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Overcoming Excipient Challenges in Spray-Dried Dispersions

Polymers and surfactants impact stability and long-term performance.

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Access to high-throughput synthesis and screening technologies has enabled the discovery of novel classes of small molecules that exhibit high potency. Unfortunately, many of these compounds suffer from poor solubility and bioavailability when administered in conventional solid-dosage forms, the preferred route of administration due to convenience and ease of use. Formulation as amorphous solid dispersions (ASDs)--most commonly via spray drying (SD) or hot-melt extrusion (HME) and more recently co-precipitation (CP)--is increasingly used to improve the performance of poorly soluble drugs. The choice of excipients for spray-dried formulations has a direct impact on the stability and efficacy of these ASDs.

Risking metastable forms

ASDs involve incorporation of the API in a metastable form within a polymer matrix. Spray-dried ASDs are prepared by dissolving the API with the polymer and other excipients in a solvent (or solvent mixture) and then removing the solvent through a rapid flash-drying process. “Metastable, amorphous forms have greater solubility and bioavailability, but because they are in a higher energy state, they desire, as do all things in nature, to move to a lower energy state, in this case via crystallization,” notes Márcio Temtem, associate director for particle design and formulation development at Hovione.

The challenge is to avoid or at least delay for a sufficient length of time (the shelf life of the product) this change in the metastable state. The key excipient in ASDs--the polymer--forms a matrix that provides this needed stabilization. The matrix disperses the API molecules, preventing any interactions between them that could lead to crystallization. API molecules trapped within such a matrix also have reduced molecular mobilities, which further reduces their potential for crystallization.

Formulation considerations

Several key factors must be considered when formulating spray-dried ASDs, such as the selection of the best ingredients to increase the “supersaturation effect” and the API/polymer ratio and the impact it may have on the stability and performance of the selected system. According to Temtem, “the API and polymer must form a true solid solution in which the polymer and API cannot be distinguished from one another and are mixed in such a way and in the right proportion that the mixture is thermodynamically and/or kinetically stable and the two compounds prefer to be together rather than apart.” Finding this “sweet spot” is achieved using various computational, high-throughput screening, and other experimental tools combined with knowledge and experience.

Processing conditions

Spray drying is just one method for preparing ASDs and may not be ideal for certain APIs or target formulations. Each method--spray drying, hot-melt extrusion, and co-precipitation--produces dispersions with different morphologies, surface areas, particles sizes, and other attributes that impact product release profiles. The manner in which the API is entrapped in the matrix is very different and thus also results in different levels of “disorder,” or in other words energy levels, according to Temtem.

Process conditions during spray drying may also impact the chemical purity of some APIs. “Although the drying technique is gentle and takes place rapidly with the API droplets protected by evaporation of the solvent, it is necessary to assess an API for degradation during drying,” Temtem observes. He adds the use of solvents can also result in the plasticization of the amorphous solid dispersion, increasing the molecular mobility and thus the potential to crystallize.

Challenges of excipient selection

The first challenges to maintaining stability in ASDs, according to Meredith Perry, associate director of pharmaceutics with Pharmatek SD, Catalent, is the need to use a polymer that is chemically compatible with the API while also being miscible and improving the supersaturation of the API in aqueous media. “Although most polymers are relatively inert, some are hygroscopic or acidic and therefore inappropriate for compounds prone to hydrolysis or acid degradation,” she states.

The second challenge is to select a solvent that provides sufficient solubility and chemical stability for both the active ingredient and the chosen polymer. “A wide range of organic solvents can be safely spray dried, so usually it’s possible to find a combination of solvents, such as polar protic and polar aprotic solvents, that meet these objectives,” Perry says.

The next challenge with ASDs is excipient selection in the solid state. Any instability previously noted in the crystalline form of the API will likely be more pronounced in the amorphous state, according to Perry. “Specifically,” she observes, “hygroscopicity is typically worse in an amorphous form due to the hygroscopicity of some polymers and the high surface area of the ASD particles. Reactivity with acids, bases, and oxidizing agents is also generally worse due to the high energy state of the amorphous material.”

Common excipients

The pharmaceutical industry favors the use of excipients that have been previously approved and have data supporting their use in humans. As a result, there are three main families of polymers used to form spray-dried ASDs, according to Temtem: cellulose-based polymers, polyvinylpyrrolidone-based polymers, and acrylate-based polymers.

Common cellulose-based polymers used in spray-dried dispersions (SDDs) include hypromellose acetate succinate (HPMCAS) and hydroxypropylmethyl cellulose (HPMC). Widely used pyrrolidone polymers include polyvinylpyrrolidone (PVP, also known as polyvidone or povidone) and copolymers of PVP with vinyl acetate. A polyethylene glycol, polyvinyl acetate, polyvinylcaprolactam-based graft copolymer has also been used extensively in ASDs. Copoylmers of methacrylates with acrylic acid in different ratios make up the third family of polymers used to form the matrices within SDDs.

“Polymer selection is the primary tool for chemically and physically stabilizing the API in an ASD because the two compounds are mixed at a molecular level,” notes Perry. For instance, HPMC capsules are often preferred over gelatin for hard shell capsules because HPMC has a neutral pH, low moisture content, and low hygroscopicity. Mannitol as a tablet excipient also meets these requirements.

In third-generation SDDs, surfactants, typically d-α-Tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS) or sodium lauryl sulfate (SLS), are often added to prevent precipitation of the API during dissolution. “Surfactants help to maintain supersaturation of the API by forming micelles and/or other 3-D structures during drug product dissolution. The API is kept in solution by preventing interaction of API molecules with one another,” Temtem explains.

Surfactant use is only effective at relatively low levels (< 5-10%); when used at higher levels, surfactants often undergo phase separation in the SDD. Due to their low melting points and sometimes low glass transition temperatures, when added to formulations in large quantities, may hinder product accumulation inside the units and result in physical and chemical stability challenges.

For compounds that are pH-sensitive, excipients with pH buffering capacity, such as citric acid and sodium bicarbonate, can have a stronger stabilizing effect on ASDs than on crystalline APIs, according to Perry. In addition, solid-dosage forms can be coated for further moisture protection. Materials such as polyvinyl acetate-based (PVA-based) coatings provide a good barrier, and can be coated more thickly than film coats to provide further protection.

Excipient developments

Excipient suppliers are taking various approaches to the development of new products for use in SDDs. Most efforts are directed at developing improved versions of existing, approved excipients given that drug manufacturers are hesitant to risk attempting to get a new drug approved with a truly novel excipient; novel excipients do not have a separate approval pathway and are only approved when a drug-product formulation in which they are used receives approval.

Thus, suppliers are looking to develop new grades of existing matrix polymers or to develop modifications to existing excipients. For instance, HPMCAS until recently was largely supplied by Shin-etsu. The company’s patent protection is expiring, and other suppliers such as Ashland and Dow are working to add this polymer to their portfolios. In addition, excipient suppliers are developing polymers with different combinations of acetate and succinate substituents to provide more options for drug developers. “These new excipients open new windows for formulators, particularly from a quality-by-design standpoint. Formulators now have many more polymer with a broad range of properties, allowing for the development of more effective products,” Temtem asserts.

Another approach is the development of higher-performance versions of existing excipients that help manufacturers optimize their production processes. Temtem notes that Dow, for instance, is developing excipients for the pharmaceutical industry that have lower viscosities and thus allow for higher solids concentrations in SD formulations and/or the ability to process spray-dried systems under milder conditions.

The development of novel excipients, or new chemical entities, is not as common but is ongoing despite the challenges in obtaining their approval. BASF, for example, is developing a new excipient with a good balance between the hydrophilic and hydrophobic moieties that provides good stabilization of APIs in solid dispersions while also maintaining supersaturation for an extended period of time, according to Temtem.

Mesoporous silica is also a substance attracting significant interest from the pharmaceutical research community as a potential excipient for ASDs. Mesoporous silica has small pores and a high surface area and has been used for many years as a catalyst in chemical processing and for various applications in the food industry. “For ASDs,” observes Temtem, “the size of the pores in mesoporous silica is ideal for trapping API molecules and preventing them from interacting. The material is advantageous because silica powder has good characteristics in terms of its flowability, which leads to improved downstream processing. Silica is also an inert material, and thus, there is no potential for interactions with the API or the GI tract.”

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