

A Systematic Review on: Hot – Melt Extrusion Technique

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Abstract- Hot-Melt extrusion is one of the maximum extensively implemented processing technology with inside the plastic, rubber and meals enterprise. Today this technology has observed its place with inside the array of pharmaceutical production operations. Melt extrusion technique are presently implemented with inside the pharmaceutical faculty for the manufacture of numerous dosage forms and formulations like granules, pellets, capsules, suppositories, implants, stents, transdermal structures and ophthalmic inserts. This review article in detail describes the melt extrusion equipment and technique. Industrial utility of this technique along with specific regions on pharmaceutical industry is illustrated. This article concludes with the overview of posted examples of the hot-melt extrusion technique.

Keywords: Hot-melt extrusion, Manufacturing operations, Extrusion geometry, Extrusion applications.

I. INTRODUCTION

Hot-melt extrusion (HME) processing was established in the early 1930s and during that time, it rapidly became the most widely applied processing technology in the plastic, rubber, and food industries. The utility of HME multiplied to the pharmaceutical industry at the start of the 1970s and changed into utilized in system and product improvement in addition to production. The first utility of HME as a production device with inside the pharmaceutical industry changed into investigated by El-Egakey et al. [1] the use of poly (vinyl acetate-co-meth acrylic acid) and epoxy resin containing a secondary amine as a polymeric carrier [1]. HME is a non-stop pharmaceutical technique that includes pumping polymeric materials with a rotating screw at temperatures above their glass transition temperature (T_g) and occasionally above the melting temperature (T_m) to attain molecular level mixing of the active compounds and thermoplastic binders, polymers, or both. This molecular mixing converts the components into an amorphous product with a uniform shape and density, thereby increasing the dissolution profile of the poorly water-soluble drug. Additionally, HME has been applied for the delivery of water-soluble drugs with numerous programs together with taste masking [2]. This interesting but difficult generation may also provide numerous blessings over traditional pharmaceutical production techniques together with shorter and extra green time to attain the very last product, environmental blessings because of the removal of solvent use, and elevated performance of drug shipping to the patient. As a result, HME has emerged as an alternative platform technology to other traditional techniques for production pharmaceutical dosage forms such as tablets, capsules, films, and implants for drug delivery via oral, transdermal, and transmucosal routes. The introduction of HME to pharmaceutical formulation development has made sophisticated equipment such as the extruder, custom designed downstream auxiliary equipment, and monitoring tools available in comparing the overall performance and product quality. This enhanced availability has supported the growth of this modern approach in pharmaceutical production techniques utilizing both single and twin-screw extruders. [1]

II. HOT-MELT EXTRUSION: EQUIPMENT AND PROCESS

Extrusion is the process of changing the physical properties of the substance by forcing it through an orifice or die under controlled conditions. The extrusion equipment is classified into 3 major classes: ram, radial screen, and roll and screw extruders. Among those, the screw extruders are the most important in the pharmaceutical industry because they continuously convert feed material to the finished form such as a rod, tube, or films. The rotating screws pressure the feed material towards the die, and the material is softened through the frictional heat developed through the barrel wall. The feed reaches the end of the screw in a viscous state that may then be forced through an orifice (or die) and moulded into the preferred form. Types of Screw Extruders Pharmaceutical screw extruders are designed primarily based totally at the preferred extrudate and are required to fulfil the current regulatory requirements for the manufacture of dosage forms.

They are classified as follows:

- A. Single-screw extruders (SSEs): smooth or grooved barrel.
- B. Twin-screw extruders (TSEs): co-rotating or counter rotating with intermeshing or non-intermeshing screws.
- C. Multi-screw extruders (MSEs): static or rotating central shaft.

Irrespective of type, feature, or technique complexity, the different extruders need to be able to rotating the screw at a given operational speed while compensating for the torque and generated shear rate from each the material being extruded and the type of screw in use. The extrusion equipment includes a motor, which acts as a drive unit; an extrusion barrel, which is often manufactured in sections and is bolted or clamped together; and a rotating screw and an end-plate die linked to the end of the barrel. This configuration in the end determines the shape of the extruded product no matter the size and shape of the screw within the stationary cylindrical barrel. The extruder product materials are bound by screw flights and a barrel wall. A central electronic control unit is attached to the extrusion unit so that you can manage the technique parameters together with screw speed (rpm), feed rate, temperatures along the barrel and the die, and the vacuum level for devolatilization. Typical electronic control panel readouts consist of the melt pressure and temperature, motor amperage, viscosity, and specific energy consumption. A schematic of an average extruder meeting is illustrated in Fig. 1 [3]

A. SSE (Single-screw extruders):

SSEs are mechanically simple device which is most widely used extruders. That device has only had slight modification to their working principles since their invention around 1897. The SSE includes one continuously rotating screw in a barrel that gives best molten material (melt) and generates a high stable pressure for a compatible output [Fig. 1]. In general, the screw design may include 20 or more turns with a pitch as like the screw diameter, thereby developing a long slender machine wherein substantial longitudinal temperature gradients can be maintained and controlled. It also gives considerable residence time, thereby allowing a sufficient degree of end-to-end mixing. Different operations may be performed in the SSE such as feeding of raw materials, conveying, melting, devolatilizing, pumping, and shaping. Mixing also can be performed for less demanding applications. The SSE gets the raw material in the feeding area after which conveys it along a flighted screw enclosed in the barrel. The SSE is flood fed through the feed hopper, and the screw rpm determines the output rate. However, they may sometimes starve fed, in which the feed system sets the mass flow rate and is not depend on screw rpm. The flights of the screw and the inner surface of the barrel form a flow channel because of the rotation of the screw. As a feature of the frictional forces in the flow channel, the SSE propels the raw materials in the direction of the proximal part of the screw. The heated barrel surface and the mechanical strength enter supplied through the screws produce a material to form a melt pool, that's inversely proportional to the solid bed size, and therefore, the melt pool will increase as a solid bed decreases. Finally, the molten extrudate is pumped through a die that imparts a particular shape for in addition downstream processing. These essential features combined with low maintenance and low cost make the HME the equipment of preference for the manufacturing of almost all extruded products.[4]

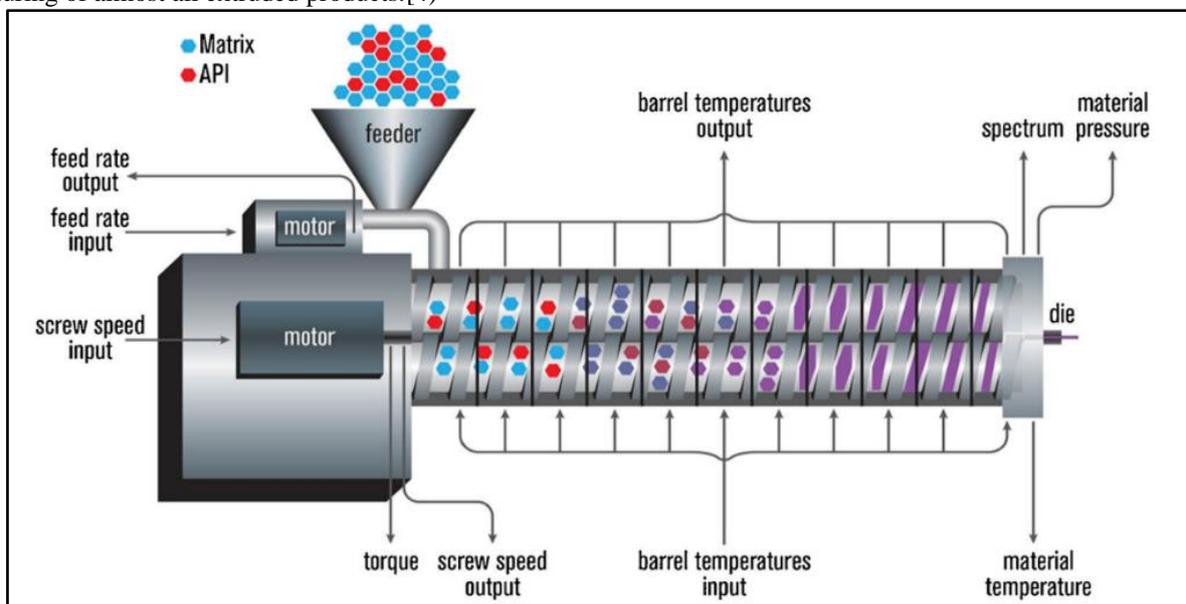


Fig.1. Schematic of typical extruder system. API active pharmaceutical ingredient

B. TSE:

The first TSE was established in the late 1930s in Italy, with the intention of mixing the mechanical actions of some available devices into a single unit. The TSE, because the name indicates, has agitator assemblies prepare up on parallel shafts [Fig. 2]. The use of screws allow different type of configurations and imposes various situations in all of the zones of the extruder, from the feeding of the materials through the hopper to the rotating screw and finally to conveying the materials to the metered pumping zone. Therefore, various types of TSEs are obtained, which every have different handling mechanisms and processing programs. The screws in the TSEs can both be co-rotating (same direction) or be counter-rotating (opposite direction). The varieties of TSEs

may be classified as completely intermeshing or non-intermeshing [Fig. 3]. The completely intermeshing TSE is the maximum famous due to the fact the layout contains a self-cleansing characteristic and, thereby, now no longer simplest reduces the non-movement however additionally prevents the localized overheating of the raw materials with the extruder. Therefore, the raw material does not rotate alongside the screw or adhere to the “first in/first out” principle of the extruder. In assessment to the completely intermeshing TSE, the non-intermeshing is much less famous with inside the blending utility because of its weaker screw interactions and decrease self-cleansing capability. These varieties of screws are frequently used to technique particularly viscous substances and for the elimination of large amount of volatile materials. The non-intermeshing TSEs aren't liable to excessive torque technology whilst processing particularly viscous substances due to the fact those screws are located one at a time from every different.

The TSE is characterized by given functions [4]:

- (a) Reduced residence time
- (b) Self-cleansing screw characteristic.
- (c) Minimum delivers.
- (d) Flexibility
- (e) Enhanced blending

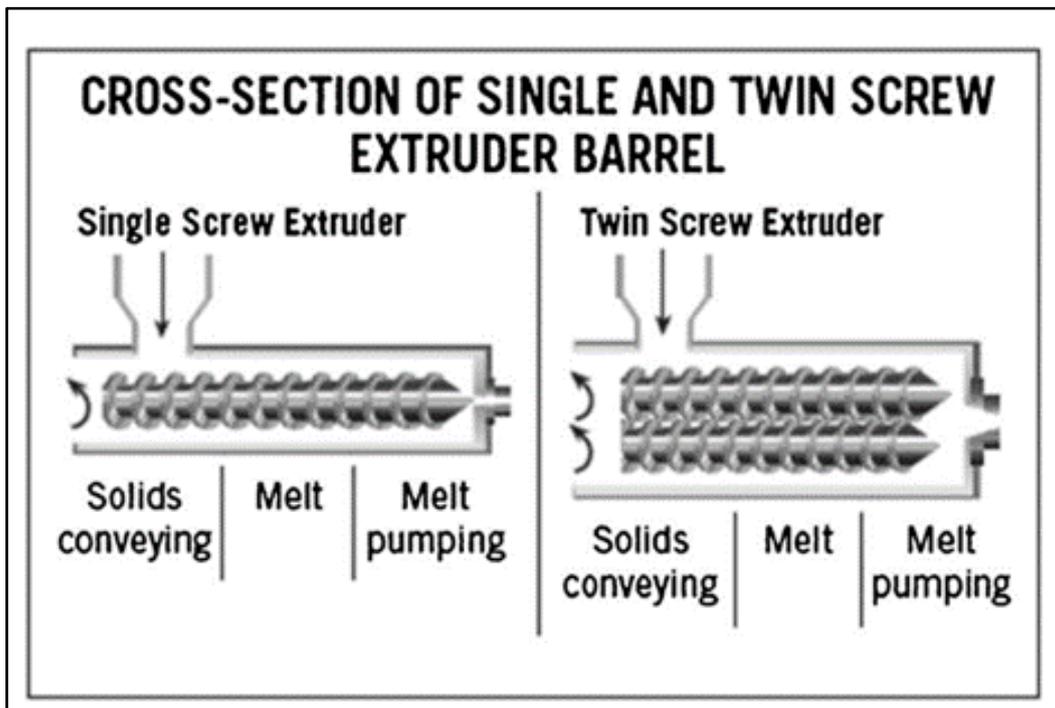


Fig. 2. Cross-section of single- and twin-screw extruders [3]

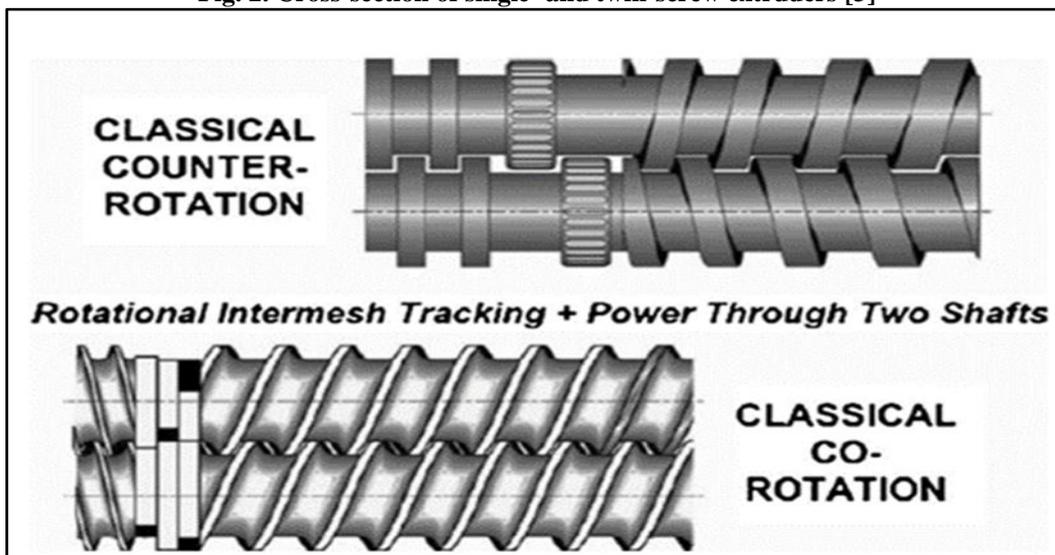


Fig. 3. Classical intermeshing co-rotating and counter-rotating screws [4]

C. MSE:

The extruders that comprise extra than screws are commonly called MSE. Depending upon the quantity of screws used withinside the extruder, the meeting may also range. For instance, if the extruder has six or 8 screws, then they're prepared in a circumferential way. On the alternative hand, if the extruder has 3 or 5 screws, then they're installation in a linear fashion, and withinside the case of the 4 screws, the extruder has a manage screw and 3 spurs [2, 5]. These preparations of the screws withinside the MSE are in no precise experience and can range relying upon the necessities of the meals and pharmaceutical industries. MSE are desired over SSE as a particularly shear-ruled float of the melted cloth in SSE effects in a massive quantity of warmth technology, which thermally degrades the cloth (thermal labile cloth). However, in MSE, because of fine displacement float withinside the intermeshing location among the screws, prevention of decay of thermal labile substances is attained [2,3].

III. MATERIALS USED IN HME

In the pharmaceutical industry the HME is needed for addition of functional excipient and complex mixtures of active ingredients in the preparation, which contain given properties [5, 6]

1. They need to meet the equal tiers of purity and protection as the ones utilized in conventional dosage forms.
2. They need to be capable of deform without difficulty within the extruder and solidify on exiting it.
3. They need to be thermo stable and keep a suitable physical and chemical balance at some point of the HME technique and after sometime between long time storage.
4. By the final dosage form desired in vitro and in vivo performance is attain.

Carriers:

The selection of carrier is depending on the drug-polymer miscibility, polymer stability, and function of final dosage form. The carriers contain water-insoluble polymers and waxes (ethyl cellulose or carnauba wax).

Polymeric carrier which is used in HME are polyvinylpyrrolidone (PVP) [6,8] or its copolymer such as polyvinylpyrrolidone-vinyl acetate (PVP-VA) [3,5], poly (ethylene-co-vinyl acetate) [3,6], various grades of polyethylene glycol (PEG) [3,7], cellulose-esters [4,7] and cellulose acrylates [3,9], polyethylene oxides (PEOs) of varying molecular weights [4], poly-methacrylate derivatives and poloxamers.

Active Pharmaceutical Ingredients (API):

For the development of desired dosage forms the physical and chemical properties of active ingredients is altered. The active ingredients may enhance or interfere with the performance of another component in formulations.

Characteristics of API:

- Solubility
- Melting temperature
- Physical State
- Lipophilicity
- Thermal Stability

Polymers:

The selection of polymers is based on the drug-polymer miscibility, polymer stability and function of final dosage form. The polymer which is selected that have thermoplastic behaviour, suitable glass transition temperature (between 50-180-degree C), High thermal stability, no toxicity, E.g. Polyethylene glycol, Eudragit, Vinyl pyrrolidone.

Plasticizers:

Plasticizers are low molecular weight substances which are useful for softening of polymers to make them more flexible. Plasticizers change the extrudate properties during the HME process and decide the release properties of the final dosage form. Plasticizer is improving processing condition, physical and mechanical properties of final product. To facilitate the extrusion and increase flexibility. Plasticizer reduces the glass transition state of polymer, processing temperature and increase the stability. E.g. Diethyl phthalate, PEG 400, Glycerol, Methyl paraben.

Overview of HME-primarily based totally advertised drug merchandise:

Current hobby in HME is developing quickly with >500 papers posted withinside the medical literature at some point of the beyond decade. HME is hired to provide extraordinary DDS, together with for oral administration: granules, pellets, films and capsules however additionally transdermal, transmucosal and subcutaneous (implants) management. Although there's a massive capacity for formulating poorly soluble tablets into ASDs, few had been commercialized so far [Table 1] Nevertheless, this fashion is honestly converting as increasingly HME-primarily based totally drug merchandise seem withinside the pipeline of many pharmaceutical companies. Lately, there had been new product submissions to the FDA and to the European Medicines Agency (EMA). In 2016, a brand new implant for the remedy of opioid dependence, containing buprenorphine, changed into authorised through the FDA. Probuphine1 is a 6- month remedy for opioid dependence, the primary to be authorised and the simplest one so far. It includes 4 subcutaneous implants of 26 mm every, positioned withinside the underside of the higher arm, supplying a non-stop and constant launch of low-dose buprenorphine. In October 2018, the FDA additionally authorised Annoveral (segesteron acetate and ethinyl estradiol vaginal machine) – a mixed hormonal contraceptive that marked the primary time a vaginal ring may be reused for 1 year. In what issues oral dosage paperwork, novel merchandise has additionally been authorised. Belsomra1 (suvorexant), an orexin receptor antagonist and the primary of its class, changed into authorised in 2014 through the FDA. It is an ASD organized through

HME to maximise BA. The crew decided on to extrude the compound with a pH-impartial solubility polymer, copovidone, and located that the pill hardness changed into associated with disintegration, dissolution and absorption. Viekirax1 (EU) [Technivie1 (USA)], authorised in 2014 through the EMA and in 2015 through the FDA, is likewise a totally thrilling product from a technical factor of view due to the fact all 3 tablets (ombitasvir, paritaprevir and ritonavir) are for my part transformed into amorphous substances through HME to beautify their BA. Only then the person extrudates are mixed, tableted and coated. Venetoclax authorised as Venclyxto1 withinside the EU and as Venclextal withinside the USA for the remedy of continual lymphocytic leukemia, is likewise synthetic through HME as a stable dispersion thanks to the very terrible water solubility. Mixtures of drug and copovidone with surfactants (Aerosil1 and Tween1) have been extruded to beautify its absorption, and the system changed into then patented, demonstrating stepped forward BA whilst synthetic through HME. More these days, Maviret1 (EU) [Mavyret1 (USA)] changed into authorised through the EMA and FDA for the remedy of continual hepatitis C. The tablets glecaprevir and pibrentasvir are poorly water-soluble and they're additionally for my part formulated as ASDs to boom the obvious aqueous solubility and acquire good enough in vivo absorption. To our information, there are already ophthalmic inserts, 4 implants and vaginal earrings authorised so far, and plenty of extra are beneathneath improvement.

Pharmaceutical form	Commercial name	Owner	Drug(s)	Therapeutic indication	Polymer	HME purpose
Ophthalmic insert	LacrisertOzurde x	Merck	-	Dry eye syndrome	HPC	Shaped (rod) system
		Allergan	Dexamethasone implantable device	Macular edema	PLG A	Shaped system
Implants	Zoladex Depot-Profact	AstraZeneca Sanofi Aventis	Goserelin Buserelin	LHRH agonist Carcinoma of the prostate gland	PLG A PLG A	Shaped(rod) system Shaped(rod) system
Devices	Probuphine (2016, USA) Implanon NuvaRing	Titan Schering-Plough NV Organon	Buprenorphine	Opioid dependence	EVA	Shaped(rod) system
				Contraceptive	EVA	Shaped(rod) system
				Contraceptive	EVA	Shaped(ring)system

Pharmaceutical improvement of HME-primarily based totally formulations: Pharmaceutical improvement targets to offer sturdy information thru the utility of systematic procedures that permit designing a best product and its production technique consistently. The facts and information accrued from improvement and manufacturing have to offer the medical expertise to guide a layout area, drug product specs and technique controls. The whole expertise of the system and technique is consolidated withinside the Common Technical Document (CTD; phase 3.2.P.2) after which used to post a brand new drug utility to the able authorities [7, 3, 27, 29]. In HME primarily based totally drug merchandise, a sturdy pre-system evaluation is the important thing to a success improvement. A step-through-step method, beginning with the thermodynamic assessment of numerous structures, accompanied through a polymer screening take a look at coupled with multivariate statistical evaluation, is beneficial to swiftly pick out the maximum promising HME structures. This is the manner to keep away from losing time, cash and attempt in failed compositions.

Thermodynamic predictions and considerations:

The choice of a appropriate service specially relies upon at the solubility and miscibility of a drug-polymer machine, polymer physicochemical houses, balance and conditions of very last dosage paperwork. Therefore, bodily and chemical houses of drug materials and feasible companies have to be cautiously evaluated earlier than beginning the improvement of HME-primarily based totally formulations. The miscibility of medication and companies is commonly one of the first troubles to be evaluated. This is critical to assure good enough drug load and chemical interactions among the additives, that's precious to optimize technique parameters and product overall performance on dissolution. However, there's no hooked up system to pick out excipients for HME to date [11]. Several techniques had been defined to be expecting miscibility with the service, commonly making use of thermodynamic predictions in an try to manual system improvement rationally. Predicting miscibility is a tough task, and the effects are crucial for the route of the improvement paintings. Some of the extra not unusual place procedures consist of the prediction of Tg of the mixture the use of the Gordon-Taylor equation (or the simplified shape through Fox), the calculation of the Hansen solubility parameters, the Flory-Huggins concept and the calculation of the interplay parameter (χ), and additionally the development of section diagrams. A evaluation of thermodynamic and computational techniques has been these days posted through DeBoyace and Wildfong. The Gordon-Taylor (or Fox) equation is a normally used method to are expecting the miscibility of drug-polymer blends withinside the pharmaceutical enterprise setting, as pondered in courses from Novartis, Merck, AbbVie, Johnson & Johnson (J&J) and Lundbeck.

One of the maximum latest examples is from J&J, in which the Gordon-Taylor equation changed into implemented withinside the evaluation of the effect of the molecular shape of sorafenib and its fluorinated shape, regorafenib, in interactions and consequent

miscibility with polymers. A fine deviation of T_g from the prediction of the sorafenib system in preference to the regorafenib one changed into a demonstration of more potent interactions, showed through NMR and computational techniques.

IV. ADVANTAGES OF HOT MELT EXTRUSION

1. Increases bioavailability of poorly soluble compound.
2. Economical process with reduced production time, fewer processing steps, and a continuous operation.
3. Capabilities of sustained, modified, and targeted release;
4. Better content uniformity in extrudates.
5. Uniform dispersion of fine particles.
6. It avoids dose dumping.
7. Clinically helpful in drug abuse.
8. HME can deliver drugs in a sustained manner and targeted drug delivery.
9. It is a potential continuous process.
10. It require less labour and equipment demands
11. HME can produce solid solutions and dispersions which results in improved solubility and bioavailability. [4, 7, 14, 24]

V. DISADVANTAGES OF HOT MELT EXTRUSION

1. The process may not be applicable for the heat liable drugs.
2. Must be relatively moisture free.
3. It include thermal process, use of limited number of polymers
4. It is not suitable for the high heat sensitive molecules. [2, 15, 23]

Limitation of Hot Melt Extrusion:

1. It need a high energy input.
2. Limited number of polymer is used for process.
3. Requires raw materials with high flow properties.
4. It is difficult to keep stability for heat sensitive drug and polymer.

VI. PHARMACEUTICAL APPLICATIONS OF HME

Solid Dispersions for Solubility/Bioavailability Enhancement:

A stable dispersion is a machine wherein one or extra energetic elements are molecularly allotted right into a hydrophilic inert service matrix. The system of an API right into a stable dispersion converts the poorly water-soluble crystalline shape to the amorphous, which will increase its solubility. Different strategies are normally used to put together stable dispersions together with the soften fusion and solvent evaporation strategies. HME is a really appropriate approach for the formation of stable dispersions, and its major gain is the technique does now no longer require solvent use. [2, 16, 22]. Therefore, the related solvent-associated balance dangers that may arise at some point of the shelf existence of the system are averted given that there's no residual solvent. Based at the configuration of the gadget and processing temperature, the TSE is rising because the maximum possible choice withinside the pharmaceutical enterprise for the manufacturing of stable dispersions We will now spotlight a few sensible examples from the literature, which gift applicable discoveries and advances withinside the utility of HME for the manufacturing of stable dispersions.

Hulsmann et al. studied the HME approach as an opportunity technique to beautify the dissolution fee of the poorly water-soluble drug 17 β -estradiol hemihydrate. Different compositions of excipients together with PEG 6000, PVP, or a vinylpyrrolidone-vinyl acetate copolymer have been used as polymers, and Sucroester WE15 and Gelucire 44/14 have been additives. The stable dispersions considerably elevated the dissolution fee in comparison to that of the natural drug or the bodily mixtures. A 30-fold boom withinside the dissolution fee changed into acquired for the system containing 17 β -estradiol, PVP, and Gelucire 44/14 at 10, 50, and 40%, respectively. The stable dispersion changed into then tableted, and the dissolution research confirmed that the development withinside the dissolution changed into maintained with the pill dosage shape [13].

Nakamichi et al. verified that the screw configuration performs an vital function in changing the crystalline and the dissolution houses of stable dispersions. Nifedipine changed into used as a version drug, and hydroxypropyl methylcellulose phthalate (HPMCP) changed into the polymer. The authors mentioned that the kneading paddle factors of the screw affected the physicochemical houses of the extruded substances and generated obvious extrudates that exhibited super-saturation in dissolution checks. The kneading paddle factors retained the cloth withinside the extruder for an extended length beneath extreme shear, and therefore, stable dispersions may be organized regardless of the running situations. In contrast, of their absence, the running situations of the system together with the screw pace and quantity of water brought to the feed cloth considerably encouraged the physicochemical houses of the extrudates. Slow screw speeds and the addition of most desirable portions of water elevated the fee of drug dissolution however did now no longer reason super-saturation [6,21].

He et al. advanced a stable dispersion of fenofibrate the use of HME generation to beautify the bioavailability of the API. These authors in comparison the results of extraordinary polymers together with Eudragit® E one hundred and polyvinylpyrrolidone-vinyl acetate copolymer S630 (PVP-VA) at the dissolution fee of fenofibrate. The extrudates have been characterised the use of differential scanning calorimetry (DSC), X-ray diffractometry (XRD), in vitro dissolution trying out, and in vivo bioavailability

research. The DSC and XRD effects found out that the fenofibrate changed into a non-crystalline nature within the stable dispersions of each polymer. The extraordinary solubility and gelling inclinations of the 2 polymers ended in extraordinary dissolution profiles for the fenofibrate. Beagle puppies have been the animal version used to evaluate the relative bioavailability of the Eudragit® E one hundred stable dispersions with micronized Lipathyl® capsules, which changed into 177.1% [16]. Sathigari et al. used HME generation to put together stable answers of efavirenz (EFV) with extraordinary polymers together with Eudragit® E PO or Plasdone® S-630 to enhance the drug dissolution fee. The drug-polymer miscibility and processability the use of HME have been showed through studying the thermal and rheological houses as a feature of drug concentration. The extrudates have been in addition characterised the use of DSC, XRD, Fourier remodel infrared spectroscopy (FTIR), and dissolution research. The XRD and DSC effects showed the life of the amorphous shape of EFV within the extrudates at some point of garage. The EFV extrudates verified a quicker launch profile than the crystalline drug did. The FTIR evaluation confirmed an interplay among the EFV and Plasdone® S-630, which decreased the molecular mobility and averted crystallization at some point of garage [14,19,20,31].

As evidenced through the above research, HME is a really possible approach for the formation of stable dispersions that can boom the dissolution charges of poorly soluble APIs and extra importantly boom their bio availabilities.

VII. EVALUATION HOT MELT EXTRUDES [16]

Thermal and chemical balance of extrudes: Thermal transitions of the polymers also are indicative of the temperature of the extrusion. The glass transition temperatures and melting factors have been measured the use of a differential calorimeter. For balance trying out of the polymers, 3 varieties of techniques have been considered, i.e. thermogravimetry, initial extrusion checks and excessive overall performance liquid chromatography. With the primary one the temperature profile weight reduction changed into recorded the use of thermobalance.

Differential Scanning Calorimetry: DSC changed into extensively used to look at the thermal houses of the cloth utilized in HME. It may be used to decide the TG and Tm wherein strength is needed or launched. It extensively utilized in drug excipient incompatibility research. It changed into extensively utilized to differentiate among amorphous and crystalline paperwork.

Thermo Gravimetric Analysis: TGA is a degree of thermally brought about cloth weight reduction as a feature of implemented temperature. TGA is significantly restrained to, studies concerning both weight advantage or loss and its frequency used for the studies of desolvation and decomposition.

Infrared Spectroscopy: IR may be used to pick out modifications in linkages among practical organizations because of structural changes or absence of crystal shape.

Applications of HME in Pharmaceutical Research:

Despite the truth that preliminary studies traits have targeted at the results of system and processing variables at the houses of the very last dosage paperwork extra latest investigations have targeted on using HME as a singular production generation of stable molecular dispersions thru the improvement of minimatrices, flavour masked formulations, and additionally sustained launch formulations in addition to paediatric formulations. Early paintings through De Brabander et al. (2000) defined the practise of matrix minitablets which changed into accompanied through in addition investigations into the houses of sustained launch minimatrices fabricated from ethyl cellulose, HPMC, and ibuprofen. Extruded minitablets confirmed minimised threat of dose dumping, decreased inter- and intrasubject variability. Very these days, Roblegg et al. mentioned the improvement of retarded launch pellets the use of vegetable calcium stearate (CaSt) as a thermoplastic excipient processed thru HME, in which pellets with a drug loading of 20% paracetamol launched simplest 11.54% of the drug after eight hours because of the tremendous densification of the pellets. As predicted, the drug launch changed into encouraged through the pellet length and the drug loading. A microbicide intravaginal ring (IVRs) IVR changed into organized and advanced from polyether urethane (PU) elastomers for the sustained shipping of UC781 (a particularly amazing nonnucleoside opposite transcriptase inhibitor of HIV1). PU IVRs containing UC781 have been fabricated the use of a hotmelt extrusion technique [14,16,31]. Moreover, a fourfold boom within the availability of propranolol within side the systemic movement changed into located whilst the HME system changed into in comparison with a commercially to be had system (Inderal). Over the closing 5 years HME has been used in large part to fabricate granules, pellets, instantaneously and changed launch capsules, transmucosal/transdermal movies, and implantable reservoir gadgets [3, 4, 9,]. For instance, with appreciate to drug management thru the oral route, molecular stable dispersions of nifedipine, nimodipine, and itraconazole had been efficiently produced the use of HME generation. Amorphous indomethacin dispersions had been synthetic the use of pharmaceutically proper hydrophilic polymers through the use of HME generation [12, 20].

Furthermore, HME studies traits have pushed focused drug shipping structures together with enteric matrix capsules and pill structures over the previous couple of years. Miller et al. have verified the capacity of HME to behave as a green dispersive technique for aggregated, nice engineering debris to enhance dissolution fee houses through improving debris' wettability. A very thrilling research of Verreck and coworkers (2006) decided using supercritical carbon dioxide (scCO₂) as a brief plasticiser at some point of the manufacture of ethyl cellulose thru HME. A tremendous discount within the processing temperature changed into done the use of scCO₂ with none disadvantageous results at the extrudate. Macroscopic morphology changed into considerably altered

because of enlargement of the scCO₂ withinside the die. The use of scCO₂ elevated the floor location, porosity, and hygroscopicity of the very last dosage paperwork. [11, 17, 24, 27, 31].

CONCLUSION AND FUTURE PERSPECTIVES

Over the beyond few decades, HME generation has emerged as an appealing novel technique for production drug shipping structures. HME has been nicely explored and documented as a non-stop, solvent-unfastened, sturdy, quick, and cost-effective production technique for the manufacturing of a huge kind of pharmaceutical dosage paperwork together with oral, topical movies, implants, and ophthalmic inserts. The SSE and TSE are steadily changing conventional batch techniques due to the steady and reproducible nature of the non-stop extrusion. There is developing hobby in HME generation due to the fact its miles appropriate for each excessive and really amazing low-dose compounds, and the gadget is extensively to be had. However, in spite of the several apparent blessings of this approach, HME isn't but a not unusual place production device for drug shipping structures. Currently, the numbers of drug merchandise available in the marketplace synthetic the use of HME are restrained due to the fact some drawbacks have impeded its great utility withinside the pharmaceutical enterprise. For instance, in comparison to different pharmaceutical strategies, HME calls for a better strength enter specially related to the shear forces and temperatures used, and some of thermolabile compounds have needed to be excluded from this technique because of excessive processing temperatures. However, modifications withinside the layout of the gadget (screw assemblies and extruder die) in addition to the addition of plasticizers may also make a contribution to lessen the processing temperatures and house time and, thereby, keep away from the thermal degradation of APIs at some point of processing.

The FDA has identified the precise adaptability of the HME generation to QbD and PAT strategies. The QbD method includes using information control and the formal layout of experiments to generate and refine the layout area at some point of the existence cycle of the product. Therefore, technique engineers are presently running intently with pharmaceutical scientists and managers to apprehend and refine the system and production technique through figuring out best threat control standards, to set up suitable manage strategies. Hot Melt Extrusion has been nicely explored and documented as a constant, solvent-unfastened, rapid and cost-effective production technique for the manufacturing of a large variety of pharmaceutical dosage paperwork, together with oral, topical movie, implants and ophthalmic inserts. HME has verified to be a sturdy technique of manufacturing some of drug shipping machine. There is growing hobby in HME generation as it's miles suitable for each accelerated and really effective low dose compounds, in addition to the gadget is normally accessible.

In conclusion, HME as a non-stop pharmaceutical production technique has colossal adaptability and capacity to update the conventional batch technique. Furthermore, with the incorporation and help of QbD and PAT procedures, the HME technique can without difficulty facilitate the scale-up from the laboratory to the industrial scale. This appealing characteristic of scalability exhibited through HME is predicted to boom the call for extrusion techniques in pharmaceutical production withinside the future.

REFERENCES

1. Kleinebudde P, Lindner H. Experiments with an instrumented twin-screw extruder using a single-step granulation/extrusion process. *Int J Pharm.* 1993;94(1):49–58.
2. Cheremisinoff NP. *Guidebook to extrusion technology.* Englewood Cliffs, NJ: Prentice-Hall; 1993. p. 23–38.
3. Steiner R. Extruder design. In: Ghebre-Sellassie I, Martin C, editors. *Pharmaceutical extrusion technology*, vol. 133. New York: Marcel Dekker, Inc; 2003. p. 19–38.
4. Verreck G. The influence of plasticizers in hot-melt extrusion. In: Douroumis D, editor. *Hot-melt extrusion: pharmaceutical application.* 1st ed. UK: John Wiley & Sons, Ltd; 2012. p. 93–112.
5. Repka MA, Shah S, Lu J, Maddineni S, Morott J, Patwardhan K, et al. Melt extrusion: process to product. *Expert Opin Drug Deliv.* 2012;9(1):105–25
6. Hancock BC, Zografi G. Characteristics and significance of the amorphous state in pharmaceutical systems. *J Pharm Sci.* 1997;86(1):1–12.
7. Cuff G, Raouf F. A preliminary evaluation of injection molding as a technology to produce tablets. *Pharm Technol.* 1998;22(6):96–106.
8. Lakshman JP, Cao Y, Kowalski J, Serajuddin AT. Application of melt extrusion in the development of a physically and chemically stable high-energy amorphous solid dispersion of a poorly water-soluble drug. *Mol Pharm.* 2008;5(6):994–1002.
9. Kazarian S. Polymer processing with supercritical fluids. *Polym Sci Ser C.* 2000;42(1):78–101.
10. Verreck G, Decorte A, Li H, Tomasko D, Arien A, Peeters J, et al. The effect of pressurized carbon dioxide as a plasticizer and foaming agent on the hot melt extrusion process and extrudate properties of pharmaceutical polymers. *J Supercrit Fluids.* 2006;38:383–91.
11. Chaturvedi, K. et al. (2018) Influence of processing methods on physicomachanical properties of Ibuprofen/HPC-SSL formulation. *Pharm. Dev. Technol.*
12. Speer, I. et al. (2018) Prolonged drug release properties for orodispersible films by combining hot-melt extrusion and solvent casting methods. *Eur. J. Pharm. Biopharm.* 129, 66–73
13. EMA (2014) CHMP Assessment report: Viekirax (ombitasvir/paritaprevir/ritonavir). Report number EMA/768346/20142014
14. Shah, S. et al. (2013) Melt extrusion with poorly soluble drugs. *Int. J. Pharm.* 453, 233–252
15. <http://www.pharinfo.net/reviews/meltgranulationtechniques/reviews>.

16. J. W. McGinity and J. J. Koleng, "Preparation and evaluation of rapid release granules using novel melt extrusion technique," American Association of Pharmaceutical Scientists, pp. 153–154, 2004.
17. D. S. Jones, "Engineering drug delivery using polymer extrusion/injection moulding technologies," School of Pharmacy, vol. 4-9, pp. 18–27, 2008.
18. H. H. Grunhagen and O. Muller, "Melt extrusion technology," Pharmaceutical Manufacturing International, vol. 1, pp. 167–170, 1995.
19. S. Singhal, V. K. Lohar, and V. Arora, "Hot-melt extrusion technique," WebmedCentral Pharmaceutical Sciences, vol. 2, no. 1, Article ID 001459, 2011
20. DiNunzio JC, Zhang F, Martin C, McGinity JW. Melt extrusion. In: Robet III OW, Watts AB, Miller DA, editors. Formulating poorly water soluble drugs. New York: Springer; 2012. p. 311–62.
21. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm. 2000;50(1):47–60
22. Breitenbach J, Magerlein M. Melt extruded molecular dispersions. In: Ghebre-Sellassie I, Martin C, editors. Pharmaceutical extrusion technology, vol. 133. New York: Marcel Dekker Inc; 2003. p. 245–60.
1. 33. Serajuddin AT. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. J Pharm Sci. 1999;88(10):1058–66.
23. Hulsmann S, Backensfeld T, Keitel S, Bodmeier R. Melt extrusion—an alternative method for enhancing the dissolution rate of 17beta-estradiol hemihydrate. Eur J Pharm Biopharm. 2000;49(3):237–42.
24. Nakamichi K, Nakano T, Yasuura H, Izumi S, Kawashima Y. The role of the kneading paddle and the effects of screw revolution speed and water content on the preparation of solid dispersions using a twin-screw extruder. Int J Pharm. 2002;241(2):203–11.
25. He H, Yang R, Tang X. In vitro and in vivo evaluation of fenofibrate solid dispersion prepared by hot-melt extrusion. Drug Dev Ind Pharm. 2010;36(6):681–7.
26. Sathigari SK, Radhakrishnan VK, Davis VA, Parsons DL, Babu RJ. Amorphous-state characterization of efavirenz-polymer hot melt extrusion systems for dissolution enhancement. J Pharm Sci. 2012;101(9):3456–64
27. J. Breitenbach, "Melt extrusion: from process to drug delivery technology," European Journal of Pharmaceutics and Biopharmaceutics, vol. 54, no. 2, pp. 107–117, 2002
28. S. S. Jana and R. Miloslava, "Hot-melt extrusion," Ceska a ' SlovenskaFarmacie', vol. 61, no. 3, pp. 87–92, 2012.
29. F. Cilurzo, I. E. Cupone, P. Minghetti, F. Selmin, and L. Montanari, "Fast dissolving films made of maltodextrins," European Journal of Pharmaceutics and Biopharmaceutics, vol. 70, no. 3, pp. 895–900, 2008.
30. F. Zhang and J. W. McGinity, "Properties of sustained-release tablets prepared by hot-melt extrusion," Pharmaceutical Development and Technology, vol. 4, no. 2, pp. 241–250, 1999.