Amorphous Solid Dispersion Using Hot-Melt Extrusion

Technology to enable many low aqueous solubility compounds.

Overview
Amorphous solid dispersions have enabled many low aqueous solubility compounds by providing enhanced oral bioavailability from the modified drug form. While there are several platform technologies and manufacturing techniques to produce amorphous solid dispersions, hot-melt extrusion (HME) is continually explored as one of the lead approaches based on having a small footprint, being amendable to continuous operation, and readily scalable. These attributes of HME trend toward more plug-and-play unit operations having a relatively lower cost of goods to manufacture compared to other technologies, making it a more appealing commercial process train.

Technology
Hot-melt extrusion is a technique for manufacturing amorphous solid dispersions, where-in the drug substance is melted or dissolved within an amorphous dispersion polymer and mixed to form a new miscible form of the drug substance. Functional excipients, including surfactants, may be added to further aid in processability, or to improve the dissolution performance of the formulation upon administration. The melt can then be extruded through a shape-forming orifice, and upon rapid cooling should remain a solid, single-phase, glassy amorphous matrix that is shelf-stable. Downstream processing equipment can be adapted to manage the extruded shape and make it amendable for additional handling. In general, these materials will be milled to reduce the particle size to a size that is appropriate to be incorporated into traditional tablet or capsule dosage form, while maintaining the performance targets for the drug.

Experience
By combining Bend Research’s breadth of solubilization technologies with our depth of fundamental understanding, we can rapidly help identify and optimize the amorphous solid dispersion formulation that can enable a drug substance. Choice formulations are identified based on our proven performance testing and physical stability model, then coupled to the HME process to assess manufacturability.

Properties of the drug, polymer, and dispersion formulation are used to vet the process space for the appropriate scale of the project. An example of this approach is described below:
1. Operating limits defined by material handling properties for a given equipment scale, configuration, and operating limits.
2. The minimum operating temperature defined by the viscosity of the formulation and torque limits for the given equipment.
3. The maximum operating temperature defined by the kinetic thermal stability of the drug, polymer, or dispersion.
4. Process interface to achieve a single-phase amorphous dispersion defined by the thermodynamic miscibility of the formulation combined with the degree of mixing that can be achieved for a given equipment scale and configuration operated at specific parameters.

Bend Research has more than a decade of experience in formulation and process development using twin-screw extruders, and has been involved in multiple process transfers and scale-ups, including an active commercial process that utilizes a 50 mm extruder. Furthermore, our experience with amorphous solid dispersions can be leveraged in further formulating solid dosage forms for oral delivery, whether the project goals are for immediate- or controlled-release forms.

**Equipment**

Bend Research is capitally invested in co-rotating, intermeshing, twin-screw extruders. Extruders exclusively for development work include a 19 mm Baker-Perkins clam-shell unit, as well as a 27 mm Leistritz unit. Bend Research also has an 18 mm Leistritz extruder and an additional 27 mm Leistritz extruder that can be utilized for both development and cGMP manufacture. Multiple loss-in-weight powder feeders and liquid injection pumps are available for inputs to the extruders, and downstream equipment includes a chilled roll for making ribbons, and a pelletizer for coarsely chopping strands or ribbons. Approximate batch sizes and throughput for the Leistritz extruders are summarized in Table 1.

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<th>Table 1. Leistritz extruder Details</th>
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<tr>
<td><strong>Equipment</strong></td>
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<td><strong>Batch Size</strong></td>
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**About Bend Research**

For more than 35 years, Bend Research has worked with clients to solve their most difficult scientific and technical problems, advancing new medicines that improve human health. This success is based on a solid understanding of scientific and engineering fundamentals, enabling Bend Research to develop, progress, and commercialize pharmaceutical technologies. The firm’s innovative drug-delivery solutions grow from a solid base of scientific and engineering fundamental understanding.

Bend Research provides formulation and dosage-form support, assists in process development and optimization, manufactures clinical-trial quantities of drug candidates in its cGMP facilities, advancing promising drug candidates from conception through commercialization. It is a leader in novel formulations, including solubilization technologies such as spray-dried dispersions and hot-melt extrusion formulations, as well as controlled-release, inhalation, and biotherapeutics.

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