



(REVIEW ARTICLE)



## Hot melt extrusion: A single-step continuous manufacturing process for developing amorphous solid dispersions of poorly soluble drug substances

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GSC Advanced Research and Reviews, 2022, 13(02), 126–135

Publication history: Received on 03 October 2022; revised on 09 November 2022; accepted on 12 November 2022

Article DOI: <https://doi.org/10.30574/gscarr.2022.13.2.0311>

### Abstract

In today's world with increasing patient population, the demand for pharmaceutical medications is increasing enormously. However, poor solubility of drug substances and underdeveloped manufacturing process are affecting the revenue of the pharmaceutical industries. Improving the solubility and establishing a robust manufacturing process is the primary prerequisite of the developmental scientists. Among various approaches amorphous solid dispersion has gained a tremendous response for improving the solubility of the drug substances. In addition, the process of hot melt extrusion has attracted the investigators from regulatory agencies and industries. The process of hot melt extrusion involves application of thermal and mechanical energy on to the processing material. The process requires no solvent and is referred as "green technique." Various factors need to be taken into consideration for developing amorphous solid dispersions. The miscibility of drug and polymer, solubility of drug in polymer, drug-polymer interactions, glass transition temperature, storage conditions majorly influence the stability of the amorphous solid dispersions systems. Though hot melt extrusion is most widely employed for developing amorphous solid dispersions still a lot of research is warranted for developing strategies to formulate high drug loading medications with improved stability. This review article mainly focuses on the instrumentation, and process for developing amorphous solid dispersions by hot melt extrusion with a small note on the various advantages and limitations.

**Keywords:** Poor solubility; Amorphous solid dispersions; Hot melt extrusion; Stability; High drug loads; Miscibility

### 1. Introduction

In today's world, improving solubility is the major challenge faced by the pharmaceutical industry. Approximately 50-60% of the new chemical entities within the developmental pipeline are said to be poorly soluble, limiting the oral bioavailability of the drug substances. Improving solubility is the primary prerequisite for developmental scientists [1–7]. For any drug substance designed to be administered in the form of intravenous (IV) dosage, improving bioavailability is not the primary concern since the drug will be directly administered in solution form. However, suitable solvents that can dissolve the entire dose and maintain the drug in a dissolved state throughout the shelf life without affecting the chemical stability need to be identified [8–12]. Compared with IV formulations, oral dosage forms have massive demand since it involves low manufacturing cost, simple process, and self-administration with no pain. The stability of oral formulations remains to be less challenging when compared with IV formulations.

Among various oral formulations such as solids and liquid dosage forms, solid oral dosage forms such as tablets and capsules have massive demand in the market. In addition, the main interest of the pharmaceutical industry lies in developing solid oral dosage forms. The stability of liquid formulations is less compared with solid oral dosage forms

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[13–17]. Also, the manufacturing and transportation of liquid medications remain expensive compared with solid formulations. Lastly, the liquid dosage forms are not unit formulations and must be dispensed each time which might result in non-homogeneous distribution of Drugs within the dispensed dose. Thus, attributing to various issues associated with liquid formulations, the pharmaceutical industries have developed their interest in manufacturing solid oral dosage forms. Among tablets and capsules, tablets are preferred attributed to their low manufacturing cost [18–21]. In addition, the adulteration of capsules is much easier when compared with tablets. Thus, the main focus of the pharmaceutical industry is to develop solid oral formulations with improved solubility and bioavailability.

For the last two decades, various applications have been investigated for improving the solubility of drug substances. The approach of improving solubility for one drug might not be applicable for another, attributing to various concerns related to the physicochemical properties of the drug substance. Among various formulation approaches that have been investigated, amorphous solid dispersions, solid crystal suspension, lipid-based formulations, the salt form of the drug, co-crystal, co-amorphous system, and cyclodextrin complexation have attracted the audience from various avenues of the pharmaceutical industries [18–28]. However, attributed to the use of solvents and lack of proper scale-up strategies, a few applications have been deemed unsuitable for commercial manufacturing [29]. In recent years amorphous solid dispersion (ASDs) has gained a tremendous response from the pharmaceutical industries for improving the solubility of drug substances. Various manufacturing strategies, such as hot melt extrusion, spray drying, fluid bed granulation, electrospinning, and kinetisol, have been investigated for developing ASDs. HME was most widely employed among the various manufacturing strategies due to its simple manufacturing and solvent-free process [30–40]. A few of the commercial formulations manufactured by the HME process are shown in Table 1. This review article mainly focuses on the instrumentation and the role of the HME process in developing ASDs, along with a note on the advantages and limitations.

**Table 1** Various commercial products developed by hot melt extrusion technology

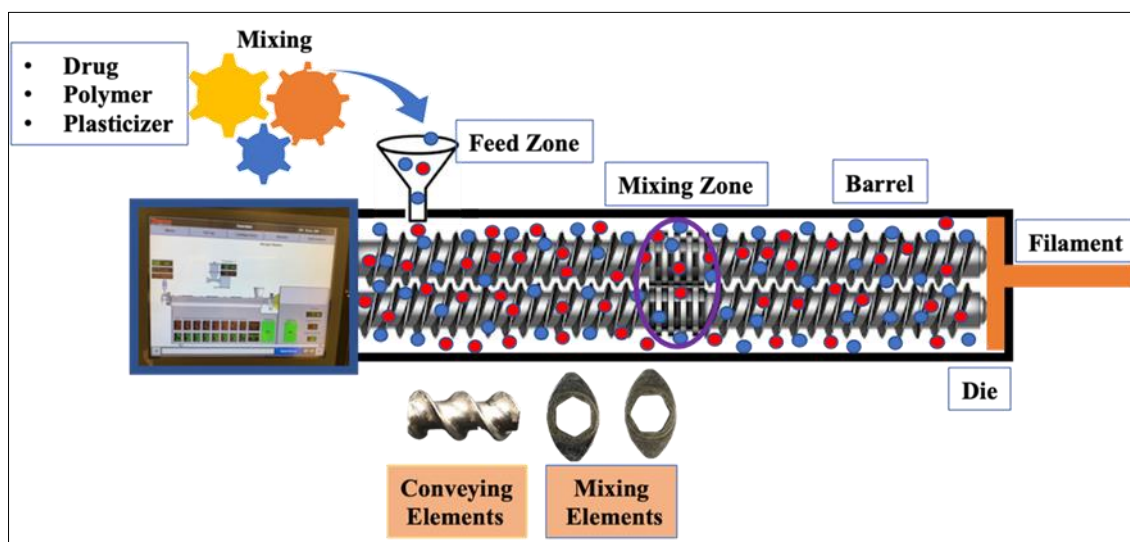
Trade Name	Drug Substance	Year of Approval
Isoptin® SR	Verapamil	1987
NuvaRing®	Etonogestrel/Ethinyl Estradiol	2001
Kaletra®	Lopinavir/Ritonavir	2007
Norvir®	Ritonavir	2010
Onmel®	Itraconazole	2010
Noxafil®	Posaconazole	2013
Belsomra®	Suvorexant	2014
Viekira® XR	Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir	2014
Venclexta®	Venetoclax	2016
Mavyret®	Glecaprevir/Pibrentasvir	2017
Lynparza®	Olaparib	2018
Braftovi®	Encorafenib	2020
Oriahnn®	Elagolix/Estradiol/Norethindrone Acetate	2020

## 2. Hot melt extrusion

In the early 1930s, the HME was initially employed in the plastic and rubber industries. Later in 1980, the suitability of HME for developing pharmaceutical medications was investigated for the first time. The hot melt extruder consists of a pair of corotating or counter rotation screws enclosed in a barrel. The extrusion process involves a metered feeding of a physical mixture into the extruder barrel. The material inside the barrel gets exposed to thermal and mechanical shear. The polymer softens and dissolves the drug at the processing temperature, forming amorphous solid dispersion. The drug is dispersed at the molecular level within the amorphous solid dispersion. The amorphous drug has improved wetting properties compared to the crystalline drug [41–47]. The material inside the barrel gets conveyed all along the length of the extruder. It is pumped outside the barrel as cylindrical filaments through a die connected at the end of the

barrel. The screw geometry inside the barrel consists of conveying and mixing elements. The primary purpose of the conveying elements is to convey the material from one zone to the other and has no mixing property. The mixing elements impart distributive and dispersive mixing to the formulation, and it has no conveying property. The mixing elements can be configured at 0, 30, 60, and 90 offset angles. With increasing offset angle, the amount of mechanical shear imparted on the processing material increases, and the conveying property decreases. Distributive mixing ensures the uniform distribution of active substances within the polymeric carrier, and dispersive mixing breaks the crystals of the drug into the smaller molecular level [48–54]. To convert the crystalline form of the drug into an amorphous form, energy greater than the lattice energy needs to be incorporated.

The primary process parameters of HME include feed rate, barrel temperature, screw speed, die temperature, process torque, and melt pressure. Apart from conveying and mixing elements, other elements include comb mixing elements, cutting edge elements, and narrow other elements. However, the role of other types of elements in developing ASDs has not been explored till today. Initially, the first type of extruder had only one screw inside the barrel, called the single-screw extruder. With increasing needs and requirements, the instrumentation has been modified to meet the needs of the pharmaceutical industries. The process of HME is also called as "green technique" since it requires no solvent for developing formulations. The other competing technology for HME is spray drying. However, the spray drying process requires a tremendous amount of solvent and remains a significant concern to the pharmaceutical industry. Hot melt extrusion can be employed for a single-step continuous manufacturing process by mounting suitable process analytical technology (PAT) tools. Among various PAT tools, near-infrared and Raman spectroscopy have been most widely investigated for developing pharmaceutical dosage forms [55–60]. Thus, attributing to various advantages, the process of HME has gained tremendous recognition in the industry. A detailed illustration of HME is shown in Figure 1. A few of the recent advancements that have been investigated for developing ASDs by the HME process are discussed below.



**Figure 1** A detailed illustration of the hot melt extruder instrumentation

### 3. Case studies

Saurabh M Mishra et al. [20] developed ASD-based tablets using a hot melt extrusion process. Within the investigation, the author has studied the effect of milling extrudates on the performance of tablets. The extrudates were milled at different speeds using different sizes of screens. The amorphous solid dispersions were developed for 20%w/w of drug load for itraconazole using hypromellose acetate succinate (HPMCAS) as a polymeric carrier. The milled extrudates were compressed into tablets using hydroxypropyl cellulose, microcrystalline cellulose, and colloidal silicon dioxide. The process of reducing the size of the extrudates has dramatically influenced the particle size, followed by the compressibility of tablets. Across the various techniques investigated, the size reduction process by chill roller has shown better compressibility of tablets compared with other techniques.

Alex Mathers et al. [21] investigated the role of drug nature in preserving the stability of ASDs. Within the current investigation, the author has developed the ASDs of indomethacin and naproxen drug substances using polyvinyl alcohol as a polymeric carrier. The ASDs were developed for a drug load of 30-50 %w/w. The developed formulations were subjected to stability at ambient conditions. Interestingly the formulations of indomethacin were found to be

stable for 24 months without any signs of drug recrystallization when stored at ambient conditions. Though the ASDs of naproxen were developed for similar drug loads using similar process parameters, the stability of the formulations was not preserved. The drug indomethacin has a good glass-forming ability compared to naproxen, which has a poor glass-forming ability. Thus, understanding the nature of drug substance plays an essential role in determining the optimum drug load for developing robust formulations.

Wenling Fan et al. [22] investigated the role of ball milling as an upstream process for the hot melt extrusion process involving the development of ASDs of high melting point drugs. Resveratrol was chosen as a high melting point model drug, and the ASDs were developed using Eudragit EPO as a polymeric carrier. The physical mixtures were prepared with drug and polymer in 1:1 ratio. The physical mixture was milled using a ball mill for different residence times and processed using HME. The formulations of ball-milled extrudates were compared with those of unprocessed physical mixtures. The formulations subjected to the ball milling process before HME have resulted in the complete conversion of the drug into an amorphous form. The formulations of unprocessed physical mixtures have resulted in the presence of the drug in crystalline form. Thus, by employing ball milling as an upstream process for HME, the ASDs of high melting point drug substances can also be developed.

Bhupendra Raj Giri et al. [23] investigated the role of sodium carbonate as an alkalizer in improving the solubility of the high melting point drug substance telmisartan. The drug telmisartan has exhibited pH-dependent solubility. The formulations of telmisartan were developed for a drug load ranging from 10-60 %w/w with sodium carbonate ranging from 0-10 %w/w. Within the formulations, the crystallinity of the drug was preserved. In the extrudates, when brought in contact with the dissolution medium, the solubilization of sodium carbonate has resulted in the formation of microenvironment pH, favoring the solubilization of the drug. Thus, the solubility of drug substances with a high melting point can be improved by employing suitable acidifiers or alkalizers within the formulation. Various formulations have been investigated by hot melt extrusion. is detailed in Table 2.

**Table 2** Various formulations have been investigated by hot melt extrusion

Active Substance	BCS class of drug	Polymers / Carriers	Process Temperature	Reference
Indomethacin	II / II / II	Eudragit E	65 - 120	[61]
Naproxen				
Ibuprofen				
Indomethacin	II / II / II	Eudragit EPO Eudragit L-100-55 Eudragit L-100 HPMCAS-LF HPMCAS-MF Pharmacoat 603 Kollidon VA64	N/A	[62]
Itraconazole				
Griseofulvin				
Carbamazepine	II	Soluplus Kollidon VA 64 HPMC E5	160	[63]
Azithromycin	II	Eudragit RL PO	150	[64]
Itraconazole	II	HPMCAS LG	160	[65]

### 3.1. Advantages

The process of HME has various advantages compared with conventional manufacturing techniques. A few of the significant advantages are discussed below:

### 3.1.1. Single-step manufacturing process

Compared with conventional manufacturing techniques such as dry granulation by roller compaction, wet granulation by high shear granulator, or fluid bed processor, the process of HME is very simple and involves single-step manufacturing. The extrudates of HME can be cut into pellets and encapsulated into empty capsule shells. Even the process of HME can be employed for continuous manufacturing by mounting suitable PAT tools to monitor the quality of the formulations. The extruder can also be utilized for the granulation process by removing the die connected at the discharge end of the barrel [66–69]. Depending on the physical state of the formulation components inside the extruder barrel, the twin screw granulation process is divided into dry, wet, and melt granulations [70–74]. The overall process view of conventional techniques is shown in Figure 2.

### 3.1.2. Green technique

The use of solvents in manufacturing pharmaceuticals is not highly recommended due to toxic side effects. The process of HME utilizes thermal and mechanical energy for converting the crystalline drug into amorphous. No solvent is utilized within the HME process; hence, it is called a "green technique." Employing solvent will not only affect the stability and quality of the dosage form, but it will also result in increased manufacturing cost since the solvents are expensive and require suitable recollecting mechanisms in place [75–79]. The ASDs can also be developed using a fluid bed processor and spray drying. However, these manufacturing techniques are limited by the use of solvents.

### 3.1.3. Solubility enhancement

In recent years increasing solubility has been the major challenge being faced by the pharmaceutical industries. By employing hot melt extrusion, the ASDs of the Drug can be developed for improved solubility and bioavailability. Apart from ASDs, the HME can also be employed to develop lipid-based formulations such as solid nano lipid particles and self-emulsifying drug delivery systems to improve solubility [80–82]. The process of HME can also be paired with the additive manufacturing process for developing patient-centric dosage forms [83–85]. Thus, HME has various opportunities in the pharmaceutical industries.

## 3.2. Limitations

Apart from various advantages of the hot melt extrusion process, it also has a few limitations that remain unaddressed today. A few of the limitations of the HME process are discussed below:

### 3.2.1. High processing temperatures

The process of HME is thermal and requires high processing temperatures for the extrusion of ASDs. The major component of the ASD formulation is a polymer. Most of the polymers exhibit high melt viscosity and require high temperatures to process. For developing ASDs, the process needs to be performed at a temperature close to the melting point or greater than the melting point of the drug substance. Thus, the process of HME requires high temperatures to develop ASDs. The polymers exhibit thixotropic behavior, where the melt viscosity decreases with increasing temperature. However, the process temperature must be maintained below the degradation point of the formulation components [86, 87]. The plasticizer's incorporation helps reduce the melt viscosity, and thereby the process can be conducted at low temperatures. However, the miscibility and stability of the formulation in the presence of a plasticizer remain questionable.

### 3.2.2. Stability of ASDs

Within the ASDs, the drug is dispersed in a high-energy molecular state. The stability of the amorphous drug is less when compared with the crystalline drug. The amorphous drug tends to recrystallize over a period affecting the quality and performance of the formulation. Various factors play an essential role in affecting the stability of ASDs. Miscibility of the Drug and polymer, the solubility of the drug within the polymer, the glass transition temperature of the ASD system, and environmental factors such as humidity and storage temperature influence the stability of the ASD. The environmental moisture acts as a plasticizer, thereby reducing the glass transition temperature of the ASD system [88, 89]. The reduced glass transition temperature influences the mobility of the drug, thereby resulting in the recrystallization of the ASD system. Thus the storage conditions play an essential role in preserving the stability of ASDs.

### 3.2.3. Downstream processing

The extrudates of the HME process can be subjected to various downstream processes. The extrudates can be cut into pellets, encapsulated, milled, and compressed into tablets. The extrudates or filaments can also be utilized for fabricating patient-centric dosage forms by fused deposition modeling three-dimensional printing. The milled

extrudates exhibit glassy nature and result in poor compressibility of tablets. The milled extrudates require more filler or diluent to obtain a tablet with suitable mechanical properties [90–92]. They are incorporating a higher amount of filler results in dose dilution with an increased size of the tablets affecting the patient population with dysphagia. Thus, more investigation is warranted to develop suitable strategies for obtaining high-drug-load formulations.

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#### 4. Conclusion

Poor solubility of the drug substances is the major problem haunting the pharmaceutical industries. Amorphous solid dispersions have gained a tremendous response among various strategies investigated for improving solubility. HME is most widely employed among various manufacturing techniques for developing amorphous solid dispersions. The process of HME involves the application of thermal and mechanical energy and requires no solvent. Thus, the process of HME is referred to as the "green technique." Hot melt extrusion is a single-step manufacturing process and is also suitable for the continuous manufacturing process. The HME can also accommodate PAT tools where the quality of the formulations can be monitored throughout the batch process. Despite various advantages, the process of HME for developing amorphous solid dispersions still needs to be investigated for developing highly drug-loaded formulations with improved stability.

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#### Compliance with ethical standards

##### *Acknowledgments*

The corresponding author would like to thank Hikma Pharmaceuticals for provide required support.

##### *Disclosure of conflict of interest*

The author declare that they have no conflict of interest.

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