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Rantanen, Jukka

Elsevier B.V.
2023-11-30

Rantanen, J, Rades, T & Strachan, C 2023, 'Solid-state analysis for pharmaceuticals : Pathways to feasible and meaningful analysis', Journal of Pharmaceutical and Biomedical Analysis, vol. 236, 115649. https://doi.org/10.1016/j.jpba.2023.115649

http://hdl.handle.net/10138/568408
10.1016/j.jpba.2023.115649

Journal of Pharmaceutical and Biomedical Analysis 236 (2023) 115649

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.journals.elsevier.com/journal-of-pharmaceutical-and-biomedical-analysis

Solid-state analysis for pharmaceuticals: Pathways to feasible and meaningful analysis

Jukka Rantanen [a,1,*], Thomas Rades [a,1,*], Clare Strachan [b,1,*]

[a] Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark
[b] Faculty of Pharmacy, University of Helsinki, Finland

ARTICLE INFO

Keywords:
Solid-state properties
Analytical techniques
Sample preparation
Product performance
Dosage form
Process analytics

ABSTRACT

The solid state of matter is the preferred starting point for designing a pharmaceutical product. This is driven by both patient preferences and the relative ease of supplying a solid pharmaceutical product with desired quality and performance. Solid form diversity is increasingly prevalent as a crucial element in designing these products, which underpins the importance of solid-state analytical methods. This paper provides a critical analysis of challenges related to solid-state analytics, as well as considerations and suggestions for feasible and meaningful pharmaceutical analysis.

1. Introduction

Employing a drug in the solid state of matter is the most common strategy and usual starting point for designing a pharmaceutical product. The main reasons for this approach are better patient compliance and product stability of solid-state systems, when compared to liquid-based products. It has been well documented that the molecular packing of both the active substance and excipients in the solid state affects the performance of pharmaceuticals [1]. Furthermore, the diversity of solid forms is, on one hand, increasing, and on the other hand, being used increasingly as a key element of product design, including single component systems (crystalline, amorphous, as well as intermediate forms of order) and multi-component systems (e.g. salt, co-crystal, and co-amorphous systems). This underpins the importance of characterizing the solid form composition of a medicinal product very carefully. At the same time, the fast development of solid-state analytical instruments, data analytical and computational methods, as well as process analytical technologies have enabled a more detailed characterization of solid matter, even as a part of complex dosage forms. A key element in risk-based drug development is the early detection of the ideal solid form based on clinical relevance [2,3]. All these developments point towards the important role of understanding solid form diversity and the selection of the most informative and feasible solid state analytical methods as a part of the overall drug development process. This paper will critically discuss these challenges and highlight the key aspects of importance for feasible and meaningful analytical characterization.

2. Selection of solid-state analysis techniques for feasible and meaningful analysis

Solid state analysis is now a central part of many (pre-)formulation research and development activities. The basis for such efforts is the convergence of technological, regulatory and financial influences: the increasing proportion and awareness of drugs with increasingly complex solid-state form behaviour can affect their pharmaceutical performance, the emergence of an array of new and improved solid state analytical technologies for both laboratory and manufacturing environments, the development of computationally feasible and user-friendly data analytical methods and platforms, regulatory authorities desiring or requiring solid state investigations, the implementation of harmonised quantitative analysis guidelines, and, finally, intellectual property considerations.

Despite the increasingly thorough solid-state analysis in (pre-) formulation development, implementing solid-state analysis that is both feasible and meaningful, i.e. predictive of pharmaceutical performance in practice, remains challenging. Firstly, it is generally not feasible to employ every possible analytical technique for a particular solid-state application. One of the first considerations is therefore, which technique(s) to use? The toolbox of commercially available solid-state

* Corresponding authors.
E-mail addresses: jukka.rantanen@sund.ku.dk (J. Rantanen), thomas.rades@sund.ku.dk (T. Rades), clare.strachan@helsinki.fi (C. Strachan).
[1] All authors contributed equally.

https://doi.org/10.1016/j.jpba.2023.115649
Received 18 May 2023; Received in revised form 12 August 2023; Accepted 13 August 2023
Available online 19 August 2023

analysis techniques is extensive, with each technology having its own theoretical and practical features, advantages and disadvantages. Additionally, new techniques, for example those based on optical technologies, continue to emerge. The principles and practical aspects of the most commonly applied techniques have been extensively described in several reviews, book chapters, and special issues of scientific journals [4–10]. There are numerous application-dependent considerations when selecting the (most) suitable technique(s) for feasible and meaningful solid-state analysis. For example:

1. What level of sensitivity, specificity and/or robustness are required?
2. Should more than one analytical method be employed?
3. How does one define when the sample is amorphous, crystalline or nanocrystalline?
4. What type of sampling is appropriate? For example, should the sample be analysed in situ in a specific environment (e.g. during processing, or administration), is sample preparation possible, and is bulk, surface or even spatially resolved sampling more appropriate?
5. How should the data be analysed and interpreted?

The first four questions are considered here through illustrative case studies and the last one, focusing on data analysis challenges, is discussed later in a separate section of this paper.

2.1. *Sensitive kind – finding the right method(s)*

In considering the first two questions, the turn of the millennium saw a flurry of activity directly comparing techniques for solid state analysis and quantification [11–13]. A good example of this is the study by Lehto et al., who directly compared seven analytical methods (X-ray powder diffraction, isothermal microcalorimetry, solution calorimetry, Raman spectrometry, differential scanning calorimetry (DSC), and gravimetric moisture sorption) to quantify amorphousness in the same spray-dried lactose samples [14]. The authors did not attempt to determine limits of detection, but rather compared the quantitative results for the same samples with the different methods. In this particular case study, the methods were largely in agreement, with the exception of DSC. Nevertheless, the authors emphasised employing multiple, preferably orthogonal (thermal, spectroscopic and/or microscopic) analysis methods to reduce the risk of erroneous quantifications. In general, a single analytical technique should not be relied upon.

2.2. *Wrecking ball - amorphous, crystalline or nanocrystalline?*

To address question three, namely "How does one define when the sample is amorphous, crystalline or nanocrystalline?", again the sensitivity of the different techniques to molecular level order in the sample must be considered. There is an order continuum from amorphous to crystalline (Fig. 1), as well as the possibility of trace level crystalline or amorphous contamination and other structural and thermal variations between differently prepared and stored solids, all of which complicate the determination of crystallinity. Different analytical techniques are sensitive to different lengths scales of order, and thus apparently contradictory results may be obtained with different analytical techniques. One such challenge highlighting this complexity is the preparation of amorphous material, for example, by milling. Mah et al. [15] employed dry ball-milling to convert crystalline glibenclamide into its amorphous form. The powder was analysed after different milling times by three orthogonal techniques: X-ray powder diffraction, XRPD (in the form of disappearance of diffraction peaks), Raman spectroscopy (as spectral changes detected with principal component analysis (PCA)), and DSC (detected as a change in onset temperature of crystallization). The samples were first "X-ray amorphous" (after 30 min of milling), then "Raman amorphous" (after 60 min) and finally "DSC amorphous" (after 180 min). These differences in sensitivity can be attributed to the different phenomena being probed by these techniques (Fig. 1). While X-ray powder diffraction is sensitive to the presence of lattice defects, Raman spectroscopy is sensitive to shorter-range intermolecular order. On the other hand, DSC induced crystallisation may be sensitive to the presence of residual crystallites during milling, which can remain at levels below the sensitivity of XRPD and Raman and/or infrared spectroscopy. It is clear with this example that a single analytical technique should not necessarily be relied upon.

Which is the most 'accurate' or, more realistically, 'meaningful'

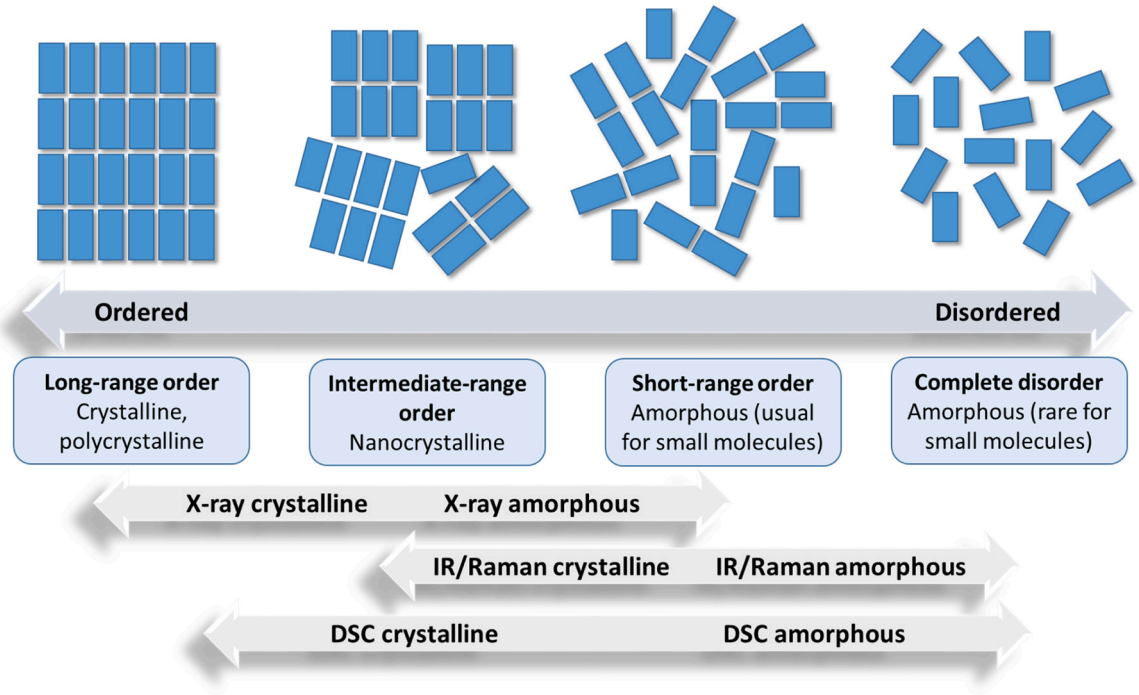

Fig. 1. Simplified schematic representing degrees of order experienced in pharmaceutical solids (not to scale) and their classifications, as well as the concept of different sensitivities to length-range order of commonly employed solid state analytical techniques. Adapted from [7,21].

analytical technique? This depends on the purpose of the solid-state analysis and the relevant critical quality attributes. If storage stability and dissolution behaviour are the primary concerns, their correlation with the crystallinity results obtained with the different techniques should be investigated. In the above example, the DSC analysis (onset of crystallinity) was the analytical technique that was best correlated with both storage stability and dissolution behavior, and therefore the most meaningful technique [15].

2.3. Nothing else matters – on the importance of sampling

Another crucial factor in technique selection is sampling: different analytical techniques have different sampling geometry, preparation, and spatially resolved analysis possibilities. Prerequisites specifically for process analytical technology (PAT) applications are considered later in this paper. Here the influence of surface versus bulk sampling on meaningful analysis is briefly considered. Some commonly available analytical methods (also depending on the sampling setup) are strongly surface biased (e.g. Fourier transform infrared (FTIR) spectroscopy with an attenuated total reflective (ATR) sampling accessory), while others have no surface bias (e.g. DSC). Crystallisation is often initiated at the surfaces of drug particles or dosage forms due to higher surface molecular mobility and stress [16–18]. As a result, more surface biased techniques can suggest faster crystallization than bulk analysis techniques. However, surface crystallinity can be a much more meaningful property to investigate than overall crystallinity when considering critical quality attributes such as dissolution (since dissolution occurs at particle surfaces) or powder flow [19,20].

The examples described involved analysis of unformulated drug or excipient. However, the principles are also applicable to multicomponent intermediates and dosage forms, with additional challenges arising due, for example, sensitivity and specificity in multicomponent systems. A recent review entitled “Industry White Paper: Contemporary Opportunities and Challenges in Characterizing Crystallinity in Amorphous Solid Dispersions” [8] succinctly encapsulates leading industrial perspectives about important theoretical and practical considerations when embarking upon solid state analysis of amorphous solid dispersions (ASDs). Numerous aspects that the paper addresses, including sensitivity (including limit of detection), specificity and capabilities of the most common and commercially available analysis techniques are relevant to other solid dosage forms, including conventional heterogenous physical mixtures.

3. Connecting solid state behaviour to biopharmaceutical performance

Whilst the link between solid-state structural properties of pharmaceutical solids and their quality attributes is increasingly understood, as briefly discussed in the previous section, the link between solid-state properties and *in vitro* and *in vivo* behavior is much less established. Since the majority of solids in pharmaceutical development are intended for oral administration, dissolution or release (and absorption) appear to be the first link between the solid dosage form and the body. Even if other routes of administration are used, such as inhalation, the drug in solid particles has to dissolve to be absorbed. As such, investigation of the link between solid properties and dissolution (*in vitro* and *in vivo*) appears of crucial importance to fully elucidate the performance of solid dosage forms. Examples of this are phase separation phenomena that might occur during storage of amorphous solid dispersions, and their consequences for dissolution [22]. Other examples include the influence of drug load in amorphous solid dispersions on the dissolution of the drug [23], as well as the presence or absence of liquid-liquid phase separation upon administration of amorphous solids [24], but also, for example, the formation of hydrates from an initially non-hydrated crystalline form of the drug during dissolution [25]. Even though it may be argued that dissolution measurements are not a solid-state characterization technique, it seems obvious that dissolution behavior should be included in the physical characterization of pharmaceutical solids, simply due to its crucial importance for the performance of the drug product.

It is advantageous to investigate these solid-state properties in an *in vitro* set up, but one might argue that ultimately, we wish to know if any of the observed phenomena actually also happen *in vivo*. There is very limited data available for example on precipitation of drug in the small intestine, and the analytical techniques currently used in the context are not particularly sophisticated with regard to solid state properties [26]. Rather it is the sampling procedure that is cumbersome, and unlikely to develop into a routine method. Thus, perhaps a better understanding and use of investigating solid-state properties upon dissolution can be gained by increasing *in vitro–in vivo* correlation between an *in vitro* method and biological performance, usually measured in pharmacokinetic studies. Progress here can be seen in the development of more and increasingly sophisticated dissolution/permeation setups [27] rather than simple dissolution measurements, but the investigation of solid-state conversions under these conditions is not as advanced as it should be. This calls for inclusion of solid-state properties (and their changes during dissolution) in any *in vitro* set up that is meant to be biorelevant, and preferably in real time. This can be achieved in more detail for example in synchrotron facilities [28] or with rapid spectroscopic (imaging) setups [29–31]. In an earlier communication, such inclusions have been described as “physico-relevant” dissolution, to name just one example [32].

Inclusion of the “fate” of, for example, an amorphous solid dispersion upon biorelevant dissolution is crucial, to understand a possible bioavailability enhancement of the formulation. It has become increasingly clear, that solubility in enabling formulations can mean a lot of different things including molecular dispersion of the drug molecules, amorphous droplets, micelles and other colloidal structures, either due to colloidal properties of the polymers used to prepare the ASD or from endogenous surfactant type molecules, such as bile salts, in the GI tract [33] (3). Here solid-state methods meet the colloidal world, and the link between or even influence of solid-state properties on the complex dissolution and absorption behavior of drugs will receive much more attention in the future.

4. Single particle solid state analysis contrasted with bulk analysis

An intriguing example of new developments in the analysis of pharmaceutical solids is the characterization of single particles, rather than the average of a collective of particles. Several spectroscopic and optical microscopy methods are potentially suitable for single particle analysis, including polarizing optical microscopy [34], various forms of Raman microscopy [35], and nonlinear optical microscopy [18]. Raman line-focus microscopy revealed the simultaneous existence of various solid forms in a single particle of nitrofurantoin upon increasing temperature [36]. Whilst this can lead to new insights, or may be important in intellectual property rights disputes, a study on a collection of the same particles using low and mid-frequency Raman showed that at least quantitatively, most of the solid forms identified in the single particle measurement played no role in the overall conversion kinetics observed in this particular case [37]. This is not to say that the investigation of single particles is not helpful; it certainly is helpful to know that these elusive polymorphic forms do appear during the transition processes, and that transition processes in a single particle can be much more heterogeneous even on the single particle level than perhaps thought before, but quantitatively such trace levels do not necessarily play a role in the overall transition process. Thus, care should be taken when comparing single particle analysis to bulk methods, as these may not lead to similar interpretations, and may come to different conclusions, that when looked at more carefully, are based on different objectives of the studies. Having said this, the possible impact of trace crystals and

nuclei on solid state transformation processes and pharmaceutically relevant properties may still need to be considered, as illustrated in analyses with for example, polarizing light microscopy [34] and coherent Raman microscopy [18].

Another recently encountered example [38] is the investigation of the cooling of single levitated droplets of a molten drug, to mimic a spray congealing process. It was found that the single levitating particle inevitably started to crystallize at the equator of the droplet, due to the fast rotation of the droplet around itself during levitation. Whilst the observations are certainly fascinating, they are most likely not mimicking the fate of a melted droplet in a spray congealing process.

Scanning probe methods (atomic force microscopy, AFM) can be used to investigate single particle level properties. This approach allows for exploring the mechanical properties of particles and particle surfaces. Nanoindentation is a well-documented approach to characterize and compare mechanical properties of different solid forms [39]. Here, one can measure elastic modulus and hardness of materials from a single particle. This approach has also been utilized for identification of 'soft', 'hard' and 'sticky' areas on particle surfaces, related to differences in the mechanical properties of amorphous and crystalline regions at the surface of a particle [40]. Scanning probe approaches can also be used to investigate dissolution processes in a dynamic mode and provide insights into mechanical properties of a crystal surface during dissolution [41]. Single particle analytical methods can also be utilized to probe the mechanical properties of a particle as a whole and use the particle as a resonator. Different vibrational modes of the resonator (a single particle) can be studied as a function of temperature and further, mechanical characteristics (Young's modulus) can be extracted from this data. Examples include properties of an amorphous sample during the glass transition [42] and dehydration of a hydrate [43]. However, it should again be noted that analyzing one single particle is a time-consuming task and results should be, similarly to scanning probe methods, evaluated critically before drawing final conclusions related to the whole particle population [44,45].

Hyperspectral imaging (HSI) is routinely used as a part of drug development and it has huge potential in high throughput solid form screening. HSI techniques have developed fast and the current instruments allow for automated particle detection and measurement of both particle size and shape parameters combined with a spectral fingerprint of each particle [46]. This has an interesting potential to be extended towards classifying the solid form composition of different particle size fractions, which is known to be critical for functionality of the powder system, such as inhalable dry powder compositions and long-acting particulate injectables. This approach will naturally increase the amount of the collected data dramatically.

5. Can real-time process measurements provide more insight into the final product?

Quality control of pharmaceuticals has been traditionally based on intensive sampling from a batch of the end-product and laboratory-based off-line analysis according to specifications of a given product. This approach does not support implementation of risk-based product design principles, personalized production and more efficient manufacturing solutions, such as continuous manufacturing. There is an increasing interest to move from intense end-product testing towards process analytical technologies (PAT), continuous manufacturing, and ultimately, to a sensor based real-time release testing (RTRT) philosophy [47]. A crucial part of this development is the implementation of PAT tools to provide information related to the solid-state properties of matter during processing.

Laboratory–based analytical instruments can provide detailed understanding of intermolecular interactions and thermodynamics of a given solid state system. Many of these analytical instruments are designed to be used *off-line* in a centralized, clean and robust laboratory environment, and cannot be easily transferred to harsh process environments exposing the instrument to e.g., dust, temperature variation, solvent exposure, and mechanical vibration. During recent decades, spectroscopic tools have been increasingly adapted and intensively implemented in processing and other harsh environments, and near infrared (NIR) spectroscopy has been almost a synonym for PAT in the early years of implementation of process analytics. The selection of spectroscopic solutions for PAT purposes has expanded and the use of, e.g., IR, Raman and terahertz (THz) can now be considered routine solutions [48]. In the future, it is expected that more and more analytical tools can be designed in a way that supports interfacing with the process environment [49].

An additional challenge with laboratory-based measurements is that they are not able to fully mimic the conditions during typical processing steps related to solid pharmaceuticals. This can include a complex interplay related to heat, mechanical stress, presence of excipients, and use of solvents during processing. Morris et al. have introduced an overview of the theoretical basis for understanding and controlling processing-induced transformations [50]. Controlling these transformations in a complex process, such as wet granulation, can be challenging. Wikström et al. have demonstrated this with an example based on interfacing of a high-shear wet granulation equipment with Raman spectroscopy [51]. They showed the effect of mixing speed in the granulator on kinetics of hydrate formation of the model compound. This type of processing involves mechanical stress related to high shear mixing, which leads to particle breakage and generation of 'fresh' crystal surfaces that are prone to solid form transformations. Combining this with the presence of granulation liquid, as well as heat generated by the process, can result in a complex series of processing-induced transformations. The overall transformation process can be even more complicated: imagine a hot melt extrusion process involving a molten polymer in contact with the active substance. Heat transfer from the molten polymer is different from the conditions inside a DSC or TGA pan, which is further complicated by shear forces present during extrusion. This has been exemplified with a case study on dehydration of nitrofurantoin monohydrate, a well-known 'isolated site hydrate' with an extraordinarily high dehydration temperature at around 120 °C. When interfacing a hot melt extruder with an *in line* Raman probe [52], it has been demonstrated that this dehydration occurs already at around 70 °C [53] in a model composition consisting of polyethylene oxide (PEO) and nitrofurantoin monohydrate. Many of these potential transformations occurring during processing will follow Ostwald's step rule. According to this rule, the less stable solid form will appear first and based on the kinetics of related transformations, multiple solid forms can be present simultaneously during processing [54] and in the worst case, the end-product can be a mixture of multiple forms [55]. On the other hand, process induced phase transformations can also be engineered to be part of product design, and controlled formation of co-crystals during granulation or with mechanochemistry [56] has been reported. An interesting alternative strategy is to use 'activation' of the product before administration using, e.g., microwaves [57] and to confirm the quality of the product with spectroscopic tools [58]. The increasing personalization of pharmaceutical products will inevitably lead to increased patient involvement [59] and decentralized production solutions [60], which underpins the need for new analytical solutions.

Innovative particle design involves also other high-energy processes, such as spray drying and the closely related electrospraying process. Spray drying is a well-established method for designing precise particle structures [61] and is readily available at a commercial scale. This process involves fast drying of the feed solution droplets, which can lead to a solid form diversity in the end-product. Lee et al. reported that the solid form of the spray-dried product can be particle-size dependent [62], which makes the process analytical challenge even more demanding. The use of small-scale process development equipment allows for, primarily, understanding the particle formation process, but secondarily, also for selecting the right process analytical tool for

process monitoring and control purposes [63].

It is evident that the analytical tools can be interfaced with the process environment and detailed information related to solid form composition can be directly collected from the moving material. Clear regulatory frameworks exist for doing this, including the US FDA PAT guidance from 2004 and the Ph. Eur. monograph 5.25 Process Analytical Technology from the late 2010 s, but careful consideration is still needed when designing the process interface, i.e., the way in which the probe interacts with the material in the process stream. The PAT tool should be able to measure the analyte of interest

1) without disturbance from other components in the product stream or properties of the process stream, such as flow dynamics and temperature changes,
2) with a relevant measurement frequency considering the kinetics of a potential phase transformation,
3) with consideration of the effective sampling volume of the analytical technique according to the risk assessment (e.g., by changing the optics in the probe), and
4) with careful design of the process interface avoiding sticking of material into the process window.

Potential transformations during processing can proceed via a solution (solution-mediated transformation) or they can appear as solid-solid transformations. This will inevitably affect the appearance and microstructure of the particulate matter, which will make the analytical task even more challenging. To address this challenge, it would be logical to combine information from different analytical instruments and follow simultaneously, e.g. particle size distribution and solid form composition of the material. An additional level of complexity can be added to this by including the analytical signal from the solution phase [64] into this combined [65] analytical challenge.

At the end of the day, investment in such complex PAT solutions should be based on the risk assessment and documented clinical need for controlling the solid form composition of the final product.

6. How do we handle all the solid-state analytical data?

Solid state analysis inherently leads to data describing the system at different levels. The overall risk assessment decision requires combining analytical results from single particles, bulk powders, and the final medicinal product. Collection of all this data is increasingly automated and we can collect information not only as a single univariate measurement result, but increasingly as complex spatial information about variation in a sample of interest. This is obvious with chemical and solid state mapping, which inherently leads to a data analytical challenge. Instead of single point univariate analytical results representing the whole sample, pixel-by-pixel analysis of the sample can be used to explore the solid form variation in the sample. Mapping approaches can be used to explore the solid form composition of the whole dosage form [18,66] or even variation at a single crystal level [36], while, however, still carefully considering the practical relevance of this mapping. This mapping will result in a ‘data (hyper)cube’, where the related mathematics are not always easily communicated. However, it should be noted that both chemical imaging and related data analysis methods already appear as monographs in the European Pharmacopoeia (5.21 Chemometric Methods Applied to Analytical Data, and 5.24 Chemical Imaging). This clearly indicates that chemical (and solid state) mapping can be considered an established methodology in the field and it should be part of the standard solid-state analytical toolbox without major concern to the complexity of related data analytics.

Fast measurement times and the improved sample preparation methods allow for time-dependent measurements on solid-state samples. These time series allow exploration of the kinetics of phase changes and the effect of external factors (e.g., temperature and water activity) on solid form stability. Coupling several spectroscopic methods has been suggested to provide more in-depth insight into solid form transformations [67,68]. The fascinating potential of this approach is that two different techniques can potentially probe different molecular interactions, which can be utilised in understanding the mechanism of changes in a given system. This has been reported by Robert et al. [69] in a study comparing simultaneous low and mid-frequency Raman measurements to investigate dehydration of crystalline small molecule hydrates. A similar philosophy is needed when considering process analytics. Combining analytical signals from several process measurements is especially important when moving towards continuously operating production lines [70,71], where robust data analysis is an absolute requirement.

The development of analytical instruments together with the development of robotics and increasing computer power results in challenges related to data. Storage, handling, and ultimately extracting the relevant knowledge from all the available solid-state analytical information can be overwhelming. High throughput preparative technologies coupled with imaging [72] and the broad arsenal of solid state analytical instruments easily can lead to a situation where the pure visual evaluation and knowledge-based decision making is not practically possible. Different data reduction methods are crucial when exploring the experimental data. In many cases, unsupervised methods (without prior system information input) can be sufficient to provide an overview of the existing data. However, when the complexity of a given system is increasing, deep learning approaches can be useful. This has been documented when exploring the crystal growth data based on optical microscopy [73]. The collected analytical data should be properly utilized in product design. Translation of a high amount of data originating from imaging at different levels (e.g., optical, scanning electron microscopy, chemical mapping), spectroscopic measurements, and high throughput screening philosophy into knowledge about the product itself often requires non-linear methods. The use of fuzzy logic in extracting knowledge from image based information has been reported [74]. This area is developing fast and the integration of data science to pharmaceutical product design is becoming a routine approach [75,76] and machine learning, including artificial intelligence, will be an important part of the broader drug product development process [77,78].

7. Conclusions

Instead of covering all possible solid-state analytical techniques, this paper focused on highlighting the areas we consider to be of most importance when analysing pharmaceutically relevant solid-state properties. An important principle in this work is to use multiple and orthogonal techniques, as well as to carefully consider the fundamental physical phenomena related to the specific method with a focus on the length of order, surface bias and sampling considerations. Many analytical methods allow for a detailed analysis at a single particle level. However, care is needed when using these results for describing a particle population and ultimately, the final dosage form. It is important to keep the patient in mind and move the solid-state analytical methods towards critical quality attributed and testing in more biorelevant conditions. Similarly, it should be noted that off-line analytical work does not always properly describe all the stress that material can be exposed to in the processing environment. Finally, the authors would like to highlight the importance of integration of data sciences into solid-state analyses.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jukka Rantanen reports financial support was provided by Nordforsk.

Data Availability

No data was used for the research described in the article.

Acknowledgements

This work has been supported by NordForsk (Oslo, Norway) - Nordic University Hub project Nordic POP (Patient Oriented Products; project number 85352).

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