Front & Center

# Enhancing the Solubility of Poorly Soluble Drugs

Studies have shown that combinatorial and high-throughput methods result in the generation of leads that are outside the limits of the Lipinski rule of 5 space (i.e., poor solubility and drug-like properties). Other studies suggest that the poor solubility of drug candidates, in addition to safety, efficacy, toxicity, and metabolic clearance issues, are drivers of lead attrition.

It has been estimated that 40% of the new chemical entities (NCEs) developed by the pharmaceutical industry are practically insoluble in water. According to Meinolf Brackhagen, senior technical service and development scientist at Dow Pharma Solutions, in a presentation delivered during CPhI Worldwide 2017 in Frankfurt, Germany, "Drug products containing low solubility compounds account for about 30% market share, and about 70% of the new drug substances in the pipeline are poorly soluble."

As a result, numerous techniques—numerous chemical and physical modifications—have been developed to enhance the solubility of these poorly soluble drugs. One of these techniques includes the manufacture of amorphous solid dispersions of drug substances in a polymeric carrier. Doing so serves two purposes, noted Brackhagen, "First, the polymeric carrier allows the preparation of stable amorphous dispersions with high solids loading, and, second, once in contact with intestinal fluids the polymeric carrier helps to stabilize the drug substance against precipitation or re-crystallization, keeping in mind that the stability, compound loading, and dispersion characteristics are characteristic of the particular drug substance."

One of these polymeric carriers is hypromellose acetate succinate (HPMCAS). HPMCAS is manufactured from hydroxypropyl methylcellulose (hypromellose) and anhydrides succinic acid and acetic acid to give hydroxypropyl methylcellulose acetate succinate with differing acetyl and succinyl content that are purified by precipitation from water. "No heavy metal catalysts are used," says Brackhagen. The material meets all requirements in the current *USP-NF* and *JPE* monographs for Hypromellose Acetate Succinate that also make it less onerous to use from a regulatory submission and documentation perspective. In addition, Dow's technical literature also states that the *USP/NF* specification for the limits on the acetyl and succinyl content are broader than the material offered by the company.

Using a variety of manufacturing techniques, HPMCAS has been incorporated into drug products such as Incivek™ (telaprevir), Zelboraf™ (vemurafenib), Kalydeco™ (ivacaftor), Noxafil™ (posaconazole), and Orkambi™ (lumacaftor and ivacaftor), presumably to improve the solubility and dissolution characteristics of these drug substances. The techniques that were used to incorporate HPMCAS into these drug products included co-precipitation, spray drying, and hot melt extrusion.

Meinolf Brackhagen, senior TS&D scientist at Dow Pharma Solutions

A line of HPMCAS, manufactured and marketed by Dow Pharma Solutions and trademarked AFFINISOL™, is available as granular and fine powders and three acetyl and succinyl contents (e.g., 7% acetyl and 16% succinyl, 9% acetyl and 12% succinyl, and 12% acetyl and 6% succinyl). In addition, Dow also offers a developmental "high-productivity" grade of HPMCAS for evaluation at customers that has the same acetyl and succinyl content and chemical and physical properties as the standard grades. "One can increase solids loading about 1.7-fold using the high-productivity grade than you can otherwise use with the standard grades, increasing productivity by a corresponding amount," noted Brackhagen. The Affinisol technical documentation also says that the same quantities of solids and high productivity-grade Affinisol in dissolved acetone, methanol, and tetrahydrofuran (THF) exhibited lower viscosities than comparable quantities of solids, standard-grade HPMCAS, and solvent over the test concentration range.

Dissolution test results comparing 25% itraconazole/HPMCAS 912 and 25% itraconazole/high-productivity HPMCAS 912 showed that the dissolution profiles were equivalent. Similar

testing also showed that as a function of dissolution, the solubility of poorly soluble drug substances such as itraconazole, ketoconazole, and phenytoin dispersed in either the standard or high-productivity grades of HPMCAS was comparable.

From a cost and productivity standpoint, compared with the standard grade of HPMCAS, the use of high-productivity HPMCAS in a spray drying process over a five-fold scale range resulted in roughly a 50% savings in time and cost at each increase in scale; the greater the scale-up, the faster the manufacturing and the greater the cost savings. "This productivity increase… could be beneficial for your timelines in the early phases," said Brackhagen.

Hot melt extrusion is another method of preparing solid dispersions. From a materials, equipment, utility, and space standpoint, spray drying and hot melt extrusion have differences that will dictate which method to use: spray dryers are available in small scale, but require a common solvent for both the drug substance and the HPMCAS. Hot melt extruders have small footprints and do not require solvents, but their use is limited to drug substances that are not thermally labile at the temperatures used in the hot melt process.

Studies by Dow show that the viscosity of hot melts of the high-productivity grade of HPMCAS is 60% lower than the standard grade. In addition, the results of Design of Experiment (DoE) studies show that the design space is also much bigger when using high-productivity grade HPMCAS. "With the high-productivity grade, we have more freedom to work with as well as better safety margins to increase or decrease throughput," stated Brackhagen. In addition to higher potential throughput, comparisons of the dissolution profiles of 40% indapamide extruded with high productivity and standard-grade HPMCAS showed that the high-productivity grade provided similar or slightly faster dissolution than the standard grade.

**"The use of high-productivity HPMCAS in a spray drying process over a five-fold scale range resulted in roughly a 50% savings in time and cost at each increase in scale."**

Heat maps resulting from Quality by Design (QbD) studies exploring the behavior of spray-dried HPMCAS substituted with a wide range of acetyl and succinyl content and poorly soluble model compounds such as itraconacole, danazol, griseofulvin, and phenytoin show that there are areas of best performance with respect to acetyl and succinyl content. In general, formulations containing HPMCAS spray-dried dispersions with higher acetyl content delay release whereas those with higher succinyl content speed release.

Building on a widely used compendial material, Dow now offers a hydroxypropyl methylcellulose grade for hot-melt extrusion (Affinisol HPMC HME). Compared to HPMC 2910, HPMC HME is soluble in water, acetone, methanol, ethanol, and methylene chloride whereas HPMC 2190 is soluble only in water, swells in methylene chloride, and is insoluble in the other solvents. Other key properties include a lower glass transition temperature (Tg) and minimal color changes at elevated temperatures, plasticizers not needed, applicability for immediate and controlled-release applications, and low moisture adsorption.

Using griseofulvin as a test compound, comparison of the dissolution profiles of pelletized hot melt extrudates prepared with different grades of HPMC HME showed that the release of griseofulvin can be controlled over a wide range; the higher the molecular weight of HPMC, the slower the release. By controlling the size of the pellets, the release can also be tailored (i.e., smaller pellets release drug substance more quickly).

The availability of excipients such as HPMCAS and HPMC HME facilitate the formulation of poorly soluble drug substances into viable and marketable drug products. In addition to enhancing solubility and tailoring drug release, these excipients also provide options for manufacturing flexibility, scale, and speed. Brackhagen also noted that the company will work with customers to develop formulations or, if needed, tailor the polymers to give formulations that deliver the desired performance.