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HOT MELT EXTRUSION FOR AMORPHOUS SOLID DISPERSIONS: THE ROLE OF RHEOLOGY AND POLYMERS IN ENHANCING DRUG SOLUBILITY AND DELIVERY

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ABSTRACT

Polymer-based drug delivery systems are essential to improve the effectiveness of poorly soluble drugs. This review was prepared as a Narrative Review of recent and previous studies on the use of hot-melt extrusion (HME) technology to produce amorphous solid dispersions (ASDs). The research focuses on the HME technique in detail, as well as on the importance of selecting a polymer based on its properties, such as molecular weight, heat transfer, melting point, and biocompatibility with the drug, which is poorly soluble or requires controlled release. It also highlights the role of rheological properties, such as viscosity and shear behavior, in controlling formulation stability, drug-polymer compatibility, and processing performance during extrusion. The review covers the most popular polymers and associated poorly soluble drugs, emphasizing their effect on melt viscosity, ease of processing, and prevention of drug recrystallization. It also discusses the effects of screw speed, thermal, and shear parameters on drug bioavailability and product quality. The main findings show that rheology control is very important for selecting HME extrusion conditions to protect heat-sensitive drugs, choosing optimal polymers, and improving the bioavailability of poorly soluble drugs. This review provides clear recommendations for identifying suitable polymers and optimum processing conditions to enhance solubility and pharmacological performance using HME.

Keywords: Twin-Screw Extruders (TSEs), Drug Delivery, Rheology, Amorphous Solid Dispersions (ASDs), Hot Melt Extrusion (HME).

NOMENCLATURE

HME	Hot Melt Extrusion
TSE	Twin-Screw Extruders

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ASD	Amorphous Solid Dispersions
Tg	Glass transition temperature

1. INTRODUCTION

It is estimated that up to 70–90% of the medications in the pharmaceutical discovery pipeline and roughly 40% of the medications currently on the market have poor water solubility. According to their permeability, most of these poorly water-soluble medications in the discovery pipeline are weak acids or weak bases, which are then further categorized as class-II and class IV pharmaceuticals under the biopharmaceutical classification system (BCS) Tan et al.,[1]. The challenge of low water solubility must be overcome. There are several ways to enhance the dissolving characteristics of weakly water-soluble compounds: Salt formation, particle size reduction, micro/nano emulsion, solubilization with a surfactant or hydrotrope, complexation, solid dispersion, and lipid formulation are some of the drug development techniques that have been created. Solid dispersion is one of the most commonly used pharmaceutical approaches owing to its simple preparation procedures Fan et al.,[2].Among these methods, solid dispersions are widely used due to their simplicity of application and their efficiency in enhancing drug solubility, as they rely on the principle of dispersing a poorly soluble drug with a polymer. One definition of solid dispersion systems is "the dispersion of one or more active substances in an inert carrier or matrix at a solid state made using the solvent, melting-solvent, or melting [fusion] methods. While the matrix is hydrophilic, the medication is hydrophobic. Simple eutectic mixes, solid solutions, glass suspensions and solutions, amorphous precipitation in a crystalline carrier, compounds, or complicated forms are all examples of solid dispersions Tekade et al.,[3].

Since the 1930s, hot melt extrusion (HME), a well-known method for creating products with consistent density and shape, has been used in the plastics sector. HME is currently being utilized in the healthcare sector to produce implants, bioadhesive films, targeted release drug delivery systems, medical devices, amorphous solid dispersion (ASD) to improve the bioavailability of poorly soluble API, and taste-masked goods Agrawal et al.,[4]**.** The pharmaceutical sector has been more interested in HME because of the many advantages this approach offers: The pharmaceutical industry has used hot melt extrusion (HME), initially created and utilized in the plastics sector, as a quick, easy, and repeatable technique for creating a variety of solid drug dosage forms for various delivery routes, including the oral route (granules, pellets, and tablets), the subcutaneous route (implants), and the transdermal and transmucosal route. Among the most extensively used applications are:

1. Masking of taste. 2. Improved dissolution of poorly soluble drugs. 3. Sustained release formulations and. 4. Nanosystem preparation Nayak et al.,[5,6].

A hot melt extruder typically consists of three sections: feeding, processing, and output. The feeder is a part of the extruder that enables materials to be fed in for additional

processing. The processing zone includes a barrel and one or two screws that rotate counter to each other or in the same direction to allow materials to pass through different areas. Depending on the requirements, the various parts of the processing zone are maintained at different temperatures. The screws are made up of conveying and kneading blocks. Conveying blocks, as their name indicates, help move materials from one zone to another. Depending on their shape, kneading blocks assist with either distributive or dispersive mixing. The physicochemical characteristics of the polymers and active substances are crucial in determining the choice of process variables such as processing temperatures, screw speed, and screw arrangement. The primary characteristics of the active ingredient that are taken into account while determining the process parameters are its melting point and degradation temperature. Similarly, when selecting polymers for hot-melt extrusion, the glass transition temperature and melt viscosity are key factors. To improve processability, the formulation may include additives like plasticizers Samanthula et al.,[7]. Most of the polymers that are used in the HME process are viscoelastic in nature and exhibit shear-thinning behaviors at elevated temperature conditions, meaning that the viscosity of melts decreases with the increase of shear rate. The HME process involves elevated temperature above the glass transition temperature (Tg) of the polymer and high shear force exerted by rotating extruder screws, which contribute to the dispersion of drug molecules in molten polymers, forming an ASD. Knowledge of rheology of the molten drug-polymer mixture is key in (i) understanding the flow properties and microstructure of melts impacted by the processing conditions, (ii) determining the miscibility/solubility of the drug polymer mixtures, (iii) optimizing the key processing conditions for the HME process including temperature and torque (motor load), and (iv) controlling the quality and performance of resultant solid dispersions (e.g., stability and release) Badruddoza et al.,[8].It must be noted that studying rheological properties provides knowledge of viscosity values and their relationship to shear rate, as well as confirming the properties of the materials used, such as molecular weight, which is one of the most important factors that must be confirmed and known for polymers, as it determines the solubility of drug mixtures. Understanding the flow behavior, determining the appropriate processing conditions, and selecting the appropriate speed and temperature for use in HME saves effort and money and does not waste time and materials, as they enable us to determine the appropriate manufacturing conditions, thus protecting the materials and preventing thermal decomposition or recrystallization.

Hot melt extrusion (HME) and amorphous solid dispersants (ASDs) have been extensively studied, but little is known about how to leverage the rheological characteristics of the drug-polymer mixture to enhance the stability and performance of heat-sensitive drugs and to save time, money, and effort before HME. Increasing the bioavailability of heat-degradable medicinal compounds, maintaining consistent product quality, and optimizing heat extrusion process conditions all depend on closing this gap.

2. METHODOLOGY OF THE REVIEW

The manuscript is underpinned by a narrative-quality critical review of the reported and recent scientific literature associated with hot melt extrusion technology as applied to

amorphous solid dispersions, which particularly touches upon polymer and pharmaceutical system rheology in relation to the extrusion process and the stability of the amorphous state. The most recent advancements in science and technology (2015–2025) have been reviewed based on scientific articles.

Research and review articles published in peer-reviewed scientific journals that related flow behavior and viscoelasticity to zero shear viscosity, storage modulus, loss modulus, as well as the performance of the HME process, were reviewed. Some old references were cited for scientific necessity to explain only basic rheology theory and fundamental physical model that are generally accepted. These ideas were referenced in recent research that either re-evaluated or used them in the context of current extrusion machines. Publications that only addressed the mechanical side of the extrusion equipment, but not also material behavior or rheological properties of the pharmaceutical-polymer system, were excluded to keep consistency with the study theme.

This review is based on a comparative and critical analysis of the published data, pointing out common findings as well as discrepancies of various studies, and connecting the studied rheological characteristics with their practical influence on mixing efficacy, physical stability of the amorphous state (good manufacturing practice), and quality aspects of final dosage forms in hot-melt extrusion applications.

3. AMORPHOUS SOLID DISPERSIONS (ASDS) FOR ORAL DRUG DELIVERY

Medication is administered orally using amorphous solid dispersions (ASDs). For drugs taken orally to be absorbed systemically, drug solubilization is essential. Regrettably, over 40% of marketed medications and nearly 90% of those in R&D pipelines are poorly soluble in water. As a result, various formulation techniques have been employed to address solubility and dissolution challenges of certain medications. Manufacturing poorly water-soluble drugs as ASDs can effectively enhance their solubility and dissolution rate. An ASD is a solid dispersion where the active ingredient is dispersed in a predominantly amorphous form within an excipient matrix. In ASDs, the amorphous form of the drug is crucial for increasing solubility. Converting the drug into an amorphous state requires no energy to break its crystal structure. Consequently, many poorly water-soluble drugs in their amorphous form achieve significantly higher apparent solubility and dissolve much faster than in their crystalline form. ASDs are also known to improve bioavailability by increasing membrane flux due to higher supersaturation. Additionally, because ASDs contain hydrophilic polymers, they are more wettable Bhujbal et al.,[9].

Depending on the type of carrier, the physicochemical stability, the physical state of the active pharmaceutical ingredient (API), and the technique used to enhance solubility, there are four main generations of solid dispersion technology. The first generation of dispersions, which are based on crystalline carriers such as sugars and urea and where the API remains crystalline, offers high thermal stability and limited dissolution rates. The second generation uses amorphous carriers, like polyvinylpyrrolidone (PVP), polyethylene

glycol (PEG), and cellulose derivatives, to improve solubility through the amorphous form of the API. However, these complexes are more prone to recrystallize and have poorer long-term stability. Third-generation systems include surfactants or carriers with emulsifying properties, such as gelucire and poloxamers, to increase physical stability, prevent recrystallization, and accelerate dissolving. Finally, the fourth generation utilizes water-soluble or insoluble carriers, such as Eudragit RS/RL and ethyl cellulose, to achieve improved solubility combined with controlled drug release. This enables the development of sustained or extended-release systems, which are especially suitable for drugs with a short biological half-life Tekade et al.,[3] as shown in Table 2. which lists instances of Amorphous Solid Dispersion (ASD) products approved by the FDA. The content is used under the Creative Commons Attribution (CC BY-NC-ND 4.0) and was sourced from Zinjad et al.,[10,11].

3.1. Advantages of Solid Dispersions

Enhanced solubility results in improved absorption and, thus, increased bioavailability. Improved patient adherence by solid dosage administration as opposed to chemical techniques, such as prodrug or salt production. Clinical studies are not required. Wide-ranging utilization Formulation and production are simple.

3.2. Disadvantages of Solid Dispersions

During processing (mechanical stress) or storage (temperature and humidity stress), the amorphous state may undergo crystallization. Moisture may increase drug mobility and promote drug crystallization, Phase separation, crystal growth, or conversion from the amorphous to the crystalline state or from a metastable crystalline form to a more stable structure during storage And poor scale-up for manufacturing Zinjad et al.,[10].

4. MANUFACTURING METHODS FOR PREPARING AMORPHOUS SOLID DISPERSIONS

In order to prevent recrystallization, the crystalline drug lattice is broken with heat or a solvent, and the mixture is then quickly chilled or dried. This process creates ASDs. Melting is used for drug-polymer mixtures, and solvent-based techniques (also known as spray drying, electrospraying, and rotary evaporation) are used for heat-sensitive medications. Since process selection has an impact on product quality, it is crucial to comprehend formulation, equipment, and process variables as well as weigh the benefits and drawbacks of each approach to choose the best one Bhujbal et al., [9].employed hot-melt extrusion (HME) to create high drug-loaded amorphous solid dispersions (HDASDs) for poorly soluble medications, such as indomethacin, ibuprofen, and naproxen, using Eudragit®E as the polymer. Design space was dominated by Flory-Huggins thermodynamic modeling, and HDASDs with high drug loading were successfully created. While DSC, X-ray scattering, FTIR, Raman, and AFM characterizations confirmed the

amorphization and stability, high-humidity tests demonstrated the improved physical stability. The study found that HME formulations can be optimized for consistent quality through predictive modeling, Tian et al[12].

4.1. Hot-Melt Extrusion Process Technology (HME)

The hot-melt extrusion method was initially developed. At the end of the eighteenth century, lead pipes were manufactured. Since then, it has been employed in the production of pipes, sheets, bags, and other products for the plastic, rubber, and food industries. With the advent of high-throughput screening, today more than half of all plastic products, including bags, sheets, and pipes, are manufactured by HME, and hence diverse polymers have been utilized to melt and form different forms for a variety of industrial and domestic purposes. The technology's (HME) capacity to offer a variety of medication delivery systems is advantageous in the pharmaceutical sector as well Tekade et al., [3].

Extrusion is the process of pushing raw materials through a heated barrel at a high, controlled temperature as well as pressure to produce a product with a consistent shape and density. Although Breitenbach was the first to introduce the development of the melt extrusion method in pharmaceutical manufacturing operations, Follonier and his colleagues first looked into the use of hot-melt technology to produce prolonged-release polymer-based pellets of various freely soluble medications. Pharmaceutical manufacturing is the primary use for co-rotating twin-screw extruders because counter-rotating devices may degrade materials due to their high pressure. These extruders are usually fully intermeshing types with self-wiping capabilities that increase efficiency and cleanliness. A higher material throughput is achieved by running the screws at greater rotational rates, which offsets the fact that the parallel spinning of the screws produces less pressure than counter-rotating systems Poulesquen et al.,[13].

On the other hand, in single-screw extruders, material movement is dependent on screw speed, whereas in twin-screw systems, it is controlled by screw configuration, resulting in faster and more efficient material transport Goffart et al.,[14]. produced immediate-release hot-melt extruded pellets containing the poorly aqueous-soluble medication Indomethacin using five different screw designs. HME was combined with a die-surface cutting pelletizer to create 1.5 mm pellets with immediate-release matrix-forming polymers such as Soluplus® and Kollidon®VA64. The study concluded that HME is a reliable method for producing pellet dosage forms by forming ASDs , Srinivasan et al.,[15].

Rheological properties of polymers and pharmaceutical excipients are important in polymer-based drug delivery systems, especially those prepared using hot-melt extrusion (HME). Understanding the flow behavior and viscosity of polymer–drug mixtures helps in selecting suitable polymers and setting appropriate processing conditions. These properties influence drug distribution within the polymer matrix and affect the quality of the final

dosage form. The addition of an active pharmaceutical ingredient, particularly at high drug loading, can change the rheological behavior of the formulation and may reduce or increase the melt viscosity. Therefore, rheological measurements, such as viscosity as a function of shear rate and temperature, are useful for adjusting extrusion parameters and ensuring stable processing. In addition, basic viscoelastic analysis can provide information about drug–polymer compatibility and melt behavior during extrusion, supporting the development of effective polymer-based drug delivery systems Aho etal., [16]. The classification of Various types of extruders used in the pharmaceutical industry Dhaval et al., [17].

5. TYPES OF SCREW EXTRUDERS

Single-screw extruders (SSEs) with barrels that are smooth or grooved.

Twin-screw extruders (TSEs): These machines use either non-intermeshing or intermeshing screws and can rotate counter- or co-rotate.

Multi-screw extruders (MSEs): center shafts that rotate or remain stationary. The various extruders must be able to rotate the screw at a specific operating speed while adjusting for the torque and generated shear rate from the material being extruded, as well as the type of screw being used, regardless of the extruder's type, function, or process complexity. A motor that serves as a drive unit, an extrusion barrel that is frequently made in pieces and fastened together with bolts or clamps, a revolving screw, and an end-plate die attached to the barrel's end make up the extrusion assembly. Regardless of the size and form of the screw inside the stationary cylindrical barrel, this design ultimately dictates the shape of the extruded output.

In the extruder process, screw flights and barrel walls hold the materials in place. The feed rate, die and barrel temperatures, vacuum level for devolatilization, and screw speed (rpm) are all controlled by a central electronic control unit that is connected to the extrusion unit. Common readouts from electronic control panels include the viscosity, motor amperage, melt temperature and pressure, and specific energy usage.

6. PROCESS CONSIDERATIONS

Twin Screw Granulator (TSG) is a complex process with a number of variables that can be changed to improve granule formulation and production. The final granule characteristics may be affected by these process variables. Important process variables that affect the granulation include pre-blending, screw rotation speed, screw configuration, the number and length of kneading zones, temperature (°C) maintenance in various zones, and feed rate (g/min or kg/h) Repka et al.,[18].

Temperature: the temperature has a big influence on the process of melt granulation. It influences the way that the drug and polymer melt, mix and harden together. The

processing temperature should not be allowed to exceed the degradation temperature of the active ingredient, especially in case when Tg of the polymer or carrier is higher than the degradation temperature of the active ingredient, when such a melt granulation process is applied. In this case, a plasticizer or a polymer with a lower Tg can be employed to reduce the processing temperature. But using TSDG, it is feasible to carry out the extrusion below the melt or glass transition temperature of ingredients in the formulation and, therefore, drying can be done with dry air rather than heat energy with shear mixing Patil et al., [6]. extrusion temperature controls the viscosity of the mixture, its flow inside the extruder, and the stability of the drug. Studying the rheological properties help us choose the optimal temperature for each formulation**.** Configuration of Screws: The number of screws and their configuration influence the mixing degree (including non-homogeneous blends), residence time, shear pressures, and temperature distribution within the extruder Srinivasan et al.,[15]. Due to the high shear in the kneading zone, having too many kneading zones can produce denser granules than using fewer mixing zones. It also increases the residence time of the blend in the extruder Kumar et al.,[19].

Screw Rotation: It affects how long the material stays in the extruder. Higher speeds reduce the residence time even though they may increase the torque needed to move the mixture, depending on the type of polymer and drug and their heat tolerance. Screw speed also affects the uniformity of the mixture and the stability of heat-sensitive drugs. In twin screw granulation (TSG), granule size is only slightly affected by speed, and this effect is more noticeable in mixtures containing very viscous polymers. Higher screw speeds can reduce the apparent viscosity of the mixture and improve the dispersion of the drug in the polymer Melkebeke et al., [20,21].

Feed Rate: is an important parameter in HME because it is necessary to maintain a constant and uniform feed rate. It gives more time for mixing, dispersion, and uniform blending of the materials. However, it should be adjusted at a rate that does not reduce productivity, because the purpose of this technique and its preference over conventional methods is to increase production rate. Care must be taken not to increase the amount of material fed to increase production volume, because this will lead to higher melt viscosity during processing and difficulty in complete mixing.

Table1 summarizes the physical and thermal characteristics of typical polymers in thermoplastic extrusions, for example, their physical form, molecular weight, water soluble matter content (WSMC), glass transition temperature (Tg) and degradation temperature(Td). These are the characteristics, which are important in terms of describing rheological behavior of the polymer melt in processing. For instance, higher molecular weight or glass transition temperature (Tg), of polymers provide increase in the viscosity of the blend which also affect in ease of processability and homogeneity in efficiency. Likewise, aqua soluble polymers can affect the melt flow and drug dispersion in the polymer matrix. Thermal stability: are the polymers decomposed much higher than the extrusion temperatures, this is also to prevent polymer decomposition during processing.

Indeed the interplay of these properties determine flow, processability and final performance of a product made by thermoplastic extrusion and the figure 1 hereunder demonstrates that rheological properties and HME parameters of drug as well polymer have a direct effect in defining specification on the final product overall.

Table 1. The Physical and Chemical Properties of Polymers Commonly Used in the Preparation of Solid Dispersions Nair et al.,[22].

Polymer	Solid-state form	Molecular Weight(g/M)	Solubility in Water	Tg/Tm(°C)	Td(°C)
PVPK-12	Amorphous	5000	High Water-soluble	120	196
PVPK-30	Amorphous	66,800-40,000	High Water-soluble	163	171
PEG-400	Crystalline	400	Moderately soluble in water	Not Applicable(NA)	NA
PEG-600	Crystalline	600	Moderately soluble in water	NA	160
HPMC-E	Amorphous	85,000-150,000	Water- soluble	141	NA
HPMCAS L	Amorphous	50,000	Above 5.0 it is Water- soluble	119	204

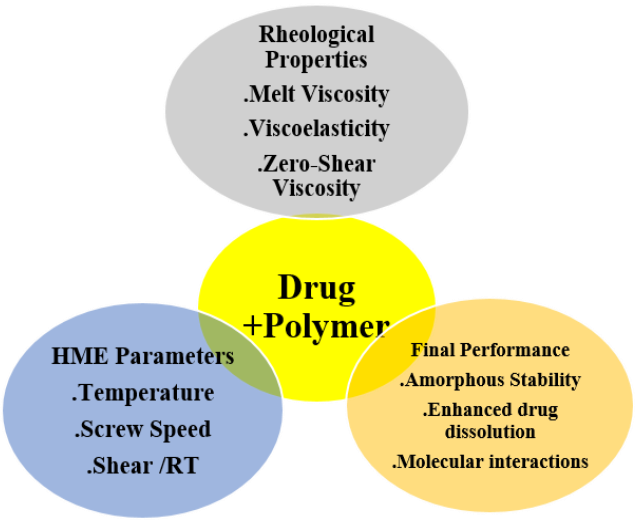

Fig.1. Schematic illustrating the relationships between the central drug-polymer system, rheological and HME Parameters and final performance.

Table 2. Lists instances of Amorphous Solid Dispersion (ASD).

Trade name	Drug name(s) \ChemicalName	Manufacturing Technique	Polymers Used	Company	Year of Approval
Prograf	Tacrolimus	Spray Drying	Hypromellose,	Astellas Pharma	1994
Nuvaring	Etonogestrel/ Ethinylestradiol	Melt Extrusion	Ethylene Vinyl Acetate Copolymer	Merck	2001
Kaletra	Lopinavir/ Ritonavir	Melt Extrusion	Co-Povidone,	Abbvie	2007
Intelence	Etravirine	Spray Drying	Hypromellose	Janssen	2008
Modigraf	Tacrolimus	Spray Drying	Hypromellose	Astellas Pharma	2009
Onmel	Itraconazole	Melt Extrusion	Hypromellose	Merz Pharma	2010
Incivek	Telaprevir	Spray Drying	Hypromellose Acetate Succinate	Vertex	2011
Kalydeco	Ivacaftor	Spray Drying	Hypromellose Acetate Succinate	Vertex	2012
Noxafil	Posaconazole	Melt Extrusion	Hypromellose Acetate Succinate	Merck	2013
Belsomra	Suvorexant	HME	PVPVA	Merck	2014
Envarsus XR	Tacrolimus	Melt Granulation	PEG	Veloxis	2015
Epclusa	Sofosbuvirc/ Velpatasvir	Spray Drying	PVPVA	Gilead Sciences	2016
Lynparza	Olaparib	HME	PVPVA	Astrazeneca	2017
Braftovi	Encorafenib	HME	PVPVA	Array	2018
Symdek	Tezacaftor/ Ivacaftorand Ivacaftor	SD	Hypromellose, Hypromellose Acetate Succinate	Vertex	2019
Braftovi	Encorafenib	HME	CoPovidone,Poloxamer188	Pfizer	2020
Qulipta	Atogepant	HME	PVPVA	Abbvie	2021

Sunlenca	Lenacapavir ^M	SD	PVPVA	Gilead Sciences	2022
Paxlovid	Nirmatrelvir / Ritonavir	HME	PVPVA	Pfizer	2023

Table 3. Show the advantages and disadvantages of HME Halagali et al.,[23].

Advantage of HME	Disadvantages of HME
An anhydrous process and no solvent are required.	High process Temperature.
Suitable for moisture-sensitive drugs.	High process knowledge required.
A water- and solvent-free process, eliminating drying steps, shrinkage issues, and safety hazards.	Cleaning is challenging, and the extruder's material requirements frequently clash with GMP concerns.
Higher drug loading capacity with improved and more consistent active ingredient release.	Reprocessing of material is difficult.
Heat-sensitive medications can be processed using a quick continuous production process that eliminates the need for drying and brief active thermal exposure.	Type and amount of Plasticizer may affect the dissolution

7. APPLICATIONS OF HOT MELT EXTRUSION (HME) IN DRUG DELIVERY

Drug administration: includes orally administered immediate-release pills, effervescent tablets, or rapidly dissolving granules. Drugs with poor water solubility exhibit improved bioavailability and dissolution, often employing solid dispersions of polymers such as PVP, PVP-VA, PEG, HPC, HPMC, Copovidone, and Soluplus.

For instance, investigated the use of hot melt extrusion (HME) technology to manufacture solid carbamazepine dispersions using Soluplus polymer, predicted the drug's miscibility with the polymer, and controlled the temperature. As demonstrated by the DSC, SEM, and FTIR test findings, the medication was uniformly dispersed within the carrier polymer, and no unfavorable chemical interactions with the polymer were detected, confirming the formation of a particle dispersion, Djuris et al.,[24].

Studied amorphous solid dispersions (ASDs) of the drug itraconazole (ITZ) utilizing Soluplus® and thermal extrusion to increase bioavailability and enhance very low solubility. Three formulations—a ternary SOL/ITZ/HP-β-CD formulation, SOL/ITZ with 2.5% AcDiSol®, and SOL/ITZ ASD—were studied and contrasted with the commercial

product Sporanox®. Dissolution trials showed improved drug release for all systems, with the preferred order being SOL/ITZ/CD > SOL/ITZ/AcDiSol® > SOL/ITZ > Sporanox®. The highest Cmax and AUC were found in SOL/ITZ/AcDiSol® rat pharmacokinetic experiments. The results highlight the importance of excipient selection and the role of Soluplus® in maintaining saturation, in addition to the challenges of linking laboratory data to in vivo outcomes (IVIVC) for BCS II medicines, Thiry et al[25]. Targeted or prolonged release via hydrophilic polymers (Eudragit, EVA copolymers).

Parenteral Drug Delivery**:** Intramuscular, intraosseous, intraocular, and subcutaneous implants. In controlled-release depot formulations, either biodegradable polymers (PLA, PGA, PLGA, PCL–PEG) or nonbiodegradable polymers (EVA, poly (ortho esters), polyanhydrides, and polyurethanes) are utilized. Protein or peptide encapsulation with controlled release kinetics.

Ocular implants**:** These devices use either nonbiodegradable (PVA) or biodegradable (PLA, PGA, and PLGA) polymers to release medications in the eye under controlled conditions Stanković et al.,[26].

8. THE RHEOLOGICAL PROPERTIES OF EXTRUDATES

In order to soften the polymer and promote the diffusion of the drug molecules through the polymer chains, high process temperatures are often required during HME Li et al.,[27]. For the drug molecules to dissolve into the polymer and produce an amorphous solid dispersion, A higher rate of medication disintegration.

Predicting how the molten material will behave during extrusion and possibly helping formulators decide whether a mixture can be processed through HME depends on examining the viscoelastic properties of a material before formulation begins. The study by Meena et al., [28]. illustrates this assessment, where they evaluated the viscoelastic characteristics of cellulose ester polymers with various substituent groups and degrees of substitution using oscillatory rheometry. Combining rheometry with thermal techniques allowed for predicting behavior during HME in the pre-formulation stage. The researchers found that the degree of substitution on the main polymer chain, chain length, and molecular weight all influence the glass transition temperature and viscoelasticity. They also discovered that Tg and viscosity increase with longer chains or higher molecular weights. Most cellulose polymers could not be extruded because of their high viscosity between Tg and the breakdown temperature. The authors concluded that HME is feasible with these systems only if an appropriate plasticizer is added.

According to several rheological studies, viscosity and viscoelastic behavior are essential for forecasting drug-polymer compatibility and optimizing hot-melt extrusion (HME) process conditions Sarode et al.,[29].

The effects of pressure coefficient (β) at high shear rate (γ) of LDPE melt flow were examined experimentally in a single pore capillary rheometer and numerically. Different die diameters and temperatures were used to extrude LDPE melt at a shear rate of 300–1500 1/s. Because of the die sizes of 1 and 2 mm and the temperatures of 150, 170, and 190 °C, pressure coefficients were examined at constant shear rates. The pressure distribution and pressure drop along the capillary die caused by the various temperatures, shear rates, and die diameters are checked using the finite element method with ANSYS/POLYFLOW. The findings indicate that when temperature, shear rate, and die diameter increased, the pressure coefficient (β) decreased. The die diameter has a moderate effect on the pressure dependency, but shear rate and temperature had stronger and weaker effects, respectively. Higher temperatures, die diameters, and shear rates resulted in more stable behavior of (β). The pressure drop values and the impact of temperature, die diameter, and shear rate (γ) on the pressure distribution are in good agreement between numerical and experimental results, Hadi et al[30].

9. EXTENSIONAL AND SHEAR FLOWS

For non-Newtonian fluids, simple shear and simple extensional flows are the most often investigated flow types. While the distance between particles on different flow streamlines varies, simple shear is a uniform flow in which fluid elements on the same streamline undergo the same deformation and the distance between them is constant, Figure 2. a. Non-uniform shear also occurs in rheometry and processing, and these are referred to as "viscometric flow." When shear is created between one moving and one stationary surface, the flow is referred to as drag flow (as previously described for the simple shear, Figure 2. a. Then, the gap height h and the moving surface's velocity v determine the shear rate in the space between the surfaces: $\dot{\gamma} = v/h$. Another kind of viscometric flow is pressure-driven (Poiseuille) flow, which is produced by the pressure gradient in a closed channel, like a pipe or tube (Fig. 2. b). The shear rate in pressure-driven flow is defined by the flow channel radius (r) and the volumetric flow rate (Q). Q: $\dot{\gamma} = 4Q/\pi r^3$ Aho etal., [16].

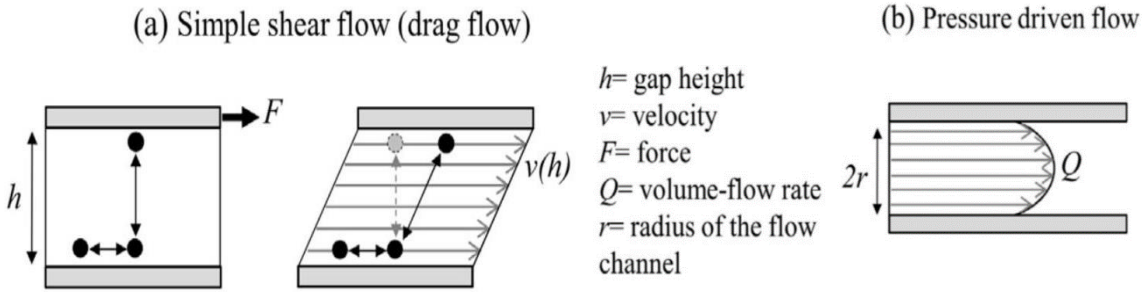

Fig. 2. Velocity streamlines in. (a) drag flow and; (b) pressure flow. The dots represent the fluid elements in the same and different flow streamlines 5.

10. DRUG-POLYMER MELT VISCOSITY AND VISCOELASTICITY

The primary rheological characteristic of drug-polymer melts that characterizes their resistance to flow under applied tension is viscosity. The viscosity of Newtonian fluids is independent of the shear rate. However, the majority of polymers utilized in the HME process have non-Newtonian, shear-thinning behavior; the entangled polymer chain molecules begin to detangle and orient along the flow direction when the polymers are subjected to significant stress or deformation. The ratio of shear stress to shear rate (τ /˙γ) is used to express shear viscosity. The first Newtonian (zero shear viscosity) plateau, transition region, shear thinning regions, and second Newtonian (infinite shear viscosity) plateau are the four segments of a typical polymer melt shear viscosity curve ,Figure 3.aCross [31]. Viscosity is constant at low shear rates, resulting in zero shear viscosity (η o). The viscosity starts to drop as the shear rate rises and usually moves into a linear region on a logarithmic plot, indicating power-law behavior. The viscosity begins to level out to the second Newtonian plateau at a high enough shear rate Chokshi et al.,[32].

Investigate the shear viscosity, shear stress, and shear pressure at a temperature of 170 °C and a shear rate range of 3–1500 s-1. Low-density polyethylene melt and nanocomposite flow characteristics were investigated numerically using POLYFLOW-Ansys version 15.0 software. According to the experimental findings, when the shear rate increased, the viscosity of the nanocomposites reduced, and the shear stress rose. For all further ratios, the pressure drop falls as the shear rate rises. The shear viscosity, shear stress, and pressure behavior of polymer nanocomposites in a capillary die, as determined by numerical analysis and experiment, show good agreement with the relevant experimental results, Latef et al.,[33].

To experimentally determine infinite-shear viscosity ($\eta\infty$) in polymer melt rheology is a daunting task. We do not have the technical capability to measure the extremely high shear rates beyond which are required, are out of scope of instruments like those used for rotational flow. Therefore, we commonly estimate the steady-state viscosity at shear rates relevant to the HME process using complex viscosity (η*) obtained from oscillatory frequency-sweep tests. As shown in Fig.3.b for Soluplus, when the Cox–Merz rule is satisfied and graphed both complex viscosity versus angular frequency and steady-state viscosity versus shear rate now coincide Cox et al.,[34].

For instance, Fig. 3.b displays the overlay of oscillation (dynamic) frequency sweep and flow sweep for Soluplus. The oscillation frequency test was conducted at higher angular frequencies (0.1 to 100 rad/s), whereas the flow sweep was carried out at lower shear rates (0.01——0.5 1/s). In order to cover the ranges typically observed in melt extrusion and injection molding operations, viscosity data acquired using both oscillatory and capillary rheometers can occasionally be merged capillary rheometer provides the steady state viscosity at greater shear rates (in the range of 1–10,000 1/s), Figure 3.c

whereas an oscillatory rheometer provides the steady state viscosity at low shear rates (often between 0.01 and 10 1/s or less) Suwardie et al.,[35].

We may infer processing circumstances with a larger shear rate in the HME process using both approaches. This decision is crucial from a processing perspective as well because the flow characteristics might be affected by the HME screw design and speed. For accurate rheological results, homogenous sample preparation is essential. Injection molding or compression has historically been used to create samples. A new vacuum compression molding (VCM) tool developed by Treffer et al. [36]offers a quick and affordable way to prepare homogenous thermoplastic samples for rheological testing Treffer et al.,[36].

By eliminating extra air, the vacuum in this instrument can stop air bubbles from forming in the sample, which could produce inaccurate rheological data. Compared to direct powder melting (RSD<8%), the measured rheological data of all manufactured polymeric samples using Soluplus, Eudragit E, and EVA Rowalit 300–1/28 using this method demonstrated great reproducibility (RSD<3%).

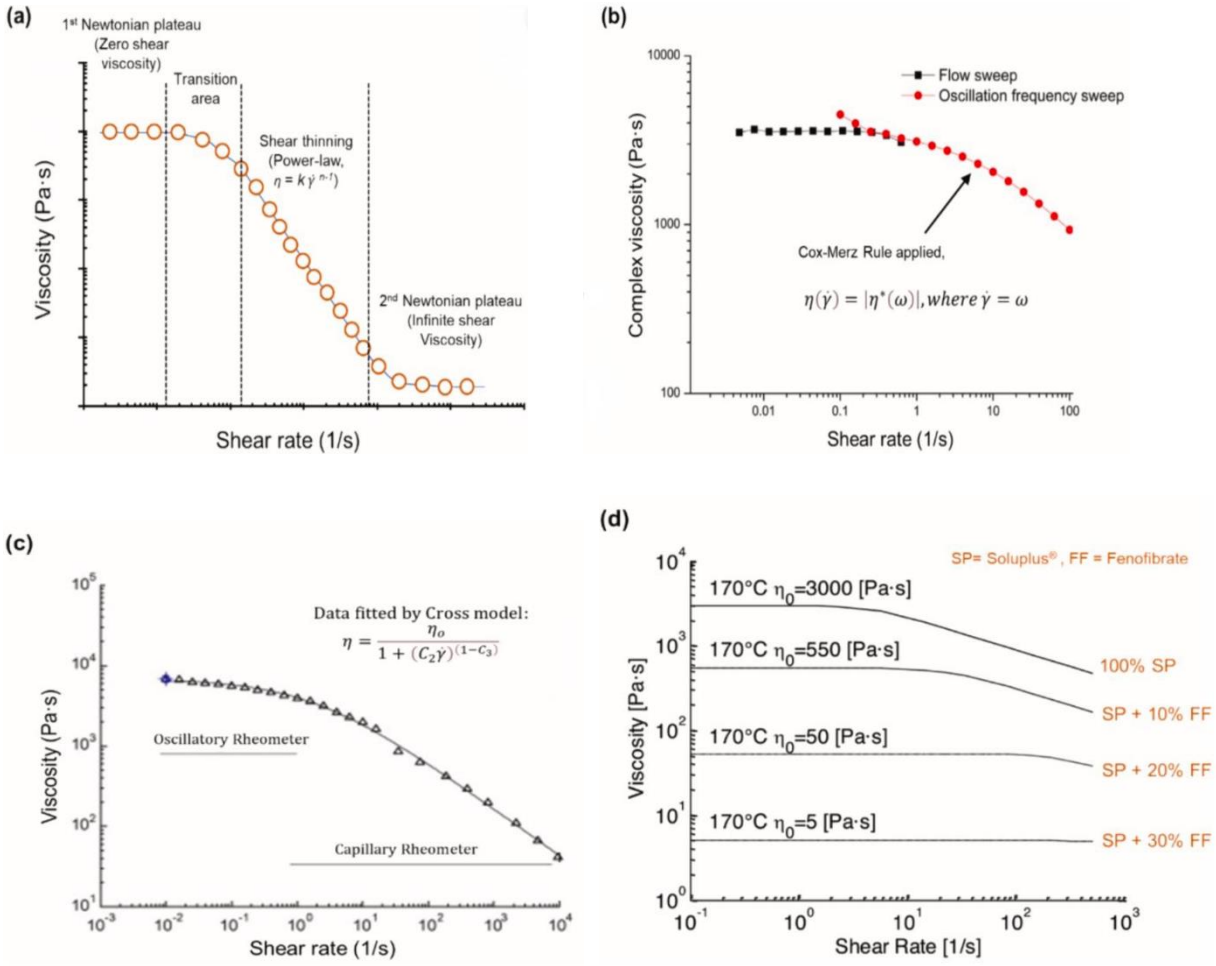

Fig.3. (a) Typical viscosity–shear rate curve for a shear-thinning polymer melt ;(b) Cox-Merz relationship for Soluplus at 160◦C. Solanki et al.,[37] ;(c) Steady viscosity of PEO at 140◦C. Suwardie et al.,[35]; (d) Viscosity as a function of shear rate for the formulations at 170◦C. Eggenreich et al .,[38].

According to reports, under particular processing conditions, the melt viscosity—rather than Tg—determines whether or not a polymer melt may be extruded Gupta et al.,[39]. As the melt viscosity increases, the torque inside the extruder can rise dramatically, overloading the motor and screws. However, excessive slips that cannot adhere to the screw and pass through the extruder die would result from too low melt viscosity, producing undercooked goods. For melt extrusion, it is therefore essential to maximize the melt viscosity. According to Meena et al.,[28], a polymer's ideal melt viscosity range is between 1000 and 10,000 Pa·s. Zero shear viscosity (η0) was frequently thought to be the most helpful measure for better understanding the relationship between the material's rheological characteristics and HME processing conditions. The data of η vs. $\dot{\gamma}$ or η* vs. ω plots, which are characterized by various mathematical models, can be used to extract this information Chokshi et al., [32]. The Cross model can be used to fit the viscosity (η) as a function of shear rate ($\dot{\boldsymbol{\gamma}}$) and produce η0.
The Cross model can be represented mathematically as follows Cross [31]:

$$\frac{\eta-\eta\infty}{\eta o-\eta\infty}=\frac{1}{1+(C2\,\dot{\gamma})^{(1-C3)}} \qquad (1)$$

Where shear rate is indicated by $\dot{\gamma}$ and zero-shear rate viscosity by ηo, infinite-shear rate viscosity η∞ ,C2, consistency and C3 a power law index-related constant. It is possible that $\dot{\gamma}$, viscosity, indicates shear rate; zero-shear rate viscosity by ηo; infinite-shear rate viscosity by η∞; C2, a measure of consistency; C3, a power law index-related constant. It is possible to set η∞ to zero to achieve more accurate curve fitting.

Figure 3 (d) shows the change in viscosity as a function of shear rate for different combinations of Soluplus and fenofibrate. The ηo values are taken from the data and compared. As drug loading increases, a decrease in ηo is observed, indicating that the drug is solubilized within the polymer. For a given drug-polymer formulation, this rheological test can help determine the necessary HME processing temperature and speed. Figure 3d displays the viscosity change as a function of shear rate for different combinations of Soluplus and fenofibrate. The values of ηo are taken from the data and compared. As drug loading increases, a reduction in ηo is seen, indicating that the drug is in a solubilized condition within the polymer. For a given drug-polymer composition, this rheological test can help determine the optimal HME processing temperature and speed. for solid dispersion products to be developed successfully, the selection of polymer carriers for HME is essential. Because polymers vary in molecular weight according to chain length and the type and degree of substitutions in the main chain, their structures have a significant

impact on both their glass transition temperature (Tg) and melt viscosity. Generally speaking, a polymer's melted viscosity at a specific temperature measures the degree of entanglement and chain flexibility of polymer chains, which determines how quickly they can move relative to each other. Higher degrees of chain entanglement in polymers with longer chains lead to higher melt viscosities. For example, in the case of HPMC, as its molecular weight increases from 25,000 Da to 150,000 Da, its melt viscosity significantly rises from 100 cps to 100,000 cps Meena et al.,[28]. Depending on temperature and shear rate, different grades have an impact on polymer flow Sarode et al.,[40]. A viscosity range of 1000–10,000 Pa·s is the standard for small-scale extrusion of neat polymers. Because plasticizers and drugs alter viscosity, commercial extruders provide greater versatility. Plasticizers that reduce melt viscosity can be used to extrude polymers with high Tg or MW Ghebremeskel et al.,[41,42]. A plasticizer is used in more than 75% of ASD medication items made by HME. Polymers are viscoelastic due to their dynamic macromolecular structures. Viscoelasticity is explained using small-amplitude oscillatory shear (SAOS), which yields the storage modulus (G′) and loss modulus (G″) as a function of angular frequency. • G′ = elastic (energy retained) • G″ = viscous (energy lost) • G″/G′ = tan δ (phase-lag). TMA and DMTA are other techniques Craig et al., [43,44]. Temperature has a major impact on viscosity and viscoelasticity. Increasing T causes chain disentanglement, which reduces viscosity. The crossover temperature (Ttanδ=1), which denotes the change from solid to liquid-like behavior, is reached when G′ = G″. This is the lowest temperature required for HME processing.

Storage and loss moduli are associated with complex viscosity (η)*:

$$|\eta^*| = \sqrt{\left(\frac{G`}{\omega}\right)^2 + \left(\frac{G``}{\omega}\right)^2} = \frac{|G^*|}{\omega} \qquad (2)$$

Where: • η* = complex viscosity • G* = complex modulus • ω = angular frequency.

In general, the rheological properties of drug-polymer systems, including shear viscosity, storage and loss moduli, zero-shear viscosity, terminal viscosity, and combined viscosity, are interrelated and collectively form the basis governing melt behavior during thermal extrusion. These parameters determine the balance between the elastic response and viscosity of the melt, directly affecting flow stability, mixing efficiency, and stress distribution within the extruder. Appropriate rheological behavior contributes to efficient dispersive mixing and ensures homogeneous drug distribution within the polymer matrix. Conversely, excessively high viscosity or dominant elastic behavior can impede melt flow and reduce mixing efficiency. Therefore, understanding and controlling these rheological properties is essential for optimizing extrusion conditions, achieving stable melt processing, and enhancing the quality and performance of polymer systems prepared using thermal extrusion technology.

11. CONCLUSION

In conclusion, this review focuses on the practical role of rheological properties in guiding the selection of key hot-melt extrusion parameters. Understanding melt viscosity, flow behavior, and viscoelastic properties of polymer–drug systems helps researchers choose processing conditions that reduce thermal and mechanical degradation, prevent material loss, and save time and effort, while ensuring the quality of the final product. Furthermore, rheology is not merely a descriptive tool but also a predictive framework for understanding the behavior of polymer-drug systems under various processing conditions. Analysis of shear and deformation mechanisms provides valuable insights into dispersion, amorphous phase formation, and drug-polymer interactions, all of which are essential for achieving homogeneous distribution and system stability. This integrated understanding contributes to enhanced process control, reliability, and industrial scalability in polymer-based drug delivery systems. In our future work, we plan to study the rheological behavior of a selected polymer system to determine the optimal extrusion parameters.

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