Importance of chemical polymorphism in modern crop protection

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Abstract

The development of agrochemical products faces many scientific challenges. After selection of an agrochemical candidate its properties will have to be optimized to guarantee best bioavailability and stability under many different conditions in various formulation types. These challenges are influenced by the solid-state properties of the active ingredient and this makes the selection of an optimized solid-state form of modern agrochemicals at early development stages very valuable. The increasing awareness of the solid state of agrochemicals is reflected in the importance of polymorphism patent applications, which may enhance the risk of litigations. This review aims to present strategies for the solid-form selection process of agrochemical development candidates. It introduces the different techniques for crystallization and analytics and demonstrates the influence of the solid state on different formulation types.

Keywords: chemical polymorphism; organic solid state; polymorphism screening; solid-state selection; crystallization; herbicides; insecticides; fungicides

1 INTRODUCTION

The organic solid state has been receiving increasing scientific attention in modern chemical chemistry. From the beginnings of Mitscherlich’s work on inorganic phases to the increasing implementation of prediction tools for solid-state screenings it has been a very long journey. Today, a number of monographs are available, which demonstrate the fascinating scientific areas of polymorphism and the importance in pharmaceutical chemistry. Unfortunately, the polymorphism of agrochemical active ingredients (a.i.) is still under-represented in the literature.

Interestingly, polymorphism is not the exception but the rule. A statistical evaluation on pharmaceutical a.i. shows that ≈80% of these molecules crystallize in more than one crystalline lattice. The evaluation of the polymorphism screenings of agrochemical a.i. at Bayer AG gave small differences to this statistic. In a number of screenings based on 76 substances, 29 of them were found to be monomorphic. Figure 1 shows the monomorphism-to-polymorphism ratio [Fig. 1(a)] and the number of polymorphic forms per a.i. [Fig. 1(b)].

We should point out that this statistical approach is based on polymorphism screenings, which are aligned to identify the most relevant solid-state forms in the most efficient way in a reduced experimental setting involving only a small number of solvents and crystallization conditions.

Polymorphs normally have different thermodynamic stabilities, melting points and enthalpy of fusion values. Additional properties such as solubility, chemical and physical stability, mechanical stability and the crystalline habitus may vary with the different modifications, and can directly affect the processability and/or the ability to build up the selected formulation type.

The evaluation of the thermodynamic stability of polymorphs is the most important topic under evaluation in polymorphism screenings. The use of the thermodynamic stable polymorph supports the uniformity of product quality by preventing agglomeration of solid-based formulation types through recrystallization of metastable forms. Based on thermoanalytical data and solubility testing as well as slurry conversion experiments, the correlation between the polymorphs has to be evaluated, resulting in the selection of the thermodynamically stable form at ambient conditions.

Currently (at the time of writing in January 2021), 289 a.i. are used in authorized plant protection products in Germany, the majority of them being solids. The most common formulation type for these a.i. are suspension concentrates (SCs), which are extremely sensitive to solid-state changes.

Besides the knowledge of crystalline phases, it is advisable to have an idea concerning the amorphization ability of the a.i. under processing conditions. Mechanical stressing can lead to a loss of crystallinity leading to the creation of an amorphous amount, which will have a dramatic influence on performance and stability of the a.i.
By contrast, the solubility ratio of polymorphs and Beckmann gives. However, in agrochemical development, nanostuctured liquid crystalline particles play in optoelectronic displays. Their special kind of molecular arrangements are well-known between crystalline and amorphous state. Mesophases with 3D order in the molecular arrangement also induces physical instability concerning recrystallization.

Today a new tendency is observed. With increasing molecular weight, the molecular structure of the a.i. contains a higher number of degrees of freedom. That supports the crystallization of hydrates and solvates or the solidification in the amorphous state and influences the solubility and bioavailability of the molecule. Hancock demonstrated that the ratio of amorphous to crystalline solubility can be dramatically high (up to a factor of 1000). By contrast, the solubility ratio of polymorphs is no higher than factor 2 to 5; for anhydrate/hydrate pairs it may be a little bit higher. The loss of a crystalline lattice makes the amorphous state highly bioavailable. Unfortunately, the missing long-range 3D order in the molecular arrangement also induces physical instability concerning recrystallization.

Liquid crystals or mesophases can be seen as a solid form in between crystalline and amorphous state. Mesophases with their special kind of molecular arrangements are well-known in optoelectronic displays. However, in agrochemical development, nanostructured liquid crystalline particles play a role as surfactants. They enable the distribution of the a.i. solution on the surface of the leaves by reducing the contact angles of the droplets sprayed on the plants. The homogeneous nucleation process. These kinds of experiments normally go along with a qualitative solubility testing to select the most appropriate solvents. Evaporation to full dryness can offer very good insights into the solid-state landscape of the candidate under research. At the laboratory scale, varying the amount of starting material may lead to different nucleation processes in one crystallizing dish. Unfortunately, this will not happen in very small compartments where the correlation between interfaces and sample amount is not feasible for solid-phase separations; this is normally the case in high-throughput screening systems. In crystallization procedures required in industry, the control of polymorphism and crystallization frequently is done by seeding the reaction mixture using the crystalline phase with the preferred crystalline lattice.

2 DIVERSITY OF THE SOLID STATE

The creation of a molecular crystalline lattice can result in different entities of crystalline forms. In one component systems polymorphs, mesophases, or the amorphous solid state may occur. These forms have the same chemical identity but can show a wide range of physicochemical properties. Probably the most frequently cited definition on polymorphs was given by McCrone, describing them as different crystalline entities resulting from the possibility to form different crystalline arrangements.

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3 HOW TO GET POLYMORPHS

3.1 Crystallization

In order to build up a crystalline lattice, the molecules have to assemble and interact with each other. The success of this process is interrelated with transport and surface kinetics. The molecules have to find each other on a phase border in more or less disordered surroundings, followed by reassembling. They have to reach the perfect location and orientation on the surface of an already built molecular group. If the molecular transport is much faster than the reassembling process on the surface, the resulting crystals may exhibit disorder in their crystalline lattice, which makes them more sensitive to mechanical stressing and can support amorphization.

The precipitation of a solid form out of solution is driven mainly by the concentration and the temperature of the observed system. By changing these parameters, the system drops out of the state of equilibrium and becomes metastable. An oversaturated solution passes through this metastable status before precipitation occurs. In this metastable area recrystallization will not take place. To start solidification the solution has to come to supersaturation first.

The precipitation will affect the system by reducing the concentration of the solute in the solution. The driving force for the homogeneous nucleation is the reduction of the Gibbs energy G as a function of enthalpy H, temperature T and entropy S.

The formation of the first clusters initiates an increase in the Gibbs energy of the system (nucleation work) followed by decrease during the growth of the small nuclei. These very small crystals have to reach a critical size (critical nucleation radius) to become stable. This size as well as the nucleation work, as a kind of activation energy for nucleation, are related to the perturbation of the equilibrium. The thermodynamic and kinetic aspects of nucleation have been described by Davey et al. and Beckmann.

3.1.1 Homogeneous nucleation process

The homogeneous nucleation takes place in some of the crystallization techniques used for polymorphism screenings and studies. Basic methods which may have a positive influence on the nucleation rate and support the polymorph control are temperature cycling, supersaturation control and altering of solvents. One of the most common is evaporation of solvents. These kinds of experiments normally go along with a qualitative solubility testing to select the most appropriate solvents. Evaporation to full dryness can offer very good insights into the solid-state landscape of the candidate under research. At the laboratory scale, varying the amount of starting material may lead to different nucleation processes in one crystallizing dish. Unfortunately, this will not happen in very small compartments where the correlation between interfaces and sample amount is not feasible for solid-phase separations; this is normally the case in high-throughput screening systems. In crystallization procedures required in industry, the control of polymorphism and crystallization frequently is done by seeding the reaction mixture using the crystalline phase with the preferred crystalline lattice.

**Figure 1.** Statistical evaluation on polymorphism screenings done on agrochemical a.i. at Bayer: (a) ratio of monomorphism versus polymorphism; (b) number of polymorphs per a.i.
3.2 Selection of an optimized, processable crystal form

The development of modern agrochemicals includes the selection of a chemical candidate with high bioavailability and unique mode-of-action. The chosen a.i. should be producible on a large scale and with reasonable costs of goods (COGs). Chemical and physical properties of the a.i. will directly influence the duration of the crystallization step and may increase COGs. For example, the resistance of filtration can be directly correlated to the crystalline habit of the a.i. Needle-like habits, as shown in Fig. 3 for the fungicidal a.i. fluopyram, influence the processability of the substance and can initiate recrystallization during storage of the product.

These properties may be different for polymorphs or pseudopolymorphic forms of the given a.i. and the selection of a crystalline form with better filtration characteristics or a more feasible crystalline habit may support to overcome these challenges.

The technical a.i. must be formulated to be used in a safe and appropriate way. In the agrochemical industry some of the most common formulation types are based on the solid state, which makes them highly sensitive to changes in the crystalline form of the active substance (Table 1).

There is a high tendency for SCs to agglomerate or solidify as a result of transitions of the solid forms, whereas emulsifiable concentrates (ECs) are very sensitive to solvate formation. The crystallization of unwanted solvates implementing one of the formulation additives is well-known and can lead to recrystallization of a less soluble form. Figure 4 illustrates the example of the solvate of the fungicide bixafen and the solvent butyrolactone which recrystallizes during the development of an EC formulation by forming an amide hydrogen bond to the carbonyl group of butyrolactone.

Many physical properties, such as solubility and flowability, can be dramatically influenced by these effects, so that the agrochemical product may become unusable, leading to customer complaints. In general, the evaluation of the thermodynamically stable form is the first step to be completed in the polymorphism screening. The characterization of this crystalline form will clarify if it is suitable for large-scale processing and if it can be formulated for a normally already selected formulation type. This polymorph has the lowest solubility in correlation with the metastable forms, which in general has an impact on the bioavailability. However, using this form prevents solid–solid transformation from a metastable to a stable form in drug product causing, for example, agglomerations.

Polymorphic forms can be monotropically or enantiotropically related (see Fig. 6). Enantiotropically related systems show temperature-dependent reversible transitions of the polymorphs, whereas monotropic systems demonstrate irreversible transformations from the metastable to the stable form only. For an enantiotropically related system, it is recommendable to determine the transition point at an early development stage, because at this point fluctuations and solid–solid transformation take place.
temperature the thermodynamical stability changes and conversion from one form to another may occur. Sometimes it may be advisable to continue the development based on alternative forms such as pseudopolymorphs (hydrates, solvates), instead of polymorphs. This may be the case if a water-based formulation is the preferred dosage form. Therefore, the selection of the most suitable crystalline form is an interdisciplinary task based on the requirements of chemical process optimization and formulation development.

3.2.1 Polymorphism screening
In order to prevent the product from unwanted quality changes it is very important to implement polymorphism screenings in the development workflow. A polymorphism screening is the first evaluation of the solid-state landscape based on a reduced number of crystallization experiments in selected solvents. The resulting samples undergo a characterization generally done by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). The aim of these types of screening is to estimate how complex the crystallization behavior of the given a.i. will be. When to perform these screenings is empirically a more or less philosophical question. Investing effort into polymorph screenings early in the discovery process versus later in the process may have its pros and cons. Starting at a very early development stage of the agrochemical product provides the opportunity to focus process and formulation optimization directly on the most suitable solid form. Additionally, an early selection of the solid form is of significant importance for toxicological studies and can help to interpret the results. Unfortunately, it implies a lot of experimental work on agrochemical development candidates which may never make it onto the market.

Alternatively, solid-state investigations at a later stage in the development process may lead to additional optimization work on manufacturing processes and formulation of products after a solid form was selected. Performing toxicological studies without knowledge of the solid-state characteristics of the a.i. in use may entail a certain amount of risk. A change in the solid-state phase between dose finding and study performance can have a dramatic influence on the kinetic solubility of the a.i. In particular, the use of the amorphous phase may lead to overdosing.

Solid-state screenings, particularly for the pharmaceutical industry, are well-described in the literature starting with the evaluation of the solubility of a.i. to be the first step which triggers all the following experimental steps, as summarized in Fig. 5.

For this investigation, the a.i. should be crystalline because the amorphous phase may have a much higher solubility and cannot be used as a kind of worst-case approach to get an idea of its behavior. Based on increasing complexity of the chemical structures of a.i., the number of crystallization screenings as a starting point is escalating dramatically.

The solubility data for the a.i. then determine the decision on performing salt or co-crystal screenings, which need to be done if the solubility of the a.i. is much too low. Especially for a.i. with a high tendency to solidify in the amorphous state this could be a suitable way to get crystalline material with optimized physico-chemical properties.

The investigation of the solid-state landscape of a given a.i. is based on different crystallization techniques, as described in Section 3. By variation of the solvent, polarity and temperature conditions, different nucleation will occur, which may lead to different crystalline forms of the a.i. The aim of polymorphism screenings is to gain an understanding of the crystalline lattice and the thermodynamic relationship of the different crystalline forms of a.i.
The transformation of polymorphs was first described by Lehmann using the terms enantiotropic conversion for a reversible process and monotropic for an irreversible effect. An enantiotropically related system has a transition temperature where both polymorphs are in equilibrium and have the identical free energy. Below this temperature, the lower melting form is the thermodynamically stable form and above it, the stability changes to the higher melting form of the a.i. The thermodynamic correlations are best described by energy/temperature diagrams (see Fig. 6), which were presented by Buerger in 1951 and Burger et al. in 1979. The evaluation of the thermodynamic behavior of different forms of an a.i. can be done by DSC and competitive slurry experiments. The evaluation of melting temperature and enthalpy of fusion values may give first hints on the thermodynamic correlation of the given crystalline forms if overlay of different thermal events is not observed.

4 CHARACTERIZATION OF CHEMICAL POLYMORPHS

The characterization of solid-state forms of an a.i. should be carried out by various techniques. Besides the most common methods including thermoanalytics, vibrational spectroscopy and X-ray diffractometry, which will be described here, there are increasing numbers of analytical tools to characterize the solid-state landscape of a technical a.i. For example, dynamic vapor sorption (DVS) can be used for the detection of hydrates and solvates of a.i. or for quantification of the amorphous amounts in technical samples. Combined systems of more than one method, like thermogravimetry/mass spectrometry, DSC/thermogravimetry and infrared (IR)- or Raman microscopy can be very useful to get most information out of very small sample amounts of a.i. Unfortunately, the downside is decreasing sensitivity of the single components in some cases.

All of these analytical methods have their strengths and weaknesses, which makes it highly recommended to use more than one technique for the analytical investigation of the solid state of an a.i.

4.1 Thermoanalytics

Because of the varying intermolecular interactions in the crystalline lattices of polymorphs, different modifications exhibit dissimilar melting points and enthalpy of fusion values. The differences vary from very low to high values. One example is the crystal forms I and II of the herbicide tembotrione (see Fig. 7), which

Figure 5. Simplified description of a solid-state selection workflow.

Figure 6. Energy/temperature diagrams of monotropically and enantiotropically related crystalline forms I (mp I) and II (mp II).
presented similar melting points but different enthalpy of fusion values and solid-state densities. 29 The evaluation of all data show that modifications I and II are monotonically related with crystal form I the stable one at all temperatures up to its melting point.

Thermoanalytical data such as melting temperatures and enthalpy of fusion values enable a first thermodynamic evaluation of the stabilities of crystalline forms based on the heat of fusion rule (HFR) stated by Burger in 1982, which correlates the melting points and heat of fusion values for the evaluation of enantiotropically or monotonically related systems. 30 It is important to underline that the higher melting form is not always the thermodynamically most stable polymorph at ambient temperature. For enantiotropically related systems the stabilities are influenced by the transition point (Tp). At temperatures below Tp the lower melting form will be the thermodynamically stable polymorph.

For the detection of the melting points several techniques are available. One of the oldest but still extremely useful methods is the Koehler heating bench, which consists of a metal band offering different temperatures going along the band length. Moving the sample placed on a specimen slide on this band will give a very fast impression of the melting behavior of the a.i. and offers very helpful information for further investigations using DSC and differential thermal analysis (DTA) techniques.

Both DTA and DSC are the most common instruments for evaluation of the thermal behavior of an a.i. These techniques measure the temperature differences of a small amount of a.i. (~5 mg) in comparison to a reference (DTA) or regulate temperature differences of a.i. and reference by power compensation (DSC). In the resulting thermograms melting points, enthalpy of fusion and other endothermic and exothermic events can be observed and analyzed (Fig. 8; Table 2).

The thermoanalytical measurements of polymorphs are highly suitable for obtaining an impression of their thermodynamic stabilities. Unfortunately, the results of the DTA/DSC measurements are influenced by many factors. 31 For example the selection of the heating rate has a strong impact on the result of the thermoanalytical experiment.

Therefore, it is highly recommended to use more than one heating rate during the evaluation process in polymorphism screenings.

The implementation of thermoanalytical investigations can give multiple information based on a very small sample amount. The combination of DSC, TGA and XRPD fits perfectly for characterization of a solid sample and will give information on the solid form, the purity, the crystallinity and the decomposition behavior. 32, 33

The interpretation of DTA/DSC results can benefit from polarized hot-stage microscopy as an additional thermoanalytical technique. If numerous events gave an overlay of signals in the resulting thermogram it can be very difficult to separate the events and make the evaluation. This can be achieved by hot-stage microscopy, which makes the events visible and the interpretation much easier.

In 1888, Lehmann described the analysis of enantiotropic systems in his book ‘Molekularphysik’. 34 This was the first implementation of hot-stage microscopy in polymorphic/allotropic inversions.

Although microscopy has various options for application, for example the recognition of hydrates/solvates or mixed crystals, the observation of sublimation, decomposition or homogeneity and, last but not least, the investigation of seeding processes, the technique is still used only infrequently. 35, 36 Looking at the broad spectrum of the physicochemical properties, which can be analyzed by microscopy and especially by thermomicroscopy, it is more than surprising. Based on the birefringence of crystalline material, polarized thermomicroscopy is a perfect tool for the investigation of phase transitions of polymorphic forms during heating up or cooling down of a given specimen. Many investigations on polymorphism using hot-stage microscopy are reported by Kuhnert-Brandstätter. 37, 38 The thermomicroscopic evaluation of the polymorphic invasion of the different forms of the fungicide fluopicolide, controlling a wide spectrum of Oomycetes diseases, gave a colorful impression of the capability of this method, which is demonstrated in Fig. 9.

Table 2. Thermoanalytical data and single-crystal X-ray structures of crystalline forms I and II of tembotrione.

| Crystal Form | Melting Point [°C] | Enthalpy of Fusion [J/g] | Density (calculated) [Mg/m³] |
|--------------|-------------------|--------------------------|-----------------------------|
| Form I       | 124               | 79                       | 1.637                       |
| Form II      | 124               | 67                       | 1.614                       |

Figure 7. Thermoanalytical data and single-crystal X-ray structures of crystalline forms I and II of tembotrione.
Besides the investigation of polymorphism, thermoanalytical techniques are highly suitable for the detection and characterization of hydrates and solvates. The elution of solvents can be directly observed by changes in the optical parameters of the specimen. The crystals will show an increase in turbidity and a decrease in transparency during heating-up, followed by a color change to brown and finally black. Using paraffin oil for sample preparation gives the opportunity to observe the loss of solvent by generating gas bubbles or even foam formation. Supplementation of TGA will help to quantify the amount of solvent lost during the heating and enables the evaluation of the molarity of the hydrate/solvate in combination with other techniques, like mass spectrometry, for example. The use of thermogravimetry for the investigation of pseudopolymorphs is described by Kuhnert-Brandstätter.

4.2 Vibrational spectroscopy (Raman and mid-IR)

The qualitative and quantitative analysis of different solid forms in a.i. and formulated products is very important to support the optimization of the chemical process as well as the formulation development, and guarantee the established drug quality. Vibrational spectroscopy has become very common technology to perform this task, because of its flexibility and simplicity in practice. In addition to desktop applications, the vibrational techniques can be used as inline devices or as combined technique, for example with DVS. In comparison with the XRPD systems, Raman and IR spectroscopy are less expensive and therefore very interesting for quality control and process analytical techniques (PAT).

The measurement principle of Raman and IR spectroscopy is the interaction of electromagnetic radiation with matter – in our case, our specimen. By absorbing a radiation quantum, the vibration of the different functional groups of the agrochemicals is stimulated. For different polymorphs and pseudopolymorphs, the surroundings and intermolecular interactions of the functional groups in the crystalline lattices are not similar, causing different electromagnetic interactions with radiation. The differences in the spectroscopic results of polymorphs can be relatively small, as shown in Fig. 10 for the insecticidal a.i. imidacloprid.

In other cases, the differences can be more obvious, which supports the evaluation of quantitative methods based on a chemometrical approach. Figure S2 compares the ATR mid-IR spectra of modifications I and II of the fungicide prothioconazole.

For mid-IR spectroscopy, the absorption of the electromagnetic radiation energy has to result in a change in the dipole moment of the molecule. In Raman spectroscopy, the monochromatic radiation shows an inelastic scattering, promoting the molecules from ground to a higher excited state of vibrational mode and
return to the first excited state, which leads to reduction in frequency (Stokes Raman Scattering). The Anti-Stokes Raman Scattering shows an increase in frequency as a consequence of transition from the first excited state of vibrational mode to the ground state, which results in an increase in frequency. The Stokes bands are more intensive and are used for the Raman spectra because the ground state of vibrational mode is well-occupied, leading to more transitions.

Most of the monochromatic radiation will be elastically scattered in all directions (Rayleigh scattering), which explains the need for very sensitive detectors and their sensitivity to fluorescence. The interaction of the monochromatic radiation with the specimen has to result in a change of polarizability to be Raman-active. Because of this difference in comparison to the mid-IR effect, both techniques complement each other perfectly. Raman spectroscopy can be used in aqueous surroundings because the interaction of electromagnetic radiation with water molecules will lead to a change in the dipole momentum of the water molecules, which makes it IR-active but Raman-inactive. That makes Raman spectroscopy very valuable for the qualitative
and quantitative analysis of formulated agrochemicals such as SCs, which are water-based. Figure 11 shows the FT Raman spectra of the herbicide metribuzin modification II and its SC formulation Sencor. The measurements were made without sample preparation and the spectra of SC Sencor and modification II are very comparable to each other.

IR spectroscopy is not sensitive to fluorescence and therefore is very useable for the analysis of wettable granules, which can be colored and may overload Raman detectors.

For quantitative solid-state characterization, different techniques can be used. The implementation of diffuse reflectance infrared Fourier transformation spectroscopy (DRIFTS) enables measurements without sample pre-preparation, so that an influence on the solid form by thermal or mechanical energy can be excluded. Based on calculated mixed spectra and multivariate calibration including different models, such as the first-order multivariate model partial least-squares (PLS) regression quantitative methods can be generated, which are perfect tools to support the development work on processes and formulations.

4.3 X-Ray powder diffraction

The difference between solid-state forms is firstly a result of variations of their crystalline lattices. Therefore, it would be interesting to analyze crystalline forms at the atomic level. X-ray radiation with its wavelength of 50–230 pm enables the interaction with the crystalline lattice and offers additional techniques to analyze the solid state. The most common approach for the characterization of solid forms is XRPD. The powder diffraction pattern is created by interaction of X-ray radiation with a powder specimen of randomly oriented crystallites. Figure S3 illustrates the XRPD pattern of modifications I and II of the fungicide prothioconazole.

The interaction of the X-ray radiation with the crystalline lattice guarantees very good sensitivity to changes in polymorphic and pseudopolymorphic forms. Without references, the method cannot provide any information concerning the chemical composition, which makes it a little too critical to use it as an exclusive technique in ‘pattern searches’. This is usually done in high-throughput approaches and can result in a high number of different patterns, with some problems with reproducibility of the recorded hits on larger scales.
Besides the highly sophisticated XRPD systems, which are expensive and have some special challenges concerning their location as a result of weight and space, desktop systems now are available which demonstrate increasing quality of data in comparison to the older systems.

In combination with other techniques like DSC and thermogravimetry, XRPD is a perfect tool for the characterization of solid forms. The evaluation of the pseudo-polymorphic landscape of azoxystrobin gives an example of the combination of thermoanalytical techniques together with XRPD and demonstrates its limitations in isostructural phases, which were overcome by implementation of temperature-related XRPD and SCRD.\textsuperscript{46, 47}

4.4 X-Ray single-crystal structure analysis and modeling

The reciprocal effect of X-ray radiation on one single crystal can demonstrate the conformational structure of the molecule in the crystalline lattice, which provides a direct insight into composition and molecular interactions, as shown in the polymorphism screening of the herbicide nicosulfuron.\textsuperscript{48}

Figure 12 shows the crystal packings of modifications I and II of the fungicide prothioconazole.

The analysis of crystalline lattices by SCRD has many advantages. Based on these data, it is possible to measure the intermolecular interactions between the molecules fixed in the lattice for interpretation on thermodynamic stabilities. The data can be used to calculate the morphology of crystals. Figure 13 shows an example where the calculated habits, done with the MERCURY software from Cambridge Crystallographic Data Centre, are compared to the recrystallized samples.

One limitation of SCRD is the need for well-defined single crystals, as recrystallization can be rather difficult. To overcome this challenge, crystalline sponges were introduced, as described for the seed dressing Metalaxyl-M and the herbicide S-Metolachlor.\textsuperscript{49}

Based on X-ray single-crystal structure analysis, the door is open for different prediction tools supporting the experimental work on solid form screenings. The progress in computational methods is amazing. The computational techniques for the prediction of crystal structures based on the pure chemical formular of the molecules were tested in blind tests initiated by the Cambridge Crystallographic Data Centre.\textsuperscript{50} Neumann et al. described the blind test approach and demonstrated the hybrid method for calculation of lattice energies based on a combination of density function theory (DFT) simulations using the Vienna \textit{Ab initio} Simulation Package (VASP) program.\textsuperscript{51} This method also is very suitable for the prediction of polymorphic stabilities. The difficulties in correlating the computational results with experimental approaches were described by Kendrick.\textsuperscript{52} Unfortunately, the virtual screenings normally lead to higher numbers of solid forms, which are sometimes not reproducible on an experimental basis.

Figure 13. Calculated morphologies of modification I and II of prothioconazole in comparison to its recrystallized sample.
5 OUTLOOK ON FUTURE DIRECTIONS

With the impending higher complexity of the molecular structure and molecular weight of the agrochemical a.i., a tendency for amorphization can be observed. The activation energy for nucleation is getting higher and the attempt to obtain crystalline material is becoming more challenging. The demand for further crystallization techniques is high and is leading to new approaches in this field.

5.1 Future challenges

At the laboratory scale, the crystallization of substances with very high nucleation activation energy can be initiated by seeding crystals of a related chemical structure. This can be used to get the first seeding material for further investigation and upscaling. Unfortunately, the additional chemical material has to be seen as an impurity and renders this approach not feasible for direct application in agrochemical industrial processes.

Heterogeneous nucleation processes get into focus. By providing artificial interfaces the activation energy for nucleation may decrease and crystallization will occur. For polymorphism control and improvement of the nucleation rate, template-induced crystallization was investigated. Additional techniques such as nonphotochemical polarization-dependent laser-induced nucleation (NPLIN), or sonocrystallization can be very interesting to broaden the spectrum of experimental settings used in polymorphism screenings.

Template surfaces as well as fluid interfaces enable the orientation of the molecules, bringing the entities closer together and supporting the arrangement of intermolecular interactions. The solid–liquid interfacial energy decreases with this process and nucleation will become possible.

Furthermore, fluid interfaces between different unmixable solvents or in emulsions can act as seeding templates. This can be very critical for ECs, which are one of the preferred formulation types for agrochemicals. One example for this effect occurred in 2009 in the EC 200 formulation Fandango, a fungicidal mixture of fluoxastrobin and prothioconazole. After years of unsatisfactory use of the agrochemicals, precipitation led to customer complaints. The comprehensive analytical characterization of the residue resulted in the structure of a mono butyrolactone solvate which was never observed during the development of the product.

This example shows that besides the knowledge of the thermodynamic stable polymorph, it is important to have an idea about the pseudopolymorphic forms. The formation of hydrates in particular can have an influence on product quality and may lead to recrystallization in spray broths. However, hydrates can be the most useful solid form in water-based surroundings if the formulation development process is based on the knowledge of these forms.

5.2 Patent protection for solid-state forms

It was demonstrated that the ability to recrystallize in different solid forms, such as, for example, polymorphs and pseudopolymorphs, may have a great impact on drug quality for a selected a.i. candidate. The selection of an optimized crystalline form may overcome process and formulation challenges such as filtration issues or agglomeration based on solid–solid transformation. Even the selection of a suitable co-crystal may have an influence on drug product properties and qualities by combining different a.i.s in one new crystalline lattice as shown in the patent application WO 2009/047043. The physical mixture of pyrimethanil and dithianon was found to demonstrate color changes and solidification during the preparation of a suspension concentrate. The provision of a one-to-one co-crystal of both a.i. led to a flowable and stable suspension concentrate.

All these investigations may support the patent protection for solid-state forms through polymorphism patent applications. A selection of agrochemical solid-state patents is shown in Table 3. Polymorphic forms, as well as hydrates, solvates, salts and co-crystals represent new varieties to chemical structures.

6 CONCLUDING REMARKS

The increasing interest in solid-state investigation and design is not only demonstrated in the pharmaceutical industry, but also has become an important part of agrochemical development of a.i.s. With the selection of the best optimized solid form at an early stage of development, there may be a very valuable impact on manufacturability, COG and agrochemical product quality. The way to obtain different forms can involve different crystallization
approaches, especially in correlation with increasing molecular weights, going along with increasing degrees of freedom of the a.i. The characterization of the resulting entities should always be done with a fundamental approach based on more than one technique, to overcome the weaknesses of the single methods. Computational polymorph screenings may support the experimental preparation to validate the thermodynamic findings.

The focus of polymorphism screenings should change from only crystallization and characterization of polymorphs to a broader approach involving the different properties of the solid forms. The selection of a solid form is always based on optimization of properties and may enable the submission of patent applications to protect the findings. These solid-state applications are of increasing interest in a highly competitive field like the agrochemical industry.

**ABBREVIATIONS**

| Abbreviation | Description |
|--------------|-------------|
| ATR          | attenuated total reflection |
| EW           | emulsion (concentrated) |
| GR           | granule |
| SC           | suspension concentrate |
| SE           | suspoemulsion |
| SL           | solution |
| WG           | water dispersible granule |
| WP           | wettable powder |

**DATA AVAILABILITY STATEMENT**

The data that supports the findings of this study are available in the supplementary material of this article.

**SUPPORTING INFORMATION**

Supporting information may be found in the online version of this article.

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