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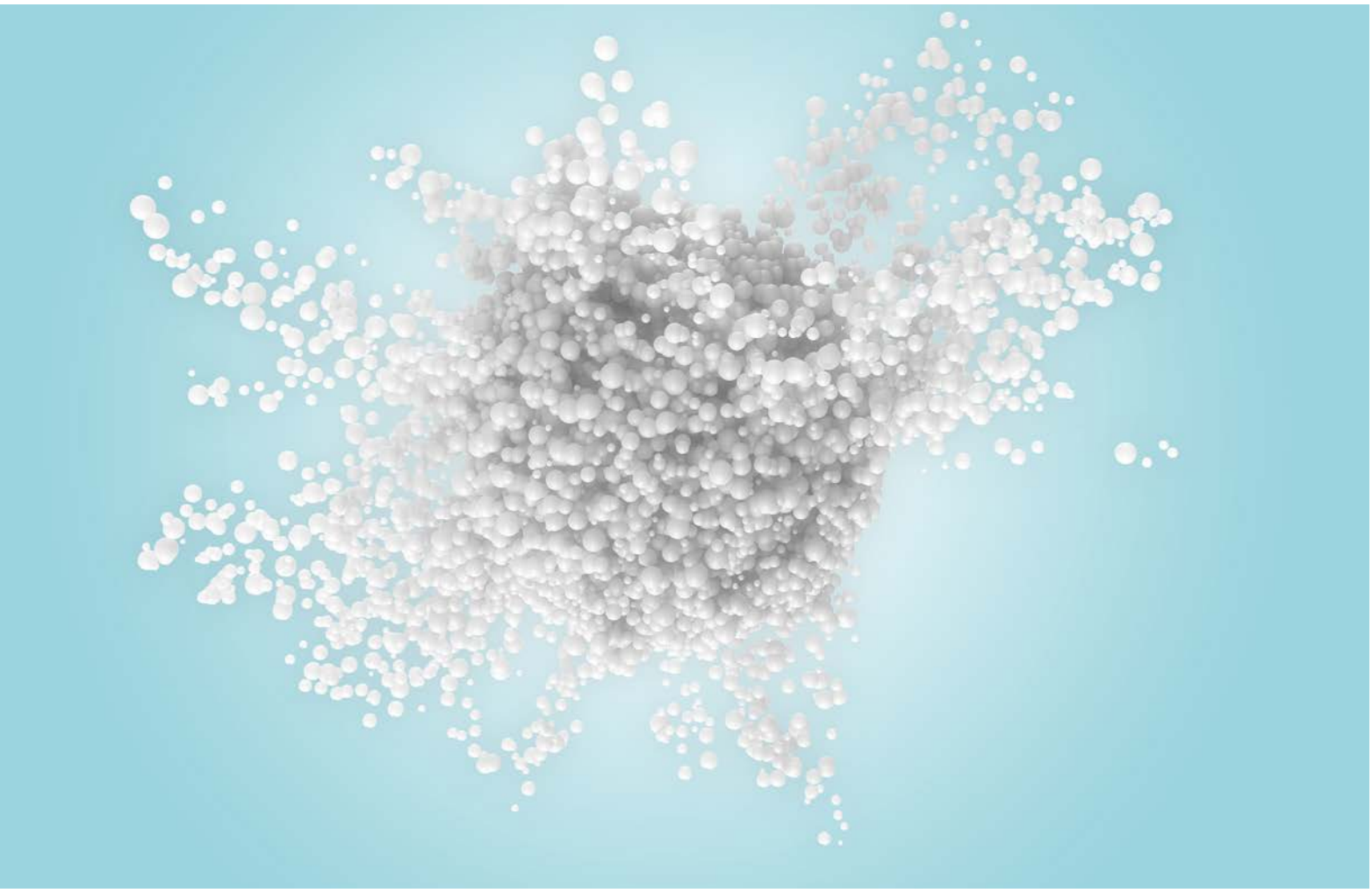

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WHITEPAPER

Critical API attributes and the major impact they can have on drug product development

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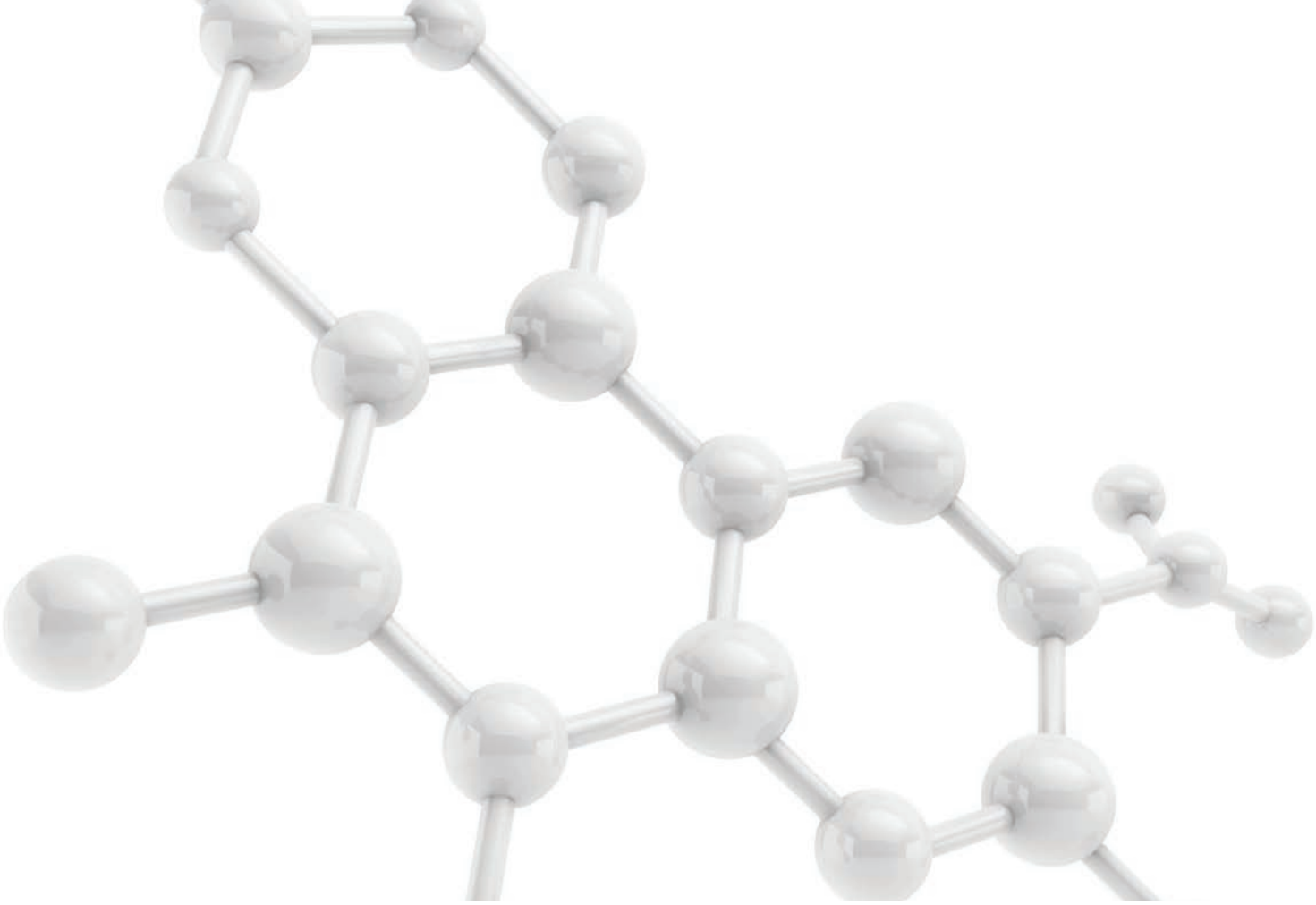

Abstract

Chemical process development of an active pharmaceutical ingredient (API) or drug substance and the pharmaceutical development of the final, formulated drug product from this API are frequently treated as independent activities in the overall process of developing a new drug.

To some extent this is born of necessity, since the drug substance must be generated and made available to pharmaceutical development before any product development activities can commence. As a result, chemical process development is often completed before the requirements of final formulation have been fully defined. However, both activities are intimately linked by the final purification and isolation step of the chemical synthesis and manufacturing process, which for solid APIs, most frequently, is a crystallization process. This final isolation should be carefully crafted to deliver the same solid form, which defines the inherent physical properties of the drug substance as well as process-dependent particle properties for every batch that is manufactured.

No matter how well-designed and robust the crystallization is, if its development lacks consideration for the particle properties required for formulation, the result may be an API that is difficult to handle or requires additional processing before manufacturing the final formulation. Conversely, not all APIs can be manipulated to deliver all attributes required for trouble-free formulation development and manufacturing activities. An integrated approach to product development can serve to avoid common pitfalls and focus efforts to where real issues exist as a result of a mismatch between the API properties and the requirements placed upon the formulated product.

API properties and their impact upon formulation

It is well known that the physical properties of an API are important in selecting the dosage form and designing its formulation to meet the drug product requirements. Some of the relevant physical properties, such as melting temperature, equilibrium solubility, crystal structure and mechanical properties dependent upon the crystal structure such as hardness of the particles, are inherent to a given crystal (e.g. polymorph, salt, solvate/hydrate, or co-crystal) modification of the API and cannot be changed. The following properties can be a result of the crystallization process employed to isolate and purify the API obtained from the final step of the chemical synthesis and can be manipulated to some extent by modifying the process conditions for the final isolation:

- crystal habit and size
- size distribution
- dissolution rate
- bulk and tapped powder density
- flowability
- static behavior
- compactibility
- wettability
- other material characterization

While the crystal habit—the external appearance and shape of the particles—is in first approximation defined by the growth behavior of individual crystal facets and therefore a consequence of the crystal structure, external factors, such as solvents and impurities in the solution from which the API is isolated, can interact with different crystal faces and modify their growth behavior. This can result in various aspect ratios or even shapes when using different solvents in the crystallization process or if synthesis routes are modified or changed, resulting in different byproducts and impurity profiles.

Similarly, size and size distribution depend upon crystallization conditions as both are a function of the number of particles generated during the crystallization process through (primary and/or secondary) nucleation as well as the growth rates of the particles. The dissolution rate of an API is a function of the surface area of the particles, which is determined by the size and size distribution and therefore also a process dependent property. All of these particle properties are key parameters and need to be taken into consideration when selecting a formulation.

Particle size matters

Equilibrium solubility under physiological conditions and dissolution rate of the API particles in the dosage form are two important factors defining release characteristics of the drug substance in the body and influence the bioavailability of the drug. Since the former is an intrinsic property of the drug substance, it is important to identify unfavorable behavior early enough in development in order to find suitable mitigating measures such as changing the solid form, e.g., selecting a salt or co-crystal for enhanced solubility or even considering amorphous API. The dissolution rate, on the other hand, is not an intrinsic property and can be modified to some extent by changing the particle size characteristics.

In order to provide a suitable range of size distributions required for studying the effect of particle size upon dissolution rate, a good understanding is required not only of the impact of crystallization conditions on particle size but also of the potential of different crystallization technologies or alternative technologies, e.g., size reduction methods, to provide the necessary particle size ranges.

Crystal habit (shape) and size distribution of the API particles can have a substantial influence upon the processability of the powder, its mixing behavior with excipients used in the formulation, and ultimately upon quality of the product. Highly anisotropic particle shapes such as needles, fibers, and plates frequently have poor flow properties, which can result in poor mixing behavior with excipients and difficulties achieving a uniform and consistent product.

Even with favorable particle shapes, problems can emerge, specifically if particle size distributions are broad or do not match the particle size distribution of the excipients employed. Broad particle size distributions can result in high compactability of the API powder which, in turn, can also lead to poor flow properties. In addition, granular convection—popularly known as the muesli or Brazil nut effect—can occur during processing.

Motion, such as vibrations, during transport and dispensing of the API, leads to spatial separation of the individual particles by size, increasing the risk of content uniformity issues in the final product. The same effect can occur if the API particle size is mismatched with the particle size of the excipients employed.

A smart approach to product development

The complexity arising from the interplay between all the factors described above suggests an alternative approach to developing a drug product that, while necessarily starting with the synthesis of the API, defines final product requirements at an early stage of development.

By keeping an eye on the drug product target profile and engineering the API to develop a drug product that meets the criteria, a better targeted development of an API with the right particulate properties can be facilitated to ensure more efficient and cost-effective product development.

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Naturally, this requires close cooperation between development chemists and solid state and crystallization specialists as well as pharmaceutical development specialists who have the requisite set of skills to identify the critical product properties and develop suitable manufacturing processes to deliver the required API properties that ensure drug product quality and performance.

It also calls for suitable organizational structures to facilitate efficient ways of working and good project management to direct and focus research and development efforts to where they are needed.

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This idea is not entirely new. To the knowledge of this author, several large pharmaceutical companies have attempted to encourage and enforce closer cooperation between chemical and pharmaceutical development with a view to creating more efficient development workstreams. The fact that this is not standard practice speaks to the challenge in implementing such an approach.

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To some extent, the challenge is built into the pharmaceutical development process itself, as mentioned above, and is a result of the necessity to synthesize and manufacture an API before it can be formulated.

It is also somewhat of a consequence of cultural differences, even between closely related disciplines, such as chemistry and pharmacy, and insufficient mutual understanding of the details of the respective disciplines.

The greatest barrier to an integrated approach, however, is the combination of cost of development of a new drug and the risk of its failure at any stage during clinical trials.

As a result, it is common to minimize development effort to the bare essentials required to enable the respective pre-clinical or clinical studies at each stage of development, delaying seemingly non-critical activities as long they can be delayed. While the cost savings inherent in this approach are obvious, the risk it entails is difficult to quantify.

While these challenges are already severe for large companies, they may appear insurmountable for small and mid-sized companies that must rely on CROs and CDMOs for their research and development work, especially if engaging with multiple partners.

Different partners may suggest different or even conflicting work packages and timelines have to be carefully managed. Simply establishing efficient communication between partners can be a challenge. Moreover, financial considerations may seem to dictate an “as little as possible” approach, increasing the risk of problems at later stages of development.

A “smart” approach, or doing the right work at the right time, does not necessarily mean significantly higher costs. In the greater scheme of things, the cost of establishing the formulation relevant properties of a new API with a view to selecting an appropriate formulation for the final product is negligible when compared to the overall cost of development. Moreover, the benefits of understanding API properties certainly far outweigh the cost of mitigating issues at a later stage, which could have been caught, addressed, and rectified earlier.

About us

Thermo Fisher Scientific provides industry-leading pharma services solutions for drug development, clinical trial logistics and commercial manufacturing to customers through our Patheon brand. With more than 65 locations around the world, we provide integrated, end-to-end capabilities across all phases of development, including API, biologics, viral vectors, cGMP plasmids, formulation, clinical trials solutions, logistics services and commercial manufacturing and packaging. We give pharma and biotech companies of all sizes instant access to a global network of facilities and technical experts across the Americas, Europe, Asia and Australia. Our global leadership is built on a reputation for scientific and technical excellence. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to Care™ program. As a leading pharma services provider, we deliver unrivaled quality, reliability and compliance. Together with our customers, we're rapidly turning pharmaceutical possibilities into realities.

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Matthew Jones joined the Thermo Fisher Scientific Linz site in 2016 and has over 25 years of experience in crystallization process development and solid state characterization. He has 12 years of pharmaceutical industry experience and has developed numerous crystallization processes for small molecule APIs for isolation, purification and particle engineering. Since joining Thermo Fisher, Matthew has established and manages a dedicated crystallization process development laboratory supporting chemical development and manufacturing across API manufacturing sites in Europe and the USA. He has also guided the modernization of and recruitment of experts for the solid state analytical laboratory in Florence, SC, establishing a state-of-the-art facility. Matthew has extensive experience in technical protein crystallization working as an assistant professor under Prof. Joachim Ulrich at the Martin-Luther-Universität in Halle, Germany. He is the author of over 50 publications, 2 patents, several book chapters as well as a book on industrial crystallization of proteins.

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