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THE USE OF HOT MELT EXTRUSION IN THE PREPARATION OF SOLID DISPERSION

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ABSTRACT

Bioavailability of a BCS class II substance can be highly affected by its formulation design. In this respect, solid dispersion in a hydrophilic carrier formulation was introduced a decade ago to resolve the problem of BCS class II substance. With that, several processing methods of the solid dispersion have been studied. Amongst the advent processing methods hot melt extrusion (HME) has appeared as a robust manufacturing method in formulating solid dispersion. The use of this method offers many advantages as compared to the other conventional methods such as environmental friendly, cost sparing and readily scalable. This review explores the use of hot melt extrusion in the preparation of solid dispersion. Besides, current trend of the investigated active pharmaceutical ingredient (API) and the recommended carrier used in this manufacturing process were summarised and categorised. Other concerns regarding the use various excipients and additives were also investigated and grouped into easily accessible format such as table. Alongside to the review, results drawn from the literature regarding the performance of the obtained HME based solid dispersion were also discussed.

Keywords: Solid Dispersion, HME and Hot Melt Extrusion, Amorphous

INTRODUCTION

Literally, solid dispersion (SD) refers to the dispersion of one or more ingredients in a solid form of continuous matrix/carrier. SD could be classified based on physical state. These include eutectics, amorphous precipitates in crystalline matrix, solid solutions, glass suspension and glass solution. Detail of the classification could be found **[1]**. SDs offer promising effects in bioavailability enhancement of poorly soluble drugs as evidenced by several publications **[2, 3]**. It is postulated that SD

formulation increases the surface area available for dissolution process via particle size reduction, and improves wetting of compounds surfaces. In amorphous SDs, further advantages are assumed to be due to the removal of crystalline drug structure **[4]**.

SD can be prepared via several methods. These include melt quenching, milling or cryo-grinding, freeze drying, co-evaporation or co-precipitation and by the means of spray drying. More recently hot melt extrusion (HME) has been introduced as an alternative to the conventional method in the preparation of solid dispersion. The use of this method offers many advantages as compared to the other conventional methods such as environmental friendly, cost sparing and readily scalable. This review will focus on use of HME manufacturing method in the preparation of solid dispersion and the materials used in this processing method.

Pharmaceutical Hot Melt Extruded Solid Dispersions

HME has appeared as a robust method for SD preparation due to its ability in producing SD system with a relatively stable products physical stability and a promising formulations performances as documented in numerous published papers **[5-10]**. The main process of this technology is to mix raw materials at the molecular level to produce an intimately mixed extrudate. The extrusion process involves different manufacturing steps, i.e. mixing, melting, homogenizing, and shaping. These processes are carried out in a single continuous step which could potentially give rise to overall cost sparing production **[11]**.

From the regulatory standpoint, melt extrusion technology is a mature engineering technology. It allows the monitoring of various parameters via typical readout information or load cell outputs. This contributes to comprehensive data documentation, good quality control and quality production **[12]**.

There are many potential formulations that could be produced by using HME manufacturing method. These include immediate release SD, targeted release dosage form **[13-16]**, multiple unit dosage forms **[17-19]**, floating dosage forms **[8, 20, 21]**, implants **[22-25]**, transdermal and transmucosal delivery systems **[26-30]**, controlled release dosage form **[6, 8, 31, 32]** as well as retarded release dosage form by the formation of nanocomposite **[33-35]**. This has attracted attention of applying HME manufacturing method in the pharmaceutical industry **[36]**.

Principles of HME

As the name implies, HME process operates under elevated temperature (at least 30-60 ^{o}C above Tg of feedstock) in order to soften the processing compound **[9]**. Mixtures of

materials, namely the active pharmaceutical ingredient (API), polymers as the API carriers and additives are passed through the feeding system and extruded in the extruder. Figure 1 depicts the HME processes range from feeding to extruding, which will be discussed in detail in next few sections.

Processes within the closed barrel encompass solubilising of API in the polymeric matrix, intense mixing of additive and dispersion of materials within the molten. At the end of barrel, high pressure imparted within the metering zone will force the molten mass extrudes through an orifice to produce a product of high density and uniformity **[13, 38]**. Subsequently, molten material is transported to the downstream equipment for final dosage designation such as melt pelletization, milling, tableting and calendaring.

The extrusion process in the extruder could be divided into three typical zones, i.e. feeding zone, melting or compression zone, and metering zone. Each of the zones has different geometrical screw design that dictates the advance of the process **[39]**.

Feeding Zone: Feeding Raw Material

The process of feeding is highly dependent on the flow properties of the feedstock. The angle between the wall of hopper and horizontal line must exceed angle of repose of the feedstock **[9]**. This is to ascertain consistent feed rate and avoid throat bridging (feeding problem when feeding material are stuck at the throat of hopper) that potentially occurs in cohesive material or fine powder that might cause erratic flow in the hopper. In order to get easy flow and good conveying of feedstock, a wide pitch and deep flight of the screw is designed in the feeding zone **[11, 40]**. **Figure 2** shows the definition of different parts of the screw extruder.

Efficiency of pumping in this zone depends on friction coefficient between the feed material and barrel or screw which allows heat dissipation from the shearing process **[9]**. The feeding process generates high pressure for subsequent transportation of feedstock to the transition or compression zone by rotating screw. For bulk solid that is prone to bridging, a driven agitator could be used as a discharge aid in feeding the raw material into the extruder **[41]**.

Transition Zone

In the transition zone, the reduction of screw pitches and flight depth form progressively narrower spacing between turning and impart a high compression pressure to the material. The materials move along the circulation in helix path of the thread. Transverse flows, drag flow, pressure flow that were generated by the increase pressure following the shallower flight depth as well as leakage are the transporting mechanisms along the barrel **[9, 11, 40]**. In this zone,

feedstock is compressed, melted, plasticized and mixed which will be further discussed in the subsequent sections.

Melting / Plasticization

Melting and plasticization processes take place in the transition zone or also known as compression zone. The heating energy is obtained from the electrical heat band that was pre-set prior to the extrusion process as well as heat dissipated from the shearing effect between the screw and material while mixing in the barrel **[11, 39, 40]**. With the heat energy, small molecule of the drug compound will be melted or diffused in the soften carrier system which causes further plasticization effect to the macromolecule polymer system.

Mixing/ Dispersion

After feeding, the processing material is transported into the mixing or dispersion zone of the hot extruder. The purpose for mixing zone of HME is to produce a highly uniform extrudate. In this zone, the mixing can be further divided into dispersive and distributive mixing **[42]**. Dispersive mixing involves the sizing or breaking of the particulate into smaller size while distributive mixing involves the homogenization of particulate within carrier with no interruption on the particle size.

The screw design in the mixing zone may influence quality of the end extrudate. **Nakamichi *et al.*, 2003**, have successfully demonstrated the important role of kneading paddle (with the twist of 30^o and 60^o) in mixing nifedipine and an enteric polymer, hydroxyprophylmethylcellulose phthalate (HPMCP). In that study, the good uniformity of extrudate was attained from the extrusion with kneading paddle as compared to the extrusion without kneading paddle. This is due the intense mixing of the mixture by kneading paddles **[43]**. Similarly, Verhoeven *et al.*, 2008, confirmed the need of kneading paddle for better extrudate quality (smooth extrudates) as compared to the extrusion of the same system without kneading paddles **[44]**.

Metering Zone

After intense mixing in the transition zone, the molten is further passed through the barrel into the "metering zone". The primary function of metering zone is to ensure uniform thickness, consistent flow and steady delivery rate through the die **[9, 11]**. The output rate of these molten material is dependent on the channel depth and length of meter zone **[9]**. Similar to transition zone, materials in this metering zone are conveyed via drag flow as well as pressure flow.

Die Pressurization

The process after the metering zone involves pressurizing of the molten material through a die with desired shape **[45]**. In some instance, extrudates emerge from the

die and undergoes 'die swell'. This phenomena is particularly happen to polymer melt where it attempts to reform from its elastic energy stored within the extrudate while being shear in the die **[46-48]**. The unintended die swelling of extrudate can be avoided by controlling the drawing force, extrusion temperature and spinning velocity **[49]**. Thus, die pressure should be monitored for desired output to match the geometry of the entangled die **[38]**.

Materials Used in HME Solid Dispersions

Active Pharmaceutical Ingredient

Intuitively, one may assume it is impossible to process thermally labile drug under HME **[50, 51]**. However, several reports have shown the successful production of pharmaceutical dosage form containing thermo labile API by means of HME. These include production of hydrocortisone films **[27]**, delta-9-tetrahydrocannabinol in polyethylene oxide matrices **[52, 53]**, thermo labile p-amino salicylic acid with assistance of CO_2as a plasticizer **[54]**, as well as protein implant, rh-interferon α-2a (IFN-α) **[55]** and somastostatin vapreotide **[24]**. **Schulze and Winter, 2009,** suggested that the solvent free HME is a good processing method for the formulation of proteins **[55]** as biological activity of the proteins could be maintained even at elevated temperature in the dry powder state rather than in aqueous media.

Some APIs appear to plasticize its carrier, such as carvedilol **[56, 57]**, chlorpheniramine maleate **[58, 59]** and etc. These APIs are good candidates for HME production owing to their better HME processability without additional external plasticizer. More examples of APIs with plasticization behaviours will be provided in section 4.4 as 'non-traditional' plasticizer.

Drug loading in the polymeric carrier may also affect the processability of HME. Schilling *et al.*, 2008, confirmed that increase drug loading of diltiazem HCL necessitated higher processing temperature and therefore increased molten flow resistance in the barrel **[47]**. Another study by De brabander *et al.*, 2003, showed that higher percentage of ibuprofen not only eased the HME process but also give rise to a good quality extrudate with an increase in drug release rate **[6]**. Therefore, thorough understanding of the APIs is indispensable for the processing concern and formulation design of HME system. **Table 1** summarised the examined APIs from the literature.

Carriers Used in HME Formulations

Over the past decade, the application of various types of carriers system has been identified. **Figure 3** shows the different generations of SD based on their carrier

systemsthat has been classified by **Vasconcelos *et al.*, 2007**.

Amongst all carriers, polymeric systems are the most commonly investigated materials in the production of solid dispersion with the inclusion of surfactants, lipids and polymer blends described in some recent studies **[32, 70, 84, 93, 96-100]**. Brief review on the use of these carriers system will be provided in the subsequent sections.

Polymers

Polymeric carriers are usually used as the dispersing agent in HME solid dispersion systems to stabilize the amorphous API. During the HME process, polymers are subjected to high shear stress, chain scission, chemical de-polymerization as well as thermal degradation **[9]**. Thus, pharmaceutical grade polymer used in HME must be able to process under relatively low temperature. Enteric polymer, pH dependent polymers and hydrophilic polymers are the commonly used polymers in fabricating pharmaceutical dosage forms. Examples of these polymers include acrylic polymer (Eudragit S100, Eudragit L100-55, Eudragit L100, Eudragit RD 100), cellulose polymer (hydroxypropyl methylcellulose), phthalate polymer and polyvinylpyrrolidon (PVP K30, vinylpyrrolidone-vinylacetate copolymer, PVPVA 6:4).

Among these polymers, hydrophilic polymers such as PVP/ PVPVA 6:4 are usually included in numerous HME compositions for immediate release solid dispersion. However, at high polymer concentration, PVP/ PVPVA 64 may result in extruder clogging due to their high glass transition temperature (> 150^{o}C) **[50]**. Other hydrophilic polymers, for example polyethylene oxide (PEO) or polyethylene glycol (PEG), xanthan gum, plasdone S-630and hydroxypropyl methylcellulose could also be added in a formulation to tailor the drug release and to yield desirable sustained release pattern **[18, 44, 101]**.

Some polymers exhibit a plasticizing effect toward other polymer in a polymers blend system. This is a benefit for HME process as the integrated polymer could aid the material transport in the hot barrel besides tailoring the drug release properties of the system **[28]**. For example, PEO 1K appeared to plasticize PEO1M and enhanced stability of the HME processed polymer **[102]**. A study performed by Lyons *et al.*, 2008, has indicated that the inclusion of poly ε-caprolactone in PEO polymer blend can function as a plasticizer in the blend by lowering melt viscosity, torque and head die pressure **[56]**.

Plasticizers Used in HME Systems

The conventional role of plasticizer is to reduce brittleness, improve flowability, and impart flexibility, toughness and strength. More specifically, it is used to change

certain physical and mechanical properties of a material. In the context of HME, plasticizers are applied to soften the polymer matrix where excessive temperature may be needed to process unplasticized based polymer that could lead to degradation or localized overheating of the polymer **[39]**. By incorporating a plasticizer, the extrusion temperature and thermal degradation of the material may be reduced **[44, 101]**. Besides, plasticizer may exert a positive influence on content uniformity of the product by promoting good flowability and mixing of the blend materials **[52]**. A study carried out by Bruce *et al*., (2005) has successfully improved the physical properties of Eudragit ®S 100 by incorporating of triethyl citrate as a liquid plasticizer **[14].**

The interest in investigating solid state plasticizers such as citric acid, PEG 8000 and methylparaben (MP) in HME system is increasing as these solid plasticizer are readily mixed in powder form prior to the extrusion at elevated temperature **[103]**. Upon extrusion, the solid state plasticizer is melted and solubilised in carrier in order to exert their plasticization effect **[13, 104]**. An example was given by Wu and McGinity, 2003, whom demonstrated that incorporation of methylparaben in the extrudates of Eudragit ® RS PO could reduce its Tg from 55^{o}C to 32^{o}C. The authors elucidated that the incorporation of methylparaben within the Eudragit ® RS PO polymer has weaken the cohesive interaction between its polymer chains and subsequently enhance its chain mobility **[103]**. Besides, citric acid was shown to alleviate the Tg of HME API-polymer system which indicates its plasticizing properties as a solid state plasticizer **[13, 14, 75]**.

The combination of both triethyl citrate (liquid state plasticizer) and citric acid (solid state plasticizer) has resulted in the good flowability of a HME API-polymer system and render the used of low processing temperature in the HME manufacturing process (Bruce *et al*., 2005). Similar attempt was carried out by Andrews *et al*., 2008, who incorporated the combination of both triethyl citrate (TEC) and citric acid in HME process of Eudragit. The authors elucidated that both TEC and acid citric have improved material flowability in the extruder, reduced Tg, and ultimately aided the extrusion process by lowering screw torque as well as die pressure. This is because TEC and citric acid are able to form hydrogen bonding with Eudragit by occupying 'active site' along the polymer and thus preventing inter-chain association **[13]**.

CO_2 is proposed to be a temporary plasticizer in HME process **[105, 106]**. Verreck and co-workers examined the effect

of CO_2 in pharmaceutical polymer such as PVP-VA 64, Eudragit E100 or ethylcellulose. It has shown that CO_2 reduced the processing temperature of HME, increased porosity and specific surface area of extrudate by forming a foam extrudate. The foam like structure of extrudates improved subsequent milling process and caused dissolution rate enhancement of the formulation **[105, 106]**. However, CO_2 was reported to exert a negative impact on physical stability of extrudate where it was shown to induce recrystallization owing to the increase in mobility and realignment of the polymer chains **[62, 106]**.

Interestingly, some APIs could intrinsically be a plasticizer for polymer. An API has to be dissolved in the polymer system in order to contribute to the plasticizing effect **[105]**. Ibuprofen was shown to possess plasticizer effect toward ethylcellulose and was known as a 'non- traditional plasticizer'**[72]**. Its effect was investigated and compared with other traditional plasticizers such as diethyl phthalate and dibutylsebacate by by Brabander *et al.*, 2002. It was elucidated that ibuprofen having equivalent plasticizer efficiency as the traditional plasticizer (diethyl phthalate and dibutylsebacate) toward ethylcellulose. The same effect was also reported in a study where API was found to plasticize Kollidon®SR (polyvinyl acetate: povidone 8:2) **[32]**. **Table 2** outlines the different types of plasticizer used in HME pharmaceutical application.

Surfactant

Surfactants such as Tween 80 and docusate sodium are regularly used in the pharmaceutical field as wetting agents and to increase solubilisation of the poorly soluble API. In the production of HME systems, the surfactant could also act as a plasticizer in the extrusion process **[101]**. Ghebremeskel *et al.*, 2007, has demonstrated the reduction in Tg of the mixture of API and polymer after the addition of surfactant into the composition of extrudate. In that study, the authors suggested that the use of surfactant could aid the extrusion process through an increase in chain mobility of polymer carrier **[101]**. More specifically, the extrusion torque of binary API-Plasdone was lowered from circa 55-65 Ncm to circa 28-30 Ncm with the addition of Tween 80 **[101]**. **Table 3** displays the example of surfactants that have been applied in HME processes.

Other additives used in HME processing

Recent investigations of HME were carried out on incorporation of nanoclay within polymeric matrix to tailor the release of API **[34, 35, 57]**. Reduction of burst release was attained by addition of polymer layered silicate as carrier for SD of ibuprofen when compared to the same formulation without

layered silicate **[33]**. Furthermore, the authors reported a reduction in tensile stress, elongation break and increment in modulus. Thence, mechanical properties of the extrudates by addition of nanoclay may be manipulated accordingly to ease subsequent downstream processes of the extrudates such as milling or compression of the extrudates systems into tablet **[33]**.

Studies have also been described whereby lipids are added to HME formulations to obtain the desired dissolution pattern **[50, 55, 93, 112-114]**. It has been shown that that the use of lipid carrier in HME produced a sustained release product with good physical stability as the hydrophobic nature of lipid had reduced the water absorption during storage **[93, 114]**. In formulations containing proteins and peptides, the inclusion of lipids in the HME process created a hydrophobic surrounding to the protein, therefore minimizing its denaturation tendency in aqueous conditions **[55]**.

Addition of other components such as waxes **[45, 73]**, pH modifiers **[14, 47, 52, 53, 65, 66]**, antioxidants **[28, 53, 102]**, lubricants **[105, 106]** and controlled water content **[43, 86]** are also possible in formulation of HME extrudates in order to obtain an optimum pharmaceutical dosage form.

CONCLUSION AND FUTURE OUTLOOK

HME offer an alternative as a manufacturing method of amorphous solid dispersion. The use of this preparation technique as a single piece of equipment does not only ease the manufacturing process but also the quality assurance of the obtain product from different batches. Many studies reported the promising results of generating solid dispersion with complete amorphization of the API which is an essential prerequisite for the enhanced dissolution rate of solid dispersion. Additives such as plasticizer, lipid, wax, and polymers blend may also be included to tailor the release pattern of the intended dosage form. Therefore, there is a great potential of developing amorphous solid dispersion using hot melt extrusion process. Other issues associated to HME product such as physical stability and dissolution performance will be further reviewed as a separate work.

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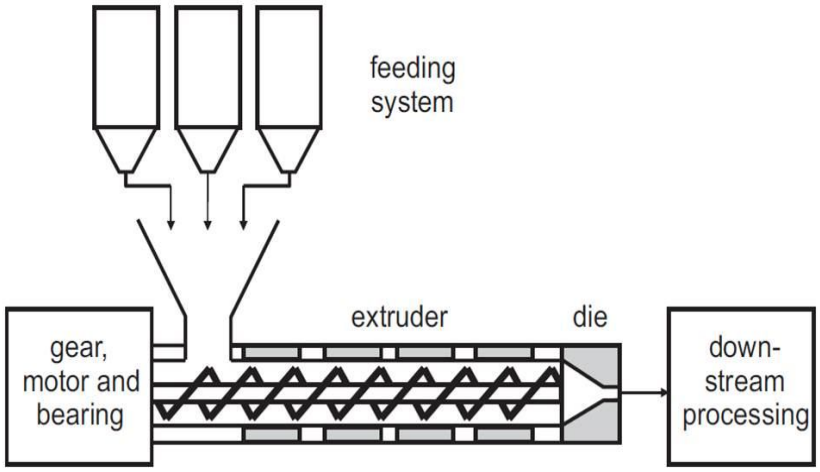

Figure 1: Schematic Diagram of a hot Melt Extrusion System [37]

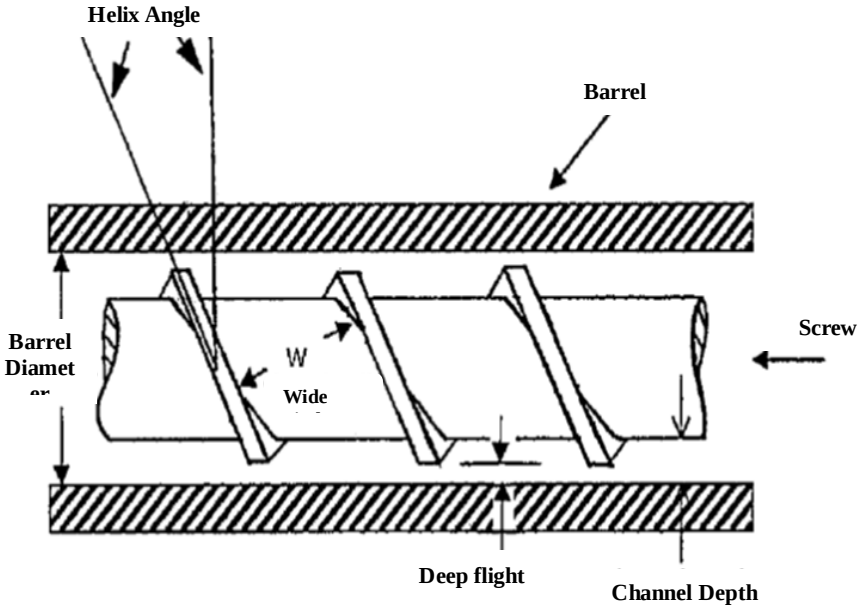

Figure 2: Diagram of a Screw Extruder [5]

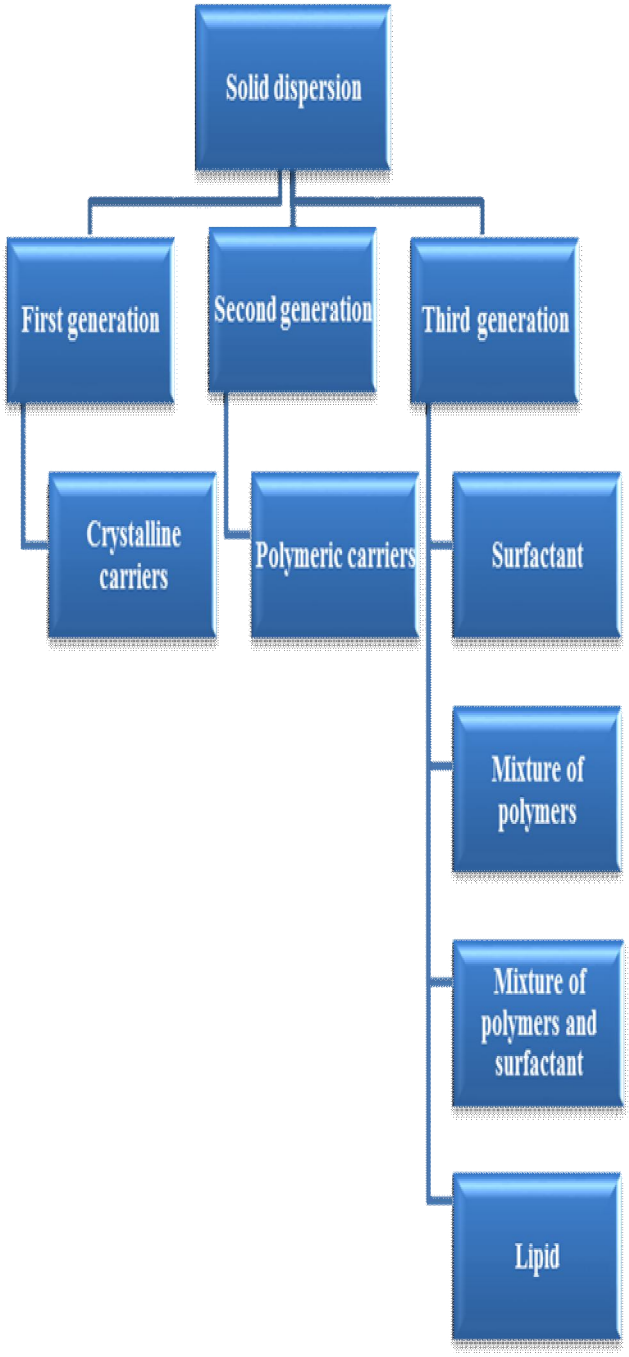

Figure 3: The Evolvement of Solid Dispersion Which Gives Rise to the Different Generations of the Formulations [95]

Table 1: APIs Used in HME Production and Characterization of HME Process

	API	Comments	references
	17β-estradiol hemihydrate	Solid dispersion of hormone was produced. The dissolution of drug was significantly enhanced	[50]
	5-amino salicylic acid (5ASA)	It appeared to create microenvironmental pH that was able to modulate the final release profile. Enteric polymer was used to target the delivery to colon.	[13, 14]
	Acetohydroxamic acid	Floating dosage form was formed by addition of $NaHCO_3$ as porous agent.	[8]
	Carbamazepine	Immediate release product was processed by HME and it showed an increase in dissolution compared to physical mixture as intimate mixing with hydrophilic polymer efficiently improved wetting.	[60, 61]
	Carvedilol	This drug was investigated in nanocomposite formulation, addition of PCL in the release pattern and impact to the process parameters. The most recent evaluation was done on the addition of CO_2 in release profile as well as recrystallization.	[56, 57, 62]
	Chlorpheniramine maleate	Floating dosage form and retarded release tablet were successfully produced by HME process.	[8, 27, 31, 63]
	Chloramphenicol	It was produced by two steps lipid plus PEG base extrusion. The final product revealed a good stability profile in 3 months accelerated studies.	[64]
	Clotrimazole	Transdermal products were developed and exhibited excellent content of uniformity. However degraded products were detected in which necessitate future investigation.	[29]
	Delta-9 Tetrahydrocannabinol Prodrug	Thermo labile properties justify the use of the component with assistance of excipients in Hot Melt extrusion process. It has been showed that its stability highly dependence on microenvironment pH of formulation.	[52, 53, 65, 66]
	Diltiazem HCl	Diltiazem HCL could bind to Eudraggit RSPO that potentially reduces the free drug. Research confirmed it does not possess plasticizing effect.	[47] *(continued)*
	Dyphilline	A derivative of theophyliine. Degradants of the product were detected thus it is at risk for long term stability.	[67]
	Etonogestrel	Controlled release co-axial fiber was prepared by single screw extruder.	[49]
	Guaiazulene Sodium	Water content is an essential key for its stabilization.	[43]
	Guaifenesin	It possessed plasticizing effect toward Eudragit L100-55. Evaluation of crystal growth inhibitor and recrystallization by nucleating agent was carried out.	[5, 68, 69]
	Hydralazine	HME hydralazine capsule was constructed by extruded hollow pipe and inclusion of drug and additive as a core.	[15]

	Hydrochlorothiazide	Ampiphilic nature of lipid and water soluble polymer in the formulation enhanced wettability of drug and thus dissolution of the drug	[70]
	Hydrocortison	A thermal sensitive compound but able to process by HME due to the inclusion of plasticizer and versatility of HME process that enable the drug to process under short residence time frame (about 2 minutes)	[27, 71]
	Ibuprofen	Sustained release ibuprofen was fabricated via polymer blends. The drug showed plasticizing effect equivalent to conventional plasticizer DEP/DBS.	[6, 17, 33, 58, 72-74]
	Indomethacin	PVA is not a suitable HME candidate for indomethacin due to immiscibility of both. It possesses good thermal stability	[75, 76]
	Insoluble microsomal triglyceride transfer protein inhibitor, R103757	It is structurally similar to itraconzole and its HME extrudates (Drug to HPMC ratio, 25:75) possessed fastest in vitro release performance relative to the film coated bead and glass thermoplastic system. No changes detected in 3 months stability test indicated its good stability profile and protection of HPMC.	[10] *(continued)*
	Itraconazole	Transdermal sustained release film intended for Onychomycosis and systemic micronized powder coupled with HME process were attempted. It's supersaturated form was found to be stabilized in Methocel E50 (HPMC E50) after pH transition from acid to neutral. It was suggested that formulation of ITZ to be carried out in controlled release manner due to the fact that rapid precipitation will take place if immediate release of drug occurred in upper GI condition which is acidic.	[2, 30, 77-84] *(continued)*
	Lysozyme	Implant of this API was produced with biodegradable polymer, polylactide co-glycolide and low MW PEG as release modifying agent.	[23]
	Lacidipine	Phase separation was observed by 2 Tg for the thermal analysis and it was further supported by solubility parameter.	[75]
	Lopinavir/Ritonavir	HME product of the combination revealed increase in bioavailability, less intra-patient variability and diminished food effect.	[85]
	Methylparaben	A 'non-traditional plasticizer'	[58]
	Metoprolol tartrate	HME extruded mini-matrices with release modifying agents and its properties were characterized by groups of researcher.	[18, 19, 44]
	Nicardipine	Floating dosage form was developed by incorporating porous agent via HME	[20]
	Nifedipine	Integration of kneading paddle in HME increases API dispersion.	[86]
	Nimodipine	Both in vitro and in vivo studies were done with HME product to select the best carrier for bioavailability enhancing effect.	[3, 87]
	Paracetamol	Tablet was prepared with layered silicate polymer to examine the influence in retard release and effect of recrystalline	[35, 88]
	Phenylpropanolamine HCl	A better particle size distribution was obtained via HME	[45]
	Propanolol HCl	Extensive first pass metabolism led to complicated analysis for evaluation of factors that may increase bioavailability of HME prepared products.	[70, 89-91]
	Theophylline	Extensive studies were carried out in formulating mini matrices, sustained release formulation, incorporation of lipid matrix as well as co-extrudate.	[32, 58, 70, 92-94]

Table 2: different Types of Plasticizer Used in HME Pharmaceutical Application

Types of plasticizer	Polymers	References
Liquid state plasticizer		
Triethyl citrate TEC (Hydrophilic)	Pre-plasticizing step with Eudragit S100 showed better results; Eudragit RD 100, Eudraagit L100-55, Eudragit RSPO, Kollidom SR (8:2), HPC:PEO (50:50, 80:20),Hydroxypropylcellulose (HPC), ethylcellulose. Its plasticizing efficiency was twice as high compared to chlopheniramine maleate in Eudragit® RSPO.	[13-15, 27, 28, 32, 44, 76, 103, 107]
Triacetin TA (Hydrophilic)	Polyvinyl acetate phthalate, ethylcellulose	[15, 44]
Dibutyl sebacate DBS (Lipophilic)	Eudragit RSPO, ethylcellulose	[44, 70, 89, 90, 103]
Diethylpthalate DEP (Lipophilic)	ethylcellulose	[44]
Acetyl Tributyl Citrate(ATBC)	HPC:PEO(50:50, 80:20),Hydroxypropylcellulose (HPC)	[27, 28]
Water content	HPMCP	[86]
Solid state plasticizer		
Traditional plasticizer		
Low MW PEO e.g., PEG 400, PEG8000	PEO1000000,HPC:PEO(50:50,80:20), Hydroxypropylcellulose (HPC)	[27-29, 102]
Sorbitol	PVP K30	[108]
Citric acid/ Citric acid monohydrate (CA MH)	Eudragit S10, Eudragit RSPO, Eudragit L100-55	[13, 14, 47]
Non-traditional plasticizer		
Carvedilol	PEO, PEO/PCL block copolymer	[56, 57]
Chlopheniramine maleate	Eudragit RS PO, Eudragit E PO, Eudragit RS30 D	[8, 58, 107]
Vit E TPGS	HPC:PEO (50:50, 80:20)	[28]
Guaifenesin	Acryl-EZE/ Eudragit L100-55 , PEO	[68, 109]
Itraconazole	Eudragit L100-55	[78] *(continued)*
Ibuprofen	Kollidom SR (8:2), ethylcellulose, Eudragit RS30 D	[6, 32, 58, 72, 74] *(continued)*
Indomethacin	Eudragit RLPO	[76]
Ketoprofen	PEO	[109]
Lidocaine HCl	Eugragit® E 100	[110]
Methylparaben	Eudragit RSPO, Eudragit RS30 D	[58, 103]

Nimodipine	**PVP/VA, Eudgragit ®PO**	**[3, 87]**
Paracetamol	**Eudragit ®EPO**	**[88]**
Temporary plasticizer		
Carbon Dioxide (CO_2)	**CO_2 is termed as 'temporary' plasticizer due to its absence in the end product of the HME system. The effect of plasticizing appears to be best in ethylcellulose followed by PVP-VA 64 and lastly Eudragit E100.**	**[54, 105, 106]**

Table 3: Example of Surfactants used in HME Process

	Surfactant	Polymer system	References
	Tween 80	**As plasticizer to Plasdone S360, Hydroxypropyl methylcellulose (HPMC) E5, Polyvinylpyrrolidaone(PVP) K30**	**[101, 111]**
	Docuste Sodium	**As plasticizer to Plasdone S360, Hydroxypropyl methylcellulose (HPMC) E5, Polyvinylpyrrolidaone(PVP) K30**	
	Sodium Lauryl sulfate	**As plasticizer to Eugragit L100, Hydroxypropyl methylcellulose (HPMC) E5**	
	Polyoxyethylene 40 stearate (Myrj-52)	**No effect in lowering Tg**	
	Poloxamer 188NF (Pluronic F68)	**No effect in lowering Tg, but showed to enhance drug release.**	**[76, 101]**