Integration of active pharmaceutical ingredient solid form selection and particle engineering into drug product design

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Abstract

This review seeks to offer a broad perspective that encompasses an understanding of the drug product attributes affected by active pharmaceutical ingredient (API) physical properties, their link to solid form selection and the role of particle engineering. While the crucial role of active pharmaceutical ingredient (API) solid form selection is universally acknowledged in the pharmaceutical industry, the value of increasing effort to understanding the link between solid form, API physical properties and drug product formulation and manufacture is now also being recognised.

A truly holistic strategy for drug product development should focus on connecting solid form selection, particle engineering and formulation design to both exploit opportunities to access simpler manufacturing operations and prevent failures. Modelling and predictive tools that assist in establishing these links early in product development are discussed. In addition, the potential for differences between the ingoing API physical properties and those in the final product caused by drug product processing is considered. The focus of this review is on oral solid dosage forms and dry powder inhaler products for lung delivery.

Introduction

The selection and nomination of the solid form (free form, salt or co-crystal and polymorph/hydrate/solvate thereof) of an active pharmaceutical ingredient (API) is an important milestone in the development of a commercial pharmaceutical product. To facilitate efficient product development, the solid form is typically nominated before the development of the commercial crystallisation process and the commercial drug product formulation and process design. It is not desirable to change the solid form once activity associated with the nomination of the commercial API and drug product manufacturing processes have commenced, as this would generally lead to substantial rework costs and project delays.

The escalation of solid form issues leading to withdrawal of marketed products or delays in launch has justifiably attracted vast amount of scientific research and regulatory focus.[1] Alternative and additional perspectives on the role of API solid form have appeared over recent years. The solid form has the potential to facilitate developability of a potential drug candidate in the preclinical stages,[2] help with acceleration of a compound during development[3] and provide intellectual property.[4] Solid form nomination is therefore of importance across all stages of pharmaceutical development and can make a substantial impact to cost and duration of the development programme. In other words meeting minimum acceptable criteria for the solid form is essential to having a developable pharmaceutical product that is enduring; however, improvements over the minimum criteria are also important to reduce time and effort in the product development phase.

The selection of the API solid form as a part of the preformulation process for pharmaceutical products has been discussed and reviewed for over 20 years.[5] However, the process by which the solid form is selected is continually being refined and improved. In general terms, solid form selection involves salt and co-crystal screening to define the solid form landscape. This is followed by polymorph screening of the free form, salts and co-crystals to...
determine the appropriate form to develop, which is generally the thermodynamically stable form. These screening approaches are covered extensively in the literature and other contributions to this special issue.

The vast majority of achievable physical attributes of APIs are set at the point of solid form selection, with both the molecular and the crystal structure becoming a canvas, and particle engineering enabling the manufacture of particles exhibiting the preferred properties from those allowed by the internal structure. Consideration should be given to integration of the API solid form into both API and drug product processes to maximise the value of the solid form selection. This review seeks to elucidate the intimate connection between solid form selection, particle engineering and API physical properties, ultimately to emphasise that a truly rational pharmaceutical development paradigm must involve solid form selection, definition of preferred API properties, determination of the preferred particle engineering approach and formulation selection as parallel activity. As an important corollary, given multiple salt or co-crystal forms for the same therapeutic agent with comparable polymorphic complexity (e.g. stability, number of polymorphs) then an ancillary set of selection criteria should be centred around the ‘canvas’ of physical properties implicit in the internal structure of each solid form considered. While an extensive side-by-side comparison would be both expensive and impractical, both emerging and established modelling tools can be used to determine the link among internal structure, API attributes and drug product (DP) manufacturability and performance. To deal with challenges with limited API availability, computational methods or useful correlations have been developed that allow the scientists designing the drug product to start to predict the role of the API on drug product attributes. Example attributes for an oral solid dosage form include, for instance, dissolution, which relates to drug product performance and content uniformity, which relates to processability.

The pharmaceutical industry uses a range of particle engineering tools to control API particle properties, from crude milling approaches to de-lump material through to sophisticated crystallisation techniques to control form, size and shape. In the context of this review, particle engineering is defined as a set of unit operations designed to deliver APIs with desirable physicochemical properties, in particular including, but not necessarily being restricted to, crystallisation, filtration, drying and milling. Generally, the potential for the solid form selection to optimise the particle properties may not be considered at the time of solid form nomination. This probably occurs because the potential for the API internal structure to influence the scope of particle engineering is not immediately obvious or there is not a quantitative definition of the particle properties needed for drug product at that time. The internal structure consists of a network of hydrogen bonds, Van der Waals interactions, and ionic and dative bonds holding the crystal lattice together, with hydrogen bonding being the prevalent type of interaction within pharmaceutical compounds. The absolute and relative strength and directionality of these interactions determines the crystallisation landscape, that is how fast a crystal will grow and what shape it will exhibit, with crystal habit also being a reflection of the symmetry within the crystal unit cell. Environmental factors, such as the crystallisation solvent or the supersaturation profile, also play a role in determining crystal shape and crystal size. For example, growth rates are face specific and will respond differently to supersaturation and solvent depending on the surface chemistry they expose, and the nature of the interactions involved in the propagation of those faces. Similarly, while the strength and direction of the interactions involved in the crystal lattice determine fracture points, the extent of particle breakage during milling will depend on the equipment and process conditions used. There has been substantial research and development relating to particle engineering API to manipulate and control particle size distribution. Probably the most significant focus of these activity has been the production of fine particles typically either for product performance (increasing the dissolution of oral low solubility drugs or the efficiency of drug delivery to the lung for inhaled products) or manufacturability (improving content uniformity of low dose products for oral dosage forms).

It has been recognised that the API particle size distribution descriptor does not take into account the anisotropic nature of crystalline materials, which has an impact on the material behaviour. This has led to a broadening of the description of the important API properties from particle size and internal structure to include particle shape and surface properties. To allow assessment of these properties, a range of analytical techniques has been integrated into pharmaceutical material characterisation including a number of high-throughput dynamic image analysis techniques to assess shape and surface characterisation techniques including atomic force microscopy (AFM) and inverse gas chromatography. These analytical techniques have been complimented by advances in approaches to access surface chemistry from the crystal structure of materials. To justify the benefit of increasing the amount of effort and time for API characterisation to include the shape (habit), surfaces and mechanical properties, it is important to be able to link those properties to the critical attributes of the drug product. Therefore, it is interesting to consider the literature in respect to their potential to impact processing and drug product performance.

During the design of a pharmaceutical dosage form the API properties, formulation components and process train can all be used to optimise the overall product performance.
and manufacturing process. This review is intended to guide the material scientist and formulator in identifying properties to measure and control during API form selection, particle engineering and formulation design. In addition, the understanding should help direct the formulation and process design components of the drug product development by highlighting the strengths and weaknesses of the API physical properties. While comprehensive overviews on the link between API and drug product exist and are cited in this manuscript, this review is aimed at consolidating the existing knowledge under a novel framework so that a multitude of quality and performance attributes normally considered during pharmaceutical development are ultimately related to a handful of ‘primary’ attributes, which are controlled through intrinsic ‘crystal lattice’ selection and during API crystallisation, isolation and particle size reduction.

The scheme in Figure 1 attempts to clarify the link between API properties, which are essentially determined by the interaction between internal structure and particle engineering, and drug product attributes commonly considered during drug product design. The schematic is somewhat simplistic, but it is useful in showing that a large number of drug product attributes are ultimately linked to only a handful of API properties – namely intrinsic solubility, particle size distribution, crystal shape and mechanical properties – which are set through the internal structure and particle engineering conditions. These API properties are also linked to each other, for instance, surface chemistry can be linked to particle morphology, which in turn is influenced by intrinsic lattice properties (and as such is dependent on solid form) and the crystallisation solvents employed. This was illustrated by a recent literature report where particle engineering was used to change the particle morphology of celecoxib, resulting in a change in the relative amount of more hydrophilic crystal faces and increased dissolution rate.\(^\text{[17]}\) Similarly, the ease of particle breakage during milling, which could be important to reach a target particle size, is linked to lattice-dependent mechanical properties such as brittleness.\(^\text{[18]}\) This approach of linking structure and property with the product performance is consistent with the principle of the material science tetrahydron.\(^\text{[19]}\) Note properties of the API that are linked only to molecular structure, such as permeability, are not included in Figure 1. In addition, while solubility is defined as having little dependence of particle size, it is known that

![Figure 1](image_url)

**Figure 1** The link between solid form selection (internal structure), particle engineering and key active pharmaceutical ingredient properties and drug product attributes.
a dependence is observed for API particles of submicron size.[20]

A detailed review of the role of API physical properties in product performance, manufacturing and stability is presented in section 2. This is followed by section 3, which reviews how solid form and particle engineering link to particle shape, size, mechanical properties and surface energy. Finally, section 4 examines the potential for differences between API attributes measured on API and those in the final drug product caused by drug product processing.

The role of API properties, solid form and particle engineering in drug product processing, performance and stability

This section focuses on the status of knowledge with respect to how API properties will influence the drug product processing, performance and stability. Examples of where models or relationships have been applied, together with strengths and weaknesses in current approaches, are discussed.

Drug product performance

For oral solid dosage forms, the objective is to get the drug to dissolve in the gastrointestinal (GI) tract to be absorbed; therefore, dissolution rate is the key performance indicator. For inhaled products, performance is defined by the in-vitro assessment of how much API is delivered to the lung, defined as fine particle mass.[21] Although inhaled products are generally locally acting, dissolution rate should be considered as it could influence residence time in the lung, particularly for low-solubility compounds.[22,23] This drug product performance section will review the role of API properties in aerosolisation performance and dissolution.

Aerosolisation performance (aerodynamic size distribution) from dry powder inhalers

The aerosolisation performance of a dry powder inhaler (DPI) is generally characterised as the in-vitro fine particle dose, which is the dose with potential to penetrate the lung in vivo. The fine particle dose is generally considered as the mass of API particles with aerodynamic diameter <5 μm in size as measured on a New Generation Impactor, Anderson cascade impactor or a multistage liquid impinger. The particles with aerodynamic diameter >5 μm are generally considered non-respirable and expected to be swallowed.

There is a substantial body of literature relating to characterisation and control of DPIs. Assessing the impact of the formulation design using functional excipients (particularly lactose) makes up a major proportion of the work. The reader is directed to other detailed reviews of this research area.[24–26] There are, however, properties of the API that should be measured and controlled independently of the specific formulation design.

It is clear that API particle size will be a critical attribute of the API for DPI products. The aerodynamic diameter \(d_a\) of an API particle is related to the particle geometric diameter \(d_g\), the effective particle density \(\rho_e\) in g/cm\(^3\)) and the dynamic shape factor of the particle (\(\lambda\)) and \(\rho_s = 1\) g/cm\(^3\) according to equation 1:

\[
d_a = d_g \sqrt{\frac{\rho_e}{\lambda \rho_s}}
\]

The relationship between the API particle size distribution and performance of the product in terms of fine particle dose is complex. Chew and Chan[27] followed by Chew et al.[28] demonstrated that the performance of a DPI was dependent on the interaction between API particle size, the air flow through the DPI device and the design of the device for two model APIs. The complex inter-relationship among API physical properties, formulation, device and testing conditions (air flow) means that generic models to predict DPI aerosolisation performance based on particle size of API have not been possible.

The potential to influence performance of a DPI using salt selection was assessed by Jashnani and Byron.[29] They found that the nature of the counter-ion did influence fine particle dose. Hydrophilic and hydrophobic counter-ions were compared with the free base of salbutamol. The study showed that the API with the lowest moisture uptake also had the most consistent performance in terms of fine particle mass across a range of humidity. However, it was recognised that the moisture content did not show a correlation with performance, and hence there were multiple factors in play driving the performance.

API particle shape for inhalation materials has been shown to influence the delivery performance. Needle-shaped particles with high aspect ratios have been shown to have improved performance as measured by deposition profiles in the lung.[30] This would be expected based on the impact of change in shape factor on aerodynamic particle size shown in equation 1. However, it is challenging to exploit the use of particle shape unless constructive particle engineering can be employed, as destructive particle engineering such as micronisation tend to create particles with reduced morphological features. In cases where constructive particle engineering is used to prepare API particles, Hooton et al.[31] demonstrated that this gives the potential for influencing the cohesive–adhesive balance through control of crystal faces.

Surface properties of API have been strongly linked to DPI performance using a range of techniques.[32] In the case of AFM there has been an evolution from using a standard silicon AFM tip to measure the pull off force with a surface through to using a tip that is functionalised using the API.
of interest. Tips functionalised with different salts of salbutamol showed different pull off forces with lactose can be correlated to the fine particle dose. The functionalised tip approach was further enhanced by Begat et al., where the size of the cohesive forces within API and excipient vs the adhesive force between API and excipient carrier particles were compared. This relationship is described as the cohesion–adhesion balance (CAB). In this work, the AFM tip was functionalised with the micronised API and the pull off force is measured in contact with large crystals of API (cohesion) or excipient (adhesion). The dominant face was used for large particles to give the most likely contact surface.

Hooton et al. built on the work of Begat et al. to show that the choice of API crystal face and excipient did influence the cohesion adhesion balance value. This is consistent with the anisotropic nature of crystals. Interestingly, work in the area of CAB has indicated that for micronised APIs used inhaled CAB ratio is consistent from particle to particle. This suggests that once API is micronised to a <5 μm size, there is a similar surface energy for particle independent of contact face for the micronised API. Thus, micronisation seems to be reducing the anisotropy of the crystal. The overall balance of adhesion to cohesion has been shown to be related to product delivery performance. Hooton et al. assessed the relationship between the aerodynamic performance of micronised salbutamol sulphate formulated with a range of sugars delivered from a DPI. They found that the increasing adhesive interaction between the salbutamol and the sugar lead to reduced fine particle performance. Furthermore, Hooton et al. showed a similar relationship for budesonide formulated with the same range of sugars. Tong et al. used inverse gas chromatography (IGC) to determine the work of adhesion and cohesion for DPI formulations. They found that the performance of the model API (salmeterol xinafoate) displayed increased cohesive strength, thus leading to reduced fine particle fraction of the dose. Interestingly, the fine particle fraction improved when lactose was added to the formulation only when the API was adhesive with respect to the lactose, with increased adhesion leading to increased FPD. This was considered to be due to the adhesion to lactose helping to break up drug–drug cohesive interactions.

In an alternative approach, Cline and Dalby were able to correlate the overall performance of dry powder blends prepared with different model API and excipients to the overall energy of the interaction between the API and the excipient in milliJoules/gram, measured using IGC. The plot of fine particle dose vs surface energy interaction was well correlated (R² = 0.93). The relationship of increasing fine particle dose with increasing interaction energy seems counter-intuitive. However, it is somewhat consistent with the work of Shur et al. who demonstrated that increasing the cohesiveness of blends leads to increase fine particle dose, where the cohesive powder was found to produce a higher fine particle mass.

The surface roughness of particles in DPIs has been assessed extensively. The majority of the research relates to the surface properties of the excipient carrier particle as this is the dominant material. However, in cases where a carrier-free DPI is developed, surface rugosity of API particles has been shown to be an important contributor to the cohesive forces between particle and hence the subsequent fine particle dose. Adi et al. showed a linear correlation between particle roughness as measured by AFM and the fine particle dose, with a doubling of the fine particle dose across the range of surface roughnesses assessed.

The performance of a DPI product is known to be related to a complex interplay between the API, the carrier particle and the device. It is challenging therefore to create generic models for DPI performance. Hickey and Xu have provided a framework for modelling aerodynamic performance data to aid formulation design based on the Langmuir equation. However, their approach currently relates to modelling aerodynamic size data to dispersion energy, which is controlled using a series of dispersion tubes to deliver the formulation and does not relate back to the physical properties of the API. Hence, it is not possible to guide the selection of the solid form or particle engineering based on this approach.

Another approach to unifying the interactions in a DPI is to consider the aerosol as a mixture of agglomerates that need to be broken to allow efficient product performance. Chan considered the structure and role of agglomerates in his detailed review of the link between particle morphology and powder aerosol performance. The strength of the agglomerate (σ) is described by equation 2 below, where Φ is the packing fraction, W is the non-equilibrium work of adhesion and D is the particle diameter.

\[
\sigma = 15.6\Phi^4W/D \tag{2}
\]

Equation 2 shows a clear link between size and surface energy through work of adhesion, plus the particle shape of the API will influence its packing Φ. Packing is clearly a critical parameter, as it has a fourth power relationship with agglomerate strength. Densification of API or API/excipient agglomerates during API micronisation or blending should therefore be avoided to maximise dispersion during aerosolisation. Furthermore, the packing density of an API agglomerate will impact on its aerodynamic size, as described in equation 1, with low-density agglomerates having a lower apparent aerodynamic size.

Overall, the body of literature indicates that solid form selection for inhalation APIs is most critical to ensure robust manufacture, consistent particle properties and chemical stability. Micronisation is most commonly used to...
achieve the required size and in these cases an API form that is physically stable post micronisation is also critical. Micronisation reduces the anisotropy of the crystal in terms of shape and surface properties; however, a constructive particle engineering approach, where possible, may allow exploitation of particle shape and roughness to improve performance. Once API particle properties are defined, formulation design provides the best opportunity for achieving high product performance and can be exploited to compensate for adverse surface properties of API. APIs that have low moisture uptake across a range of relative humidities might also be beneficial, while those that are highly adhesive to lactose or highly cohesive should perhaps be avoided. Discussion on the role of solid form on the physical stability of API once micronised can be found in the section entitled Shelf life (Stability).

**Dissolution**

Delivering a suitable and repeatable bioperformance of an oral dosage form is an important design criterion. To this end, the dissolution of a drug product is typically one of the key performance attributes of an oral solid dosage form, as it is the first step to achieving good bioavailability. There are two stages to the dissolution process; first, the dosage form must disintegrate and then the API must dissolve. Generally, immediate release oral solid dosage forms are designed to disintegrate quickly (in less than 15 min). In addition, dissolution of API from DPIs and suspension metered dose inhalers (MDIs) in the lung may be important, particularly for low-solubility compounds.

Methods have been developed to attempt to simulate API dissolution. These methods are based upon the diffusion-controlled model for solid dissolution which was developed by Noyes and Whitney (equation 3) late in the 19th century, and then subsequently modified by Nernst.\(^{47}\)

\[
\frac{dM}{dt} = DS/h(C_s - C_t)
\]

where the rate of dissolution is \(dM/dt\), the saturated solubility of the drug is \(C_s\), the concentration of the drug at time at time \(t\) is \(C_t\), the surface area of drug in contact with the liquid media \(S\), the thickness of the drug layer exposed to the dissolution media (diffusion layer) \(h\) and the diffusion coefficient \(D\). The key factors that can be controlled during the form selection are the saturated solubility of the API \((C_s)\) and the surface area available for dissolution \((S)\). The surface area is inversely related to the particle size of the API for a given mass. Hence, by increasing the solubility or decreasing particle size, dissolution rate can be increased. The enhancement of the solubility using form selection is the most extensively researched area with respect to solid form selection and has been described elsewhere\(^{48}\) and within this special issue.

Johnson\(^{49}\) recently compared the two lead methods for modelling dissolution developed by Lu et al.\(^{44}\) and Wang and Flanagan\(^{40}\) used in commercially available software such as Gastropus (Simulations Plus Inc., Lancaster, California, USA), Simcyp (Simcyp Limited, Sheffield, UK), Intellipharm PKCR (Intellipharm, Niantic, CT, USA) and PK-Sim (Bayer Technology Services GmbH, Leverkusen, Germany). In this paper, Johnson compared experimental dissolution data for two low-solubility compounds (cilostazol and hydrocortisone) at two particle sizes with simulations generated using the two methods. In summary, Johnson concludes that both methods were able to simulate the experimental data for micron size particles, although there were significant differences in the diffusion layer thickness chosen to give the best fit. In addition, Johnson recommended that more drug and also larger particle sizes are needed to refine the methods and increase confidence in predictions. It is important to note that these models for simulating an oral solid dosage form assume rapid disintegration and spherical particles that are fully wetted.

The impact of particle shape on surface area was considered by Lu et al.\(^{44}\) They measured the dissolution rate of coarse particles with a cylindrical morphology and observed that a better fit for the dissolution rate was achieved by taking into account the shape. Dali and Carstensen\(^{50}\) completed an elegant experiment where they looked at the relative dissolution rate of different crystal faces on single crystals. They showed that the shape factor changes considerably during the dissolution process, and, as such, changes in shape can be accounted for by applying the Hixson–Crowell cube root law. Thus, consideration and control of crystal shape may be important for low-solubility compounds, purely from its impact on the total surface area.

Lippold and Ohm\(^{51}\) showed that the wettability of powder had a significant impact on its dissolution rate. They compared the intrinsic dissolution rate of a range of powders with the contact angle measurements and demonstrated that there was a relationship between contact angle of the solvent and dissolution rate. Where the contact angle was low (<40°), and hence wetting relatively high, consistently high dissolution was achieved, which was assumed to be complete wetting. However, as the contact angle increased indicating poorer wetting, the rate of dissolution dropped dramatically. This work implied that there are two considerations with respect to the surface area component of the dissolution process, namely the total surface area, and the proportion of the total surface area that is wettable by the solvent of interest.

To build on the work of Lippold and Ohm\(^{51}\) and Lu et al.\(^{44}\) that assume an average contact angle over the whole particle, it is important to consider the anisotropic nature of...
crystals and that each face has its own specific surface properties. Modi et al.\(^{[11]}\) assessed the impact of particle shape (crystal habit) on the dissolution rate over and above the effect on total surface area using celecoxib as a model API. Particles with different morphologies were crystallised and fully characterised in terms of their material properties. One batch was crystallised as acicular particles and the other as plate-like particles. Both batches were observed to have the same polymorphic form and very similar particle size and surface area. Molecular modelling showed that the plate-like particles should have more relatively polar surface than the acicular particles. This was supported experimentally by surface characterisation using contact angle and X-ray photoelectron spectroscopy. The two batches were tested for dissolution and bioavailability in an animal model, dosed as suspension. The results indicated the plate-like batch with the higher relative area of more polar faces on the crystal also had a significantly faster in vitro dissolution rate and higher in-vivo bioavailability in an animal model. This work indicates that, as well as the total surface area, the relative polarity of the surface is important. This is consistent with the work and conclusions of Lippold and Ohm.\(^{[31]}\)

Molecular dynamics modelling of drug crystal dissolution has recently been carried out by Gao and Olsen\(^{[52]}\) that supports the argument that the chemistry of each crystal face is important. In this work, the crystal structure of paracetamol was used to simulate the structure of a very small crystal made up of repeating unit cells. A ‘water box’ was then built around the crystal and allowed to relax; then dissolution was simulated. This modelling work provided several interesting insights into crystal dissolution. It clearly showed that dissolution as modelled was not a random process and that different crystal faces dissolve at different rates. In addition, it was highlighted that corners and edges dissolve more rapidly than any of the faces. The prediction that the edges of crystals should dissolve more rapidly than the surfaces was supported by experimental observations. The increased dissolution rate at edges was also predicted for crystal imperfections or defects. Thus, a key conclusion was that the increase in dissolution observed by engineering fine particles may be due to the relative increase in edges and defects created by making smaller particles as well as surface area increase.

It is clear from the literature and modelling that API solid form solubility is key to achieving good dissolution. In cases where highly soluble APIs are not available, particle size reduction can be used to enhance dissolution. Furthermore, the literature indicates that, during particle engineering, consideration should be given to trying to increase the proportion of polar surface area. Modelling suggests that edges and surface defects, which are likely to be influenced by destructive particle engineering techniques, may also enhance dissolution. Overall, there are models in place that the material scientist can use to select an appropriate solid form and particle engineering approach. Enhancement of the models to take into account surface polarity may be of value in the case of relatively hydrophobic drugs where wetting could play a role in dissolution. If the required dissolution rate cannot be achieved by solid form selection and particle engineering, there are a multitude of formulation tools that could also be applied, although a dissolution fix using API solid form and particle engineering would likely lead to a more simple drug product formulation and process.

**Processability**

For low-dose products, the particle size of the API can become a factor in achieving good dose uniformity across the batch. This is because larger particles can represent a significant quantity of the overall dose, and hence the presence or absence of a large particle or particles in a dosage form can lead to a product outside an acceptable range of potency. There have been a number of methods developed for the relationship of API particle size distribution vs the content uniformity of potency of the product\(^{[33,34]}\) based on the random mixing theory for powders.\(^{[33]}\)

Zhang and Johnson\(^{[56]}\) demonstrated that the modelling of content uniformity gave valuable insights. They employed an approach to modelling content uniformity where the potency of API per dosage form is simulated by distributing the particles evenly across dosage forms. Where there were too few particles for one to be put in every dosage form, the particles are placed at regular intervals to retain a mass balance for the entire batch. Simulation of the content uniformity using this approach was compared with experimental data for jet-milled API of two size distributions and found to give a useful prediction of the probability of meeting the US Pharmacopeia (USP) content uniformity specification. Through application of the equation derived by Yalkowsky and Bolton,\(^{[34]}\) they generated a nomogram of the relationship between maximum acceptable volume median diameter that would have a 99% probability of meeting USP stage 1 content uniformity, the skewness of the particle size distribution and dose. Importantly, this method gave an equivalent prediction to that of Yalkowsky and Bolton,\(^{[34]}\) which gives increased confidence to the reliability of the method. The model also allows some valuable insights into the relationship between API particle size distribution and risk of failing content uniformity specification. For example, narrowing the distribution with of \(D[v, 0.9]/D[v, 0.5]\) from 4 to 2 increases the maximum acceptable \(D[v,
0.5] by fourfold (note that in Figure 2a and 2b, \(d_{50}\) denotes \(D[v,0.5]\) and \(d_{90}\) denotes \(D[v,0.9]\)).

Huang and Ku\textsuperscript{58} enhanced the connection of the model to the USP specification by building on the work of Rohrs et al.\textsuperscript{57} to generate a nomogram that includes the probability of passing Stage 1 or Stage 2 testing to USP (905), as shown in Figure 2b. Similar to Rohrs et al., they were able to simulate change in skewness of the distribution as dose drops for a specific API size distribution and made very similar conclusions with respect to the significant impact of applying a cut-off with respect to particle size at the top end of the distribution. Interestingly, they did note that for fine particles there could be significant particle agglomeration, and hence the agglomerate size distribution would be a better descriptor for the prediction of the blend content uniformity.\textsuperscript{59} This observation will be discussed further in a later section of this review.

The surface properties of materials have also been shown to influence the distribution of powders during blending. Ahfat et al.\textsuperscript{60} showed that spreading coefficients determined from the contact angles of powders predicted the spreading of powders during blending. These surface interactions are not considered by content uniformity models and may not be relevant to the overall blending uniformity. However, they would be particularly important where the API is a fine material and adhesive mixing mechanism dominates,\textsuperscript{61} as is the case for DPIs. The spreading coefficient approach has been extended to wet granulation to predict the spreading of granulation solutions over APIs to select granulation binder.\textsuperscript{62} Furthermore, Thielmann et al.\textsuperscript{63} used IGC to show that there were significant differences in the wettability of model hydrophilic and hydrophobic particles, which lead to granules with very different properties.

The particle size of the API can be linked to the segregation potential once mixing of API and excipients is achieved. Ideally, the particle size of the API should be very similar to the excipients to minimise the risk of segregation of a random (non-interacting) mix. To have acceptable flow, many of the main excipients used for solid dosage forms tend to be in the 50–100 \(\mu\)m range. Therefore, the principle of size-matching API to excipient is often overruled for low-dose or low-solubility products by the drive to get fine particles to allow the potential to achieve a homogenous mix or improved dissolution. This reduction in size also has the benefit of moving the blend from a random (non-interacting) mix to a ordered (interacting) mix, which means segregation potential is generally reduced.\textsuperscript{61}

Achieving suitable powder flow is critical to some unit operations for tablet and capsule manufacturing processes.
The physical properties of the solid form of an API particularly the particle size distribution are known to be important to flow. Mullarney and Levy[64] have modelled the relationship between particle size distribution and powder flow. The partial least squares model generated a four-parameter model based on key particle size descriptors. They reported that the modelling approach worked best for API and excipients as separate relationships. From the modelled data, they were able to generate a decision tree to help guide particle size selection with relation to flow behaviour, which could be used to help guide particle engineering for APIs.

To allow the patient to take a consistent amount of formulated API, a unit dosage form is usually prepared. In the case of tablets, which are the most common oral solid dosage form, this requires compression of the powder blend. When designing a tablet formulation, it is important that the tablets are mechanically strong and have minimum sticking of the blend to tablet punches. The mechanical properties of an API are influenced by the solid form[63] and will impact on tabletability of a formulation, particularly for high drug loadings. Recent work by Perumalla and Sun[66] demonstrates the significance of assessing mechanical properties, specifically tabletability, as part of solid form selection. Roberts[65] provides a detailed review linking structure and mechanical properties. When considering the internal structure of the API, he suggests that consideration should be given to achieving a sufficiently high cohesive energy and also hydrogen bonding functionality in layers or sheets leading to slip planes and hence lead to reasonable plasticity. Plasticity facilitates densification during compression and increased surface contact between materials, which is critical to achieving a strong compact. In addition to the internal structure, it is important to consider that mechanical properties can be influenced by the anisotropic nature of API. For example, tabletting performance has been shown to be substantially influenced by API shape,[67] which was attributed to shape influencing the orientation of slip planes in the crystal. The surface properties of an API can also contribute to mechanical strength, and a trend that increasing surface energy for the same bonding area leads to increased tensile strength was demonstrated by Fichtner et al.[68] This was built on by Modi et al.[69] who demonstrated that specifically the dispersive (non-polar) component of the surface free energy is the main contributor to this increase in compact strength.

Tablet sticking and picking can also be a significant problem for tablet dosage forms. This occurs when, over repeating compression cycles, material adheres to the punch faces causing aesthetically poor quality tablets.[70] Tablet sticking has been shown to be multifaceted, being linked to API properties, formulation and processing conditions. It is clear, however, that in general, placebo tablets do not stick and hence the API is considered critical to tablet sticking. Wang et al.[71] demonstrated a relationship between molecular interaction of a series of APIs with an iron superlattice and sticking, which support the importance of the API molecular structure in sticking potential. Waknis et al.[72] extended the modelling by assessing the impact of particle shape on sticking using two morphologies of mefenamic acid. This work indicated that the proportion of polar surface area is an important factor with respect to punch sticking. Work assessing metal adhesion during encapsulation work is expected to follow the same trends. This is supported by experimental work from Podczeck,[73] which indicates that the polar Lewis base surface properties of materials are in rank order to adhesion during encapsulation.

The content uniformity and segregation of an API are principally controlled by the particle size distribution, and as such particle engineering is the dominant factor over form selection. The same is true, but to a lesser extent, for flow which is influenced by particle size but also particle shape. Models for content uniformity and flow can be used to guide the material scientist. In cases of high-dose and low-solubility APIs, there will be a compromise with respect to size to achieve dissolution and flow, which will likely lead to a granulation approach being required for drug product processing. In the case of tabletability and tablet sticking, solid form selection and particle engineering both provide significant contributions in terms of achieving suitable mechanical and surface properties. Another potential compromise area could be on surface polarity, as this seems to be detrimental to punch sticking, but can lead to increased dissolution rate.

**Shelf life (stability)**

The shelf life of a drug product can be determined by the chemical or physical stability of the API in the formulated product. There have been a number of well-publicised physical stability issues for marketed products.[74] However, physical stability issues related to the API are minimised by selecting the thermodynamically stable form of the API and assessing the impact of drug product processing on the form during formulation and process design. Physical stability issues with respect to the API are possible with high-energy processing such as jet milling, which is the standard industrial process for obtaining a respirable size distribution of an API for DPIs. This is because, as well as causing size reduction, the high energy often leads to disruption or disordering of the API crystal lattice.[75] This damage to the crystal lattice is often referred to as process-related disorder. API with process-related disorder is often observed to recrystallise back to the crystalline form with time and under certain humidity or solvent vapour pressures.[75]
During this recrystallisation, particle size enlargement of the API is observed and the surface properties of the API are likely to change. This can be important for oral products by leading to reduced dissolution and is of particular importance for DPIs through significant impact on the fine particle dose. Two aspects of the process related disorder may be considered important: the physical stability of the disorder under different environmental conditions and the amount of disorder present. Often the material scientist will attempt to simulate the ‘worst-case scenario’ physical properties of the API using the amorphous phase. Nearly all quantification tests for process-related disorder use the amorphous phase as a reference standard. With these considerations in mind, the material scientist should have a thorough understanding of the amorphous phase of the API when developing an inhalation product. Understanding to show that the API amorphous phase can either be controllably removed by conditioning or is physically robust might be considered as part of solid form selection. There are a few constructive particle engineering approaches that can be used to prepare respirable particle of API (e.g. Chiou et al.\cite{76}) that could be expected to create a crystalline and therefore more physically stable particle; however, they are not commonly used.

Chemical degradation of API commonly defines the shelf life of a drug product. It has been shown that different polymorphs or salts of an API have different chemical stability.\cite{77,78} The crystal structure of the API may be important in chemical stability. On rare occasions, the structure of the API may leave it prone to degradation through the location of the reactive groups in the crystal structure; this is referred to as topochemistry.\cite{79} In addition, the presence of molecular level pores in the crystal structure may leave the reactive groups more prone to reaction.\cite{80} The level of disorder or amorphous content of an API has also been shown to influence stability, with increased disorder usually but not always leading to decreased stability.\cite{81,82} Moisture uptake by APIs has also been shown to have a marked impact on the chemical stability. Guerrieri et al.\cite{83} produced a model for the degradation rate (\(K_{prot}\)) of a range of salts of procaine based on the moisture uptake (\(W\)), saturated solubility of API in the moisture layer (\(C_s\)) and the stability of the aqueous layer (\(k_{aq}\)), as shown in equation 3, indicating that the degradation in this API is dominated by the solution state.

\[
K_{prot} = k_{aq} \times W \times C_s
\]  

\(3\)

During formulation development, the stability of an API and API in drug product is typically measured experimentally under accelerated conditions.\cite{84} It has been observed that typically the stability of API can be significantly influenced by mixing with excipients.\cite{85} Generally, the degradation rates are found to increase as drug loading is decreased so accelerated studies are carried out at low drug loadings. The process of making a dosage form will require the API to come into contact with other materials (excipients) to form interfaces. The underlying causes of the change in stability are multifactorial and will be product specific. However, they could be related to the creation of defects or disorder during processing, and the intimate contact of API and excipient surfaces.

Solid form and particle engineering can have a major impact on chemical stability. For solid state reactions, consideration should be given to reactive functional groups in the API structure and how they are expressed in the crystal morphology. In addition, it would be preferred to have an API that can be prepared in a highly crystalline form with low propensity for disorder during processing and low hygroscopicity. In cases where pH-dependent degradation may occur, consideration should be given to the impact of the counter-ion on pH micro-environment.

**Summary in relation to solid form selection**

Solid form selection is a continually evolving process, which is critical to both API and drug product design and processing. Physical properties of the API, such as solubility, stability, hygroscopicity and mechanical properties, are routinely considered as part of solid form selection. Traditionally, following solid form selection, particle engineering conditions are selected to control the size distribution of the API. In some cases, the knowledge and understanding is sufficient that relationships or computational methods exist to link API attributes to drug product attributes. In addition, there is growing evidence in the literature that the particle shape and surface properties of an API can also make a significant impact on the product performance for oral solid dosage forms and particularly DPIs. The solid form selection and particle engineering used for an API ultimately defines the attributes of the API. However, it is clear that the two activity are not mutually exclusive and hence should be considered in tandem, as shown in Figure 1.

It is critical to consider the particle engineering requirements that might be needed at the point of solid form selection. To do this, it is necessary to understand what properties would be expected to be required for a particular dosage form type. A challenge is that the solid form selection generally comes early in development where specifics of the formulation and process have not been locked down. The methods or models described in this section can be used retrospectively to assess risks once an API has been produced, but more importantly in the context of solid form selection they can be used to help guide the appropriate properties needed from the API solid form. Kougoulos et al.\cite{87} provided a detailed example of application of
content uniformity and the dissolution models, together with modelling of accelerated stability data. Based on the impact of fine particles on chemical stability and coarser particles on content uniformity and dissolution, they derived a target particle size specification for $D_{v0.1}$ and $D_{v0.5}$. Furthermore, they were able to select the most appropriate particle engineering technology for the API by assessing the potential to meet the target size, although there was discussion of the potential for applying models for guiding or setting API property specification.\cite{11,16} The paper by Kouguoulos et al. is one of only a few industrial examples. This example shows the value of models in guiding particle engineering but is important when applying models consideration is given to the assumptions inherent in the models and how that will impact on the output.

It is critical that solid form selection is carried out with a drug product perspective in mind. This would be facilitated by having a general set of API criteria in mind to guide the solid form selection. It would be expected that this approach would consider the manufacturing, performance and stability requirements for the dosage form and then translate them back into the attributes of the API required. There is substantial discussion and investigation in this area providing guidance on the selection of the best manufacturing process for an API, with the aim of developing a ‘Manufacturing Classification System’\cite{85}. For example, Hancock (as cited by McCormick\cite{86}) provides an example of such approach for the manufacturability component for an immediate release direct compression tablet, and the recommendations are summarised in Table 1.

An understanding of the optimal API properties would provide an advantage when trying to build those properties into the API through solid form selection and particle engineering, to make the process design and development more facile. To maximise the value of this philosophy at the time of solid form selection, it is important to consider how the scope for modifying other physical properties of the API is influenced by the solid form selected.

**The link among solid form, particle engineering and particle shape**

Solvent and additives can either modify the binding motifs that propagate through the crystal by forming H-bonded adducts such as solvates or cocrystals, or simply interact to different extents with each type of chemical groups expressed at each crystal face. Specifically, the rapid growth of edges and corners of a crystal is associated with the propagation of strong and directional intermolecular interactions, while less energetic interactions are associated with experimentally observed crystal faces.\cite{9} For habit modification to be effective, the solvent or additive must be capable of selectively disrupting an H-bonding pattern that is involved in the growth of one or a few of the crystal faces. This is important in the context of this review because different polymorphs, or more generally different solid forms, could have different susceptibilities to crystal habit modification, and a situation could be envisaged where an inability to modify an adverse crystal habit for one solid form could justify a switch to a different one. It therefore follows that the ability to model how sensitive an internal structure/solid form is to habit modification would be advantageous in terms of informing solid form selection. Indeed, if the overall crystal habit is dominated by one interaction that is significantly stronger than others present in the crystal lattice (for instance, as highlighted by the persistent presence of an extremely acicular habit even after crystallisation at low supersaturation from a variety of diverse solvents), selective disruption might prove non-trivial or impossible.

In general, it could be expected that different polymorphs could exhibit different ‘structural handles’ on crystal shape determined by the specific interactions and packing present.

<table>
<thead>
<tr>
<th>Property</th>
<th>Parameter Description</th>
<th>Target Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particle size and shape</td>
<td>$D_{v0.1}$ (mean volume diameter)</td>
<td>$&gt;30 \mu m$</td>
</tr>
<tr>
<td></td>
<td>$D_{v0.9}$</td>
<td>$&lt;1000 \mu m$</td>
</tr>
<tr>
<td></td>
<td>Aspect ratio</td>
<td>$&lt;1.5$</td>
</tr>
<tr>
<td>Powder flow</td>
<td>Effective angle of friction</td>
<td>$&lt;41^\circ$</td>
</tr>
<tr>
<td>Powder density</td>
<td>Bulk</td>
<td>$&gt;0.5 \text{ g/ml}$</td>
</tr>
<tr>
<td></td>
<td>True</td>
<td>$1.0–2.5 \text{ g/ml}$</td>
</tr>
<tr>
<td>Tableting performance</td>
<td>Dwell time sensitivity</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Compression force</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Compression stress</td>
<td>20–125 MPa</td>
</tr>
<tr>
<td>Compact mechanical properties (at $\sim 0.85$ solids fraction)</td>
<td>Tensile strength</td>
<td>$&gt;1.0 \text{ MPa}$</td>
</tr>
<tr>
<td></td>
<td>Brittle fracture Index</td>
<td>$&lt;0.2$</td>
</tr>
<tr>
<td></td>
<td>Indentation hardness</td>
<td>75–250 MPa</td>
</tr>
</tbody>
</table>

in their respective crystal structures. Of course, similar expectations can be extended to other crystal forms of a given molecule, including hydrates/solvates, salts and co-crystals. Indeed, examples of polymorphs displaying different morphologies in the same solvent have been reported, for example, for 2,3,5-trimethyl-1,4-diacetoxybenzene.[87] However, while the ability to predict the impact of a solid form modification on the availability of more favourable physical properties would be tremendously attractive, it also remains elusive. Indeed, in a recent review, Aakerøy et al. stated that ‘primary structural motifs, governed by relatively strong interactions, often display considerable consistency, . . . whereas weaker and less defined interactions can dramatically alter the 3D arrangements.’[88] This can be illustrated, for instance, through sulphathiazole, of which 5 different anhydrous polymorphs have been reported.[89] Strikingly, despite remarkable similarity in packing, conformation and H-bonding, for instance between forms II and IV, radically different morphologies are observed.[90] Moreover, none of the reported polymorphs appear to be sensitive to solvents in terms of crystal habit. This is especially remarkable in the light of the reported selective isolation of metastable forms from certain solvents,[90] indicating that solvents can interfere with nucleation without necessarily impacting crystal growth.

The application of molecular modelling to the prediction of the impact of solvents, impurities or additives on crystal shape is a very fertile research area and one too complex to fully discuss here. The reader is referred to a review by Schmidt and Ulrich,[91] which contains a useful summary of methodologies reported in the literature.

As well as having an impact on crystal shape, solvents can of course engage in H-bonding with the product, resulting in the formation of solvates, which in turn could display a completely different set of interactions compared with the crystal lattice of the unsolvated host, thus unlocking additional opportunities for particle engineering. Nangia and Desiraju compiled a survey of structures in the Cambridge Crystallographic Data Centre and ranked commonly used solvents in terms of their propensity to form solvates.[92] Of course, the selection of API solvates presents some challenges, not least the consideration of regulatory aspects around residual solvent levels.[93]

An additional piece of the puzzle was added by Aakerøy et al.,[94] who have compared the complexity of solid form landscape for salts vs co-crystals, which again is relevant here on account of different particle engineering opportunities potentially available with different crystal lattices. In their assessment, Aakerøy and co-workers concluded that salts are much more prone than co-crystals to show unexpected molecular compositions, including both additional components in the lattice such as solvents, and unexpected stoichiometries. This assessment, focused on cases where at least one carboxylic acid group was present, concluded that carboxylic acid groups are more easily satisfied when uncharged (compared with charged) and that the difference between salts and co-crystals is further exacerbated when no obvious donor, for example, an –NH₂ group, is present in the counter-ion or co-former.

To provide some degree of comparison between the growth rates of different solid forms of the same species, growth morphologies and attachment energies were calculated by the Authors for a series of carbamazepine derivatives, with results reported in Table 2. While the calculations simulate the morphology and growth characteristics of crystals grown in vacuum,[95] and as such do not take into account industrially relevant factors such as crystallisation solvent and supersaturation, they provide some useful pointers. Firstly, the calculations show that different solid forms could indeed provide a significant morphological landscape and that, through judicious solid form selection, more desirable product crystal shapes might become acces-

Table 2  Calculated vacuum growth morphologies and attachment energies for a number for carbamazepine solid forms. Calculations were performed using Materials Studio. CSD refers to the corresponding entry in the Cambridge Structural Database.

<table>
<thead>
<tr>
<th>CSD reference</th>
<th>Form description</th>
<th>Predicted growth morphology</th>
<th>Range of attachment energies (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBMZPN02</td>
<td>Anhydrous form 3</td>
<td>Diamond-like</td>
<td>−42.0 to −67.31</td>
</tr>
<tr>
<td>CBMZPN03</td>
<td>Anhydrous form 2</td>
<td>Needle</td>
<td>−88.5 to −398.6</td>
</tr>
<tr>
<td>CBMZPN12</td>
<td>Anhydrous form 4</td>
<td>Hexagonal plate</td>
<td>−63.3 to −161.1</td>
</tr>
<tr>
<td>CBMZPN16</td>
<td>Anhydrous form 5</td>
<td>Octagonal plate</td>
<td>−56.9 to −151.2</td>
</tr>
<tr>
<td>FEFNTO3</td>
<td>Di-hydrate</td>
<td>Hexagonal prism</td>
<td>−26.2 to −115.5</td>
</tr>
<tr>
<td>CRBMZ401</td>
<td>Acetone solvate</td>
<td>Hexagonal prism</td>
<td>−19.7 to −45.5</td>
</tr>
<tr>
<td>LOKFB</td>
<td>Isonicotinamide co-crystal, form 1</td>
<td>Hexagonal plate</td>
<td>−20.0 to −59.1</td>
</tr>
<tr>
<td>LOKFR01</td>
<td>Isonicotinamide co-crystal, form 2</td>
<td>Prism</td>
<td>−38.9 to −148.0</td>
</tr>
<tr>
<td>XAYGIP</td>
<td>Hydrochloride salt</td>
<td>Needle</td>
<td>−31.3 to −59.0</td>
</tr>
</tbody>
</table>

Structures were first optimised using COMPASS with forcefield assigned charges, then growth morphologies and attachment energies were calculated using the same forcefield and charges, with the exception of the hydrochloride salt, for which ESP charges were used following DMol³ structure optimisation (medium quality, GGA/PBE functional, no DFT-D correction, DND basis set). Refer to Materials Studio documentation for further information on COMPASS and the parameter settings used for these simulations.)
The relationship among solid form, particle size and particle engineering

Historically, the main physical property of the API other than the solid form that has been considered is the particle size distribution. The primary measures for success of particle engineering have been achieving a suitable particle size distribution while maintaining the preferred solid form in a crystalline state. Particle engineering for the control of API size and size distribution has taken two distinct approaches:

- Constructive particle engineering. Where the particle is built up from molecules of API, for example, crystallisation.
- Destructive particle engineering. Where larger than required particles of API are comminuted to deliver particles with the required size, for example, milling or micronisation.

During crystallisation, particle size and its distribution are ultimately determined by the interplay between nucleation, crystal growth, attrition and agglomeration. The link between environmental crystallisation conditions and nucleation/growth has been described in many textbooks (e.g. Mullin) and is outside the scope of this review. In essence, supersaturation plays a key role in determining the balance between nucleation (formation of new particles) and growth (of existing particles), with the latter favoured at lower supersaturation and resulting in fewer, larger crystals in comparison with an analogous crystallisation conducted at higher supersaturation. In addition, key components of the classical nucleation and growth equations display a dependence on lattice properties, for example, the alpha factor, which is a descriptor for surface roughness, are directly linked to the bond energies in the crystal. Furthermore, De Yoreo and Vekilov describe crystal growth as a balance between attachment and detachment of growth units from a growing crystal surface, with both phenomena linked to structural factors.

In general, it is difficult to make any kind of prediction of crystal size based on polymorphism alone. While different polymorphs will likely have different mechanical properties and surface properties, and hence could be susceptible to different tendencies to break or agglomerate in a solution environment, it is also true that Ostwald’s rule of stages predicts an initial transition via metastable forms, which complicates a direct experimental assessment of the link between polymorphism and crystal growth rates. In addition, a comprehensive literature search on a comparison of growth rates between compounds of pharmaceutical interest and their salts and co-crystals returned no hits. The latter is perhaps not surprising, considering that some of the preparative methodologies involved in co-crystals formation, such as solvent-drop grinding, might not be amenable to crystal growth measurements by conventional means.

To summarise, there is limited data in the literature to allow a meaningful comparison of growth rates of different solid forms, and a thorough experimental investigation across multiple compounds of pharmaceutical interest would be very valuable in confirming whether these differences in growth rates are observed, and in assessing their extent in realistic industrial crystallisation conditions.

The relationship among solid form, particle engineering, mechanical properties and surface energy

While the relationship among internal structure, particle engineering, mechanical properties and surface energy is difficult to deconvolute, nevertheless some good insights are available in the literature. For example, the flow of materials can be linked to surface energy among other factors, and in turn work by Bandyopadhyay and Grant has shown that surface energy is linked to face-specific attachment energies, implying that a change in morphology will result in a change in bulk surface energy. The relationship between mechanical properties and particle engineering, including a consideration of solid form, has been covered in Chow et al.‘s excellent review on engineering of pharmaceutical materials, where, for instance, the differing mechanical properties associated with different hydrated forms of magnesium stearate, a common pharmaceutical excipient, are cited.

The impact of both structural factors and particle properties controlled through particle engineering has been discussed in the literature. Broadly speaking, the mechanical properties of pharmaceutical materials are defined by the hydrogen-bonding framework defining their internal structure, and in particular the role of strength and directionality of the H-bonds in defining the network of interactions and the presence of slip planes in the crystals.

Shariare et al. discuss some of the basic predictive approaches for the estimation of mechanical properties of APIs, namely those based on interplanar d-spacing, on the calculation of elastic constants and on attachment energies.

The general conclusion is that estimates based on d-spacing are appropriate for crystals that are isotropic in nature; however, for anisotropic materials, a more complex framework that describes the ease of lateral displacement and hindrance to it because of the molecular roughness of the slip planes as well as plane-plane detachment energy is required. Khomane and Bansal\cite{100} postulated that the difficulty in reliable prediction of mechanical properties arises from the role that large numbers of weak H-bond interactions can play.

Conversely, Shariare \textit{et al}.,\cite{104} and Modi \textit{et al}.,\cite{69} related the impact of morphology, that is, a property that can be controlled during particle engineering, to the mechanical properties of pharmaceutical materials. Specifically, Shariare \textit{et al}.,\cite{104} considered the impact of different ibuprofen morphologies on the fracture mechanism and the critical brittle–ductile transition, and rationalised their findings in terms of location of cleavage planes. In addition, from the latter, the polar or non-polar character of the faces exposed after comminution was described using a structural framework, which was then verified through experimental measurements of surface energy. Modi \textit{et al}.,\cite{69} focus on the impact of crystal morphology on compactability and interparticulate bonding strength. In the case of celecoxib, these studies revealed that a plate morphology offered superior compactability compared with acicular crystals, and again the observations were rationalised on the basis of crystal and surface chemistry.

A complementary perspective on the link between crystal shape and mechanical properties of bulk materials was offered by Waknis \textit{et al}.,\cite{72} Their study of the adhesion behaviour of mefenamic acid with different crystal shapes indicated that sticking of API on tablet press punches during compression operations involving long dwell times can ultimately be modulated through adjusting the contribution of hydrophobic (less ‘sticky’) and hydrophilic crystal surfaces.

While much emphasis has been placed on the role of crystal shape, primarily because of the emergence of improved modelling tools that have enabled prediction and rationalisation of observed behaviour to a level of accuracy hitherto unattainable, the importance of additional particle properties that are controlled during crystallisation and other particle engineering operations is also known and well documented. For example, the fracture mechanism of any material is known to change below a critical particle size that is compound dependent and is known as the critical brittle–ductile transition point.\cite{102} Additionally, Shariare \textit{et al}.,\cite{102} elegantly define the role of defects by describing the dependence of mechanical properties on coherent length, that is, the effective contact area between slip planes, which is in reality defined by the length over which planes are structurally ordered, with the latter usually being limited by defects and being smaller than particle size itself. Consequently, particle engineering operations that could give rise to a higher level of defects could result in materials that are easier to fracture because the effective size of the slip planes is decreased.

The prediction of face-specific surface energy was first approached by Hartman\cite{105} with a method, based on attachment energy calculations, that is still used in more contemporary studies, for example, by Shariare \textit{et al}.,\cite{102} The postulated link between surface energy and attachment rates described by equation 4:

\[
\gamma_{hkl} = \frac{Z d_{hkl} E_{hkl}^m}{2V}
\]

with \(\gamma_{hkl}\) as the face-specific surface energy for face \(hkl\), \(d_{hkl}\) the corresponding lattice spacing, \(E_{hkl}^m\) the attachment energy and \(Z\) the number of molecules in the unit cell.

An extended comparison in terms of surface energies between different solid forms of the same active ingredient has not been reported; however, a series of predictions can be made using known solid forms of carbamazepine using the approach proposed by Hartman.\cite{105} The results are shown in Table 3. These calculations are based on the attachment energy values reported in Table 2 using equation 4.

### Table 3 Predicted surface energies for different solid forms of carbamazepine based on equation 4. CSD refers to the corresponding entry in the Cambridge Structural Database

<table>
<thead>
<tr>
<th>CSD reference</th>
<th>Form description</th>
<th>Predicted surface energy for the most dominant crystal face (kcal/mol(\AA))</th>
<th>Predicted surface energy for the least dominant crystal face (kcal/mol(\AA))</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBMZPN01</td>
<td>Acetone solvate</td>
<td>0.0752/(001)</td>
<td>0.0327/(11-1)</td>
</tr>
<tr>
<td>CBMZPN02</td>
<td>Anhydrous form 3</td>
<td>0.0584/(011)</td>
<td>0.0988/(020)</td>
</tr>
<tr>
<td>CBMZPN03</td>
<td>Anhydrous form 2</td>
<td>0.0242/(2-10)</td>
<td>0.0291/(2-21)</td>
</tr>
<tr>
<td>CBMZPN12</td>
<td>Anhydrous form 4</td>
<td>0.0430/(200)</td>
<td>0.0469/(111)</td>
</tr>
<tr>
<td>CBMZPN16</td>
<td>Anhydrous form 5</td>
<td>0.0384/(002)</td>
<td>0.0274/(102)</td>
</tr>
<tr>
<td>FEFNOT03</td>
<td>Di-hydrate</td>
<td>0.0706/(020)</td>
<td>0.0978/(1-1-1)</td>
</tr>
<tr>
<td>CRBMZAO1</td>
<td>Acetone solvate</td>
<td>0.0752/(001)</td>
<td>0.0327/(11-1)</td>
</tr>
<tr>
<td>LOKFIB</td>
<td>Isonicotinamide co-crystal, form 1</td>
<td>0.0794/(001)</td>
<td>0.0888/(1-1-1)</td>
</tr>
<tr>
<td>LOKFR01</td>
<td>Isonicotinamide co-crystal, form 2</td>
<td>0.0371/(011)</td>
<td>0.0522/(101)</td>
</tr>
<tr>
<td>XAYGIP</td>
<td>Hydrochloride salt</td>
<td>0.0520/(010)</td>
<td>0.0790/(100)</td>
</tr>
</tbody>
</table>
The data show that, on one hand, a diverse range of surface energies can be accessed through different solid forms, but also that the overall change in surface energy resulting from a change in morphology is very limited (and possibly of no practical significance) for some of these solid forms such as anhydrous forms 2 and 4, whereas a more marked change in surface energy is seen, for example, between the two isonicotinamide polymorphs. In addition, although this set of data only encompasses a limited number of solid form entities, there seems to be no discernible relation between surface energy and the ‘type’ of solid form, for example, free species, hydrate, salt or co-crystal.

The focus of earlier sections has been on understanding which API physical properties might be modified or controlled through solid form selection and particle engineering to aid design of a robust process leading to a drug product with required performance. This approach assumes that the properties of the API measured at release are not modified during downstream drug product processing. This will be the focus of the final section of this review.

### Solid form and particle properties of the API after drug product manufacture: potential for change during process or inappropriate prediction of drug product attributes

The testing of an API batch at release is often the last time the API is directly characterised, although the impact on its quality can be assessed further down the line through indirect measurements such as drug product potency or dissolution. The characterisation provides the information to go into predicting or modelling the drug product performance. This assumes that the API physical properties are not impacted by the drug product processing. Over the last decade, there has been increased focus on the potential for the drug product process to influence the properties of the API, which then leads to changes to the drug product quality attributes either at release or on stability.

A key consideration is the potential for change of the solid form (phase transformation) during drug product processing. There are many cases documented in the pharmaceutical literature of where the crystal form of the API has been changed during drug product processing.[106,107,108]

To understand this risk, it is recommended to map out the range of conditions (e.g. temperature, pressure, water activity and composition) that the API is exposed to during processing.[109] The potential for change can then be significantly reduced by selection, if possible, of the most physically stable solid form of an API at ambient conditions and the environmental conditions the API is exposed to during manufacture. Govindarajan and Suryanarayanan[110] reviewed the potential for phase transformation and provided a detailed summary of the potential mechanism of form conversion in drug product, as shown in Figure 3. They conclude that it is much more challenging to characterise the API in the final drug product than as a pure API because of the potentially low concentration of API and the multicomponent nature of the formulation. With this in mind, it is good practice to simulate the drug product processing step on the pure API and assess solid form changes as part of the solid form nomination process.[6] However, it

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![Figure 3](image-url)  
**Figure 3** Schematic representation of process-induced phase transformations (adapted from Govindarajan and Suryanarayanan[110]).

can be challenging to simulate the exact environmental condition during processing and the micro-environment at the excipient–API interface in the drug product. For example, the potential for a salt form to break back to its original free form during processing is very much dependent on the micro-environment in the drug product and hence challenging to simulate.\[111\]

Particle properties can also be affected by drug product processing, as shown in Figure 4. The effects are separated into the three key API particle properties of size, shape and surface. Sometimes the changes in API properties are produced by design. For example, coating APIs with different microsized lubricants was shown to improve flow,\[112\] but most often the changes are unexpected and only detected through a change in the drug product quality attributes. Advances in analytical techniques used to assess API in drug product allow the material scientist to make quantitative analysis of particle properties.\[113\]

Changes in physical properties for the neat API compared with the API in drug product can result either in an increase or a decrease in the particle size. Reduction in particle size is caused by high energy drug product processing leading to fracture or attrition of the API. Gamble et al,\[114\] provide an excellent example of tracking the API particle properties through a typical drug product process using a chemically selective imaging system (Morphologi G3S-ID, Malvern Instruments, Malvern, UK). This work demonstrated the potential for size reduction during processing. Interestingly, they showed that low shear blending and commilling did not significantly impact on the size, whereas the force feed system used for the roller compactor did cause measureable size reduction. Based on the literature on the impact of downstream processing on API particle properties, it is expected that higher aspect ratio particles would be most likely to undergo size reduction. In addition, it would be expected that API that has already undergone mechanical processing such as milling or micronisation would not be prone to any further size reduction.

A larger apparent API particle size in drug product can be caused by agglomeration. These agglomerates then act as primary particles with respect to their impact on drug product attributes such as content uniformity\[59\] and, in some instances, dissolution. Often these agglomerates are present because of cohesive API properties.\[115\] The apparent particle size of an API in drug product will be a balance of the primary particle size, cohesive forces and the level of dispersion energy applied through blending. Therefore, it is often possible to increase de-agglomeration by increasing shear forces during blending.\[116\] In some cases, it may be appropriate for the API particle size test to be designed based on the dispersion mechanism observed in the drug product so as to detect changes in cohesive properties as well as primary size as part of API characterisation and release.

Surface properties of a crystalline API are dependent on the internal structure and morphology, which control the surface functional groups. Therefore, any changes in morphology due to fracture and comminution may influence the surface properties. Furthermore, disorder in the crystal lattice caused by high energy processing\[75\] would also lead to change in surface chemistry. In addition apparent changes in the surface properties of the API can be caused by intimate interaction with excipients. These can be by design to improve attributes such as powder flow and dissolution\[117\] or unintentional such as over-lubrication of API leading to poor dissolution.\[107\]

Overall, there are numerous examples of where unexpected changes or differences in the apparent particle

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**Table 1**

<table>
<thead>
<tr>
<th>Changes in API Particle Attribute during Drug Product Processing</th>
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<tbody>
<tr>
<td>Size Difference</td>
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<tr>
<td>Shape Difference</td>
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<tr>
<td>Surface Difference</td>
</tr>
</tbody>
</table>

**Figure 4** Schematic representation of potential drug product process induced changes in active pharmaceutical ingredient particle attribute.
properties of API in the drug product when compared with the measurement on the API have led to unpredicted issues with drug product performance. Hence, in cases where the apparent size, shape or surface properties of the API may be critical to the drug product performance, it is important to track those properties through the drug product process to aid with API and drug product process design.

Conclusions

There is a substantial body of literature to assist the translation of solid form and particle properties into drug product performance. The selection of the solid form together with its potential to impact the particle properties should be considered in the context of the material science tetrahedron (Figure 5).[19] The tetrahedron concept considers the connection among structure, properties and ultimately product performance. In the context of this review, solid form selection provides the structure, which is then combined with particle engineering to provide the properties. The balance of application of solid form vs particle properties to provide API with properties matching the drug product requirement will depend on the specific circumstances. However, in general, it could be considered that the expected relationship of form vs particle influence is shown in Figure 1. Overall, this schematic is intended to lead to the following conclusions. First of all, most or all of the key drug product attributes considered during pharmaceutical product development can be linked to only five API physical properties, which in turn are intimately connected. Second, anisotropy of crystals and differences in surface chemistry as a function of API crystal shape can play a key role in determining the drug product attributes, for example tabletability, fine particle dose and dissolution. Finally, these physical properties are linked to the internal structure of the API – set at the time of solid form selection – and are controlled through particle engineering, with internal structure representing the canvas of achievable properties that can be modulated through particle engineering.

There are established models to predict product performance based on API properties (e.g. dissolution linked to particle size, shape and solubility). Further development of these models so that they are linked back to API structure will facilitate increased integration of the solid form and particle engineering into the product design. Solid state chemical stability in particular provides a substantial challenge, but could perhaps provide the biggest reward in terms of time and cost saving during drug product development.

API property selection (form and particle) provides an important design option to achieving the most facile development of a drug product, in contrast with options that deal with API issues through formulation or process fixes. A truly holistic strategy for drug product development should focus on linking solid form selection, particle engineering and formulation design to both exploit opportunities to access simpler manufacturing operations and prevent failures due to incomplete understanding of the impact of API properties on drug product performance, processing and stability. As the understanding of the link between API crystal structure and its properties improves, the integration of solid form selection into drug product design will be further enhanced. Where the properties of the API are critical to the overall performance of the drug product, care should be taken to maintain them appropriately through the drug product processing steps.

Declaration

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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Integration of API solid form selection


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