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Hot melt extrusion technology, approach of solubility enhancement: A brief review

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ABSTRACT

During the developmental process, there is an estimated 40 to 70% incidence of delay or failure for new drug entities due to poor biopharmaceutical properties such as poor solubility, poor permeability and poor chemical stability. Hot melt extrusion (HME) technology may provide the answer. HME, a solid-dispersion technology, has gained popularity in the pharmaceutical industry as a means of improving the solubility of drugs. HME has several areas of application, including bioavailability enhancement, oral controlled release, the production of advanced controlled release forms, and melt granulation. HME can be used to create many dosage forms and is compatible with process analytical technology. It is a continuous process with less offline testing, fewer operator interventions, and can be scaled up easily to improve efficiency and decrease operating costs. This review encompasses the brief idea about instruments, materials, optimization of process and applications of HME.

Keywords: Solubility, Hot melt extrusion, Screw design, Optimization, Polymer.

INTRODUCTION

The advent of high through-put screening in the drug discovery process has resulted in compounds with high lipophilicity and poor water solubility. Solubility enhancement of such compounds is a major challenge to formulation scientists. Various approaches have been adopted to address this including preparation of solid dispersions and solid solutions. Since the early 1930s, Hot-melt extrusion (HME) was established and has been used predominately in the plastics manufacturing industry and also in the food industry [1]. The most relevant technologies for the manufacture of solid dispersions are melting of excipients or fusion method [2], embedding of drug by means of spray drying [3], co-evaporation, co-precipitation [4], freeze-drying [5] and roll-mixing or co-milling [6, 7]. The word 'extrusion' is derived from the Latin 'extrudere', which literally means to press out or to drive out. 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 [8]. This technology has been used in various industries like

agrochemicals, detergent additives, sweeteners, food processing and more recently in pharmaceuticals. In pharmaceutical industry HME has been used for various applications like [7]:

- Improving the dissolution rate and bioavailability of the drug by forming a solid dispersion or solid solution.
- Controlled release of the drug.
- Taste masking of active pharmaceutical ingredient.

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 [1]**.** HME differs from simple extrusion in that, polymer, drug and excipient blends are mixed thoroughly in the molten state in this process, needing no solvents for granulation. The molten polymer serves as the thermal binder. Simple extrusion process uses aqueous or organic solvents for wetting the powder blend for granulation. It is a time consuming process since drying step is critical. Use of solvents in this process may degrade the drug and residual solvents may be present after drying **[**8]. The advantages and disadvantages of HME technology have been enlisted in table 1.

Table 1 Advantages and disadvantages of HME [9, 1].

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

Components of the formulation

Hot melt extruded dosage forms are complex mixtures of active drug and excipients. The excipients may be broadly classified as matrix carriers, release modifying agents, bulking agents and various additives. The excipients can impart specific properties to melt extruded pharmaceuticals in manner similar to those in traditional dosage form [1].

1) Drug

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 organic 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. As an initial assessment, the thermal, chemical and physical properties of the drug substance must be

characterized. 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 solid solution 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 [10].

2) Polymers

Polymers are the most important excipients in HME formulations. They have their characteristic glass transition temperature (Tg) and melt at temperature little above their Tg. Molten or softened polymers act as binders for granulations, thus requiring no solvents. Mixing occurs thoroughly in the molten state and the drug is embedded in the polymeric matrix. Polymers having Tg below the drug degradation temperatures have been widely utilized as thermal binders and retardants for melt extrusion processing [8]. The various polymers for HME have shown in table 2.

Table 2 Pharmaceutical grade polymer for HME [11].

Chemical name	Tradename	Tg(^{0}C)	Tm(^{0}C)
Polyethylene glycol	Carbowax®	-20	35-65
Polyethylene oxide	PolyOx™	-50	60-80
Hydroxypropyl cellulose	Klucel®	0	180-210
Ethyl cellulose	Ethocel®	133	180-250
Hydroxypropylmethyl cellulose	Methocel®	160-170	190-200
Poly(dimethylamino ethyl methacrylate-co- methacrylate ester)	Eudragit® E	50	160-170
Ammonio-comethacrylate copolymer	Eudragit® RS	64	-
Poly(vinyl pyrrolidone)	Kollidon®	-	-
Poly(vinyl acetate)	Sentry® Plus	35-40	-

3) 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. Plasticizers are added to HME formulations to facilitate the extrusion of the material and to increase the flexibility of the extrudate. This approach may reduce the likelihood of degradation problems that are associated with temperature sensitive drugs or polymers [12]. The choice of suitable plasticizer depends on many factors, such as plasticizer-polymer compatibility and plasticizer stability. The plasticizer lowers the Tg of the polymer which is desired condition during HME process. A reduction in polymer Tg depends upon the plasticizer type and concentration. A reduction in processing temperatures may improve the stability profile of the active compound as well as the polymer carrier. Plasticizers also lower the shear forces needed to extrude a polymer, thereby improving the processing of certain high molecular weight polymers [13, 14]. The thermo-chemical stability and volatility of the plasticizer during processing and storage must also be taken into consideration [1]. Some of the plasticizers used in HME are diethyl phthalate, triacetin, triethyl citrate, acetyl triethyl citrate, acetyl tributyl citrate, propylene glycol, glycerin, dibutyl sebecate, dibutylsorbiton monolaurate, PEG 400 and glycol triacetate etc. [8].

3) 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 HME process. 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. They are most effective when used in a closed system where oxygen cannot be replaced once it is consumed. Chelating agents such as edentate disodium (EDTA) and citric acid are another type of preventive antioxidant that decreases 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 HME processing for e.g. waxy material like glyceryl monostearate has been reported to function as a thermal lubricant during hot-melt processing. Vitamin E has been reported to plasticize polymers and enhance drug absorption [15].

4) Equipments

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. The extruder is typically composed of a feeding hopper, barrels, single or twin screws, and the die and screw driving unit. Figure 1 shows schematic diagram of HME equipment.

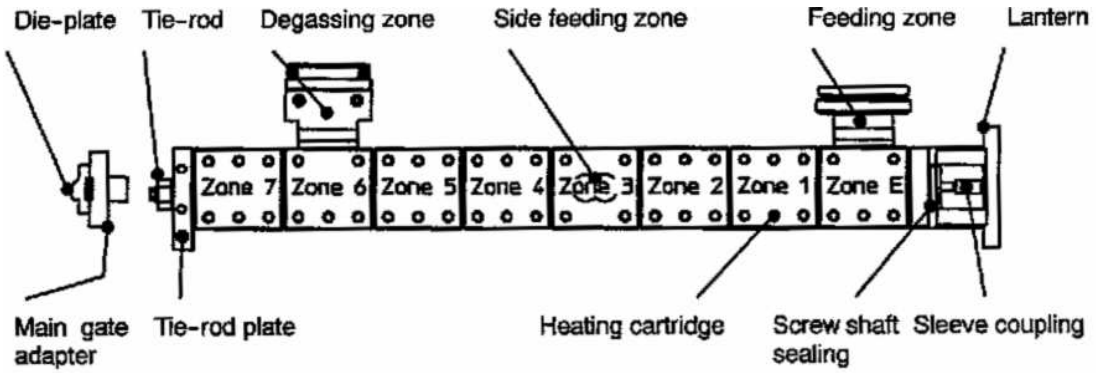

Figure 1 Heating barrel co-rotating screws for HME [16].

During this process, different zones of the barrel are preset to a specific temperature. A blend of the thermoplastic polymers and other processing aids are fed into the barrel of the extruder through the hopper and transferred by a rotating screw inside the heated barrel. Temperatures of different sections of the barrel are controlled by electrical heating bands and monitored by thermocouples. The materials inside the barrel are heated mainly by the heat generated due to the shearing action of the rotating screw. The molten mass is eventually pumped into the die, attached to the end of the barrel. The extrudates are subjected to further processing by auxiliary downstream devices. The auxiliary equipment for the extruder mainly consists of a heating/cooling device for the barrels, a conveyer belt to cool down the product. 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. A screw extruder consists of three distinct parts:

1. A conveying system for material transport and mixing
2. A die system
3. Downstream auxiliary equipment for cooling, cutting and/or collecting the finished product

The design of the extrusion screw has a significant influence on the efficiency of the hot-melt extrusion process. The functions of the screw are to transfer the material inside the barrel and then to mix, to compress, to melt the polymeric materials and to pump the molten mass through the die. Several parameters are used to define the geometrical features of the screw [16, 17]. The various equipment parameters affecting extrusion process have been shown in table 3.

Table 3 Equipment parameters [18, 19].

Parameter	Comment
A. Screw design	a) Compact and transfer the feed stock in to the barrel of machine b) Affect the performance of feeding section because of friction between feed stock, at the surface of screw and barrel
B. Screw configuration	a) Alters the production method as different screw elements like feed rate, metering is optimised for particular application.
C. Screw speed	a) It must be optimised b) At very high speed, degradation may occur due to melt fracture
D. Die design	a) Controls physical shape of the molten extrudate b) Die swelling- The viscoelastic properties of polymer melt are able to recover some of the deformation imposed by screw inside the barrel during extrusion

a) Single screw extruders

Single-screw extrusion is a fundamental operation for polymer processing. It is used to increase pressure within a polymer melt, allowing extrusion through a die or injection into a mould. Although a relatively simple process, single screw extrusion does not possess the mixing capability of a twin-screw machine and is, therefore, not the preferred approach for the production of pharmaceutical formulations [17].

b) Twin screw extruders

Twin-screw extrusion offers the pharmaceutical formulator a rapid, continuous process that has much better mixing capability than single screw extrusion. Moreover, twin screw extrusion provides a more stable melting process, shorter residence times and significantly greater output. Industrially, twin screw extrusion has become extremely favourable because of process practicality and the ability to combine separate batch operations into a single continuous process, thus increasing manufacturing efficiency. This extruder characterised by short residence time, self wiping screw profile, minimum inventory, versatility, superiority. 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 [20,21]. Typical twin screws have been shown in figure 2.

Figure 2 Intermeshing profiles of twin screws

Process of Twin screw HME

Feeding & melting zone (1): In the first process zone (feeding zone) the polymer and any required adjuvants are fed into the extruder via a gravimetric solid feeder. In the melting zone, the polymer is melted by the use of dispersive and distributive screw elements. Depending on the product specifications it can be beneficial to feed a premix of raw materials into the upstream feeding zone.

Incorporation of additional components such as APIs (2&3): Downstream of the melting section, additional solids (depending on the product requirements), liquids or the API are added. In some cases, it can be beneficial to add the API nearly at the end of the process section to decrease the thermal stress on the API. Although the residence time of the material in the melt extruder is already very short, adding the API downstream in the process section can also reduce the API residence time (and thermal exposure) to an absolute minimum.

Discharge section (5): The pressure build-up zone is located at the end of the extruder upstream of the die or other integrated downstream equipment. The pressure consumed by the upcoming subsequent unit (e.g. die face pelletiser) has to be generated in the discharge zone.

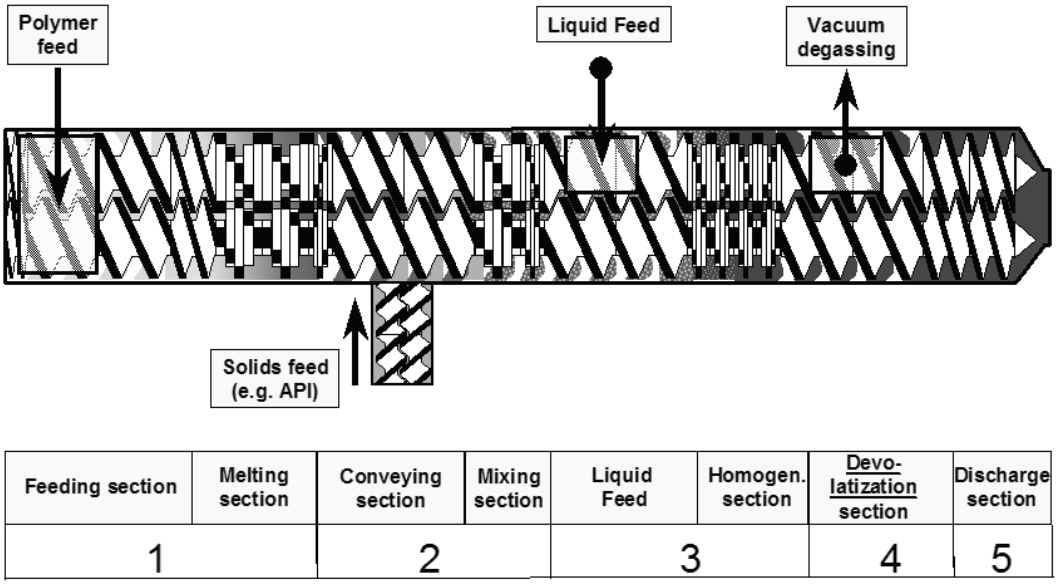

Figure 3 Diagram of the individual process steps in a Coperion twin-screw extrude [16]

Devolatilisation zone (4): Just before the end of the process section the product is devolatilised. Due to the axially open screw channels in the co-rotating twin screw extruder, the devolatilisation zone must be sealed by completely filled zones on either side of the devolatilisation opening to prevent extraction of components that have not yet been incorporated from upstream zones. The conveying elements in the devolatilisation zone are designed to operate partially filled to provide as large a product surface as possible for devolatilisation and also to prevent product discharging through the vent.

Evaluation of HME formulations [1]

Evaluations of formulations produced via HME can be evaluated by several methods. The evaluation methods can be used to differentiate between solid solutions (molecularly dispersed

drugs) and solid dispersions (physical mixtures of drug and carrier). In general, dispersions in which no crystallinity can be detected are molecularly dispersed.

1. Differential scanning calorimetry (DSC)
DSC has been widely used to study the thermal properties of the material used in HME. It can be used for determination of Tg and Tm in which energy is required or liberated. It is also used for the study of drug excipient incompatibility studies. It also used to differentiate between amorphous and crystalline forms.

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.

2. X-Ray diffraction pattern (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. However, the sensitivity of the XRD technique is limited and cannot generally detect crystallinity of less than 10%.

3. 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.

4. Nuclear Magnetic Resonance (NMR)
Solid state nuclear magnetic resonance (NMR) has been used to probe the crystallinity of materials. Although any NMR-active nucleus can be studied, most efforts have focused on ^{13}C investigations.

5. Microscopy
Microscopy is one of the best methods to study the crystalline properties of hot-melt extrudates. 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.

New development in HME
The coupling of extrusion and supercritical CO_2 (sc-CO_2) technologies has broadened the field of application of extrusion processes. The first applications of sc-CO_2-assisted extrusion were developed for the agro-food industry 20 years ago. However, most thermoplastics are potential candidates for sc-CO_2-assisted extrusion. The main advantage of introducing sc-CO_2 in the barrel of an extruder is its function as a plasticizer, which allows the processing of molecules which would otherwise be too fragile to withstand the mechanical stresses and the operating temperatures of a standard extrusion process. In addition, the dissolved CO_2 acts as a foaming agent during expansion through the die. It is therefore possible to control pore generation and growth by controlling the operating conditions. New challenging opportunities are expected in the field of pharmaceutical applications, like the possibility of mastering microcellular foam manufacture for making solid dispersions of a drug with controlled release. In tissue engineering

the possibility of making biodegradable scaffolds allowing new cell colonization and tissue regeneration is also very promising technology [22]. CO_2 acts as a plasticizer for polyvinyl pyrrolidon vinyl acetate 64 (PVP-VA 64), Eudragit® E100 and ethyl cellulose 20 (EC20) cps, allowing for a reduction in processing temperature. Thermal properties were not changed for PVP-VA 64 and Eudragit® E100 after carbon dioxide treatment, while for EC 20 cps the crystalline content was altered as a function of CO_2 pressure and temperature. The morphology was changed to a foam-like extrudate after CO_2 treatment, which improved milling of the polymer samples [23-25].

Optimization of HME process

Optimization of the melt extrusion process is a must before proceeding for any formulation.

parameters like screw configuration and screw speed; process parameters like temperature, melt viscosity and flow, melt pressure; and formulation parameters like physicochemical properties of the polymer and drug, drug-polymer miscibility and compatibility, glass transition temperature of the polymers, type of plasticizer and the desired drug release from dosage forms have a strong impact on the final product and its performance. Characterization of physico-mechanical properties of drug, polymers to assess their suitability for this process and the effect of formulation, process and equipment parameters on the product performance must be considered. Table 4 shows the parameters are to be considered during optimization of HME process.

Table 4 Parameters for optimization of formulation [26-30]

Parameter	Comment
Formulation parameters	
A. Physicochemical properties of the drug- particle size and shape, flow properties, moisture content, particle geometry, bulk density	a) Affects extrudability
B. Thermal stability – DSC, DTA	a) Prediction of the miscibility of drug and polymer b) Compatibility of drug and polymer c) Determination of Tg
C. Rheology	a) Assessing drug polymer miscibility b) Confirming the thermal analytical findings c) Estimating motor load
D. Extrusion temperature and motor load	a) Extrusion temperature is kept higher than Tg or Tm
Formulation development parameters	
A. Drug	a) Must be stable at processing temperature b) Compatible with the excipients
B. Selection of polymer	a) Critical factor and selected on the basis of rheological and thermal properties b) Tg less than drug degradation temperature
C. Selection of plasticizer	a) Can alter the rate of drug release b) Polymer plasticizer compatibility

Applications of HME Process

General Application

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. 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 [16].

Applications in the Pharmaceutical Industry

HME is considered to be an efficient technique in developing solid molecular dispersions and has been demonstrated to provide sustained, modified and targeted drug delivery resulting in improved bioavailability. HME process is 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, and transdermal systems. In pharmaceutical industry the melt extrusion has been used for various purposes, such as [31, 32]

1) Masking the bitter taste of an active drug.
2) Formation of polymer-drug solutions/dispersions:
- Increased drug solubility
- Increased drug dissolution rate

3) Formulation of controlled release dosage forms (including implants).
4) Formulation of targeted release dosage forms.

Overview on latest research on HME

Application of proper formulation techniques and novel manufacturing processes such as Kinetisol® dispersing process, it is possible to prepare solid dispersions without the aid of solvents or plasticizers, which may translate into improved physicochemical properties and increased homogeneity of the solid dispersion [33]. Kinetisol® dispersing is a new fusion based manufacturing that utilizes a combination of frictional and shears energies to rapidly produce solid dispersions. This technique has been successfully employed for the production of hydrophilic solid dispersions and plasticizer-free solid dispersions containing temperature-sensitive polymers such as Eudragit L 100. It is possible to produce amorphous solid dispersions of thermally labile active ingredients using fusion methods [34]. Thin films of lidocaine, using matrix of HPC and HPMC have been successfully prepared by HME technology resulted in retardation of lidocaine release [35]. HME processing has been used to mask efficiently the taste of bitter active substances e.g. ibuprofen and preparation of granules for orally disintegrating tablets [36]. By using ethyl vinyl acetate polymers proved to be promising matrix formers using HME technology to manufacture oral sustained release tablets without the addition of a plasticizer [37]. Nano/micro-dispersions of ritonavir are formed upon dispersion of melt extrudate in aqueous medium. The melt extrudate show improved dissolution rate and drug release properties of ritonavir compared to the crystalline raw material and thereby also enhance the bioavailability of ritonavir [38]. Yano et al have been observed that the dissolution rates of indomethacin from extrudates manufactured by melt extrusion and wet extrusion with hydroxypropyl β cyclodextrin (HP-β-CD) are significantly higher than that of the physical mixture of indomethacin and HP-β-CD [39]. HME processing of ketoprofen with sulphobutyl ether of β cyclodextrin (SBE_7-β-CD; Captisol®) at an extrusion temperature close to the melting point of ketoprofen (100 °C) and considerably lower than the melting point of SBE_7-β-CD (approximately 235 °C) resulted in an intimate dispersion of ketoprofen was seen to be superior to that of dispersions prepared by co-grinding, freeze-drying, and heat-treatment [40]. HME and die face pelletisation of starch melts have been found to be an interesting approach for continuously producing spherical pellets with a very narrow particle size distribution [41]. Tablets prepared by HME technology, containing 25% w/w 5-amino salicylic acid (5-ASA) and Eudragit S100 have shown controlled release of 5-ASA in pH 7.4 phosphate buffered media [42]. HME process has been used to prepare a bi-layered cylindrical co-extrudate for the purpose of developing a theophylline sustained release dosage form [43]. Enteric matrix pellets of theophylline have been prepared using Eudragit S100 as matrix material with a diameter below 1 mm [44]. HME have been successfully used to manufacture gastro-resistant matrix tablets consisting of Eudragit L100-55, demonstrating that HME techniques may be used as an alternative to conventional enteric film coating processes [45]. Influence of xanthan gum parameters (concentration and particle size) on the *in vitro* release of ibuprofen from ethylcellulose mini-matrices manufactured by HME have been studied by Verhoeven et al [46]. HME have been used for itraconazole and HPMC 2910 5 mPa s 40/60 w/w, results in an

amorphous solid dispersion whereby the polymeric carrier prevents crystallization of the drug substance during cooling. This result shows enhanced *in vitro* dissolution compared to the physical mixture containing the crystalline drug substance [48]. It has been proven that addition of methylparaben to the Eudragit RS PO polymer which results in an increase in the polymer chain mobility during hot melt extrusion and reduced both the Tg and the melt viscosity of the polymer [49]. It was observed that as the amount of filler present in the matrix increased then the extent of dissolution time increases. This effect could be of use for extended release dosage forms. The agar filler system have been explored and proved to be a viable alternative to microcrystalline cellulose as a filler system in hot melt extruded dosage forms [50]. HME of starch based formulations have a promising new pharmaceutical technique for the continuous production of matrix formulations for controlled drug delivery [51].

CONCLUSION

Hot-melt extrusion, a process used to disperse or dissolve a drug in a molten polymer, has become increasingly important in pharmaceuticals due to the possibility of dissolving poorly soluble drugs in a solid solution. It is a very important method for solubility enhancement and major advantage over conventional techniques for manufacturing of sustained release matrices. It is the continuity of different process steps like mixing, melting, homogenizing and shaping, can be carried out on a single machine. The resultant product yields matrices with excellent homogeneity. Optimization of process parameters and selection of polymer are the critical factors during HME process. These factors are considered because HME process takes place at higher temperatures. HME can be used to create many dosage forms and is compatible with process analytical technology. It is a continuous process with less offline testing, fewer operator interventions, and can be scaled up easily to improve efficiency and decrease operating costs.

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