15% (w/w) as moderately hygroscopic
- >15% (w/w) as very hygroscopic

Determination of stability information to be submitted in registration applications is documented in the ICH Q1A (R2) guideline "Stability Testing of New Drug Substances and Products" [71]. For chemical and pharmaceutical process purposes, the characterization of hydrates in suspensions of organic solvents with water (binary or ternary mixtures) with specified water activity is recommended [72, 73]. For further and detailed description of terms and relations, the chapter "Hygroscopicity and Hydrates in Pharmaceutical Solids" in [22] is recommended reading.

Eventually, the solid that incorporates a solvent may have various natures. It may be a neutral form, a salt, a cocrystal, or combinations thereof. Consequently, numerous variations of compounds may be formed. It appears to be a science on its own to classify and name such compounds accordingly [74].

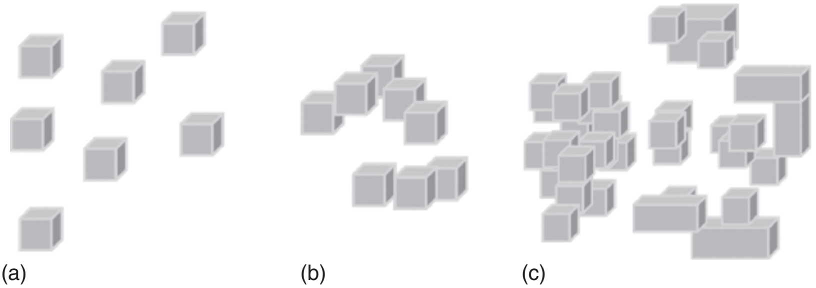

Figure 1.12 (a) Dispersed primary particles, (b) aggregates, and (c) agglomerates.

1.1.8.7 Dispersed Primary Particles, Aggregates, and Agglomerates

Crystals distributed as isolated primary particles in a suspension form a dispersion, i.e. a phase that is equally distributed in another phase. Due to attractive forces, the individual crystals may find each other and stick together and eventually form bigger particles constituted by the smaller ones. Depending on the attractive forces and the nature of bridges formed, aggregates and agglomerates may be distinguished as secondary particles (see Figure 1.12). While in aggregates (from latin aggregare, "group, attach"), multiple particles are connected by physical interaction or adhesion, agglomerates (from latin agglomerare, "mass together, join forces") are formed by multiple particles that are grown, sintered, or melted together, and thus form new or bigger particles that cannot be easily separated into the original constituents. However, in literature the two terms are often used interchangeably.

Aggregates may easily separate during post-crystallization procedures like filtration, washing, or application of tiny mechanical forces processing into primary particles, whereas agglomerates are more stable against size reduction. However, mechanical forces may cause formation of smaller particles by attrition or breakage of the agglomerates.

1.1.8.8 Particle Size and Particle Size Distribution (PSD)

Particle size considers individual particles with respect to length, width, and height or the volume as the product of these three measures as well as the morphology. Properties of these individual particles are homogeneity, stability against breakage, solubility, and dissolution rate.

Particle size distribution (PSD) considers a collective of particles, namely, their amount, distribution (with respect to size and mass), volume (e.g. tapped volume), and surface. Collective properties are separability, miscibility, tendency for agglomeration or aggregation, flowability, tapped density, and bulk density.

1.1.9 Investigating and Understanding the Polymorphic Landscape

Defining the objective at the beginning is one of the most important advices to follow in project management. Project goals may be formulated, e.g. according to the S.M.A.R.T. principles, i.e.

- specific
- measurable

- achievable
- relevant
- time bound

Easier said than done when it comes to the solid form. Assuming the intention is to administer the medication as a solid dosage form, e.g. as a tablet or as capsule, then probably the desired dose range can be estimated and the desired range for particle size can be specified, at least to a certain level. However, the number of isolatable polymorphic forms, potential solvates, types of salts, or cocrystals that can be achieved along with the particular properties relevant for successful drug development are unpredictable based only on the molecular structure. The timeframe for the project can certainly be set by management. Unfortunately, this may not be enough time to explore the polymorphic landscape with all its valleys, mountains, bright plains, and dark rivers. Every solid form project has its peculiarities. Every single compound behaves differently. Therefore, approaches to explore the landscape must be defined. Yet, the number of potential parameters to set for screening studies, like temperatures, pressures, solvents, methods for preparation, mixing, additives, and so forth, constitutes a really big experimental space. Reduction to practice necessarily decreases the number of experiments to an affordable and executable subset. However, the selection made depends on individual expertise and experiences of the operator(s) and the limits set by regulations and the institution the team works for.

These investigations yield, under the selected conditions, materials that have specific properties. This determines the first aspect of discovering the polymorphic landscape, the formation routes and their parameters lead to a smaller or bigger zoo of new compounds, i.e. polymorphs, solvates, salts, and the like. When determining the properties of compounds formed, a part of the investigation is aiming to identify the chemical and physical stability. The latter refers to potential transformation pathways and interrelationships, i.e. phase transitions, between polymorphic forms including solvation and desolvation.

A summary of all the findings or “polymorphic landscape” collected for a compound over time supports future development, manufacturing, and evaluation of next-generation products. It guides further optimization of synthesis, crystallization, and downstream processing, as well as formulation efforts with respect to operational space.

An example for a polymorphic landscape is given based on a paper on a methanol solvate of thiamine hydrochloride [75]. This may not reflect all possible polymorphic forms and solvates; however, the abstract of the paper mentions that thiamine hydrochloride (**THCl**) forms a monomethanolate (**MM**) upon exposure of crystalline thiamine phases (thiamine hydrochloride hemihydrate/**HH**, nonstoichiometric hydrate/**NSH**, and anhydrate/**AH)** to anhydrous methanol (solvent and vapor). Also, desolvation of **MM** at 50–80 °C resulted in the formation of a poorly crystalline intermediate which crystallized to **AH** at elevated temperatures (≥150 °C). When exposed to water vapor (11–75% RH, RT), **MM** transformed to **HH** (**NSH** was detected at ≤40% RH), while exposure to polar solvent vapor resulted in direct formation of **AH**. **MM** was stable in the presence of nonpolar (benzene and hexane) solvent vapor […] [75]. Hence, the abstract can be visualized as “polymorphic landscape” in a diagram (Figure 1.13).

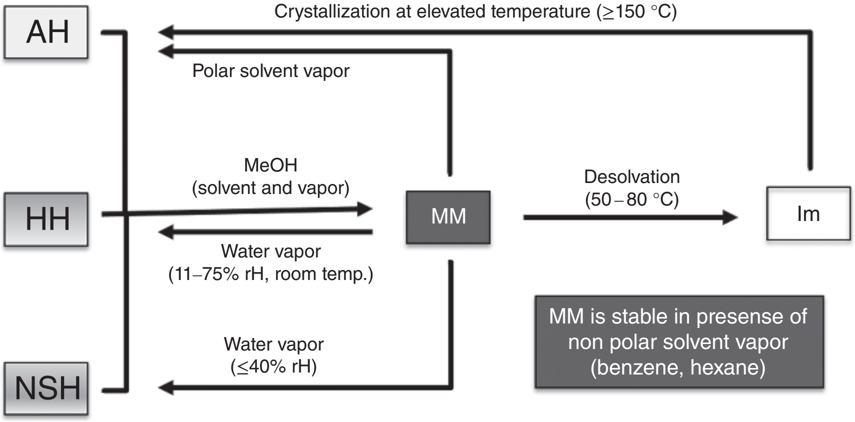

Figure 1.13 Polymorphic landscape derived from experimental findings. MM, mono-methanolate; AH, anhydrate; HH, hemi-hydrate; NSH, non-stoichiometric hydrate; Im, intermediate form; MeOH, methanol; rH, relative humidity.

1.1.10 Performing the Crystallization

The rational starting point for every crystallization (process) is the understanding of the solubility profile of the compound that shall be isolated [76–78]. In addition, it is advisable to know the accompanying impurities and their solubility profiles, too. It is worth to mention that the impurity profile can vary depending on the selected synthesis route [24].

In pharmaceutical industry, crystallization is predominantly conducted from solution. Reasons for this is that the organic synthesis is typically performed in solution and the reaction product can readily be crystallized from the system. Crystallization from the melt might be an option if the compound has sufficient thermal stability. Crucial for the selection of the crystallization method from solution (evaporative, cooling, anti-solvent, pH shift, or a combination thereof) is the solubility curve of the compound and the meta-stable zone width (MSZW). Once these data are determined and available for the selected compound–solvent system, the crystallization behavior can be investigated.

The MSZW determines the conditions under which the compound can remain in a supersaturated solution without spontaneous nucleation. The meta-stable zone is typically the range of conditions under which seed material (dry or in suspension) is added to initiate controlled crystallization. The seed has to be thoroughly characterized and selected with respect to polymorphic form, morphology, PSD, and amount. In general, it is recommended to perform crystallizations with seeding because this allows better reproducibility and control of PSD, yield, and crystalline form of the product.

As supersaturation is the driving force for crystallization, the process conditions have to be adjusted accordingly over time as by formation of the solid material, the supersaturation decreases. Typically, process conditions like mixing, temperature, anti-solvent addition, or vacuum are governed so that the growth of the particles is according to the desired crystalline form, morphology, PSD, and impurity profile.

Inclusion of impurities (residual solvent, by-products, reagents) into the product is usually not desired.

In addition to textbooks [32, 33, 35], further viable sources for an introduction into the basics of detailed investigation of solubility profiles and approaches for sophisticated industrial crystallization process optimization is presented on the websites of suppliers, like Technobis crystallization systems (www.crystallizationsystems.com) or Mettler Toledo Autochem (www.mt.com).

1.1.11 Objectives for the Optimization of Crystallization Processes and Solid-State Properties

There are various reasons to spent time and resources during development and manufacturing on the optimization of crystallization processes and solid-state properties.

Of particular importance is that the synthesis route and related conditions like process parameters and chemicals may change during the lifespan of a compound and its way of production. Consequently, any change may have an effect on the resulting solid form. This lesson is taught in reports about “Concomitant” [79], “Disappearing”, “Reappearing” [25–27, 80], or “late appearing” [81] polymorphs. Joel Bernstein has summarized this insight with “…the polymorph obtained, or the polymorphic mixture obtained, depends on the synthetic route to the desired material. It is probably more correct to state that as usual, the polymorph or polymorphic mixture depends on the crystallization conditions, and these will clearly differ in the solvent/reagent/product compositions resulting from different synthetic conditions and routes” [24].

Synthesis routes typically change from early R&D, over chemical, process, and pharmaceutical development until DS and dosage form manufacturing, in general caused by optimization attempts. It is of utmost importance to understand that all these efforts have to take in count and consequently require surveillance and control of the resulting solid polymorphic form and its properties. Considerable impact may have all steps that define or deal with the solid form, including, but not limited to, crystallization, separation, drying, storing, formulating, transporting, and packaging along with parameters and conditions of those processes. In addition, transformation, like scale-up, technological transfer to or from Contract Research Organizations (CRO) and Contract Development and Manufacturing Organizations (CDMO), even in-house transfer to other production sites or manufacturing equipment, should be accompanied by solid-state expertise and responsible risk management.

1.1.12 Implementation of In Silico and Simulation Techniques

One appropriate mean to support risk management is consulting in silico techniques that simulate the physical or chemical behavior of a reaction system or process. Simulation is based on mathematical models and therefore the fields of applications, efficiency, and limitations depend on the information about the reaction or process that is available and can be drilled down to descriptive equations and numbers.

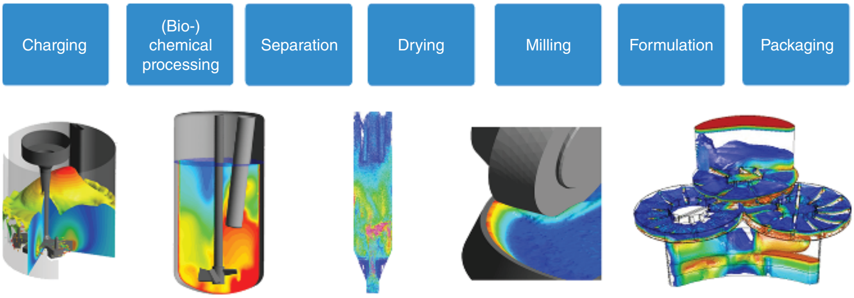

Figure 1.14 Various applications for simulation of chemical and pharmaceutical unit operations. Source: Courtesy of aixProcess GmbH, Aachen, Germany.

Knowledge about computational methods addressing pharmaceutically relevant topics for solid-state applications like crystal structure prediction, solubility prediction, and formulation design in industrial contexts was collected by Abramov in 2016 [82].

Fortunately, engineering aspects are well addressed by simulation, too. Simulation is applicable for many unit operations and in the world of chemical and pharmaceutical sciences (Figure 1.14). The basic principles as well as the evolving capabilities due to development in underlying theories, algorithms, and increasing availability of computational power are well reported [83–87].

It is worth noting that engineers and chemists typically have different educational backgrounds and probably as a consequence different perspectives to address and look at processes. Both may think in formulas. Yet the understanding and viewpoint are different. While an engineer primarily visualizes his process understanding in “mathematical formulas” and flow diagrams, the chemist illustrates processes with “molecular formulas” and chemical reactions thereof. The use of simulation packages to describe and understand processes is a helpful mean to bring the worlds together and illustrate engineering and chemical aspects to simplify mutual communication.

Theories about, e.g. fluid dynamics, mechanical, material, and thermal properties are readily available through databases and simulation software packages for various engineering tasks.

Consequently, basic information packages from laboratory scale experiments along with easily accessible geometrical information of equipment for scale-up or manufacturing can be fed into models. The subsequent insights enhance understanding of the underlying situation and potential challenges as well do they simplify communication according to the proverb “a picture says more than a thousand words” (see Figure 1.15).

Very often mixing is identified as critical process parameter (CPP) for crystallization processes. Affecting process parameters like dosing rates, locations for addition, order of addition, filling volumes, temperature profiles, propeller geometries, and related properties like power number and shear rates are quite often just estimated based on experiences or simple assumptions. On a higher level, crystallization

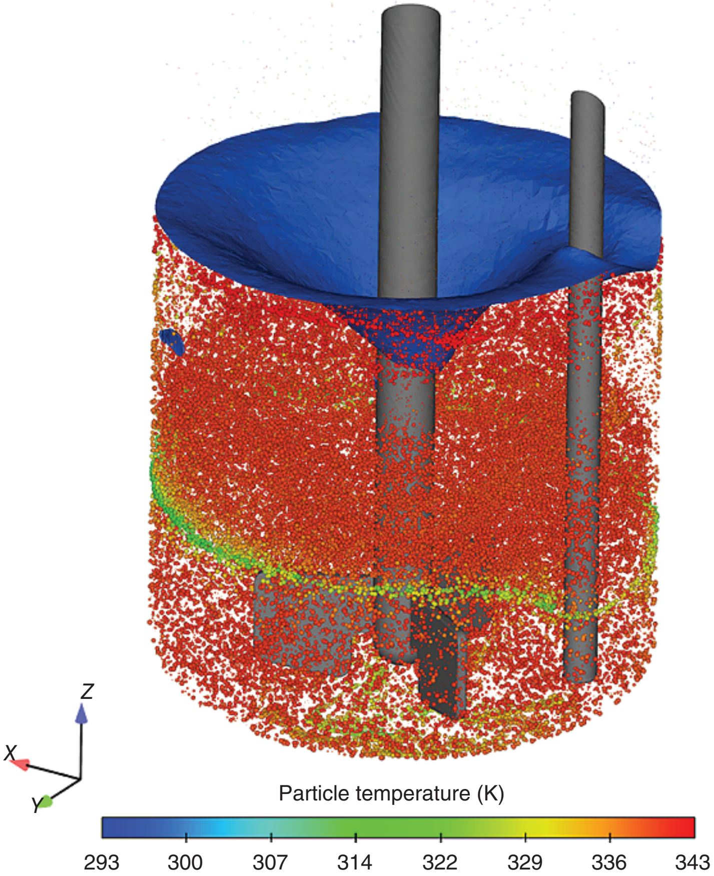

Figure 1.15 Calculated temperature distribution after seeding in a cooled mixed vessel in 100 l scale. Source: Courtesy of aixProcess GmbH, Aachen, Germany.

can be described by nucleation and growth kinetics and chemical reactions by reaction kinetics. Introducing such information into the simulation models require more efforts but could then lead to additional insights on the evolution of PSDs or by-product formation or decomposition.

Upon scale-up or site transfer, not all conditions and properties from the original (e.g. lab scale or CRO) equipment can be kept constant. Decisions, naturally supported by a risk assessment, must be taken.

As an example may serve the in silico investigation of a stirred vessel and a look at the calculated temperature distribution (compare Figure 1.15). Due to specific mixing properties of the equipment under consideration, stagnant zones evolve during mixing. Therefore, some regions are exposed somewhat longer to the cooled wall of the vessel. Consequently, this leads to cold spots (or zones) where unintended spontaneous nucleation of a supersaturated solution may happen well before the temperature probe that is located in another zone, that might probably better mixed, indicates that the temperature elaborated for seeding in lab experiments is reached.

In analogy, for chemical reactions this may be transferred to a heated vessel, where hot spots evolve inducing accelerated decomposition related with an undesired (and certainly unexpected) out-of-specification purity profile.

According to quality by design (QbD) principles, implementation of simulation approaches supports multidimensional exploration of the design space. This comprises rational process design and understanding of processes and equipment parameters. Identification of CPP combined with application of scale-up principles may serve to minimize, e.g. batch-to-batch variations and enhance overall process and product quality.

Simulation-related engineering efforts may be overcompensated by reduced costs for less chemicals, reagents, energy, re-working, disposal of failed attempts, as well as avoiding selection of unsuitable equipment and the like. In addition, mechanical forces can be derived from the calculations that may point to material stress or enhanced exposition to corrosion. This information may support preventive maintenance of manufacturing equipment. Many industries like automotive, aerospace, and chemical industry established the opportunity for more efficient and rapid development as well as optimization of manufacturing processes provided by simulation techniques. As part of a rational and properly coordinated development and manufacturing strategy, simulation techniques make sense to be implemented responsibly also into pharmaceutical R&D and manufacturing.

As such, surveillance of processes as well as continuous improvement and operational excellence is feasible. Besides data and information acquisition and interpretation by enhanced statistical interpretation through ML techniques or AI approaches, physical modeling by means of simulation brings additional efforts and insights.

As an entry point to overcome hesitations, often the application of simulation techniques as a "firefighting" tool is used in critical projects. This is an appropriate and suitable approach to learn about the opportunities before implementing simulation as part of strategy and daily business.

1.1.13 Saving the Investment – Addressing Intellectual Property Rights

Eventually, all measures can be drilled down to enhance profit or safety. However, approaching those final objectives, several intermediate targets can be accessed by investigating the crystallization process or the solid-state landscape.

As there are

- increasing yield
- reducing initial amounts of materials
- increase energy efficiency (e.g. heating, cooling, and drying routines)
- reduce potential threads for people and environment (e.g. avoid dust by larger particles)
- reduce reaction and overall processing times
- identification and control of CPPs for chemical and pharmaceutical operations
  - improve purity, reduce amount of by-products

  - understand the affect of synthesis routes, different impurity profiles, and the fate of impurities on resulting solid forms and morphology
  - understand the impact of morphology (flowability, filterability, compatibility)
  - optimize isolation steps (filtration, centrifugation), consider morphology
  - increase washing efficiency (e.g. reduce solvents or repetitions)
  - optimize drying (e.g. reduce time or energy, target desired polymorphic form)
  - understand impact of process conditions and routines
- enhance physical or chemical stability
  - understand impact of
    - light
    - humidity or moisture
    - temperature
    - mechanical forces (e.g. pressure, shear forces)
  - prevent alteration of solid form
  - optimize storage conditions and packaging
  - enhance shelf live

Besides understanding and gaining control of technical aspects of solid form properties and processing, the other important aspect to invest into solid-state activities is an additional chance to protect IP rights. Particularly, the pharmaceutical industry invests huge amounts of money into R&D and commercialization. However, there is high risk to not get a return on investment for many projects. Therefore, successful projects, i.e. those where eventually a medication reaches the patient, have to cover also the investments of the failed attempts. A system, worldwide established to protect IP rights, i.e. preventing others from exploiting efforts invested into R&D and commercialization, is the international patent system (PCT). It is recommended to educate (solid-state) scientist with the basics of the patent system. A starting point may be training on proper documentation and communication of experiments and results. Building close relationships and establishing cooperation in interdisciplinary teams, including scientists and patent attorneys, enhance mutual understanding for limitations, requirements, and challenges. Furthermore, it encourages innovation, which starts with an idea but takes a long way until market decides on failure or success of a product.

1.1.14 Concluding Remarks

As with all attempts to describe a complex matter, this chapter has been able to address only some of the topics that are relevant in the context of solid form development and processing, foremost in the pharmaceutical industry. It is of utmost importance to understand that properties and behavior of all types of solid materials, not just API, require attention along the development and manufacturing chains. Knowing and controlling the particularities of solid materials is an essential asset for all stakeholders, regardless of dealing with scientific, technical, or business aspects.

Risk-based management should include timely investment in solid-state activities and foster an appropriate work environment and infrastructure to avoid huge time lagging and money-intensive efforts to resolve problematic situations and ensure undisturbed marketization of DSs and DPs. Besides ensuring proper and timely technical development, the protection of IP rights and eventually the freedom to operate is a must and convincing aspect to invest into solid-state-related activities.

List of Abbreviations

(A)NDA	abbreviated new drug application
API	active pharmaceutical ingredient (used as synonym for DS)
bn	billion (10^9)
CRO	Contract Research Organizations
CDMO	Contract Development and Manufacturing Organizations
CPP	critical process parameter
DP	drug product
DS	drug substance
DSC	differential scanning calorimetry
DVS	dynamic vapor sorption
eCTD	electronic Common Technical Document
ELN	electronic laboratory notebook
ERP	enterprise resource planning
HMI	human–machine interface
HPLC	high-performance liquid chromatography
IB	investigators brochure
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
ICIQ	Institut Catalá d'Investigació Quimica
IP	intellectual property
IR	infrared spectroscopy
LC–MS	liquid chromatography coupled with mass spectroscopy
LEA	lab execution and analysis system
LIMS	lab information system
MSZW	meta-stable zone width
NMR	nuclear magnetic spectroscopy
PCT	patent cooperation treaty (international patent system)
PDF	pair distribution function
PLC	programmable logic controller
PLS	Prozessleitsystem, i.e. distributed control systems (DCS)
PSD	particle size distribution
QA	quality assurance
QbD	quality by design
R&D	research & development
rH	relative humidity
SCADA	supervisory control and data acquisition
SCXRD	single-crystal X-ray diffraction
ssNMR	solid-state nuclear magnetic resonance spectroscopy

T	temperature
TGA	thermogravimetric analysis
XRPD	X-ray powder diffraction

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