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Review Article

A Review on Hot Melt Extrusion Coupled Novel Drug Delivery Systems

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Abstract

The utilization of hot melt extrusion (HME) technology for new applications is increasing in recent years, as evidenced by the many published reports in the last five years. Because of its process automation and low-cost scale-up qualities, which decrease labor expenses and capital investment. HME has emerged as an essential technology for drug delivery applications in pharmaceutical research and manufacture. The novel application of the HME process provides a promising alternate approach in the formulation of novel drug delivery systems. The present review discusses the importance of HME in the development of novel drug delivery systems with the review of relevant case studies.

Keywords: hot melt extrusion, novel drug delivery, pharmaceutical research

1. INTRODUCTION

Patients have traditionally preferred oral administration of medications, and it remains the most convenient and industrially relevant delivery method. However, many recently created chemical entities have low water solubility, which is a significant problem because medication solubility is frequently a rate-limiting stage in intestinal drug absorption, lowering bioavailability [1–4]. Innovative formulation platforms and tactics for novel oral drug delivery technologies are rapidly being developed to address this issue and increase therapeutic efficacy and safety[5,6]. The range of nano-systems in the oral drug delivery area includes liposomes[7,8], solid lipid nanoparticles[9,10], nanocrystals[11–13], liposomes[8,14], polymeric nanoparticles[15–17] which are obtained via specialized techniques such as high pressure homogenizer (HPH)[18,19]. Typically, nano-systems exhibits stability issues caused by agglomeration[20]. Thus, drying techniques such as lyophilization or specific stabilizers are added to inhibit agglomeration or improve the stability of nano-systems[21–24].

Hot melt extrusion (HME) has been an important processing method in the pharmaceutical industry over the last three decades, and its use to make innovative pharmaceutical products is driving its growth[25]. The majority of pharmaceutical companies are adopting HME technology to improve the dissolving profile of poorly water-soluble pharmaceuticals, hence increasing bioavailability[26–28]. HME has recently been investigated for a variety of applications, and it has proven to be effective in the development of diverse drug delivery systems[29]. HME was used to develop pharmaceutical cocrystals[30], salts[31], amorphous solid dispersion systems[32–34], self-emulsifying drug delivery systems[35], twin-screw granulation[36–40], abuse-deterrent formulations[41–43], three-dimensional (3D) printing filaments[44,45]. The schematic illustration of HME application in various novel drug delivery systems are presented in Figure 1.

HME process consists of a motor, barrel, rotating screw and die. Of which, barrel, screws, feeder are main components for the optimization of extrusion process. The barrel can be heated to soften and reduce the viscosity of polymer. Screws helps in mixing, transporting and subsequently force the melt through a die. The feeder aids in transfer of the materials from feeding section to the barrel. HME process comprises of three steps i.e., melting, mixing and shaping [46].

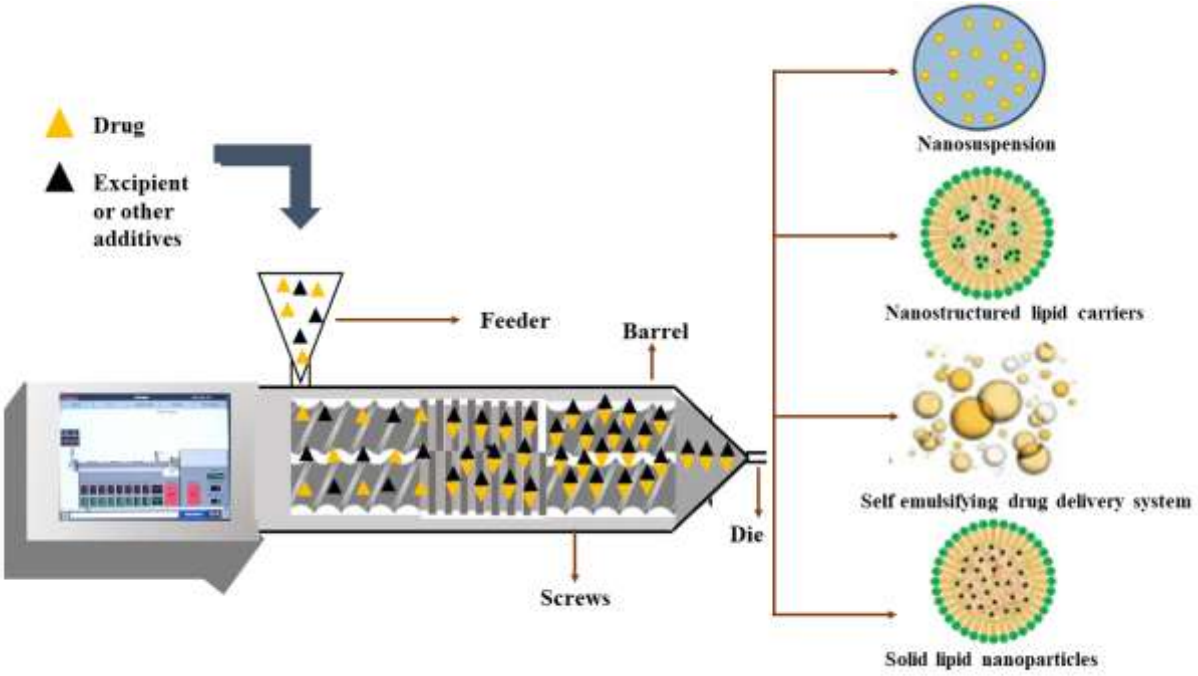

Figure 1. Schematic representation of HME application in various novel drug delivery systems.

Screw elements in different configurations can be incorporated into the barrel to achieve either low or a high shear. Varying the arrangement of conveying and kneading elements in different offset angles (30°, 60° (forwarding) and 90° (neutral)) provides different screw configurations[47]. The main purpose of conveying elements is to push the solid material within the barrel, whereas kneading elements are used for mixing, dispersing and also to provide mechanical shear to the solid material. The main mechanisms involve insider the extruder are dispersive and distributive mixing. The distributive mixing ensures homogenous distribution of active pharmaceutical ingredient throughout the polymer matrix. Whereas dispersive mixing acts by breaking down solid material, polymer or any agglomerates to a molecular level due to more shear stress by the screw elements present in the mixing zone [48]. Usually, combination of distributive and dispersive mixing is desired while developing the delivery systems like of amorphous solid dispersions. The ratio of outside screw diameter/inside screw diameter is an important design parameter of the HME process. Because this ratio dictates the free volume and torque level of the extruder. Another important considerations during HME processing are barrel temperature and screw speed [49].

The barrel temperature chosen for HME process should be above the glass transition temperature but below degradation temperature of the polymer and it can be above or below the melting temperature of API. The barrel temperature influences the melt viscosity, a low barrel temperature shows high viscosity and torque. Whereas high barrel temperature reduces viscosity and torque but the API and polymer may prone to degradation [50].

Screw speed can affect the degree of material fill, shear rate and mixing efficiency of the extrusion process. Moreover, screw speed has an impact on residence time of the material within the barrel[51].

2. HME-NANOTECHNOLOGY

The advent of nanoscience and nanotechnology has had a significant impact on existing drug administration systems. Nanotechnology boosts the efficacy of patient recovery due to its nanometer-scale formulations, which has piqued the interest of various pharmaceutical firms [52,53]. Drug delivery methods based on nanotechnology are an effective way to overcome the low bioavailability of some active ingredients. To date, various ways for manufacturing nanotechnology-based medication delivery systems have been established (e.g. nanoparticles, nanocrystals, and nanoemulsions). The necessity for multistep, nanotechnology-based procedures is the major difficulty that all of these techniques face batch-processing manufacturing has a number of advantages. limitations, such as batch-to-batch inconsistency in the manufacturing process the quality of the final product and the relatively high costs. When compared to those for continuous processing, there are more steps involved. As a result, it is critical to design new procedures that deliver all of the benefits of existing ones. medication delivery products based on nanotechnology, and can get around the restrictions of traditional methods.

Nanomedicine has spread into the pharmaceutical sector due to its smaller particle size and improved dissolving qualities. It entails prolonged drug release, reduced recurrent dose administration, and increased cellular absorption, all of which improve the efficacy of the therapy. Because of the various procedures needed, traditional techniques frequently experience challenges such as inconsistent batch uniformity and a relatively greater cost. To overcome these challenges, researchers are turning to HME technology to develop oral and topical nano systems that are both safe for living tissues and have distinct features. The traditional batch-based technique is still employed to create nanotechnology-based drug delivery systems such as nanocrystals, nanostructured lipid carriers (NLC), nanosuspension, and solid nanoparticles. HME has recently been investigated in combination with other formulation techniques for the preparation of nanotechnology-based goods such as solid lipid nanoparticles (SLNs), nanocrystals, and self-emulsifying drug delivery systems[54]. Summary of HME application in various NDDS presented in Table 1.

Table 1: Properties of HME based novel drug delivery systems [35,55,56]

Delivery system	Active	Excipients	Evaluation parameters	Key findings
HME-SLNs	Fenofibrate	Trimyristin, Glyceryl stearate, Stearic acid, Glyceryl dibehenate, Glycerol distearate	Particle size, polydispersity index, encapsulation efficiency, in vitro drug release	The developed HME-SLNs demonstrated better process control and size reduction compared to the conventional process of hot homogenization. The dissolution profile of HME-SLN was faster than that of the crude active and a micronized marketed fenofibrate formulation. Increase in drug absorption from HME SLN formulations as compared to the crude drug and marketed micronized formulation.
HME-SMEDS	Carvedilol	Capric/caprylic triglycerides, (diethylene glycol monoethyl ether, (hydroxypropyl methylcellulose acetate succinate	Powder X-ray diffraction, drug content, Particle size, polydispersity index, Reconstitution efficiency, in vitro drug release, scanning electron microscopy, , optical microscopy	The HME-SMEDDS retain the drug release in pH 1.2 with complete drug release in pH 6.8. The highest temperature and recirculation time during HME led to a rapid and complete microemulsion reconstitution and drug release in pH 6.8.
HME-Nanosuspension	Clotrimazole	Soluplus®, microcrystalline cellulose 101	Polarized Light Microscopy, Differential Scanning Calorimetry, X-ray Powder Diffraction, Fourier Transform Infrared spectroscopy, In Vitro Dissolution, Loss on drying, Redispersibility Index Measurement	An optimized drying process by HME can help maintain the integrity of nanosized particles by preventing its agglomeration in the presence of moisture and heat energy. HME drying process resulted in achieving higher process yield and optimum moisture content.

2.1. HME-SOLID LIPID NANAOPARTICLES

SLNs have an inner solid lipid core stabilized by surfactant/emulsifiers on the surface. SLNs are typically spherical in shape, with average sizes ranging from 100 nm to 1000 nm. They outperform liposomes, polymeric NPs, and emulsions in terms of drug loading capacity and stability when compared to liposomes. High pressure homogenization and solvent evaporation are commonly utilized to prepare SLNs[57,58]. SLNs were also created by combining HME with lipids with good coat-forming characteristics, resulting in a smooth particle surface and improved dispersibility. Trimyristin, tripalmitin (Dynasan1 116), glyceryl dibehenate (Compritol1 888 ATO), SA, and glyceryl distearate can be used to do this (Precirol1 ATO 5)[59,60]

Khinast et al. identified the potential use of HME in conjunction with an internal devolatilization process (nano-extrusion) to create a one-step process for converting a liquid-stabilized nano-suspension into a solid formulation, resulting in a continuous processing technology for solid nanoformulation production[61]. Baumgartner et al. identified a potential application for HME by designing and developing a one-step nanoextrusion process for manufacturing solid nanoparticle formulations by directly feeding the nanosuspension into HME equipment, with the solvent being continuously removed via devolatilization. The authors employed Soluplus® as the polymer and phenytoin as the water-insoluble model medication. The solubility of phenytoin produced as a nanosuspension and then as a nanoextrudate increased significantly more than that of the bulk phenytoin powder. Because of the enhanced effective particle surface area, the produced solid nanoformulations had a faster dissolving rate (100 percent drug release in 5 minutes)[62].

Another recent study by Ye et al. created a one-step processing technique for nanocrystal production by combining HPH with HME. Efavirenz, a BCS class-II medicine used to treat human immunodeficiency virus type I infection, was chosen as the model drug in this investigation[63]. The nanosuspension was first prepared in a high-pressure homogenizer, then mixed with Soluplus® in the extruder barrel, and the water was evaporated. Scanning electron microscopy, zeta particle size analysis, and differential scanning calorimetry were employed to characterize the particle size and crystallinity of the final product/active pharmaceutical ingredient (API) in this research. The authors came to the conclusion that conjugating HPH with HME is a promising approach.

Patil et al. showed that conjugating HME with HPH may be used to successfully create SLNs. HME was used to meltemulsify the particles, while HPH was employed to decrease the particles to nanoscale size. The model drug was the poorly water-soluble BCS II drug fenofibrate. The optimal SLN formulation obtained using the HME-HPH approach has particle sizes of less than 200 nm, according to the findings. The dissolution profile of the SLNs prepared using the HME-HPH approach was found to be faster than that of the crude drug and SLNs prepared using conventional methods, according to the authors[55].

2.2. HME-SELF-EMULSIFYING DRUG DELIVERY SYSTEMS

Self-microemulsifying drug delivery systems (SMEDDS), which are lipid-based formulations made up of an isotropic mixture of oils, surfactants, and co-surfactants, can produce submicron o/w emulsions. SMEDDS are isotropic combinations of oil, surfactant, and one or more cosurfactants or cosolvents that

offer lipophilic medicines in fine dispersion rather than crystalline form, facilitating drug release from the dispersed oil droplets following oral administration under gentle agitation given by GI motility [64]. The creation of tiny droplets when two immiscible liquids come into touch with each other due to a reduction in interfacial tension between those two phases was commonly referred to as self-emulsification [65]. This ability to self-emulsify contributes to increased drug absorption rate and extent, as well as consistent in vivo profiles[66]. After being diluted by GI fluids, SEDDS interact with mixed micelles and are digested by enzymes in the presence of endogenous materials such as bile salts and pancreatic lipase, leading in the development of various colloidal structures such as lipid vesicles and mixed micelles[67]. This structural alteration is important in medication solubilization because it prevents drug precipitation, creating a favorable environment for improving bioavailability [68,69].

SMEDDS has also demonstrated strong therapeutic benefits[70]. The liquid form of SMEDDS, on the other hand, necessitates the use of costly soft gelatin capsules. The oily ingredient in the capsules can also drain out. Liquid SMEDDS (L-SMEDDS) may also be chemically unstable, resulting in drug precipitation[71]. In this regard, the usage of solid SMEDDS (S-SMEDDS) has been advocated as a more appropriate strategy, as it reduces production costs while also improving stability, patient compliance, and dose accuracy. Solid systems are less irritating to the gastrointestinal mucosa, which improves safety. SMEDDS and SEDDS are meant to improve oral bioavailability by increasing the solubility of poorly soluble medications and spreading them along their gastrointestinal tract transit [72]. Solid SEDDS are a practical way to improve dose accuracy, stability, and ease of manufacture. The advantages of SEDDS and solid dosage forms are combined in this liquid SEDDS form. Adsorption of liquid SEDDS onto solid carriers to form free-flowing powders is the traditional approach for preparing solid SEDDS [69]. HME is a commercially scalable solution for continuous manufacturing of dosage forms[46]. Liquid SMEDDS (LSMEDDS) have been incorporated into powders utilizing a variety of processes, including adsorption on solid carriers, wet granulation with a high-shear mixer, spray drying, extrusion/spheronization, and traditional wet and melt granulation [35].

Silva et al. recently described the development of carvedilol solid SEDDS using an extruder and Velsan® CCT (capric/caprylic triglycerides) as an oil phase, Plurol Isostearique® (polyglyceryl-6-isostearate, Plurol) as a surfactant, and Transcutol HP® (diethylene glycol monoethyl ether) as a co-surfactant using a magnetic stirrer, liquid SEDDS was made in the traditional manner. Using solid carriers HPMCAS/HPC and microcrystalline cellulose in a mortar, the formulations with satisfactory emulsifying qualities were transformed into solid SEDDS. The mixture was then extruded with a twin-screw hot melt extruder, and the extrudates were treated for further processing. The amorphous nature of the API in the prepared solid SEDDS was confirmed by PXRD investigations. In pH 6.8 media, the extrudates made with the lowest drug load at the maximum processing temperature and recirculation time released the drug quickly. This recent article on the use of HME in the manufacture of pharmaceuticals[35]. This recent article on the use of HME in the formation of solid SEDDS highlights a new application for HME in the creation of a variety of pharmaceutical drug delivery systems.

2.3. HME-NANOSUSPENSION

For improved medication stability and commerciality, a nanosuspension (crystalline or amorphous) is eventually dried into solid powders. Before drying, matrix formers are invariably added to the nanosuspensions to generate stable dried nanoparticles. Sugars have been widely used as matrix formers due to their ability to embed and/or adsorb drug nanoparticles, as well as their superior hydrophilicity, which promotes drug particle disintegration. Some of the most frequent matrix formers used during the drying of nanosuspensions are mannitol, lactose, and trehalose [73–75]. Generally, nanosuspensions are produced via either topdown or bottom-up processes. Top-down techniques rely on milling, high pressure homogenization, and pulsed laser fragmentation to reduce the size and break down of massive materials into nanometer-sized particles[76]. The bottom-up technique is based on supersaturated solution precipitation. It is often used to make nanosuspensions in bulk solutions as well as single droplets. This approach is employed in several pharmaceutical procedures, including solvent-anti-solvent technology, supercritical fluid processing, spray drying, and emulsion-solvent evaporation[77,78].

Gajera et al., [56] developed clotrimazole nanosuspension using HME. The nanosuspension was delivered directly into the extruder via a separate feeding system in order to remove the excess moisture and obtain dried nanosuspension. To aid the evacuation of excess moisture, a vacuum assembly was placed at the rear end of the extruder. Flash evaporation is used to devolatilize nanosuspension, and the application of adequate vacuum pressure precludes any moisture content accumulation in the finished product. During the extrusion process, the nanoparticles become embedded in the polymer and matrix material, resulting in a stable dried product. Furthermore, using the design of experiments (DoE) technique, HME process parameters for solidifying nanosuspension were improved and confirmed.

3. CONCLUSION

HME has become one of the preferred technologies over traditional techniques in pharmaceutical research for development of novel drug delivery systems. Manufacturing processes such as HME that generate a product in a continuous manner is gaining importance for manufacturing novel drug delivery systems. The ability of a HME to generate a product dispersion of nanoparticles appears to be a promising platform technology for improving medication solubility and bioavailability while also increasing patient compliance. However, in order to optimize therapy, these novel drug delivery strategies must be further studied in vivo. Finally, emerging applications involving HME, such as the development of SMEDS and SLNs must be verified further.

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