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HOT MELT EXTRUSION: PROCESS PARTS ASPECTS AND KOLLIPHOR USES

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ABSTRACT

Originally adapted from the plastics industry, the use of hot-melt extrusion has gained favor in drug delivery applications both in academia and the pharmaceutical industry. Several commercial products made by hot-melt extrusion have been approved by the FDA, demonstrating its commercial feasibility for pharmaceutical processing. Hot-melt extrusion is an efficient technology for producing solid molecular dispersions with considerable advantages over solvent-based processes such as spray drying and co-precipitation. This review provides discussion of the formulation and processing aspects of hot-melt extrusion. This Review article mainly focus on the parts-Extruder and techniques used in Hot Melt Extrusion. This Review article also focuses on use of Kolliphor in Hot Melt Extrusion and their's different types.

INTRODUCTION

Hot melt extrusion technique:- For decades, the value of "continuous processing" in the pharmaceutical industry has been recognized. Hot-melt extrusion (HME) is a manufacturing process widely used in plastics industry, and has significant potential as a continuous pharmaceutical process.[1]

Polymers for HME should have thermoplastic behavior to enable the melt extrusion process; they have to be stable at extrusion temperature, have a suitable Tg of 50–180 °C, low hygroscopicity and no toxicity since larger amounts of the polymer are used Hot melt extrusion always produce a solid dispersion.[20]

Extrusion in Hot Melt Extrusion

Extrusion codisperse the crystalline drug and amorphous polymer by applying the energy of friction and softens the polymer.[20][9]

With respect to the purpose of improving or changing the physical characteristics of given substance and its conversion to suitable shape and size, extrusion is performed by passing the substance through die under controlled conditions.

And in this case, extrusion is performed by using hot melting of substances.

Generally, wet extrusion is more preferred than dry extrusion (solvent free) because in wet extrusion, extrudates have a superior finish due to the softening, plasticizing, and ripening action of the solvents. wet extrusion under low temperatures and pressures with minimum friction is required because the polymer is explosive when overheated using dry extrusion processes.[10]

Among different types of extruder (Ram, roll, radial), screw extruder is used widely in pharmaceutical industry due to advantage of high uniformity and homogeneity than others.

Technical parts used in Hot Melt Extrusion

In hot melt extrusion, heat is used to control the viscosity and ease of flow of substances.
This technique contains the following parts

1. Conveying System:- which carries the material and involves both distributive and dispersive mixing of drug and polymer.[5]
-feeding zone
-heating barrel.
-screw driving unit (single, twin, or multiple screw)

2. Die system:- which forms the material into definite shape (tablet, film, pellets, granules)

3. downstream processing

Feeding zone

In these, the starting material is fed from a hopper directly in to the feed section, which has deeper flights or flights of greater pitch. This geometry enables the feed material to fall easily

into the screw for conveying along the barrel. The pitch and helix angle determine the throughput at a constant rotation speed of the screws.

Pumping efficiency of the feeding section is dependent upon the friction coefficient between the feed materials and the surface of the barrel and screw.

The feedstock must have good flow properties. This requirement is usually met by insuring that the angle of the feed hopper exceeds the angle of repose of the feed materials.

Force feeding device such as a mass flow feeder or side stuffer can be used to direct the feedstock onto the rotating screw.

Inconsistent material feed may result in a "surge" phenomenon that will cause cyclical variations in the output rate, head pressure, and product quality.

Heating barrel

The temperature of the melting zone (barrel) is normally set 15–60°C above the melting point of semi-crystalline polymers. polymers with low melt viscosities and high thermal conductivities exhibit a more efficient melting process. Solidified polymer components can block the channel if melting is incomplete and result in a surge of material around the blockage.

Temperature of all the barrels are independent and can be accurately controlled from low temperatures (30^{o} C) to high temperatures (300^{o} C) degradation by heat can be minimized. The glass transition or melting temperatures of polymers and drug usually determines the barrel temperature.

Material is transported as a solid plug to the transition zone where it is mixed, compressed, melted and plasticized. Compression is developed by decreasing the thread pitch but maintaining a constant flight depth or by decreasing flight depth.

The melt (peudoplastic flow) moves by circulation in a helical path by means of transverse flow, drag flow, pressure flow and leakage; the latter two mechanisms reverse the flow of material along the barrel.

The function of the metering zone is to reduce pulsating flow and ensure a uniform delivery rate through the die cavity.[2]

Screw Driving Unit (single, twin or multiple screw)

In heating barrel, screw designs are present which allow the extruder to perform a mixing and reduction of particle size in addition to extrusion. screw design was the dominant factor in determining the content uniformity of the extrudates.

The space between screw diameter and width of the barrel is normally in the range of 0.1-0.2 mm.

The heat required to melt or fuse the material is supplied by the heat generated by friction as the material is sheared between the rotating screws and the wall of the barrel. High friction along the barrel and low friction at the screw interface contribute to efficient mass flow in the feed section.[3]

Screw is the basic unit of extruder and its design decides the requirement such as high or low shear. Dimensions of the screws are given in terms of L/D ratio, which is the length of the screw divided by the diameter. in a pharmaceutical pilot scale extruder, the screws range from 18 to 30 mm.

The extruder may be single, twin or multi screw extruders.[4]

Single Screw Extruder (SSE)

It is invented in 1897.

It is smooth or grooved barrel.

Screw design may consist of 20 or more turns with a pitch similar to the screw diameter, thereby creating a long slender machine in which substantial longitudinal temperature gradients can be maintained and controlled manner.

Once screws are reduced to less than 18 mm, the screw becomes weak and solids transportation is far less reliable. To overcome these shortcomings, a vertical screw, driven from the discharge end, may be used.

There are three basic functions of a single screw extruder: solids conveying, melting and pumping.

After solids conveying the flight depth begins to taper down and the heated barrel causes a melt to form. The energy from the heaters and shearing contribute to melting. Ideally, the

melt pool will increase as the solid bed reduces in size until all is molten at the end of the compression zone. Finally, the molten materials are pumped against the die resistance to form the extrudate.

In the SSE, the friction between the materials, the rotating screw, and the barrel allows the material to rotate and push forward, which generates heat. Therefore, increasing the screw speed increases the frictional heat and elevates the temperature, which may degrade heat sensitive drugs.

Single-screw extruders do have the advantage over twin-screw extruders in terms of their mechanical simplicity and more reasonable cost.

Twin Screw Extruder (TSE)

It is invented in 1930.

Twin screw extruder has has two agitator mounted on parallel shafts and rotate together with the same direction of rotation (co-rotating) or in the opposite direction (counter rotating) and are often fully intermeshing.

Co-rotating shafts have better mixing capabilities as the surfaces of the screws move towards each other. This leads to a sharp change in mass flow between the screw surfaces.[4,5] As the screws rotate, the flight of one screw element wipes the flank of the adjacent screw, causing material to transfer from one screw to the other.[11]

Counter-rotating designs are only utilized when very high shear regions are needed.counter-rotating twin-screw extruders suffer from disadvantages of potential air entrapment, high-pressure generation, and low maximum screw speeds and output. Corotating twin-screw extruders can be operated at high screw speeds and achieve high outputs, while maintaining good mixing and conveying characteristics.[5]

There are two types of TSEs can be further classified as fully intermeshing or non-intermeshing. The fully intermeshing TSE is the most popular because the design incorporates a self-cleaning feature and, thereby, not only reduces the non-motion but also prevents the localized overheating of the raw materials with the extruder.

TSE heating is controlled from outside sources as the intermeshing screws push the material forward with the relative motion of the flight of one screw inside the channel on the other. Therefore, in the TSE, heat generation is independent of the screw speed.

Compared to the SSE, the intermeshing co-rotating of the TSE provides better mixing, producing a more homogeneous solid containing finely distributed and dispersed active compounds.

Typical TSE barrel section would be 44:1 L/D long. Therefore, the intermeshing TSE may be configured for up to 60:1 L/D, whereas the no intermeshing TSE can be specified at a 100: 1(8).

Twin-screw extruder is characterized by the following descriptive features: -

1. Short residence time:- 5-10 min.
2. Self wiping screw profile
3. Minimum inventory

Multiple Screw Extruder (MSE)

It contains more than 2 screws and due to positive displacement flow in the intermeshing region between the screws, prevention of degradation of thermal labile materials is attained in MSE which is advatangous (such as easier material feeding, higher kneading and dispersing capacity, lower tendency to overheat, higher process productivity and flexibility, and better control of process parameters) over SSE and TSE.

Continuous monitoring of Hot melt extrusion

Continuous manufacturing (CM) processes via hot melt extrusion is important because conventional batch processes of manufacturing have several drawbacks (e.g., poor controllability, low yield, and difficult scalability, batch-to-batch variation)

Continuous monitoring will ease this process in many ways for the industry, enabling it to cut costs by converting processes from batch to Continuous monitoring along with appropriate real-time monitoring using PAT tools for the implementation of QbD.

Process analytical technology (PAT) initiated by the FDA is used for the in-line monitoring of critical product parameters (attributes) linked to the product quality.

Aspects of process development in a continuous mode of operation is the thorough analysis and understanding of (residence time distributions) RTD via the processing steps and descriptions of the degree of intermixing at each the processing step.

Scale-up of the CM of pharmaceuticals using HME processes can be assessed by optimizing the heat transfer of the barrel, where the scale-up of the manufacturing will entirely dependent on the heat transfer. In this method, the surface area for heat transfer is taken to be equivalent to the barrel surface area.

Analytical Tools applied for Pharmaceutical HME Monitoring

process analytical tools applied for pharmaceutical HME monitoring and control analytical tools in HME will enable the 'quality by design' (QbD) approach introduced by the Food and Drug Administration.[4]

Analytical techniques mentioned in this review are either in-line or on-line applications. On-line measurements involve the diversion of a small part of the product from the process stream which is then presented to an analyser. The sample is returned to the process stream. In-line techniques (invasive or non-invasive) are located directly in the process stream and provide information without removing the samples from the process stream.[1]

Near infrared spectroscopy (NIR)

It is one of the major process analytical tools applied for pharmaceutical HME monitoring and control.

NIR spectroscopy to predict

1. Quantity in hot-melt extruded films via a developed partial least squares (PLS) model.
2. monitor and predict drug content and to evaluate the solid state of the extrudates before exiting the die.[6]
3. Real time predictions of the API loading (% w/w) and surfactant loading. Two transmission NIR probes were mounted in a die adapter where e first probe is used to send the light through the melt, and on the opposite side of the melt channel, a second probe captures this signal and sends it to the detector.
4. To study the impact of process design and scale up on residence time distributions (RTDs) and on composition disturbances caused by feeding issues. RTD measured by adding a single drop of blue food colouring to the extruder feed inlet and measuring the optical response at the die adapter.

5. In-line transmission NIR measurement system allowing the determination of the composition of a multicomponent melt stream at the exit of a twin screw extruder.
6. Off-line NIR spectra were taken at several points along the extruder screws to examine the dynamics of the cocrystal formation.

Others like Raman spectroscopy, ultraviolet/ visible (UV-VIS) spectroscopy, fluorescence spectroscopy, terahertz (THz) spectroscopy, nuclear magnetic resonance (NMR) spectroscopy, ultrasound techniques and rheological techniques are also used as process analytical tools applied for pharmaceutical HME monitoring and control.

Pharmaceutical Applications of HME

Polyvinyl polymers

PVP Polymers (Kollidon, Kolliphor, Kollicoat)are hard to extrudate due to high values of Tg or Tm, melt viscosities and smaller difference between $T_{(degradation)}$ and T_g (M).

1) Kollidon

Kollidon is a sustained-release minimatrices used in the oral controlled drug delivery system. it is one of the prolong release excipient consisting of polyvinyl acetate and polyvinyl pyrrolidone in the ratio of 8: 2.[12]

Polymer	Glass transition temp.(^{0}C)
Kollidon + 0% TEC	38.2
Kollidon + 5% TEC	27.9
Kollidon + 10% TEC	18.6

Highly pure polymer grades such as Kollidon® 30 and Kollidon® 90 F were not used in HME process due to higher molecular weight(34). Kollidon VA 64 perform as a release rate enhancer by decreasing the hardness of the tablets.[14]

Polymer	% release rate within 24 hours
10% Kollidon	76
20% Kollidon	94

Viscosities of Kollidon polymer is high and has stiff flow due to higher value of tan δ(greater than 1). Kollidon VA 64 copolymer acts as a binders, granulating agent, retardants and film formers.[16]

Polymer grade	Molecular weight	Glass transition temperature(Tg)	Moisture content(%w/w)	Degradation Temperature(°C)	Processing temp.[37]
Kollidon 12 PF	2000 to 3000 D	72(lowest)	2	196	100-110
Kollidon	7000 to	140	4.5	217	120-130

17 PF	11000 D				
Kollidon 25	28000 to 34000 D	153	6	166	-
Kollidon 30	44000 to 54000 D	160	6	171	135-145
Kollidon 90 F	1000000 to 1500000 D	177	3.5	194	160-170
Kollidon VA 64	45000 to 70000 D	105(due to copolymerization with pvp)	2.5	270	-

2) Kolliphor

Kolliphor P 407, also called as Poloxamer 407 which made up of both hydrophobic and hydrophilic parts, chemically it contains an ester of natural D-α-tocopheryl succinate with polyethylene glycol 1000. It was found that thermal degradation temperature of Kolliphor P407 is above the 300^0C. Kolliphor is used as a solubility or dissolution enhancer which has a low melting point and orally safe to be used.[18,19]

Polymer	Molecular weight	T_m(^{o}C)
Kolliphor TPGS	1.5kDa	39

3) Kollicoat

Kollicoat IR is a polyvinyl alcohol-polyethylene glycol graft copolymer, a water soluble polymer, a free-flowing powder and a film forming polymer. It is developed as a coating polymer for instantly release tablets. DSC study of kollicoat shows that glass transition temp. of 37.4^0C and T_m at 209^0C.[15,17]

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