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Review Article

Unlocking Drug Potential by Enhancing Poor Drug Solubility and Bioavailability through Hot-Melt Extrusion

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ABSTRACT

Today's drugs, not all usually soluble and easy to formulate drug actives, they might be potent drug molecules at their specific target, they can never become a successful therapy, or molecule, or product if they are not able to reach the target where they are active. So, what we are targeting in this for is making these molecules bioavailable. So, this is what we want to achieve and it can be done by the melt extrusion process. The key point of this review was to establish the relationship between a novel technology, solubility and the bioavailability profile through Hot Melt Extrusion (HME) in order to reshaping the Pharmacokinetic (PK) and Pharmacodynamic (PD) landscape for poorly soluble drugs. Tailoring the PK and PD with HME solid dosage form was shown to be affected by the physicochemical properties of the carrier matrix used. With the help of HME technology by dissolving these crystalline drug actives in a molten polymer matrix and pre-dissolved form and that makes it much more bioavailable and this enhanced the performance of such drug actives and in many cases. It is that what actively enables such molecules to at all become a drug product and a therapy. Compared to the traditional methods of developing drug products, HME is a key the gate to enhance in delivering the drug products to avoid patient compliance. A report says there are lots of developments in pharmaceutical APIs with poor solubility and improving their solubility is quite challenging. The effective formulation needs characteristics carriers and polymers that are suitable for the HME technology that has been discussed here. HME has been proven as an effective choice for the conventional ways of producing tablets, films, implants, etc. that can be administered orally, transdermal and transmucosal. This review paper adds knowledge of supercharging sluggish drugs by the use of HME and it can put the punch back in pharmaceutical industries and should use these recent developments to employ and develop cutting-edge drug delivery systems to avoid patient compliance.

Keywords: Hot-melt extrusion, Solubility, Polymers, Pharmacokinetics and Pharmacodynamic, APIs.

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INTRODUCTION

Melt extrusion process could be efficiently applied in order to enhance the solubility, stability and further to improve the poor physical properties of the drug substance. The numbers of poorly soluble APIs are undoubtedly keep rising with the development of new drug products and most of these kinds of drug products are already entering the development pipeline. Using Hot Melt Extrusion (HME) to convert basic ingredients and excipients into a homogenous solid of a uniform shape, it also permits the dissolution of APIs into a polymer to develop a matrix called an Amorphous Solid Dispersion (ASD). HME is a widely known and distinct characteristic in the pharmaceutical sector within the application of increasing the bioavailability of drugs and improving the PK-PD performance of Active Pharmaceutical Ingredients (APIs). It also enhanced Biopharmaceutical Classification System (BCS) drugs which apparently less soluble and less dissolution rate and permeability e.g. Class II and IV. This technology is rapidly gaining significant attention in the pharmaceutical industry, especially in targeted therapies like oncology. It is crucial for anyone working in this field to have a thorough knowledge of HME.[1]

In this article, we look over the improvement of PK-PD of Class II and IV BCS compounds by increasing solubility, PK and PD profile in formulations, helped improve poorly soluble drugs by using the HME technique, formulation design, as well as processing technologies and materials, characterization and

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comparative study between HME and regular formations and development.

Hot Melt Extrusion Reinvents Drug Profiles for Enhanced solubility, Absorption and Action

Owing to the importance of solubility, new techniques are needed in order to achieve the intended outcome in drug development by improving the PK-PD profile, drug disposition and APIs solubility for the development of targeted drug delivery systems. The PK-PD profile allows for the dissociation of drug-carrier complexity and pharmacological variables, which occurs throughout the process of disposition as a result of endogenous and exogenous factor. It has also been used to enhance the understanding of the *in vivo* behaviors complicit and facilitate in drug delivery development. A drug's absorption and elimination from the body are quantitatively measured through pharmacokinetic profile. Pharmacodynamic modeling evaluates the pharmacological effects of drugs over time with consideration of significant rate-limiting mechanisms of action. An effect that is relevant to effectiveness should be the pharmacodynamic endpoint that is taken into account. And the response should be quantified and validated for precision, accuracy, reproducibility and specificity. The development of new technologies can improve the knowledge of the delivery systems of physicochemical characteristics and the interactions of physiological systems that represent blood flow, expression of enzymes, cell life span and transporters.[2]

Over 40-70% of new APIs fail to match their ranges because of poor solubility and permeability during the product development process. Due to this, the researcher faces difficulty introducing new chemicals because of bioavailability and PK-PD profiles, which are basically due to poor solubility. Physical and chemical challenges are overcome by using multiple approaches during the development of pharmaceutical products, including solid dispersion, micronization, co-solvent, pH adjustment, complexation, surfactant, salt formation, nanotechnology, polymorphs and hydrotophy. As a way to increase the bioavailability of drugs, solid dispersion develop by HME is currently gaining an interest in the pharmaceutical sector because of its applications, simple manufacturing process and cost-effectiveness.[3] Drugs that are poorly soluble have lower absorption, which results in inadequate and variable bioavailability as well as side effects on the gastrointestinal mucosa.[4] Solubility is one of the most crucial factors in achieving the correct drug concentration within the bloodstream to get the desired pharmacological outcomes, which is the result of the solute dissolving to make a homogeneous system in a solvent. Low water solubility is a fundamental obstacle in both in the development of new chemical substances and generic drug formulations.

Reshaping the poorly soluble APIs

There are different techniques can be used to increase the drug solubility like physical modifications (Micronization, nano-suspension, polymorphs, amorphous forms and co-crystallization) and chemical modifications (pH, buffer, derivatization, complexation and salt formation).[5]

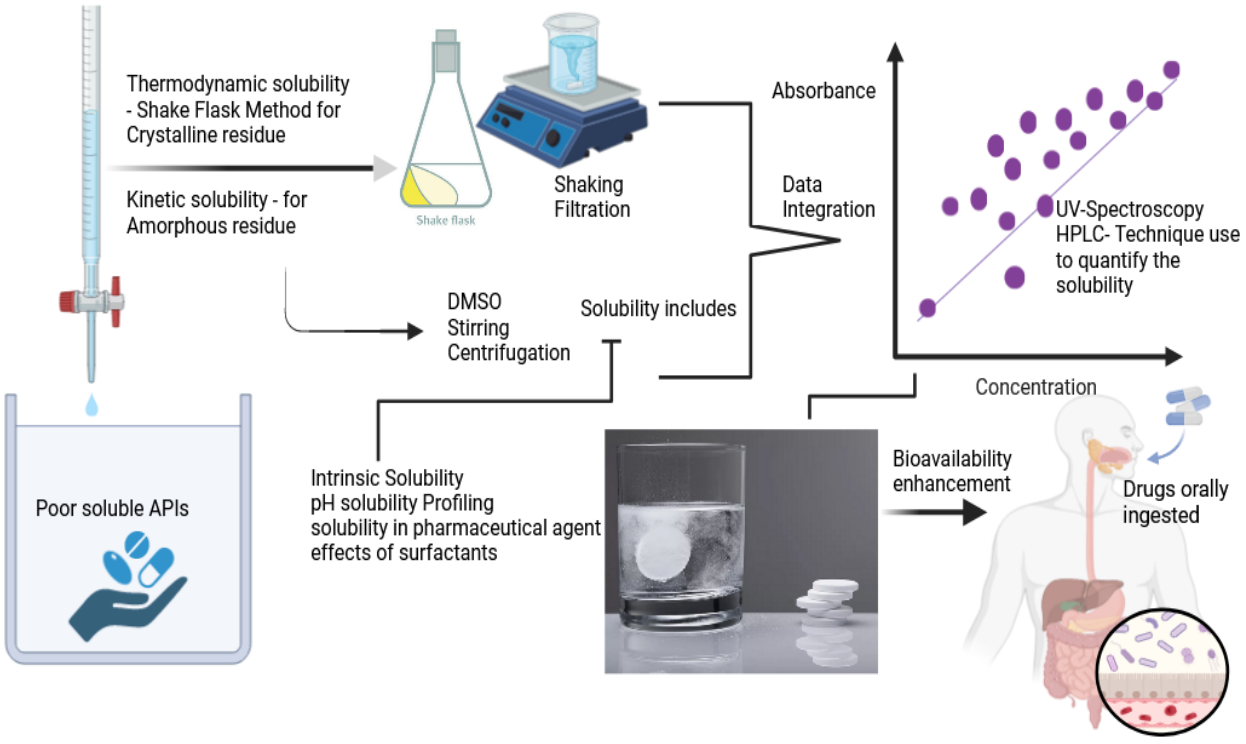


Figure 1: Drug solubility method, quantification and bioavailability enhancement.

Solubility is < 1 mg/mL, absorption is inadequate and solubility needs to be improved using various technologies. Poor bioavailability is the main issue in developing of oral dosage forms and it can be influenced by dependent variables like; permeability, dissolution rate, biotransformation, pre-systemic metabolism and low permeability, poor solubility and efflux mechanisms are the causes of less bioavailability.[6,7] As per the source, there are many techniques that can be used to make drugs that aren't more soluble. The technologies are chosen depending on characteristics of the drugs under consideration, the kind of the excipients is being selected and the anticipated dose form.[8,9]

Experimental methods for quantifying solubility

The drug solubility can be determined by following methods:

Determination of thermodynamic solubility

The shake-flask method is the simple, accurate and approved solubility method for poor soluble APIs because of faster and reproducible. Briefly, the pharmaceutical agent is over-added to the solubility medium. The solid phase needs to be brought into equilibrium with a saturated solution with the addition of pharmaceutical agent. If more solids are added, the solution of pH and, consequently, the drug's solubility could change if an acidic or basic pharmaceutical is dispersed in medium. The amount of time needed for the surplus solid to equilibrate with the dissolved drug can vary based on the dissolving rate and agitation method used and usually it achieves within 24 hr. The synthetic technique depends on a laser beam tracking the concentration of the solid drug. The drug could dissolve if a specific amount of solvent is added or if the temperature changes (Figure 1).[10]

Determination of kinetic solubility

The kinetic solubility is measured using a stock solution; it gives the maximum solubility, ease of automation, precision and fastest precipitating species of the compound and it is often determined by adding co-solvent DMSO and the fact that it works best with chemicals with a solubility of more than 10-6 molars. UV-spectroscopic and HPLC techniques are the ones that can be used for determination (Figure 1).[11]

Hot Melt Extrusion Expedites the Journey of Underperforming Drugs

ASDs have been prepared by using HME is used on a massive scale in order to increase the solubility and dissolution rates of poorly soluble compounds.

Sekiguchi and Obi were the ones who initially proposed a method to produce fast-acting solid dispersion dosage forms. Briefly, the physical mixing of a drug and water-soluble carriers is heated until it melts. The drug and carrier used here should be thermostable. Then the melted complex is stirred gradually and solidified on ice; later, the solid mass is broken down, pulverized, sieved and compressed. The % weight of the drug is based on the binary system, carrier of choice and melting point.[12] As discussed above the Solid dispersions are a one method for enhancing the API's solubility and bioavailability. Soluplus polymeric solubilizer was developed especially for formulation by HME. Different concentrations are taken a consideration for surfactants, such as graft copolymer composed of PEG, Lutrol, were used in combination with amphiphilic Soluplus as a primary solubilizing agent to examine their effects on formulation processing by HME.[13] In order to establish the Developability Classification System (DCS), the BCS parameters are adjusted for the intended dose of the given chemical. Orally given DCS IIa and DCS IIb drugs absorption is constrained by their rate of dissolution and solubility respectively.[14,15]

Hot-Melt Extrusion Process and Equipment

HME is a novel processing method in the development and formulation of molecular dispersions of APIs with polymers and lipid matrices that led this method to get modified, controlled and targeted drug delivery.[16-19]

HME is a technique of transferring raw materials through a die under controlled, regulated circumstances to develop products of uniform shape and density.[20] It has been used for many different drug delivery formulations including solid dosage forms that increase drug bioavailability. It is a continuous, solvent-free multi-step processes. The material of excipients like diluents, Plasticisers or polymers mix with APIs via heat and pressure treatment causes the products get melts and produce uniform shape and density for use of different applications.[21]

The HME process is optimised by an electronic control system in a screw extruder that can change the screw speed, temperature and pressure. Under the influence of heat and shear force or stress, the screw extruder produces a homogeneous blend that alters the qualities of the final product. Single-screw and twin-screw extruders have two different types of screws inside the extruder that are used for different mixtures of materials as they pass through the barrel. An image shows the arrangement of many parts of the machine (Figure 1).

The single screw extrusion system is having a single rotating screw inside the barrel including compression; feed and metering zones were there which cause a shift in pressure in each zone that produces the mixture of API and excipients (Figure 2).

Screw Extruder

The gearbox and driving unit of the electric motor turn the screw at a predetermined speed. Temperature controllers are attached to the barrel's heating and cooling components to keep the temperature under control. The properties of the plastic material, the screw and barrel assembly's construction and the operating conditions of the system all affect the screw and barrel assembly's capacity to extrude a particular material. The single screw

extrusion is particularly ideal for high viscous materials because of its uninterrupted movements which create high pressure (Figure 2).[22]

Twin-screw HME is a continuous process that improves the solubility of APIs.[23,24] The screw was placed side by side and each screw can rotate either same or opposite direction. This method developed heat and shear energy to produce the ASD of an API into a polymer carrier.[25,26] Since it is a continuous process, it's better to use it in combination with an in-line analytical method to enable real-time monitoring of material quality.[27,28] Twin screw extruders provide a number of benefits over single screw extruders, including faster transit times, less inclination to overheat and simpler material input and dispersion capacity. HME has been integrated as a key formulation and development process in the pharmaceutical industry during the past ten years as a result of a combination of growing pressure from regulatory bodies and improvements in knowledge about ASDs. To date, there have been 25 products approved by the FDA that were made using this technique.[29]

Extrusion System Elements

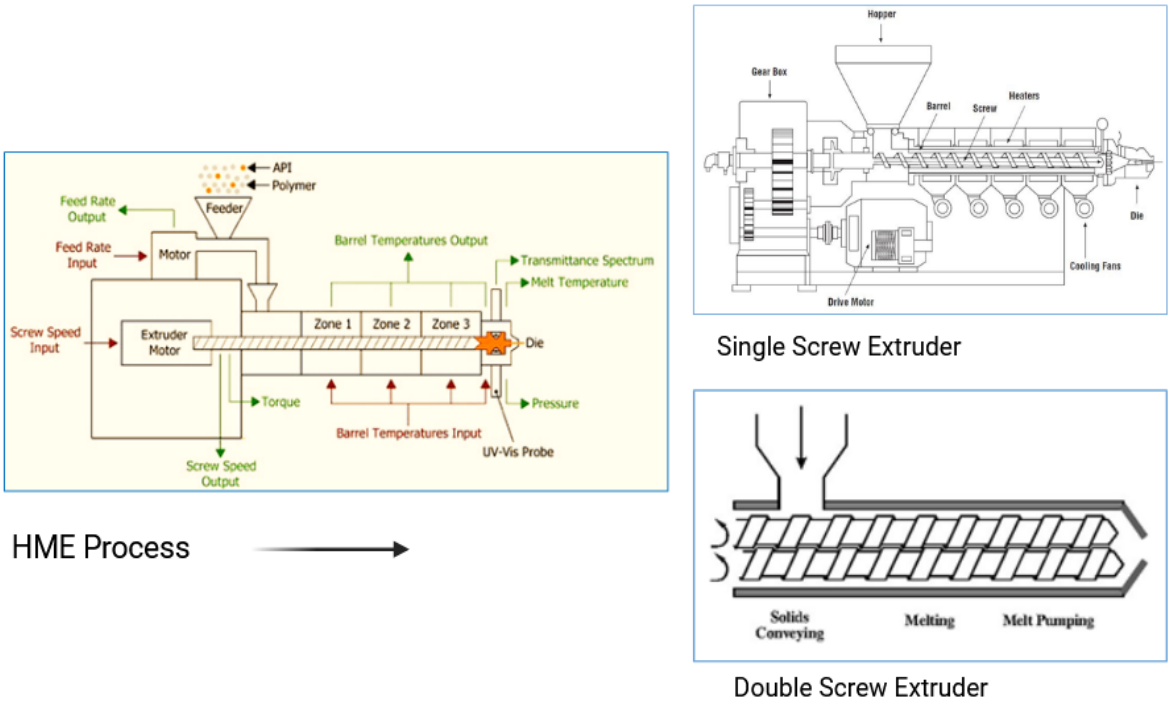
The physical properties of the substances can be altered by changing the extrusion process when a substance is driven through an orifice or allowed to die on the HME under controlled. The component of HME extruder include a motor, an extrusion barrel, rotating screws in the barrel and die which is connected at the end of the extruder.[18] A thermoplastic screw can be divided into six different zones. Different polymer varieties have different screw designs.[30] Such as: Feeding Zone, Melting Zone, Mixing Zone, Metering Zone, Venting Zone and Die Shape (Figure 2).

Several factors are involved in the design and optimisation of the HME process.[31,27]

Factors include the right tools, the mass feed rate and the process temperature and shear forces.

Physiochemical variables: characteristics of the drug and excipients, compatibility of the mix's physical and chemical components and stability considerations.

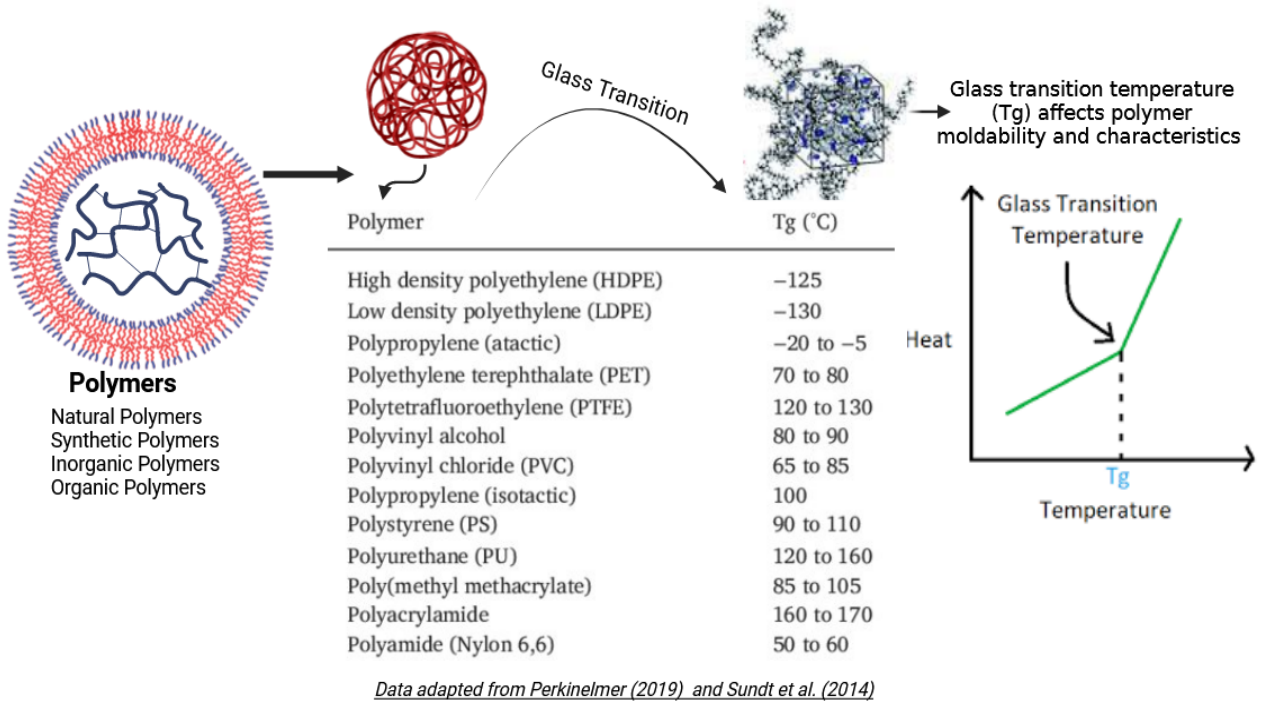
Formulation parameters: Drug-polymer solubility and interactions, rheological characteristics, physical state and drug dissolution from extrudes.



Screw can be divided into six different zones. Different polymer varieties have different screw designs.

- Feeding Zone: Transfer materials from the hopper to the barrel.
- Melting Zone: Melt the substance by heating it, which lowers its viscosity.
- The mixing zone: Transverse, flow, and pressure flow, leakage are used to move material in a helical pattern.
- Reduce the pulsing flow of molten mass in the metering zone.
- Venting Zone: Eliminate gases and flammable substances.
- Die shapes include rounds, ribbons, and films.

Figure 2: Schematic representation of the Hot Melt Extrusion Process, Extruder and Elements



Polymer	Tg (°C)
High density polyethylene (HDPE)	−125
Low density polyethylene (LDPE)	−130
Polypropylene (atactic)	−20 to −5
Polyethylene terephthalate (PET)	70 to 80
Polytetrafluoroethylene (PTFE)	120 to 130
Polyvinyl alcohol	80 to 90
Polyvinyl chloride (PVC)	65 to 85
Polypropylene (isotactic)	100
Polystyrene (PS)	90 to 110
Polyurethane (PU)	120 to 160
Poly(methyl methacrylate)	85 to 105
Polyacrylamide	160 to 170
Polyamide (Nylon 6,6)	50 to 60

Data adapted from Perkinelmer (2019) and Sundt et al. (2014)

Figure 3: Hot Melt Extrusion based polymeric formulation their Glass Transition Temperature.

HME process can be optimised by using Process Analytical Technologies and Experimental design.

Components Used In HME to Increase Solubility

Polymers and carriers

There are several types of polymers that can be used to increase solubility; these are listed in Figure 3 and glass transition affects polymer characteristics in terms of moldability, tensile strength and transparency.[14] Drug-polymer stability, miscibility and function of the final dosage form all play major roles in the choice of polymer for solubility enhancement.

Use of Polymers in Drug Delivery

Polymers such as PVP and HPMC are excellent binders that increase the production of granules and enhance the flow and compaction characteristics of tablet formulations.

The polymeric excipients that are used in intermediate release tablets are also used in "bulk-out" capsule fills.

Polymers have been tested for their capacity to prolong the time of gastric retention by adhering to the stomach mucous membrane and floating above the contents of the stomach, respectively.

The patient must maintain a therapeutic effect to avoid compliance by using an extended or sustained release dosage form. And the most common polymers are cellulose derivatives such as; Ethyl cellulose and cellulose acetate, as well as polyvinyl acetate.

Polymers play a key role, especially in targeted drug delivery systems. It prevents degradation or release in the stomach and small intestine and ensures a controlled release in the proximal colon.

Site-specific mucoadhesive polymers, which have advantages like; increased polymer residence time, improved penetration, enzymatic inhibition and site-specific adhesion.

Plasticisers

Plasticizers usually consist of low-molecular-weight substances that can molten polymers to increase their flexibility. Plasticizers lower the processing temperature and Tg, which eventually improves the stability of the polymer and the drug. By expanding the free volume between polymer chains, plasticizers lower a polymer's Tg and melt viscosity.

Glass Transition Temperature (Tg)

Tg determines when a polymer transitions from a hard, brittle state. As soon as it reaches this temperature, carbon chains begin to move. At this stage, the temperature at the edge of the solid state causes the amorphous region to change from a stiff to a flexible state, more like a viscoelastic rubbery state. The space between the molecular chain's doubles at this temperature. Semi-crystalline polymers' viscoelastic qualities enable flexibility, which is necessary for packaging materials. The amorphous component of a semi-crystalline material has a feature called the Tg. When the temperature goes below Tg, the molecules of amorphous materials stay frozen in place and behave like solid glass. Although plastic materials with stiff and rigid molecular structures exhibit a greater Tg, plastic materials generally have a lower Tg. The Tg, which varies for each polymer having an

amorphous structure, is a useful indicator of whether a certain material is more appropriate for flexible or rigid applications.[32-34] The polymers are designed to function below their glass transition point. An example of this is a tool with a hard plastic handle. If the glass transition temperature were below the working temperature, the plastic handle would be flexible to allow one to grab it and use it effectively (Figures 3 and 4).

The type and quantity of the plasticizer determine whether the polymer Tg decreases. They enhance the finished product's physico-mechanical characteristics. There are several types of plasticizers available, which are listed in Figure 5.

Factors affecting the glass transition temperature

Polymer chains with stiffening groups have less flexibility and have higher Tg values. Dipole forces, H-bonding and other stronger intermolecular forces reduce the chain's mobility, which raises the value of Tg. Tg grows as the m.w. of the polymer does because Tg is linked to molecular weight. Depending on the relative humidity of the exposure, moisture may function as a plasticizer and cause a material to reach equilibrium moisture content by slowly diffusing through it. Results, in a lower Tg. For determining Tg, we use Differential Scanning Calorimetry (DSC), Thermo-Mechanical Analysis (TMA) and Dynamic Mechanical Analysis (DMA).

Other processing Aids

The stability of polymers can be improved by adding antioxidants such as butylatedhydroxytoluene and butylatedhydroxyanisole. Vitamin E, acid receptors and/or light absorbers can be added to polymers that are prone to degradation to increase their

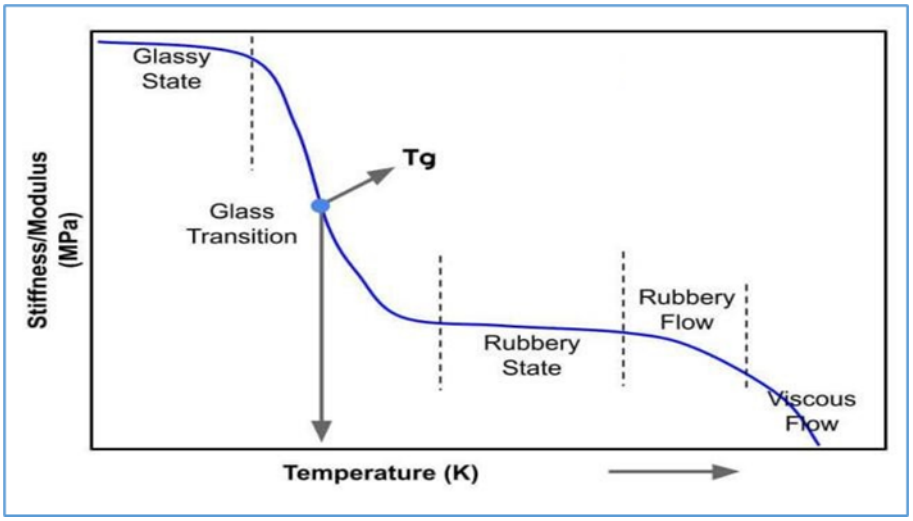
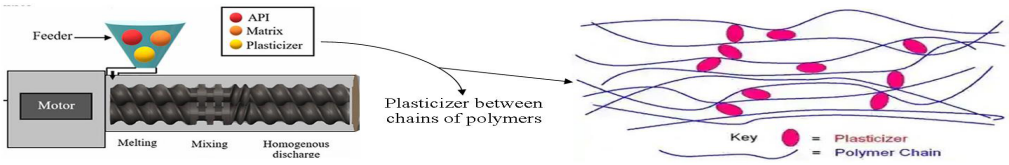


Figure 4: Graph of glass transition temperature plotting the temperature and stiffness of a material.



Plasticisers Type	Examples
Citrate esters	Triethyl citrate, tributyl citrate, acetyl triethyl citrate, acetyl tributyl citrate
Fatty acid esters	Butyl sterate, Glycerol monosterate, stearyl alcohol
Glycol derivatives	Polyethylene glycol, propylene glycol
Phthalate esters	Diethyl phthalate, dibutyl phthalate, dioctyl phosphate
Sebacate esters	Dibutyl sebacate
Vitamin E TPGS	D-alpha-tocopheryl polyethylene glycol 1000 succinate
Miscellaneous	Triacetin, Mineral oil, castor oil

Figure 5: Types of Plasticizers.

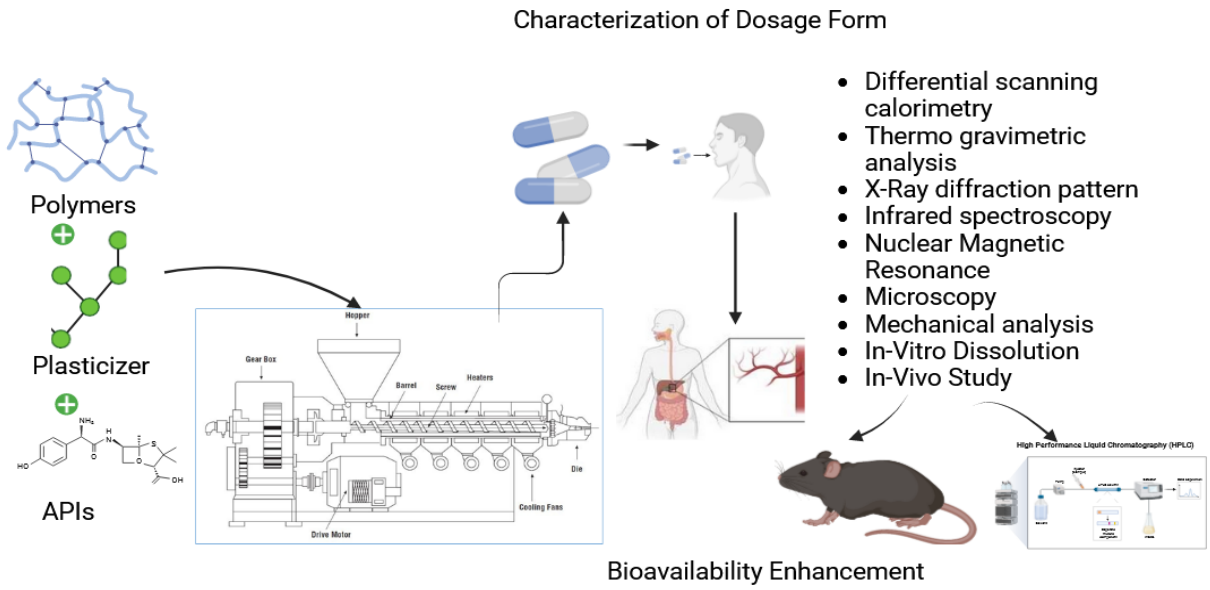


Figure 6: Characterization of Dosage form made by HME Technique.

Table 1: Drug formulation by using HME Technology.

Petereit, *et al.*	Taste-masked granules of verapamil HCl using HME and the anionic methacrylate co-polymer Eudragit.
Pimparade, *et al.*	By extruding a mixture of caffeine citrate with ethyl cellulose, a plasticizer, and mannitol to speed up drug release, showed that HME was a useful technique for disguising the bitter taste of caffeine citrate. In order to create a one-step procedure for turning a solid formulation developed by adding a liquid-stabilized nano-suspension.
Khinast, *et al.*	HME in conjunction with an internal devolatilization procedure, resulting in a continuous method of processing for the production of solid nano-formulations.
Ye, *et al.*,	HPH and HME were coupled to create a one-step processing technique for the creation of nanocrystals.
Patil, *et al.*	SLNs can be successfully produced by conjugating HME with HPH.
Cassidy, *et al.*	Reported a photosensitizer-containing oral formulation for HME-targeted medication delivery to the colon. The formulation, which has been included in the medication as polymer, plasticizer TEC, and photosensitizer, was extruded using a twin-screw extruder with Eudragit® S 100 as the polymer.
Miller, *et al.*	Reported a supersaturated itraconazole-targeted intestine delivery method for better oral absorption using HME. In this investigation, amorphous solid itraconazole dispersion with Eudragit® was made using 20% and 40% Carbopol® 974P.
Sax and Winter	Studied triglyceride-based implants made by mixing a number low-melting lipids with glycerol tristearin and extruding them through a twin-screw process.
Park, *et al.*	Studied a durable clotrimazole or nystatin-containing denture adhesive film for oral candidiasis.
Dierickx, *et al.*	Co-extrusion was used by Dierickx et al. to create fixed-dose combination micromatrices. A multilayer dosage form was created that combined polycaprolactone for metoprolol tartrate's sustained release and PEO/PEG for hydrochlorothiazide's quick release.
Daurio, *et al.*	Demonstrated that the production of co-crystals of carbamazepine-saccharin, caffeine-oxalic acid, theophylline citric acid and nicotinamide-trans-cinnamic acid is feasible and scalable using twin-screw extrusion.
Moradiya, *et al.*	Successfully observed co-crystals of saccharin and carbamazepine in a 1:1 ratio.
Crowley MM, *et al.*	HME is a technology that has promise for improving the dissolution of poor soluble drugs.
Chokshi RJ, *et al.*	By using hydrophilic polymers to improve the drug's wetting, deagglomeration, and micellization are responsible for the improvement in dissolution by HME.

stability. Additional chelating agents, like citric acid and EDTA, Ascorbic acid and other reducing agents can also be employed as antioxidants.[35-37]

Characterization Methods

The physicochemical properties of the HME were determined using a variety of techniques. Since both the API and polymer are exposed to high temperatures during the HME process, it stands to reason that APIs with extremely high melting points or those that are thermally labile present a high concern.[38] The n numbers of procedures can be used to evaluate the extrusions produced by the extruder. Additionally, these methods can be used to distinguish between solid solutions and dispersions.[31] ASDs are being utilised more frequently to support drug development and have effectively produced a number of commercial goods. To comprehend how solid dispersions promote bioavailability, numerous experiments have been done. The enhanced bioavailability of ASDs is caused by a number of circumstances. First, the crystalline medication's transformation into its amorphous form increases its apparent solubility, which in turn improves bio performance, particularly when the drug is absorbed quickly. Second, through increasing API wettability, reducing particle size and stabilising the dissolved drug, the spread of API within the matrix of polymers influences drug dissolution. The capacity of an amorphous dispersion to increase the rate of dissolution and keep the concentration of drug in solution.[39] *In vivo* evaluations of the pharmacokinetic characteristics of solid amorphous dispersions can be done in rodents and non-rodents. A single dose of the drug would be administered after an overnight fast with free access to water. Before and 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h post treatment, blood plasma samples are taken into a K-EDTA-coated tube. Acetonitrile and water are used to dilute the samples 50/50. HPLC-MS/MS analysis is performed on the supernatants following centrifugation at 3000 rpm for 5 minutes (Figure 6).[39]

A Study of HME Technology and Drug Formulation

The physicochemical properties of APIs are influenced by the extrusion process and formulation. With the addition of excipients, the properties of poor water-soluble drugs also have a significant impact on *in vitro* dissolution and *in vivo* performance. The majority of research suggests a combination of additives or polymers, such as plasticizers, surfactants, low-TG polymers, pH modifiers, disintegrant and diluents, to enhance the HME process and regulate drugs (Table 1).[36,40-52] HME has a number of advantages over commonly used pharmaceutical formulations.[53]

The HME method is a continuous, controlled process with twin screw technology that yields an API that is consistently dispersed in the carrier matrix.

Since the HME process is based on amorphous solid dispersion in a carrier matrix, which offers flexibility in downstream processing and the capacity to produce a variety of formulation types.

HME allows the use of taste-masking methods;

Compounds that are insoluble in water have increased solubility and bioavailability;

Non-ambient, solvent-free procedure;

An economical procedure that runs continuously and has a shorter production time;

Sustained, customized and targeted release capabilities;

Active component criteria for compressibility are not necessary;

Stability at various pH, moisture levels and safety when used on people; Uniform dispersion of small particles;

Production of a variety of performance dosage forms with less unit operations.

CONCLUSION

Establishing the relationship between Pharmacokinetics (PK, concentration vs. time) and Pharmacodynamics (PD, effect vs. time) is an important tool in the discovery and development of new drugs in the pharmaceutical industry, especially the poor soluble molecules. The PK/PD relationship offers a pharmacokinetic foundation for estimating the therapeutic index and supports the design of effective dosage regimens for clinical proof-of-concept trials that are driven by pharmacokinetics and biomarkers. Based on abundant literature available in public domain, it can be concluded that use of HME, can be an effective formulation, the solubility and bioavailability of BCS class II and IV molecules can be increased depending on the drug's solubility in the polymer, drug physical state, or crystalline state. The *in vitro* and *in vivo* release characteristics of the drug can be significantly influenced by its physical state in the formulation. It entails treating a polymeric material above its Tg and usually over its Tm to achieve molecular-level mixing between the API and polymeric excipients through the use of heat and mechanical energy. We can state that the development of solid dispersions by using HME can be the most appropriate method for the development of pharmaceutical oral solid dosage forms. HME is not only cost-effective and time-saving, but it is also simple to increase in size, making it a perfect method for industrial production.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

HME: Hot Melt Extrusion; **PK:** Pharmacokinetics; **PD:** Pharmacodynamics; **APIs:** Active Pharmaceutical Ingredients; **ASD:** Amorphous Solid Dispersion; **BCS:** Biopharmaceutical Classifications; **PEG:** Polyethylene Glycol; **DSC:** Developability Classification System.

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