Hot Melt Extrusion

Hot melt extrusion (HME) is the process of applying heat and pressure to melt a polymer and force it though an orifice in a continuous process. HME is a well known process, developed to produce polymer products of uniform shape and density, and its industrial application dates back to the 1930’s. It is one of the most widely applied processing technologies in the plastic, rubber and food industries and is used to prepare more than half of all plastic products including bags, films, sheets, tubes, fibers, foams, and pipes. HME has more recently been applied to the health-care industry where it is used to manufacture medical devices and to mix active pharmaceutical ingredients (APIs) with polymers to enhance the API’s bioavailability or prepare precursors for thermoplastic drug-eluting devices such as subcutaneous and intravaginal implants and intravaginal rings. This technical brief discusses the equipment and principles of HME with a particular emphasis on its use in the pharmaceutical industry.

HME is carried out using an extruder – a barrel containing one or two rotating screws that transport material down the barrel. Extruders consist of four distinct parts:

1. An opening though which material enters the barrel, that may have a hopper that is filled with the material(s) to be extruded, or that may be continuously supplied to in a controlled manner by one or more external feeder(s),
2. A conveying section (process section), which comprises the barrel and the screw(s) that transport, and where applicable, mix the material,
3. An orifice (die) for shaping the material as it leaves the extruder,
4. Downstream auxiliary equipment for cooling, cutting and/or collecting the finished product.

The HME process is shown schematically in figure 1.

There are two types of extruders: single and twin screw extruders (see figure 2). Single screw extruders are primarily used for melting and conveying polymers to extrude them into continuous shapes, whereas twin screw extruders are used for melt-mixing polymers with additional materials (pigments, fillers, reinforcing, and APIs), and for devolatilization. In the production of pharmaceutical formulations, which require homogeneous and consistent mixing of multiple formulation ingredients, a twin screw extruder is preferred because the rotation of the intermeshing screws provides better mixing to produce a homogeneous solid containing finely dispersed API particles, or a solid-solution of API in polymer. This can improve the dissolution rate and bioavailability of poorly-water soluble API formulations. Uniformly distributed API is also a pre-requisite for the production of drug-eluting devices with intra- and inter-batch reproducibility of drug-release kinetics.

Melting is accomplished by frictional heating within the barrel, and for twin-screw extruders, as the materials undergo shearing between the rotating screws and between the screws and the wall of the barrel as they are conveyed. The barrel is also heated with heaters mounted on the barrel, or cooled with water. The barrel section temperatures are usually optimized so that the viscosity of the melt is low enough to allow conveying down the barrel and proper mixing, while keeping temperatures low enough to avoid thermal degradation of the materials.

The screws of a twin screw-extruder are usually to provide different types of mixing and conveying conditions at various zones in the barrel. During product development, modular screws with multiple elements (figure 3) fitted on a common shaft, allow the tailoring and optimization of the screw design for each product. Sections of the screw can be designed to perform particle-size reduction, mixing and conveying functions. The length of
the screw in relation to the barrel diameter (the L/D ratio) is chosen to optimize the degree of mixing and the number of zones required to achieve the final product characteristics. An example of a complete modular screw is shown in figure 4. Single-piece production screws may be built to the same design as the development screws, but are easier to clean for cGMP compliance.

Rotation of the screws creates distributive and dispersive mixing (figure 5). Distributive mixing maximizes the division and recombination of the materials while minimizing energy input by mixing with low extensional and planar-shear effects. This uniformly blends the materials but does not significantly reduce dispersed material particle size and yields minimal thermal and shear degradation of sensitive materials.

Dispersive mixing applies extensional and planar shear fields to break the dispersed materials to smaller size, ideally using energy at or slightly above the threshold level needed to break them down.

The use of different mixing elements allows the twin screw extruder to perform both particle-size reduction and mixing so that the APIs can be incorporated into the polymer in dispersed form or, if the API solubility in the polymer is high enough, in dissolved form.

Since the extrudate cools rapidly on exiting the extruder, any API that is dissolved in the polymer at the mixing temperature may be unable to recrystallize on cooling, leading to supersaturated solid solutions. In such cases stability of the product must be closely followed as recrystallization of the API over long time-scales is possible, especially at elevated storage temperatures and high API loadings, and may impact the shelf life of the final product.

There are two families of twin screw extruders: high-speed energy input (HSEI) twin-screw extruders, which are primarily used for compounding, reactive processing and/or devolatilization, and low-speed late fusion (LSLF) twin-screw extruders, designed to mix at low shear and pump at uniform pressures. Screws may be co-rotating (self-wiping), or counter-rotating (calendar gap), see figure 6, with most extruders used for mixing being co-rotating.

Different types of exit dies are used to shape the extrudate to the desired profile. These dies include sheet and film dies used in transdermal film applications, strand dies used for medical tubing and some drug-eluting devices, shape dies used in blow moulding, and co-extrusion dies used in reservoir device designs. Different downstream auxiliary components are also used in the finishing process, including water baths and air knives for cooling, conveyor belts for moving the extruded product from the die to the end of the line, strand-cutters for cutting the extrudate into tubing or rods, and spoolers for extrudate collection. Pelletizers are used for cutting the extrudate into smaller pieces for direct capsule filling and in the case of some devices for injection molding to form the final product.

HME allows the API to be mixed with the polymer under the minimum of shear and thermal stress and hence with the formation of minimal process-related API degradants. Antioxidants are often included within the formulation, and the short residence time in the barrel (typically on the order of minutes) also helps to minimize thermal degradation especially compared to batch mixing and other compounding processes.

One strategy for controlling drug elution kinetics from devices such as intravaginal rings involves an extension of the simple extrusion technique. Simultaneous extrusion of a drug-loaded core strand with a release-controlling polymer sheath that encapsulates the core in a single co-extrusion process produces a two-layer core-sheath strand. A specially designed extrusion head is fed by two perpendicular extruders – one supplying the core composition, the other supplying the sheath material. The core-sheath strand is cut and the ends connected to make the final device.

HME provides product developers of medical devices, dissolving oral dosage forms and drug-eluting devices with a process option that maximizes API mixing with polymer, while minimizing API degradation, and even opens the door to products that cannot be prepared by other means.

References

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