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Hot melt extrusion: Improving solubility of poorly soluble compounds

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Abstract

Solving solubility challenges before they become long-term issues is critical for the success of your small molecule project. One potential development and manufacturing option to address solubility challenges is implementing a hot melt extrusion (HME) strategy to manufacture amorphous solid dispersions (ASDs).

Leveraging HME solutions can result in solvent-free processing, reduced cost of goods (COGs), and continuous manufacturing. As you build out your HME strategy, there are a variety of considerations around pharmaceutical applications, formulation, and processing to ensure your strategy is flexible, robust, and comprehensive.

Introduction

Hot melt extrusion (HME) technology was adapted from the plastic and food industries to the healthcare industry due to its applicability in development of novel and effective formulations. HME is a continuous manufacturing process where active ingredients, polymers, and processing aids are fed into a hot melt extruder (**Figure 1**) and subjected to high shear and temperatures to form a homogenous matrix of desired characteristics. Typically, a hot melt extruder consists of a screw-barrel system, die, and post extrusion equipment for cooling, shaping, and cutting the extrudate. Each component in the extruder has a unique function which altogether influences the properties of the final product. The selection of barrel temperature is dependent on several factors, such as:

- The degradation temperature of the drug and polymer.
- The glasses transition temperature, and/or the melting point of the polymer—based on whether the polymer is amorphous, crystalline, or semi-crystalline polymer.
- The melting point of the drug and the processability of the formulation.

The screw consists of morphologically different elements which perform different unit operations including conveying, mixing, and kneading of the ingredients. The screw speed, regulated by the motor, is responsible for generation of shear as a result of the frictional forces between the ingredients, both the screw elements, and the barrel. The screw configuration, speed, and length of the barrel dictate the residence time of the ingredients. In the extruder, the residence time plays a significant role in the processing as it influences both the degradation kinetics of drug and polymer, as well as the final product characteristics.

The use of HME technology in the pharmaceutical industry has been steadily increasing due to its capability to manufacture products with properties such as enhanced bioavailability, abuse deterrence, and modified release, without the need of a solvent.

Several commercial products have been approved and are produced using HME technology. KALETRA™ NORVIR™, and ONMEL™ are examples of the US FDA approved tablet dosage forms prepared using HME technology for improved bioavailability. NuvaRing®, IMPLANON™, and OZURDEX™ are examples of implants developed using HME technology approved by the FDA.

Formulation and processing considerations for HME process

Development of pharmaceuticals using HME requires desired characteristics using HME requires meticulous investigation of active pharmaceutical ingredients (APIs)/ polymer properties which helps in deciding on the formulation and processing variables.

Thermal properties

Careful evaluation of thermal properties is necessary to establish the suitable barrel temperature. For solubility enhancement, the selected barrel temperatures should range between the glass transition temperature (Tg) and melting point (MP) and the degradation temperatures to ensure complete conversion of the crystalline state to amorphous state, while avoiding thermal degradation of the components. Generally, Differential Scanning Calorimetry (DSC) is used as an analytical tool to understand the thermal properties of API's and polymers.

Figure 1: Hot melt extruder

Drug-polymer miscibility

The drug and polymer need to be completely miscible to achieve maximum solubility—supersaturation—and to minimize the risk of phase separation and crystallization of drug from the polymer (**Figure 2**). Comparison of the Tg of the drug and polymer alone and the physical mixtures of drug and polymer obtained by modulated DSC, serves as important information for drug-polymer miscibility. Theories such as Flory-Huggins theory and group contribution theory can be used to predict thermodynamic stability of the extrudate by considering the interactions between the drug and the polymer. This information can help in deciding the maximum drug loading that can be achieved with a given drug and polymer.

Mechanical properties

Materials should undergo acceptable levels of deformation —thermoplastic—to be suitable for hot melt extrusion. Viscosity obtained from melt rheological studies of the drug-polymer combination gives an idea about the mechanical suitability of the material for the extrusion process.

Materials having acceptable mechanical properties would not overshoot the torque beyond the limitations of the equipment. Viscosity is dependent on several factors such as molecular weight of the polymer, temperature, and addition of processing aids like plasticizers. Melt viscosity at different temperatures of the drug-polymer can establish temperatures of the extrusion zones to limit the screw torque within the instrument's capability.

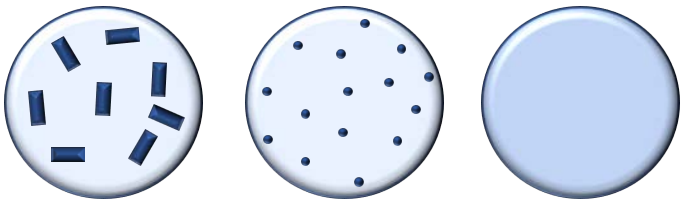

Figure 2: Solid state characteristics of crystalline, amorphous, and molecular solutions

Pharmaceutical applications

Hot melt extruders are used for a wide range of pharmaceutical applications such as solubility enhancement, preparation of abuse deterrent formulations, modified release formulations, implants, and continuous granulation.

Solubility enhancement

Hot melt extruders are primarily used for improving the solubility of poorly soluble compounds. Despite numerous high throughput screening techniques for selection of molecules with desired characteristics, more than 40% of the new chemical entities (NCEs) in the drug developmental stages face the challenge of aqueous solubility.

Although capable of eliciting the desired pharmacological response, many molecules with poor solubility cannot be commercially developed.

Although capable of eliciting the desired pharmacological response, many molecules with poor solubility cannot be commercially developed. Moreover, drug molecules having poor aqueous solubility require frequent administration of medicaments to reach the required blood concentrations, leading to unwanted side effects. Improving the solubility of poorly soluble drugs would clear some of the roadblocks to reach the public.

Hot melt extrusion is a solvent free solubility enhancement technique to disperse or dissolve the crystalline low soluble molecule in the hydrophilic polymer to convert into amorphous highly soluble state. HME is advantageous compared to other solubility enhancement techniques because the solvent-free continuous process eliminates time-consuming steps, such as drying.

Preparation of abuse deterrent formulations

Regulatory bodies are constantly trying to prevent drug abuse by encouraging the development of abuse deterrent formulations for drugs with abuse potential. Formulations containing controlled substances are abused by crushing and insufflation, chewing, and extracting, among others. Abuse deterrent formulations resist damage of the formulations by gelling or being crush resistant. Hot melt extrusion of abuse potential drugs with polymers like high molecular weight poly (ethylene oxide) would make the formulations tamper resistant with desired drug release.

Preparation of modified release formulations

The drug release from the dosage forms are often modified with an intent to solve the shortcomings of immediate release dosage forms. Modified release dosage forms can be designed to delay drug release, to protect the drug from the harsh environment of the stomach, to deliver the active substance to a particular site, or to extend the duration of action. Based on the requirement, hot melt extrusion technology can be used to develop modified release formulations by using polymers of different molecular weights to sustain the drug release or polymers with functional groups to selectively release the drug at a particular site.

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Taste masking

Products administered orally account for around 60% of all the pharmaceutical products in the market. Of these, most are bitter and leave an unpleasant feeling after swallowing, which is something pediatric patients are particularly sensitive to. The bitter taste of medicines can be masked by extruding the active ingredients with suitable polymer and down processing the extrudate into powder or pellets as required.

Continuous granulation

Continuous manufacturing of pharmaceuticals is gaining importance because of the advantages it offers over batch processing. Continuous processing involves fewer steps and is thereby a quicker and more reliable process than a batch process.

A hot melt extruder can be converted to a twin-screw granulator for continuous processing through simple modifications like open discharge instead of die at the end of barrel and a pump for dispensing of liquid binder into the barrel. In addition, continuous granulation by twin-screw granulators may allow for variable batch sizes and real time monitoring of the product through process analytical technology.

Preparation of implants

Implant preparation (**Figure 3**) using HME technology is advantageous over other techniques due to its ability to load higher quantities of drugs and avoidance of solvents and surfactants in the manufacturing process.

Polymers which are biodegradable and suitable for an extrusion process like poly (lactic-co-glycolic acid) (PLGA) are used for preparation of implants. Several commercial products like NuvaRing® and IMPLANON™ are available as contraceptive devices in the market.

Scale-up of hot melt extrusion process

From a small-scale extruder to a large-scale extruder, a scientific approach is necessary to scale-up the manufacture of pharmaceuticals. Parameters like specific mechanical energy, product temperature, and residence time distribution of the ingredients need to be identical at both small-and large-scales.

This provides a starting point for scale-up processes. These parameters can be adjusted by modulating parameters like feed rate, screw speed, and temperature profiles. Additionally, the extruders used for the small- and large-scale need to be geometrically similar in terms of length and diameter, screw diameter ratio, outer and inner diameter, and the screw design.

Based on the process limiting factors, the scale-up strategies can be classified as volumetric, power, and heat transfer:

- Volumetric scale-up: In case of volumetric scale-up strategy, an identical mean residence time of the ingredients is targeted to achieve a successful scale-up. The mean residence time of ingredients can be determined by use of tracer or by NIR or Raman spectroscopy.
- Power scale-up: Identical specific mechanical energy consumed by the small-scale extruder and large-scale extruder is the basis for power scale-up of a hot melt extrusion process. The specific mechanical energy involved in an extrusion process is calculated by considering the power and throughput of the process on the proposition that screw geometry, fill percentage, and equivalent screw speed are the same among the extruders.
- Heat transfer scale-up: The heat transfer scale-up is based on the degree of fill, barrel surface area, temperature gradient—between the ingredients and the barrel, and the residence time. The heat transfer coefficients need to be similar for a successful scale-up using this strategy.

Apart from these strategies, simulation-assisted models like Akro-Co-Twin Screw® and Ludovic® are commercially available which consider temperature, pressure, fill ratio, viscosity, shear rate, energy consumption, and residence time distribution as outputs.

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Thermo Fisher Scientific capabilities

Micro-pellets

Thermo Fisher Scientific is equipped with two hot melt extruders coupled with a micro-pelletizer for preparation of multi-unit particulate systems (MUPS). These pellets can be further coated to provide characteristics such as delayed or sustained release. The size of micro-pellets ranges from micrometers to a few millimeters (**Figure 3**).

Figure 3: Micro-pellets prepared from HME

Cut rods

Cut rods are like micro-pellets in preparation except the size of cut rods are larger compared to the micro-pellets. The size of cut rods ranges from millimeters to a few centimeters (**Figure 4**).

Figure 4: Cut rods prepared from HME

Figure 5: Granules prepared from HME

Granulation

Thermo Fisher Scientific can develop both solvent-free melt granulation and wet granulation processes for the continuous manufacture of granules which can be further processed to prepare final formulations (**Figure 5**).

Conclusion

Hot melt extrusion technology is seeing a rapid growth in the pharmaceutical industry due to its ability to solve the challenges involved in formulation development of drugs. It can be used effectively to develop pharmaceutical formulations of the highest quality with a thorough understanding of the process.

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Thermo Fisher Scientific provides industry-leading pharma services solutions for drug development, clinical trial logistics and commercial manufacturing to customers through our Patheon brand. With more than 65 locations around the world, we provide integrated, end-to-end capabilities across all phases of development, including API, biologics, viral vectors, cGMP plasmids, formulation, clinical trials solutions, logistics services and commercial manufacturing and packaging. We give pharma and biotech companies of all sizes instant access to a global network of facilities and technical experts across the Americas, Europe, Asia and Australia. Our global leadership is built on a reputation for scientific and technical excellence. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to Care™ program. As a leading pharma services provider, we deliver unrivaled quality, reliability and compliance. Together with our customers, we're rapidly turning pharmaceutical possibilities into realities.

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Srinivas Ajjarapu is a research scientist within the pharmaceutical development team at Thermo Fisher Scientific's site in Cincinnati, Ohio. Srinivas supports the product development team by providing technical input and assisting with both formulation and process development. Srinivas received his PhD from the University of Mississippi where his research was focused primarily on projects funded by the FDA and NIH and formulation development using hot melt extrusion. Prior to joining Thermo Fisher Scientific, he worked with Sun Pharma for the US and Canada regulatory affairs team, where his responsibilities included providing regulatory approaches to products in the developmental stage, filing dossiers, and responding to queries from regulatory agencies.

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Venkata Raman is a research scientist on the pharmaceutical development team at Thermo Fisher Scientific which provides services for early development and tech transfer projects. His research experience spans over nine years which includes four years of industrial experience in generics from India. Experience includes immediate and controlled release solid dosage forms as well as early and late stage development work. He received his PhD from the University of Mississippi and his research there included the formulation of amorphous solid dispersions and controlled release via hot melt extrusion technology.

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