EXPANDING THE COMMERCIAL OPTIONS FOR PREPARATION OF AMORPHOUS SOLID DISPERSIONS

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Spray drying (SD) and hot-melt extrusion (HME) are commercially proven and accepted amorphous solid dispersion (ASD) technologies for the enhancement of the dissolution and bioavailability of poorly soluble drugs. These approaches are not suitable for all APIs, however. Hovione, in addition to offering non-ASD solutions such as nanomilling and cyclodextrin complexation, is developing an effective coprecipitation technology platform to address this key market need.

ENHANCING SOLUBILITY WITH ASDS

Solubility in physiological fluids is a prerequisite for high bioavailability of drug substances. For many APIs that exhibit poor water solubility, bioavailability can be enhanced by preparing the product in an amorphous rather than a crystalline form. Amorphous compounds, because they lack long-range order, typically have higher apparent solubilities and faster dissolution rates than their crystalline counterparts. On the other hand, they present some challenges in drug formulation due to their reduced physical and chemical stability compared to crystalline materials.

Formation of a solid dispersion of an amorphous API in a polymeric matrix can often improve its stability. Amorphous solid dispersions (ASDs) therefore provide a means for preparing amorphous drug formulations with higher apparent solubilities and faster dissolution rates as well as the stability required for safe and efficacious medicines.[1]

ASDs are most commonly produced via spray drying (SD) or hot-melt extrusion (HME). A wide variety of approved polymer excipients are available for the formulation of ASDs. The specific polymer and preparation method are dictated by the characteristics of the API and the desired properties of the formulated product, including the dose and form (tablet, capsule, etc.).

DETERMINING THE BEST METHOD

As mentioned above, on the commercial scale, spray drying and hot-melt extrusion are the two main methods used to prepare ASDs. The solubility of the API in organic solvents and its melting point are the two key properties that are considered when determining the best method for ASD formation. HME applicability is limited to APIs with low melting points and non-thermal labile drugs, while SD is in practice limited only by API solubility in organic solvents. In some cases both technologies are applicable, and the formulator must consider additional factors in order to select the optimum solution.

There are also cases, however, where neither HME nor SD is ideal, particularly APIs with high melting points (>200 °C) and limited solubilities in volatile organic solvents. For these 'brick dust' compounds, which are increasingly prevalent in the drug industry pipeline, either an alternative method for ASD formation is required,

or a non-ASD approach must be adopted (such as nanomilling or complexation with cyclodextrins; see Table 1).

Amorphous solids can be generated using a number of different techniques beyond SD and HME. Solvent-free methods include vapor condensation, supercooling of a material in the liquid state, and disruption of a crystal lattice in the solid state via grinding. Solvent-based methods involve precipitation of the API from solution, and include solvent evaporation via various methods and freeze drying. To date, these different methods have generally only been performed on smaller scales.

Coprecipitation of an API and a polymer is, on the other hand, an attractive option for problematic APIs that are also scalable. There has been in fact one drug (Zelboraf®, vemurafenib, from Roche) produced at large scale via a solvent-controlled precipitation process.[2]

PRACTICAL COPRECIPITATION

Improvement of the coprecipitation process is, however, needed to make the technology more attractive for commercial drug formulation and manufacturing. Hovione, a leader in spray drying, is developing new techniques for coprecipitation that will allow its use as a robust and reliable third-platform technology for ASD generation.

The approach we have taken involves the use of microfluidization.[3] In this solvent-controlled precipitation (SCP) process, the API and polymer are dissolved in one solvent and mixed with a second, antisolvent in which the ingredients are insoluble (alternatively, the polymer can be dissolved in the API antisolvent). The two streams interact under carefully controlled conditions in a microreactor. These conditions are selected to allow the formation of an API-polymer coprecipitate consisting of agglomerates of nanoparticles. The nanoparticles have very high surface areas and thus unique physicochemical properties.

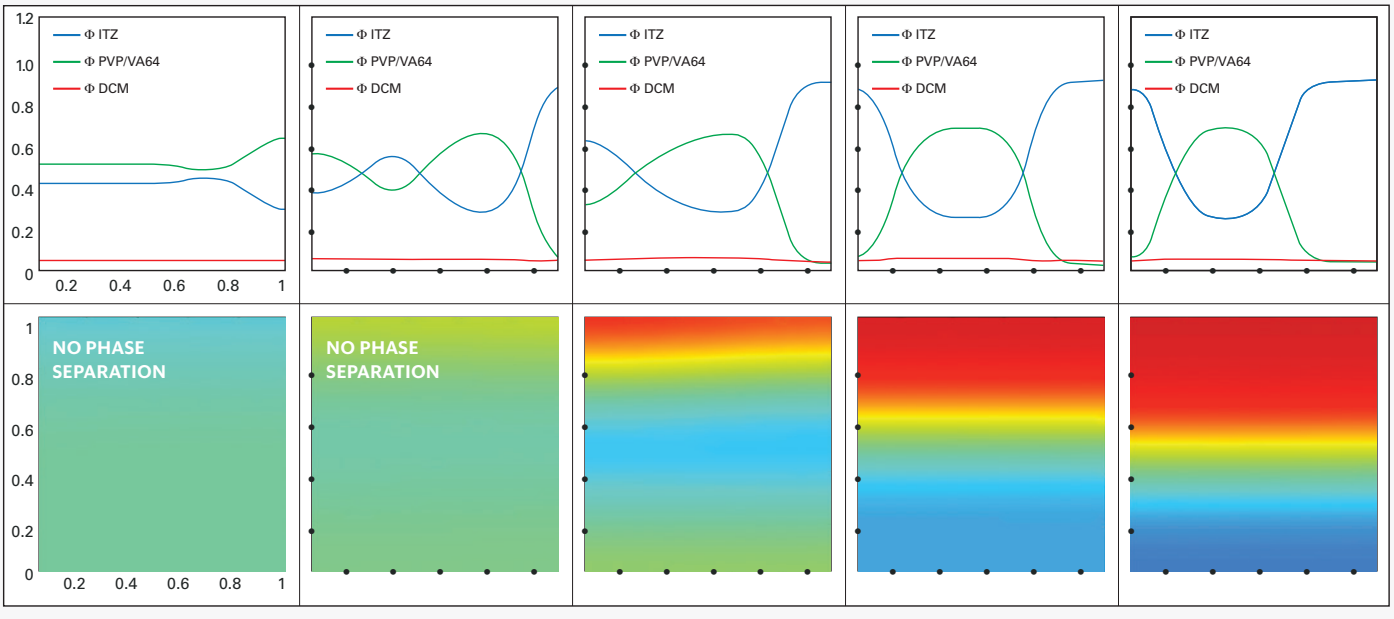
One advantage of the technology over spray drying is the ability to use polar, high-boiling solvents (dimethylacetamide and dimethylformamide, for instance). In addition, compared to HME, coprecipitation is a low-temperature process that can be used for thermosensitive APIs. The novelty of our approach to SCP at Hovione is the use of microreactors and microfluidization to promote the contact between streams. The feed concentrations and rates, API/polymer ratio, and mixing conditions (temperature, time, etc.) have a direct impact on the critical quality attributes of the materials produced.

Traditionally, coprecipitation processes have been performed in stirred reactors with shear mixing, which provides limited control over the actual mixing conditions. In our process, however, the particle size, size distribution and morphology, as well as the level of nanoparticle aggregation, can be finely controlled due to the uniform mixing conditions generated in the microreactor using an assisted microfluidization process. As a result, this new SCP technology is highly attractive for enhancing the bioavailability of BCS Class II compounds with poor solubilities. The suspensions containing the coprecipitates may be isolated by conventional means, as filtration or centrifuge or dried via spray drying to yield spray-dried nanocomposite microparticles.

THE USE OF MICROFLUIDIZATION TECHNOLOGY ALLOWS FOR FINE CONTROL OF THE PARTICLE SIZE, SIZE DISTRIBUTION, DENSITY AND OTHER CHARACTERISTICS CRUCIAL TO DRUG PERFORMANCE.

TABLE 1

Drug: **Polymer Ratio** (%W/W)



FORMATION OF A SOLID DISPERSION OF AN AMORPHOUS API IN **A POLYMERIC MATRIX CAN OFTEN IMPROVE ITS STABILITY.**

WHEN ASDS ARE NOT AN OPTION

Even with access to coprecipitation, there are times when solubility enhancement for APIs cannot be achieved through the preparation of an amorphous solid dispersion. There is consequently a need for non-ASD alternatives in such cases. Nanomilling and inclusion complexation with cyclodextrins are two additional options.

The nanomilling process at Hovione predominantly involves a step of microfluidization to produce the nanoparticles, followed by isolation via spray drying to isolate the materials or microencapsulate the APIs. As with the coprecipitation process, the use of microfluidization technology allows for fine control of the particle size, size distribution, density and other characteristics crucial to drug performance.

Inclusion complexation with cyclodextrins is another established method for increasing the solubility of poorly soluble APIs. Hovione has a license with Ligand to access their Captisol® technology (sulfobutyl ether β-cyclodextrin) for formulation screening; that provides access, at the proof-of-concept stage, to one of the most successful cyclodextrins in the field. As with the development of ASD solutions, processes based on nanomilling and inclusion complexation with cyclodextrins need to be developed with scale-up to commercial production in mind.

ACCELERATING FORMULATION DEVELOPMENT

While we have built a great reputation in particle engineering, particularly on our process development capabilities and the ability to take any process from the lab to commercial scale, we have also started developing strong foundations in formulation development. One example of the latter is our proprietary software (Ternarius) for the development of ASDs. Thermodynamics, diffusion and solvent evaporation kinetics were incorporated into a mathematical model, allowing formulators to identify promising formulations without the need to consume any API.[4] Additionally, this tool provides guidance to reduce the number of physical experiments that must be performed, therefore saving time and expensive API.

We are also developing methodologies for the rapid evaluation of the potential *in vitro* and *in vivo* performance of compounds formulated using different ASD and other platform technologies for enhancing bioavailability. These methods take into consideration the target tissue(s), formulation type, and dosage (among others) to predict the most appropriate solution.

CONCLUSION

The improvement of solubility has become a crucial subject for many drug candidates under development today. Access to the best solution for bioavailability enhancement ensures the highest likelihood for successful formulation of these challenging compounds.

Hovione is therefore continuing to extend its expertise and capabilities in spray drying while developing other enabling technologies such as hot-melt extrusion, a novel coprecipitation platform technology, and alternative techniques for APIs not suited to ASD formation.

Our extensive experience with many different types of poorly soluble compounds has also provided us with a great basis to develop state-of-the-art methodologies for accelerating formulation design and process development, allowing for more rapid and cost-effective identification of optimum solutions. P

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