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Comprehensive Review on the Hot Melt Extrusion: Design and Applications

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ABSTRACT: Hot melt extrusion (HME) is the process of embedding the drug in a polymeric carrier and is used since the early 1930s, predominantly in the plastic manufacturing industry. HME has emerged as a versatile and innovative technology in pharmaceutical formulation development. Despite the remarkable progress in HME, challenges such as process variability, scale-up issues, and regulatory considerations persist. The review encompasses a thorough examination of the extrusion process, highlighting the critical design considerations, equipment parameters, and material choices that influence product quality. The article provides a detailed analysis of the various applications of hot melt extrusion in pharmaceuticals, ranging from enhancing drug solubility to formulating sustained-release dosage forms and combination products. This comprehensive review explores the intricate aspects of hot melt extrusion, focusing on its design principles and diverse applications in the field of pharmacy.

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INTRODUCTION:

The majority of medications are administered orally in solid dosage forms due to the numerous advantages associated with it. The most commonly developed solid oral dosage forms are tablets, capsules, powders, and granules. Although tablet and capsule dosage forms are most popular and hence a lot of information about these dosage forms is available. However, granules are neglected as the dosage form, though they are used to prepare tablets by compression, and used to fill the capsules. Hence, detailed information on granules and the methods used to prepare the granules needs elaborative discussion.

Granules, one of the solid oral dosage forms, are made up of dry aggregates of powder particles that are combined with one or more medicines, along with or

without other components or excipients. Due to the wide surface area provided by the small powder particles and the high solubility of the other ingredients or excipients used in the formulation, it is primarily used for low-toxicity, high-dose drugs that are typically taken with or without water [1].

Advantages of granules over other dosage forms [1,2]:

- Granules have excellent and uniform flow properties than pharmaceutical powders and hence they are recommended for preparation of tablets and other medications.
- Granules have a higher compressibility than powder.
- The granules have a uniform particle size, making their content more uniform than that of powder.
- Granules are preferred to powders for making solutions because they are easier to moisten by a solvent than pharmaceutical powders.
- In the pharmaceutical business, granules reduce or control dust during the production process.
- Different forms of granules, including coated, gastro-resistant, and modified-release granules, can be formulated for medication, however, the powder has some restrictions.
- Granule-based tablets are always better for coating than tablets made by compressing powder.
- Granules are physically and chemically more resilient against ambient factors such as humidity, light, temperature, etc. than powder because they have a smaller surface area than powder.
- Different granulation techniques are available to create granules that are suited for active pharmaceutical ingredients (API) and excipients that are sensitive to moisture as well as those that are not.

Disadvantages of granules [1,2]:

- The major disadvantage of granules is that they are much less comfortable for the patient to dispense and carry as compared with tablets or capsules.
- It is difficult to formulate active pharmaceutical ingredients (API) that are hygroscopic or deliquescent, amorphous oxygen-sensitive, and volatile.
- To perform the granulation process an experienced person is required.
- It needs special storage conditions; these types of medicine should be stored in a dry place to prevent moisture degradation.
- Compared to tablets, pills, and capsules, the dosage of the granules may not be accurate as they have a stable dose, high precision and lowest variability.
- It includes several processing steps and takes more time, energy, and space; hence, it is a costly technique.
- Granules are not suitable for the administration of potent drugs with low doses; however, the manufacture of tablets and capsules is a more appropriate option for low-dose products.
- It cannot protect against the unpleasant odor and taste of the drugs.

In general, several types of granules are used for medication, including effervescent granules, coated granules, and gastro-resistant granules.

METHODS OF GRANULATION:

Granulation, a word derived from the Latin phrase granulatum, which means grain, is a process of expansion of powdered particles to shape grain-like agglomerates. In the pharmaceutical industry, the granules obtained from the particles of the active pharmaceutical ingredient (API) and excipients blend are further efficiently processed into stable dosage forms.

Based on the binder and process used, the granulation techniques are-classified into:

- Wet granulation.
- Dry granulation.
- Extrusion and Spheronization.

Although first two granulation methods mentioned above are commonly used for the preparation of granules, Extrusion Spheronization is one of the innovative and new techniques available for the preparation of granules.

Extrusion:

Extrusion is a multistep process used to prepare extrudes of uniform size. Material is forced through an opening to create rod-shaped particles of uniform diameter, which are then spheronized using spheronizer to get the pellets, or granules [3].

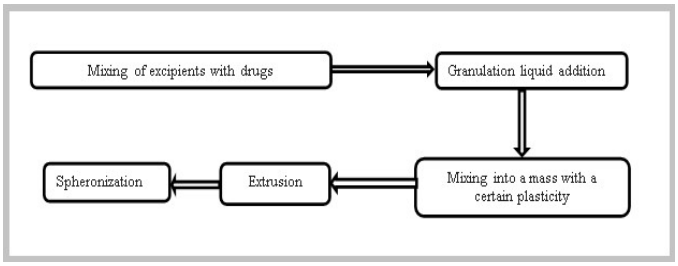

Fig 1. Flow chart of extrusion process.

The compression increases the mass density, resulting in the formation of pellets. Flow chart for the extrusion process is depicted in Fig 1.

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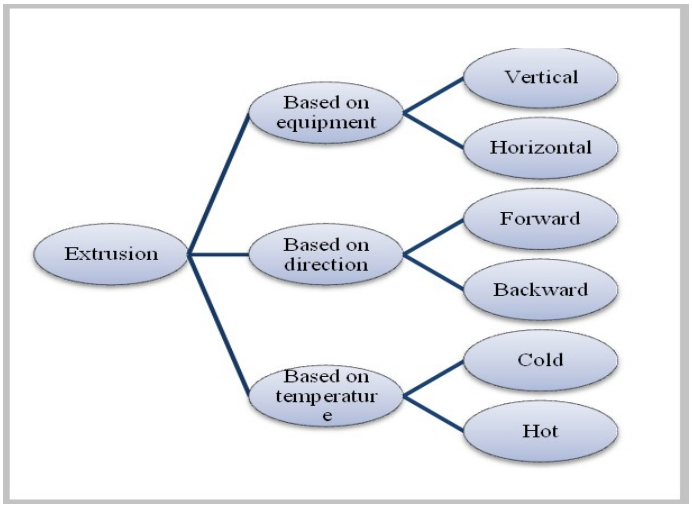


Fig 2. Types of extrusion [7].

Extrusion equipment includes rams, radial screens, and roller and screw extruders. Among these, screw extruders are the most important in the pharmaceutical industry for continuous conversion of feed material into final shapes such as rods, tubes, or sheets. The supplied material is extruded toward the die by the rotating screw, and the material is softened by frictional heat developed through the walls of the barrel. The feed reaches the end of the auger in a viscous state and can be forced to form extrudes of desired shape through an orifice (or die) [4-6].

Extrusion equipment is mainly classified into three classes based on equipment, direction, and temperature and details of each class is being depicted Table 1.

HOT-MELT EXTRUSION (HME):

It is the most widely applied technique in the plastics industry and has been demonstrated recently to be a viable method to prepare several types of dosage forms and drug delivery systems. Hot-melt extruded dosage forms are complex mixtures of active medicaments, functional excipients, and processing aids. HME also offers several advantages over traditional pharmaceutical processing techniques. HME is the continuous process of melting a polymer and forcing it through an orifice using heat and pressure. HME is well-known for its development of uniform-size and high-density polymer products [8,9].

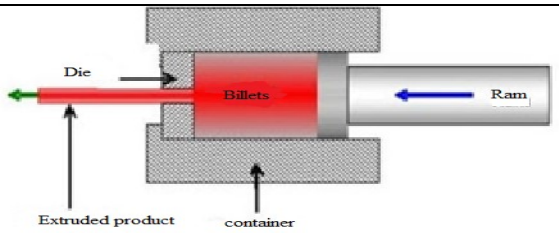
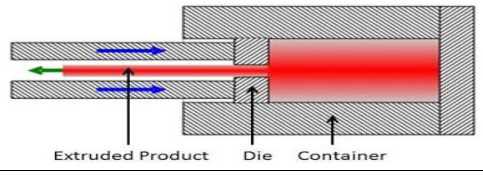
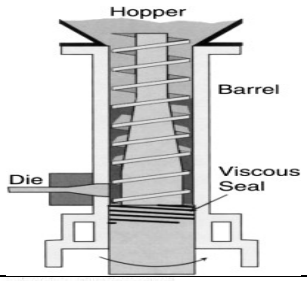
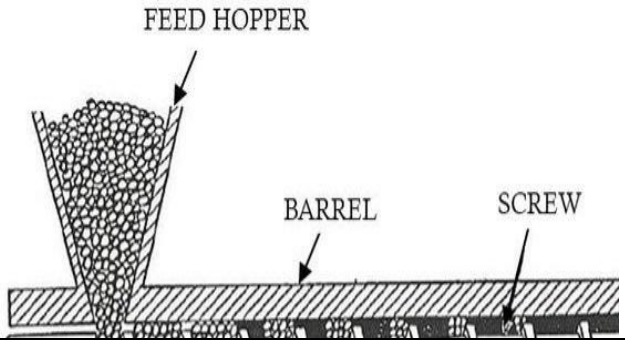
Joseph Brama first developed HME technology in the eighteenth century for the manufacture of lead pipes. It is one of the most widely used processing technologies in the plastic, rubber, and food industries, accounting for more than half of all plastic products such as bags, films, sheets, tubes, fibers, foams, and pipes. The pharmaceutical manufacturer has benefited greatly from the development of hot melt extrusion [10-12]. HME has been used in the healthcare industry to manufacture medical devices and combine active pharmaceutical ingredients with polymers.

HME is a method during which raw materials (polymers, drugs, and different excipients) are unit tense into the feeder and mixed at high temperatures by rotating screws before being gone through a die to make a product of uniform size and form [13].

Advantages of HME [3,5]:

- Continual procedure.
- Maximum output.
- Non-solvent method.
- Improves the solubility and bioavailability of drugs that are poorly soluble in water.
- No further downstream processing is necessary.
- Useful for active pharmaceutical ingredients with a low compressibility index.
- Relatively stable thermodynamically.

Table 1. Classification of extrusion equipment.

Forward extruder: Also called direct extrusion,the die is stationary and pressure is applied to the ram. As the billet extrudes through the die the pressure required to maintain flow progressively decreases with decreasing the length of the billet in the container	
Backward extruder: Also called indirect extrusion where the ram is stationary and the die moves. Extrusion is constant with increasing ram travel.	
Vertical extruder: Billet and die are vertical in equipment. Easier alignment between the ram and tools. Higher rate of production. Uniform deformation.	
Horizontal extruder: The layout of the operation is horizontal. Deformation is non-uniform due to the temperature difference between the top and bottom parts of the billet. Floor space is needed. Proper alignment is needed	
Cold extruder: Cold extrusion is done at room temperature or near room temperature. The advantages of this over hot extrusion are the lack of oxidation, higher strength due to cold working, closer tolerances, better surface finish, and fast extrusion speeds if the material is subject to hot shortness	
Hot melt extruder: The melt extrusion name itself indicates that process where material requires high temperatures to melt. This means it is done above the material's recrystallization temperature to keep the material from work hardening and to make it easier to push the material through the die	

➢ There is minimal oxygen exposure in the extrusion channel.

Disadvantages of HME [4]:

➢ Thermal process.

➢ Requires raw materials with high flow properties.

➢ Hot melt extruders oblige high-energy input, predominantly because of the temperature and shear forces.

➢ Not appropriate to compounds that are heat labile.

Equipments:

The extruder, which typically consists of one or two rotating screws inside of a stationary cylindrical barrel, is therefore the essential component of HME. It offers melting, mixing, kneading, venting, and extrusion of the materials inside the barrel [16].

The steps involved in the extrusion process can be broken down into the following categories [17]:

- Feeding the extruder through a feeder.
- Mixing, grinding, reducing particle size.
- Flow through the die.
- Extrusion from the die and additional downstream processing.

Extruders used for the hot melt process can be divided into three types based on the number of screws used.

Single screw extruder (SSEs):

SSEs are the most widely used extruders as they are mechanically simple devices and have been slightly modified in operational principles since its invention around 1897 [19].

The SSE consists of one continuously rotating screw in a barrel that results in good quality molten material (melt) and generates a high stable pressure for a consistent output. In general, the screw design may consist of 20 or more turns with a pitch similar to the screw diameter, thereby creating a long slender machine in which substantial longitudinal temperature gradients can be maintained and controlled. It also provides considerable residence time, thereby permitting an adequate degree of end-to-end mixing.

Single-screw extruders consist of three zones as shown in Fig 3 [15,22].

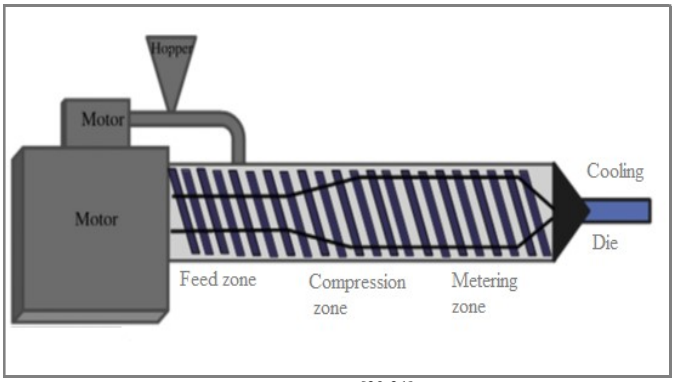


Fig 3. Single screw extruder [20,21].

***Feed zone*:**

The single-screw extruder receives the raw material in the feeding zone with very low pressure by increasing the screw pitch and/or the screw flight depth, larger than that of other zones to allow for consistent feeding from the hopper and gentle mixing.

Compression zone:

The compression zone consists of other steps such as mixing, kneading, and venting. The pressure is increased by decreasing the screw pitch and/or the flight depth to effectively impart a high degree of mixing and compression.

Metering zone:

Finally, in the metering zone, the molten extrudate is pumped through a die that imparts a definite shape for further downstream processing. In addition to the three zones, downstream auxiliary equipment for cooling, cutting, and collecting the finished product is employed.

Twin screw extruder (TSEs):

The first TSE was brought in the 1930s in Italy, to combine the mechanical actions of several existing devices into a single unit. The TSE has two agitator assemblies mounted on parallel shafts as shown in Fig 4 and 5.

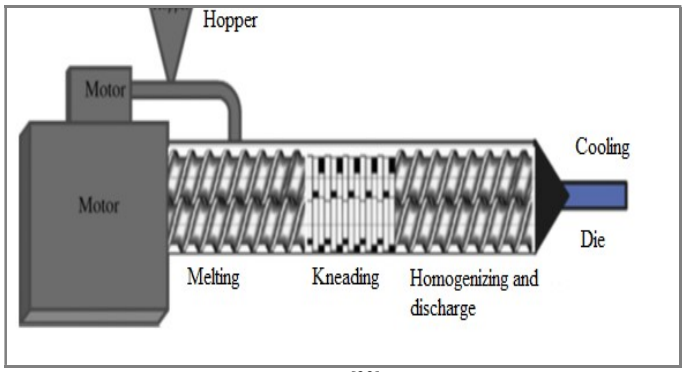


Fig 4. Twin screw extruder [22].

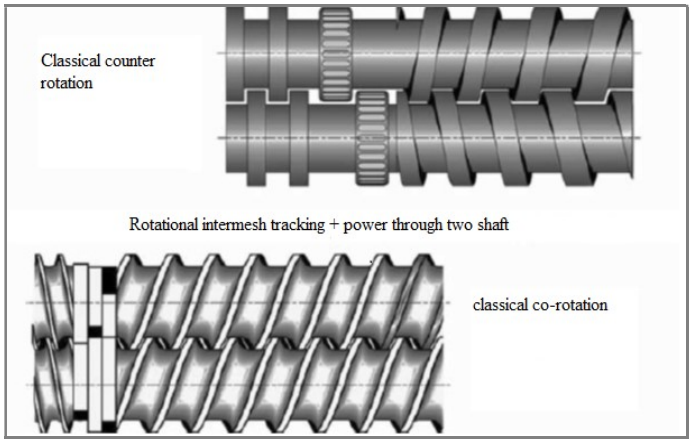


Fig 5. Twin Screw Rotation.

The forms of twin-screw extruders may be similarly labeled into fully intermeshing and non-intermeshing.

The fully intermeshing kind is commonly used because of the self-cleansing function and decreases non-motion via means of stopping localized overheating of raw substances with the extruder.

The non-intermeshing kind is not used much because of its weaker screw interactions and decreased self-cleaning capability. Both kinds are frequently employed to process extremely viscous materials like rubber. However, because these screws are positioned apart from one another, the non-intermeshing type is resistant to high torque generation when processing highly viscous materials.

The rotation of the screws in twin screws may either be co-rotating (same direction) or counter-rotating (opposite direction) [4,15,22].

TSE is characterized by the reduced residence time, self-cleaning screw feature, minimum supply, flexibility and enhanced mixing.

Multi screw extruder (MSEs):

Extruders with more than two screws are commonly referred to as MSE. The assembly may differ depending on the number of screws used in the extruder. These screw arrangements in the MSE are not unique and may vary depending on the needs of the food and pharmaceutical industries. MSE is preferred over SSE because SSE's highly shear-dominated flow of the melted material generates a large amount of heat, which thermally degrades the material (thermolabile material). However, in MSE, due to positive displacement flow in the intermeshing region between the screws, thermolabile materials are protected from degradation [4,23]. The difference between single screw extruder and Twin screw extruder is shown in Table 2.

Table 2. Difference between SSEs and TSEs [13].

Single screw extruder (SSEs)	Twin screw extruders (TSEs)
In SSE, there is only one screw.	The two screws allow for easier feeding and increased kneading and dispersing capacity.
A greater propensity to overheat	Less propensity to overheat
Less Productive	More productivity
Limited mixing power	TSEs co-rotational intermeshing improves mixing
Prolonged residence	Short residence time

Materials used in the HME process:

Hot melt extruded dosage forms are a complex blend of functional excipients and active ingredients. Matrix carriers, release-modifying agents, bulking agents, lubricants, antioxidants, thermal lubricants, and miscellaneous additives are some general categories of functional excipients used in HME as shown in Table 3.

Ideal material characteristics to be used for HME are easy to melt, easy to solidify upon exit, materials must be as pure as possible, and a requirement is that each compound be thermally stable [7].

APPLICATION OF HOT MELT EXTRUSION:

Solid Dispersion:

One or more active ingredients are molecularly distributed into a hydrophilic inert carrier matrix in a system known as solid dispersion. The poorly water-soluble crystalline form of an API is changed to the more water-soluble amorphous form during the formulation process to create a solid dispersion. To prepare solid dispersions, a variety of methods, such as melt fusion and solvent evaporation, are frequently used [4].

HME is a particularly appropriate technique for the formation of solid dispersions, and its main benefit is that the method does not need solvent use. Therefore, the associated solvent-related stability risks may occur throughout the formulation. Based on the configuration of the instrument and process temperature, the TSE is rising because it is the most viable possibility within the pharmaceutical industry for the formation of solid dispersions [24].

Granulation:

To create solid dosage forms like tablets and capsules, granulation of powder blends is a common unit operation. Granulation is typically done in a batch process using well-established technologies like fluidized bed granulators, rotating drums, pans, high-shear mixers and/or cyclones, and roll compactors/press rolls [34-36]. TSG is the method used for bulk material transfer to the mixing zone. At the discharge point, the material is then collected as granules after being kneaded to form agglomerates, either with or without the assistance of particular binders in the formulation [37,38].

Twin-screw granulation (TSG) has been discovered to be a very attractive method for granulation, however, because of the many benefits it offers, including continuous automated production at higher throughput, flexibility (due to the granulator screws' modular setup inside a TSG), the ability of the screws to self-clean, real-time monitoring, ease of scaling, improved product quality, reproducibility, cost-effectiveness, need for less space, etc. Twin-screw granulation results in higher

Table 3. Commonly used excipients in HME and its purpose [13, 24-33].

Material	Purpose	Examples
Carriers polymeric and non- polymeric	The active ingredient is contained in a carrier formulation that frequently consists of one or more "meltable" substances and other useful excipients in hot-melt extruded drug delivery systems. Typically, wax with a low melting point or a polymer serves as the meltable substance. In the creation of a hot-melt extruded dosage form, the choice of an appropriate carrier is crucial. The processing conditions are frequently determined by the carrier's characteristics. The release of the active ingredient from the final dose form can be regulated by the physical and chemical properties of the carrier	Polyethylene oxide, Polyethylene glycol, Hydroxypropyl methylcellulose, Hydroxypropyl cellulose, Eudragit® E, Soluplus®, Polyvinylpyrrolidone, hydroxypropyl methylcellulose acetate succinate, Hydroxypropyl methylcellulose phthalate, Ethyl cellulose, Ethylene vinyl acetate, Polyvinyl acetate, Poly (L-lactic acid), Poly (lactic-co-glycolic acid), Poly (glycolide), Polycaprolactone, Silicone, Polyurethanes
Plasticizer	Plasticizers are typically low-molecular-weight substances that can soften polymers to increase their pliability. To optimize the processing conditions during the production of the extruded dosage form or to improve the physical and mechanical qualities of the finished product, the use of polymeric carriers in HME frequently necessitates the introduction of a plasticizer into the formulation.	Phthalate esters: (Dimethyl, Diethyl, Dibutyl, Dioctyl Phthalate), Fatty acid esters (Butyl stearate, Glycerol monostearate), Citrate esters (Triethyl, Tributyl, Acetyl triethyl, Acetyl tributyl citrate), Sebacate esters (Dibutyl sebacate), Vitamin E TPGS (D- α-tocopherol polyethylene glycol 1000 succinate), Polyethylene glycol, Propylene glycol, Polyethylene oxide, Triacetin, Surfactants (Polysorbates, Polyethylene glycol monostearate), Carbon dioxide
Lipid matrices	To make HME processing easier, other materials were used. Waxy materials have been documented to serve as a thermal lubricant during hot-melt extrusion.	Microcrystalline wax, Stearic acid, Carnauba wax, Glyceryl dibehenate, Glyceryl palmitostearate, Glyceryl trimyristate, Triglyceride tripalmitin
Other processing aids	The preferential oxidation of reducing agents protects drugs, polymers, and other excipients from attack by oxygen molecules.	Swelling agents: Croscarmellose sodium, Sodium starch glycolate, pH modifiers: Citric acid, Pressurized CO2: foaming agent, Antioxidants: Butylated hydroxytoluene, ascorbic acid, Effervescent agent: Sodium Bicarbonate, Preservative: Methyl Paraben

porosity granules and is accompanied by very brief residence times [24,38,39].

Pellets:

Pellets are often made by utilizing HME wherever the material is initially extruded either with the assistance of an extruder followed by pumping through a die, at last cooled, and cut manually or with the help of a pelletizer. Desired dose strengths may be achieved without form Granulation or method changes using pellets [41,42].

Pellets supply the chance to mix many active parts, incompatible drugs, or medicines with totally different release profiles within the same indefinite quantity unit [43,44]. Pellets are widely used to improve taste properties by mixing with food additives. Pellets are often made efficiently using HME technology, followed by an additional process employing a strand pelletizer [24].

Taste masking:

For formulation scientists, creating pleasant oral dosage forms for the pediatrics market while masking the taste of naturally unpleasant-tasting medications has become a huge challenge. There is a need for a system that prevents the API from interacting with the sense of taste, thereby minimizing or eliminating the unpleasant sensory response. HME has not yet been used in any commercial pediatric medications, but there is a pressing

need for more dependable, affordable, and easily scalable taste masking advanced technology. It extends the shelf life of the product and is continuous, less time-consuming, scalable, and applicable to drugs that are sensitive to moisture. A tool for effective taste masking is choosing the right masking agent at the necessary drug-excipient ratio [24,44].

Films:

Solvent-casting techniques are the foundation of most current film manufacturing technologies. The selection of suitable solvents is constrained by the unsafe nature of the majority of organic solvents, residues even after drying, and complex processing conditions, while the disposal of the associated waste may be unsafe to the environment and human health.

As a result, the pharmaceutical industry currently uses HME technology to prepare to beat the constraints of solvent-casting ways [45,46].

Oral controlled release:

Compression, such as roller compaction or tableting, is the most common manufacturing method for sustained-release dosage forms. Deformation occurs at the points of contact between the drug and excipient particles, increasing the compression force and densifying the formulation composition. Plastic deformation occurs in ductile materials like microcrystalline cellulose, whereas brittle materials like lactose experience brittle fracture. A prepared sustained-release drug-delivery system has successfully used a TSE process. Thermal plastics that are easily processed in a TSE include widely used polymeric drug-release retardants like Eudragit RS, ethyl cellulose, and hydroxypropyl cellulose. Corotating (or counter rotating) twin screws are used to feed and move polymeric drug-release retardants inside the heated barrel during the extrusion process. The rotating screws' shearing effect causes the polymeric materials to soften. The molten mass is then forced through the die, which is screwed onto the end of the barrel, and changed into various shapes. The extrudate can either be directly formed into a dosage form or ground into granules and then compressed using a conventional method to create the final dosage form [45,46].

Nanotechnology:

Nanotechnology based drug delivery systems like nanosuspension, solid lipid nanoparticle (SLN), nanostructured lipid carriers (NLC), nanocrystals, and nano-emulsion are continuously being prepared using the traditional batch-based approach. The traditional methods often face problems such as inconsistent batch quality and reasonably higher costs due to the various steps involved [47].

To overcome these limitations, researchers are forgoing developing oral and topical Nano-systems by adopting HME technology that would be safe for the living tissues and hold unique characteristics. The sophisticated HME technique is now used to fabricate the above-mentioned Nano-systems in a single-step process or by coupling with a high-pressure homogenizer/probe sonicator to further reduce the particle size [48].

The development of nanomedicine using this technology has proven to be valuable as it minimizes batch-to-batch variability, product cost, and processing time. Several publications favor the practicability and benefits of continuous manufacturing HME technique for the development of organic and inorganic [25].

CONCLUSION:

HME has proven to be a robust method of producing numerous drug delivery systems and therefore it is useful in the pharmaceutical industry enlarging the scope to include a range of polymers and APIs that can be processed with or without plasticizers. HME is a solvent-free, robust, quick, and economy-favored manufacturing process for the production of a large variety of pharmaceutical dosage forms.

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