

Time to Put the Spotlight on the Substance of your Drugs through Solid-form Development

The global pharmaceutical industry generated more than \$1.25tr in revenue in 2019, up from \$1.2tr in 2018¹, and the final figures for 2020 are expected to be even more impressive. With this expansion, it is no surprise that the space is growing ever more competitive.

In such a fast-paced environment, pharmaceutical companies need to do all they can to ensure their products – no matter whether they are new innovations or improvements to existing active pharmaceutical ingredient (API) solids – stand out in the market. Even marginal gains in therapeutic effect or the cost of manufacturing can make all the difference to whether a product succeeds or fails to make an impact.

The question facing pharmaceutical companies is: how to achieve these all-important enhancements? As John Mykytiuk at Sterling Pharma Solutions explains, the answer to this question lies in perfecting the physical characteristics of the API solid itself through solid-form development.

Even with the turmoil of the ongoing COVID-19 pandemic, the pharmaceutical industry has continued its impressive legacy of innovation. Over the last year, it has produced not only new coronavirus therapies and vaccines at an unprecedented pace, but has delivered exciting new treatments for a variety of other serious medical conditions as well.

The European Medicines Agency (EMA) recommended 97 new medicines for authorisation by European Union (EU) Member States in 2020, and 39 new active substances². This is up from 66 new medicines and 30 new active substances the year before. The story is the same in the US, where the Food and Drug Administration (FDA) approved 53 novel therapies last year³, up from 48 in 2019⁴.

In this fast-paced environment, pharmaceutical companies are under more pressure

than ever before to produce therapies – new or improved – that can outpace those of competitors, by being more efficacious or more cost-effective. Even the smallest enhancements can make a big difference in terms of success.

With this in mind, it is crucial that pharmaceutical companies make every effort when developing new drugs, or enhancing existing treatments, to optimise their effectiveness and simplify the required manufacturing process.

However, the process of optimising a drug is more than simply looking at its chemical make-up, or the delivery method. It's vital to also consider the physical characteristics, from the packing of the API's molecules, to the shape and size of its individual particles – a process known as “solid-form development”.

The Impact of a Drug's Solid Form

The physical make-up of an API plays a key role in the optimisation process for any API, whether a new substance or an existing one, due to its effect on the behaviour of the drug in the manufacturing process and subsequently in the human body.

It is possible for an individual API to have multiple possible crystal lattice packing arrangements – a phenomenon known as “polymorphism”. On top of polymorphism, the range of possible shapes and sizes of API particles results in very different consequences in terms of the drug's behaviour.

For example, all these factors can impact on an API's solubility in water or in other solvents, with repercussions for therapeutic effect.

A poorly water-soluble API might have reduced bioavailability – meaning less of it can enter the bloodstream when introduced to the body to have an active effect. This undermines its efficacy as a treatment, requiring more frequent dosing to maintain therapeutic blood levels, with consequences for patient convenience and adherence.

The molecular structure of an API polymorph also has ramifications for formulation

manufacturing efficiency. It can affect the melting point of the substance, meaning that energy used during drug product manufacture may change the form. More complex salt, cocrystal, hydrate and solvate formation processes may be required to produce the target version or polymorph. In addition, particle size reduction such as milling operations may be needed to achieve the required particle shape and size. All of these will impact on an API solid's commercial feasibility.

Given the impact of these physical characteristics, it is clearly vital that drug companies take steps to identify the most appropriate polymorph and other features if they want to produce commercially successful drugs.

Moreover, the physical properties of an API – including the polymorphs, salts, cocrystals, hydrates, particle shape and size – form a key part of product patents. Taking this into account, investing in appropriate solid-form development can identify the preferred physical properties. In doing so, it can not only help ensure the success of a drug product, but can help safeguard a company's intellectual property (IP), protecting it from the competition.

The Search for the Right Physical Profile

Identifying the right physical characteristics for an API requires drug companies to consider many factors.

The thermodynamic behaviour of an API polymorph – the structural stability of the solid and how it changes over time – including its mechanical properties, such as brittleness, compressibility or ductility, are crucial to determine, due to their impact on manufacturing.

Likewise, the surface texture of an API particle can impact its solubility and therefore bioavailability. It can also affect how API particles interact with each other, with irregular surfaces potentially leading to the particles clumping together, with consequences for dosing.

In addition, the surface properties can affect how it responds to its surroundings



or its ability to absorb water or dissolve, its responses to light via photodegradation, and how the API is handled and drug product packaged.

The kinetic properties of an API, meaning how particles dissolve in a medium, such as PBS or biorelevant media, is another important characteristic to consider, as it can impact on bioavailability and, therefore, efficacy.

Finally, and as important to consider, is the chemical purity of the API. Drug developers must identify any impurities in the API in order to be able to develop a manufacturing process capable of controlling them effectively to ensure optimum health and safety.

Considering the Formulation

In addition to optimising the efficacy of the API, it is necessary to consider how the physical characteristics of an API will impact on other factors in the development process.

In particular, the API's physical properties must be appropriate for the formulation of the finished drug product to ensure optimum performance in the final delivery method – whether oral, parenteral or inhalation.

The interaction of a formulation's components with the API has a vital part to play in the therapeutic effect of the drug, as well as the shelf-life of the product.

All of this highlights the vital role played by the solid form of an API on therapeutic

effect. Perfecting the physical characteristics of a substance is vital to achieve the most effective product.

Optimising the Process, Enhancing Efficiency

Once the appropriate properties have been determined, drug companies must then carefully consider how they can reproduce them consistently during the manufacturing process in an efficient manner.

It is crucial to achieve this goal, as the cost of producing the API will impact profitability for the finished product. With this in mind, to ensure the product succeeds on the market, any manufacturing process must be able to minimise production costs to maximise profit margins.

The time it takes to manufacture and refine an API directly impacts the cost of production. Solid-form development can identify ways to simplify the manufacturing process for the API, helping to streamline the scaling and commercialisation process, so companies can benefit from a return on their investment (ROI) more quickly.

Enhancing synthesis processes to produce the API is an important first step in reducing production time. Even more important, though, is the filtration and drying of the produced API, be it a new chemical entity, NEC, or existing material. The right methods can wash and isolate the desired drug substance, eliminating impurities and achieving consistent chemical purity and solid-form characteristics from batch to batch of API.

Finding an effective method for both filtration and drying is key to ensuring any API's commercial viability and can be addressed through crystallisation development.

However, filtration and drying on their own may not always be enough to ensure consistency across a batch of API, as the dried particles may still be irregular in size and shape. Therefore, it may be necessary to incorporate milling or micronisation into the manufacturing process to reduce the API particle size and achieve an optimum profile.

This step can add time to the production process, so it is important to find solutions at earlier stages in the development cycle to eliminate the need for particle size reduction. Better filtration procedures can reduce waste, while improvements to drying can reduce the amount of additional processing, such as milling, further downstream. This can ultimately reduce the cost of manufacturing, increasing eventual ROI for the drug compound.

Seeking Expert Solid-form Development Help

It is clear that solid-form development has a vital role to play not just in delivering more effective drugs for patients, but also in minimising manufacturing costs and optimising productivity for drug companies.

Despite the importance of this stage in the drug innovation journey, pharma companies, regardless of their size, often do not have the expertise or infrastructure to carry out the investigative processes needed to identify the ideal physical properties

of an API, and optimise manufacturing processes.

However, it is possible to outsource the solid-form development process to expert partners. A growing number of contract development and manufacturing organisations (CDMOs) are offering specialised material sciences services, including expert teams and dedicated infrastructure and capacity, in order to help drug companies to develop their API solid.

When engaging a CDMO for solid-form development services, though, there are some investigative processes that are essential for effective and comprehensive solid-form development. If they want the best possible support, drug companies should ensure that their CDMO partner offers the following investigations:

1. Polymorphism investigation – to identify the polymorph that not only offers the greatest therapeutic effect, but also has the thermodynamic qualities and chemical stability required to ensure commercial viability.
2. Salt/cocrystal investigation – to improve the solubility of the API and identify ways to improve it for optimum bioavailability and manufacturing feasibility.
3. Pre-formulation evaluation investigation – to optimise the API's solubility as well as chemical and mechanical stability for the needs of the formulation.
4. Flow characteristic determination – to understand how the formulation will flow through processing equipment and delivery device to customise both for optimum performance.
5. Crystallisation development – to devise the most effective and efficient process to reproduce the target API characteristics consistently.
6. Bulk particle manipulation – to determine whether particle size reduction such as milling is needed following isolation of the drug substance, to achieve an appropriate particle shape and size.

In addition to offering these, it is important that drug companies work with

CDMO partners that offer the flexibility and capacity to meet their solid-form development needs.

More and more CDMOs are investing in dedicated material science facilities and teams to deliver specialist support in this area – working with these, drug companies can ensure the highest possible standard of solid-form development.

Work with Experts to Shape the Perfect API Particle

Solid-form development lays the groundwork not just for therapeutic effectiveness, but also for commercial viability, so it is vital that sufficient time and attention is dedicated to this part of the drug development process. Failure to do so can result in drugs that are unnecessarily expensive to make, without adding value to healthcare professionals and patients, ultimately undermining their market value.

By engaging with CDMOs that specialise in solid-form development, however, companies can minimise the risk of this occurring. The right partner can give them the guidance and support they need to live up to the pharmaceutical industry's reputation for innovation, delivering better, more cost-effective therapies that transform patients' lives.



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John Mykytiuk obtained his degree in chemistry and PhD in polymerisation reaction kinetics from the University of Bradford. Following two post-doctoral positions at Sussex University, he joined Cyanamid GB as part of a drug development group. John then moved to a CRO, Evotec/Aptuit, where he was involved in chemical process research and development including solid state investigations. John then moved to Onyx Scientific to take up a role to develop solid state services where he was involved with numerous and diverse solid state investigations. John now leads the solid state activities at Sterling Pharma Solutions encompassing physico-chemical characterisation, salt and polymorphism investigations, crystallisation development and particle characteristics.