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ROLE OF MELT EXTRUSION IN THE ENHANCEMENT OF BIOAVAILABILITY

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ABSTRACT

Starting from plastic industry, today melt extrusion has found its place in the array of pharmaceutical manufacturing processes. Melt extrusion processes are currently applied in the pharmaceutical field for the formulation of variety of dosage forms such as granules, pellets, tablets, implants, transdermal systems & ophthalmic inserts. This technology represents an efficient pathway for increasing the solubility of poorly soluble drugs. The process forms a solid dispersion where the drug is presented in an amorphous & molecularly dispersed state in a carrier. This leads to an increase in solubility, as no lattice energy has to be overcome during dissolution. Melt extrusion is considered to be an efficient technology in the field of formulation of solid dispersions to improve bioavailability with particular advantages over solvent processes. This article highlights on the technology of Hot Melt Extrusion (HME).

INTRODUCTION: Oral delivery is preferred route for drug administration over the other routes due to its own advantages. Candidature for oral drug delivery should have following properties-

1. Adequate aqueous solubility,
2. Sufficient absorption through gut,
3. Metabolic stability & no efflux.

Advances in combinatorial chemistry & HTS generated large number of drug molecules, of which many are poorly soluble posing bioavailability problems. Also impact of lipophilic receptors leads to the generation of lipophilic drugs which possess poor dissolution rate thus poor bioavailability. Almost 40% of drug candidates fail to show therapeutic response due to poor solubility [2].

Importance of solubility in Bioavailability: Bioavailability is the extent of therapeutically active drug that reaches the systemic circulation & thus will be available at the site of action. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility behavior of a drug is one of the key determinants of its oral bioavailability. In recent years, the number of poorly soluble drug candidates has increased tremendously.

The formulation of poorly soluble drugs for oral delivery presents a challenge to the formulation scientists. The rate and extent of dissolution of the active ingredient from any dosage form often determines the rate of extent of absorption of the drug. An active agent given orally, it must first dissolve in gastric and/or intestinal fluids before it can then

permeate the membranes of the GI tract to reach systemic circulation therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption [1].

This article focuses on the use of solid dispersion technology to improve the dissolution characteristics of poorly water-soluble drugs and in turn their oral bioavailability. The method discussed is Hot Melt Extrusion (HME). In case of poor water soluble drugs, dissolution is the rate-limiting step in the process of drug absorption. Drug with poor water solubility have been shown to be unpredictably and slowly absorbed compared with drugs of higher solubility. Therefore, a better oral, parenteral, or topical formulation can be developed by increasing the water solubility of the drugs.

Formulation challenges with Poorly Soluble Drugs [12]:

- Poor dissolution rate.
- Low & variable bioavailability.
- More potential for food effect.
- Inability to deliver high doses for toxicity studies.
- Difficulty in the development of parenteral formulations.

Factors affecting Solubility [29]:

1. **Molecular size** - Molecular size will affect the solubility. The larger the molecule or the higher its molecular weight the less soluble the substance. Larger molecules are more difficult to be surrounded with solvent molecules in order to solvate the substance.
2. **Polarity** - Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents.
3. **Polymorphism** - The capacity of a substance to crystallize in more than one crystalline form is polymorphism. Polymorphs can_vary in melting points. Since the melting point of the solid is related to solubility, so polymorphs will have different solubilities.
4. **Particle size** - The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent, so increase in solubility.
5. **Nature of Solute & Solvent** - Same solute can dissolve to different extent in different solvents.
6. **Temperature** - Temperature will affect solubility. If the solution process absorbs energy then the solubility will be increased as the temperature is increased. If the solution process releases energy then the solubility will decrease with increasing temperature. Generally, an increase in the temperature of the solvent increases the solubility of a solid solute.
7. **Pressure** - For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility. For solids and liquid solutes, changes in pressure have practically no effect on solubility.

Methods of Solubility Enhancement [2, 29]:

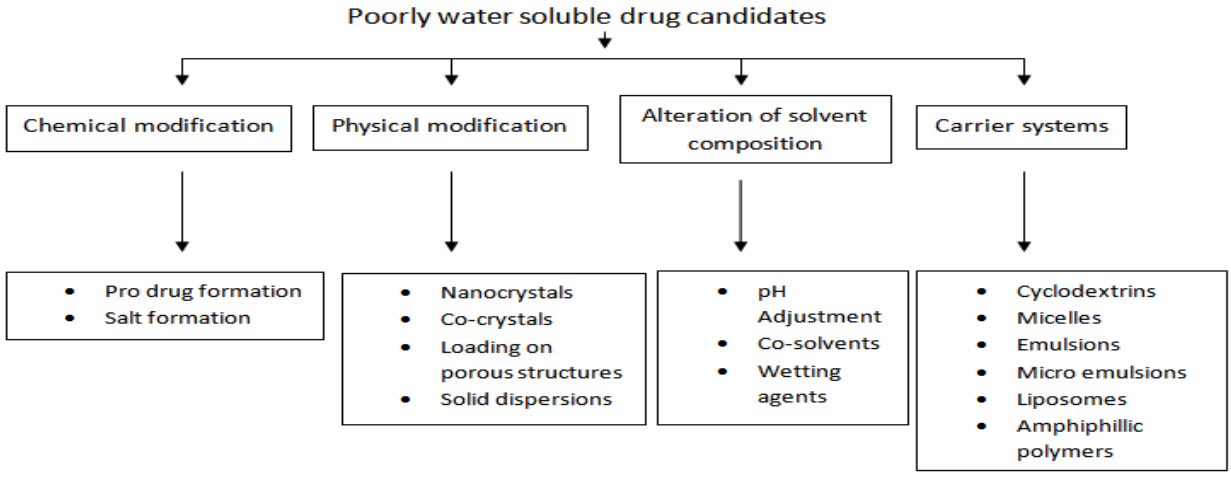


FIG.1: METHODS FOR ENHANCING SOLUBILITY

1. **Solid Dispersions [10, 16]:** "The term solid dispersion (SD) is defined as the dispersion of one or more active ingredients (hydrophobic) in an inert carrier or matrix (hydrophilic) at solid state prepared by the melting (fusion), solvent, or melting-solvent method". The drug can be dispersed molecularly, as amorphous particles (clusters) or as crystalline particles. Therefore, based on their molecular arrangement, six different types of solid dispersions can be distinguished. Moreover, not the preparation method but the molecular arrangement governs the properties of solid dispersions.

Types of Solid Dispersions:

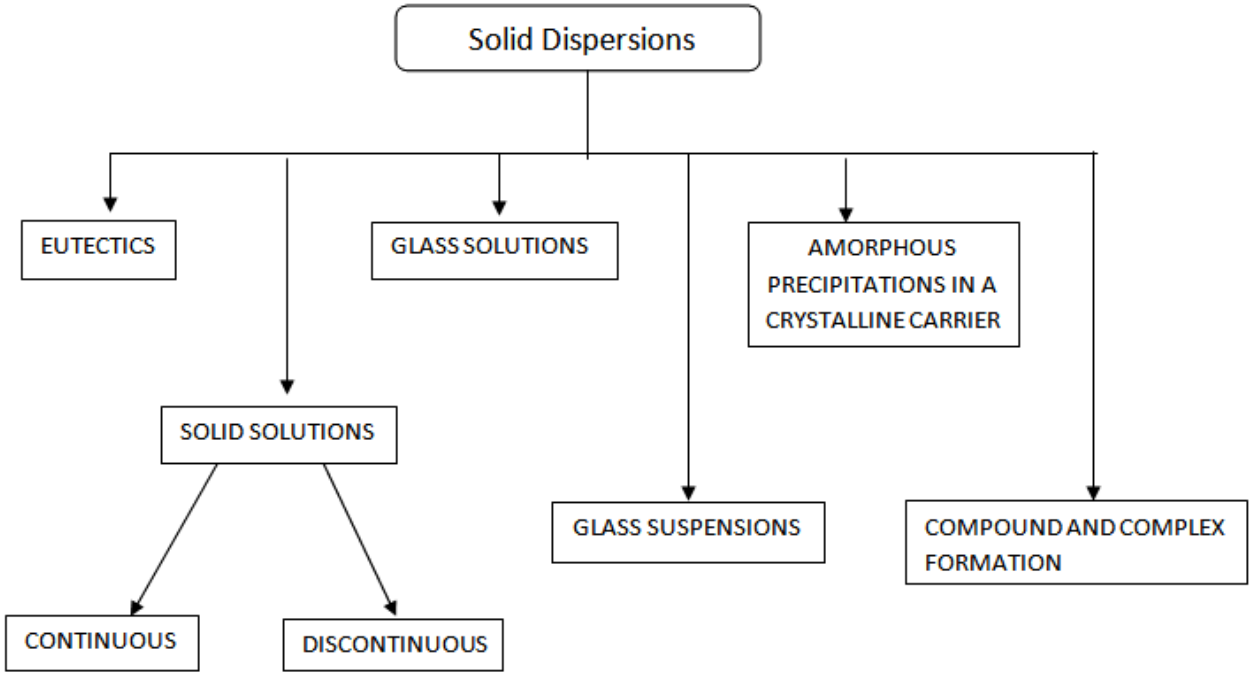


FIG. 2: TYPES OF SOLID DISPERSIONS

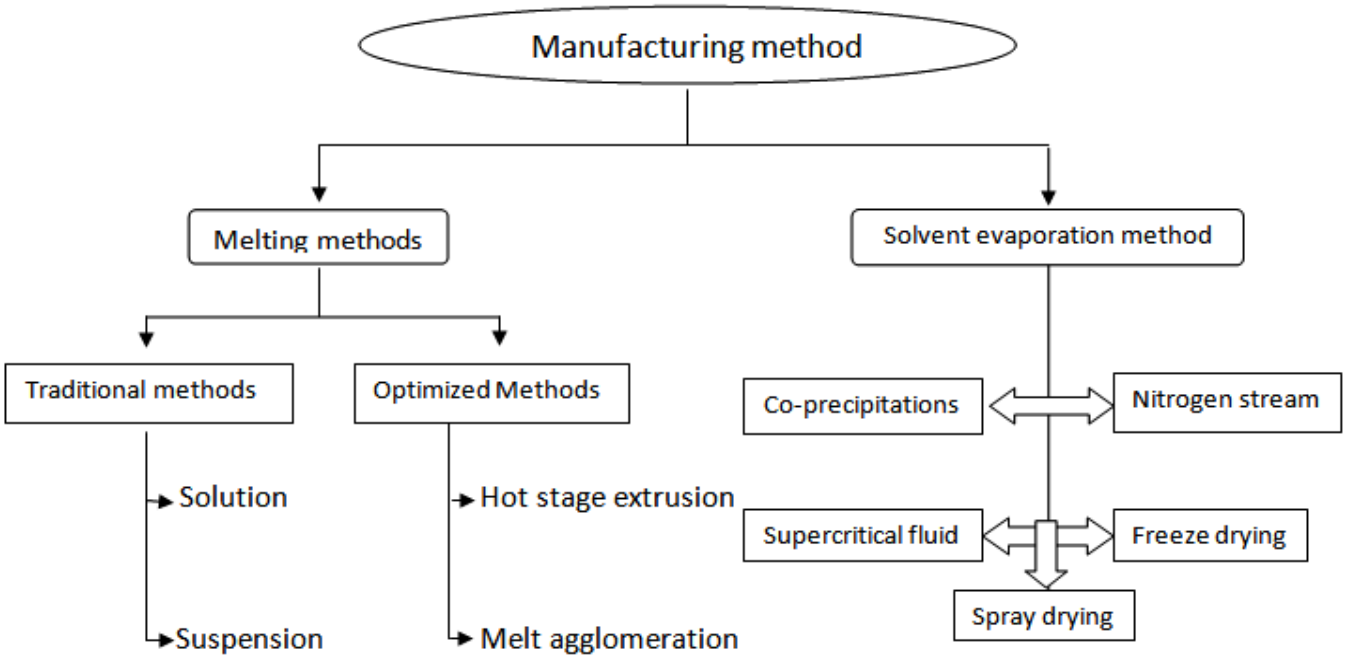


FIG. 3: MANUFACTURING METHODS FOR SOLID DISPERSIONS

The solid dispersion approach to reduce particle size and therefore increase the dissolution rate and absorption of drugs was first recognised in 1961, by the melting (fusion) method, solvent method, or fusion solvent-method. Novel techniques include rapid precipitation by freeze drying, usage of supercritical fluids, spray drying and melt extrusion. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone, polyethylene glycols, Plasdone-S630. Many a time surfactants may also be used in the formation of solid dispersion.

Hot Melt Extrusion (HME): Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971. It has been reported that melt extrusion of miscible components results in amorphous solid solution formation, whereas extrusion of an immiscible component leads to amorphous drug dispersed in crystalline excipient. The process has been useful in the preparation of solid dispersions in a single step [2].

HME is an efficient technique for producing solid molecular dispersions with considerable advantages over solvent based process. HME can be broadly defined as the process of embedding drug in polymeric carrier under controlled conditions of temperature, shear, & pressure to generate wide variety of finished products. Extrusion involves conversion of raw materials in to products of uniform shape & density by forcing through a die under controlled conditions.

HME differs from simple extrusion in that, polymer, drug and excipient blends are mixed thoroughly in the molten state in this process, needing no solvents for granulation. The molten polymer serves as the thermal binder. Simple extrusion process uses aqueous or organic solvents for wetting the powder blend for granulation [12]. It is a time consuming process since drying step is critical. Use of solvents in this process may degrade the drug and residual solvents may be present after drying.

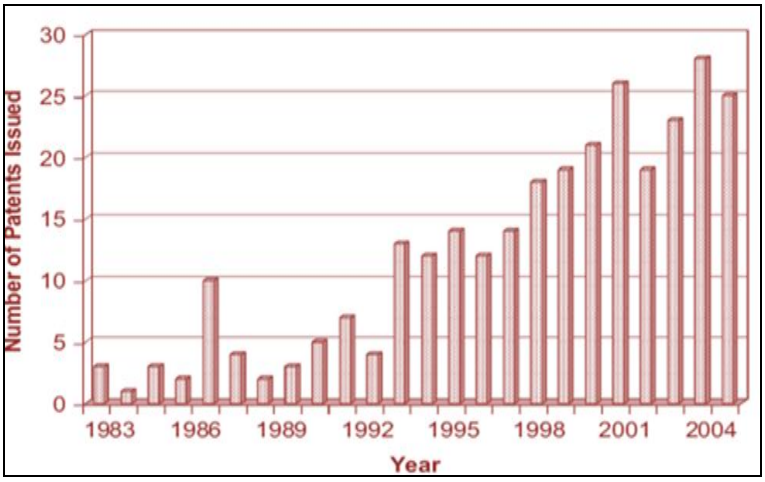
Melt extrusion process are currently applied in the pharmaceutical field for the manufacture of a variety of dosage forms and formulations such as granules, pellets, tablets, suppositories, implants, stents, transdermal systems and ophthalmic inserts.

History: The word 'extrusion' is derived from the Latin 'extrudere', which literally means to press out or to drive out. Extrusion is the process of converting a raw material into a product of uniform shape and density by forcing it through a die under controlled conditions. Industrial applications of extrusion process dates back to 1930s**.** The extrusion process was invented for the manufacturing of lead pipes by Joseph Brama at the end of the 18th century.

Melt extrusion technique has found its place in the array of the pharmaceutical manufacturing operations which is evident from the increasing number of patents and publications in the scientific literature with over 100 papers published in the last 12 years. Hot melt extrusion is mainly used to produce homogenous matrix formulations of the drug. Previously mainly used for mfg of plastic products like plastic sheets, & pipes, the process is currently also used in pharmaceutical industry for manufacturing of variety of dosage forms & formulations[2, 15].

Pharmaceutical interest in HME

Numbers of patents have been found to be increasing with years.



GRAPH: NUMBER OF PATENTS FOR HME FROM YEAR 1983 TO 2004

Advantages of HME:

TABLE 1: ADVANTAGES OF HME

FEATURE	BENEFIT
Solvents not required	Environmentally friendly, economical; No residual solvent in final product.
Continuous process	Fewer unit batches required; Efficient scale-up from laboratory to large-scale production.
Intense mixing and agitation achieved	Improved content uniformity.
Compressibility not required	Useful for powders with low compressibility index.
Polymers serve multiple purposes	Less number of excipients required; Cost effective.
Greater thermodynamic stability than that produced by other hot-melt methods	Fewer tendencies toward recrystallization.

Principle: It works on the principle of forcing a raw material or blend through a die or orifice under set conditions such as temperature, pressure, rate of mixing and feed-rate, for the purpose of producing a stable product of uniform shape and density.

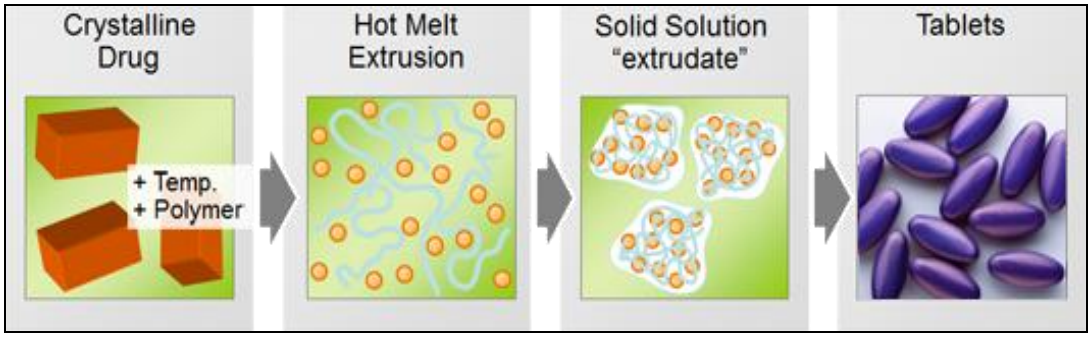


FIG.4: PRINCIPLE OF HME

Materials used in HME: For a pharmaceutical material to be processed by HME, it must be able to soften easily inside the extruder and solidify upon its exit. The materials must meet the same levels of purity and safety as for those prepared by traditional techniques. Most of the raw materials used in hot-melt extruded pharmaceuticals have been used in the production of other solid dosage forms such as tablets, pellets, granules, transdermal, and transmucosal systems. Thermal stability of the individual compounds is a prerequisite for the process, although the short processing times encountered in this process may not limit all thermolabile compounds [8, 9].

Hot-melt extruded dosage forms are complex mixtures of active medicaments and functional excipients. Functional excipients may be broadly classified as matrix carriers, release modifying agents, bulking agents, antioxidants, lubricants, and miscellaneous additives. The selection and use of various excipients can impart specific properties to hot-melt extruded pharmceuticals in a manner similar to those in traditional dosage forms.

The incorporation of plasticizers may lower the processing temperatures necessary for HME thus reducing drug and carrier degradation. Drug release from these systems can be modulated by the incorporation of various functional excipients.

The dissolution rate of the active compound can be increased or decreased depending on the properties of the rate-modifying agent. For systems that display oxidative or free radical degradation during processing or storage, the addition of antioxidants, light absorbers may be used [14].

Basically excipients are divided into four main types as

A. Active pharmaceutical ingredient (API),

B. Carrier,

C. Plasticizer &

D. Antioxidants & other processing aids.

A. **Active pharmaceutical ingredient (API)**: The properties of the active drug substance often limit the formulation and processing choices available to the pharmaceutical scientist in the development of dosage forms. HME is an anhydrous process, which avoids potential hydrolytic degradation pathways. In addition, poorly compactable materials can be prepared as tablets without a compression process by cutting an extruded rod to the desired dimensions. As an initial assessment, the thermal, chemical, and physical properties of the drug substance must be evaluated. Depending on the unique properties of the drug substance and the other materials in the formulation, the drug may be present as undissolved particles, a solid solution, or a combination in the final dosage form. The state of the drug in the dosage form may have a profound impact on the processability and stability of the product [14].

B. **Carriers**: In hot-melt extruded drug delivery systems, the active compound is embedded in a carrier formulation often comprised of one or more thermoplastic or meltable substances and other functional excipients. The meltable substance is generally a polymer or low melting point wax. The selection of an appropriate carrier is important in the formulation and design of a hot-melt extruded dosage form.

The properties of the carrier often dictate the processing conditions. The physical and chemical properties of the carrier can control the release of the active compound from the final dosage form.

The incorporation of a low melting point compound into a low melting point wax may form a eutectic mixture or reduce the melting point of the mixture preventing the formation of a solid dosage form. Carriers used in hot-melt extruded dosage forms have included water insoluble polymers and waxes such as ethyl cellulose or carnauba wax in which the rate of drug release are diffusion controlled [7].

Water soluble polymers have included hydroxypropyl cellulose, polyethylene oxide, poly vinyl pyrrolidon etc. in which the drug is released by a diffusion and erosion mechanism.

TABLE 2: POLYMERS USED IN HME

Chemical name	Use
PEG	Plasticizer, modified release
Polyethylene Oxide	Plasticizer, immediate & controlled release
Hydroxy propyl cellulose	Controlled release
Methacrylate Co-Polymer	Immediate & controlled release
PVP	Immediate & controlled release
Ethyl Cellulose	Sustained release

c. **Plasticizer**: Plasticizers are typically low molecular weight compounds capable of softening polymers to make them more flexible. The use of polymeric carriers in HME often requires the incorporation of a plasticizer into the formulation to improve the processing conditions during the manufacturing of the extruded dosage form or to improve the physical and mechanical properties of the final product. Plasticizers are able to decrease the glass transition temperature and the melt viscosity of a polymer by increasing the free volume between polymer chains.

Plasticizers have also been found to facilitate the fusion process of semicrystalline polymers. Less energy is usually required to melt semi-crystalline polymers following the addition of one or more plasticizers [7]. With the addition of a plasticizer, a HME process can be conducted at lower temperatures and with less torque.

Generally, both the active ingredient and the polymer will be more stable during the extrusion process due to these improved processing conditions. Plasticizers used for the preparation of pharmaceutical dosage forms must have good efficiency, stability, polymer plasticizer compatibility and permanence.

TABLE 3: VARIOUS PLASTICIZERS USED IN PHARMACEUTICAL DOSAGE FORMS

TYPE	EXAMPLES
Citrate esters	triethyl citrate, tributyl citrate, acetyl triethyl citrate, acetyl tributyl citrate
Fatty acid esters	butyl stearate, glycerol monostearate, stearyl alcohol
Sebacate esters	dibutyl sebacate
Phthalate esters	diethyl phthalate, dibutyl phthalate, dioctyl phosphate
Glycol derivatives	Polyethylene glycol, propylene glycol

d. **Anti-oxidants & other processing aids**: The excessive temperatures needed to process unplasticized or under plasticized polymers may lead to polymer degradation. The stability of polymers that are susceptible to degradation can be improved with the addition of antioxidants or light absorbers during HME.

E.g. polyethylene oxide has been reported to be protected from free radical and oxidative degradation by the incorporation of an antioxidant. Antioxidants are classified as preventive antioxidants or chain-breaking antioxidants based upon their mechanism. Preventive antioxidants include materials that act to prevent initiation of free radical chain reactions. Reducing agents, such as ascorbic acid, are able to interfere with autoxidation in a preventive manner since they preferentially undergo oxidation. The preferential oxidation of reducing agents protects drugs, polymers, and other excipients from attack by oxygen molecules. Chelating agents such as edetate disodium (EDTA) and citric acid are another type of preventive antioxidant that decrease the rate of free radical formation by forming a stable complex with metal ions that catalyze these reduction reactions [7, 12].

Other materials used to facilitate HME processing are waxy materials like glyceryl monostearate which have been reported to function as a thermal lubricant during hot-melt processing. Vitamin E TPGS has been reported to plasticize polymers and enhance drug absorption.

Types of extrusion processes[14,15]

a. Ram extrusion

b. Screw extrusion

a) **Ram extrusion:** Ram extrusion operates with a positive displacement piston or ram capable of generating high pressures to push materials through the die. During ram extrusion, materials are introduced into a heated cylinder. After an induction period to soften the materials, a ram pressurizes the soft materials through the die and transforms them into the desired shape. High-pressure is the operating principle of ram extrusion. This technique is well suited for the precision extrusion of highly valuable materials.

The ram exerts modest and repeatable pressure as well as a very consistent extrudate diameter. The major drawback of ram extrusion is limited melting capacity that causes poor temperature uniformity in the extrudate. Also, extrudates prepared by ram extrusion have lower homogeneity, in comparison with extrudates processed by screw extrusion

b) **Screw extrusion:** A screw extruder provides more shear stress and intense mixing. At a minimum, a screw extruder consists of three distinct parts: a conveying system for material transport and mixing, a die system for forming, and downstream auxiliary equipment for cooling, cutting & collecting the finished products. Individual components within the extruder are the feed hopper, a temperature controlled barrel, a rotating screw, die and heating & cooling systems.

Equipment: HME equipment consists of extruder, downstream auxillary equipments, & other monitoring tools used for performance & product quality evaluation [11].

Extruder: At the most fundamental level, an extruder consists of a platform that supports a drive system, an extrusion barrel, a rotating screw arranged on a screw shaft and an extrusion die for defining product shape. Typically, process parameters are controlled via connection to a central electronic control unit. The extrusion drive system generally comprises motor, gearbox, linkage and thrust bearings; whereas the barrel and screw is commonly utilized in a modular configuration [19].

Simple single screw arrangements consist of only a single rotating screw inside a stationary extruder barrel, while more advanced machines involve twin-screw systems utilizing either a co-rotating or counter-rotating configuration.

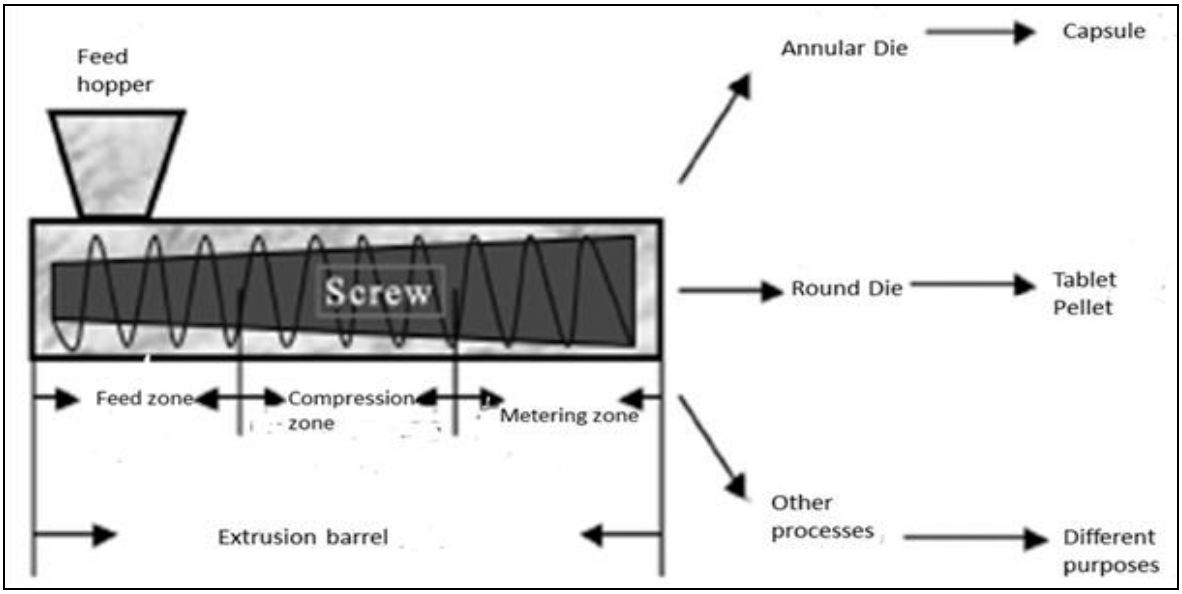


FIG.5: BASIC INSTRUMENTATION OF EXTRUDER

A simple single screw extrusion system comprises one rotating screw inside a stationary barrel that may be conveniently subdivided into three distinct zones: feed zone, compression zone and metering zone. The depth and/or pitch of the screw flights differ within each zone, generating variable pressure along the screw length (zone dependent). Because of the large screw flight depth and pitch, the pressure within the feed zone is very low, allowing for consistent feeding from the hopper and gentle mixing of API and excipients. The primary function of the subsequent compression zone is to melt, homogenize and compress the extrudate so that it reaches the metering zone in a form suitable for extrusion.

Consequently, the compression zone must impart a high degree of mixing and compression to the material. This is achieved by decreasing the screw pitch and/or the flight depth, resulting in a gradual increase in pressure along the length of the compression zone. The final section, the metering zone stabilizes the pulsating flow of the matrix, thus ensuring the extruded product has a uniform thickness. Constant screw flight depth and pitch helps maintain continuous high pressure to ensure a uniform delivery rate of molten material through the extrusion die and, hence, a uniform product.

Individual components within the extruder are the feed hopper, temperature controlled barrel, rotating screw, a die and heating/cooling elements.

Additional systems include mass flow feeders to accurately meter materials into the feed hopper, liquid and solid side stuffers, vacuum pumps for degassing, pelletizers and calendaring equipment. Standard process control and monitoring devices include zone temperature and screw speed with optional monitoring of torque, drive amperage, melt pressure and melt viscosity. Temperatures are normally controlled by electrical heating bands and monitored by thermocouples [11, 12].

Types of extruders currently available are single and twin screw extruders. Single screw extruder is considered as the basic form of the extruder that simply melts and forms the material. Mixing ability is poor compared to twin screw extruders. There is a possibility of degradation of material due to heat generation caused by the longer residence time of material. Single screw extruders are an economical option for melt processing but are not ideal for compounding mixtures of plastics with solids or liquids.

HME by single screw extruder is a viable method for preparing sustained release wax granules for tablets having low dose of drugs and for tablets prepared with excipient having widely different densities from API. Twin screw extruders were introduced in late 1930s. They provide excellent mixing of the powder materials for melting and forming during this process. Different types of twin screw extruders are available, depending on the manufacturer and for meeting specific market needs.

The two main types of twin screw machines are co-rotating and counter rotating which have different screw rotations in the barrels.

Single Screw Extruder [19]: The single screw extruder is the most widely used extrusion system in the world. One screw rotates inside the barrel and is used for feeding, melting, de volatilizing, and pumping. Single screw extruders can be either flood or starve fed, depending upon the intended manufacturing process. Single screw extruders are continuous, high-pressure pumps for viscous materials that can generate thousands of pounds of pressure while melting and mixing. Most extruder screws are driven from the hopper end. Single screw extruders accept material into the feed section and convey materials along a flighted screw enclosed in a barrel.

Single screws are typically flood fed; where the hopper sits over the feed throat and the screw RPM determines the output rate. Sometimes these devices are operated under starve fed conditions, where a feed system sets the mass flow rate and is independent of screw RPM.

There are three basic functions of a single screw extruder: solids conveying, melting and pumping. The forwarding of the solid particles in the early portion of the screw is a result of friction between the material and the feed section's bore. After solids conveying the flight depth begins to taper down and the heated barrel causes a melt to form. The energy from the heaters and shearing contribute to melting. Finally, the molten materials are pumped against the die resistance to form the extrudate.

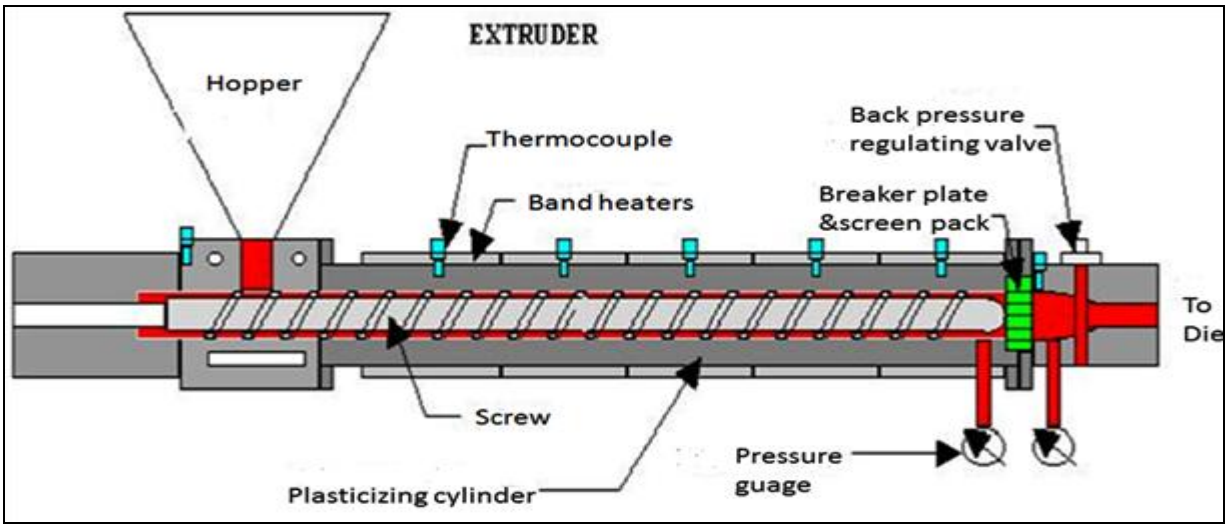


FIG. 6: SINGLE SCREW EXTRUDER

Twin Screw Extruder: The first twin-screw extruders were developed in the late 1930s in Italy, with the concept of combining the machine actions of several available devices into a single unit. As the name implies, twin-screw extruders utilize two screws usually arranged side by side.

In a twin-screw extruder, the screws can either rotate in the same (Co-rotating extruder) or the opposite (counter-rotating extruder) direction. The counter-rotating designs are utilized when very high shear regions are needed as they subject materials to very high shear forces as the material is squeezed through the gap between the two screws as they come together. Also, the extruder layout is good for dispersing particles in a blend.

Generally, counter-rotating twin-screw extruders suffer from disadvantages of potential air entrapment, high-pressure generation, and low maximum screw speed and output.

Co rotating twin-screw extruders on the other hand generally of the intermeshing design, and are thus self-wiping. They are industrially the most important type of extruders and can be operated at high screw speeds and achieve high outputs, while maintaining good mixing and conveying characteristics. Unlike counter-rotating extruders, they generally experience lower screw and barrel wear as they do not experience the outward "pushing" effect due to screw rotation. These two primary types can be further classified as non-intermeshing and fully intermeshing.

The fully intermeshing type of screw design is the most popular type used for twin screw extruders. This design itself is self-wiping, where it minimizes the non motion and prevents localized overheating of materials within the extruder [16].

The design of the screw has a significant impact on the process and can be selected to meet particular requirements such as high or low shear. In an extrusion process, the dimensions of the screws are given in terms of L/D ratio, which is the length of the screw divided by the diameter For example, an extruder screw that is 1000 mm long and has a 25 mm diameter exhibits a 40:1 L/D.

Typical extrusion process lengths are in the 20 to 40:1 L/D range, or longer. Extruder residence times are generally between 5 sec and 10 min, depending upon the L/D ratio, type of extruder, screw design, and how it is operated. The size of an extruder is generally described based on the diameter of the screw used in the system, i.e., 18-27 mm extruder (pilot scale) as compared with 60 mm extruder (production scale). Most screws are made from surface coated stainless steel to reduce friction and the possibility of chemical reactions.

The die is attached at the end of the barrel. The shape of the die dictates the physical form or shape of the extrudate. Generally, the cross section of the extrudate will increase upon leaving the die, a phenomenon known as “die swell” depending on the visco-elastic properties of the polymers [11]. The auxillary equipment for extruder consists of a heating/cooling device for barrels, downstream equipment to collect the products. Monitoring devices on equipment include temperature gauge, screw speed controller, pressure gauge & extrusion torque monitor.

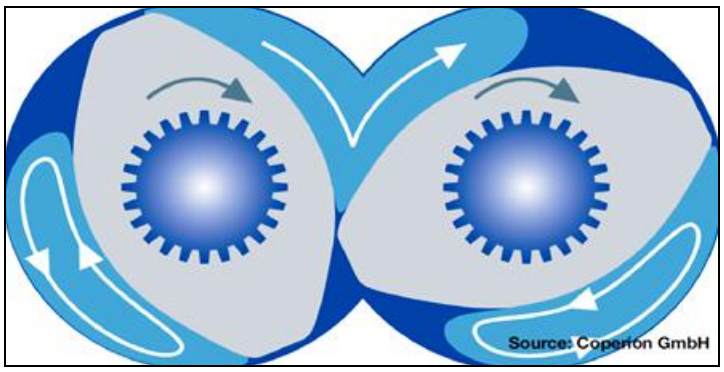


FIG. 7: TWIN SCREW EXTRUDER

Advantages of twin screw extruders-

- High kneading potential
- High dispersing capacity
- Easier material feeding
- Less tendency to overheat (stable melting process)
- Shorter & constant residence times
- Significant greater output.

Downstream Auxillary Equipment: A wide variety of downstream systems are available following the extrusion process. Cooling the extrudate may be in the form of air, nitrogen, on stainless steel conveyors or rolls, or in water. Pellets or shapes may be extruded and wound or cut-to-length. Co-extrusion allows the possibility of complex properties from a single structure, which can be beneficial for time-release products. Film and lamination systems are used to combine melt extrusion with substrates for transmucosal and transdermal applications.

For film applications, chill rolls, and torque winders are used to rapidly cool and collect the extrudate. Film thickness can be adjusted by changing the die opening, the mass flow rate introduced into the extruder, screw speed, the rotation speed of the chill rolls, or the torque winder. The chill roll temperature also influences the properties of the film and may be adjusted with appropriate downstream devices.

Other Monitoring Tools: Used for performance & product quality evaluation. Monitoring devices on HME equipment include temperature gauge, screw speed controller, pressure gauge & extrusion torque monitor.

Extrusion Process: The different zones of the barrel are pre-set to specific temperatures prior to the extrusion process. The feedstock must have good flow properties. This requirement is usually met by insuring that the angle of the feed hopper exceeds the angle of repose of the feed materials. When this prerequisite is not met, the feedstock tends to form a solid bridge at the throat of the hopper resulting in erratic flow.

In these situations, a force feeding device such as a mass flow feeder or side stuffer can be used to direct the feedstock onto the rotating screw As the feedstock is moved along the length of the barrel, thermal energy is generated by shearing, imposed by the rotating screw and from conduction from the barrel via electrical heating bands. Pumping efficiency of the feeding section is dependent upon the friction coefficient between the feed materials and the surface of the barrel and screw. The friction on the inner surface of the barrel is the driving force for the material feed, whereas the friction at the surface of the screw restricts forward motion of the material.

High friction along the barrel and low friction at the screw interface contribute to efficient mass flow in the feed section. Clearly, the bulk density, particle shape, and compression properties of the raw materials impact the feeding efficiency. Material transfer should be efficient in order to maintain an increase in pressure in the compression zone and the metering zone. The pressure rise in these zones insures efficient output of the extrudate. The temperature of the melting zone is normally set 15-60°C above the melting point of semi-crystalline polymers or the glass transition temperature of amorphous polymers. The efficiency of the melting process depends on the polymer properties and the extruder design. In general, polymers with low melt viscosities and high thermal conductivities exhibit a more efficient melting process [24].

Changes in the screw design are sometimes warranted to improve the melting process and improve mass flow through the extruder. Processing conditions depend on the chemical stability and physical properties of the thermal polymer. Melt viscosity, molecular weight, glass transition temperature, and melting point (in the case of a semicrystalline polymer) should be considered to establish appropriate processing parameters. Polymers are subjected to a mechanical shear stress imposed by the rotating screw, and thermal stress due to the relatively high processing temperatures and pressures. Plasticizers, antioxidants, thermal lubricants, and other additives are often included in the formulation to address stability concerns [25].

Characterization of HME Products [26, 29]:

A) **Drug-carrier miscibility**:

a) Hot stage microscopy;
b) DSC;
c) XRD;
d) NMR

B) **Drug-carrier interaction**:

a) FT-IR spectroscopy;
b) Raman spectroscopy;
c) Solid state NMR

C) **Physical structure**:

a) SEM (Scanning Electron Microscopy);
b) Surface area analysis

D) **Surface properties**:-

a) Dynamic Vapor Sorption;
b) Atomic force microscopy;
c) Inverse gas chromatography

E) **Amorphous content**:

a) Polarised light optical microscopy;
b) Hot stage microscopy;
c) DSC;
d) XRD

F) **Stability**:

a) Isothermal calorimetry;;
b) DSC

G) **Dissolution enhancement**:

a) Dissolution;
b) Intrinsic dissolution

Applications: In pharmaceutical industry the melt extrusion has been used for various applications like-

1. Improving the dissolution rate and bioavailability of the drug by forming a solid dispersion or solid solution.

2. Controlling or modifying the release of the drug.

3. Masking the bitter taste of a drug.

4. HME process is currently applied in pharmaceutical field for production of variety of dosage forms such as granules, pellets, tablets, implants & transdermal systems.

5. It produces particles of uniform size with narrow size distribution and good flow properties. Pellets composed of different drugs can be blended and formulated in single unit dosage form that facilitates delivery of two or more chemically compatible or incompatible drug at the same or different site in GI tract. Pellets are frequently used in controlled release delivery system as it facilitates free dispersion of spheroids in the GI tract and offer flexibility for further modification. It improves the safety and efficiency of active ingredient.

HME offers several benefits over the traditional formulation which makes it more attractive with respect to commercialization and ease of operations [27].

Formulation development by HME: The selection of an appropriate carrier compound is important in the formulation and design of a hot-melt extruded dosage form. Depending on the physical and chemical properties of the drug substance and the other excipients in the formulation, the drug may be present as undissolved particles, a solid solution, or a combination in the final dosage form. The state of the drug in the dosage form may have a profound impact on the processability and stability of the product.

Hot-melt extruded dosage forms are complex mixtures of active drug and functional excipients like matrix carriers, release-modifying agents, bulking agents, and various additives. The excipients can impart specific properties to melt extruded pharmaceuticals in manner similar to those in traditional dosage form.

CONCLUSION: Today melt extrusion technology represents an efficient pathway for enhancement of dissolution of poorly soluble drugs. The drug is dissolved in a polymer to improve dissolution of poorly water-soluble drugs or can be present in crystalline form for sustain release applications. The high shear mixing that occurs in the barrel of the extruder during processing ensures good content uniformity of the active material in the finished product.

Furthermore, the availability of a wide range of thermo-analytical and microscopic techniques allow for the characterization of physical and chemical stability of actives and/or excipients used in the melt extrudate with good predictability. The potential of automation and reduction of capital investment and labor costs have made HME worthy of consideration. High-energy input mainly related to shear forces and temperature may pose problems in manufacturing of heat labile actives by HME. This can be overcome in most cases by proper designing of the extrusion equipment and optimizing operating conditions. The possibility of employment of a broad range of polymers, plasticizers and/or processing aids has opened an arena for continued research.

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