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RECENT ADVANCES IN HOT MELT EXTRUSION TECHNOLOGY

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ABSTRACT

Melt extrusion process which is well known in the polymer and food industry is now being used for pharmaceutical manufacturing to create innovative new formulations and is a continuous process of mixing and designing moldable materials. It is one of the most widely applied processing techniques useful for preparing solid dosage forms, granules, pellets, suppositories, implants, stents, ophthalmic inserts, transdermal and transmucosal drug delivery systems. Also this technique is used in Taste Masking, Solubility Enhancement, and Sustained-Release Pellets Manufacturing. Several advantages over other techniques include cost and performance benefits such as a faster path to FDA approval for new compounds, possible re-indication for existing active pharmaceutical ingredient (APIs), controllable bioavailability, possible lower doses, and probable lower production costs. Hot-melt extrusion efficiently produces solid molecular dispersions with considerable advantages over solvent-based processes such as spray drying and co-precipitation. In general, high temperatures have to be applied to extrude polymeric carriers. Melt extruded dosage forms are complex mixtures of API, excipients, and polymer carrier which are blended using single and twin-screw extruders, molten thermoplastic polymers during the extrusion process can function as thermal binders and/or drug release retardants. A typical extrusion line consists of the material feed hopper, basic extruder, the extrusion die, the calibration units, the haul-off, the saw, and finally the treatment devices for final finishing and handling. This technology is suitable for both high dose and potent compounds. Thus, this review summarizes in detail all the aspects of melt extrusion.

HISTORY: The advent of high through-put screening in the drug discovery process has resulted in compounds with high lipophilicity and poor solubility. Increasing the solubility of such compounds is a major challenge to formulation scientists [1]. Then after Joseph Brama invented the extrusion process for the manufacturing of lead pipes at the end of the eighteenth century. However, hot-melt extrusion was not applied in the plastics' industry until the mid-nineteenth century, when it was first introduced into a wire insulation polymer coating process [2].

Hot-melt extrusion (HME) is an established process that has been used since the early 1930s, predominately in the plastics manufacturing industry, but also in the food processing industry.

INTRODUCTION: Extrusion can be simply defined as the process of forming a new material (the extrudate) by forcing it through an orifice or die under controlled conditions, such as temperature, mixing, feed-rate and pressure.

During formulation development, new drug entities experience failures or delays which include poor biopharmaceutical properties, lack of efficacy, and high toxicity. Poor biopharmaceutical properties such as poor solubility, poor permeability, poor chemical stability, etc. are responsible for almost 40% of the above development issues. In relative terms, the overall rate of absorption of new drug entities is affected more frequently by its solubility than by its permeability. Poor solubility is the most common challenge faced by formulation scientists.

Numerous formulation approaches have been used to enhance the oral bioavailability of poorly soluble drug molecules which includes the formulation of amorphous systems. These formulation efforts are based on the disruption of the three-dimensional long-range molecular interactions present on crystalline drug molecules. These amorphous phases possess higher solubility, higher dissolution rate and consequently higher bioavailability when compared with the crystalline drug molecule. These amorphous systems also have different mechanical properties when compared to either crystalline drug alone or its physical mixtures.

Melt quenching is amongst the above few industrially feasible manufacturing means of amorphous systems. This method produces amorphous pharmaceutical systems by rapidly cooling molten physical mixtures of drugs and hydrophilic polymers process usually called as "Solid Dispersion, (SD)" in which drug particles/molecules are homogeneously distributed throughout a polymeric hydrophilic matrix. When the molten material is passed through an orifice then the method or technology is called "Hot Melt Extrusion, (HME)."

HME processes possess some characteristics, which are especially advantageous for the manufacture of SDs. HME is essentially a solvent-free process. HME equipment is modular, thus, different unit operations might occur in a single and continuous extrusion process. Specific unit operations are a result of the combination of barrel type and screw elements as well as temperature and pressure applied to specific modules. For example, depending on modules settings, unit operations such as mixing and melting might occur mainly in some specific zones of the extruder. By means of screw speed variation, residence time is also controlled. **Figure 1** shows a typical array of modules and screws for a twin-screw extruder.

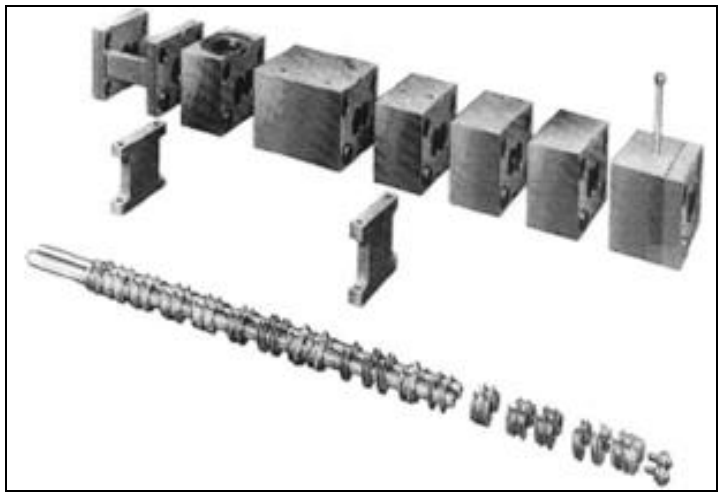

FIGURE 1: TYPICAL ARRAY OF BARRELS AND SCREW ELEMENTS OR MODULES IN A TWIN-SCREW EXTRUDER

The selection of polymer(s) and extrusion conditions are critical during formulation development of SDs of poorly soluble drug molecules by HME technology. The polymer is selected to ideally ensure complete miscibility and therefore maximum molecular interaction with the drug molecule in both the molten state as well as upon cooling with reasonable chemical and physical stability. Extrusion variables, such as extrusion temperature(s), must be selected by considering both the melting point of the drug as well as the Tg value(s) of the polymer(s).The aim of this investigation is to enhance the dissolution rate of a poorly water soluble pharmaceutical agent by means of its formulation as SD.

Definition:

1. **HME** is the process of embedding drug in a polymeric carrier [3].
2. **HME** is the process of converting a raw material into a product of uniform shape and density by forcing it through a die under controlled conditions [4].

3. **HME** can be simply defined as the process of forming a new material (the extrudate) by forcing it through an orifice or die under controlled conditions, such as temperature, mixing, feed-rate and pressure [5].

Advantages [6, 7, 8, 9]: HME offers several advantages over traditional pharmaceutical processing techniques including:

1. Enhanced bioavailability of poorly soluble compounds.
2. Economical process with reduced production time, fewer processing steps, and a continuous operation.
3. Clinically advantaged dosage forms, such as drug abuse and dose dumping deterrent technology.
4. Sustained modified and targeted release capabilities.
5. Better content uniformity was obtained from the HME process among granules of different size ranges.
6. There are no requirements on the compressibility of active ingredients and the entire procedure simple, continuous and efficient.
7. Uniform dispersion of fine particle occurs.
8. Good stability at varying pH and moisture levels.
9. Safe application in humans due to their non-swellable and water insoluble nature.
10. Reduced number of unit operations.
11. Production of a wide range of performance dosage forms.
12. Production of a range of geometries.
13. Processing in the absence of solvents and water.

Disadvantages [6, 8]:

1. Thermal process (drug/polymer stability).
2. Flow properties of the polymer are essential to processing.
3. Limited number of available polymer
4. Requires high energy input.
5. The melt technique is that process which cannot be applied to heat-sensitive materials owing to the elevated temperatures involved.
6. Lower-melting-point binder risks situations where melting or softening of the binder occurs during handling and storage of the agglomerates.
7. Higher-melting-point binders require high melting temperatures and can contribute to instability problems especially for heat-labile materials.

Industrial applications:

General: Extrusion technology is extensively applied in the plastic and rubber industries, where it is one of the most important fabrication processes. Examples of products made from extruded polymers include pipes, hoses, insulated wires and cables, plastic and rubber sheeting, and polystyrene tiles. Plastics that are commonly processed by extrusion include acrylics (polymethacrylates, polyacrylates) and cellulosics (cellulose acetate, propionate, and acetate butyrate), polyethylene (low and high density), poly propylene, polystyrene, vinyl plastics, polycarbonates, and nylons [3]. In film extrusion, the polymer melt is extruded through a long slit die onto highly polished cooled rolls which form and wind the finished sheet. This is known as cast film.

In the food industry extrusion has been utilized since 1930 for pasta production. A widely used versatile technique combines cooking and extrusion in a so-called extrusion cooker [4].

In the animal feed industry, extrusion is most commonly applied as a means of producing palletized feeds [6].

Applications in the Pharmaceutical Industry:

Drug Delivery Technology: In pharmaceutical industry the melt extrusion has been used for various purposes, such as

i. Improving the dissolution rate and bioavailability of the drug by forming a solid dispersion or solid solution(SD or SS)

ii. Controlling or modifying the release of the drug

iii. Masking the bitter taste of an active drug

The bioavailability of an orally administered drug mainly depends on solubility and permeability. Due to advent in the drug discovery process the resultant compounds are often high molecular weight and highly lipophilic and exhibits poor solubility [7]. Scientists have tried to address solubility issues by improving solubility and dissolution rate, preparatition of SD or SS.

The most relevant technologies for the manufacture of solid dispersions are melting of excipients or fusion method [8], embedding of drug by means of spray drying [9], co-evaporation, co-precipitation [10], freeze-drying [11], and roll-mixing or co-milling [12, 13].

Lately, melt extrusion technology has evolved as an efficient manufacturing technique, to disperse or dissolves the drug in molten polymer, forming a SD or SS and is convenient technology for poorly water soluble drugs. The essential advantage of the melt process in this domain is formation of solvent solid dispersions [14, 16].

By definition, SD and SS can be differentiated based on the molecular state of the drug in the carrier matrix. If the drug is dissolved at molecular level i.e. the drug forms one phase system with polymer, it is referred as a solid solution; whereas, if the drug is in a two phase system with polymer and forms a microcrystalline dispersion, it is generally referred to as a solid dispersion [15, 17].

Improvement in bioavailability with these systems is primarily based on improving dissolution rates [18, 19]. In the case of a SD, this is achieved by improvement in the wetting behavior of the hydrophobic drug as well as deagglomeration and micellization of the drug with hydrophilic polymers, in case of SS, improvement in dissolution rate is due to the high energy amorphous nature of the drug. Thermodynamically, solid solutions are more unstable compared to solid dispersions because in the solid solution the drug exists in a high energy amorphous form [20], which is prone to precipitation or crystallization under environmental stress such as moisture and heat, especially during processing and storage of the drug products [21-24]. Glass transition temperature (Tg) has long been seen as the predominant factor governing the physical stability of the solid solution. The higher the Tg of system the better the thermodynamic stability [25]. The solubilizing and stabilizing effects of the polymer and interactions with the drug are often far greater importance for the physicochemical stability of solid solutions [26- 31].

PROCESS AND EQUIPMENT: HME equipment consists of an extruder, auxiliary equipment for the extruder, downstream processing equipment, and other monitoring tools used for performance and product quality evaluation [32]. The extruder is typically composed of a feeding hopper, barrels, single or twin screws, and the die and screw–driving unit (**Figure 2**). The auxiliary equipment for the extruder mainly consists of a heating/cooling device for the barrels, a conveyer belt to cool down the product and a solvent delivery pump. The monitoring devices on the equipment include temperature gauges, a screw-speed controller, an extrusion torque monitor and pressure gauges.

The theoretical approach to understanding the melt extrusion process is therefore, generally presented by dividing the process of flow into four sections [33]:

1) Feeding of the extruder.

2) Conveying of mass (mixing and reduction of particle size).

3) Flow through the die.

4) Exit from the die and down-stream processing.

Generally, the extruder consists of one or two rotating screw inside a stationary cylindrical barrel. The barrel is often manufactured in sections, which are bolted or clamped together. An end-plate die, connected to the end of the barrel, determines the shape of the extruded product (**Figure 2 and Figure 3**).

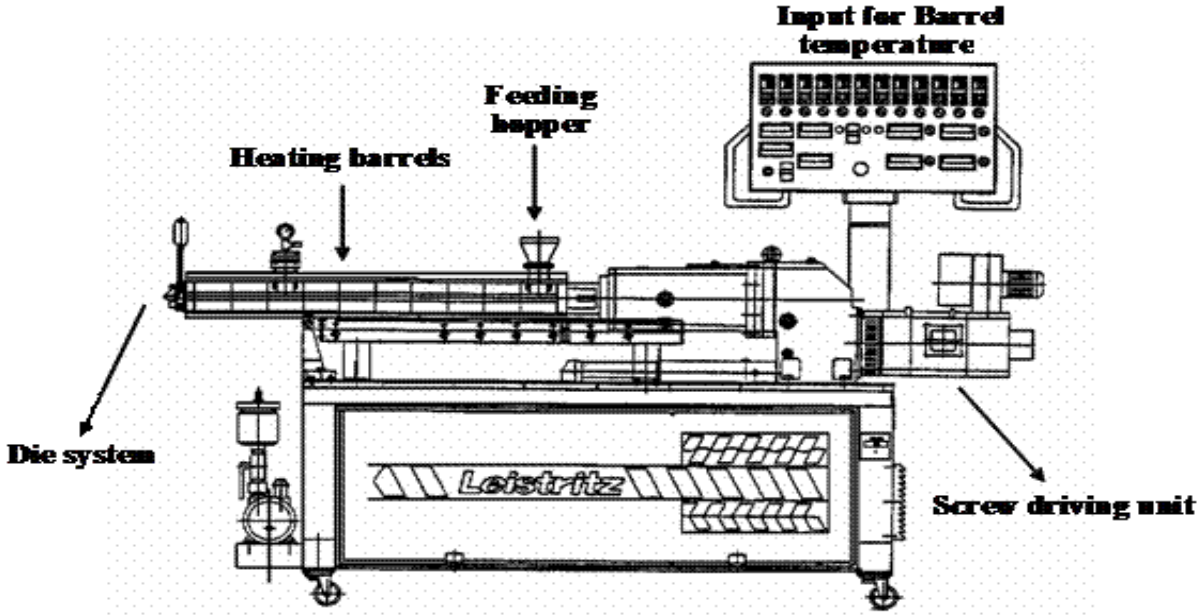

FIGURE 2: MICRO-18 TWIN SCREW CO-ROTATING LEISTRITZ EXTRUDER

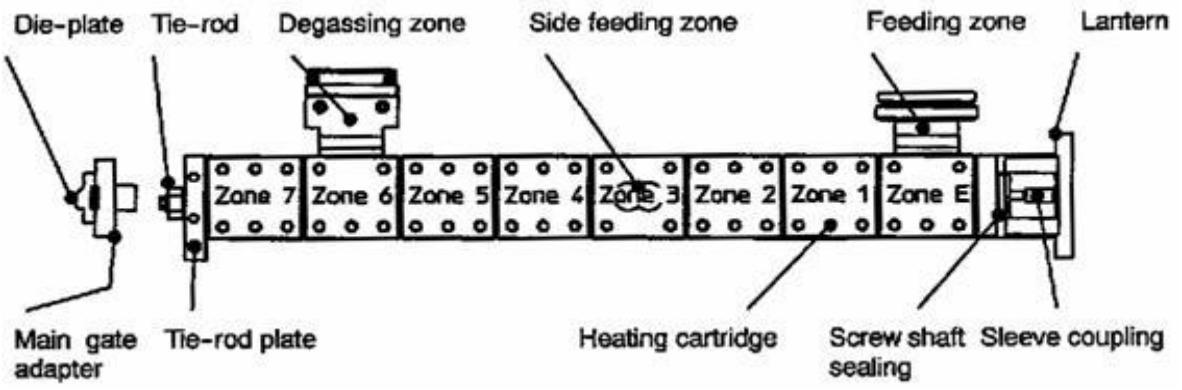

FIGURE 3: HEATING BARRELS AND CO-ROTATING SCREWS FOR HOT-MELT EXTRUDER

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 in combination with electric or liquid heaters mounted on the barrels [34]. Modifying screw designs allow the extruder to perform a mixing and reduction of particle size in addition to extrusion, so that material can be blended into the extrudate or even dissolved [35].

The extrusion channel is conventionally divided into three sections: feed zone, transition zone, and metering zone (**Figure 4**). The starting material is fed from a hopper directly in to the feed section, which has deeper flights or flights of greater pitch (**Figure 5**). 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. The 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 while maintaining a constant thread pitch [36].

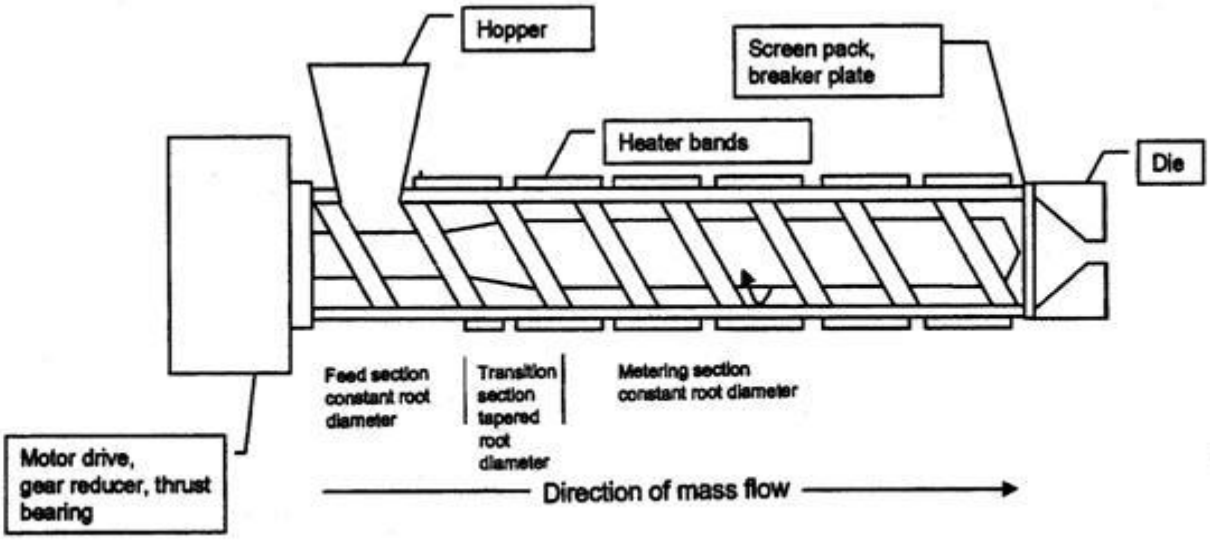

FIGURE 4: COMPONENT PARTS OF SINGLE –SCREW EXTRUDER

Both methods result in increased pressure as the material moves along the barrel. The melt 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 space between screw diameter and width of the barrel is normally in the range of 0.1-0.2 mm [34].

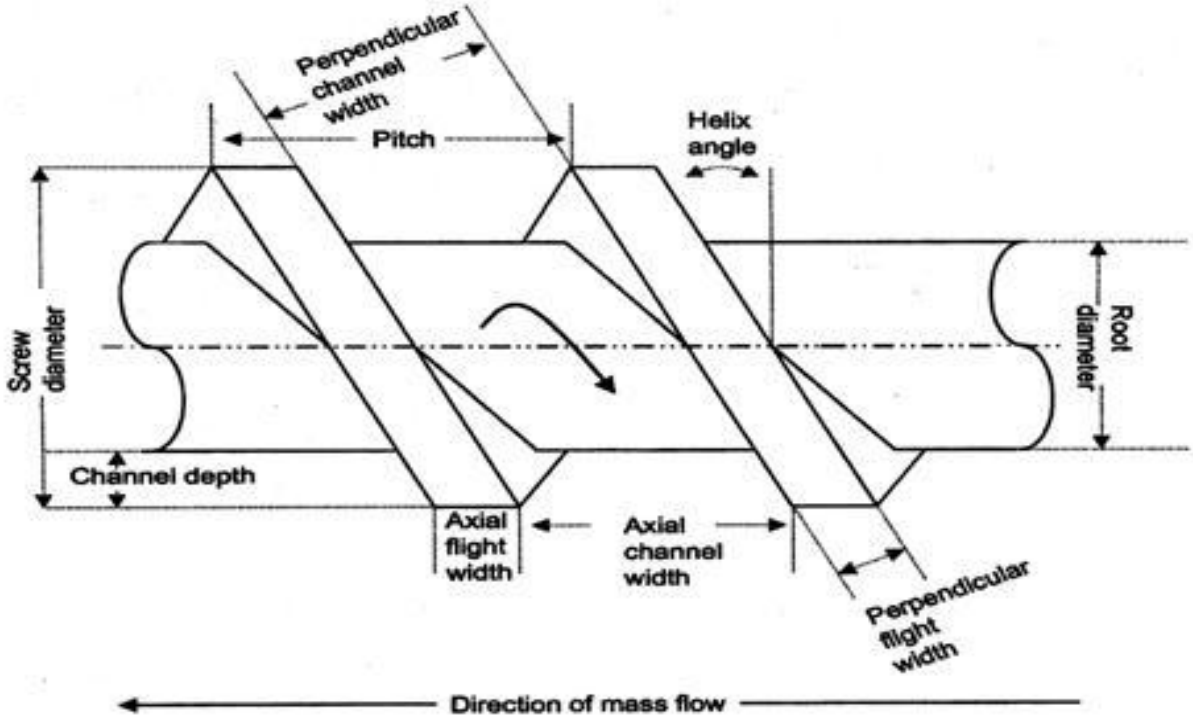

FIGURE 5. EXTRUSION SCREW GEOMETRY

The material reaches the metering zone in the form of a homogeneous plastic melt suitable for extrusion. For an extrudate of uniform thickness, flow must be consistent and without stagnant zones right up to the die entrance. The function of the metering zone is to reduce pulsating flow and ensure a uniform delivery rate through the die cavity [33].

The twin-screw extruder has two agitator assemblies mounted on parallel shafts, these shafts are driven through a splitter/reducer gear box 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 [33, 34]. 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. In this manner the material is transported along the extruder barrel.

The twin-screw extruder is characterized by the following descriptive features [34]:

1) **Short residence time**: The residence time ranges from 5-10 minutes depending on the feed rate and screw speed.

2) **Self wiping screw profile**: i.e. the flight of the one screw wipes the root of the screw on the shaft next to it, ensures near complete emptying of the equipment and minimizes product wastage on shutdown.

3) **Minimum inventory**: Continuous operation of the equipment coupled with the continuous feeding of the material helps in reducing inventories of work in progress. This is important when processing valuable or potentially hazardous materials.

4) **Versatility**: Operating parameters can be changed easily and continuously to change extrusion rate or mixing action. The segmented screw elements allow agitator designs to be easily optimized to suit a particular application. Die plates can also be easily exchanged to alter the extrudate diameter. This allows processing of many different formulations on a single machine, leading to good equipment utilization. Polymers with a wide range of viscoelastic and melt viscosities may be processed and even fine powders may be directly fed into the system.

5) **Superior mixing**: The screws have various mixing elements which impart two types of mixing, distributive mixing and dispersive mixing. The distributive mixing ideally maximizes the division and recombining of the material while minimizing energy. The dispersive mixing ideally breaks droplet or solid domains to fine morphologies using energy at or slightly above the threshold level needed. This mixing aids in efficient compounding of two or more materials in the twin-screw extruder.

Typical twin-screw laboratory scale machines have a diameter of 16-18 mm and length of four to ten times the diameter. A typical throughput for this type of equipment is 0.5- 5 gm/min. As the residence time in the extruder is rather short and the 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 [34].

Extrusion processing requires close monitoring and understanding the various parameters: viscosity and variation of viscosity with shear rate and temperature, elasticity and extensional flow over hot metal surfaces. [37]. The controlling and main monitoring parameters are barrel temperature, feed rate, screw speed and motor load, melt pressure respectively.

i. **Barrel temperatures:** The glass transition (Tg) or melting temperatures of polymers and drug usually determines the barrel temperature

ii. **Feed rate and screw speed:** The constant feeding rate and screw speed throughout the process is important as the combination of these two factors establishes the level of fill in extruder [34]. Due to constant feed rate and screw speed, there will be a constant amount of material in the extruder and thus the shear stress and residence time applied to material remains constant.

iii. **The motor load and melt pressure:** These parameters depend on feed rate and screw speed. With constant feed rate and screw speed these parameters depend upon the molecular weight of polymer and drug as well as polymer miscibility in binary mixtures [33].

Materials used in HME: The materials used in the production of hot melt extruded dosage forms must meet the same level of purity and safety as those used in traditional dosage forms. Most of the compounds used in production of hot-melt extruded pharmaceuticals have been used in production of other solid dosage forms such as tablets, pellets, and transdermals.

The materials used in hot melt extruded products must possess some degree of thermal stability in addition to acceptable physical and chemical stability [32].

HME dosage forms are complex mixtures of active drug and functional excipients [matrix carriers, release-modifying agents, bulking agents, and various additives] [38]. The excipients can impart specific properties to melt extruded pharmaceuticals in manner similar to those in traditional dosage form [39].

Active Ingredient: The properties of the active drug substance often limit the formulation and preparation options available, in the development of an acceptable dosage form. HME offers many benefits over traditional processing techniques. This is a relatively new technique to the pharmaceutical industry. The process is anhydrous, thus avoiding any potential drug degradation from hydrolysis following the addition of aqueous or hydro alcoholic granulating media. In addition, poorly compactable materials can be incorporated into tablets produced by cutting an extruded rod, thus eliminating any potential tableting problems seen in traditional compressed dosage forms.

Depending on the unique properties of the drug substance and the other excipients in the formulation, the drug may be present as undissolved particles, a SS, or a combination in the final dosage form. The state of the drug in the dosage form may have a profound impact on the processability and stability of the product [32].

Polymer Systems: In HME drug delivery systems, the active compound is embedded in a carrier formulation comprised of one or more meltable substances and other functional excipients. The meltable substances may be polymeric materials [40-43] or low melting point waxes [44, 45]. The selection of polymer for HME process mainly depends on drug–polymer miscibility, polymer stability and function of final dosage form.

A variety of carrier systems have been studied or used in hot-melt extrusion dosage forms. Such carrier systems include polyvinylpyrrolidone (PVP) [46] or its co-polymer such as polyvinylpyrrolidone-vinyl acetate [47] , poly(ethylene-co-vinyl acetate) [38], various grades of polyethylene glycols, cellulose ethers [48] and acrylates [49], various molecular weight of polyethylene oxides [43], poly methacrylate derivatives and poloxamers. Amongst the different classes of biodegradable polymers, the thermoplastic aliphatic poly (esters) such as poly (lactide) (PLA), poly (glycolide) (PGA) and copolymer of lactide and glycolide, poly (lactide-co-glycolide) (PLGA) have been used in extrusion. Starch and starch derivatives have been applied along with low molecular weight excipients like sugars and sugar alcohols and waxes [50, 51].

The basic prerequisite for the use in melt extrusion is the thermoplasticity of the polymers or that of the respective formulation.

Plasticizers: The use of polymeric carriers usually requires the incorporation of a plasticizer into the formulation in order to improve the processing conditions during the manufacturing of the extruded dosage form or to improve the physical and mechanical properties of the final product [32]. Plasticizers are added to HME formulations to facilitate the extrusion of the material and to increase the flexibility of the extrudate, which may reduce the degradation problems that are associated with temperature-sensitive drugs or polymers [52].

The choice of suitable plasticizer depends on many factors, such as plasticizer-polymer compatibility and plasticizer stability. Triacetin [38], citrate esters [41, 53] and low molecular weight polyethylene glycols [38, 43, 53] have been investigated as plasticizers in hot-melt extruded systems. The plasticizer lowers the Tg of the polymer as for production. A reduction in polymer Tg depends upon the plasticizer type and level [32].

A reduction in processing temperatures may improve the stability profile of the active compound [53] and/or of the polymer carrier [38, 43]. Plasticizers also lower the shear forces needed to extrude a polymer, thereby improving the processing of certain high molecular weight polymers [43, 53]. The thermo-chemical stability and volatility of the plasticizer during processing and storage must also be taken into consideration [53-57].

The incorporation of plasticizers may lower the processing temperatures required in hot-melt extrusion, thereby reducing drug and carrier degradation. The dissolution rate of the active compound can be increased or decreased, depending on the properties of the rate-modifying agent [32].

Other Processing Aids: The excessive temperatures needed to process unplasticized or under plasticized polymers may lead to polymer degradation. The stability of polymers that are susceptible to degradation can be improved with the addition of antioxidants, acid receptors and or light absorbers during hot melt extrusion. Antioxidants are classified as preventive antioxidants or chain breaking antioxidants based upon their mechanism. Preventive antioxidants include materials that act to prevent initiation of free radical chain reactions.

Reducing agents, such as ascorbic acid, are able to interfere with autoxidation in a preventive manner since they preferentially undergo oxidation. The preferential oxidation of reducing agents protects drugs, polymers and other excipients from attack by oxygen molecules. These antioxidants are sometimes called oxygen scavengers.

Chelating agents such as edetate disodium (EDTA) and citric acid are another type of preventive antioxidant that decrease the rate of free radical formation by forming a stable complex with metal ions that catalyze these reduction reactions.

Other materials have been used to facilitate hot-melt extrusion processing. Waxy materials like glyceryl monostearate have been reported to function as a thermal lubricant during hot-melt processing. Vitamin E TPGS (d-alpha tocopheryl polyethylene glycol 1000 succinate) has been reported to plasticize polymers and enhance drug absorption.

EVALUATION [34]: Evaluation of Formulations Produced via HME that Contain High API Loading is done using several methods, depending upon type of dosage form developed.

1. **Differential Scanning Calorimetry (DSC):** Thermoanalytical methods include those that examine the system as a function of temperature. DSC has been widely used to study the thermal properties of materials used in hot melt extrusion. DSC can be used for the quantitative detection of transitions (melting point, Tg) in which energy is required or liberated (i.e. endothermic and exothermic phase transformations).

   Generally, the HME is scanned and compared to a physical mixture of the drug, polymeric carrier and other excipients. The lack of a melting transition in the DSC scan of the hot-melt extrudate indicates that the drug is present in an amorphous rather than crystalline form.

2. **Thermo Gravimetric Analysis (TGA):** TGA is a measure of thermally induced weight loss of a material as a function of applied temperature. TGA is limited to studies involving either a weight gain or loss, and is commonly used to study desolvation and decomposition. TGA can be used as a screening tool for the thermal stability of materials used in HME.

3. **X-Ray Diffraction (XRD):** XRD is also used to characterize the crystalline properties of hot-melt extruded dosage forms. The principle of XRD is based on Bragg's law, in which parallel incident X-rays strike the crystal planes and are then diffracted at angles related to the spacing between the planes of molecules in the lattice. Crystallinity is reflected by a characteristic fingerprint region in the diffraction pattern.

   If the fingerprints of the drug and carrier do not overlay one another, the crystallinity of the drug and polymer following HME can be determined. Thus, XRD can be used to differentiate between solid solutions, in which the drug is amorphous, and solid dispersions, in which it is at least partly present in the crystalline form, regardless of whether the carrier is amorphous or crystalline. However, the sensitivity of the XRD technique is limited and cannot generally detect crystallinity of less than 10%.

4. **Infrared Spectroscopy (IR):** IR can be used to detect changes in bonding between functional groups due to structural changes or a lack of crystal structure. IR can be used to differentiate between peaks that are sensitive to changes in crystallinity from those that are not.

5. **Nuclear Magnetic Resonance (NMR):** Solid state NMR has been used to probe the crystallinity of materials. Although any NMR-active nucleus can be studied, most efforts have focused on 13C investigations.

6. **Microscopy:** Microscopy is one of the best methods to study the crystalline properties of HME. Both optical and electron methods are suitable to examine the surface morphology of samples to probe for the presence of crystalline particles or amorphous domains. It is also possible to obtain reliable particle size information using these techniques.

MARKETED PRODUCTS: The interest in HME is growing rapidly. The US and Germany hold approximately more than half (56%) of all issued patents. In spite of this increased interest, there are few commercialized HME pharmaceutical products currently marketed. There is no. of companies using HME as a drug delivery technology including **Pharma Form** (TX, USA) and **SOLIQS** (Germany). SOLIQS has developed a proprietary **Meltrex** formulation and redeveloped a protease inhibitor combination product, **Kaletra**, for the treatment of human immunodeficiency virus (HIV). Moreover, HME **Kaletra** tablets were shown to have significant advantages for the patient compared with the previous soft gel capsule formulation, such as reduced dosing frequency and improved stability.

SOLIQS has also developed a fast-onset **ibuprofen** system and a sustained release formulation of **verapamil (Isoptin SRE)** that was the first directly shaped HME product on the market [5]. In the same instance there is number of products which has been developed by no. of companies using HME as drug delivery technology and this technology is becoming a robust in the field of pharmaceuticals.

CONCLUSIONS AND OUTLOOK: Today HME technology represents an efficient pathway for manufacture of drug delivery systems. Resulting products are mainly found among semi-solid and solid preparations. The potential of the technology is reflected in the wide scope of different dosage forms including oral dosage forms, implants, bioadhesive ophthalmic inserts, topical films, and effervescent tablets.

Formulations with high API loading, extended release properties and excellent content uniformity can be successfully prepared via HME. HME-prepared tablets exhibited exceptional tablet hardness and friability results over control samples produced via direct compression.

The drug can be present in crystalline form for sustain release applications or dissolved in a polymer to improve dissolution of poorly water soluble drugs. The possible use of a broad selection of polymers starting from high molecular weight polymers to low molecular weight polymers and various plasticizers has opened a wide field of numerous combinations for formulation research.

Drawbacks of the technology are often related to high energy input mainly related to shear forces and temperature. The design of screw assemblies and extruder dies are two major areas, which have significant impact on product quality and degradation of drug and polymers. Drugs which are sensitive to elevated temperatures can be processed successfully when the residence time is short compared to conventional processes like sterilization. Success of this technique is dependent on the processibility (and stability) of the drug and/or polymers and optimization of this technique requires fundamental knowledge of the physicochemical properties of the drugs and polymers.

Work in this field is increasing and the literature published reveals many novel and interesting aspects of this technology such as in-situ salt formation, fast dispersing systems with foam like structures, complex formation in the melt, and nanoparticles released from molecular dispersions manufactured by melt extrusion. HME appears to be a viable approach to produce dosage forms that contain high API loadings and exhibit controlled release behavior. It is a valuable technique for poorly soluble APIs.

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