

A REVIEW ON HOT MELT EXTRUSION FOR SOLUBILITY ENHANCEMENT OF POORLY WATER-SOLUBLE DRUGS

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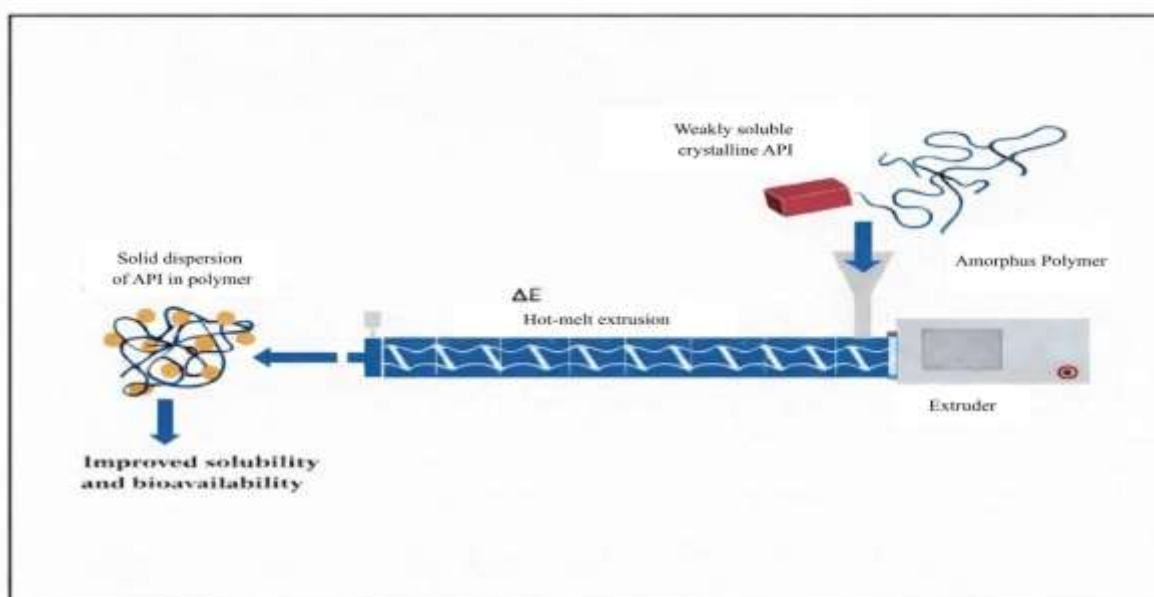
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ABSTRACT

This review focuses on using the hot melt extrusion to increase the solubility of weakly water-soluble medications, especially those in Biopharmaceutical Classification System Classes II and IV. Research publications, review papers, and pharmaceutical reports pertaining to hot melt extrusion and solubility improvement techniques were used in a thorough analysis of the published literature. Key aspects such as Hot Melt Extrusion process design, extrusion parameters, and formulation components including polymers and plasticizers were reviewed. The mechanism responsible for solubility enhancement, especially amorphous solid dispersion formation, was analyzed. Common characterization techniques like X-Ray Diffraction, Differential Scanning Colorimetry, Fourier Transform Infrared spectroscopy, and in-vitro dissolution studies were also reviewed to assess formulation performance. In addition, recent studies focusing on polymer selection, process optimization, and future formulation strategies for improving the stability and performance of Hot Melt Extrusion- based systems were also considered. The reviewed research show that by converting crystalline pharmaceuticals into stable amorphous dispersions inside polymeric matrix, Hot Melt Extrusion efficiently improves medication solubility and dissolution.

Index Terms: Amorphous Solid Dispersion, Drug Bioavailability, Hot Melt Extrusion, Polymer Carriers, Solubility Enhancement, Weakly Water-Soluble Drugs,

Graphical Abstract:



1. INTRODUCTION

The drug must be soluble and permeable in the gastrointestinal tract in order to have an impact after being taken orally. The BCS classification, seen in figure 1, was developed to classify pharmaceuticals based on their intestinal permeability and water solubility [1]. Using surface active agents, making solid dispersions, and synthesizing water-soluble prodrugs are some of the recommended solubilization techniques [2,3]. To prepare SD, the HME method—a well liked manufacturing technique that increases the rate of dissolution of poorly aqueous-soluble pharmaceuticals by converting them to an amorphous form at high pressure and temperature and then uniformly dispersing the drug into the water-soluble polymer—was chosen. [4–6]. Additionally, it is a commonly used production technology that turns pharmaceuticals that are poorly soluble in water into an amorphous state at high temperatures and pressures, which then uniformly distributes the drug into the water-soluble polymer to speed up the rate of dissolution [7-10]. Two of the fourteen commercially available medications are either weakly aqueous-soluble or have a specific absorptive component, which results in lower, more time-consuming and expensive operations, not to mention ethical concerns about using animals. These factors have made computer simulation-based PBPK modeling more crucial. Furthermore, PBPK modeling is currently needed to address absorption following oral administration for pharmacological evolution [11,12]. To control drug permeability, one must comprehend biologically pharmacokinetics (PBPK). pharmacokinetic and absorption observations, require increasingly time-consuming and expensive procedures, computer simulation-based PBPK modeling has grown in importance because to ethical concerns over the use of animals. Furthermore, PBPK modeling is currently necessary to solve these problems for pharmaceutical evolution [13,14] Approximately 250 pharmaceutical businesses have used the PBPK modeling simulation 28 software [12]. Pharmacokinetics and real world absorption data can be more precisely predicted by employing computer simulation programs to build PBPK models [15]. Additionally, it reduces the amount of time and money the pharmaceutical business spends on IVIVC (in vitro-in vivo correlation) studies [13]. A major advancement in computer modeling has made it possible to represent all absorption carriers and distribution channels [16–20].

Table 1. Classification of drugs based on solubility and permeability according to BCS [1]

Class	Solubility	Permeability	Drugs
Class 1	High	High	Chloroquine
Class 2	Low	High	Carbamazepine
Class 3	High	Low	Metformin
Class 4	Low	Low	Furosemide

2. HOT MELT EXTRUSION: PROCESSING METHOD AND INSTRUMENTATION

The capacity of hot melt extrusion (HME) technology to create sophisticated drug delivery systems and improve medication bioavailability has drawn a lot of interest in pharmaceutical research. This technique has evolved into a reliable manufacturing approach for dispersing or dissolving drugs within a polymer matrix to form solid dispersions or solid solutions.

Hot melt extrusion involves forcing a blend of drug and polymer through a heated barrel under controlled temperature, pressure, and mechanical shear to produce a uniform product with desired shape and density. A typical melt extruder consists of heating barrels, screws, die assembly, and additional auxiliary equipment. To guarantee constant product quality, auxiliary parts like temperature control systems, pumps, solvent delivery units, and cooling conveyor belts are utilized.

Commercial scale extruders are capable of producing outputs ranging from 5–20 kg per hour. As seen in figure 1, A feeding hopper, barrel, single or twin screws, die section, and screw-driving system are the extruder's primary parts. Monitoring instruments such as temperature sensors, pressure gauges, screw speed controllers, and torque measurement devices are used to maintain process control. Because twin-screw extrusion offers effective mixing and consistent medication dispersion inside the polymer matrix, it is frequently chosen in pharmaceutical manufacture. However, single-screw extrusion is also widely used depending on formulation requirements.

The screws are mounted on a shaft and configured at different angles such as 0°, 30°, 45°, 60°, and 90°. These screws can operate either in the same rotational direction or in opposite rotational directions (counter-rotating), depending on the required mixing efficiency and processing conditions. The following zone can be found in an extrusion barrel with an extruder [21].

Material Feeding Zone: The zone is responsible for transferring the material from the hopper into the barrel.

Material Melting Zone: In this area, the substance is heated or melted to reduce its viscosity.

Drug-Polymer Mixing Zone: In this zone, drag flow, pressure-driven movement, transverse mixing, and small leakage effects all have an impact on the spiral-like pathway that material travels along inside the barrel.

Material Metering Zone: In order to produce a consistent result, it helps to lessen the pulsating flow of molten mass.

Venting and Degassing Zone: Eliminate any gasses and volatile compounds produced during processing.

Extrudate Shaping Zone: The die may have a film, ribbon, or circular shape. Extrusion can be carried out without a die in some circumstances, such as controlled release applications.

Different zones have different screw flight pitches and depths, which causes pressure variations along the screw's length depending on the zone. The screw arrangement, which is thought of as the extruder's heart, is made up of the many elements used in the various zones.

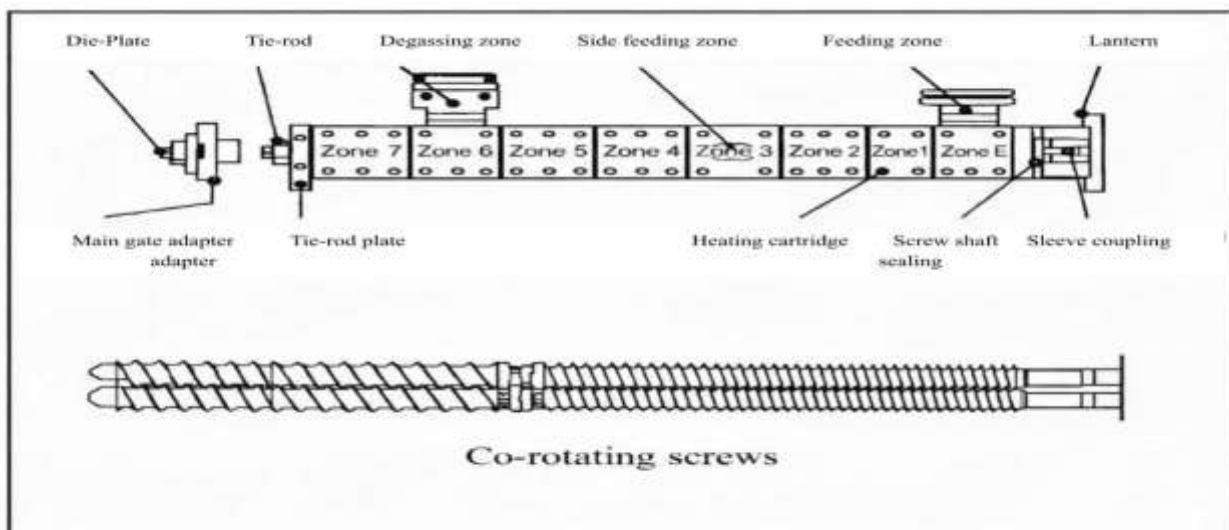


Figure 2. Diagrammatic Illustration of Extruder [21]

2.1 KEY PROCESSING PARAMETERS IN HOT MELT EXTRUSION

The extruder's various zones allow for the independent heating of each barrel section to reach the necessary processing temperature profile. The kinds of pharmaceutical applications and excipients utilized determine the extruder's temperature profile [21,22]. The extrusion process can be enabled by directly controlling or monitoring the following process parameters.

Barrel temperatures: The glass transition temperature or melting point of the polymer utilized, the drug's degradation temperature, and the method of application all affect the extrusion temperature profile of different zones [23, 24].

Feed rate and screw rotation speed: Both feed rate and screw speed affect how much material is within the extruder. Stable processing conditions depend on maintaining steady feeding and screw rotation. The amount of material inside the extruder stays constant when the feed rate and screw speed stay constant, which produces consistent shear stress and residence duration during processing.

Melt viscosity of polymeric system: The molecular weight of the polymer being utilized and the barrel temperature both affect melt viscosity.

Melt pressure during extrusion: Since melt pressure and melt temperature are the best indicators of extruder performance, they are the most crucial metrics. Their values make process issues clear. However, because it is impacted in a complicated way by altering additional process variables like temperature profile and screw rotation speed.

Melt processing temperature: The actual temperature at which a blend begins to melt is known as the melt temperature. It depends on viscous heat dissipation, barrel temperature, and melt pressure.

Die section temperature control: The viscosity and pressure required to overcome the die's resistance and produce output are indirectly determined by the die's temperature.

Vacuum level during venting: High heat during extrusion can produce a variety of gases that could become trapped in the finished product and affect its quality. As a result, vacuums are employed to efficiently remove gasses, which enhances the extrudes' quality.

Extrusion Die configuration: The extrudes' shape is determined by the die's design.

2.2 MATERIALS EMPLOYED IN HME FOR SOLUBILITY IMPROVEMENT

Polymers and Carriers: By melting the polymers and distributing or dissolving the drug in the molten polymer, Hot melt extrusion (HME) is widely applied to enhance the bioavailability of drug molecules, especially those exhibiting limited aqueous solubility. Table 1 summarizes the many types of polymers that can be used for solubility augmentation. The choice of polymer for improving solubility is primarily influenced by the final dosage form's function, polymer stability, and drug–polymer miscibility.

Table 2: Frequently Polymers Used in HME for Solubility Enhancement [25]

Polymer Name	Commercial Name	Glass Transition Temperature $T_g(^{\circ}\text{C})$	Melting Temperature ($^{\circ}\text{C}$)
Polyethylene glycol	Carbowax	-20	35-65
Hydroxypropyl cellulose	klucel	0	180-210
Hydroxypropyl Methylcellulose	Methocel	160-170	190-200
Copolymers of ethylene	Lutrol F-127	-	57
oxide and propylene oxide	Lutrol F-68	-	55

Plasticizers: Generally speaking, plasticizers are compounds with relatively low molecular weight substances that soften polymers to increase their flexibility. Plasticizers lower the glass transition temperature (T_g), which lowers the processing temperature and eventually increases the drug's and polymer's stability. By raising the intermolecular distance between polymer chains, plasticizers lower a polymer's melt viscosity and glass transition temperature (T_g). The kind and concentration of the plasticizer determine a decrease in polymer T_g . They enhance the finished product's physico-mechanical characteristics. Table 2 summarizes the various types of plasticizers that are available.

Table 3: Frequently Used Plasticizers in Pharmaceutical Formulations [25]

Category	Common plasticizers
Citrate based plasticizers	Tributyl citrate (TBC), acetyl tributyl citrate(ATBC), acetyl triethyl citrate(ATEC), triethyl citrate(TEC)
Fatty acid derivatives	Butyl stearate, , stearyl alcohol, glycerol monostearate
Glycol based plasticizers	Propylene glycol, Polyethylene glycol
Sebacate derivatives	Dibutyl sebacate
Phthalate derivatives	Diethyl phthalate

Additional Processing Aids: Degradation of polymer can occur from the high temperatures required to process unplasticized or under plasticized polymers. Antioxidants (butylated hydroxyanisole, butylated hydroxytoluene, and vitamin E), acid receptors, and/or light absorbers during extrusion can increase the stability of polymers that are prone to degradation [25]. Another kind of preventive antioxidant is a chelating agent, such as citric acid and edetate disodium (EDTA). Antioxidants can also be derived from reducing agents like ascorbic acid. employing these methods [26, 27].

3. SOLUBILITY ENHANCEMENT MECHANISM IN HOT MELT EXTRUSION

3.1 Methods for Developing Amorphous Solid Dispersions

In 1961, Sekiguchi and Obi developed a practical method that overcomes many of the limitations and improves the bioavailability of drugs with limited aqueous solubility. To establish a eutectic combination of the pharmaceuticals with water-soluble carriers, this process-later dubbed solid dispersion-involves melting the physical mixes of the medications [28]. Solid dispersion is defined as ‘dispersion of one or more active ingredients at molecular to microcrystalline level in an inert carrier or matrix at solid state’. Physiologically inert carriers, which can be easily water-soluble or water-insoluble for formulations needing rapid or modified release, respectively are used to make solid dispersion [29]. By decreasing the particle size and increasing the surface area of poorly water-soluble medications, solid dispersion enhances their solubility, dissolving rate, and oral bioavailability [30]. A matrix made up of at least two components- a poorly soluble drug and a solvent carrier that is mostly hydrophilic-is referred to as a solid dispersion [31]. An inert water-soluble carrier is used to disperse the drug in a solid state [32].

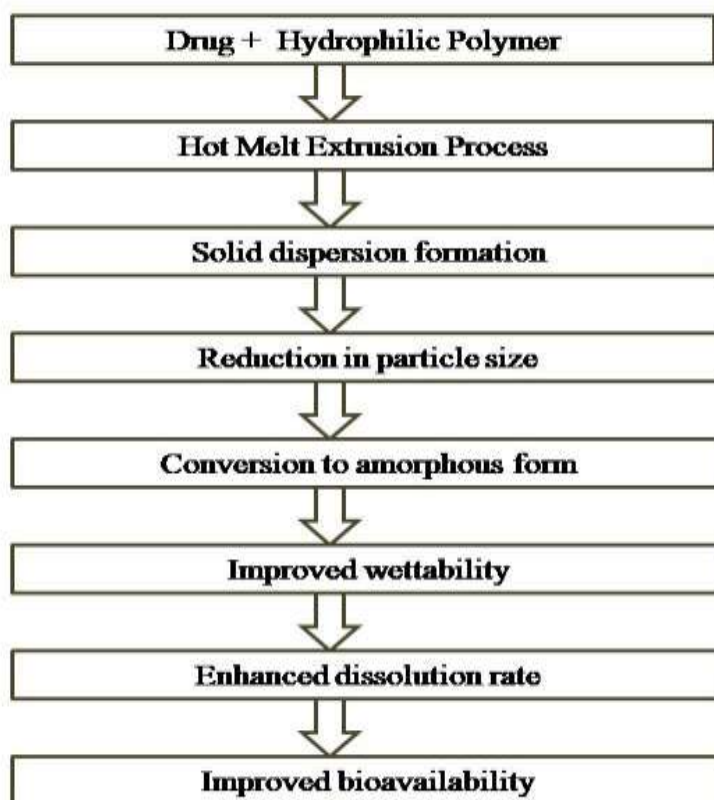


Figure 2. Mechanism of Solubility Enhancement Using Solid Dispersion Approach [28]

3.2 TECHNIQUES FOR PREPARATION OF SOLID DISPERSIONS

3.2.1 Hot Melt Fusion Technique

This direct melting method's primary benefits are its affordability and ease of use. Using this method, the medication and a hydrophilic carrier are physically blended and heated until a homogenous molten liquid is produced. After that, the molten material is quickly cooled while being constantly stirred—usually in an ice bath to enable solidification. After solidifying, material is broken up into smaller pieces, ground into a powder, and sieved. With the use of appropriate tableting excipients, the resulting powder can subsequently be crushed into tablets. A binary system's composition—that is, the choice of carrier and the weight percentage of the drug substances in the system—determines its melting point. For solid dispersions to form, the medication and carrier must be compatible in the molten state using the hot-melt method. The drug's and the carrier's thermo stability is another crucial need [33].

3.2.2 Preparation of Solid Dispersions by Solvent Evaporation Method

The first people to dissolve the medication and the carrier in a single solvent and then evaporate the solvent under vacuum to create a solid solution were Tachibana and Nakamura. This allowed them to create a solid solution of the very water-soluble carrier povidone with the highly lipophilic β -carotene. Because the solvent evaporation method removes organic solvents at relatively moderate temperatures, both the medicine and the carrier are protected from thermal degradation, which is one of its main advantages. However, the drawbacks of this approach include the increased preparation costs, the challenge of eliminating the organic solvent entirely (from a regulatory standpoint), the drug's chemical stability may be negatively impacted by even minute amounts of leftover solvent. Thus, during formulation, selecting suitable volatile solvent that is compatible with the medication and carrier is crucial and the challenge of replicating crystal formations [33].

4. CHARACTERIZATION TECHNIQUES FOR FORMULATIONS

Extrudates from the extrusion process can be assessed using a variety of analytical methods. These techniques aid in distinguishing between solid solutions, in which the medication is uniformly dispersed at the molecular level, and solid dispersions, which are physical mixes of drug and carrier [34].

4.1 Thermal Stability Evaluation Using TGA: The thermal stability of materials treated by hot melt extrusion is evaluated by thermogravimetric analysis (TGA). By tracking weight changes during heating, this method is frequently used to investigate solvent removal and material degradation. TGA provides information about thermally induced weight changes by calculating changes in a sample's mass as a function of temperature.

4.2 Thermal Behaviour Analysis by DSC: Thermal transitions involving energy absorption or release, such as the glass transition temperature (T_g) and melting temperature (T_m), can be identified using differential scanning calorimetry (DSC). It is also useful for assessing possible drug-excipient incompatibility and distinguishing between crystalline and amorphous forms in extrudates.

4.3 Drug-Polymer Interaction Study Using IR Spectroscopy: By examining variations in distinctive absorption peaks, infrared spectroscopy is utilized to assess drug-polymer interactions. Changes in these peaks could be a sign of changes in the formulation's molecular interactions and crystallinity.

4.4 Crystallinity Assessment by XRD Analysis: The crystalline quality of hot-melt extruded compositions is investigated using X-ray diffraction (XRD). The presence of crystalline structures is indicated by distinctive peaks in the diffraction pattern. However, when crystallinity is present in very small amounts—typically less than 10%—XRD's sensitivity is limited and it could miss it.

4.5 Morphological Evaluation Using Microscopy: An efficient method for analyzing the structural properties of hot-melt extrudates is microscopy. Optical or electron microscopy can be used to examine the materials' surface characteristics to detect crystalline particles or amorphous areas. Furthermore, microscopy provides useful information regarding particle size distribution.

4.6 Structural Characterization by NMR: To assess molecular interactions and identify modifications in the bonding between functional groups, solid-state NMR spectroscopy is employed. This method also helps assess the formulation's degree of crystallinity.

4.7 Mechanical Property Evaluation of Extrudates: To determine the plasticity and brittleness of extrudes, tensile strength and elongation must be measured.

4.8 In- vitro Drug Release Study: Establishing a release profile to represent in-vivo performance.

5. HME IN PHARMACEUTICAL DRUG DEVELOPMENT

5.1 Role of HME in Pharmaceutical Manufacturing

The HME process is widely recognized as an efficient technique for producing molecular dispersions and enhancing the effectiveness of medication delivery. This technique makes it possible to create prolonged, regulated, and site specific drug delivery systems with improved bioavailability. Lozenges, pellets, pills, suppositories, implants, stents, and transdermal systems are among the dosage forms made using HME in pharmaceutical manufacture. Additionally, the pharmaceutical industry uses melt extrusion technique for a variety of formulation applications. [35].

1. Covering off an active drug's unpleasant taste.
2. Polymer-drug dispersions and solutions:
 - Enhanced solubility of drugs
 - A higher rate of drug dissolution
3. Creating dose forms with controlled release, such as implants.
4. Creating dosage formulations with tailored release.

5.2 General Uses

Extrusion technology is widely acknowledged as a significant production method, especially within the rubber and plastic sectors. Extrusion methods are frequently applied for manufacturing of goods like pipes, tubing, insulated wires, rubber sheets, plastic films, and polystyrene components. Additionally, from the early 20th century, extrusion technology is extensively applied in the food business, particularly for the production of pasta products. Extrusion cooking is a widely used food processing method that utilizes heat, pressure, and mechanical shear to treat food items. [36].

6. FUTURE PERSPECTIVES

HME is considered a successful method for creating amorphous solid dispersions that increase solubility and bioavailability for drugs with limited aqueous solubility. This method offers a number of benefits over traditional methods, such as continuous processing and the removal of organic solvents. [37].

Several studies have attempted to minimize thermal degradation of drugs during HME, HME was able to develop and successfully sell two amorphous solid dispersion products from Abbott laboratories that contained heat-sensitive medications. However, just a few heat-sensitive medications were evaluated in the majority of the articles that suggested ways to stop thermal degradation, but only evaluated a small number of heat-sensitive medications; information on drug potency and associated compounds was unavailable. More research should be done to see whether the described techniques would be successful for more temperature-sensitive medications [38].

Furthermore, as intermolecular interactions affect many characteristics of solid dispersion, including dissolving behavior, physical stability, and chemical stability, future study should concentrate more on the interactions between drug and polymer. Additionally, this kind of research might offer crucial data for formulation improvement and polymer selection. Further investigations should focus on the microscopic structure of solid dispersion and how it relates to physical stability and dissolving behavior. Phase separation below the phase size of roughly 50 nm cannot be characterized by commonly used methods like XRD and DSC, which likely causes recrystallization during storage. Phase separation within solid dispersion, drug distribution, and drug solubility/miscibility in polymers may all be better understood with the use of some novel approaches. Understanding the macroscopic behavior of solid dispersion requires knowledge of thermodynamics in addition to the microscopic structure [39].

Additionally, choosing the right polymer is essential to a successful HME formulation because different medications and formulation goals require different polymers. Through interactions with the medication or other mechanisms, an appropriate polymer carrier can help increase the drug's solubility, physical stability, and bioavailability. However, only a few polymers are suitable for application in HME. Thus, new research areas include the synthesis of novel appropriate polymers (like Soluplus® [40–41], EVA [42], PEG-PVA, and PVP VA/PEG mixtures for HME [43].

Recent reports of HME improving the solubility of herbal extracts, such as ginsenosides and bifendate, indicate a novel use for HME. Although there remain a lot of issues and difficulties with HME, currently developments are expected to establish this technology as a highly valuable tool in drug development [44–45].

7. CONCLUSION

This review concentrated on methods for improving the solubility of drugs with limited aqueous solubility that fall into classifications II and IV of the Biopharmaceutics Classification System (BCS), with a special focus on hot melt extrusion (HME) technology. Through the creation of amorphous solid dispersions and improved drug–polymer interactions, HME has emerged as a reliable and commercially viable technique for improving the solubility and dissolution performance of drugs among the various techniques described in the literature. The reviewed studies emphasize that stable formulations with enhanced biopharmaceutical performance are largely dependent on the proper selection of polymers, plasticizers, and processing conditions. Understanding the amorphization, stability, and release characteristics of extruded systems relies on characterization techniques as thermal, structural, and dissolving studies. Despite several obstacles

including the risk of thermal deterioration and long-term physical, recent advancements in polymer development, low-temperature extrusion techniques, and process analytical technologies are anticipated to substantially increase the use of HME despite certain obstacles such thermal degradation risk and long-term physical stability issues. All things considered, hot melt extrusion is a continuous, scalable, solvent-free manufacturing platform featuring substantial potential for the creation of oral dosage forms of medications with low solubility and is probably going to continue to be a crucial enabling technology in pharmaceutical innovation in the future.

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