

Amorphous solid dispersions have enabled the successful formulation and advancement of 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 a leading approach based on mature process understanding, small process footprint, continuous operation and readily scalable. These attributes allow for more of a plug-and-play unit operation, resulting in relatively lower manufacturing costs and making it a more appealing commercial process train.

Proven Technology

Hot-melt extrusion is a technique for manufacturing amorphous solid dispersions in which the drug substance is melted or dissolved within a dispersion carrier and mixed to produce and stabilize the amorphous form of the drug substance. Functional excipients, such as surfactants, are often added to further aid in processability or improve the dissolution performance of the formulation upon administration. The melt is extruded through a shape-forming orifice and, upon rapid cooling, remains a solid, single-phase, glassy amorphous matrix that is shelf-stable. Post-extrusion processing equipment can be adapted to manage the extruded shape, making it amendable to downstream processing into a dosage form. In general, these materials are milled to reduce the particle size to be incorporated into a traditional oral solid dosage form such as a tablet or capsule, while maintaining the desired release profile for the drug.

Extensive Experience

By combining Capsugel's depth of solubilization technologies with our fundamental understanding of pharmacokinetics, we can rapidly help identify, prototype and optimize an amorphous solid dispersion formulation that improves the bioavailability of a low aqueous solubility drug substance. Formulation selection is based on our proven in vivo predictive dissolution performance testing and physical state stability modeling, then coupled to the HME process to assess manufacturability and throughput.

Capsugel 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. And 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 extended-release forms.

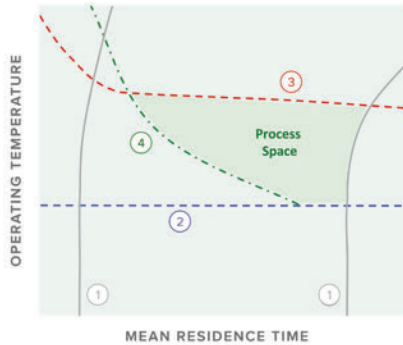


Modular screws are assembled on high torque splined shafts.

Hot-Melt Extrusion Technology

Well-Defined Process

Properties of the drug, polymer and dispersion formulation are used to vet the process space for the appropriate scale of the project.



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

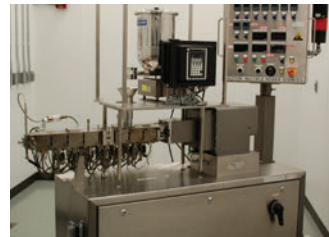
Advanced Equipment

We utilize a range of co-rotating, fully intermeshing, twin-screw extruders, feeders and post-processing equipment. Extruders exclusively for development work include a 19 mm Baker-Perkins clam-shell unit, as well as 18 mm and 27 mm Leistritz units. We have additional 27 mm and 18 mm Leistritz extruders exclusively used for cGMP manufacturing. Multiple loss-in-weight powder feeders and liquid injection pumps are available for inputs to the extruders; downstream equipment includes chilled rolls and a pelletizer for coarsely chopping strands or ribbons.

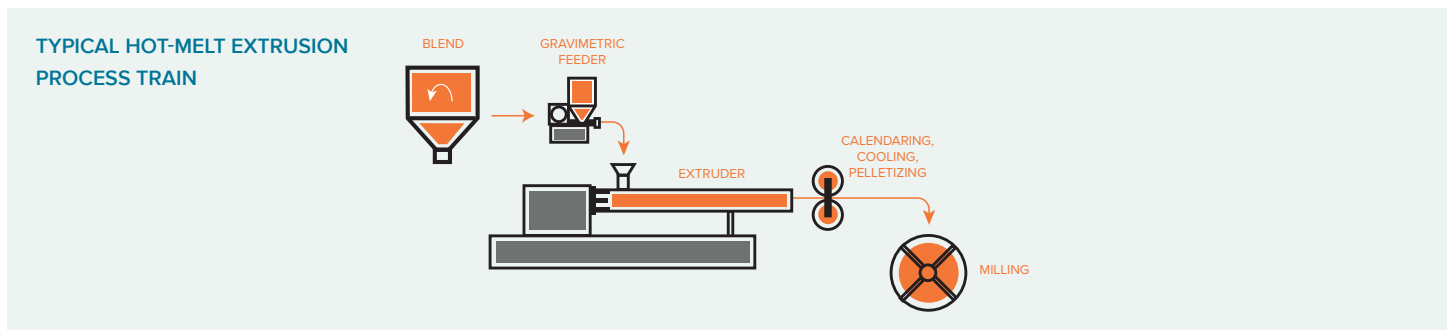
TABLE 1. LEISTRITZ EXTRUDER DETAILS

Equipment	18 mm	27 mm
Batch Size	> 300 grams	> 1.0 kilograms
Throughputs	0.3 to 6 kg/hr	1 to 20 kg/hr

18 MM LEISTRITZ EXTRUDER



27 MM LEISTRITZ EXTRUDER



Learn more about how Capsugel's Hot-Melt Extrusion Technology can address your bioavailability challenges.

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