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Review Article

Novel Applications of Hot Melt Extrusion Technology

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Abstract

Hot melt extrusion (HME) technology was introduced to pharmaceuticals in the 1970s for manufacturing and product development. Since then, there were several developments in HME technology to utilize it effectively for the manufacturing of pharmaceuticals. Though the primary purpose of HME technology remains to be solubility enhancement through the preparation of amorphous solid dispersions, it also has various other applications like dry granulation, abuse-deterrent formulation, continuous manufacturing, film preparation, implants, sustained release formulations, etc. The purpose of this review article is to consolidate the information related to applications of HME technology in the pharmaceutical industry.

Keywords: Hot melt extrusion, poorly soluble drugs, continuous manufacturing, solid orals, and applications.

Introduction:

Hot melt extrusion (HME) technology initially used in the plastic industry was introduced into the pharmaceutical industry due to its widespread applications. Since its inception in the pharmaceutical industry, there have been several formulations that were developed with help of HME. HME also gained traction in the pharmaceutical industry due to recent recommendations of regulatory agencies to shift to continuous manufacturing from batch processing[1-5].

Typically, a hot melt extruder consists of feeding, processing and output region. The feeder is part of the extruder where incoming materials are introduced into the extruder for further processing. The processing region consists of a barrel and either a single screw or twin screws which rotate in the same direction or counter to each other facilitating the movement of materials through different sections [6]. The different sections of the processing region are maintained at different temperatures based on the requirement. The screws consist of a mixture of conveying and kneading blocks. As the name indicates, the conveying blocks help in transferring material from one zone to another zone. Kneading blocks based on their shape help in either dispersive mixing or distributive mixing[7, 8].

The physicochemical properties of active ingredients and polymers play a decisive role in the selection of process parameters like screw speed, processing temperatures and screw configuration. Melting point and degradation temperature are the major properties of the active ingredient which are considered in setting the process parameters. Likewise, glass transition temperature and melt viscosity are critical parameters in the selection of polymers for hot melt extrusion. Additives like plasticizers may be included in the formulation to improve the processability[6, 9].

Several regulatory agencies have been encouraging continuous processes due to the robustness of the process due to low batch to batch variability. The hot melt extrusion process can be in the continuous manufacturing of pharmaceuticals due to its design and versatility in the preparation of various dosage forms. Several process analytical technologies (PAT) like in-line near-infrared (NIR) spectroscopy, UV/Vis spectroscopy, rheometry, etc. can be built into the extruder making it favorable for continuous manufacturing[10-12].

Applications of HME technology:

HME technology is used in the preparation of various dosage forms which help in solubility enhancement, abuse deterrence, implant preparation and others. The adaptability of the equipment to be modified makes it suitable to use as manufacturing equipment for films, implants, semi-solid dosage forms, etc. Case studies and relevant information has been discussed later to discuss the applicability of HME technology in the manufacturing of these dosage forms[13].

Solubility Enhancement:

The oral route is the preferred route of drug delivery due to ease of administration, patient compliance, non-invasiveness and others. However, in order to be formulated as an oral route, the drug needs to have minimum solubility to reach systemic circulation. Unfortunately, most of the drugs suffer from poor aqueous solubility to be administered an oral route. In such cases, modifying the drug as amorphous solid dispersion or as co-crystals may be helpful in improving the solubility when alternate approaches like salt formation or pH modification are not possible[14].

Amorphous Solid Dispersions (ASDs):

Amorphous solid dispersions are prepared by dispersing the sub-micron drug particles in hydrophilic polymers. Reduction in size results in the amorphization of drugs leading to increased entropy. Polymers prevent in agglomeration of these drug particles by arresting their movement.

Satish et al. prepared ASD of efavirenz, a low soluble anti-viral drug using HME technology, as an alternative to conventional and nanoformulations[15, 16]. The dissolution rate of efavirenz was improved with polymers Eudragit EPO and Plasdone S-630. The extrudates were characterized by DSC, XRD and FTIR techniques. Dissolution studies indicate that the dissolution rate of ASDs was improved compared to the crystalline drug. FTIR studies indicate an interaction between the drug and Plasdone S-630 was responsible for the stability of the ASDs[17].

Nimodipine belongs to a class of calcium channel blockers used in brain damage caused by subarachnoid hemorrhage. Nimodipine solid dispersion was prepared with hypromellose methyl succinate (H type) using HME technology. The ASDs were characterized using DSC, powder XRD, hot stage microscopy and SEM. The performance of ASDs was studied through in-vitro dissolution studies and in vivo pharmacokinetic studies in Sprague-Dawley rats. The results from these studies reveal improved solubility, dissolution rate and bioavailability with ASDs[18].

In another study, ASDs of nifedipine and efavirenz prepared through HME technology using hydroxypropyl methylcellulose acetate succinate (HPMCAS) were investigated for processability, dissolution and stability. ASDs were studied through DSC and XRD techniques. Both techniques confirmed the amorphous nature of the drug in the ASDs and were found to be stable for three months at 40ºC/75% RH[19].

Another study on different grades of HPMCAS, Eudragit RSPO, Eudragit FS100, Kollidon VA64 and Plasdon K-29/32 was performed to study the supersaturation kinetics of nifedipine. Binary and ternary ASDs were prepared using the mentioned polymers. Solubility studies indicate that HPMCAS-HG and HPMCAS-HG + LG combinations of nifedipine resulted in the highest improvement in solubility and delay in induction of nucleation compared to ASDs of other polymers. Ternary ASDs of nifedipine/HPMCAS-LG/HPMCAS-HG, and nifedipine/ HPMCAS-LG/Eudragit FS100 systems showed maintenance of supersaturation levels with enhanced dissolution due to synergistic effect[20].

Co-crystals:

Co-crystals are used to improve the solubility and dissolution rate of poorly soluble drugs. However, production of co-crystals requires large quantities of solvent and is a tedious process. HME technology can be used to manufacture pharmaceutical co-crystals through a grinding machine which could a solvent free-approach.

In a study, co-crystal of aripiprazole and adipic acid were manufactured using HME technology. Adipic acid acts as a co-former. Soluplus was used at 5% to improve processability. The co-crystals were characterized through DSC, FTIR, NMR, p-XRD, SEM and hot-stage microscopy. FTIR spectra indicated the formation of new crystalline material through a non-covalent interaction between the drug and co-former[21].

Meciej et al prepared co-crystals of theophylline and nicotinamide through a matrix-assisted co-crystallization approach. The effect of semi-crystalline and amorphous polymers on co-crystallization was studied. The results reveal that the use of a semi-crystalline polymer, poloxamer led to the formation of co-crystals embedded in a polymer matrix and increased the efficiency of the process. While the use of an amorphous polymer, Soluplus resulted in partially amorphous composites[22].

Carvedilol co-crystals were produced using nicotinamide as a co-former through HME technology. The drug and nicotinamide ratio of 1:2 was selected and purged through HME by altering the barrel temperatures and shaft speed. The products were analyzed using different characterization techniques like DSC, PXRD, FTIR techniques and the shape of the co-crystal was studied using SEM. The solubility and dissolution rate of the co-crystals was compared with carvedilol. XRD results indicate that the 2θ value of the product was different from carvedilol suggesting drug-co-former interaction. The data also shows improvement in solubility and dissolution rate of carvedilol co-crystals compared to carvedilol[23].

Melt Granulation:

Melt granulation is performed by agglomeration of fed powders during the granulation process by modulating the barrel temperature below the melting temperature of API but above the glass transition temperature (T_g) or melting temperature of the binder used.

A high-dose modified-release tablet formulation of imatinib mesylate was prepared using melt granulation technology using a twin screw extruder. Hydroxypropyl cellulose (Klucel HF), Ethylcellulose and a combination of HPMC K100M and ethyl cellulose 100cP were used as polymers/binders for the study with magnesium stearate as a binder. A mixture of API and polymer was subjected to a processing temperature of 185ºC which is below the melting point of the API. Confocal Raman spectroscopy was used to confirm that API remained in as crystalline state without melting[24].

Twin-screw melt granulation was utilized in improving the solubility of fenofibrate using Gelucure 48/16 as a solubilizer and Neusilin US2 as a surface adsorbent. Different granules were prepared based on altering the ratio of API, Gelucire 48/16 and Neusilin US2. The in vitro dissolution showed that an increase in Neusilin US2 levels resulted in a decrease in dissolution but improved stability. An increase in Gelucire 48/16 led to slower disintegration and dissolution[25].

Continuous manufacturing:

Continuous manufacturing is gaining attention in pharmaceutical manufacturing due to low batch to batch variability thereby improving the quality of the product[26]. Twin screw extruders are already used in the continuous manufacturing of new commercial products like Orkambi, Prezista, etc. Several researchers have shifted the focus to developing pharmaceutical products through a continuous process using twin screw extruders[27].

Voriconazole topical cream was prepared using oil and a non-aqueous polyethylene base through a continuous process. A non-aqueous hydrophilic base was selected to prevent the degradation of voriconazole due to water. Transcutol P and a combination of camphor and menthol were studied as

permeation enhancers. The O/W cream was found to be stable for 3 months without degradation[28].

In another study, Oil in water emulgel was prepared by extrusion process. Lidocaine was used as a model drug. Several emulgels were prepared by altering the process variables like screw speed (100, 300 and 600 rpm) and barrel temperature (25°C and 60°C). The prepared emulgels were characterized for pH, water activity, globule size distribution, and in vitro release rate. It was found that higher screw speed resulted in smaller globules and higher drug release from emulgels compared to emulgels prepared at lower screw speed[29].

Films:

HME technology is also used in the preparation of buccal films. Buccal films can be used for local action and improving bioavailability by avoiding first-pass metabolism[30-32]. Buccal films of clotrimazole were prepared using HME technology. A combination of HPMC and PEO was used as polymeric carriers and polycarbophil was used as bioadhesive material. A process temperature of 125-130°C was used for extrusion. The results indicate that the drug content and content uniformity of films were within the specifications. The films also possessed adequate bioadhesive strength[33].

3D Printing coupled HME technology:

Recently, HME technology was explored to produce personalized medicines by coupling 3D printing. The extrudates prepared through hot melt extrusion of drugs and polymers are used as starting material for 3D printing. Fused deposition modeling is used to prepare personalized medicines from extrudates like 3D printed microneedles, pediatric formulations, etc[34]. Microneedles have certain advantages like to initiate quick action or improving bioavailability as they can directly route the drug into the systemic circulation[35].

Protein Drug Delivery:

Formulating protein drug delivery systems is challenging as proteins are prone to physical and chemical degradations[36]. HME technology was explored to deliver a model protein lysozyme through protein/poly(lactide-co-glycolide) (PLGA) implants. Lysozyme stability was studied using DSC, FTIR, HPLC and biological activity. Formulations were optimized to have high drug loading. The optimized formulation was successful in delivering the lysozyme for a minimum of 60 days without initial bursting[37].

Nanoparticulate Drug Delivery:

Nanoparticles have several advantages improving solubility, improving bioavailability, targeting drug release capability, controlled drug release capability and others[38-47]. Fenofibrate solid lipid nanoparticles were prepared using HME technology using a quality-by-design approach. HME was used for melt emulsification and high-pressure homogenization was used for size reduction. The combination proved to produce SLNs with a consistent particle size of less than 200 nm. The *in vitro* release showed better release of SLNs prepared through combination and HME and high-pressure homogenization to micro fenofibrate formulation[48].

Conclusion:

HME technology since its advent into the pharmaceutical industry has been explored in the preparation of various dosage forms. Researchers are constantly trying to fill the gaps associated with specific drugs by employing novel technologies. In the years to come, HME technology may replace some of the conventional technologies to produce pharmaceuticals with more quality.

Interest Declaration:

The authors declare that there is no conflict of interest.

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