1

Aspects for Developing and Processing Solid Forms

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1.1 Aspects for Developing and Processing Solid Forms

1.1.1 Introduction

Due to progressing through time and space, we constantly learn and forget. We lose things out of sight and focus on the ones that are of most importance and interest. Consequently, we cannot keep pace on every single field of technology and science. Career pathways are manifold. It is fairly natural that people in management positions who take over the responsibility to direct companies, departments, or groups cannot be experts in all the domains falling under their responsibility. Therefore, they have to educate themselves and rely on their staff, employees, team members, suppliers, contract organizations and consultants, and the assessments delivered. Decisions are made on such a base. Those decisions determine the commercial fate of the business, which in turn determines the well-being of those who gave input into the decisions. A circle of life? Will just the fittest survive?

1.1.2 Education and Personal Background

Some lack of knowledge and understanding of impact and relations may occur especially in fields that are typically not in the focus of a general chemical, medicinal, or pharmaceutical curriculum. Organic compounds constitute the majority of active pharmaceutical ingredients (API) very often in the form of crystalline solids. Nevertheless, solid-state-related topics for organic compounds are treated in introductory organic synthetic textbooks, like the *Organikum* [1], just on a few pages that do not go much into the details. Crystallization (including selection of the solvent, recrystallization, and crystallization from the melt) is explained in two pages, and structure analysis by means of X-ray is mentioned in another page.

Besides, still a predominant perception of solid-state characterization techniques, in particular X-ray powder diffraction (XRPD), is that the investigations are expensive. Admittedly, XRPD is not as widely distributed and readily accessible as spectroscopic and chromatographic techniques. Consequently, solid compounds

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and dosage forms are primarily characterized by the analytical techniques that are easily available. It is perfect to assess purity profiles and determine the solubility and dissolution profiles. Unfortunately, it is not sufficient to analyze the liquid state because that does not reveal much about the properties of the material in the solid state. Additional processing knowledge is also needed to design and modify solid-state properties.

Our current position, our educational background, as well as the social and technical environment that surrounds us determine the perception of threads and opportunities.

As long as during chemical development or production, solid-state-caused obstacles can be overcome by some, maybe magic and not really understood, measures that everything is fine or, more precisely, appears to be fine, at least for the moment. No further resources, time, and money are invested to understand the cause–effect relations. How long will this satisfaction for saving money last? Who is eventually paying the bill for lack of thoroughly understanding the processes and interdependencies? The advice is to implement solid-state experts into CMC or other development and processing teams. Taking the advantage and benefit from the different perspective, they can add to discussions and innovations.

In the past 20–30 years, solid-state development became more and more important in the pharmaceutical industry. Many treatises in print and online cover a broad variety of aspects that can be subsumed under the roof of solid-state development. This concerns not just molecules that are API but also many other compounds classified as fine chemicals, agrochemicals, explosives, or those having a relevance for nutrition products. The eye-catching word is mainly "polymorphism" that, along with similar terms like "polymorph" and "pseudo-polymorph" or terms often discussed in the context like "hydrate", "solvate", "salt", "cocrystal", "co-crystal", or "amorphous", was and still is worthwhile to cause attention.

The attention culminated to a hype that has today become a scientific and commercial important field of sound investigation to ensure proper development and subsequent successful marketability of products in general. However, in the world of pharmaceuticals, the interest is beyond commercial aspects related to ensuring safety and efficacy of the products dedicated to reduce suffering from diseases or curing patients.

Consequently, many stakeholders are involved in solid-state research, development, manufacturing, and commercialization. But it is also the other way round. Chemists and pharmacists who are active in the field of development and processing of solid compounds have lots of interfaces to other departments from which they get or to whom they deliver information and materials as exemplified for a crystallization laboratory in Figure 1.1.

Obviously, every single discipline can consider itself as the most important and thus justifies its position in the center of this representative arrangement. Actually, the center of Figure 1.1 only represents the point of view and maybe the self-conception. Solid-state development, particularly for pharmaceutical applications, is a complex and ever-changing setup involving and needing lots of disciplines for successfully mastering the development and manufacturing workflows.

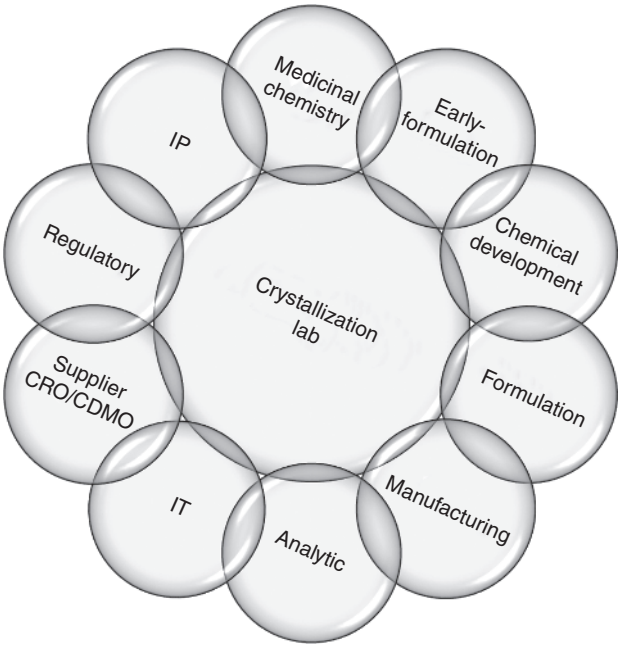

Figure 1.1 The crystallization laboratory – integrated in pharmaceutical development and manufacturing.

Looking behind the scenes, stepping somewhat back from the science but without neglecting the importance of a sound understanding of the basics and the implementation of solid-state-related processes is the intention of the following chapters constituting this edition. Every chapter was contributed by someone who is an expert in his or her particular field, someone who illuminates the aspects of his or her domain with the awareness of being a part of the whole. While reading the chapters, consider its topic as standing in the center of the arrangement (Figure 1.1). Development and processing of solid compounds and forms is apparently enlightened from different perspectives. Therefore, some aspects are covered not just by one author. When there is light, then there is shadow. Not every aspect can be treated, especially because the chapters were intentionally written from a subjective standpoint and perspective. Personal preferences, experiences, and peculiarities directed the content. Other perspectives and considerations may well exist.

Solid-state development and processing is nothing that can be handled as an isolated aspect of pharmaceutical R&D or manufacturing, although a lack of general understanding of the foundations, disregarding the essential impact the solid state has on process and eventually product quality, is surprisingly still around in the industries.

This is understandable from one perspective. Dedicated experts are typically required to address the many topics showing up in the course of pharmaceutical research and particular pharmaceutical development and manufacturing. All of them are well trained and have skills in their particular sciences or businesses.

Education at university is focusing on the formation of domain experts. As a drawback, less time is typically available to look to the left and to the right, forward and beyond of the own field of expertise.

As a consequence, all those experts eventually involved in versatile R&D and manufacturing teams have the duty to ensure that their colleagues (or "interfaces") also get an understanding of the impact of their particular field of expertise for the whole process and vice versa. All participants in R&D and manufacturing processes have the obligation to accentuate the need and significance of the topics addressed by themselves and their laboratories or departments. There is a necessity for people having the capability to act as coaches, teachers, and trainers; devoted to their field of expertise but not trapped therein; on the contrary, open minded and willing to share knowledge. People dedicated to draft, construct, and maintain their part of the development and production, as well as of business processes.

Getting the knowledge out of the heads. What is important to share? What should others know about your business? Besides sciences, what is also important to communicate to make industrial and commercially oriented environments work?

The intention is to cover the most essential topics in industrial, mainly pharmaceutical, environments that are related to the manifold of properties and characteristics solid compounds have.

1.1.3 Societal Impact – Fishing in Foreign Waters

The societal impact or the impact of society – human being are creating the society they live in and individuals are formed by the society they live in. Dealing with societal, economical, and historical impact on science and business is typically not a field harvested by a solid-state expert. Other businesses and sciences treating sociological relations, management, or national economy usually consider topics like this. Professionals in these fields have experiences, tools, and know the sources for research and how to investigate developments and interrelations. Therefore, the following is layman's reflection on societal aspects.

1.1.3.1 Motivation

Why trying to cover this topic? First, because it is interesting. Second, it has some relevance to start with this consideration now. As long as individuals are present who eyewitnessed or even designed the initial pharmaceutical solid-state development, or worked on the implementation of the current status, it is possible to get insights not just based on figures and statistics. They can talk and report about motivations, desires, challenges, dead ends, hopes, and obstacles. The dimension of personal experiences and observations is important and worth to be told.

A comparison might help. It is a bit as if a chemist, well educated and trained in organic chemistry, attempts to cover topics related to solid-state aspects, like designing a crystallization process or investigating a solid-state landscape. Why are not the experts doing the job? Answers are manifold: "Not a big task, let's just have a look", or there is no solid-state expert around, or the expert is packed with other projects, or

nobody is aware that a solid-state expert would probably have a different perspective and appropriate education, better tools, and experiences to do the job.

Usually the attempt to "just let's do it" fails. It might lead to some results. Maybe that these results are good enough to decide that, probably at a first glance, no further investigation is necessary or meaningful. Time will show whether the project dies or whether it is interesting enough to follow up.

"Just let's do it" reflects the approach in this part of the section to consider mutual interaction between people or society and pharmaceutical solid-state chemistry. Unfortunately, these economical and societal aspects of pharmaceutical solid-state development and about the historical development-related interactions between society and science are not yet covered accordingly. There is a hope that in future someone will do so properly.

While reflecting this challenge with others, the response was like "who could be interested and would spent time on reading?" Maybe nobody is interested. However, there are always people acting for some years in their field of expertise and have observed and contributed to changes. Certainly, these individuals are curious to read a summary and a reflection about the topic and fields of expertise they spent years of their lives on.

The likelihood for realizing such a project is naturally larger for widespread general topics like computer technology or popular sciences like flights to the moon, exemplified by [2–6].

The hope is that someone picks up the idea and starts with economical, societal, and historical research on this small but important niche in pharmaceutical science with more adequate means, knowledge, and resources than attempted here.

1.1.3.2 The Personal Dimension

Any action consequently leads to a reaction. Probably, every student of natural science has heard in the first physics lectures about Isaac Newton who formulated this as his third law of motion "Law III: To every action there is always opposed an equal reaction: or the mutual actions of two bodies upon each other are always equal, and directed to contrary parts" [7].

This consideration is not limited to physical bodies moving in the three-dimensional physical world. There is also always an impact in a nonmaterial sense, an impact on ideas, thoughts, and desires. This impact is the essence of advancement in general and technological progress in particular. Realization of progress is only possible because the fourth dimension, time, is also affected. Progress is not possible without a change of states in time. The qualitative and quantitative identification of change is only possible if a prior state is compared to a later state of a system or society.

Being asked by one of the series editors if I am interested to edit a book on pharmaceutical solid-state development, it took me a while to make my decision. I wondered, what can I, what can we as authors, contribute to the society of solid-state experts or community of people who strive to learn about solid-state development and processing that has not yet been reported before? Moreover, it was not just me among the authors who has asked himself this question.

Before I decided to dive into this project, my understanding was that everything of importance for investigating the solid state was already told. In this very moment, while typing these lines and editing the contributions of the other authors, I am convinced that this is certainly not the case.

For sure, progress is always made and there will always be new developments and new inventions and discoveries, as in all sciences. In addition, there will be old, sometimes forgotten, stories told in a new fashion. Actually, this is not what I had in mind.

What in particular is untold is our subjective perception and perspective. Having the opportunity to write from and about someone's subjective position in this area is an argument that is convincing to start editing and writing. The burden and chance to communicate our very personal view on the "Solid-State development and processing of pharmaceutical molecules" is appreciated. We have the chance to communicate about those aspects and topics we personally consider of being of interest and value for the community. We have the chance, and responsibility, to make a personal selection of scientific themes, topics, references, and examples that are worthwhile to address in the context of industrial tasks. We have the chance to act, to influence, and impact. This will for sure lead to reactions: affirmative or contrary. Regardless of its nature, every reaction will itself be of further impact on personal thinking and therefore on thinking of the community.

This is already a societal impact of solid-state development. People, certainly not for the first time, agreed to spend a significant part of their time to restitute partly to the society what they received from others. There were many who taught and trained them to acquire and prosper particularly specialized and sometimes singular and rare skills. The motivation that drives each individually can be manifold. It might be the chance to spread the personal view, it might be the chance to summarize and share a particular sequence of business life, it might also be to face a particular personal challenge, and it might well be the option to publish and to promote personal career. It might be something else or a mixture of the preceding. These willing authors differentiated themselves from those who objected to contribute. Some of those who rejected concluded a personal calculation that taking the time to contribute is not what they like to do or that it would not pay off for them or their business. Some questioned if anyone might read the chapter, the book. Some were stopped by illnesses, by other duties, or by supervisors who preferred seeing them to work (in a more direct manner) for the company or protected them to not burn themselves. Solid-state development and processing as well as many of the other branches in the pharmaceutical value chain with all their facets have for sure a societal impact and are impacted by society.

1.1.3.3 Beyond the Impact on Individuals

The aforementioned addresses the personal dimension of societal impact. There is another dimension, an even larger one worth to be addressed. What is the impact that the investigation of the solid state has on organizations? How do these organizations act, develop, and influence science, regulations, businesses, and consequently societies?

It was Albert Einstein who realized that the experience of a chronological sequence, which we usually call history, depends on the perspective of the observer and whether events appear to be (i.e. are) simultaneous or one after the other. Apart from this relativistic point of view on events, the speed of experiencing and learning for human beings is usually chronological. "Standing on the shoulder of giants", often attributed to Isaac Newton, but going back at least to the twelfth century [8], summarizes how the accumulation of knowledge and progress establishes. Individuals learn from and build on the experiences of others. The essence of enterprises, often praised, sometimes forgotten (as reflected by the term human resources), is the sum of all the individuals working for these companies. One way to reflect on their collective achievements is that economical figures illustrate the financial value of a company. Besides, there is also a social value. There are examples where the social value of an organization correlates with the economic value [9].

1.1.3.4 Understanding the Market – Not an Easy Task

In particular, the pharmaceutical industry in Europe itself, represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA), annually presents their economic and societal contribution [10, 11].

There are other potential sources for data, like statistical offices. Unfortunately, figures are usually not broken down to an extent where the impact of solid-state-related activities becomes visible. This same issue occurs with official statistical data acquired, for example, by the German statistical office (Statistisches Bundesamt, DESTATIS) as published in the GENESIS-online database (https://www-genesis.destatis.de) or the European Commission as published in the Eurostat database (https://ec.europa.eu/eurostat/web/science-technology-innovation/data/database).

Because the categories are very generally defined (see Table 1.1), no information can be derived and assigned particularly to the impact of such a niche like "solid-state activities" on turnover or number of employees.

Even harder it is to get corporate data broken down to the affect and effect of pharmaceutical solid-state activities. According to national laws, companies may have

Table 1.1 Categories in the German DESTATIS GENESIS-online database (as of 2019-08-14).

Code	Content (category)	Translation of content
WZ08-72	Forschung und Entwicklung	Research and Development
WZ08-721	Forschg.u.Entwicklg. in Natur-u.ä. Wissenschaften	Research and Development in natural and similar sciences
WZ08-7211	Forschung und Entwicklung in Biotechnologie	Research and Development in biotechnology
WZ08-7219	Sonstige Forschg.u.Entwicklg. von Naturwiss. u.Ä.	Other Research and Development in natural and similar sciences
WZ08-74	Sonst. freiberufl.,wissenschaftl. u. techn.Tätigk.	Other self-employed, scientific, and technical activities

the obligation to publish their financial results. In Germany, e.g. public companies (AG) listed on the stock exchange and companies with limited liability (GmbH) disclose their accounting documents on a yearly basis to the operator of the Federal Gazette (i.e. Bundesanzeiger) or deposit them in the business register (i.e. Handelsregister) [12]. The data can be accessed via the Internet [13].

Following this approach to get insights into the historical development of solid-state-related businesses, it has to be taken into account that the level of detail is quite coarse as it lists the cumulative financial results of the enterprises per year. Therefore, possibly none of the financial figures can be attributed to solid-state departments or even smaller working groups being just a part of a bigger chemical or pharmaceutical company.

Nevertheless, if the business of a company is mainly focused on solid-state-related services, the historical financial figures of this company can be considered, with some approximation, to reflect the development of solid-state services over the years. Maybe not as a representative *pars pro toto* but at least as an example.

On the German market, the company Solid-Chem GmbH, located in Bochum, is one of these focused companies. According to the company philosophy [14], they investigate the solid-state chemistry of products and offer consulting and scientific support with also covering aspects dealing with drug products (DPs). Data about the company are available in the Bundesanzeiger. The company may serve, at least for the period of data published, as an example that reflects, based on its financial results, the necessity and importance of solid-state investigations and services for the chemical and pharmaceutical industry. Unfortunately, data published in the Bundesanzeiger are not as comprehensive and telling as one might wish. In general, nothing is said about the number of employees and the wages paid nor is there information on the types of projects.

Another indication for the increased interest in pharmaceutical solid-state activities is the acquisition of companies formerly specialized in the investigations of solid-state topics and their implementation into larger contract development and manufacturing organizations (CDMO), exemplified by

- SSCI, originally founded in 1991, acquired in 2006 by Aptuit, and since 2015 a division of Albany Molecular Research (AMRI).
- Crystallics, originally founded in 2000, acquired by Ardena in 2016.
  In the years between, the solid-state facilities were part of several splits and mergers.
- Pharmorphix, originally founded in 2003, acquired by Johnson Mathey in 2015.
- Solid Forms Solutions, acquired by Avista Pharma early in 2018 subsequently acquired by Cambrex end of 2018.

Another observation is expansion of formerly focused expertise into service providers with an extended portfolio as well as formation of associations, as there are, for example,

- Solvias
- Crysforma, as part of ICIQ (Institut Catalá d'Investigació Quimica)

- APC
- CMAC

Although there are examples that the pharmaceutical industry divests solid-state expertise, several CDMO have established in-house solid-state expertise to support development and manufacturing but may or may not offer this expertise as a separate service for third parties.

1.1.3.5 Benefits of an Interdisciplinary Mindset

There may be other approaches to get telling data. Maybe professional data providers or chemical or pharmaceutical societies have a deeper insight into the figures of their individual or corporate members. Maybe newspapers or major business consulting companies have a database that might give more answers about the societal impact and impact on society if properly analyzed and publicly distributed. Business, literature, or patent databases may, and certainly do, serve as a source, and the contents might be crawled by data mining algorithms. Data analytical tools could eventually process the results with respect to

- publications, posters, conferences, whitepapers, webinars, and seminars
- business figures, financial data, merger & acquisitions
- applications, granted patents, application status (active, inactive)
- dates, to put everything in chronological order
- occurrence of terms in title, abstract, description, example, and claim
- terms like polymorphism, salt, cocrystal, modification, Form A … Form Z, Form I … Form XVIIIC, Form α … Form Ω, and so on
- various solid-state characterization techniques
- companies, assignees, inventors
- … and more …
- … and combinations thereof

As an example to demonstrate, the opportunities of combining several sources like patent and financial data may serve the valuation analysis for Norvasc® in which the attractiveness, i.e. sales threshold, to circumvent a secondary salt patent was estimated for products in the United States to be about $1.5 bn [15].

Such results combined with insights gained from sociological or historical research might generate new knowledge and understanding of relationships. This will certainly happen if data use rights and privacy laws allow and someone identifies a financial advantage or business case.

1.1.4 The Basis for Mutual Understanding

Terms used in science typically get a definition to provide a common base for conversation. Unfortunately, different actors think that different definitions are meaningful and correct to express the situation. Therefore, a range of definitions for terms evolve throughout time and space and a jargon is formed, while we are permanently exchanging thoughts to simplify and speed up communication and interaction.

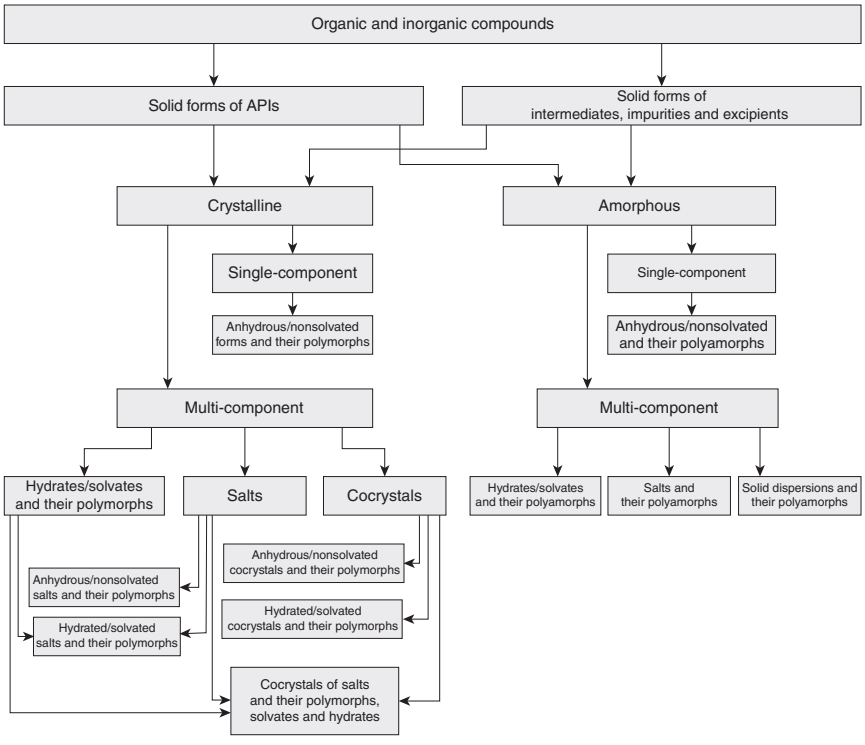

Figure 1.2 The complexity of solid compounds in pharmaceutical applications. Amended chart based on Aitipamula et al. [16].

Figure 1.2 illustrates an attempt to categorize the diversity of solid forms. Various potential combinations of solids can be formed by combining single components. In principle, the following categories apply:

- Nature of compound
- Degree of crystallinity (amorphous–crystalline; i.e. unordered–ordered)
- Number of components (single–multiple) and ratio
- Type of components (liquid–solid; aqueous–nonaqueous)
- Nature of bonding, type of interaction (ionic–π–π interaction–van der Waals)
- Number of solid forms having the same composition (polymorphism)
- Homogeneity (purity, ideality) of the solid arrangement (pure–mixed phases; solid solutions)

To make the image complete, combine elements from these categories.

A consideration of basic principles, terms, and aspects is provided and discussed throughout the years in details elsewhere, exemplified, without claiming completeness, by [17–35] and all the references mentioned therein.

The following sections and chapters emphasize some of the prerequisites and aspects to provide a base for a better understanding for solid-state aspects of small molecules and the enormous impact on chemical and pharmaceutical development and processing.

1.1.5 Crystallization is a Separation, Not a Separated Process

Crystallization is the separation process that leads to solid crystalline material and is as such, together with other separation techniques, responsible for 40–90% of the spent capital and operating costs of industrial production [36].

Why crystallization? Crystallization is an acknowledged and well-established purification step suitable to deplete impurities like by-products, unreacted reagents, catalysts, or residual solvents introduced by the preceding synthesis. Therefore, crystallization is a perfectly suited unit operation to separate valuable material from waste or material that is supposed to be used in other value chains.

Moreover, why crystalline solid material? Materials in crystalline solid state generally exhibit superior stability properties than in amorphous or liquid state. Alteration processes like decomposition and chemical reaction (e.g. oxidation) are reduced due to low mobility of the constituents compared with amorphous or liquid state.

In course of the organic synthesis and the subsequent crystallization procedure, the solid material is in the suspension still in contact with solvent and impurities from the reaction. At this stage, in the slurry, changes in the solid form may continue to happen. Thermodynamically, more stable forms can evolve from metastable modifications or solvate formation can happen since at lower temperature another region of stability might have been reached. Due to increased concentration unintended precipitation of byproducts or impurities can happen or addition compounds may form.

To further purify the desired material, typically filtration or centrifugation followed by washing of the filter cake is applied subsequently. With respect to the solid form, this should happen with some care because solvate formation or exchange of the solvate in solvated forms can take place as well as pre-drying with flow of air or inert gas may lead to desolvation of solvated forms.

Often the separation is followed by a drying routine to remove residual solvent and increase flowability of the solid material. Besides changes in particle size caused by agglomeration or breakage, also a change of the solid form may happen as described earlier. In addition, since generally thermal energy is introduced by raising the temperature level, polymorphic forms may interconvert. Reduced pressure is commonly applied, which may lead to unexpected behavior in contrast to atmospheric pressure conditions. Especially drying of solvates to a defined stage requires thorough knowledge and investigation of the phase diagram to avoid producing material that is not according to the desired outcome.

Transport and storage may expose the drug substance (DS) or other materials, like reactants, intermediates, or excipients, to conditions that can also affect the solid state. Consider temperature changes by moving drums from the production hall to a storage place that has a different temperature or exposes the material from time to time to sunlight. Besides condensation of moisture, additional drying due to temperature changes may have an effect on the polymorphic or solvate form. Furthermore, mechanical forces can result in changes of particle sizes and morphology.

Eventually a formulation process like tableting can affect the solid state of the DS as the DP is produced. The variety of formulation processes comprises multiple

chances to impact the solid form of the DS. Thermal stress and mechanical forces may alter the physical form of the DS as well as bring it in contact with excipients being potential sources for moisture or water or even partners for chemical interaction. Upon storage and transport, the final DP should also not alter its properties.

This process chain described earlier [31] illustrates the embedding of the crystallization in a broader context. Although crystallization is the first step where solid properties can and should be addressed, subsequent process steps may alter and modify solid characteristics and must therefore be considered and understood as well.

Additional aspects complete the image of integrated solid-state development and processing. Figure 1.3 illustrates interrelating tasks and duties that have to be managed and handled during solid-state development and processing. It all starts with setting up the scene. Define the objective(s) that shall be reached. Organize and establish the infrastructure necessary to reach the goal. This comprises availability of suitable equipment and materials as well as experienced and well-educated staff or teams who are prepared and trained to perform the required tasks. Next is designing the experiments and/or processes. Think about what is required and necessary to reach the objective as fast and as cheap as possible with sufficient quality. Select the types of analytics suitable to monitor proceedings and confirm quality. Develop and establish analytical methods and sampling (drawing and handling) procedures. Confirm that initial thoughts were correct or adopt if necessary. Subsequently, solid formation processing sets in. Experiments to investigate and optimize or processes to reproducibly conduct crystallization and formulation as well as downstream procedures like isolation and drying have to be set up. Not to forget the installation of efficient delivery pathways to analytical operators, clients, or patients. As part of all these processes, knowledge generation happens. People and organizations learn permanently. Learning should be as effective as possible to reduce development efforts or enhance manufacturing capacity. Additional value can be generated by efficient communication between all stakeholders participating in those development and manufacturing processes. Digitalization of

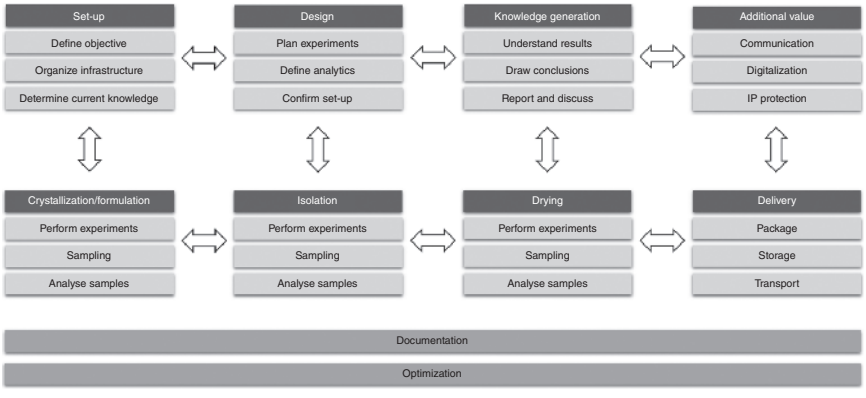

Figure 1.3 Tasks and duties for solid-state development and processing.

technical and business procedures is advised wherever meaningful and applicable to ensure effectiveness and reliability. Understanding mutual requirements and needs is important to reduce overall efforts, enhance performance, and reduce costs. Certainly, the efforts should pay back and value preserved by protecting the intellectual property (IP) generated. Along all these procedures and processes, documentation and optimization must take place. Otherwise, quality cannot be guaranteed and knowledge gets lost if not distributed within the organization while costs increase and performance stagnates.

Always keep in mind that tasks should never be considered from an isolated perspective. Interact, exchange, and attempt to resolve issues jointly. However, not necessarily at the stage where they pop-up or cause trouble. Strive to overview the complete processing chain. Try to get external input by consultancy, give internal teams the chance to reflect their achievements, and support further progress. Identify causes and effects and establish the solution where overall costs and burden are least. Probably, isolated budgets and task forces optimizing solely their particular field of responsibility are the worst approaches – at least from a scientific or an engineering point of view.

1.1.6 Some Early Information About Solid-state Properties

It may happen that synthetic chemists may not even be aware that they are describing important properties of the materials used as starting materials (reactants) for a reaction or as outcome thereof (products, by-products) in the synthesis procedure that is documented in the (electronic) laboratory notebook. This information may be very valuable initial information for a solid-state or formulation scientist when it comes to further investigation and development of the compound. Table 1.2 illustrates some types of solid-state-related information that could be extracted and questions that may arise from synthesis descriptions. As a consequence, the more detailed such a procedure is documented, the more information can be derived.

A basic training for synthetically working staff is recommended to teach them about what may be relevant information for subsequent solid-state investigations. For example, failing attempts with other solvents for extraction or some early solubility tests are worth to be documented and to be handed over when the synthesis is transferred to another lab, e.g. for resynthesis, further optimization, or scale-up. However, even more important is a clear, extensive, and unambiguous documentation that enables someone who wants to reproduce the results or wants to scale-up the reaction to do so.

1.1.7 Digitalization (Not Only) in the Laboratory

1.1.7.1 Prerequisites – Technology and People

Digitalization is more than digitization. While the latter means transferring analogue data into a digital version, i.e. scanning a piece of paper to create an electronic JPEG or PDF document, the former term “digitalization” is more comprehensive. The Gartner IT Glossary [37] defines digitalization as “the use

Table 1.2 Example for a synthesis procedure.

Description	Information on properties
A 250-ml three-necked flask was charged with 105 ml ethanol 1.30 g (56.5 mmol) and reactant **1**	Solubility of reactant **1** in ethanol is >1300 mg/105 ml, i.e. >12.4 mg/ml
After the reactant 1 was dissolved upon stirring, 4.70 g (49.9 mmol) compound 2 in 20 ml ethanol and 8.56 g (69.6 mmol) compound **3** were added.	Reaction time for dissolution (not specified) Was compound **2** dissolved or suspended?
The solution was boiled under reflux and moisture exclusion for 2½ hours.	Was it a solution from the beginning or dxfissolve the reactants slowly upon reaction? The reaction (or reaction product) is sensitive to hydrolysis.
The next day, the ethanol was distilled off and the residue was dissolved in 35 ml of 5% sodium hydroxide (NaOH) solution	Reaction product is stable at elevated temperature, stable under basic conditions and soluble in NaOH ($c = 5\%$) Was it a solution or suspension the other day?
The solution was extracted five times with 20 ml *tert*-butyl methyl ether (TBME) in a separating funnel	Product is soluble in TBME
Subsequently, the solvent was stripped off yielding some grams of a yellowish crystalline powder	Evaporation crystallization is possible The color may indicate that some impurities remained How has crystallinity been proved? by XRPD? Which crystal form resulted? Evaporation may lead to amorphous material or metastable polymorphs Is cooling crystallization also possible?

of digital technologies to change a business model and provide new revenue and value-producing opportunities; it is the process of moving to a digital business."

Referring the example of scanning the paper, digitalization addresses the causes and effects of doing the scan. "Scanning" could bring additional value by reducing shelf or storage room for archiving; applying object character recognition techniques to the electronic document enables searching for terms and implementing the data in more complex business process, e.g. for electronic implementation of the scanned data into an Electronic Lab Notebook (ELN).

However, looking into laboratories today, one might get the impression that digitalization is yet a challenging task, and digital transformation, as remarked by Gartner [38] "can refer to anything from IT modernization" and is indeed interpreted as anything related to IT. Initiatives by senior management [39] eventually force actions in the laboratories. However, this desirable situation finds its

limitations in reality. Machine learning (ML), for example, is a topic of general interest and concern. Unfortunately, there is a lack of experiences and competences and if there are no resources or budget for data analysts or data scientist than it is advised to companies to educate employees from R&D (i.e. domain experts) in these technologies [40]. As long as this expertise has not yet entered laboratories, even implementation of basic digitalization solutions does not take place everywhere. Still, experiments are documented in paper lab notebooks and Excel sheets are (mis)used as databases and represent the foundation of the daily work in many enterprises. Basic principles of database practices (e.g. normalization) are not always applied. Information is filled into Excel sheets in a manner that would require additional, yet unnecessary workload to tidy the data for automated analysis by ML techniques. As an example, spreadsheet cells become united to look nicely or become filled with unformatted and inconsistent types of data. Hopefully unknowingly, but consequently increased efforts are necessary to extract the information automatically, yet even manually. Therefore, training in basic IT principles is essential to raise the chance to modernize, i.e. digitalize, laboratory workflows.

In the end, it is all about people, their attitude, habits, and "kingdoms." The latter refers to another important preventer of rapid and exhaustive implementation digitalization: the tendency of protecting and shielding domain areas, like synthesis, biological or analytical data, and reports from external (but in-house) inspections or accesses. Being afraid of nonexperts to misinterpret data or tear information out of the original context leads to establish protection routines, either physical or organizational barriers.

Consequently, advice for starting (or accelerating) digitalization is to identify domain experts who have an affinity and attitude toward IT topics and love to develop visions and who have the ability to transport these visions to their colleagues and encourage progress in digitalization and empower these talents to reorganize workflows, if necessary beyond borders of laboratories or departments. To prevent frustration, it is recommended to harvest the low-hanging fruits first, i.e. start small in an area, e.g. laboratory, that is under supervision of the domain expert and select primarily staff willing to follow suggestions for innovative solutions. Educate domain experts not just in technological topics, but also encourage continuous professional development of soft skills, like innovation management or leadership.

1.1.7.2 Connect Data and the Right Information from Synthesis and Analysis

Not only for solid-state experiments, there is a necessity to connect information from synthesis with analytical data. Especially in light of digitalized workflows, proper naming of samples is necessary to facilitate the interpretation of results. In industrial environments, often multiple experiments are performed in short time or even in parallel.

Awareness of which experiments shall be and were performed and at what stages samples should be or were taken as well as proper coding of the experiments and especially the samples and their characterization, i.e. the analytical results,

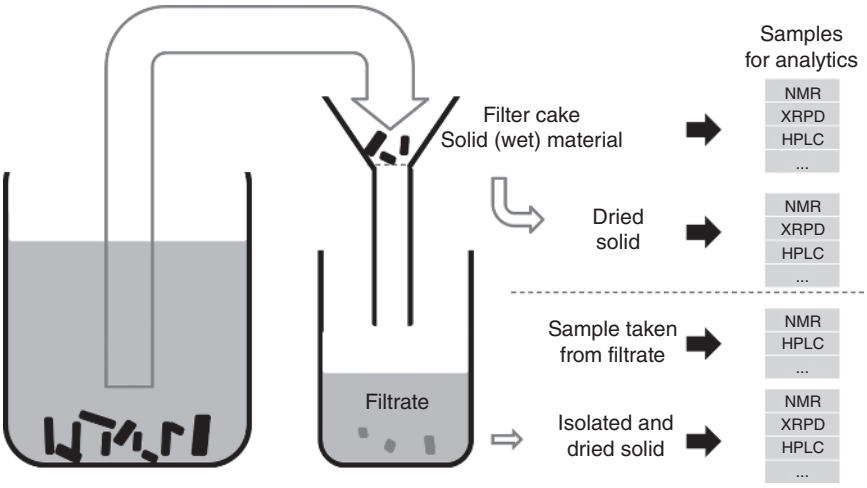

Figure 1.4 Sampling procedure for a filtration process.

is key for accurate and quick interpretation and consequently knowledge generation.

Figure 1.4 illustrates potential sampling steps for a filtration. During isolation of a solid from a suspension, various solid materials occur. First, there is the filter cake. Depending on the filtration procedure applied, it may be pre-dried applying an air or nitrogen flow going through the wet solid. This filter cake is typically transferred to a dryer (e.g. a vacuum oven), where it is usually dried until no further mass loss is observed. Below the filter, there is the filtrate, which is a liquid and it occurs that subsequent precipitation or crystallization happens out of the filtrate. This accidently generated solid material should subsequently also be isolated and analyzed in a wet or dried state. These considerations on awareness on sampling procedures apply not only to laboratory experiments but also to piloting and manufacturing of DSs and DPs.

To understand material properties and changes throughout the process, first the right information must be derived. For example, in case of the filtration experiment, the wet filter cake should not be exposed unconsciously to subsequent sample preparation when the solid form, maybe a solvate, shall be determined by XRPD. Sample preparation like drying or storing the sample in a fridge may alter the solid form, and consequently, false conclusions can be drawn from the analytical investigations. Even worse, when the sample shall be investigated by various analytical methods (probably in different laboratories) and each sample is treated differently on its way to the measuring device. The results coming out of these investigations may not reveal a clear picture, i.e. the results are inconsistent. For example, it maybe that thermal gravimetric analysis (TGA) reveals a mass loss indicating existence of a mono-solvate, but the XRPD shows the pattern of an ansolvate.

A prerequisite to be able to collate analytical results accordingly is meaningful naming or coding of experiments, materials, and samples. It sounds obvious but

unfortunately, sometimes not enough care is spent on the coding of samples that enables

(a) correct assignment to the process step where and when the samples were taken
(b) automatic collation in a data management system of the results of various analytical methods.

An inefficient approach of sample naming is attempting to type "all" information about the synthesis conditions (e.g. temperature, solvent, catalyst used) or material properties (e.g. enantiomer, solid form) in the sample name. This may work for exploratory experiments where one single researcher tries to keep track of his (initial) efforts for a small project but is doomed to fail in a professional industrial workflow involving multiple users and laboratories.

The solution to keep track of synthesis conditions and analytical information efficiently is some kind of data management system. That may be a paper notebook, but the analogue format of paper lacks flexibility to replicate, analyze, visualize, aggregate, and report information. Today, an electronic format, a digitalized solution, appears to be mandatory. Worksheets may do the job but far more efficient, especially in complex industrial organizations, are dedicated systems like electronic laboratory notebooks (ELNs), laboratory information systems (LIMSs), databases for the various analytical datatypes, knowledge management platforms, or interconnected combinations of those systems. These systems can simplify ensurance of data integrity and should be properly selected to match the individual needs of the laboratories and users and their roles. Furthermore, it should not be forgotten that implementing, maintaining, extending, and developing such systems enforces overhead which typically is not appreciated by senior management. The business case considering efforts and returns must be made up by every organization itself.

1.1.7.3 Contributions and Choices

Sometimes it is hard to find the appropriate equipment, be it hard- or software, that fits to the needs of the laboratory or the staff working there. One reason might be that decisions on product features are often driven by manufacturers on technical reasons, causes to ensure compatibility to older systems, or by innovative minds prospecting and anticipating future needs. Quite intelligent is approaching the customers and listening to the "voice of the customers" [41] or even better identifying the needs unknown or not even expressed by the customer as propagated by innovation management. It is attributed, probably falsely, to Henry Ford that customers would rather wish "faster horses" instead of thinking in new, innovative dimensions like "cars" [42]. Fortunately, the latter approach is followed as witnessed by numerous questionnaires, conferences, or user group meetings organized or sponsored by manufacturers. Serving not only to raise awareness about latest product developments (i.e. promotion) but also to get a better understanding about the market's desires is a driving force. Eventually raising market share and turnover is the ultimate goal for the manufacturer. Nevertheless, reaching this objective is under control of the customers in the laboratory that claim their needs, decide for systems, and continuously raise their voice and actively contribute to device, system,

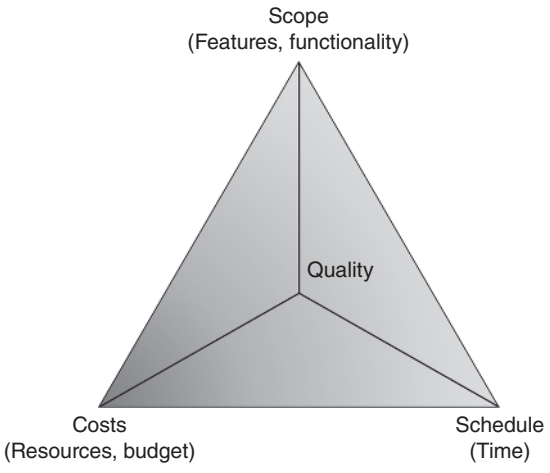

Figure 1.5 Triangle of project management.

and software development. It is worth to spend some resources (time and budget) on contributing to systems that are business critical for the respective laboratory. Giving feedback on bugs, naming desired changes or modifications for interfaces, or expressing functional requirements is essential to direct system suppliers in the right, the customer's, direction. If the supplier is not willing or able to listen and act, then customers have the choice to vote with their feet.

However, what is the right direction to go? Which device or system fulfills the needs of the various stakeholders best? One foundation is to get an overview on the market and understand pros and cons of the various solutions. Define your objective and requirements first, identify your current standpoint, and then identify the various paths to proceed and options you have. Evaluate appropriate solutions and suppliers. Make use of the various tools to get market transparency. Go to fairs, attend conferences, attend webinars and seminars, and search the Internet for product information. However, be careful with experiences posted anonymously. Find advice you can trust. Either by recommendation of colleagues or by other customers you might have identified on focused user group meetings. Weigh disadvantages and advantages. What is a disadvantage for the other one might be advantageous for you and vice versa. Be aware that good decisions require efforts on your side. The options you have reflect the triangle of project management (Figure 1.5). In the center, you get the maximum of quality with the most comprehensive scope instantaneously at no costs. Real live projects are always a trade-off. If you do not have persons with the right skills, you can spend money hiring them. If you do not have the money, you will get poorer quality or a less number of requirements sufficiently addressed or it will take longer time to finish the project. Eventually risk management tells at what levels the project is managed at best.

1.1.7.4 Application of Digitalization

Certainly, the main and basic starting point is digitalization of the general daily work. Historically, introduction of calculating machines and substitution of type- and telewriters can be considered as the starting point for the digital revolution

reaching to the masses. Today, knowledge in basic office solutions, like text processors, spreadsheets, email programs, and ability to search the Internet, is a basic request in all job announcements.

In addition, more specific talents are ask when it comes to complex tasks and applications that are more and more part of industrial workflows, exemplified by the ability to insert basic information into information systems and knowledge of how to query databases. Often welcomed expertise are skills to create databases and write software applications, starting with macros or python scripts for data analysis but leveling up to implementation of automated data analysis by means of ML or artificial intelligence (AI) or more complex software solutions implemented in the laboratory workflow.

A part of these requirements is a necessity to apply and transfer general digitalization solutions to applications in the expert domain. Staff and management need to familiarize with domain-specific software. In the field of solid state, there are numerous analytical devices in use that create data files that need to be evaluated, interpreted, and understood. This process is often be accompanied by third-party software that, for example, calculates physicochemical properties, simulates XRPD pattern, visualizes, analyses, or predicts crystal structures. Last, but not least, it is important to have an idea, if not a vision and thorough experience, how individual available and potential solutions can be assembled and integrated to enhance comfort, efficiency, and reliability of daily tasks and build a seamless workflow. Figure 1.6 might give an impression on the various levels and complexity for digitalization solutions in a laboratory environment. However, it has to be considered that the complexity of implementation and use of software solutions always go hand in hand with

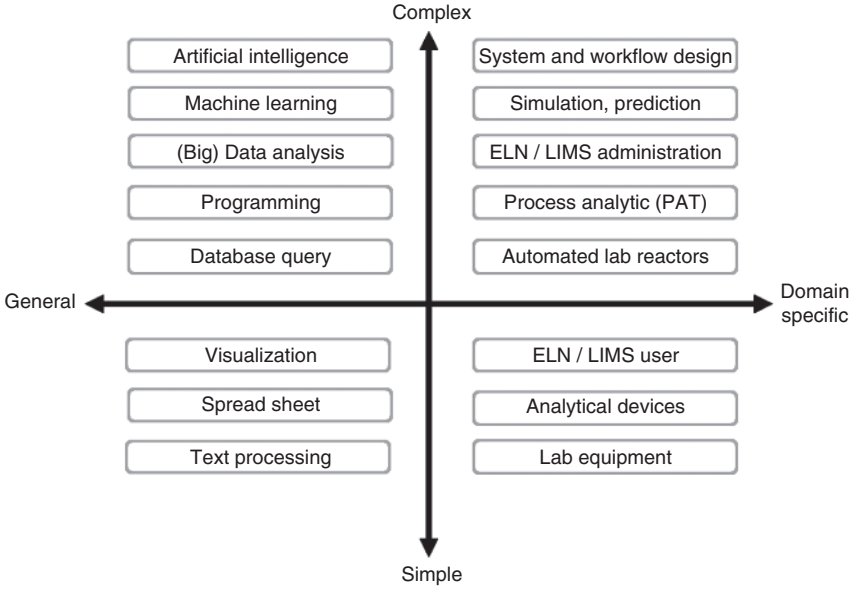

Figure 1.6 Level and complexity of digitalization.

the skills of the users. Furthermore, application of general tools for domain-specific purposes always requires domain experts that support design, implementation, and maintenance.

1.1.7.5 Fully Digitalized Infrastructure

Categorization of the various IT systems used within a laboratory in hierarchical order with respect to complexity and criticality for business aspects is meaningful. This supports definition of objectives and where to start (or continue) digitalization. A pyramid naming the types of systems visualizes for a single department or laboratory this hierarchy. From bottom to top, the number of devices typically decreases, whereas the complexity and criticality increase. First, interdependencies with this departmental pyramid should and must be considered. Remove ideological and technological barriers. Ensure seamless mutual interoperability of the systems as well as data integrity. Next, identify and implement critical interfaces to ensure effortless operation of the departmental systems. Focus on satisfying the needs of all stakeholders – within the pyramid and beyond. Start with simple and most useful tasks and progress with the more complex and less important ones. Never forget justification of actions by ensuring return of investment, competitive advantages, or fulfilling regulatory requirements.

Last, try to interconnect systems of various departments and external contributors wherever meaningful (Figure 1.7).

Exemplified for a solid-state laboratory and displayed on a more detailed IT and laboratory system and technology level, a fully integrated IT environment (Figure 1.8) comprises systems like

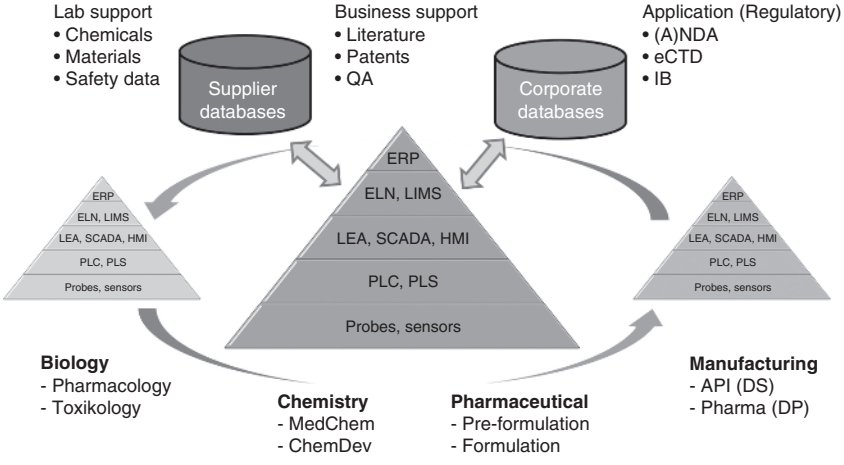

Figure 1.7 Hierarchy and Interoperability of departmental IT systems. ERP, enterprise resource planning; ELN, electronic laboratory notebook; LIMS, lab information system; LEA, lab execution and analysis system; SCADA, supervisory control and data acquisition; HMI, human–machine interface; PLC, programmable logic controller; PLS, Prozessleitsystem, i.e. distributed control systems (DCS); DS: drug substance; DP: drug product; QA: quality assurance; (A)NDA: abbreviated new drug application; eCTD, electronic Common Technical Document; IB, investigators brochure.

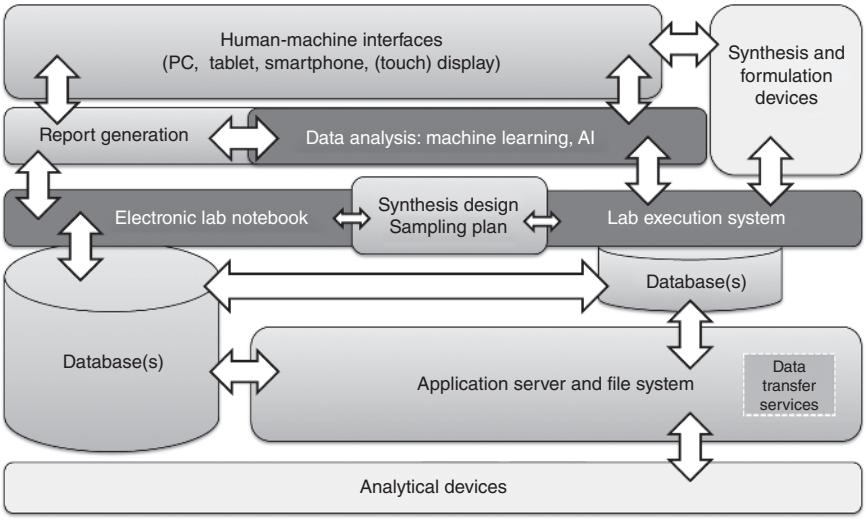

Figure 1.8 Fully digitalized IT and lab system landscape for a solid-state laboratory.

- (Automated) lab reactor systems (synthesis and formulation devices)
- analytical devices (X-ray, spectroscopy, imaging, chromatography, stability, dissolution, PAT probes)
- server and automation services (hardware, software)
- design and planning tools
- ELN and database systems
- data analysis and reporting tools
- human–machine interaction (HMI) devices (PC, tablets, smartphones, etc.)

Such fully digitalized infrastructures (Figure 1.8) have already been successfully implemented in the past. Many efforts are required to configure and adopt out-of-the box solutions and interfaces between the systems. However, attempts to harmonize data exchange standards may simplify implementation and maintenance. Yet, skilled staff and professional support is a prerequisite for implementation, optimization, and maintaining integrated high-end systems operable. One of the most important aspects, as for many projects and business processes, is communication. Communicate and discuss

- needs to keep stakeholders satisfied and
- intended changes to ensure seamless and continuous interoperability of systems.

1.1.8 Basic Terms and Concepts in the World of Solid State

1.1.8.1 Crystalline and Amorphous

Typically, a crystalline material is understood as having long-range order in all three dimensions of space (see Figure 1.9a).

Order means periodic arrangement of smaller units (atoms or molecules) that is mathematically described by symmetry operators. The International Tables of

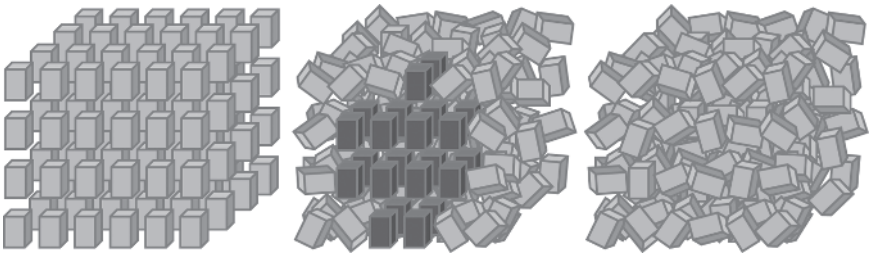

Figure 1.9 (a) Arrangement with long-range order, (b) mainly amorphous, arrangement without long-range order, to some extent local order exist, (c) completely amorphous.

Crystallography lists 230 space groups that represent the manifold of arrangements of potential symmetry elements that are used to describe periodicity in crystal structures [43].

Amorphous material lacks the periodicity over a longer range (see Figure 1.9b and c). Therefore, an X-ray powder investigation would not result in a pattern with narrow and distinct reflexes but with one or more broad halos. The borders may be fuzzy. Local order and its extent may be recognized with solid-state nuclear magnetic resonance (ssNMR) spectroscopy [19, 44] or pair distribution function (PDF) analysis applied to XRPD [45–48].

Various analytical methods can be used to determine qualitatively and with additional efforts quantitatively whether a sample is mainly or partially crystalline or amorphous. For example,

- Microscopy
  - Crystalline samples of pharmaceutical compounds often exhibit birefringence. The sample must be analyzed using polarized light using cross-polarized optical filters.
- X-ray diffraction
  - Crystalline samples diffract radiation in the wavelength of X-rays (e.g. copper radiation has a wavelength of c. 1.54×10^{-10} m). This results in either distinct diffraction spots in case of single-crystal diffractometry or reflexes in an X-ray powder diffractogram.
  - Even in case of no distinct Bragg reflexes present, a powder diffractogram can be used to determine the extent of short-range and long-range order, e.g. by applying the methodology of fast Fourier transform (FFT) analysis and PDF analysis.
  - Single-crystal X-ray diffraction (SCXRD) data are important to simulate the XRPD based on the structure to confirm phase analysis. Furthermore, SCXRD enables the determination of identity including the absolute stereo configuration of compounds.
- Thermal analysis
  - Differential scanning calorimetry (DSC) may reveal glass transition, melting, and phase transitions.
  - TGA may show mass loss (solvent) or decomposition.

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

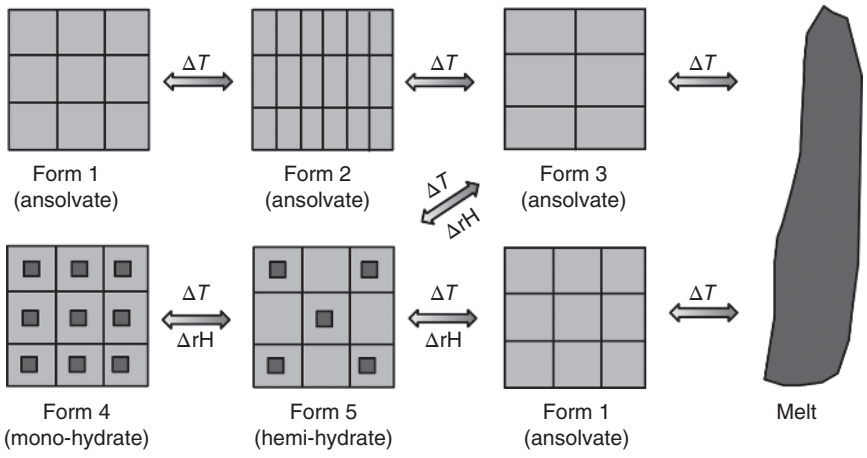

Figure 1.10 Schematic representation of potential interconversions between polymorphic and hydrated forms and melt upon changing temperature (ΔT) and/or relative humidity (ΔrH). Pathways depend on conditions.

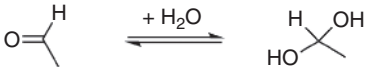

Figure 1.11 Acetaldehyde, a geminal diol – an organic compound "containing" water.

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].

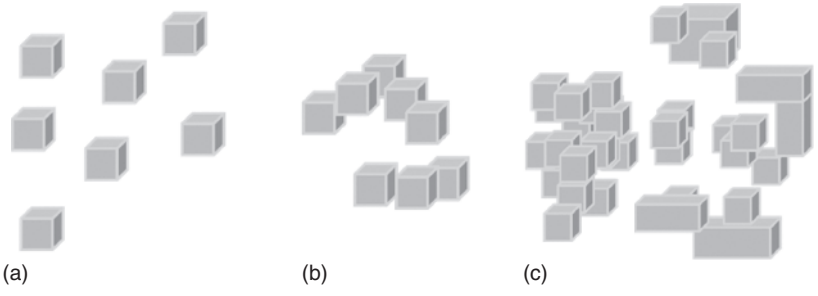

Figure 1.12 (a) Dispersed primary particles, (b) aggregates, and (c) agglomerates.

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).

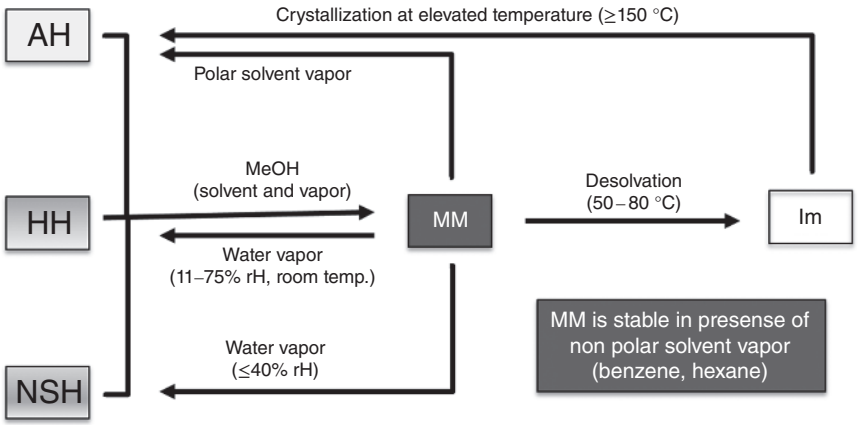

Figure 1.13 Polymorphic landscape derived from experimental findings. MM, mono-methanolate; AH, anhydrate; HH, hemi-hydrate; NSH, non-stoichiometric hydrate; Im, intermediate form; MeOH, methanol; rH, relative humidity.

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.

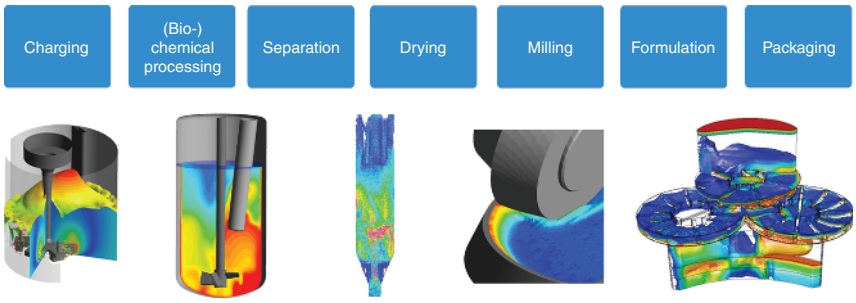

Figure 1.14 Various applications for simulation of chemical and pharmaceutical unit operations. Source: Courtesy of aixProcess GmbH, Aachen, Germany.

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

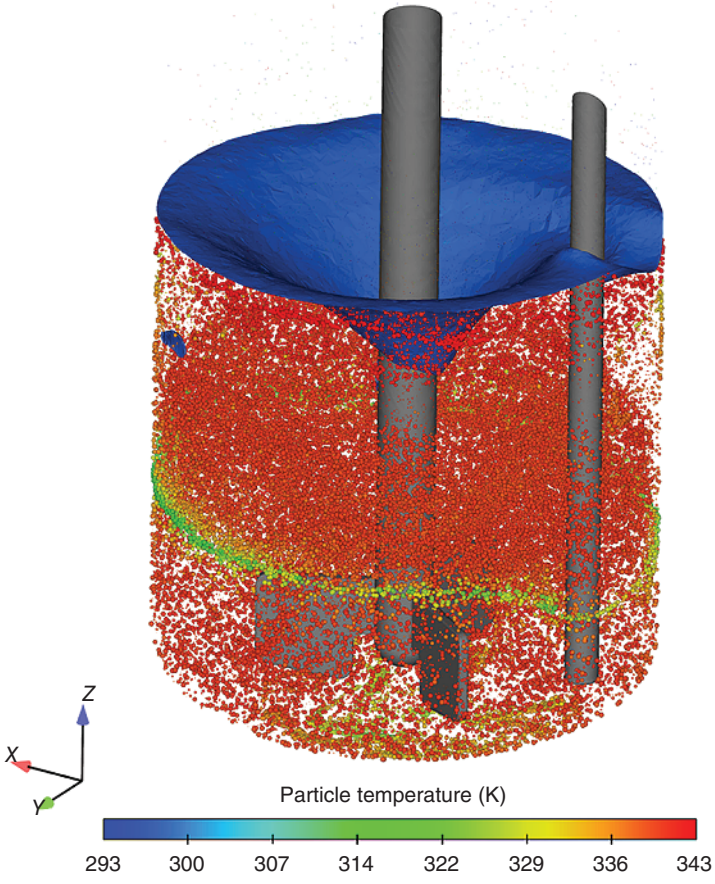

Figure 1.15 Calculated temperature distribution after seeding in a cooled mixed vessel in 100 l scale. Source: Courtesy of aixProcess GmbH, Aachen, Germany.

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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