Oral solid dose

Overview of hot melt extrusion and its pharmaceutical applications

1. Introduction

Hot melt extrusion (HME) technology was adapted from the food and plastic industries to the healthcare industry due to its applicability in development of novel and effective pharmaceutical formulations. HME is a continuous manufacturing process wherein the active ingredients, polymers, and processing aids are fed into the extruder and subjected to high shear and temperatures to form a homogenous matrix of desired characteristics. Typically, a hot melt extruder consists of 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 influence the properties of the final product. The selection of barrel temperature is dependent on several factors like the degradation temperature of the drug and polymer, the glass transition temperature and/or the melting point of the polymer (based on whether the polymer is amorphous, crystalline, or semi-crystalline), the melting point of the drug, and the processability of the formulation. The screw consists of morphologically different elements which perform different unit operations like conveying, mixing, and kneading of the ingredients. The screw speed, regulated by the motor, is responsible for the generation of shear as a result of the frictional forces between the ingredients and 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 over time due to its capability to manufacture products with properties like 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 some 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.

Figure 1. A hot melt extruder.

2. Formulation and processing considerations for HME

Development of pharmaceuticals of desired characteristics using HME requires meticulous investigation of active pharmaceutical ingredients (API) and polymers to help decide formulation and processing variables.

2.1 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 degradation temperatures and the glass transition temperature (T_g) or the melting point (T_m) 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 and polymer.

2.2 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/crystallization of the drug from the polymer. Comparison of the T_g of the drug and polymer alone and the physical mixtures of drug and polymer obtained by modulated DSC serve as important information for drug–polymer miscibility. Several theories like the 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.

2.3 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 including 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.

3. Pharmaceutical applications

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

3.1 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 new chemical entities (NCEs) in drug developmental stages face the challenge of aqueous solubility. Many molecules with poor solubility cannot be commercially developed although capable of eliciting the desired pharmacological response. 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 low-soluble crystalline molecule in the hydrophilic polymer to convert into highly soluble amorphous state. Hot melt extrusion holds a number of benefits among other solubility enhancement techniques like its solvent-free process, lack of time-consuming drying steps, and having fewer number of steps being a continuous process.

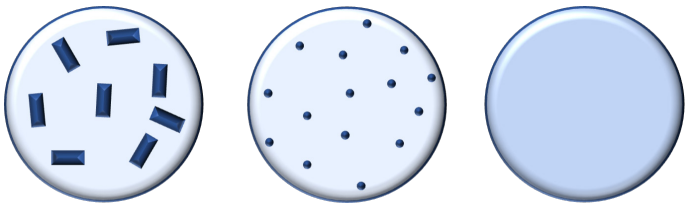

Figure 2. Solid state characteristics of crystalline, amorphous, and molecular solutions.

3.2. Preparation of abuse deterrent formulation

Drug	Crystalline	Amorphous	Molecularly dissolved
Polymer	Amorphous	Amorphous	Amorphous
Thermodynamic stability	Almost stable	Unstable (kinetically controlled)	Stable (drug below saturation solubility)

Regulatory bodies prevent drug abuse by encouraging the development of abuse deterrent formulations for drugs with abuse potential. Formulations containing controlled substances can be abused by crushing and insufflation, chewing, and extracting. Abuse deterrent formulations resist damage of the formulations by gelling or by being crush-resistant. Hot melt extrusion of drugs that have high abuse potential with high molecular weight polymers like polyethylene oxide would make the formulations tamper-resistant with desired drug release.

Figure 3. Abuse deterrent formulations.

3.3. Preparation of modified release formulations

Drug release from dosage forms are often modified with an intent to solve the shortcomings of immediate release. Modified release dosage forms can be designed to delay the drug release, protect the drug from harsh environment of the stomach, deliver the active substance to a particular site, or to extend the duration of action. Based on the intended use, hot melt extrusion 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.

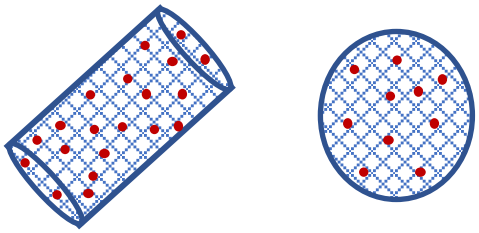

Figure 4. Drug entrapped in polymer matrix.

3.4. Taste masking

Products administered through oral route account for ~60% of all pharmaceutical products in the market. Of these, most products are bitter and leave an unpleasant feeling after swallowing. Pediatric patients are particularly sensitive to these unpleasant flavors. The bitter taste in medicine can be masked by extruding the active ingredients with a suitable polymer and down processing of the extrudate into powder or pellets as required.

3.5. Continuous granulation

Continuous manufacture of pharmaceuticals is gaining prominence due to its advantages over batch processing. Continuous processing involves fewer steps and is thereby quicker and much 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 the barrel and a pump for dispensing 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.

3.6. Preparation of implants

Implant preparation using HME technology is advantageous over other techniques due to its ability to load higher quantities of drug and avoid 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 the NuvaRing® and IMPLANON™ are available as contraceptive devices in the market.

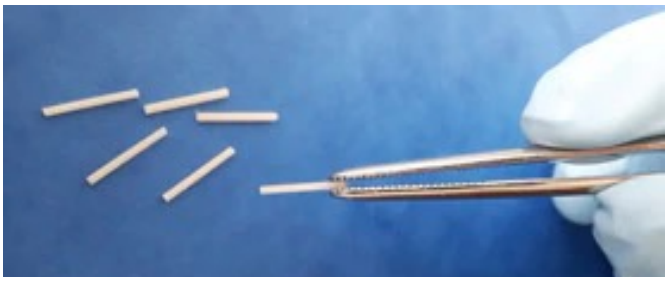

Figure 4. Implants prepared using HME technology.

4. Scale-up of hot melt extrusion process

A scientific approach is necessary to scale up the manufacture of pharmaceuticals from a small-scale extruder to a large-scale extruder. Parameters like specific mechanical energy (SME), product temperature, and residence time distribution of the ingredients need to be identical at both small-scale and large-scale, which provide a starting point for the scale-up process. These parameters can be adjusted by modulating parameters like feed rate, screw speed, and adjusting temperature profiles. Additionally, the extruders used for the small scale and large scale need to be geometrically similar in terms of length/diameter ratio (L/D), screw diameter ratio (outer diameter/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.

4.1. 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.

4.2. Power scale-up

Identical specific mechanical energy (SME) consumed by the small-scale extruder and large-scale extruder is the basis for power scale-up of the hot melt extrusion process. The SME 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.

4.3. 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 the Akro-Co-Twin Screw™ model and Ludovic model are commercially available which consider temperature, pressure, fill ratio, viscosity, shear rate, energy consumption, and residence time distribution as outputs.

5. Capabilities of Thermo Fisher Scientific

5.1. Micropellets

Thermo Fisher Scientific is equipped with hot melt extruders coupled with micropelletizer for preparation of multi-unit particulate systems (MUPS). These pellets can be further coated to provide characteristics like delayed or sustained release. The size of micropellets range from micrometers to a few millimeters.

Figure 5. Micropellets prepared from HME.

5.2. Cut rods

Cut rods are similar to micropellets in preparation except the size of cut rods are larger compared to the micropellets. The size of cut rods range from millimeters to a few centimeters.

Figure 6. Cut rods prepared from HME.

5.3. Granulation

Thermo Fisher is capable of developing both solvent-free melt granulation and wet granulation process for continuous manufacture of granules, which can be further processed to prepare final formulations.

Figure 7. Granules prepared from HME.

6. Conclusions

Hot melt extrusion technology is seeing rapid growth in the pharmaceutical industry due to its ability to solve many challenges associated with traditional methods in drug. With a thorough understanding of the process, hot melt extrusion can be used to alter properties to enhance solubility, deter abuse, and modify the release profile to develop high quality pharmaceutical formulations.

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