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A promising method to enhance the solubility of poorly water soluble drug by using hot-melt extrusion technique

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Abstract

More than 40% of new chemicals are of poor solubility, it causes poor bioavailability. Several techniques are available to increase the solubility of drugs, such as converting the drug into salt form, complexion, co-solvency, particle size reduction, nano-suspension, cryogenic technique, modification of crystal habit etc. Hot melt extrusion has increased wide acknowledgment in the recent past. Over the past recent three decades modern flexibility has permitted hot melt extrusion (HME) is to increase wide acknowledgment and has just settled its place in the wide range of assembling activities and pharmaceutical research advancements. HME has just been exhibited as a vigorous, novel system to cause strong scatterings so as to give time controlled, changed, broadened, and focused on medicate conveyance bringing about improved bioavailability just as taste covering of bitter Active Pharmaceutical Ingredients (APIs). Hot melt extrusion is one of the efficient technique for improving the solubility of hydrophobic drugs by forming solid dispersion. It is a solvent-free process and time taken for the production is less. The process involved in this technique include, weighing/feeding, Melting, Mixing, Venting, Extrusion, Cooling, Pelletizing. Solubility of many drugs have improved by utilizing hot melt-extrusion technology. In this review, a detailed overview about Solubility enhancement of drugs by hot-melt extrusion and its applications are discussed. This review summarizes the importance and uses of solid dispersion technique for improving the solubility of poorly soluble drugs

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INTRODUCTION

At present, many novel APIs possess low solubility and poor bioavailability after oral administration. So, it is necessary to increase solubility and the permeability of the drug and to improve the bioavailability (Vasconcelos *et al.*, 2007). Almost 60% of the formulation available in the market is oral administration. Nowadays much stress is given to drug discovery towards the identification of hydrophobic molecules for oral administration (Juma *et al.*, 2008). To enhance the dissolution and bioavailability of hydrophobic drugs, several technologies such as co-solvency, micellar solubilisation, micronization, chemical modification, hydrotropy, pH adjustment, solid dispersion formation, complexion, etc. (Vemula *et al.*, 2011). The new technology introduced into the industry in the year 1991 by Warner-Lambert used Hot-melt extrusion method to increase the solubility of hydrophobic drugs. Commercial use of extrusion process was

introduced in the year 1930. The method of Hot-melt extrusion was initially used for the manufacturing of lead pipes during the last part of eighteenth century. Palletized feeds are produced by extrusion method, which is most commonly applied in the production of animal feed. Food and Plastic industry also uses HME technique. Development of API molecular dispersion into various polymers has been done by HME. This HME process also used to make the drug more palatable. The several research groups evaluated that HME increases dissolution rate of hydrophobic drugs and to modify the drug release. Extrusion is a process that converts a raw material into a uniform shaped product. The process involves the process of grinding the raw material with the help of a rotating screw under a specific temperature after which it passes through a die under controlled condition (Repka *et al.*, 2008). HME is widely discussed in both the academic level as well as in the pharmaceutical industry for the range of applications it possess such as dosage forms like tablet and capsule. Extrusion should produce consistent product flow through relative heating and cooling under continuous process. This technique is reviewed based on the overall prospective of its various elements, processing technologies and novel formulation and development in oral drug delivery (Crowley *et al.*, 2007).

SOLUBILITY

One of the main challenges in pharmaceutical formulations is the drug solubility and its bioavailability. IUPAC defines solubility as the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent (Savjani *et al.*, 2012). Oral administration of drugs is more common because of the cost effectiveness, patient compliance and ease of administration (Krishnaiah, 2010). Poor solubility is associated with BCS Class **II** and IV, which in turn leads to poor bioavailability of drugs. Examples of class **II** and IV drugs given in (Table 1).

Importance of Solubility Enhancement:

Solubility is considered as one of the important parameters for the drug to reach the systemic circulation to elicit required therapeutic action. In order to influence therapeutic plasma concentration, hydrophobic drugs always need high doses. Most of the new chemical entity and generic drugs often face solubility related problems to a greater extent. When the drug is administered orally, the main rate limiting step associated with this route is solubility. Water is the universal solvent, used in almost all the pharmaceutical formulations. Drugs with poor solubility, decreases the dissolution and absorption of drugs, thereby leading to poor bioavailability of drugs (Vogt *et al.*, 2008). USP and BP solubility criteria given in (Table 2).

Techniques of Solubility Enhancement

1. Physical Modifications given in (Table 3)
2. Chemical Modifications given in (Table 4)
3. Miscellaneous Methods given in (Table 5)

Hot melt extrusion process

The expertise (HME) has verified to be a strong technique of producing copious drug delivery system and consequently the HME is established to be valuable in the pharmaceutical industry. Hot melt extrusion is a method of pumping a raw material into the product of uniform shape and density at elevated controlled temperature and pressure. Breitenbach first introduced the hot melt extrusion process in the pharmaceutical manufacturing (Breitenbach, 2002). The Follonier and his co-workers first said about the hot melt technology to manufacture sustained release polymer based pellets (Andrews *et al.*, 2009). To understand the process of the hot melt extrusion (Figure 1) the whole procedure of HME in the following,

1. The extruder is fed through the hopper
2. Mixing, grinding, particle size reduction, venting and the kneading.
3. Pass through the die
4. Exit from the die and downstream processing

The extruder has feeding hopper, barrels, single or twin screws, die, and screw driving unit.

HME is a process that changes a powder blend into uniform shaped product by compacting the powder or mixture. In the process of HME the active drug along with plasticisers and other additives are passed through a die and orifice under controlled conditions of temperature and pressure.

The extruder consists of two types

1. Single screw extruder
2. Twin screw extruder

Single Screw Extruder (SCE)

Single screw extruder are widely used as its mechanism is simple and have only slight alterations have

Table 1: Examples of class II and IV drugs

S.No	Class **II** drugs	Class IV drugs
1	Chlorpromazine	Amphotericin B
2	Diclofenac	Chlorothiazide
3	Digoxin	Colistin
4	Erythromycin	Furosemide
5	Ibuprofen	Mebendazole

Table 2: USP and BP solubility criteria

S.No	Descriptive term	Part of solvent required per part of solute
1	Instantly soluble	Less than 1
2	Freely soluble	1 to 10
3	Soluble	10 to 30
4	Less soluble	30 to 100
5	Lesser soluble	100 to 1000
6	Hardly soluble	1000 to 10,000
7	Practically insoluble	10,000 and over

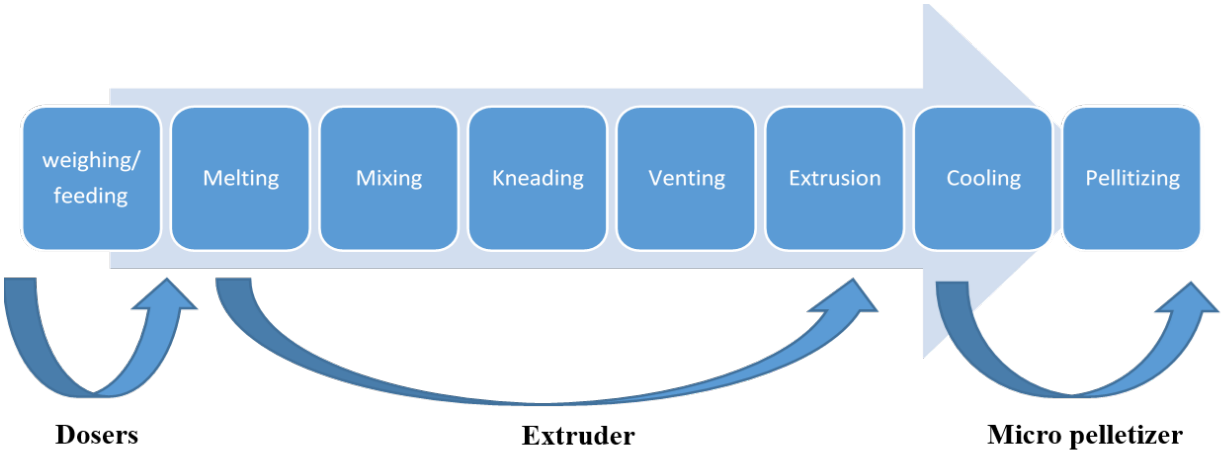

Figure 1: Schematic diagram of the HME process

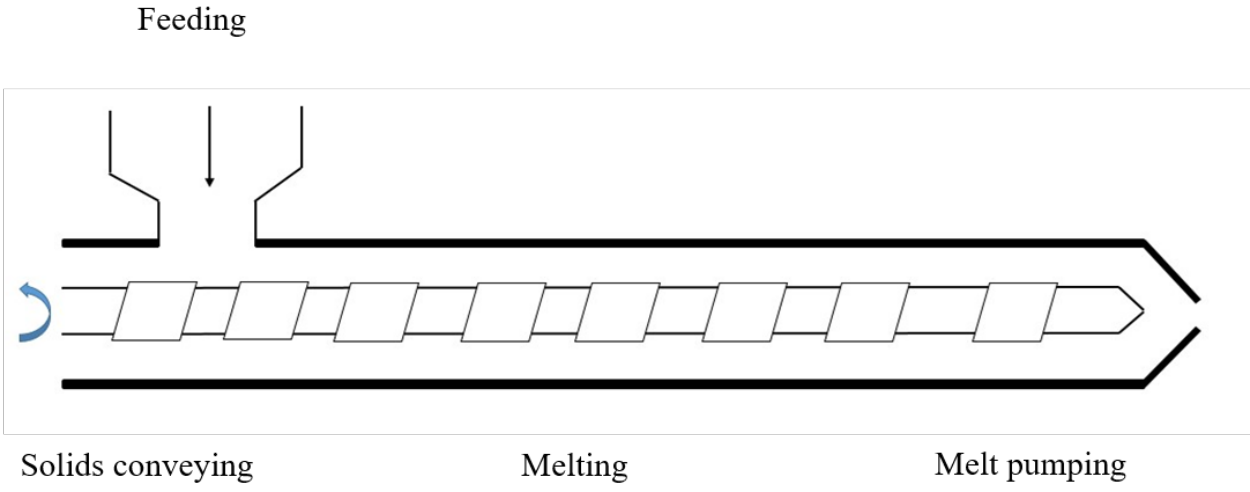

Figure 2: single screw extruder

Table 3: Physical modification

S.No	Solubility Enhancement Technique	Description
1.	Particle size reduction	Particle size is inversely proportional to the surface area. As the particle size decreases, (which increases the exposure of particle in the solvent) the solubility of the drug increases. Micronization: Increased dissolution of fenofibrate more than 10 folds (Vogt *et al.*, 2008; Chaumeil, 1998)
2.	Solid dispersion	With the help of highly soluble carriers, poorly soluble drug release occurs, which creates a large surface area and increases the solubility (Huang and Dai, 2014). Techniques: Hot Melt Extrusion and Solvent evaporation.
3.	Nano- suspension	In the absence of matrix material, solubility increases by suspending the poorly-soluble drug in dispersion. (Agrawal and Patel, 2011). Techniques: High Pressure homogenization, Precipitation Technique, Combined precipitation and homogenization, Media milling.
4.	Cryogenic Techniques	Solubility is enhanced by the formation of amorphous drug particles (nanostructured), with high porosity. (Leuenberger, 2002). Techniques: Ultra-rapid freezing, Spray Freezing onto Cryogenic Fluids, Spray Freezing into Cryogenic Liquids, Spray Freezing into vapour over liquid.
5.	Modifications of Crystal Habit	Crystal Engineering: With the help of polymorphs, hydrates/solvates, solubility of hydrophobic drugs can be increased. Polymorphs - Metastable form is associated with enhanced solubility. Hydrates/ solvates – Eg) Comparing to non-solvated polymorphs, antidiabetic drug glibenclamide isolated from pentane and toluene possess more solubility. (Ritika and Aggarwal, 2012).

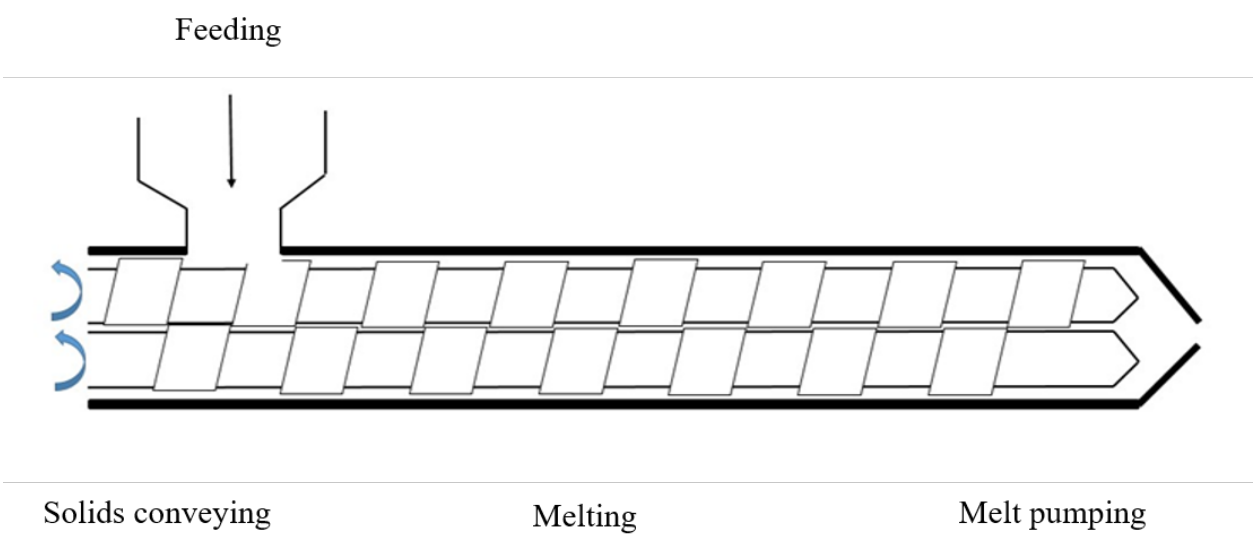

Figure 3: twin screw extruder

Table 4: Chemical modification

S.No	Solubility Enhancement Technique	Description
1.	Salt Formation	Solubility of acidic and basic drugs can be increased by converting the drug into salt form.e.g. Aspirin, theophylline, and barbiturates. (Serajuddin, 2007)
2.	Complexation	By inserting non-polar molecule into the cavity of another molecule (host), inclusion complexes are formed. Most commonly used host molecule is cyclodextrin, surface of which makes them water soluble. (Uekama *et al.*, 1998). Techniques: Microwave Irradiation Method.
3.	pH Adjustment	With pH change, hydrophobic molecules are dissolved in water, by protonation and de-protonation. Once after adjusting the pH, stable and soluble ionisable compounds are choosen.
4.	Co-Solvency	For increasing the solubility of poorly soluble compounds, co-solvents (mixture of water /water miscible solvent) are used. Eg) PEG 300, propylene glycol, or ethanol.
5.	Hydrotropy	More concentrated alkali metal salts increases the solubility of BCS Class-2 molecules. Other examples are Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate.

Table 5: Miscellaneous methods

S.No	Solubility Enhancement Technique	Descriion
1.	Super critical Fluid Technology	Carbon-dioxide is mostly used in SCF. Particles are formed, when drug is dissolved using supercritical CO2 and sprayed with lower pressure. SCF produces sub-micron level particles, which increases the solubility.

to be made to their basic operational principles from their invention from 1897. In single screw extruder the good quality molten [melt] material obtained when it is rotated continuously between rotating screw in a barrel. A high stable pressure is generated to maintain continuous output. It produces a high steady pressure for an unfailing output. The screw inside the barrel has 20 or more screws akin to that of the diameter of the screw towards its longitudinal axis creating long slim machine where considerable longitudinal temperature can be preserved and controlled. Single screw extruder can be used to perform different processes like raw material feeding, transmission, melting, de volatizing, pumping and moulding. Mixing can also be done for less challenging applications.

This Single screw extruder (Figure 2) receives the raw material from feeding area and then passes it towards the flighted screw enclosed within the drum. The Single screw extruder is fed via hopper, and output rate is determined. Screw flight barrel inner surface is fixed in such a way that it provides optimum clearance for the feed and acts as a flow canal during the gyration of the screw. A melt pool is induced by the hot superficial part of the barrel and the machine-driven energy input delivered by the screw. This is inversely related to the bed size of the solids. When the volume of melt pool increases the solid bed decrease. The melted extrude obtained is transferred into the die to provide a defined shape and additional processes.

The process of HME is having the combined advantage of low cost of maintenance and low cost of production. These applications of the HME makes it the most preferred equipment for the production of products that are prepared by extradition products. (Repka *et al.*, 2007).

Table 6: Currently marketed products

Name/company/drug	Route of administration	Polymer
ozurdex®, Allergan (dexamethasone)	Ocular insertion	Hydroxypropyl cellulose
Zoladex®, Astra Zeneca (goserelin acetate)	Subcutaneous insertion	Poly(lactic-co-glycolic acid)
Implanon®,Merck (etonogestrel)	Subcutaneous implantation in the inner side of the upper arm	Ethylene-vinyl acetate
Nuvaring®,Merk (etonogestrel/ethyl vinyl estradiol)	Intravaginal ring	Ethylene-vinyl acetate
Norvir®,Abbott (ritonavir)	Oral tablet	PEG-glyceride
Kaletra®,Abbott (lopinavir/ritonavir)	Oral tablet	Polyvinylpyrrolidone/polyvinyl alcohol
Onmel®,Merz (itraconazole)	Oral tablet	Hydroxypropyl methylcellulose
Gris-PEG®, Pedinol (griseofluvin)	Oral tablet	Polyethylene glycol
Covera-HS®, Pfizer (verapamil)	Oral tablet	Hydroxypropyl cellulose
Eucreas®,Novartis (vildagliptin/metformin HCL)	Oral tablet	Hydroxypropyl cellulose
Zithromax®, Pfizer (azithromycin)	Oral tablet	Pregeltinized starch

Twin Screw Extruder (TSE)

The first Twin screw extruder was invented in late 1930's in Italy. The main aim of this invention is to combine the principles of many machines into a single unit. Twin screw extruder (Figure 3) as the title says it consists of two separate agitators assembled within the parallel arrangement of the shafts. These two screws render different configuration and likewise provide diverse environments in all regions of the extruder from feeding of the raw feed through hopper to the gyrating screw and in the end to pass the material to the metered pumping zone. (Crowley *et al.*, 2007; Thiele, 2018). TSEs is further categorised into fully intermeshing or non-intermeshing. In this fully inter-meshing is the most prevalent one.

Pros and Cons of HME

The technique of HME have many advantages in relation with pharmaceutical processes such as

(a) Increases solubility and bioavailability of the poorly aqueous soluble drug

(b) Solvent less method

(c) Fewer processing step and continuous operation

(d) Reduced production time

(e) Good stability at changing pH and moisture level

(f) Content uniformity of the extrudes

(g) Sustained, modified and targeted release capabilities

(h) Life cycle management.

However HME has some disadvantages

(a) Not suitable for thermally liable drugs

(b) Mainly not useful for the high heat sensitive molecules such as proteins

(c) Requires high energy input (Ridhurkar *et al.*, 2016)

Possible mechanism of action

In HME the mechanism involved in the conversion of crystalline form to amorphous is mainly based on the hydrogen bonds. The hydrogen bonds are formed as a result of the interaction between a lone pair of an electronegative atom and hydrogen atom that exists extensively between the drug and polymer. The hydrogen bonds are predominantly an electrostatic interaction, but it can also act as covalent bonds with directivity. Another mechanism involved is dipole-dipole interaction that exists between polar molecules. This is also a kind of

electrostatic interaction. This combination of electrostatic interaction can lead to the formation of positive and negative charges at both ends of the molecules. These charged ends can attract other charged ends of molecules. But this mechanism is rarely observed in drug polymer interactions. Another possible mechanism that can contribute to the HME process is Van der Waals force. It exists in almost all systems in the forms of attractive and repulsive forces. Van der Waals force has little contribution to the process of HME.

The ionic interaction is the strongest interaction between the drug and polymer whereas hydrogen bond is the most prominent bond. The relative strength of the four types of bonds present in the drug-polymer interaction is in the sequence of ionic interaction>hydrogen bond>dipole-dipole interaction>van der Walls interaction.

Enhancement of solubility and bioavailability using hot melt extrusion technology:-

Solid dispersions can be formed using hot-melt extrusion technique, which converts crystalline (poorly water soluble) to amorphous (Highly water soluble) form of drug, thus enhancing the solubility of the drugs in water and it also increases the bioavailability of drugs (Patil *et al.*, 2016). Hot melt extrusion technology is mainly for poorly soluble drugs to improve the solubility and bioavailability. The rate of dissolution of poorly soluble drug 17-β estradiol hemihydrate solid dispersion (17β-estradiol, PVP, and Gelucire 44/14 at 10, 50, and 40%) using HME was increased by 30 folds in the year 2000 (Hülsmann *et al.*, 2000). In 2012, Efavirenz solid solutions was prepared using HME Technology employing two polymers (Eudragit E PO or Plasdone S-630), in which Efavienz extrudes showed faster release than crystalline form (Sathigari *et al.*, 2012). In 2013, HME technology was employed in the formulation of carbamazepine (CBZ) as solid dispersions using a new amalgamation of Soluplus and the HF grade of the polymer hydroxypropyl methylcellulose and acetate succinate to improve the solubility and the physical and chemical stability of the solid dispersion product was studied. As a result, release of CBZ was increased when the concentration of Soluplus was increased. From these studies, it was confirmed that hot melt extrusion technique increases both the solubility and bioavailability of drugs (Djuris *et al.*, 2013). In 2014, Solid dispersion of Ginkgo biloba extract (GBE) done using HME technique involving a spray-dried powder carrier matrix, PVP-VA 64: Kolliphor RH 40 (85:15), increased the dissolution rate and oral availability of the extract. GBE showed 30% release in first 2 hours, whereas GBE-SD Showed 93% release in first 20 min. Similarly, maximum Cmax and AUC were observed to increase in GBE-SD than GBE, when administered to Sprague-Dawley rats (Wang *et al.*, 2015). In 2015, hot melt extrusion was utilized to prepare Soluplus®/TPGS-based solid dispersions to increase oral bioavailability of valsartan equipped with twin-screw systems. Drug release and Oral absorption was observed to increase in SP and TGPS based SD. Hence, it can be concluded that, hot melt extrusion increases dissolution and oral absorption of valsartan (Cho *et al.*, 2015). In 2016, Improvement of Solubility, permeability and oral absorption of Psychoactive natural product (piperine) were studied using hot melt extrusion, the dissolution studies established drastic increase in the release of drugs in 10% and 20% w/w piperine/Soluplus(®) extrudes up to 95% and 74%, respectively. It also exhibited more than 160- and 45-fold increase in the solubility in water, respectively. Further, permeability studies established the increase of piperine absorption of 10% w/w piperine/Soluplus (®) extrudes to a range of 158.9 μg/5 ml in comparison with pure piperine at 1.3 μg/5 ml in 20 min (Ashour *et al.*, 2016). In 2017, studies were conducted on solid dispersion of the drug itraconazole prepared by HME for improvement of bioavailability in the framework of the Three Rs rule. Solid dispersion formulations made of itraconazole (ITZ) and Soluplus® were formulated by HME. An increase in the C_{max} and Area Under the Curve were observed after the administration of all three formulations in comparison levels after the use of Sporanox® which are as follows,

SOL/ITZ/AcDiSol®>SOL/ITZ/CD>SOL/ITZ>Sporanox®

(Thiry *et al.*, 2017). In 2018, hot melt extrusion for the preparation of aripiprazole- loaded pH modulated solid dispersions was utilized and studied. From the study, it can be concluded that HME increased the solubility and bioavailability of aripiprazole (McFall *et al.*, 2019). In 2019, Oral Bioavailability enhancement of Ziprasidone Hydrochloride (ZH) SD by Hot-Melt extrusion with Plasdone-S630 and HPMCAS-HF and with no food effect was studied**.** Pharmacokinetics studies indicated that the bioavailability of ZH-SD formulation had no significant difference in fasted and fed state, and the C_{max} and AUC of ZH-SD were two fold higher than Zeldox® in fasted state. This indicated that ziprasidone has achieved a desired oral bioavailability in fasted state and no food effect (Xue *et al.*, 2019). From the studies carried out using Hot-melt extrusion, it is evident that solid dispersion formed by HME enhances both the solubility and Oral bioavailability of drugs.

Overall application of HME

Extrusion plays an important role in several industries, especially in rubber and plastic industries. Products made from melt extrusion includes polystyrene tiles, wires, rubber sheeting cables etc. Plastic extrusion is part of production of many plastic products. (Breitenbach, 2002). In food production, extrusion used in the production of pasta, in pet food industry and veterinary science, the production of plants, or injection moulding uses extrusion. (Maniruzzaman *et al.*, 2012a; Wedlock and Wijngaarden, 1997) The formulation of pvp melt that are fast dispersing forms of drugs that are poorly soluble drugs in crop protection field (Wedlock and Wijngaarden, 1997). HME in pharmaceutical industry had achieved in a strong place having a superior aspects compared to the conventional methods like spinning and grinding (Mcginity and Koleng, 1997). HME also emerged as a newer technique in pharmaceutical application and improves the attributes and efficacy of formulated products (Repka *et al.*, 2006). In the field of pharma manufacturing HME is used for several applications for example

1. Improving the rate of dissolution
2. Bioavailability drugs that are poorly soluble
3. Release control of the drugs
4. Making the drug palatable
5. Preparation of thin film formulations (Morales and McConville, 2011).

During drug discovery drugs with high lipophilicity and higher molecular weight are obtained, these drugs will be of low solubility, due to the arrival of high throughput screening (HTS). (Zheng *et al.*, 2007) Several methods are available to increase the rate of dissolution and solubility of solid dispersion, among them, HME has been the best process to prepare solid molecular dispersion (Maniruzzaman *et al.*, 2013; Zheng *et al.*, 2007).

Pharmaceutical applications of hot melt extrusion

At present, hot melt extrusion is a widely utilized technology in Pharmaceutical Research in various fields of drug delivery. Microencapsulation is one of the commonly used techniques for delivering the drug into the areas of the GIT without getting affected by the environment of the system. Use of Hot melt extrusion in encapsulation reduces the usage of solvents and also makes it a cost-effective technique. In 2004, a sustained-release system consisting of hot-melt extruded ethyl cellulose cylinders containing a Hydroxypropyl methylcellulose (HPMC) – Gelucirecore was prepared, which is an example of HME incorporated microcapsules (Mehuys *et al.*, 2004). HME Technology can also be used for targeted delivery of drugs. In 2008, the HME technology was used to formulate the oral absorption of itraconazole (ITZ) by the targeted intestinal delivery of the supersaturated drug (Miller *et al.*, 2008). One of the drawback associated with solid oral dosage form is bitter taste. HME can be used to make the drug palatable by producing solid dispersion with taste masking polymer. In 2012, Taste masking of paracetamol was done by HME. The results revealed that HME is capable to mask the taste of unpleasant drugs (Maniruzzaman *et al.*, 2012b). Films in pharmaceutical industry, is used in drug delivery and as dressing in wound healing. Solvent casting is commonly used to prepare films. As this method is associated with numerous disadvantages, hot melt extrusion can be opted as an option to overcome the drawbacks associated with solvent casting. In 2014, Antifungal denture adhesive film for oral candidiasis was developed by hot melt extrusion technology (Park *et al.*, 2015). HME technology is also used in the preparation of implants. HME technology is also used in the preparation of nanoparticles. In 2014, HME was utilized to produce solid lipid nanoparticle (SLN) of fenofibrate (Patil *et al.*, 2015). In 2006, Floating hot-melt extruded tablets can be also used for the gastro retentive controlled drug release system.

Currently marketed HME products

The interest in hot melt extrusion is growing rapidly. Around 56% of issued patents are in US and Germany. Many marketed product are available in the market that are produced by HME. Many companies have employed HME in their product manufacturing given in (Table 6).

CONCLUSIONS

HME method by and large has proven to be an effective method for increasing the solubility and bioavailability of the water insoluble drugs. The mechanism of converting the crystalline drug to amorphous form was effective in increasing the solubility of the drug. Every component in the process of HME is highly modifiable. The selection of the polymer to be used in the process and the exit die for shaping material. However, the success of the HME process depends mainly on the proper equipment, personnel and facilities. Solvent less and continuous fashion of operation makes HME more economic and labour friendly. It replaces traditional process,

as HME is a continuous pharmaceutical manufacturing process. Moreover, scale-up of HME from lab scale to commercial scale is possible by applying QbD and PAT approaches. Thus, demand towards HME will increase in pharmaceutical manufacturing in the future.

Conflict of Interest

None.

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