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HOT-MELT EXTRUSION TECHNIQUE: A REVIEW

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ABSTRACT

Hot-melt extrusion is one of the most widely applied processing technologies in the plastic, rubber and food industry. Today this technology has found its place in the array of pharmaceutical manufacturing operations. Melt extrusion process are currently applied in the pharmaceutical field for the manufacture of a variety of dosage forms and formulations such as granules, pellets, tablets, suppositories, implants, stents, transdermal systems and ophthalmic inserts. This review article in detail describes the melt extrusion equipment and process. Industrial application of this process along with specific areas on pharmaceutical industry is illustrated. This article concludes with the overview of published examples of the melt extrusion process.

Keywords: Hot-melt extrusion; Manufacturing operations; Extrusion geometry.

INTRODUCTION

Hot-melt extrusion is one of the most widely applied processing technologies in the plastic, rubber and food industry. Currently, more than half of all plastic products, including plastic bags, sheets and pipes are manufactured by this process [1,2].

Recently melt extrusion has found its place in the array of the pharmaceutical manufacturing operations. Several research groups have evaluated this technology to achieve enhancement in dissolution rates for poorly water soluble drugs, to modify drug release and transdermal passage of the drug.

Extrusion 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 (1). Extrusion can be operated as a continuous process, which is capable of consistent product flow at relatively high throughput rates. An extruder consists of two distinct parts: the conveying system which transports the material and imparts a degree of distributive and dispersive mixing, and the die system which forms the material into the required shape. Extrusion may be broadly classified into a molten system under temperature control or a semisolid viscous system. In molten extrusion, heat is applied to the material in order to control its viscosity and enable it to flow through the die. Whereas, semisolid systems are multiphase concentrated dispersions containing a high proportion of solid mixed with liquid phase [3].

Process and Equipment

Hot-melt extrusion equipment consists of an extruder, auxiliary equipment for the extruder, downstream processing equipment, and other monitoring tools used for performance and product quality evaluation [2]. The extruder is typically composed of a feeding hopper, barrels, single or twin screws, and the die and screw driving unit (Figure 1). 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.

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The theoretical approach to understanding the melt extrusion process is therefore, generally

presented by dividing the process of flow into four sections [4]:

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 1 and Figure 2) 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 [5].

Most commercial extruders have a modular design, providing a choice of screws or interchangeable sections which alter the configuration of the feed, transition, and metering zones. This makes it possible to modify the process to meet particular requirements, for example, from standard to high shear extrusion or addition of solvent and evaporating the solvent form material. 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 (Figure 3). The various screw and die design available and practical considerations of thermoplastic extrusion are reviewed by Whelan and Dunning [6].

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 [7]. 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 [5].

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 [4].

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. In such case, the agitator element wipes both the surface of the corresponding element on the adjacent shaft, and the internal surfaces of the mixing chamber and ensures a narrow and well-defined residence time distribution. In general, 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. In this manner the material is transported along the extruder barrel.

The twin-screw extruder is characterized by the following descriptive features [5]:

1) Short residence time: The residence time in the twin-screw extruder in a typical extrusion processes ranges from 5-10 minutes depending on the feed rate and screw speed.

2) Self wiping screw profile: The 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^oC) to high temperatures (300^oC) degradation by heat can be minimized [5].

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. Today, extruders allow in-process monitoring and control of parameters, such as the temperature in the extruder, head and die as well as pressure in extruder and die [8]. The main monitoring and controlling parameters are barrel temperatures, feed rate, screw speed, motor load and melt pressure. Barrel temperature, feed rate and screw speed are controlling parameters and motor load and melt pressure are monitoring parameters.

i) **Barrel temperatures:** The glass transition 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. This is critical to the process, because it governs the balance between the weak and strong mass transfer mode. 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.

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 [9]. This process is often referred to as profile or line extrusion in which the shape of the extrudate, such as a tube, is determined by the die. The extrudate profile proceeds horizontally to the cutoff equipment, which controls its length. Profiles may be further processed, for example, as in film extrusion, blow molding, or injection molding [9].

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. Plastic packaging film is also formed by blow extrusion, where tubular film is produced by melt, usually vertically, through an annular-shaped slit die. The extruded tube is inflated by air to form a large cylinder. Blow molding refers to a process where the plastic is heated to a melted or viscous state and section of molten polymer tubing is extruded usually downward from the die head in to an open mold. The mold is closed around it, sealing it at one and. Compressed air is blown into the open end of the tube, expanding the viscous plastic to the walls of the cavity, thus forming the desired shape of the container. During injection moulding the molten plastic is not extruded but rather injected into a cavity and then solidifies. The mould is then opened and the article is removed.

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 [10].

In the animal feed industry, extrusion is most commonly applied as a means of producing palletized feeds [11]. The manufacture of implants by extrusion or injection moulding is another field of application in the veterinary field.

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

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 of high throughput screening (HTS) in the drug

discovery process the resultant compounds are often high molecular weight and highly lipophilic and exhibits poor solubility [12]. Scientists have tried to address solubility issues by various pharmaceutical interventions. Today among the many methods available to improve solubility and dissolution rate, preparation of solid dispersions and solid solutions has gained vast attention.

The most relevant technologies for the manufacture of solid dispersions are melting of excipients or fusion method [13], embedding of drug by means of spray drying [14], co-evaporation, co-precipitation [15], freeze-drying (16), and roll-mixing or co-milling [17, 18].

Lately the melt extrusion technology has evolved as an efficient manufacturing technique, to disperse or dissolves the drug in molten polymer, forming a solid dispersion or solid solution. It is the convenience of the technology that gives new hope to the solid dispersion and solid solution approach as a delivery system for poorly water soluble drugs. The essential advantage of the melt process in this domain is its solvent free formation of solid dispersions [19].

Sekiguchi and Obi were first to report the melting or fusion method [20]. In 1974 solid dispersions of drugs were described as a relatively new field of pharmaceutical technique and its principles play an important role in increasing dissolution, absorption and therapeutic efficacy of the drug [21].

By definition, solid dispersions and solid solutions 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 [20, 22]. Improvement in bioavailability with these systems is primarily based on improving dissolution rates [23, 24]. In the case of a solid dispersion, this is achieved by improvement in the wetting behavior of the hydrophobic drug as well as deagglomeration and micellization of the drug with hydrophillic polymers. In case of solid solutions, 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, [25] which is prone to precipitation or crystallization under environmental stress such as moisture and heat, especially during processing and storage of the drug products. Two major factors that stabilize solid solutions are intermolecular interactions between the drug and the carrier [26-28] and the viscosity of the carrier [29]. Glass transition temperature has long been seen as the predominant factor governing the physical stability of the solid solution. The higher the glass transition temperature of system the better the thermodynamic stability [30]. 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 [31-34]

Since solid dispersions were introduced in 1961 [20], an immense amount of research has been done in this area. However, very few solid dispersion systems have been marketed. These include a griseofulvin-polyethyleneglycol dispersion (Gris-PEG marketed by Wander), Cesamet a nabilone-PVP (polyvinyl pyrrolidone) preparation (marketed by Lilly) as well as a formulation of toglitazone (Rezulin marketed by Parke-Davis) which was withdrawn from the market for toxicology related issues to the drug. Several implants containing a LHRH agonist for parentral use have become commercially available, such as geoserelin (Zoladex) or buserelin (Depot-profact) embeddings in poly(lactide-coglycolide) (PLGA) [35].

The troglitazone formulation in PVP was actually manufactured by melt extrusion (ref.). Melt extrusion technology has proven to be a suitable method for the production of controlled release reservoir systems consisting of polyethylene vinylacetate (EVA) co-polymers. Based on this technology, two controlled release systems Implanon and Nuvaring have been developed [36].

Application of melt extrusion as a drug delivery technology

For over two decades, the value of continuous processing in the pharmaceutical industry has been recognized. The potential of automation and the reduction of capital investment and labor costs have made hot-melt extrusion worthy of consideration [37].

Until recently, hot-melt extrusion had not received much attention in the pharmaceutical literature. Pellets comprising cellulose acetate phthalate were prepared using a rudimentary ram extruder in 1969 and studied for dissolution rates in relation to pellet geometry [38]. More recently, production of matrices based on polyethylene and polycaprolactone were investigated using laboratory scale extruders [39, 40]. Mank et al., reported in 1989 and 1990 the extrusion of a number of thermoplastic polymers to produce sustain-release pellets [41]. A melt extrusion process for manufacturing matrix drug delivery system was reported by Sprockel and co-workers [42].

In 1994 Follonier and co-workers investigated hot-melt extrusion technology to produce sustained-release pellets [43]. Diltiazem hydrochloride, a relatively stable, freely soluble drug was incorporated into polymer-based pellets for sustained-release capsules. Four polymers were considered for extrusion trials, namely ethylcellulose,

cellulose acetate butyrate (CAB), poly (ethylene-co-vinyl acetate) (EVAC) and polymethacrylate derivative (Eudragit RSPM). The plasticizers included triacetin and diethyl phthalate. The porosity of the formulations was assessed using mercury porosimetry. The pellets produced, exhibited a smooth surface and low porosity. The in-vitro release of the drug was biphasic, with the CAB and EVAC pellets giving the lowest release rate. In a later study, Follonier et al. examined different parameters influencing the release of diltiazem hydrochloride from hot-melt extruded pellets [44]. These parameters included polymer type, drug/polymer ratio, and pellet size. The authors incorporated various polymer excipients such as croscarmellose sodium (Ac-Di-Sol) and sodium starch glycolate (Explotab) into the formulations to vary the drug-release rate. These pellets could be applicable for incorporation into hard gelatin capsules. With optimization techniques and formulation, it is apparent that hot-melt extrusion of these and other sustained-release pellets is a viable drug delivery technology.

Aitken-Nichol and co-workers investigated the viability of hot-melt extrusion technology in 1996 for the production of thin, flexible acrylic films for topical drug delivery [45]. One of the advantages they pointed out was that the delivery manufacturing process is not restricted by solvent concerns. The investigation compared cast films with various extruded films. They also studied the effect of types and levels of plasticizers using the model drug lidocaine HCL; on the glass transition temperature (Tg) and the mechanical properties of high density polyethylene (HDPE) and Eudragit E-100 extruded films. Eudragit E-100 was the primary thermoplastic polymer extruded. The authors found that hot-melt extrusion was viable technology for the production of free films of this acrylic resin. Triethyl citrate (TEC) was an acceptable plasticizer for Eudragit E-100. The authors concluded that the differences in the dissolution and ductile properties between cast films and extruded films were due to amount of drug dissolved in the polymer. The dissolution rate of lidocaine HCL was affected by the drug loading, in contrast to the solvent cast films tested.

Transdermal and transmucosal drug delivery systems are frequently produced by films cast from organic or aqueous solvents. Repka and co-workers discussed the numerous disadvantages accompanying these techniques, including long processing times, environmental concerns and excessive costs [46]. In 1999 they used Killion melt extruder to produce hydroxypropyl cellulose (HPC) films employing a. Polyethylene glycol 8000 (PEG 8000) 2%, triethyl citrate (TEC) 2%, acetyltributyl citrate (ATBC) 2%, and polyethylene glycol 400 (PEG 400) 1% were the plasticizing agents studied. In addition, either hydrocortisone 1% or chlorpheniramine maleate 1% was incorporated into the films as a model drug. The influence of these plasticizers and drugs on the physical-mechanical properties of the films such as tensile strength, percentage elongation, and youngs modulus were investigated. The authors observed that a pure HPC film could not be produced without incorporation of a plasticizer due to high stress exhibited in the extruder. With exception of PEG 400, all the plasticizers investigated demonstrated adequate stability throughout the duration of the study. Although PEG 400 initially exhibited excellent plasticizer qualities for HPC films, it was found to be unstable in all parameters tested. Chlopheniramine maleate proved to be an excellent plasticizer for HPC, providing mechanical stability for the hot-melt extruded film, and was chemically stable for up to 12 months. Hydrocortisone was shown to be a good plasticizer comparable to the conventional plasticizers studied. However, the chemical stability of drug incorporated into HPC films was shown to be a function of processing temperature and residence time in the extruder.

Another application of hot-melt extrusion was described by Miyagawa, Sato, and co-workers in 1996 and 1997 [47, 48]. They studied the controlled release and mechanism of release of diclofenac. These researchers utilized a twin-screw compounding extruder to prepare wax matrix granules composed of carnauba wax, the model drug, and other rate controlling agents. Their first investigation [47] showed that a wax matrix with high mechanical strength could be obtained even at temperatures below the melting point of the wax. Dissolution release profiles of diclofenac from wax matrix granules were strongly influenced by the formulation of the granules. The rate-controlling additives that were varied in the formulations included hydroxypropyl cellulose, methacrylic acid copolymer (Eudragit L-100), and sodium chloride. The authors emphasized the advantages of using twin-screw extruder for wax matrix tablets, such as low temperatures, high kneading and dispersing ability, and low residence time of the material in extruder. The investigators concluded in a second study [48] that selection of rate-controlling agents based on physicochemical properties (solubility and swelling characteristics) had significant impact on the properties of wax matrix granules prepared by this extrusion process.

Zhang and McGinity [49] in 1999 investigated the properties of polyethylene oxide (PEO) as a drug carrier and studied the release mechanism of chlopheniramine maleate (CPM) from matrix tablets. In these extruded tablets, PEG 3350 was included as a plasticizer to facilitate processing. The molecular weight of the PEO, the drug loading percentage, and the inclusion of PEG were all found to influence the processing conditions and the drug release properties of the extruded tablets. An increase in the percentage of PEG 3350 increased the release rate of the drug. PEG 3350 is composed of the same structural unit as PEO. The hydration and dissolution rate of the

entire matrix system were thus accelerated due to the presence of the plasticizer. When CPM loading was increased from 6 to 12%, no change in the percentage of drug release with respect to time was observed. There was a slight increase when the drug loading reached 20%. This study conveyed the reproducibly of dissolution data from tablets manufactured by hot-melt extrusion.

Similar study was conducted by Zhang and McGinity in 2000 [50]. The objective of this study was to investigate the properties of poly vinyl acetate (PVA) as a retardant polymer and to study the drug release mechanism of theophyline from matrix tablets prepared by hot-melt extrusion. The release rate of the drug was shown to be dependent on the granule size, drug particle size, and drug loading in the tablets. As the size of hot-melt extruded theophyllline/PVAc granules was increased, there was a significant decrease in the release rate of the drug. Higher drug loading in the hot-melt granules also showed higher release rates of drug. Water-soluble materials such as PEG 400 and lactose were demonstrated to be efficient release rate modifiers for this system.

McGinity and Koleng in 1997, employed hot-melt extrusion technology for the preparation of rapid-release granules [51]. In this investigation, a hot-melt extrusion process was used to granulate acetaminophen and filler excipients with low molecular weight polyethylene glycols. The resultant granules were combined with additional excipients (disintegrant and lubricant) and compressed into tablet compacts. Drug release from bulk granules and tablets were compared containing 15 to 25% polyethylene glycole 6000. The drug release from granules was improved over that from tablets. Tablets containing 15% polyethylene glycol released more than 80% of the drug after 30 min as required for acetoaminophen tablets in the USP 23.

In similar study Perissutti and co-workers (2002) applied hot-melt extrusion technology to improve dissolution of carbamazepine [52]. The aim of this research was to use a ram extruder to directly prepare a fast release dosage form with uniform shape and density, containing poorly water soluble model drug and polyethylene glycol 4000 (PEG 4000) as a hydrophilic carrier and low melting binder. The investigation revealed that the extruded mixtures of an equivalent composition exhibited more rapid release than simple physical mixtures.

H lsmann and co-workers worked on hot-melt extrusion to improve solubility and dissolution of 17-Estradiol hemihydrate, a poorly water soluble drug [53]. Different compositions of excipients such as PEG 6000, polyvinylpyrrolidone or a vinylpyrrolidone-vinyl acetate-copolymer were used as polymers and Sucroester WE 15 or Gelucire 44/14 as additives. The solid dispersions resulted in a significant increase in dissolution rate when compared to the pure drug or to the physical mixture. A 30-fold increase in dissolution rate was obtained for a formulation containing 10% drug, 15% PVP and 40% Gelucire ^{TM} tablets.

Nakamichi and co-workers prepared a floating sustained release dosage form composed of nicardipine hydrochloride and hydroxypropylmethylcelluloseactate succinate, using twin-screw extruder [54]. By adjusting the position of the high-pressure screw elements in the immediate vicinity of the die outlet, and by controlling the barrel temperature, a puffed dosage form with very small and uniform pores was obtained. It was shown that the puffed dosage form prepared by twin-screw extruder, consisting enteric polymer was very helpful as a floating dosage form that was retained for long period in the stomach.

In a later study Nakamichi and co-workers also investigated the role of the kneading paddle and the effect of screw revolution on the preparation of a solid dispersion using twin-screw extruder [55]. The authors concluded that the kneading paddle element of the screws play an important role in changing the crystallinity and dissolution properties of a solid dispersion of nifedipine and hydroxypropylmethylcellulose phthalate.

Along with literature describing the in vitro performance of solid dispersions a number of melt extruded solid dispersions have been examined in human clinical studies.

The antiretroviral agent, loviride when melt extruded to a solid molecular dispersion in HPMC showed remarkable, lower food effect compared to capsules [56].

Antifungal compositions of intraconazole were prepared as solid dispersions using the melt extrusion process. In a limited number of volunteers these tablets gave an area under the curve (AUC) in the fasted state that was 2.3 times the AUC of the marketed reference capsules [57].

Materials used in hot-melt extrusion technology

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 use in production of other solid dosage forms such as tablets, pellets, and transdermals. The materials must possess some degree of thermal stability in addition to acceptable physical and chemical stability. The thermal stability of each individual compound and of the composite mixture should be sufficient to withstand the production process. Hot-melt

extruded dosage forms are complex mixtures of active drug and functional excipients. The functional excipients may be broadly classified as matrix carriers, release modifying agents, bulking agents, and various additives [58]. The excipients can impart specific properties to melt extruded pharmaceuticals in manner similar to those in traditional dosage form.

Active ingredient

The properties of the active drug substance often limit the formulation and preparation option available to the pharmaceutical scientist in the development of an acceptable dosage form. Hot-melt extrusion, a relatively new technology to the pharmaceutical industry, offers many benefits over traditional processing techniques. The melt extrusion process is anhydrous, avoiding any potential drug degradation due to hydrolysis following the addition of aqueous or hydroalcoholic granulating media. In addition, poorly compactable materials can be incorporated into tablets produced by cutting an extruded rod, eliminating any potential tableting problems seen in traditional compressed dosage forms [58]. The active ingredient should be thermally stable to be melt-extruded and thus an initial assessment of thermal, chemical and physical properties of the drug substance is very essential. Depending on the unique properties of the drug substance and the other excipients in the formulation, the drug may be present as undissolved i.e. solid dispersion or completely dissolved in polymer i.e. solid solution in the final dosage form. The state of the drug in the dosage form may have profound impact on the processibility and stability of the product [59].

In addition to thermal degradation, the active compound may interfere with the functionality of the other components in the formulation. Oxprenolol hydrochloride was shown to melt under melt extrusion processing conditions, which lowered the viscosity of the extrudate to yield material with poor handling properties. In similar work preparing dosage forms by injection molding, Cuff and Raouf [60] reported that the fenoprofen calcium inhibited hardening of a PEG-MCC matrix, resulting in an unusable product. Lidocaine was also shown to effectively lower the Tg of Eudragit E/HDPE flms [61], and hydrocortisone demonstrated a time-dependent lowering of the glass transition temperature of hydroxypropyl cellulose (HPC) films [62].

Polymer systems: The selection of polymer for hot-melt extrusion 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) [63] or its co-polymer such as poly vinylpyrrolidone-vinyl acetate [64], poly(ethylene-co-vinyl acetate) [44], various grades of polyethylene glycols [52], cellulose ethers [65] and acrylates [66], various molecular weight of polyethylene oxides [49], 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 [67, 68]. The basic prerequisite for the use in melt extrusion is the thermo plasticity of the polymers or that of the respective formulation.

Plasticizers

The choice of suitable plasticizer depends on many factors, such as plasticizer-polymer compatibility and plasticizer stability. Triacetin, citrate esters, and low molecular weight polyethylene glycols have been investigated as plasticizers in hot-melt extruded systems. The plasticizer lowers the glass transition temperature (Tg) of the polymer as well as the processing temperature necessary for production. A reduction in polymer Tg depends upon the plasticizer type and level. A reduction in processing temperatures may improve the stability profile of the active compound and/or of the polymer carrier. Plasticizers also lower the shear forces needed to extrude a polymer, thereby improving the processing of certain high molecular weight polymers. The thermo-chemical stability and volatility of the plasticizer during processing and storage must also be taken into consideration [62, 69, 70].

The materials used in the production of hot-melt extruded forms are the same pharmaceutical compounds used in the production of more traditional systems. Thermal stability of the individual compounds is a prerequisite for the process, although because of the short processing times not all thermolabile compounds are excluded. The incorporation of plasticizers may lower the processing temperatures required in hot-melt extrusion, thereby reducing drug and carrier degradation. Drug release from these systems can be modified by the addition of various functional excipients. The dissolution rate of the active compound can be increased or decreased, depending on the properties of the rate-modifying agent. For systems that display oxidative or free-radical degradation during processing or storage, the addition of antioxidants, acid acceptors, and/or light absorbers may be advised [59].

Figure 1. Micro-18 Twin screw co-rotating Leistritz extruder

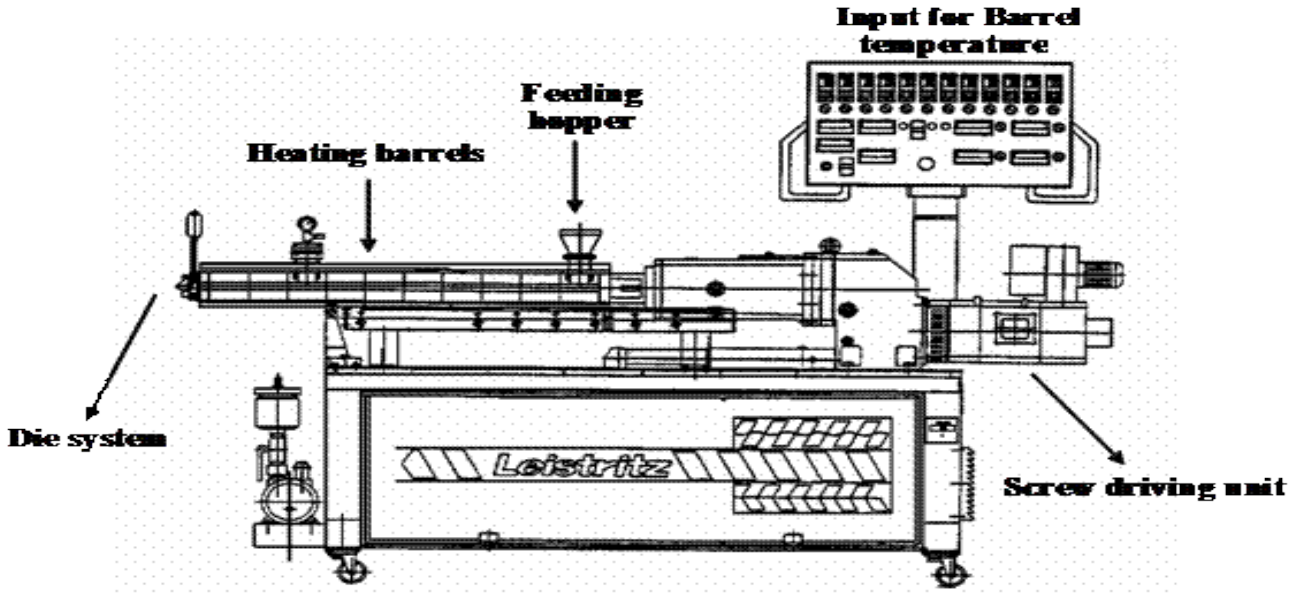
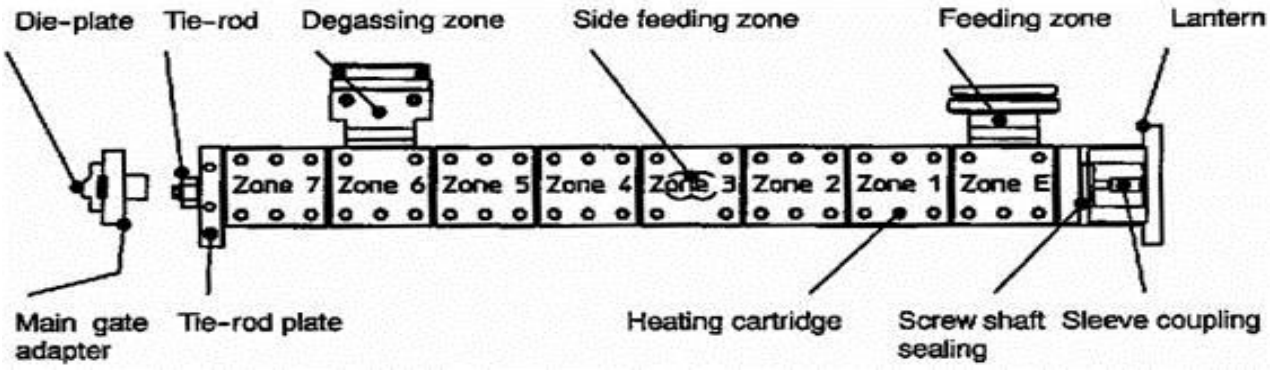


Figure 2. Heating barrels and co-rotating screws for hot-melt extruder

Heating barrels



Co-rotating screws

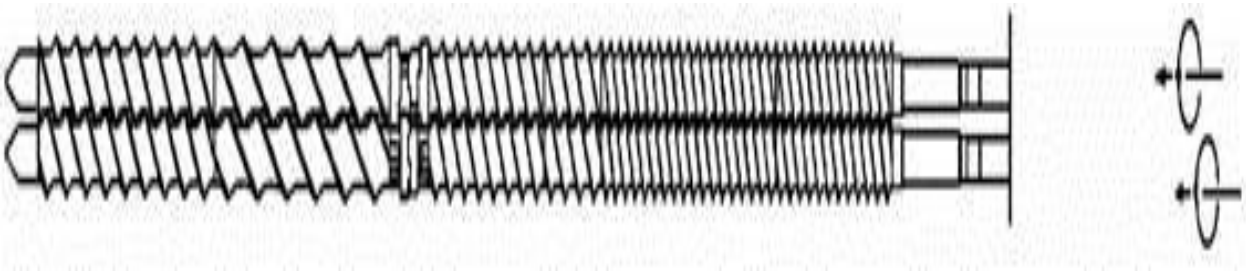


Figure 3. Screw and kneading elements

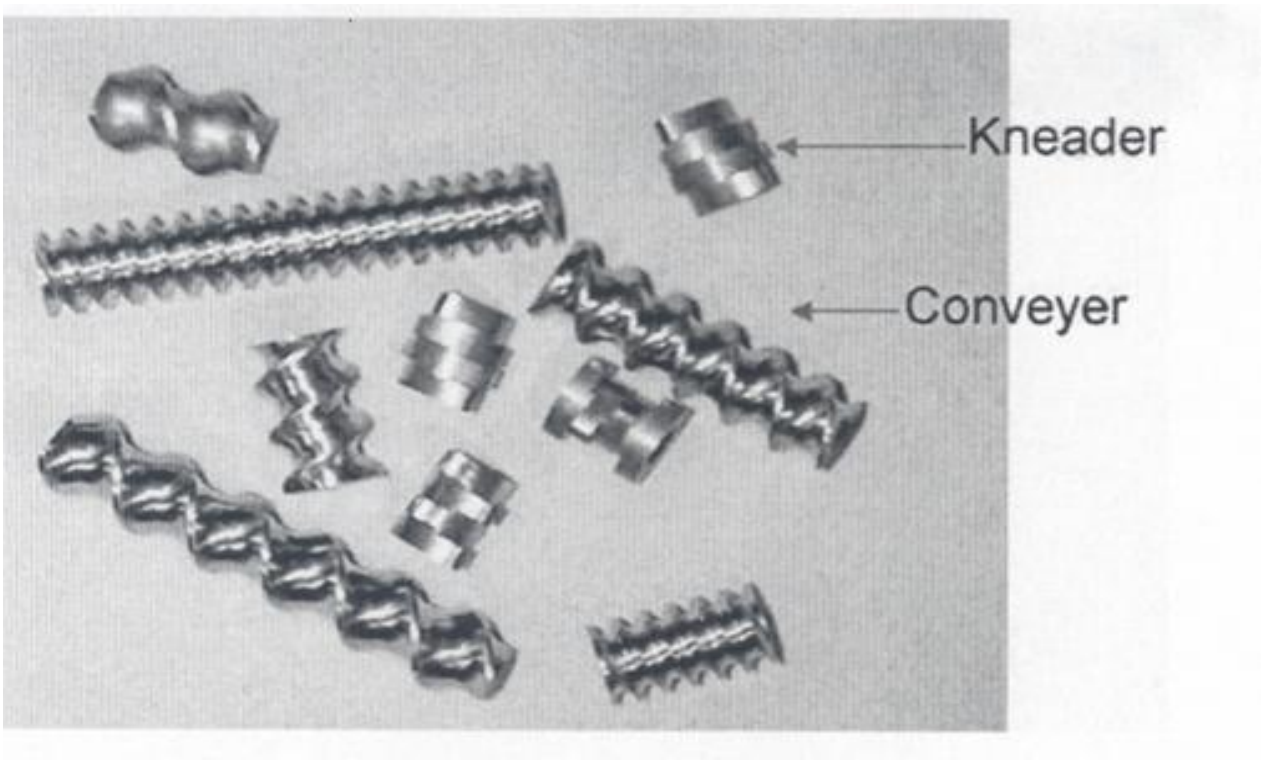


Figure 4. Component parts of single screw extruder

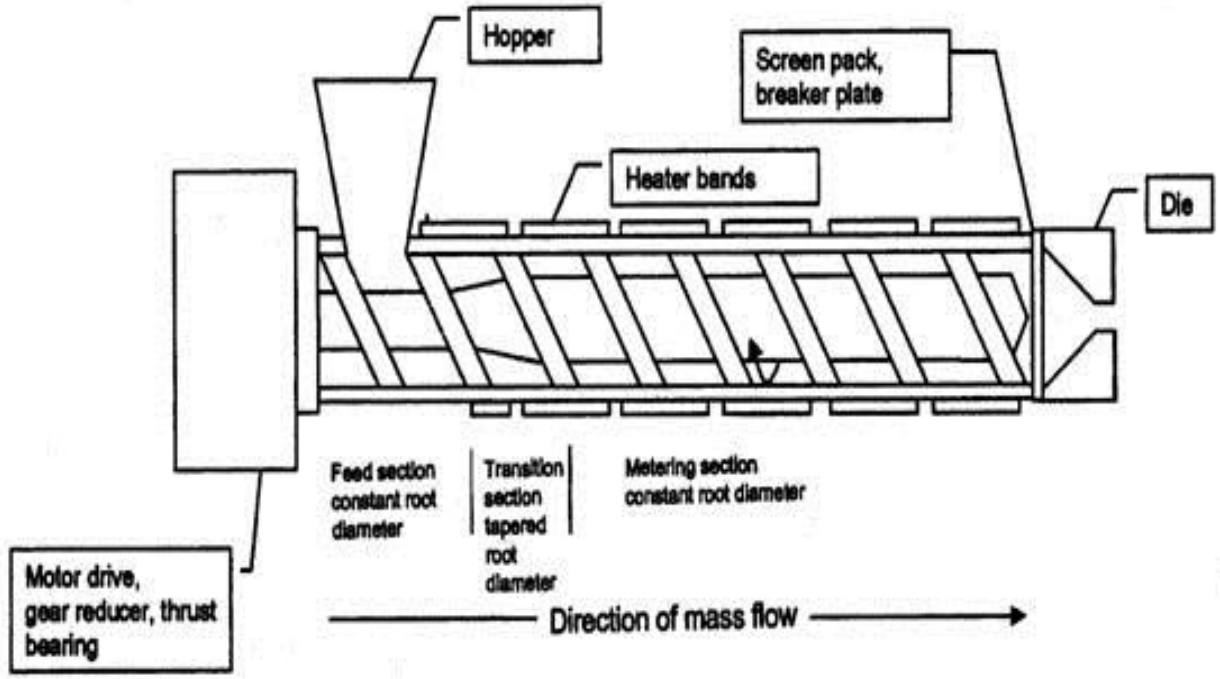
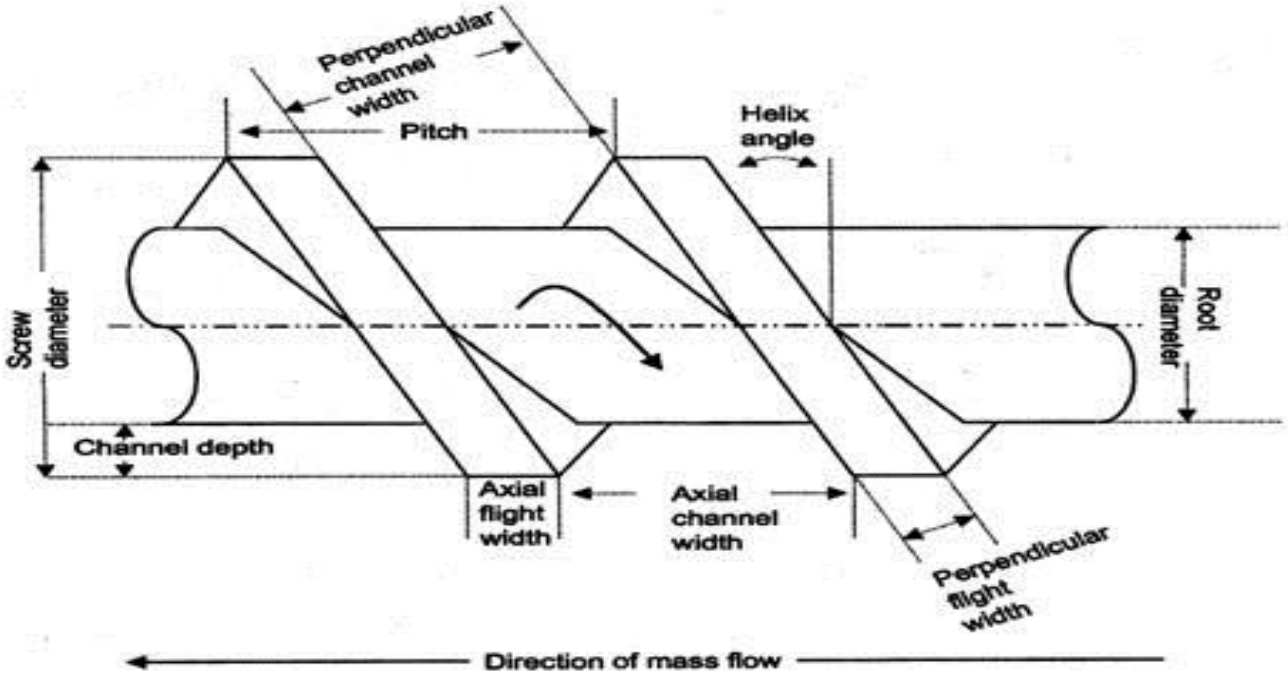


Figure 5. Extrusion screw geometry



CONCLUSION

Today melt extrusion 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. In addition, the physical state of the drug in an extrudate can be modified with help of process engineering and the use of various polymers. 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. This is where process engineering becomes significant. 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.

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 naoparticles released from molecular dispersions manufactured by melt extrusion.

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