The prevalence of poorly soluble active pharmaceutical ingredient (API) molecules in the drug development pipeline has increased the popularity of solubility-enhancing formulations for oral tablet drug products. This article discusses the benefits of creating spray-dried dispersions to improve API solubility.

API molecules intended for oral administration are often categorized using the Biopharmaceutical Classification System (BCS), which indicates the primary factors affecting API bioavailability and, subsequently, directs the formulation strategy required to support the drug product’s development. The system uses the API's solubility and permeability characteristics to place the compound into one of four categories, as shown in Figure 1.
An API is considered "highly soluble" when the highest clinical dose strength will dissolve in 250 milliliters or less of aqueous media over a pH range of 1 to 7.5 at 37°C. For permeability assessment, an API is considered to be "highly permeable" when the extent of the API absorption (parent drug plus metabolites) in humans is greater than or equal to 90 percent of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.

Trends suggest that the majority of API candidates currently in the development pipeline have a BCS Class II rating [1], meaning that they require a solubilization strategy to promote oral bioavailability and maximize the chance of clinical success.

Traditional methods of processing an API for an oral tablet dosage form have used micronization to reduce an API's particle size, which increases its overall surface area and promotes faster dissolution. However, for many Class II APIs, micronization doesn't sufficiently improve API solubility to achieve the desired clinical outcome. While the micronization makes the API particles dissolve faster, the dissolved API may quickly precipitate in vivo before it can be absorbed. This means that today's drug developers must identify more complex techniques for improving and sustaining the solubility of poorly soluble APIs prior to their inclusion in tablets or other solid oral dosage forms.

**Spray-dried dispersions**

One well-documented, commercially validated technique for enhancing API solubility is to prepare the poorly soluble API as an amorphous dispersion within a carrier polymer using a spray dryer. The amorphous state of the API means that there are no highly ordered or crystalline interactions between API molecules, which leads to higher solubility in water, relative to a crystalline API. However, an amorphous API tends to be unstable and will recrystallize unless stabilized. A spray-dried dispersion (SDD) places the API molecule in a polymer-mediated solubilized state and maintains that amorphous state during transition through the patient's gastrointestinal (GI) tract.

You can prepare an SDD quite easily by dissolving both the API and polymer in a suitable solvent that can be readily evaporated (such as acetone or methanol). It's important that the API and polymer both be completely dissolved, otherwise crystalline API may appear in the final SDD. The solution is then delivered into a spray drying unit, which quickly converts the solution into droplets. These droplets dry rapidly in-flight as they travel from the top of the spray dryer to the outlet. The solvent's rapid evaporation traps the API-polymer mixture in the amorphous state and produces a low-density solid particle. The dried SDD material then goes through a post-drying step to ensure complete removal of the solvent.

Often, the goal of SDD design is to achieve the ideal in-vivo solubility-enhanced API molecule profile. A crystalline API slowly dissolves but never exceeds its equilibrium solubility limit, as indicated by the light blue line in Figure 2. An SDD's amorphous nature ensures rapid initial API dissolution (referred to as "spring"), as shown by the red line in Figure 2. Following this rapid spring dissolution, the API continues to dissolve over time in the intestinal milieu in a supersaturated state maintained by the presence of the SDD's polymers. The dried SDD material then goes through a post-drying step to ensure complete removal of the solvent.

While polymer selection for an SDD is dependent on the nature of the API, several well-characterized polymers have been shown to be successful, including hydroxypropyl methylcellulose (HPMC), hydroxypropyl methylcellulose acetate succinate (HPMC-AS), and polyvinylpyrrolidone (PVP). Using biorelevant characterization dissolution methods, you can determine the API's propensity for precipitation in the GI tract, which will steer your polymer selection and help determine drug loading limitations.
You can initially manufacture SDD prototypes in batch sizes as small as 500 milligrams to characterize the API-polymer matrix. Techniques such as differential scanning calorimetry (DSC) and x-ray powder diffraction can determine the API-polymer homogeneity and miscibility within the matrix and confirm the amorphous nature of the prototype. Using DSC, you can also determine the formulation’s glass transition temperature, which is a key predictor of the SDD’s physical stability. This allows you to evaluate the formulation’s propensity to crystallize or destabilize during long-term storage.

Researchers often use SDDs (routinely administered as a suspension) in early-phase clinical studies. This provides rapid clinical evaluation of the SDD, which is appropriate to determine the API exposure and confirm that the solubilization approach has been successful. However, a conventional tablet format is often the desired drug product form for proof of concept or patient trials.

**SDD tablet development**

Successfully developing an SDD into an oral tablet requires that you pay attention to certain considerations during formulation. First, the typical drug load for an SDD is 40 percent, but the acceptable target weight for most tablets is less than 1 gram, which limits the amount of extragranular excipients you can incorporate into the tablet formulation. Second, you must optimize the SDD’s particle size to be small enough to ensure rapid dissolution but not so small that the formulation segregates during processing or storage.

SDD tablet development must ensure effective in vivo tablet disintegration, which is necessary to expose the SDD for initial wetting and subsequent dissolution in the GI tract. SDDs often contain traditional tablet ingredients, with the balance between disintegrants and fillers optimized using small compaction studies and dissolution testing. After identifying the lead formulation compositions, the next step is to optimize the key process parameters that affect critical product characteristics, such as solid fraction (relative density) during manual slugging, ribbon thickness during roller compaction, and tablet hardness during compression.

**SDD tablet characterization**

To characterize an SDD tablet formulation, you must perform standard tests to build a data package, including assay, related substances, and content uniformity. The dissolution test is a critical characterization tool, because the API’s release rate is reliant on the disintegration rate of the tablet, the subsequent exposure of the SDD for wetting, and the resultant API dissolution. Using a variety of dissolution media can help to provide a robust understanding of both the initial API release and the subsequent maintenance of the solubilized state at different pH values, mimicking the movement of the drug product through the patient’s GI tract.

**Future outlook**

The use of SDDs as an enabling technology for poorly soluble APIs is common for early-phase clinical development programs. For example, Quotient has developed more than 250 SDD clinical-stage products in the past decade, with more coming on each year. As products such as these advance through clinical development toward approval, it seems clear that SDDs will become an increasingly common approach for developing new oral tablet drug products.

**References**


Nikki Whitfield is vice-president, CDMO services at Quotient Sciences, Nottingham, UK (www.quotientsciences.com). She has 23 years of experience in the pharmaceutical industry, including development, transfer, and scale-up of both early-phase and late-phase spray-dried, inhaled, and topical products for both the European and US markets.