Hot Melt Extrusion: A Review of Recent Developments.

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Abstract: Hot-melt extrusion (HME) is a solvent-free, continuous, and efficient process for producing various pharmaceutical dosage forms. HME has gained significant attention in the pharmaceutical industry due to its ability to enhance the solubility and bioavailability of poorly soluble drugs, develop abuse-deterrent formulations, and create customized drug delivery systems. This review aims to provide an overview of the recent advancements and applications of HME in the pharmaceutical field. The review discusses the fundamental principles of HME, including the equipment, process parameters, and commonly used materials. It highlights the advantages of HME over conventional techniques, such as improved drug dissolution, enhanced stability, and reduced manufacturing steps. The review also explores the various applications of HME in pharmaceutical development, including: Solid, Abuse-deterrent drug delivery, gastro retentive drug, taste masking of bitter APIs using polymeric carriers, preparation of films for buccal, transdermal, and wound healing applications and veterinary medicine, such as the development of long-acting injectable formulations and taste-masked dosage forms for animals. The review highlights the recent advancements and applications of HME in the pharmaceutical field, demonstrating its potential to improve drug delivery and patient outcomes.

Keywords: Hot Melt Extrusion, Continuous Manufacturing, Form Conversion. Veterinary Medicine.

I. INTRODUCTION

The HME technique was effectively applied in the plastics sector in the 1930s after it was first shown to be effective in the production of lead pipelines towards the 18th century's end (1). After that, HME developed into a cutting-edge method of processing that allows for the creation of dispersion of API molecules into various matrices of lipid or polymer. Targeted, modified, prolonged, and time-controlled drug delivery has been demonstrated with this approach (2).

The ability of HME to create a range of dosage forms for drugs, including capsules, tablets, films, and inserts for transdermal, transmucosal, and oral drug delivery, has drawn significant interest from the pharmaceutical industry as well as from academic institutions (2). HME helps in making it feasible to process heat-sensitive substances or thermally unstable agents, including proteins, amino acids, and thermosensitive medications (3). HME works so well that it can replace some common techniques like spray drying and roll spinning.

In the HME procedure, Drugs and excipients that are pushed through an extruder having revolving screw components at degrees typically higher than the glass transition temperature (Tg) of polymers and frequently higher than the melting point (TM); lipids may be utilized in place of polymers (3). Drugs and excipients like lubricants, binders, additives, and so forth melt in the barrel to create molecular mixing, which produces extrudates with higher quality and better content uniformity (4, 5).

e FDA's (Food and Drug Administration) process analytical technology (PAT) scheme, is used to develop and analyze methods for managing multiple unit operations through the measurement of the parameters of critical processes that could influence key quality characteristics during the active extrusion process to achieve end product quality, is one of HME's main advantages. The process is well-proven (6). This is definitely a bonus because HME will easily go together with continuous manufacturing (CM) and a high degree of automation can be incorporated which will produce products which are highly reproducible. CM can be carried out by controlling the restrictions discovered during the processing of batches by calibrating certain instrument settings (7). For this reason, HMEs are now being combined with downstream ancillary devices like a 3-D printer (8), a high pressure homogenizer (9) and a

pelletizer (10). The usage of these paired equipments, as well as the US FDA's PAT system, allows for easy scaling up from lab to production scale.

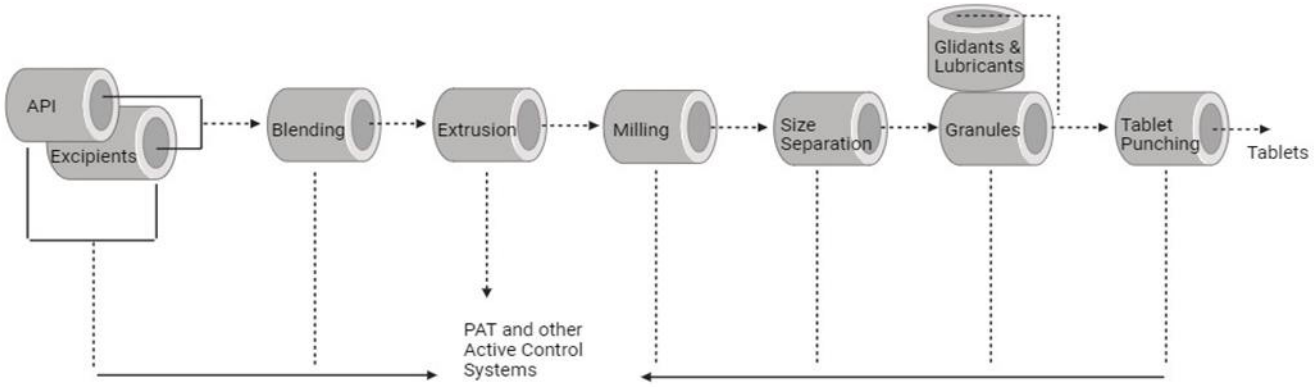

Figure 1 – Workflow of continuous manufacturing using HME

Figure 1 illustrates the various steps where PAT systems will be incorporated of continuous manufacturing of tablets.

Two goals are pursued in this review piece. The first is to fully describe the HME procedure and the materials used in it, as well as the roles of the designed extrusion instrument components. The second is to offer an overview of the application of HME technology in various drug delivery systems such as 3-D printed dosage forms, abuse-deterrent systems, GRDDS (gastro retentive drug delivery systems), implants, taste masking systems and drug-loaded films. Many formulations used in veterinary clinics today are formulated and intended for consumption by humans, with little attention to anatomy, physiology, and biochemistry between animals. The scarcity of commercially available medications specialized to veterinary pharmacotherapy needs additional research in this field (11).

II. Basic Workflow & Process Technology in HME.

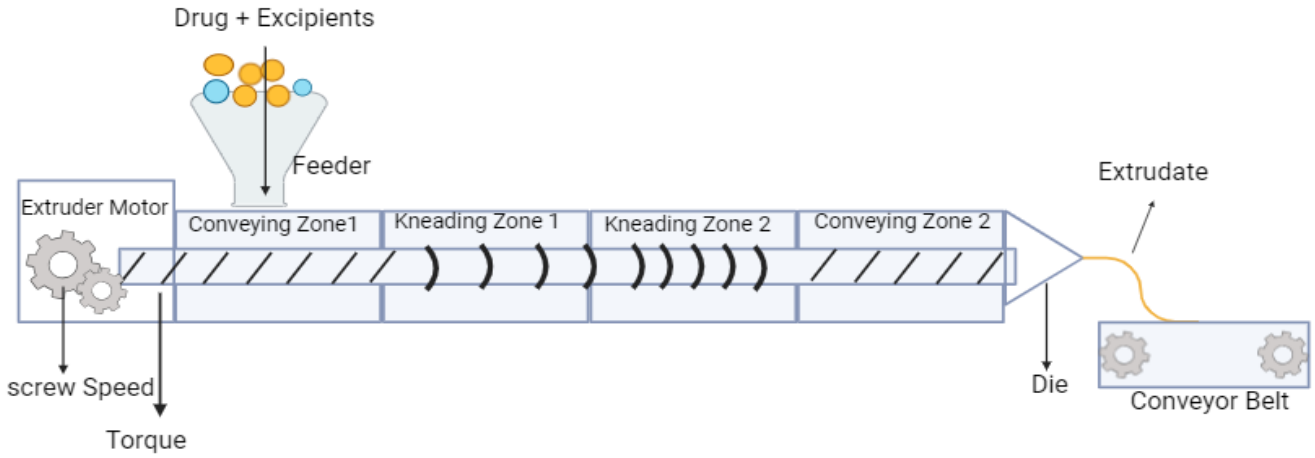

Figure 2 – Schematic View of Hot Melt Extruder.

This figure illustrates the working of a typical Hot Melt Extruder.

El-Egakey et al (12) first demonstrated the uses of HME in the pharmaceutical domain, their demonstration used poly (vinyl acetate-co-methacrylic acid) and an epoxy resin with a secondary amine as a carrier material. Extrusion is the procedure of passing raw materials through a barrel to produce a uniformly shaped and dense result, in hot melt extrusion-controlled heat and pressure are applied to raw materials, and the barrel is heated as well, the heat and pressure should be enough to melt our raw materials (13).

By categorizing the complete HME compaction process, the scientific approach to comprehending the HME process may be summarized as follows. (14)

(A) Extruder flowing through a hopper

(B) Combining, crushing, sifting, Venting, and kneading,

(C) Passing down the die, and

(D) Extrusion from the die and further downstream processing.

A fixed cylindrical barrel with one or more than one co-rotating/counter-rotating spinning screws within is what makes up an extruder. It is usually constructed in segments to shorten the duration of molten materials that need to remain inside the barrel. After that, the barrel's parts are bolted or secured together. The length of the barrel can therefore be changed based on the various raw material types that are employed. The shape of the extruded materials determines the end of the barrel to which an end-plate die is attached.

III. Extruder Types – Single Screw and Double Screw.

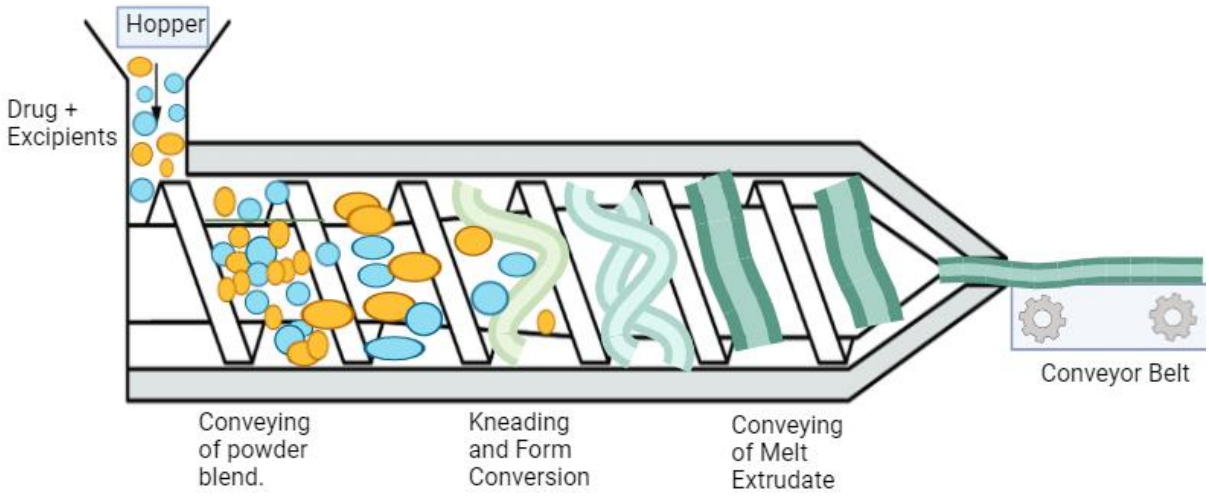

Figure 3 – Cross Section of Single Screw Extruder.
This figure illustrates the flow of material inside a single screw extruder.

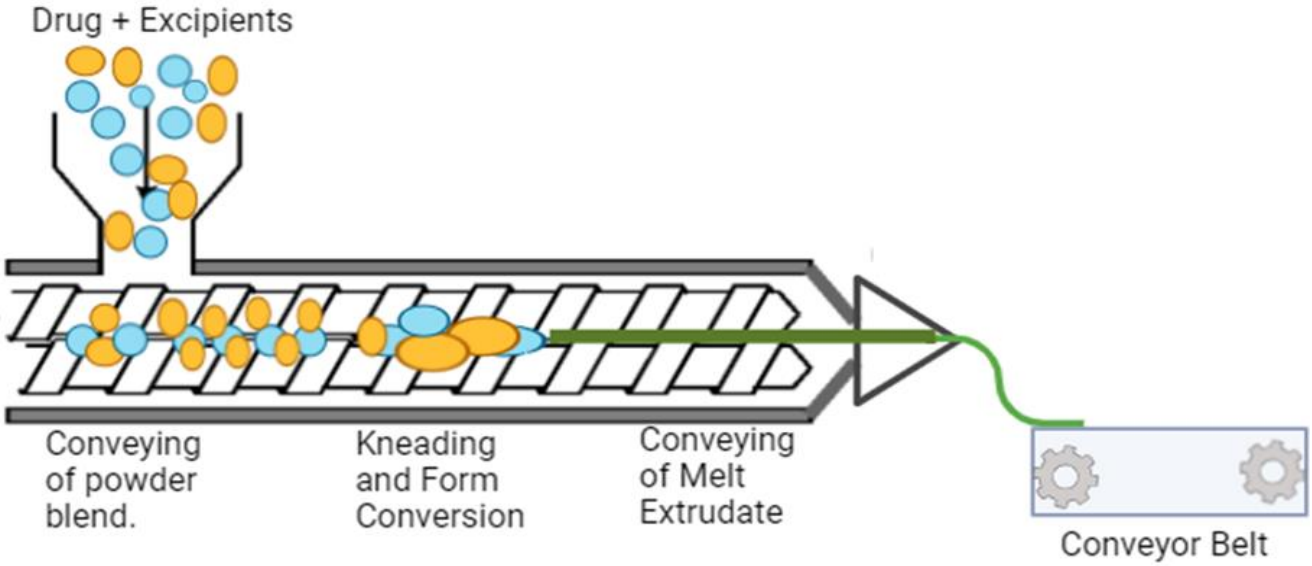

Figure 4 – Cross Section of Twin Screw Extruder.
This figure illustrates the flow of material inside a twin screw extruder

The basic need for all extruder types is that their single or twin screws must compensate for the torque and ensuing shear rate produced by the extruding substance while rotating at a sufficient predefined functional speed (15). There are two types of extrusion barrels: the Single Screw Extruder (SSE) which uses a single spinning screw, and the Twin Screw Extruder (TSE) which uses two counter-rotating/co-rotating screws. A standard extrusion setup consists of an extrusion barrel, a spinning screw, an extrusion die, and a motor that acts as a drive unit, not considering the size or kind of screw placed in the immobile barrel (14). A central electronic controller attached to the extrusion machine (16) controls the screw speed, temperature, and pressure. This electronic control system has a monitoring function as well.

A single-screw extruder comprises a revolving screw placed inside a still barrel (13). Because of their simple shape and inexpensive cost, SSE is commonly used in the plastics sector; however, their use for manufacturing dosage forms is limited due to their poor mixing capabilities. TSE was created to overcome the limitations of SSE. Two agitator units are mounted on opposite shafts to make up this configuration. The sizes of pharmaceutical extruder screw models range from 11 – 150 mm, which has a typical L/D ratio of 20 – 40:1, with 30 L/D being more frequent for pilot scale and even higher in production variations (17). These screws are frequently manufactured of surface-coated stainless steel for preventing the chances of any chemical reactions and friction (18).

A typical one-screw extruder has three distinct zones: feed, processing, and metering. Processes including mixing, kneading, and venting can also be carried out in the processing zone, which is often referred to as the compression zone. However, mixing is ineffectual when performed with the standard conveying screw component with a helical structure. Thus, a functional mixing component is required to prepare molecularly dispersed solid dispersion (SD) (19). Installing a bi-lobed kneading or mixing screw component to the screw was necessary due to the previously mentioned issue with a conveying screw component which was unable to provide sufficient blending (20). Different pressures are experienced along the screw's length throughout each of the zones due to variations in the pitch and depth of the axial and perpendicular screw flights. The pressure inside the feed zone is often kept low in order to facilitate continuous feeding via the hopper and moderate blending of an API, polymers, and additional excipients. As a result, the screw flight depth and pitch are kept larger than those in other zones. At this stage of the process, the extruder's pressure is quite modest, but as we proceed away from the feed zone, it gradually increases. By decreasing the screw pitch and/or the flight depth, this procedure allows the pressure to gradually increase over the length of the compression zone, providing the material with a high degree of mixing and compression. (13 & 17). Within each zone, Furthermore, the compressor zone not only homogenizes but also compresses the extrudate, allowing it to reach the barrel's final portion (metering zone) in a processing-ready state. The last zone, the metering zone, guarantees that the extruded end product has a consistent thickness, shape, and dimension while stabilizing the effervescent flow of the matrix. To maintain continuous high pressure and a steady delivery rate at which extrudates via the extrusion die, resulting in a uniform extruded product, a screw flight depth and pitch must be constant and steady.

The TSE has various advantages over SSE, including improved API mixing with other excipients, resulting in a homogenous mixture, self-cleaning capabilities, a lower tendency to overheat (owing to superior melt temperature control), and a shorter residence time. TSE will be categorized as 'intermeshing' or 'non-intermeshing'. The intermeshing TSE type is the utmost prevalent as it includes an auto-cleaning mechanism in the design, which avoids non-motion while also preventing the extruder from locally heating raw materials. An intermeshing configuration allows for a higher level of conveyance and significantly shorter dwell times. The non-intermeshing TSE is not as much of prevalent in blending applications as the fully intermeshing TSE because of its reduced capacity for auto-cleaning and weaker screw contacts. Non-intermeshing TSEs, on the other hand, are not vulnerable to excessive torque production while handling very viscous substances since they are not interconnected. As a result, these screws can be utilized to treat extremely viscous materials and extract sizable amounts of volatile chemicals (21). Furthermore, when a barrel lengthens, a screw's proportions alter, it generally increases with the length of the barrel. Additionally, the arrangement of the screws themselves can be altered because of the employment of complex designs such as kneading blocks, reverse-conveying and forward-conveying components, and other methods which are used for enhancing or managing the required level of mixing (22).

IV. Commonly used materials in the HME process

To run the HME process effortlessly and constantly and for the production of the desired product, an in-depth pre-formulation research must be carried out and on the basis of the findings a sensible selection of an Active ingredient, carrier, and excipient must be done. When processed by HME, the medicinal substance breaks inside the hot barrel and

solidifies as it exits the die. Every component of HME should be free of contamination, satisfy the safety and efficacy standards, and be of the highest quality (23). Even though the materials will pass from the heated barrel within a short period of time, i.e., anywhere from 10 secs to 10 mins (Depends upon L/D, screw design, extruder type, and operating speed). High thermal stability is always desirable in order to limit the likelihood of degradation. However, the use of thermolabile materials is not entirely restricted (24, 25) in reality, to maintain a constant flow of substances during the process, The ideal extrusion temperature is 20–30°C higher than the carrier material's Tg. However, it shouldn't be higher than the temperature at which any of the components inside degrade (26).

A meltable component and a functional additive are used to create a carrier system for the API's embedding. The polymeric or non-polymeric carrier system might be present. If the carrier is polymeric, it can be biodegradable (27) or non-biodegradable (28). Non-polymeric systems used are often waxes and lipids with low melting point (MP) (29, 30).

The compatibility studies amongst the APIs and carrier should be carefully considered for dosage forms that employ a non-polymeric carrier component. A wax with low MP may produce a eutectic combination when another low melting point component is added. Additionally, it might lower the mixture's melting point, which would stop the final formulation from coming out as expected (23). During the melt extrusion process, waxy substances such as carnauba wax (29) and glyceryl monostearate (31) are identified to serve as a thermal lubricant.

When employing a polymeric carrier, a plasticizer may be added to the polymeric carrier to either reduce the procedure temperature used in the HME procedure, or increase the mechanical and physical qualities of the targeted dosage form.Plasticizers are typically low molecular weight compounds that helps in softening of polymers to increase their flexibility. They function by raising the free space between polymer chains, which lowers a polymer's Tg and melt viscosity (32,33). Some examples of plasticizers used are fatty acid esters, phthalate esters, Vitamin E TPGS, citrate esters, propylene glycol, polyethylene oxide etc. During the HME process, pressurized CO2, which is known to act as a foaming agent, also had a plasticizing impact. (34, 35). The use of plasticizers has been seen to lower the melting temperature of polymers; examples of this include hydroxypropyl cellulose (38), PVP VA 64 (35), Eudragit® EPO (37), hydroxypropyl methylcellulose acetate succinate (39) and EthocelTM 20 cps (36), Sometimes due to the usage of certain APIs like Ibuprofen, chlorpheniramine maleate and hydrocortisone usage of plasticizers may not be required because these drugs can act as a plasticizer during the HME process (40, 41, and 42).

V. HME Applications

By utilising HME as a continuous manufacturing technology, many researchers are currently refocusing their efforts on developing dosage forms; the sections that follow discuss their research and accomplishments.

A. Three-Dimensional Printing

Pharmaceuticals can be produced using a variety of 3D printing techniques. The very first tablet approved by the Food and drug administration using 3D printing is Spritam®, contains levetiracetam, which is used to treat epileptic seizures, and is centered on the powder bed binding process (Zip Dose technology) (43).

Table 1 – Dosage forms made by coupling HME with 3D printing.

Pressure Assisted Microsyringes (PAM) (44), Precise Extrusion Deposition (PED), Fused Deposition Modeling

(FDM) or Fused Filament Fabrication (FFF), and Multiphase Jet Solidification (MJS) (45) are examples of extrusion-based 3D printing techniques. Pressure is used in extrusion-based 3D systems to push material into liquid (such as premixed pastes or inks) or molten mass (with the help of heat), which is then printed into the required 3D shape (46).

Real-time monitoring and control are necessary when combining HME with any extrusion-based 3D printing as a continuous manufacturing process to make sure both phases are coordinated. Recently, several methods have been investigated as PAT tools for HME, including Raman, NIR, MIR, FTIR, and UV/VIS. However, these tools can only be used to a limited extent in FDM 3D printing for pharmaceuticals. PAT tools are nondestructive and offer continuous, high-throughput material screening throughout the manufacture of pharmaceutical products. (S Tambe- 45,46, 43,47,48,49).

Borujeni et al. (50) synthesized carbamazepine (CBZ) matrix tablets using ethyl cellulose, hydroxypropyl cellulose (HPC), as the matrix polymeric material, and triethyl cellulose as a plasticizer to achieve zero-order kinetics. Sufficient

plasticizing effect during the process is essential for smooth operations. This plasticizing effect can be achieved either by the addition of a plasticizer (such as triethyl cellulose), because of the drug's plasticizing impact (as in the case of Ibuprofen containing formulation) or a combination of both. The absence of a plasticizer would result in brittle filaments which will break under the pressure of moving gears.

Similarly, many formulations using HME & FDM 3D printing have been developed that showcased Sustained Release

Drug used	BCS classification	Route of Administration	Dosage Form	Polymers	Reference
Carvedilol	BCS Class II	Oral	Cylindrical extended-release tablet.	Hydroxypropyl cellulose, Affinisol™ 15LV, Kolliphor® TPGS, Eudragit® EPO, Kollidon® SR,	82
Pramipexole	BCS Class I	Oral	Cylindrical immediate-release tablet.	Eudragit® EPO, Poly (ethylene) oxide	83
Riboflavine-5'-phosphate sodium	BCS Class III	Oral	Capsule for Enteric release.	Eudragit® L100-55, polylactic acid, polyethylene glycol 400,	84
Baclofen	BCS Class III	Oral	Caplet for immediate release.	Polyvinyl alcohol, sorbitol	85
Hydrochlorothiazide (HCT)	BCS Class III	Oral	Caplet for immediate release	Parteck® MXP (PVA)	86
Indomethacin (IND)	BCS Class II	Oral	Bottle, Heart shaped tablet.	Hypromellose acetate succinate, PEG	87
Aripiprazole	BCS Class IV	Oral	Orodispersible films.	Polyvinyl alcohol	88
Quinine	BCS Class I	Parenteral	Hollow cylindrical implant for sustained release.	Eudragit® RS, Ethylcellulose polycaprolactone, and poly (Lactide) (PLLA)	89

(SR) profile such as Dronedarone HCL preparation for cardiac arrhythmia (51), SR formulation containing Theophylline (47).

The absence of quantitative tools for characterization to assess the filament's printing capacity is one of the primary problems with the FDM application. To address this problem, Xu et al. (52) looked at three texture analysis techniques in addition to a metric called "Toughness" that quantifies the evaluation of filaments for FDM.

Coupling 3D printing with HME provides great benefit over conventional methods as this setup avoids one size fits all approach and presents versatility and accessibility for various applications.

B. Abuse-Deterrent Drug Delivery System

The prescribed dosage form, particularly opioid analgesics used to treat pain conditions, has been identified as being easily abused (nonmedical use or misuse) by several government health organizations as well as Non-Governmental Organizations. People usually take these medications at larger dosages than prescribed or physically modify the dosage form, by methods like crushing, grinding, or milling, to experience ecstatic or sedating effects. (53). There are various ways to abuse drugs, including oral consumption, nasal insufflation, parenteral injection, and smoking (inhalation) (54). In order to create abuse-deterrent (AD) preparations, the most popular approaches are to mechanically stiffen a dosage form, make it harder to crush or grind, add gelling agents to increase the viscosity of aqueous extract (55), and restrict intravenous intake. Drug misuse can also be reduced by creting formulations that are not satisfactory or pleasant,

slowing down the release of the drug, incorporating bitter excipients, or rendering the substance unfit for inhalation (56). (57, 58).

Given that the main purpose of any dose form is to administer medication and not to deter their release, this makes the process of developing an AD dosage form very difficult. Research is going on towards the use of employing HME to develop AD formulations. Some of them are discussed here.

Loperamide has frequently been abused by taking more than 30 or so tablets together to gain euphoria and it has also been used by those individuals who are fighting opioid withdrawal. The easy availability makes this social problem even worse.

An HME-based tablet dosage form was created by Nukala et al. (59), which contains pH-responsive polymers (Kollicoat® Smartseal 100P and Eudragit® EPO) and a trace amount of base (L-arginine). The rationale behind the selection of these excipients was the possibility that the release of loperamide when several tablets are ingested simultaneously may be efficiently controlled by L-arginine and other components arranged in a pH-dependent polymeric network. This is because the large amount of L-Arginine incorporated in the polymeric network would raise the ph of the surrounding medium and prevent the ph sensitive polymer from releasing Loperamide, this deterrent mechanism would only kick if large number of dosage forms are consumed together thereby preventing abuse.

Other examples would include the preparation of an aversion liquid-filled capsule (Siddhant Palekar, aversion liquid-filled capsule), the aversion liquid would result in instant gelation and formation of large non-snortable particles. Siddhant Palekar et al used Metformin as their model drug, the model drug loaded polyvinyl alcohol (PVA) filaments were prepared using HME and 3D printer was used to shape it in the style of a capsule. The aversion solution to be employed in these capsules was formulated by blending sudan black and sodium polyacrylamide starch in oil base. Arun Butreddy developed a formula for ER pellets that inhibit intravenous misuse. (60) using high molecular weight polyethylene oxide, xanthan gum as a gelling agent and Acetaminophen as a model drug. In comparison to plain PEO pellets, the PEO in addition to the xanthan gum-based formulation had a greater viscosity, injection pressures, and smaller syringeable volumes. In addition, physical manipulation tests such as crushing and thermal manipulation (oven and microwave) were carried out. It demonstrated that the pellets were undamaged, extremely rigid, and resistant to manipulation that would circumvent ER properties. The behavior mentioned above of the pellets was showcased because of xanthan gum's quick hydration and swelling tendency, which made it difficult to draw it using a syringe (syringeable), as well as to perform IV injections using a syringe.

Table – 2 Application of HME to create abuse-deterrent, nanosuspension, multi-component system, and semi-solid dosage forms.

Drug Used	BCS Classification	Route of Administration	Dosage form	Polymer	Reference
Metformin	BCS Class III	Oral	Egg Shaped tablet (Abuse deterrent System)	Polyvinyl alcohol, sorbitol	90
Ibuprofen	BCS Class II	Oral	Tablet with Co-crystals.	Nicotinamide is the coformer.	91
Ketoprofen	BCS Class II	Topical	Topical gel.	Kolliphor® P407	92
Clotrimazole	BCS Class II	Topical	Nanosuspension	Soluplus®, microcrystalline cellulose	93
Lidocaine	BCS Class I	Topical	Polyelectrolyte complex (sustained release)	Eudragit® L100-55	94
Naproxen	BCS Class II	Oral	salt	Meglumine (MEG),	95

				Soluplus®, Kollidon® VA64, Kollidon® K30	
Progesterone	BCS Class II	Parenteral	Sustained release depot injection	Poly (lactic-co-glycolic acid) (PLGA) copolymers (lactide: glycolide molar ratio of 50:50)	96
Theophylline	BCS Class I	Oral	Co-crystal.	Nicotinamide as co-former, polyethylene oxide, HPMC AS, Kollidon® VA64	97

C. Implants

HME technology is being used to develop several types of implantable drug delivery systems. Some of them are mentioned here: Intravaginal ring (IVR) made up of Polyether Urethane (PU) elastomers that contains anti-hiv drug UC 781 showcased sustained delivery of the drug.

A microbicide intravaginal ring (IVR) for the continuous delivery of UC781, a highly efficient nonnucleoside reverse transcriptase inhibitor of HIV, was designed and created using polyether urethane (PU) elastomers. Hot-melt extrusion was employed to make PU IVRs containing UC781. UC-781 is classified as a non-nucleoside reverse transcriptase inhibitor (NNRTI) thiocarboxanilide. It is a topical microbicide designed to target AIDS.

The use of Tenofovir's oral dosage has been proven to be effective against HBV and is known to increase the life expectancy in HIV infection. However, missing a dose is associated with increase in the duration of infection, to mitigate this, Simpson et al. (61) developed subcutaneous implants of Tenofovir alafenamide for subcutaneous administration. Antiretroviral medication could be delivered via these long-acting reservoir implants for more than ninety days.

The formulation was in pressed pellet form which was prepared by extruding polyurethane (PU) tubing and drug via HME.

Since HME process can be carried out even at lower temperatures therefore it can also be used for the formulation of proteinaceous drugs. This is because at lower temperatures the risk of heat induced protein denaturation is very low. Coss´e et al. (62) conducted a study wherein they developed PLGA-based biodegradable implants that contain proteinaceous drug using HME. In the study the processing temperatures of the extruder were carefully controlled, temperature of initial zone of extruder was kept at 90 ◦C and the end point of extruder was kept at 60 ◦C. It is noteworthy to acknowledge that the drug's residence period within the extruder is relatively short,this also contributes in lowering the risk of protein & peptide denaturation due to heat.

D. Gastro retentive Drug Delivery System (GRDDS)

For any GRDDS gastric retention is a fundamental characteristic. To achieve gastric retention HME technology provides a variety of mechanisms.

Fabian J Simons et al (63) using HME developed hollow tubes which were sealed at both ends, such tubes would resist gastric emptying by floating in the gastric fluid. The drug chosen was Metformin, its crystals were incorporated in the tube wall which in turn was made up of Eudragit® RS PO and E PO. This formulation could release the drug in sustained release format from anywhere to 4 hours to 12 hours, depending upon the amount of the drug loaded in the matrix, the study also demonstrated that the drug loading in the polymer matrix could be as high as 80% w/w without the risk of burst release. Buoyancy was mostly reliant on the ratio of outer diameter to inner diameter this means amount of the drug loaded in the polymer matrix could be adjusted depending upon the desired potency of the drug, without running the risk of affecting the buoyancy.

One more study was performed by Manjeet Pimparde et al (64) in which the authors prepared GRDDS that would resist gastric emptying by a dual mechanism. The two mechanisms were bio-adhesiveness and buoyancy. The drug chosen was felodipine and was in a crystalline form but it went from being in crystalline state to an amorphous state during the melt-extrusion procedure, where it was disseminated and "frozen" in the polymer matrix. The polymer matrix was made up using Hydroxypropyl cellulose and Hypermellose. These floating bioadhesive foam pellets which were loaded with the amorphous solid dispersion of felodipine were created in a single step of HME. These pellets had the appearance of foam pellets because of the porosity which was imparted to them due to the expansion of CO2. The CO2 was generated by Sodium Bicarbonate which was also incorporated during HME process. Naturally the percentage Sodium Bicarbonate incorporated was found to affect the buoyancy the most. Invivo drug release studies found that it was controlled till 12 hours.

E. Taste Masking

Bitter API taste masking is a major difficulty in the manufacture of orally disintegrating tablets (ODT). By employing flavor-masking polymers to make solid dispersions, HME is a successful method for masking the bitter tastes of a variety of APIs and preventing the patient's taste buds from coming into touch with the bitter medications.

In research, Sultan M. Alsheri et al. (65) employed Eudragit to formulate the medication utilizing HME and solid dispersion technology, thus masking the bitter taste of mefenamic acid. Based on the results of the FT-IR, SEM, and dissolving tests for the extrudates, two ideal formulations (20% and 25% drug loads) have been selected for the formulation of the oral disintegrating tablets (ODTs). Manufactured ODTs were seen to possess not only the desired taste-masking action but also good friability and a short disintegration period. All extruded formulations and the ODTs were found to be chemically and physically stable after testing for six months at 40 °C/75% RH and twelve months at 25 °C/60% RH, respectively.

In another study conducted by Andreas Gryckze et al (66), the unacceptable taste of Ibuprofen (IBU) was masked by dispersing the drug in methacrylate copolymer (Eudragit) matrix, solid dispersions of the drug, and the polymer matrix was prepared using HME processing. To make ODTs from the granules, a direct compression technique was employed. During the compression process, several ratios of super disintegrants, such as crosslinked polyvinylpyrrolidone and sodium croscarmellose, were utilized to produce tablets with the appropriate hardness.

F. Films

Films are thin sheets that are made by using one or more polymers, plasticizers may or may not be incorporated in their formulation, and these films have been used as drug delivery devices. The most extensively used approach for film casting is the solvent casting method, in which the polymers are allowed to dissolve in an appropriate organic solvent to produce a viscous gel, which then is poured over a suitable cast, and the organic solvent is then allowed to vaporize. This leaves behind the polymeric film. Many of the organic solvents used are hazardous to human health and the residual solvent which is left after the drying process can negatively affect human health (67-70). This is one drawback of this method of film casting other drawbacks include decreased film elasticity when aging is taken into account (71).

When it comes to film casting, there are certain advantages of using HME. For instance, there are fewer manufacturing stages and no solvents are used. In actuality, among the primary advantages of HME is its capacity to produce extrudates in a single processing step, which is extremely cost-effective. There is also no necessity for compressing the active components and excipients together. A more consistent distribution of fine particles is made possible by thoroughly mixing the polymer before it is melted into a molten state. HME films are produced using a simple procedure that involves mixing the right quantity of polymer, medication, and plasticizer into an evenly powdered mix before feeding it to the hopper into the already heated extruder and transferring it into the heated barrel via the rotating extruder screw. It is possible to create homogeneous sheets with thicknesses that are typically less than 1 mm (7). For the finished film to be flexible and simple to handle and easily applicable at the action location, the plasticizer is needed. In order to ensure that the film remains adhered to the mucosal surface long enough to facilitate drug absorption or action, a bio adhesive material may also be required at times.

By combining HME and 3D printing, Rasha M. Elkanayati and colleagues (73) created mucoadhesive oral films for treating xerostomia. The primary saliva-stimulating components in their composition were Xylitol and Adipic acid, with Polyethylene Oxide N80 (Polyox-N80) serving as the polymeric carriers. Upon quantification of the adipic acid concentration in the printed films by high-performance liquid chromatography, the results indicated a consistent film composition and a satisfactory medicine release. More than eighty percent of the adipic acid was released in fifteen minutes, and thirty minutes later, it was entirely discharged. The DSC thermographs of the printed compositions revealed that the adipic acid was dispersed throughout the polymer.

Dilipkumar Suryawanshi et al. (74) developed orodispersible films (ODFs) loaded with vitamin B12 (Cyanocobalamin) using the film-forming polymer Soluplus® employing the hot-melt extrusion method. The amount of Soluplus®, glycerine, and menthol in the combination had a substantial influence on the time of disintegration, tensile strength, dissolving, and rate of permeation of the films. When put through physicochemical characterization experiments, melt-extruded films produced satisfactory findings. All melt-extruded films broke down quickly and completely dissolved within 10 minutes. Ex-vivo permeation experiments showed that melt-extruded films had a higher cyanocobalamin permeability than normal drug solution. Cyanocobalamin was uniformly distributed across the surface of the tailored film, as revealed by SEM and AFM measurements. The stability of cyanocobalamin after HME processing was verified by Raman spectroscopy.

G. Applications of HME in veterinary medicine.

The safety and efficacy of medicine for species other than humans is also equally important. Therefore, before administering a dosage form to any species, it is essential to conduct pertinent pharmacokinetics and pharmacological studies of the dosage form. These studies will help us develop appropriate dosage form for our species of interest. Scientists are now looking into HME in the context of animal medicine in order to fully reap the advantages of this technology. To provide the best possible therapy for animals, HME can develop personalized, customized, and sustain pharmaceutical delivery systems. This lowers the financial and time costs while also limiting the stress that animals experience from management, dosing, and confinement. (75, 76).

A broad-spectrum livestock antibiotic of the chloramphenicol (CAP) family is Florfenicol (FF). FF has some disadvantages, including hydrolysis at low pH levels, bacterial resistance, and stomach irritation. To find a solution Xu et al (77) utilized HME to formulate an enteric formulation of FF containing AquaSolve™ (Hypromellose Acetate Succinate- HPMCAS) as the polymer. For the characterization of the HME extrudate several analytical techniques were carried out namely differentiating scanning calorimetry (DSC), thermogravimetric analysis (TGA), powder X-ray diffraction (PXRD), and fourier transform infrared spectroscopy (FT-IR). In a three-stage dissolution analysis, it was found that >80% of the loaded FF was released in the phosphate buffer media while only 10% of the loaded FF was released in the acidic media. Pharmacokinetic studies were carried out in which the prepared formulation exhibited longer t1/2 and longer mean resident time (MRT) than FULAIKA® (commercially sold FF product).

A method called ballistic drug delivery allows the drugs to be delivered from a secure distance without the need to confine the animal (78) Such a transportation method has many benefits. Some of its characteristics include multiple drug delivery, adaptability in designing hollow reservoir systems to accommodate different combinations (solid, semi-solid, or liquid); customized dosages for a single person (animal-specific systems based on age, gender, species, etc.); minimal or no interaction from wild animals without the need for anesthesia; and treatment that is reasonably priced. treatment. The possibility of using HME technique and 3-D printing as a prototyping technique to create and distribute drugs used in animal has recently caught the attention of academics.

Long et al. (81) created a formulation with biodegradable projectiles containing progesterone (2, 5, and 10% w/w) and PLA as a carrier using HME in conjunction with additive manufacturing (3-D printing). After the additive-manufactured projectiles were assessed for their in vitro drug release, the scientists observed that the manufactured projectiles were effectively able to extend the drug release for an extended period (>5 months) at a predetermined rate. Veterinarians frequently have to compel an animal to take a tablet or pill by forcing the oral solid dose from deep within its mouth while administering medication orally. However, the process carries a high risk of failure as the animal may simply spit out the tablet. Another way is to ask owners/caretakers to put the medication in between pieces of meat, cheese, or other food items (79). The animal can ingest the medication owing to this procedure, although it is also possible that there might be a decreased bioavailability due to drug-food interaction. Therefore, even in the case of veterinary dosage forms, taste masking is an equally important step in the formulation of bitter drugs. One such attempt was made by Yan et al (80) in which they used the polymer Eudtagit® EPO to mask the taste of Tilmicosin. The usage of the macrocyclic antibiotic telmicosin in veterinary hospitals is restricted due to its strong bitter taste. Tilmicosin was extruded with Eudtagit® EPO at a 30% drug loading temperature and screw speed of 100 RPM at 135 °C. In the study, the prepared formulation was compared with two marketed products of Tilmicosin. First was Pulmoil® which is a commonly marketed product premix, drug release studies showed similar drug release patterns in both formulations but the developed formulation showed a higher taste masking effect. The other marketed product with which the developed formulation was compared to was enteric-coated granules called Tilexin. The developed formulation showed higher bioavailability.

VI. Recent scenario of Patents on HME.

Given how useful HME technology is for drug formulation & drug delivery, there is a lot of academic and industrial study being done to determine how to market such goods. The limitations of traditional medication delivery methods are driving researchers to innovate, which is increasing the number of HME patents. A description of a few of the most current HME inventions can be found in the table number 3.

Table 3 : Recent patents granted to inventions that used the HME process.

Serial Number	Patent Number	Patent title	HME details	Drug	Patent issue year	Reference
1	US10596118B2	Solid dispersions	HME was used to develop solid dispersions of Ospemifene to achieve higher solubility and bioavailability.	Ospemifene	2020	98
2	US10493033B2	Oxidation-stabilized tamperresistant dosage form.	HME was used to develop a dosage form by the process of thermoforming. The developed dosage form was found to have hardness of 300N	Oxymorphone HCl	2019	99
3	US10034883B2	Poorly soluble drugs of Mesoporous dosage forms	HME is utilized to give solid dispersions which in turn enables homogenous covering. This invention reduced the total amount of required polymer material which was normally used for same process.	Rivaroxaban, IBU	2018	100
4	US9867786B2	Alkaline labile drugs containing Stabilized compositions	This patent(s) details the development of a bioadhesive system using HME that incorporates an alkali-sensitive medication, acidic excipients, and an alkaline thermoplastic polymer.	Testosterone	2018	101
5	US9980974B2	Intraocular implants	To deliver Prostamide for	Prostamide	2018	102

		containing prostamide and their application techniques	a long time using biodegradable intraocular devices that contain polymers like PLA, PLGA, etc.			
6	US10265270B2	Decoquinate solid dispersion, a method of preparation, and its use.	A solid combination containing 5–30% decoquinate, 60–90% polymer, and 0–10% detergent was made using HME.	Decoquinate	2019	103
7	WO2015071394A1	formulation of chemicals by hot-melt extrusion that are sparingly soluble.	The creation of sparingly-(water)-soluble compounds is described in the patent, along with its application as (or within) a dietary supplement or feed item that uses HME to boost bioavailability and stability.	Carotenes	2018	104
8	WO2018178295A1	Valsartan with sacubitril-containing stable hot-melt extrudate	The process described in the patent involves employing HME to create solid edible forms of dosage (granules or pills) that contain a solid dispersion of valsartan and sacubitril in a polymeric matrix..	Sacubitril and Valsartan.	2018	105
9	US9827202B2	Extrusion of modified-release multi-particulates	The formulation, manufacturing, and embedding of modified-	Theophylline	2017	106

		using hot-melt method	release multi-particulate granules in thermoplastic polymer, lipophilic matrix, or a combination thereof are all described in the patent. It also discusses the creation of enteric matrix pellets using HME in a single process, eliminating the need for additional film coating and the use of organic solvents.			
10	US20170119669A1	a stable HME formulation including small medication particles.	In this invention, HME technology was used to distribute tiny amounts of the drug into a solid, soluble polymer. The created product that has been released has steady released characteristics for an extended period of storage	Itraconazole, Danazol	2017	107
11	EP2837391B1	The hot-melt extrusion composition, hot-melt extrusion carrier, and hot-melt extrudate production process all involve the utilization of hypromellose acetate succinate.	In this innovation, HPMCAS was used as a carrier while HME was used to make formulations.	Nifedipine	2017	108

12	US9642809B2	pharmaceutical formulations with controlled release for extended effects.	In this innovation, a layered pharmaceutical composition for oral medication delivery was constructed by sandwiching a solid middle layer between 2 outside layers.	Hydrocodone, Morphine, Oxycodone, Paracetamol	2017	109
13	US9757466B2	Techniques and materials to discourage misuse	Formulations designed to discourage misuse were made with a minimum of 10% w/w PEO, HPC, and an appropriate disintegrant.	The current idea allows for the use of any drug, medically appropriate drug salt, drug derivative, drug analog, drug homolog, or polymorph.	2017	110
14	US10555986B2	Supplemental food made from natural products using a hot-melt extruder method.	The mixture, which is made by scattering flavonoids from natural extracts using melt mixing or extrusion in the polymer medium, is described in the application. This research looked into a new nutritional supplement that contained the naturally occurring compound epicatechin.	Epicatechin, Cacao	2020	111

VII. Conclusion

HME process is an important concept in designing of new dosage forms for various types of diseases and conditions in humans as well as animals because it is a relatively simple and straightforward technique. This technique can also be coupled with a lot of other processes which enables continuous manufacturing of medications, this enhances its industrial applicability.

It should be viewed as a paradigm-shifting technology as with only minor equipment and process modifications it has been able to create a number of products that were once believed to be outside the purview of this process.

Future technologies will need to develop the procedure and optimize the apparatus and output design in order to overcome the disadvantage of the HME method's high energy intake requirement. Given the developments in

formulation science, polymer chemistry, and PAT equipment and technology, HME would surely have a prominent position in the market.

LIST OF ABBREVIATIONS:

Sl. No.	Abbreviation Used	Full Form
1	HME	Hot Melt Extrusion
2	PAT	Process Analytical Technology
3	PLA	Polylactic Acid
4	FDA	Food and Drug Administration
5	SSE	Single Screw Extruder
6	TSE	Twin Screw Extruder
7	MJS	Multiphase Jet Solidification
8	FFF	Fused Filament Fabrication
9	FDM	Fused Deposition Modeling
10	PED	Precise Extrusion Deposition
11	PAM	Pressure Assisted Microsyringes
12	HPC	Hydroxypropyl Cellulose
13	GRDDS	Gastro retentive Drug Delivery System
14	ODFs	Orodispersible Films
15	AFM	Atomic force microscopy
16	SEM	Scanning Electron Microscope
17	FT-IR	Fourier Transform Infrared spectroscopy
18	PXRD	Powder X-ray Diffraction
19	TGA	Thermogravimetric analysis
20	DSC	Differentiating Scanning Calorimetry
21	CAP	Chloramphenicol
22	MRT	Mean Resident Time

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