Review Article

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Recent Advances in Hot Melt Extrusion and Its Applications

Ratnaprabha P. Kinikar[1]
ORCID: 0000-0002-9045-406X
Ashwin B. Kuchekar[1]*
ORCID: 0000-0003-0496-6059

[1] School of Pharmacy, Dr. Vishwanath Karad, MIT WPU, Kothrud, Pune-411038, Maharashtra, India

Corresponding author:
Ashwin Kuchekar
School of Pharmacy, Dr. Vishwanath Karad, MIT, WPU, Kothrud, Pune-411038, Maharashtra, India
Tel: +91-9420627436
E-mail: ashwin.kuchekar@mitwpu.edu.in

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ABSTRACT

Over the decades the outcome of industrial compliance, manufacturing process, formulation and development, Hot Melt Extrusion (HME) also expanded the acceptance. As a result of industrial adaptability, it has developed itself into a wide range pharmaceutical research development. New drug entities face failures or delays during formulation development, including poor biopharmaceutical properties toxicity, lack of efficacy, or both. To overcome such obstacles, the HME technique is preferred one. In comparison to conventional techniques, its use is increasing because of its process, solvent free nature, cost effective, and on-line manufacturing. For achieving different applications, several dosage forms can be produced by altering the design of equipment and adapting a modified processing condition.

Keywords: Hot Melt Extrusion, Screw, Plasticizer, Solubility, Granules

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INTRODUCTION

Hot melt extrusion (HME) was introduced in the mid-nineteenth century in the plastic industry for the production of plastic bags, sheets, and pipes. After several modifications, special designs and quality of equipment are widely used in the pharmaceutical sector. HME is a process in which raw materials are introduced to an extruder having rotating screws. During the mixing of materials, two forces are generated: one is heat, and the other is shear force. Under these two forces, drugs and other excipients are melted and mixed uniformly to obtain the desired quality. This molten mass is further processed by downstream ancillary equipment to achieve the desired shape and dosage form of the product. Ghalanbor et.al produced implants of thermosensitive proteins or amino acids like Poly(lactic-co-glycolic acid using the HME technique to improve stability. The temperature of the extruder is generally above Tg (glass transition temperature) and occasionally above the melting point of the polymer. HME technology has been used to create 3D printed dosage types, taste masking, co-crystals, films, nanotechnology, implants, abuse-deterrent, microencapsulation, semi-solids, gastro-retentive drug delivery systems, the twin-screw granulation technique and solid dispersions. [1-5]

Based on their capacity, pharmaceutical HME is classified into development scale and production scale equipment. For R & D and clinical purposes, development scale extruders are used in which very less quantities of material are available, while larger quantities of material are needed for production scale. However, complex scenarios such as high temperatures during processing and energy input, shear rates and a lack of HME compatible excipients may have inhibited wider adoption of this technology. Withstanding the above drawbacks, employing innovative techniques such as Quality by Design technique, process analytical technology, and instrument modifications, which include design and geometry of screws, different shapes of dies, as well as the use of suitable additives like swelling agents (sodium starch glycolate), pH modifiers (Citric acid), foaming agent (CO2), and effervescent agent (Ascorbic acid), they can be overcome. [6-7]

For achieving desirable product quality and a variety of products, HME is used in conjunction with 3D printers as downstream ancillary equipment, as well as pelletizers and high-pressure homogenizers. Improvement in the efficiency of HME is obtained by using a PAT tool and QbD. They can help improve safety, avoid batch losses, and meet requirements. HME may make a major contribution to the on-line manufacturing platform, which is accomplished by optimising particular equipment parameters to manage batch processing limitations. Raman and near-infrared (NIR) spectroscopy, rheometry and UV/Visible spectrophotometry can provide in-process quality control and an awareness of the extrusion process, achieving high end-product quality. [8-11]

EQUIPMENT DESIGN and PROCESS

For the first time, El-Egakey et al. looked into hot melt extrusion as a manufacturing apparatus in the pharmaceutical sector. The HME technique consists of a hopper, an extruder, a screw, die or orifice, and ancillary downstream equipment and numerous controlling tools to ensure that the machinery is in good working order and that the extrudates are of the highest possible quality. The entry point of the extruder is a hopper into which raw materials are added. With the help of a single or twin screw, these materials are mixed and conveyed. This extruder comes out of an orifice known as a die, and the desired shape is obtained. There is no need for any die for formulations like co-crystals, salts, microsystems, granules, solid dispersions, semi-solids, or nano systems. [12]

The screws are grouped as single screw extruder (SSE), twin screw extruder (TSE) and multi-screw extruder (MSE) (Table.1). In the plastic industry, SSE is used due to its cost effectiveness and simple equipment design, but not in the pharmaceutical sector due to its poor mixing ability. In the 1930s in Italy, the twin screw extruder was invented. Two agitators are sited on a parallel shaft having co-rotating and counter-rotating screws, i.e., screws rotate in the same direction and different directions, respectively. This screw has two types, i.e., intermeshing and non-intermeshing screws. The gap between the shafts is similar to the diameter of the screw, which is known as a non-intermeshing screw. In contrast to this, in intermeshing screws, the centreline gap between the shafts is much less than the diameter of the screw. As compared to SSE, intermeshing TSE gives improved mixing in a homogenous solid system where the whole API is uniformly dispersed with other excipients. TSE has some silent features like self-cleaning

capability, shorter residence time, and low heating. Reduced wastage takes place due to the complete draining of material from the barrel, and it is beneficial when API has higher costs. The Multi-screw extruder (MSE) screw number ranges from two to four. Scale of the model for screws of extruder vary from 11 - 150 mm, with a length of the screw to its outside diameter ratio of 20 to 40:1, with 40 L/D being the most popular. Screw configuration is an important central element of HME operation in which capacity to convey and blend is considered. The helical screw does not deliver the effective mixing of API. But it is overcome in the case of a mixing screw/bi-lobed kneading where the efficient mixing of material is obtained.[13-15]

While extrusion is regarded as a one-step procedure, the process may be divided into subprocesses for better understanding.

- Material introduced into the extruder by the hopper
- Mixing of materials, discharging, and material extrusion
- Pumping-out through die
- existing raw material into the downstream process

The drug and raw materials are fed into a warmed extruder with dual/single screws and an orifice to create a final product with the desired size and shape. Parameters which are controlled in this process are rate of feeding, speed of screw and barrel temperature, while monitoring parameters are motor load and melt pressure. In the extruder, to obtain a constant amount of material, residence time, and steady shear stress applied to the material, the feeding rate of the materials and speed of the screw should be constant during the operation. The screw speed and feed rate have an effect on the motor load and melt pressure. To extruder screws are firmly fixed, and their special mixing geometry permits high-shear distributed mixing, resulting in the appropriate dispersive and distributive action (Figure 1). Screw speed, melting point, barrel fill, size of particle of materials, screw configurations and residence time are managed and observed in order to achieve a consistent and homogeneous product through the HME process. Various downstream ancillary elements now play a part in the extruded product's finishing, forming, and analysis. Chill rolls, conveyor belts, pelletizers and strand cutters are examples of these. [16-19]

Siyuan Huang et. al. has struggled to extrude heat sensitive drugs such as gliclazide by taking advantage of this benefit to reduce their sensitivity to higher extrusion temperatures and shorter residence times. HME is a versatile method for preparing solid dispersions transdermal, taste-masked preparations, topical products owing to the modifications made by scientists. A large number of patents and research papers have laid out a wider range of processes that could be effectively conducted using HME, contributing to innovative commercial products. The HME has established itself as a technology pioneer in the pharmaceutical industry due to its flexibility and ease of use. [20]

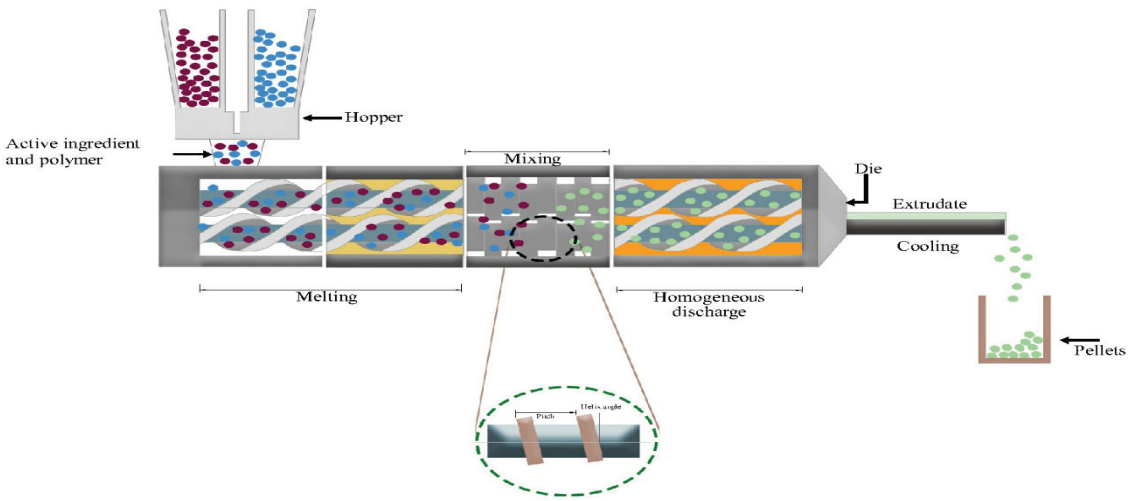

Figure 1. A twin-screw extruder of the HME process

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COMPOSITION OF HME MATERIALS

A pharmaceutical portion deforms within the heated extruder during HME processing and upon departure it solidifies. All products used in HME should be of equivalent integrity and effectiveness, and they should be free of contamination. For the selection of an API, various drug delivery systems are used, additives and carriers are needed in order for the HME process to run smoothly and continuously in order to obtain the target product. While materials stay within the heated barrel of the equipment for 10 sec-10 min (depends on L/D, design of screw, extruder type, and speed of operation), to minimise the chances of any possible degradation, higher thermal stability requirements will always be appreciated. The use of thermolabile products, on the other hand, is not prohibited by HME.[22]

1.Carrier

The selection of a specific carrier must be crucial in the design and preparation of a HME dosage form. The active ingredient is typically coated in a carrier mixture that often contains "meltable" material and additives. The melted material is usually a wax or a polymer with a low melting point. The carrier's physicochemical characteristics will alter the active compound's release from the end product. The compatibility of the active ingredient and the carrier should be considered in systems that use nonpolymeric carrier materials. Eutectic mixture is formed. A compound having a low melting point is added to a wax with a low melting point (MP), or the MP of the mixture is reduced, due to which solid dosage forms are inhibited. The carrier material chosen has a leading effect on the kinetics of drug release from hot-melt extruded formulations. To control the rate of drug release with the aim of covering the granules, waxes and polymers (water insoluble) such as carnauba wax or ethyl cellulose, have been used as carriers in hot-melt extruded dosage types (Table.2). [23,24]

2. Plasticizer

A plasticizer is a low molecular weight chemical compound that softens polymers and makes them more flexible. The addition of a plasticizer to the formulation throughout the processing of the extruded dosage form in order to advance manufacturing conditions or to improve the final product's mechanical and physical properties. An HME process can be performed with less torque at lower temperatures and with the addition of a plasticizer. Because of the improved manufacturing conditions, both the polymer and the drug product would be more stable during extrusion. Use of plasticizers in the manufacture of dosage forms must be effective, stable, polymer

Table 1. A commercial list of pharmaceutical-grade extruders [21]

Manufacturer	Extruder	Diameter of screw (mm)	Capacity* (kg/hr)	Screw type
Thermo Scientific	Pharma mini HME micro-compounder	Variable diameter	0.01 - 0.2	Conical co & counter rotating
	Pharm 11 parallel twin screw compounder	11	0.02 -2.5	Co-rotating multiple elements
	Pharma 16 HME	16	0.2 – 5	
	Pharma 24 HME	24	5 – 20	
	Pharma 36HME	36	20 - 100	
Leistritz	ZSE 18 HP PH	18	0.5 – 7	Co-rotating
	ZSE 27 HP PH	27	2 – 60	
	ZSE 40 HP PH	40	20 - 180	
	ZSE 50 HP PH	50	60 - 300	
DSM	DSM Xplore twin-screw micro-compound	Different diameter	--	Conical co & counter rotating

Table 2. Carriers used in HME [25]

Trade Name	Chemical Name	T_g(°C)	T_m(°C)
Kollidon®	Poly (vinyl pyrrolidone)	168	-
Avicel® PH 101	Microcrystalline cellulose	-	-
Eudragit® E	Poly (dimethylaminoethylmethacrylate-comethacrylic esters)	50	-
Sentry® plus	Poly (vinyl acetate)	35-40	-
CIBA HI	Epoxy resin containing secondary amine	80-100	-
Lunacera®Paracera®	Microcrystalline Wax	-	-

plasticizer compatible, and long-lasting. In hot-melt extruded systems, citrate esters, PEG (low molecular weight) and triacetin have been studied as plasticizers (Table.3). Surfactants, in addition to acting as solubilizers, have recently been demonstrated to be powerful plasticizers in the production of solid dispersions by HME. [26,27]

The drug itself will act as a plasticizer on occasion, including ibuprofen (IBP) and chlorpheniramine maleate. In 2002, Brabander characterized the plasticizing property of IBP and found that rising IBP concentrations lowered the glass transition temperature, which specifies the plasticizing effect. Repka (2001) studied that in the case of chlorpheniramine maleate, it acts as a plasticizer along with increasing elongation and lowering tensile strength. [28,29]

3.Other aids

Processing unplasticized or under plasticized polymers at high temperatures can cause polymer degradation. Antioxidants, and/or light absorbers may be added to polymers that are prone to degradation during HME to increase their stability. Based on their mechanism, antioxidants are categorised as either chain-breaking antioxidants or preventive antioxidants. Since oxidants, such as ascorbic acid, preferentially undergo oxidation, they can act as a preventative measure against autoxidation. Another form of preventive antioxidant is chelating agents like edetate disodium (EDTA) or citric acid. To make HME processing easier, other materials were used. Waxy materials such as glyceryl monostearate have been documented to serve as a thermal lubricant during hot-melt extrusion. Plasticization of polymers and improved drug absorption have been confirmed with vitamin E TPGS (Table.4). [30]

APPLICATIONS OF HOT MELT EXTRUSION

Some researchers focused their efforts on evolving dosage forms with the use of hot melt extrusion as an on-line manufacturing technology, and their findings were published. With the advances in conventional drug delivery systems, important growth has been made in the development of novel drug delivery systems based on hot melt extrusion technology.

1.HME along with three-dimension printing

Aprecia Pharmaceuticals created the first FDA-approved 3D-printed tablet, Spritam®, for treating epilepsy seizures. Resin-based 3D systems, extrusion-based systems, droplet-based systems, and powder-based systems are among the 3D printing technologies being investigated for various pharmaceuticals. The material is extruded under pressure in extrusion-based 3D systems, either as a liquid (premixed pastes or inks) or molten mass (heat-assisted). The outline of the extruded filament is 3D printed. The extrusion-based systems are fused deposition modelling (FDM)/fused filament fabrication (FFF), multiphase jet solidification (MJS), pressure-assisted micro syringes (PAM), and precise-extrusion deposition (PED) (Table 5). [31,32]

The company Stratasys®, trademarked FDM, which uses HME to produce filament with preferred properties for 3D printing (Figure 2). In FDM, before being applied layer by layer, a thermoplastic polymer filament is expelled and warmed through a noz-

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Table 3. Plasticizers Used in HME [27]

Name	Example
Fatty acid esters	glycerol monostearate, butyl stearate
Phthalate esters	dimethyl, diethyl, dibutyl, dioctyl phthalate
Surfactants	polyethylene glycol monostearate, docusate sodium, polysorbates,
Citrate esters	tributyl citrate, triethyl citrate, acetyl tributyl citrate, acetyl triethyl citrate,
Sebacate esters	dibutyl sebacate

Table 4. Aids for processing HME [30]

Aids	Example
Swelling agents	sodium starch glycolate, croscarmellose
pH modifiers	Citric acid
Foaming agent	CO_2 (Pressurized)
Antioxidants	BHT, BHA or ascorbic acid
Effervescent agent	Sodium Bicarbonate
Preservative	Methyl Paraben

Table 5. Extrusion based system of 3D printing

Sr. No	Extrusion based system	Specification
1	Fused deposition modelling (FDM)	Heating of filament, Poor Z resolution, Good XY resolution, Low operating cost and maintenance
2	Pressure-assisted micro syringes (PAM)	3D printing does not necessitate any prior thermal processing, establish thermosensitive drug delivery systems, Pressure is used to extrude viscous semiliquid or paste substance from a syringe.
3	Precise extrusion deposition (PED)	More appropriate than FDM and MJS, no need of filament, Pellets and granules can be processed
4	Multiphase jet solidification (MJS)	Extrusion of a melted paste layer by layer through a heated jet nozzle to create a three-dimensional product

zle. After each layer is deposited, the build platform moves down, and another layer is deposited on top of the previous layer. As the process progresses, the build platform moves vertically downward while the nozzle moves horizontally. Computer-aided design modelling allows for the formation of virtually any form or geometry object by layering on top of each other (Table 6). [33]

2. Solid dispersions by HME Solubility/ bioavailability enhancement

The most well-known applications of HME are the formulation of solid dispersions for the purpose of increasing solubility. By obtaining amorphous shape by crystalline shape of the active ingredient having low solubility by dissolving it in an inert carrier leads to higher solubility of that active ingredient. The amorphous structure has a faster dissolution rate

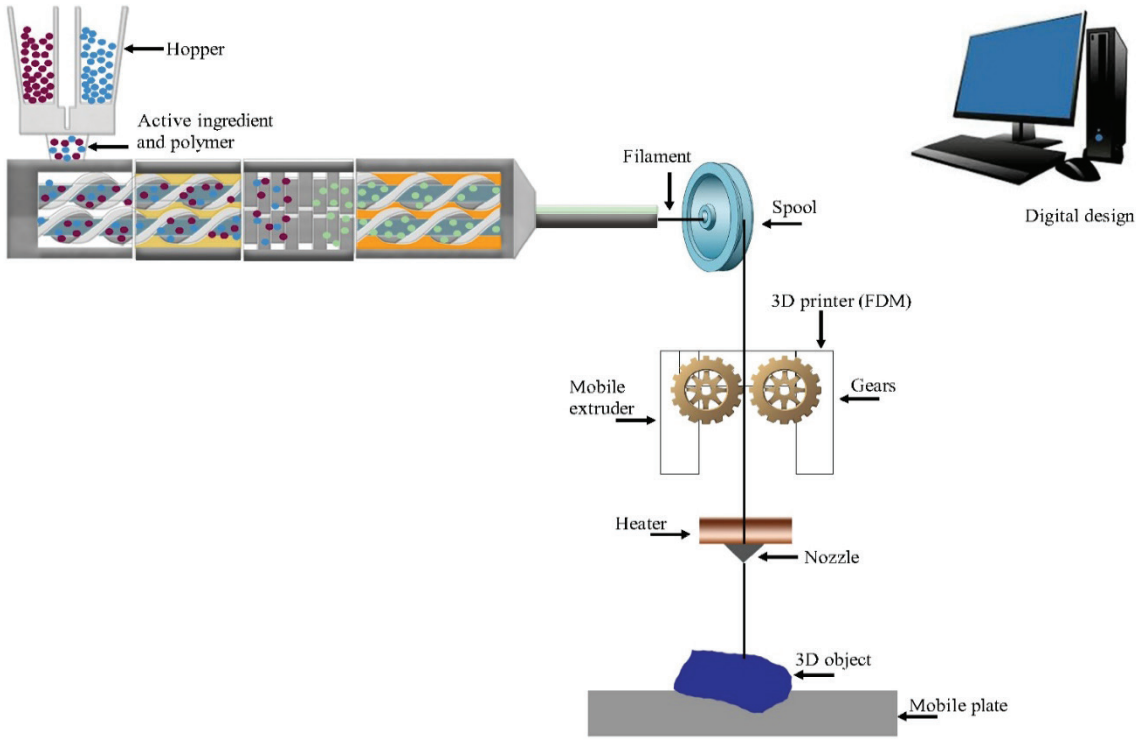

Figure 2. FDM 3D printing with HME

Table 6. Dosage forms developed by 3D printing [33-36]

Drug	Description	Use	Temperature (◦C)	Shape
Aripiprazole BCS class IV	Films made with a combination of FDM and HME technology had a positive dissolution rate and were equivalent to solvent cast films.	Antipsychotic	172 ◦C	Oro-dispersible films
Baclofen BCS class III	To combat drug errors that result in inadequate efficacy due to disorganised formulations, a tailored dosage type for paediatric patients has been developed.	Muscle relaxant	170 ◦C	Caplet-shaped (mini)
Indomethacin (IND) BCS class II	HME was used to create paediatric medicines with enhanced palatability by mimicking Starmix® 'candy-like' and sweets printing formulations using fusion deposition modelling.	NSAIDs	40–120 ◦C	Various shaped 3D printed tablet
Pramipexole BCS class I	An IR 3D printed tablet with a small dose (API-1 mg), few inactive ingredients, no need for any disintegrating agents.	Parkinson's disease	120–130 ◦C	Cylindrical shaped

and kinetic solubility can cause supersaturation of the API, increasing the bioavailability of compounds that are badly water soluble in the gastrointestinal fluid. The amorphous substances have greater free energy, which makes them thermodynamically metastable and entropically drives them to a highly stable crystalline state. Rather than using a pure amorphous active ingredient, researchers have attempted to stabilise the amorphous shape using other additives, resulting in the formation of amorphous solid dispersions (ASDs) in which composition is made up of a single-phase mixture of active ingredient and stabilising polymers. [37]

Equipment designs, processing conditions and material properties (polymeric carriers and API) are all intertwined in melt-extrusion-produced amorphous

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solid dispersions. In comparison to other traditional techniques such as melt fusion and solvent evaporation, HME technology has proven to be the most effective and efficient method for without the use of solvents in the production of SDs. During the wide-ranging development of solid dispersions, QbD techniques and effective design of experiment strategies will assist researchers in achieving consistent quality goods. [38]

Excipients with slow screw speed, lipid excipients (low melting), less moisture content, and a small number of particles were found to be effective in preventing void formation. Using HME technology to treat a variety of ailments, many researchers are actively testing and developing ASDs of various medicaments.

Sarabu et al. also looked into the stability and dissolution of amorphous solid dispersion made with Nifedipine and Efavirenz, the effect of different grades of hypromellose acetate succinate (HPMCAS) using HME technology. Even after three months of stability testing at 75% relative humidity at 40°C, the formed ASDs maintained their amorphous existence. With HPMCAS grades, Nifedipine solubilized better than Efavirenz, as per the research.[39]

3. Abuse-deterrent (AD) drug delivery systems

To achieve euphoric or sedative effects, one usually takes a higher-than-recommended dose or tampers with the manually manipulating shape or design of a product via a process such as grinding, crushing, or milling. United States regulatory bodies have determined that the dosage form that has been prescribed, especially to treat pain problems such as opioid analgesics used, may be easily abused (nonmedical usage or misuse). Drug abuse can take many forms, including oral, inhalation, nasal, parenteral.

Two of the most popular ways to create AD preparations are raising the tensile strength of a formulation to make it harder to grind/crush, and also making it more viscous so that it prevents IV abuse by adding gelling agents (Figure 3). Additionally, by reducing drug release or inserting unpleasant excipients to make it unsuitable for inhalation, dosages that are less effective or unpleasant may be designed to help avoid drug abuse. Due to its ease of availability, the anti-diarrheal drug Loperamide is often dubbed "poor man's methadone." Many people abuse this drug by taking higher doses, usually higher than 30 pills, to produce a seductive effect or to complete the need of opioid addiction. Nukala et al. used HME to build a loperamide AD and create a tablet dosage type with polymers (pH-sensitive-Kollicoat®, Smartseal 100P, and Eudragit® EPO) and a base (L-arginine). The process was done at a 250-rpm screw speed at 150° C. [40]

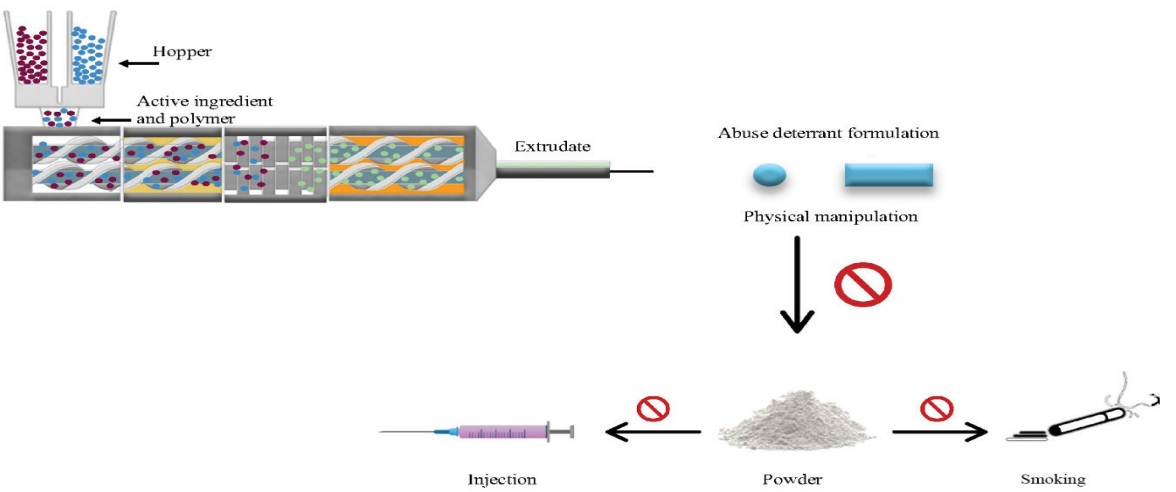

Figure 3. Methods and routes of abuse drugs and its formulation by HME

4. Co-extrusion

Co-extrudates were made up of two concentrically arranged polymer matrices: a lipophilic centre and a hydrophilic coat. The co-extrusion method involves processing two or more ingredients at the same time via an outlet with two or more orifices, at the end product merging (Figure 4). It is used in bi-layer or multi-layer tablet preparation. Management of two incompatible active ingredients or a changed release mechanism with an outer layer that protects the inner layer can be achieved by HME. [41]

Using an HME technique, Almajaan et al. produced a concentric multi-layered FDC. The aim was to attain different release behaviour from a single dose: Immediate release from the outer layer and Sustain release from the heart, respectively. Antihypertensive medications were selected to be hydrochlorothiazide and losartan potassium. [42]

5. Shaped drug delivery systems

When the melted extrudate leaves the extruder, it is formed into the proper cross-section by the extrusion die (flat, annular). The important aspect of the former drug delivery system is the configuration of the orifice that gives the extrudate the optimal configuration, dimension and shape. Shaped drug delivery systems can help monitor drug release by changing the region of the extrudate via geometrical variations (Figure 5).

5.1 Films

Thin films are used in a variety of drug delivery systems, including buccal, oral, sublingual, transdermal, ocular and vaginal, and can have both local and systemic effects. Because of their ease of swallowing and self-administering with their rapidly dissolving properties, thin films have emerged as a new drug delivery mechanism. Bio-adhesive films are being produced to increase the product's effectiveness by allowing the drug to be released over a longer period of time. For the production of implants and films, solvent-casting is the most widely used method. [43]

The solvent casting method is advantageous because it is a low-cost continuous process in which solvents are not required. Hot melt extrusion films are made by adding the drug, plasticizer, and film-forming polymer before passing them through a pre-heated hopper and moving them into the barrel (pre-heated) by a revolving screw. The molten state of the polymer, combined with mixing, allows for more uniform fine particle dispersion, which results in the drug's molecular dispersion improving bioavailability. Medicated solvent cast films also face a challenge in terms of drug uniformity.

5.2 Pellets

Pellets can be made using HME, in which the material is extruded using a melt pump or an extruder, then pumped through a die, chilled, and diced either

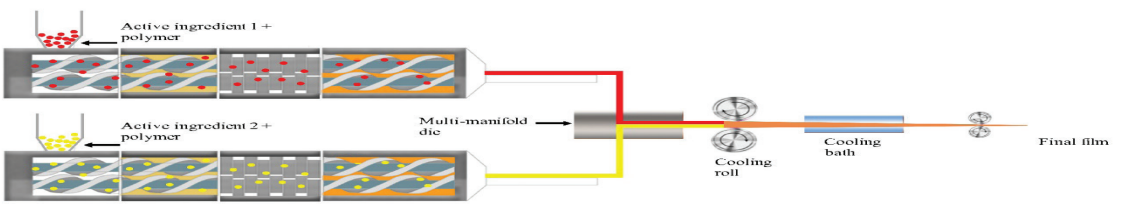

Figure 4. Coextrusion process with HME

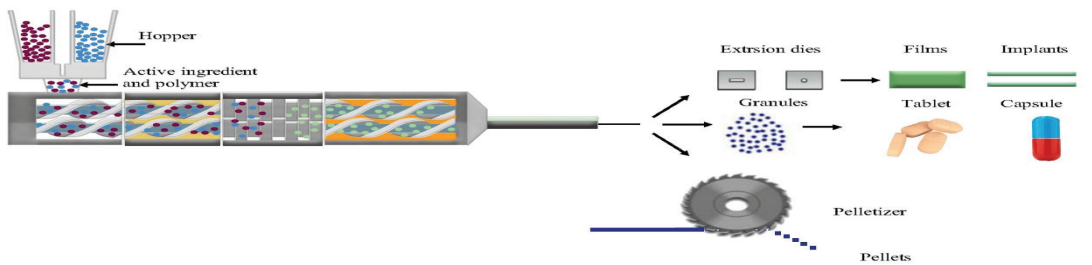

Figure 5. Formulation of various shaped drugs using HME

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manually or with the help of a pelletizer. Pellets may also be used to achieve desired dose strengths without changing the formulation or procedure. These systems have outstanding flow properties as well. The pellet drug delivery system has a number of advantages, including the ability to design and build a reliable oral drug delivery system with a great deal of versatility (suspension, tablet, capsule, sachet). Pellets are often blended with food additives to increase palatability. HME technology makes it simple to process pellets, which can then be further processed with a strand pelletizer. The temperature of the strand pelletizer's inlet and the pelletizer's ingestion speed has an effect on the final pellet consistency. [44]

For the paediatric population, pellets containing diclofenac sodium (Df-Na) were created by Vithani and Douroumis using HME technology to create Compritol® 888 ATO. The process was carried out at temperatures ranging from 50 to 75°C. The use of HME technology to produce high-quality pellets on a continuous basis means that even when a poorly soluble material is used, conventionally prepared pellets must be coated to prevent rapid drug release. HME's pellets are unique in that they're used for either IR or CR applications, based on the characteristics of the matrix polymer. [45]

5.3 Granules

Granulation is a particle-to-particle agglomeration process that improves the properties of materials, including tabletability, flowability, and homogenisation for easier management and downstream processing. Due to real-time monitoring, self-cleaning capacity of the screws, simple scalability, improved product consistency, and reproducibility, twin-screw granulation (TSG) is an appealing solution for granulation. Raman and 3D high-speed imaging camera, NIR spectroscopy, spatial filter velocimetry, photometric stereo imaging, and centred beam reflective measurements. For real-time monitoring processing, analytical tools are introduced for the TSG operation. [46]

5.4 Solid Implant

"Implantable drug delivery systems" are drug delivery devices that are inserted into the system and release drug (s) for a specific time period at a certain rate. In terms of increased residence time at the specific site, targeted and sustained drug delivery, minimized toxic effects, and abuse-deterrent properties, these systems outperform conventional methods. The ability to control the rate of mass extrusion by changing the extrusion speed and conveyer is a viable technique for obtaining consistent-quality implants. Oral solid dosage types do not face the same difficulties and requirements as implants.

Cosse et al. used HME technology to produce PLGA-based bio-degradable implants including a TSE protein. The chance of high-temperature protein denaturation during the extrusion step is greatly reduced since hot melt extrusion can be handled at minimum temperatures and for a minor time. The processing temperatures (initial-90°C and final-60°C) were set at 90°C and 60°C, respectively, to obtain effective PLGA workability and minimize thermal stress on the protein. In the extrusion process, both 5 mm and 9 mm extruders were used in this study by carefully monitoring the temperature. Novel drug delivery systems with special geometries and release actions can be designed with the help of HME for successful therapy. Using HME technology, effective implants with multiple APIs can be created quickly today. [47]

6. Semi-solid drug delivery systems

The development of semi-solids through hot melt extrusion is a less time-consuming and one-step process due to the direct melting and blending of the ingredients. The HME technique used to produce a variety of semisolid products such as creams, ointments, and gels. Mendonsa et. al. developed the poloxamer gel using the HME technique. The end extruded product is free of air bubbles, so no cooling units or de-aerators are needed, as with traditional methods. Since the barrel's screw elements play such a significant role in mixing, no additional scrapers or agitators are needed (Figure 6). The screw components are also important in the size reduction of particles. The high kneading and dispersing process of the mixing material leads to homogeneous distribution of the active ingredient in the melt mix with no lumps of the aqueous and oil phase when the aqueous and oil phases are mixed together. In addition, semi-solid manufacturing operations can be altered by applying different phases to different areas of a barrel to obtain the desired product quality while lowering the retention time for heat-sensitive products. Heat treatments in order to boost dosage stability and enhance the drug's thermodynamic effect on the transdermal membrane. [48-52]

7. Microencapsulation

Microencapsulation is a method of encapsulating, dispersing, or dissolving a drug material (core) within a coating material or matrix. As a result, a physical barrier is formed between the central agent on the inside and the outside atmosphere. The use of HME for drug encapsulation has a number of benefits, including the need for very few to no solvents, which lowers costs. It may also be used to mask the taste of unpleasant APIs and protect sensitive drugs. By enclosing the drug, it is easy to deliver it directly to a specific region, preventing any deterioration or harmful pH condition system that may interfere with it once it is administered. [53,54]

Using the HME method, Khor et al. produced microcapsules of quercetin by adding excipients such as zein or shellac, carnauba wax, for taste masking. Both microencapsulated formulations (zein, shellac) displayed good taste masking efficiency with carnauba-wax encapsulated powders. Based on the findings, HME microencapsulation may be a promising technique for creating taste-masked products, shielding drugs from the atmosphere. [55]

8. Self-Micro-emulsifying Drug Delivery Systems (SMEDDS)

SMEDDS (Self-Microemulsifying Drug Delivery Systems) is an isotropous blend of oils, surfactants, and possibly cosolvents with co-surfactant. SMEDDS are prepared to enhance the solubility of drugs having low soluble drugs. All these materials are introduced into the hopper where they are blended with the help of the screw in the barrel and a mix of SMEDDS is obtained. When these SMEDDS are introduced to an aqueous phase like gastrointestinal fluids, they emulsify into o/w emulsions and form agitations due to gastrointestinal motilities. Liquid SMEDDS have a few disadvantages, such as the need for costly soft gelatine, which leads to oily materials leaching out of the capsules. It may also be prone to chemical instability, resulting in API precipitation. Solid Adsorbing liquid SMEDDS onto a suitable solid carrier yields a free-flowing powder. As a result, solid SMEDDS is a good choice for improved bioavailability and durability, high permeability, easy availability, and precise dosing. [56-58]

9. Nanotechnology

Because of its lesser particle size and better dissolution characteristics, nanomedicine has spread into the pharmaceutical industry. It involves extended drug release, decreased repeated dose administration and improved cellular absorption, all of which improve the therapy's efficacy. Traditional approaches often encounter issues such as unreliable batch consistency and a relatively higher cost as a result of the numerous steps involved. To address these difficulties, researchers are turning to HME technology to create oral and topical nano systems that are both healthy for living tissues and possess unique properties. The conventional batch-based approach is still being used to make nanotechnology-based drug delivery systems including nanocrystals, nanostructured lipid carriers (NLC), nanosuspension, solid

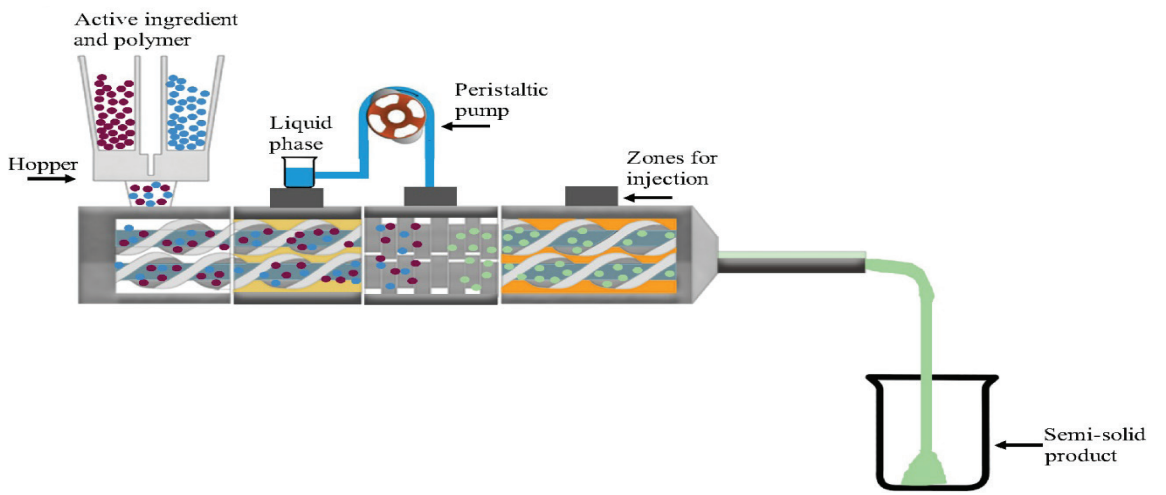

Figure 6. Formulation of Semisolid dosage form using HME

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lipid nanoparticle (SLN) and nano-emulsion. The advanced hot melt extrusion technique is now being used to formulate the aforementioned nano-systems in a unit phase or in combination with a probe sonicator/homogenizer (high-pressure) to further minimise the size of the particles. This technology has proven to be beneficial in the production of nanomedicine because it reduces batch-to-batch inconsistency, cost of production, and processing time. [59-63]

10. Co-crystallization by HME

By increasing stability, solubility, and delivery without altering the drug's physiologic functions co-crystals are formed to improve drug bioavailability. The co-crystallization system utilises a biomolecules synthon method, in which a drug's pharmacodynamic and pharmacokinetic properties are altered to improve the drug's poor aqueous solubility. A pharmaceutical co-crystal is made up of two main components: a drug and a co-former. The collaboration between a drug and a co-former is intensified in the HME process due to high shear and vigorous mixing, results in the formation of co-crystals without using solvents. Noncovalent bonds, such as H-H bonds, Van der Waals bonds, electrostatic interactions, and halogen bonding are used to interact between the drug and the co-former. [64]

Co-crystals are invented by Fernandes and Rathnanand using hot melt technology to enhance the solubility of carvedilol. A gravimetric screw feeder was used to feed a 1:2 mixture of carvedilol and nicotinamide into the barrel at 20 rpm. When hydrophobic carvedilol interacts with nicotinamide, its polarity is increased, which leads to an improvement in its potency. With a speed of 175 rpm, the four separate heating regions were set to 32°, 85°, 90° and 92°C respectively. Co-crystals increased its solubility by 4.79-fold, as equated to pure carvedilol, which was tested during the IV drug release analyses. The co-crystallization method was significantly affected by the processing parameters, which improved when the screw speed and temperature were modified (by fixing the temperature above the eutetic melting point co-crystals are formed). As a result, using QbD to better understand the effect of HME parameters on co-crystal formation is needed. [65]

CONCLUSION

Hot melt extrusion has been considered as a feasible solution for the advancement of drug delivery systems, despite being a relatively recent invention in the pharmaceutical sector. Since continuous extrusion is stable and repeatable, conventional batch processes are replaced using single and twin-screw extruders. For solubility improvement, online production, and PAT tools, HME has been widely used. In addition, this "green" technology expense, solvent-free, was presented and evaluated for product viability with 3D printing Fused Deposition Modelling (FDM) applications. In pharmaceutical science, HME has surpassed conventional techniques as a preferred technology for the production of novel drug delivery systems. HME was used to study a variety of drug delivery methods, including oral, parenteral and topical routes. The creation of these novel drug delivery systems was aided by the availability of wide spectrum HME polymers and excipients.

It covers a wide range of endless opportunities and technologies, including 3D printed dosage formulations, co-extrusion, AD formulations, semi-solids, chronotherapeutic drug delivery, nanotechnology, co-crystals, twin-screw granulation, and other uses.

It has some drawbacks, such as limited numbers of excipients are available, it is not suitable for sensitive microbial species, and maintenance of each piece of equipment is required. Since HME allows for the online manufacturing of dosage forms for a wide range of applications, this continuous manufacturing platform provides a real opportunity to address the pharmaceutical industry's crisis. HME, a paradigm-shifting tool, has been used to produce many items previously thought to be outside the reach of this method with only minor equipment and process modifications.

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