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# Hot-Melt Extrusion (HME) Is Advanced Approach for Development of Solid Self Emulsifying Drug Delivery System

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**Abstract:** The pharmaceutical industry is paying more and more attention to hot-melt extrusion (HME), but this technology's promise for creating solid self-emulsifying drug delivery systems (S-SMEDDS) has not yet been fully realized. The numerous published publications over the past five years show that hot melt extrusion (HME) technology is increasingly being used for novel applications. Because it has low-cost scale-up capabilities and process automation, which reduce labour costs and capital expenditure. HME has become a crucial technique for pharmaceutical manufacturing and research applications involving drug delivery. In the development of new drug delivery systems, the novel use of the HME method offers a promising alternate strategy. Through a discussion of pertinent case studies, the current review examines the value of HME in the creation of innovative drug delivery systems.

**Keywords:** Hot Melt Extrusion, Solid Self-Emulsifying Drug Delivery System, Liquid Self-Emulsifying Drug Delivery System, Spray Drying, Melt Granulation.

## 1. INTRODUCTION

There are lots of drugs molecules which are recently approved has poor aqueous solubility which further affect the desired bioavailability. There is a big challenge for formulation development for such type of drug molecules. Last many decades there is many novel drug deliveries approached are applied for bioavailability enhancement.

The development of self-emulsifying drug delivery systems (SEDDS) has shown to be a clever strategy for delivering highly hydrophobic substances while increasing their bioavailability.

It is a lipid-based drug delivery technology, which has the benefit of improving solubilisation of active ingredients by creating a lipophilic milieu and concentration gradient that guides drug transport to the right intestine absorptive regions. The efficacy of such a delivery system in vivo depends more on how it behaves in the gastrointestinal tract than on its particle size. Lipid-based formulations provide effects that mimic the consumption of food. The system's lipids are quickly broken down in the colon, and the broken down by products are solubilized by bile salt-lecithin mixed micelles, forming a fine colloidal dispersion that improves absorption (Etezadi et al., 2020, Joyce et al., 2019).

By creating a stable dispersion of the lipid/oil and aqueous phases with the use of surfactants and co-solvents, it is possible to lower the interfacial tension between the two phases and produce a stable biphasic system, which is how lipid-based drug delivery systems (LBDDS) are made (Chang et al., 2015). Lipids, surfactants, and co-solvents are key LBDDS components that are tested in accordance with medication and formulation criteria.

The four categories of LBDDS are determined by their makeup. There are four types of emulsions: Type-1, which only contains oil and lipids without any surfactants or co-solvents; Type-2, which combines oil and lipid with a water-insoluble surfactant to create stable emulsions like Self-Emulsifying Drug Delivery Systems (SEDDS); Type-3,

which combines oil and lipid with a water-soluble surfactant and more hydrophilic components to create Self-micro-emulsifying Drug (Williams, et al., 2014).

The preparation technique is chosen based on the necessary formulation parameters, such as particle size, dispersity index, homogeneity, etc., after the composition of the lipid phase has been optimized for drug accommodation. The majority of preparation methods involve high shear mixing, which reduces the size of the lipid droplets and produces a homogenous dispersion. These methods include high pressure homogenization, high pressure atomization (spray drying), micro-fluidization, and high frequency sonication. All of these methods have been employed in the past, but they all have a number of problems, related to excipient and drug, degradation with polymorphic alterations at high melt temperatures including residual aqueous phase, impacting the formulation's stability. While batch processing methods like sonication and homogenization have a reduced product yield, continuous processing methods like high-pressure homogenization and micro-fluidization have narrow channels that may get clogged by lipid accumulation in the system. The yield value for sonication and homogenization was found very low which is insufficient for industrial scale-up. Additionally, these methods demand expensive maintenance, increased time commitment, and labour-intensive scaling from pilot to industrial size. So the scientist is focussed on Hot Melt Extrusion (HME), a technique with continuous processing capabilities and large-scale output, can be employed to address the above technological issues HME is a process in which raw materials are processed at high temperatures and pressures while being continuously mixed and subjected to shear force to produce a product that is uniformly disseminated. In this procedure, the drug goes through a thermal transition and combines with the carrier matrix to generate an amorphous dispersion.

HME is a widely utilized method for creating formulations for medications with low water solubility that have increased entrapment efficacy and enhanced bioavailability (Butreddy et al., 2021b, Butreddy et al., 2022, Butreddy, 2022). Since HME offers additional advantages like negligible heat exposure with short barrel residence time, avoiding formulation overheating/reheating, and continuous processing capabilities that save time, lower the cost of production, and eliminate batch-to-batch variability, it has been widely used to prepare LBDDS including Solid Lipid Nanoparticles (SLN), Nano emulsions, nanostructured lipid carriers, lipid implants, etc.

## 2. LIQUID SELF-EMULSIFYING DRUG DELIVERY SYSTEM

An isotropic or homogenous mixture of drug, synthetic or natural oil, solid or liquid surfactant, and co-surfactant is referred to as a SEDDS. SEDDS having the potential to create fine oil in water (o/w) emulsion formulation following slight agitation induced by peristaltic movement, followed by dilution in the gastrointestinal (GIT) aqueous fluid (Agubata et al., 2014).

Self-micro emulsifying drug delivery system (SMEDDS) and self-Nano emulsifying drug delivery system are the two forms of SEDDS (SNEDDS). While SMEDDS generate oil-in-water micro emulsion with oil globule sizes in the range of 100-250 nm, SNEDDS form oil-in-water Nano emulsion spontaneously with oil droplet sizes of less than 100 nm (Vasconcelos et al., 2018).

### 2.1. Composition of SEDDS

**Oils:** A certain amount of oils can solubilize the lipophilic drug. It can promote self-emulsification and enhance the percentage of lipophilic drugs carried by the intestinal lymphatic system, which increases absorption from the GI tract, making it the most significant excipient (Shah et al., 1994). Different levels of saturation in long- and medium-chain triglyceride oils were used in the construction of SEDDSs. Due to its composition and physiological benefits, modified or hydrolysed vegetable oils have made a significant contribution to the success of SEDDSs (Charman et al., 1992). The conventional medium-chain triglyceride is being replaced by novel semi-synthetic medium-chain triglyceride oils, which contain surfactant characteristics (Shah, et al., 1994).

**Surfactant:** SEDDSs are made with non-ionic surfactants that have high hydrophilic-lipophilic balance (HLB) values (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc.). To create a stable SEDDS, the typical surfactant strength varies between 30 and 60% weight-for-weight of the formulation. Surfactants have a high HLB

and hydrophilicity, which facilitates the quick spreading of the formulation in aqueous media and/or the immediate generation of o/w droplets. Due to their amphiphilic nature, surfactants can dissolve or solubilize hydrophobic drug molecules at relatively high concentrations. This can allow for the drug molecules to remain in the body longer and prevent precipitation of the drug within the GI lumen (Khoo et al., 1998).

**Cosolvents:** Large volumes of hydrophilic surfactants or the hydrophobic medication may be dissolved in the lipid base with the aid of cosolvents such as diethylene glycol monoethyle ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, tetrahydrofurfuryl alcohol polyethylene glycol ether (Glycofuro), etc. Sometimes these solvents function as cosurfactants in microemulsion systems.

## 2.2. Potential advantages of these systems include

- Enhanced oral bioavailability facilitating dose decrease.
- More constant temporal absorption patterns of drugs.
- Drug(s) are selectively directed to a certain GIT absorption window,
- Defence against the harmful environment in the gut for the drug(s).
- Delivery profile management
- Less variation, taking into account food influences
- Safeguards delicate drug substances
- Significant drug loads
- Dosage types that are liquid or solid

## 2.3. Disadvantages

SEDDS liquid formulations have a number of drawbacks, including limited dosage form options, low drug loading capacity, drug leakage, and low stability.

## 3. SOLID SELF-EMULSIFYING DRUG DELIVERY SYSTEM EXCIPIENTS

Solid Self-emulsifying drug delivery system other than oil, surfactant, co-surfactant contains adsorbent or solid carrier. There are the list of excipients used in solid self-emulsifying drug delivery system depend on solidification technique.

1. Silica based adsorbent or carrier Such as silicates, micronised or amorphous silica (Sylysia®), silicon dioxide, fumed silica (Aerosil®) and Magnesium trisilicate., Magnesium hydroxide or magnesium aluminometasilicate (Neusilin®) Calcium silicate; and Porous dibasic calcium phosphate anhydrous (Fujicalin®). Cross-linked sodium carboxymethyl cellulose and/or cross-linked polymethyl methacrylate and Talcum crospovidone (Sanghai et al., 2013, Mandić et al., 2017) are used for adsorption and hot Melt extrusion.
2. Aerosil® 200, lactose, Mannitol, microcrystalline cellulose, are used as carrier for wet granulation method (Cho et al., 2016, Dixit and Nagarsenker, 2008, Franceschinis et al., 2015).
3. Lactose, maltodextrin, Hydroxypropyl cellulose, hydroxypropyl methylcellulose, and microcrystalline cellulose are used as Hydrophilic carrier and Crospovidone and silica are used as hydrophobic carriers for spray drying method.

4. Cryoprotectant are used for freeze drying method such as trehalose, sucrose, maltose, glucose and mannitol, are sugars (do Vale Morais et al., 2016).

### 3.1. Advantages of Solid SEEDS Include

- Increased adherence by the patient.
- Improve the reproducibility and stability of oxidation.
- Easy-to-use process control.
- Stable thermodynamics.
- The GIT's spontaneous production of liquid SEDDS.
- Improve permeability while reducing release rates with a longer gastric residence time.
- Better solubilization than traditional dosage forms.
- Selective drug targeting for a particular GIT absorption window.
- Preserving drug crystallization and precipitation post emulsification at the GIT (Tang et al., 2008, Potharaju et al., 2020).
- The use of lipophilic drug molecules with rate-limiting stages in the dissolution process (Suvarna, 2017).

### 3.2. Solidification Technique

Instead of employing the traditional method, liquid SEDDS (L-SEEDS) can be converted to solid dosage forms by applying modern techniques such adsorption to solid carrier, melt granulation, spray drying, freeze drying, and melt extrusion.

**3.2.1 Melt Granulation:** Melt granulation is a process that combines binders that melt at low temperatures to produce powder agglomeration. Melt granulation has many advantages over traditional wet granulation, and is sometimes known as thermoplastic palletization or one-step processes. As meltable binders, several forms of semisolid liquid and solid are used. With the melt granulation process, it is important to regulate a number of variables, including the impeller speed, mixing duration, viscosity, and particle size of the binders (Yetukuri and Sudheer, 2012, Mandić et al., 2017). It is a continuous technique that offers consistent excipient and drug dispersion (Mahapatra et al., 2014).

**3.2.2 Spray Drying:** in the Spray drying method atomization of solution produced by the emulsification of carrier and liquid SEEDS carried out into drying chambers under a controlled temperature and airflow conditions where the volatile solvents is evaporating which lead to formation of dry particles. Resultant dry particles are used for further process (Baek et al., 2014, Čerpnjak et al., 2015).

**3.2.3 Freeze Drying:** At lower temperatures and pressures, the frozen aqueous phase in liquid self-emulsifying formulations can be sublimated to create a powder, which when reconstituted with an aqueous phase yields a fine micro- or Nano-emulsion (Singh et al., 2014, do Vale Morais et al., 2016). This drying method so involves freezing the product to solidify it before sublimating the solvent to produce a lyophilized molecular dispersion. To avoid the slight stresses that the lipid bilayers experience during freezing and drying, cryoprotectants are periodically added.

#### 3.2.4. Adsorption to Solid Carriers

The process of converting liquid SEDDS into SSEDDS known as adsorption on solid carriers is widely used. This technique includes blending liquid SE formulations onto solid carriers in a blender to produce free-flowing powders from liquid SE formulations. The finished powder is then compressed into tablets or further combined with other excipients before being added to capsules.

Cross-linked polymers, high surface area colloidal inorganic adsorbent materials, or nanoparticle adsorbents can all be used as solid carriers. Examples include silicates, silica, talc, magnesium trisilicate, magnesium hydroxide, cross-linked sodium carboxymethyl cellulose, cross-linked polymethyl methacrylate, and crospovidone. These cross-linked polymers can help create favourable conditions to sustain drug dissolution and also help slow. Additionally, a variety of solid nanoparticle adsorbents are used in the formulation of SSEDDS, including porous silicon dioxide, carbon nanotubes, carbon nanohorns, fullerene, and charcoal (Sarpal et al., 2010, Shah et al., 2012, Taksande et al., 2011, Singh, 2015, Kanjani et al., 2016, Khedekar and Mittal, 2013).

**3.2.5. Melt Extrusion:** Melt extrusion is a solvent-free technique that produces SSEDDS from SEDDS and has a high drug loading capacity of roughly 60%. By passing a raw material having plastic qualities through a die at a controlled temperature, pressure, and product flow, extrusion turns that material into a formulation with consistent shape and density (Gursoy and Benita, 2004, Tang et al., 2008, Betageri, 2019, Yetukuri and Sudheer, 2012, Mallikarjun and Babu, 2011, Almeida and Tippavajhala, 2019, Ramesh et al., 2016, Kansara et al., 2015). Summary of solidification technique of Liquid SEDDS of different drugs is presented in Table 1.

**Table 1: Solidification of Liquid self-emulsifying drug delivery by different technique**

Drug	Matrix	Description	Solidification technique	Ref.
Dapson	Aerosil	Development of solid self-microemulsifying drug delivery (S-SMEDDS) of dapsone (DP) by adsorbing on neusilin US2 and spray drying with aerosil 200. The optimized formulation of LSMEDDS (F8) containing capryol 90 (10 percent w/w), Tween 80 (67.5/5 w/w), and labrasol (22.5 percent w/w) showed the smallest particle size and (10.3) and Solid SEEDS particle size $87.5 \pm 4.95$ with yield 30.6% to 42.66%.	Spray drying	(Mahore et al., 2021)
Resveratrol	Colloidal silicone dioxide	A solid self-emulsifying drug delivery systems was developed by using the spray-drying approach, to increase the solubility of resveratrol (RES). Three surfactant systems, soy phosphatidylcholine (SPC), eumulgin® HRE-40 (EU), and sodium oleate (system A); SPC/Tween®80 (TW) and sodium oleate (system B); and SPC/EU/TW (System C), were tested along with cod liver oil. System C produced the highest incorporation (21.26 mg/ml). The highest yield solid self-emulsifying drug delivery systems (80.12) were made with colloidal silicon dioxide (CSD).	Spray drying	(Aloisio et al., 2019)
Methotrixate	Calcium silicate	To create a novel solid self-microemulsifying drug delivery system (SMEDDS) that contains methotrexate (MTX) and has improved bioavailability and photostability. Spray drying liquid SMEDDS with	Spray drying	(Kim et al., 2019)

		the solid carrier produced the solid SMEDDS. The liquid SMEDDS droplet size of 189.336.61 nm and the solid reconstituted particle size of 126.734.32 nm were used to optimize the formulation.		
Bambuterol hydrochloride	Microcrystalline cellulose:aerosil	The solid self-emulsifying drug delivery system of bambuterol hydrochloride was prepared by adsorption technique using microcrystalline cellulose:aerosil mixture as the adsorbent. The formulations were optimized with droplet size of solid SEDDS100 and 300 nm.	Adsorption to solid carrier	(Saggar et al., 2019)
Iloperidone	Syloid XDP and Aerosil 200	Solid self microemulsifying drug delivery system (SMEDDS) and liquid compact (LSC) of Iloperidone were developed (ILO) for improvement of oral bioavailability. The composition of formulation Capmul MCM, Labrafac WL 1349 as oils, Lauroglycol 90 and PEG 600 as surfactant and co-surfactant. Syloid XDP and Aerosil 200 were optimized as carrier and coating material in the ratio of 15:1 w/w for liquid solid formulation.	Adsorption to solid carrier	(Suram et al., 2020)
Piroxicam	Neusilin US2 (magnesium aluminosilicate)	Solid self-micro emulsifying drug delivery system was prepared by adding liquid self-micro emulsifying drug delivery system with Neusilin US2 and filled in hard gelatin capsule. The droplet size and PDI value of optimized batch was found to be 138.8 nm respectively 0.519 with drug content 98%.	Adsorption to solid carrier	(Pattewar et al., 2018)
Osthole	Ethyl cellulose (EC) and Eudragit S100.	Solid self-microemulsifying drug delivery system (S-SMEDDS) of osthole was developed by spherical crystallization technique. liquid self-microemulsifying drug delivery system (L-SMEDDS) of osthole was formulated with castor oil, Cremophor RH40, and 1,2-propylene glycol. The optimized osthole S-SMEDDS had a high yield ( $83.91 \pm 3.31\%$ ) and encapsulation efficiency ( $78.39 \pm 2.25\%$ ).	Spherical crystallization technique.	(Sun et al., 2018)
Fenofibrate	Santa Barbara Amorphous-15 (SBA-15) mesoporous silica and Aerosil® 200 with soluplus	Novel supersaturated Solid self-emulsifying drug delivery system (super-SMEDDS) was developed by combining SSEDSS with appropriate precipitation inhibitor to overcome the thermodynamically instability and precipitation rapidly prior to absorption, resulting in compromised bioavailability. Particle size of Solid self-emulsifying drug delivery system $125.23 \pm 1.50$ nm while supersaturable solid	Supersaturable solid precipitation inhibition	(Quan et al., 2017)

	(inhibitor)	having 132.78±1.27 nm.		
Paclitaxel	Aerosil 200	Paclitaxel (Ptx) solid-self-emulsifying drug delivery system (S-SEDDS) was created using the spray drying approach to increase Ptx's low bioavailability (BA). According to their solubilizing power, 10% oil (ethyl oleate), 80% of a surfactant mixture (Tween 80: Carbitol, 90:10, w/w), and 10% of a cosolvent (PEG 400) were selected. The prepared S-SEDDS had mean droplet sizes of 16.9 1.53 nm, zeta potentials of 12.5 1.66 mV, and encapsulation efficiencies of 56.2 8.1%, respectively.	Spray drying	(Cho et al., 2016)
Atorvastatin	Lactose (Lactochem® powder)	Liquid and solid self-emulsifying drug delivery systems (SEDDS) for poorly soluble atorvastatin was developed by spray drying technique. The liquid formulation was optimized by droplet size and zeta potential of CF 3 (188.1 ± 1.48 –30.2 ± 1.21) and OF 2 (190.5 ± 1.28–32.0 ± 3.20). Solid formulation have Particle size 330 nm with entrapment efficiency 52-53 % (EE). Better solubilisation properties were exhibited by solid formulation OF2 in-compare to liquid SEDDS formulation.	Spray drying	(Czajkowska-Kośnik et al., 2015)

This review emphasizes on the hot melt extrusion as technique for the development of S-SEDDS.

#### 4. HOT MELT EXTRUSION

HME is a process in which raw materials are processed at high temperatures and pressures while being continuously mixed and subjected to shear force to produce a product that is uniformly disseminated. It is made up of a revolving screw, barrel, motor, and die. The viscosity of the polymer can be lowered and softened by heating the barrel. Screws aid in blending, moving, and ultimately forcing the melt through a die. The feeder facilitates the movement of materials from the feeding area to the barrel. The primary elements for the extrusion process' optimization are the barrel, screws, and feeder. Three steps make up the HME process: melting, mixing, and molding (Patil et al., 2016). To achieve either a low or a high shear, screw components in various configurations can be integrated into the barrel. Different screw configurations are possible by varying the offset angles of the conveying and kneading parts (30°, 60° (forwarding), and 90° (neutral) (Sarabu et al., 2022). While kneading elements are used to mix and disperse solid materials as well as give them mechanical shear, conveying elements' primary function is to drive solid materials through the barrel. Dispersive and distributive mixing are the primary internal extruder mechanisms. A uniform distribution of the active medicinal component throughout the polymer matrix is guaranteed by the distributive mixing process. The screw elements located in the mixing zone, (Maniruzzaman et al., 2012) cause dispersive mixing to act by breaking down solid material, polymer, or any agglomerates to a molecular level. Usually, when creating delivery systems for amorphous solid dispersions, a combination of distributive and dispersive mixing is desired. One crucial design factor for the HME process is the outside screw diameter to interior screw diameter ratio. Because the extruder's free volume and torque level are determined by this ratio. Barrels' temperatures and screw speeds are two more crucial factors to take into account when processing HME (Ghosh et al., 2012). The barrel temperature selected for the HME process can be either above or below the melting point of API. It should be above the glass transition temperature but below the polymer degradation temperature. The melt viscosity is influenced by the barrel temperature; a low barrel temperature



manifests as high viscosity and torque. While a high barrel temperature decreases viscosity and torque, it may be more susceptible to deterioration of the API and polymer (Martin, 2016). The degree of material fill, shear rate, and mixing effectiveness of the extrusion process can all be impacted by screw speed. Additionally, the screw speed affects the material's residence period inside the barrel (Maniruzzaman and Nokhodchi, 2017).

#### 4.1. Advantages of HME Technique

- Enhanced solubility lead to better bioavailability of poorly water soluble drugs.
- Solvent-free technique at non-ambient condition.
- Fewer processing steps with reduced production time having continuous operation lead to economically benefits.
- Different release pattern can be obtain such as sustained, modified, and targeted.
- Extrudates with better content uniformity.
- Compressibility of active ingredients can be avoid;
- Dispersion of fine particles obtained uniformly.
- High stability in hostile environment in GIT.
- Few steps process having production of a wide range of dosage forms.
- There is the option of range of screw geometries (Maniruzzaman et al., 2012, Jones, 2008, Grunhagen and Muller, 1995).

HME, however, also has certain drawbacks. The main drawbacks of HME are the thermal process (drug/polymer stability), the use of a small number of polymers, high flow properties of polymers, and the requirement of excipients that are inappropriate for molecules that are relatively more heat sensitive, such as proteins and some microbial species (Grunhagen and Muller, 1995).

#### 4.2. Application of HME in different drug delivery

HME has recently been investigated for a variety of applications, and it has proven to be effective in the development of diverse drug delivery systems. HME was used to develop self-emulsifying drug delivery systems, twin-screw granulation, pharmaceutical cocrystals, abuse-deterrent formulations, three-dimensional (3D) printing filaments, salts, amorphous solid dispersion systems, tablet formulation. The summary of solidification of different drug delivery system by Hot Melt Extrusion technique is given in Table 2.

**Table 2: Solidification of many in drug delivery system by HME technique**

Drug	Matrix	Description	Types of DDS	Ref.
Celecoxib, efavirenz or fenofibrate	E-173 kDa, Kollidon® 17 PF	S-SNEDDS was prepared by co-extrusion of liquid SNEDDS (L-SNEDDS) by using polymeric carriers containing celecoxib, efavirenz or fenofibrate as model drugs.	Solid SMEDDS	(Schmied et al., 2022)
Active ingredients	Soluplus® and Kollidon® VA-64	With Kollidon® VA-64 and Soluplus®, develop continuous pilot-scale solidification and characterisation of self-emulsifying drug delivery systems (SEDDSs). A Coperion 18 mm ZSK18 pilot plant-scale extruder was used for HME, and polymer and SEDDS were split-fed at 10, 20, and 30% by	Solid SMEDDS	(Zupančič et al., 2022)

		weight, respectively.		
Fenofibrate	Gelucire 48/16 and Neusilin US2	To increase the solubility and dissolution of fenofibrate formulations (granules), a one-step continuous twin-screw melt granulation technique was developed employing Gelucire® 48/16 and Neusilin® US2 as the solubilizer and surface adsorbent.	Tables with a hard matrix, of granules	(Sarabu et al., 2021)
Quetiapine Fumarate	Gelol(glycerol monostearate lipid matrix, Klucel EF(HPC-EF), Kollidon®VA64 and Kollidon®12PF as hydrophilic binders	The effect of hydrophilic binders on the stability of lipid-based sustained release matrices of quetiapine fumarate produced by the continuous twin screw melt granulation technique to prevent dose dumping in the matrices.	Lipid-Based sustained release matrix.	(Nyavanda et al., 2021)
Aripiprazole succinic acid (SA) and nicotinamide		The current study shows how to use the hot melt extrusion (HME) method to create multicomponent solid forms of aripiprazole (ARP) using succinic acid (SA) and nicotinamide (NA) as cofomers.	Pharmaceutical cocrystals	(Butreddy et al., 2021a)
Acetaminophen	Polyethylene oxide and gelling agent	Hot Melt Extrusion Method Produced Long Release Pellets for Abuse Deterrent Potential: Category-1 In-Vitro Assessment.	Abuse-deterrent formulations	(Butreddy et al., 2020b)
Aripiprazole (ARP) adipic acid (ADP)	Soluplus polymeric matrix (SOL)	To increase cocrystals' solubility and dissolution rate, make them using the solvent-free hot melt extrusion (HME) process.	Pharmaceutical cocrystals	(Butreddy et al., 2020a)
Loperamide	Eudragit® EPO and Kollicoat® Smartseal 100P	Hot melt extrusion was used to create filament after loperamide was molecularly distributed into the stomach soluble cationic polymers Eudragit® EPO and Kollicoat® Smartseal 100P. The L-Arginine content of the tablets (Eudragit® EPO (SJU1) and Kollicoat® Smartseal (SJU2) made from filaments was optimized.	Multi-dose oral abuse deterrent formulation	(Nukala et al., 2019a)
Opioid	PVA	Instant Release with Abuse Deterrent Using 3D printing technology, an egg-shaped tablet known as an egglet was assessed and optimized for mechanical manipulation, drug release, and extraction. A viable tool for creating patient-tailored, quick release abuse deterrent formulations could be HME combined with FDM 3D printing.	Abuse Deterrent Immediate Release Egg-Shaped Tablet	(Nukala et al., 2019b)
Carvedilol	Colloidal silicon dioxide, MCC, HPMCAS/HPC and talc	Liquid SMEDDS were produced, and carvedilol was employed as a class II model drug. The resulting microemulsions mean size, polydispersity index (PDI), and zeta potential were calculated. The lipid mixture and HPMCAS were then combined using a twin-screw hot-melt extruder to produce the extrudates. 94.71% 5.17% of CARV content, no stability issues.	Solid SMEDDS	(Silva et al., 2018)
Naproxen Meglumine	Soluplus® PVPVA64 PVPK30	Employing the reactive melt extrusion approach, in situ salt production between naproxen and meglumine was demonstrated. The processing temperatures for extrusion were set at a level substantially above the melting points of the different parts. ASDs made from NPX-MEG exhibit greater solubility and stability.	Salt formation	(Liu et al., 2017)
Haloperidol, Maleic acid		The impact of operating temperature and screw configuration on salt formation. Less crystalline salt was produced while operating at temperatures closer to the melting point of salt. When high shear mixing zones were added, complete conversion to salt occurred as opposed to partial conversion at lower processing temperatures.	Salt formation	(Lee et al., 2017)

Indomethacin, Arginine	Copovidone	IND-ARG CAM was successfully prepared using the melting-solvent method. The addition of copovidone enhanced the IND's non-sink dissolving behavior.	Amorphous Solid Dispersions	(Lenz et al., 2017)
Atorvastatin		The solid SMEDDS were produced by utilizing adsorption and melt granulation processes. The solid SMEDDS functioned as immediate releasing capsules after quickly reconstituting to an excellent microemulsion in 1-3 min, with a release of 94.62% at the end of 30 min.	Solid SMEDDS	(Nanda Kishore et al., 2015)
Aripiprazole		Fast-dissolving oral film preparation comprising aripiprazole Kim et al EP2883540 2015	Mouth dissolving film	(Yong SK, 2015)
Mefenamic acid		Mefenamic acid taste-masked oral disintegrating tablets with enhanced solubility via molecular interaction produced by hot melt extrusion technology.	Taste-masked oral disintegrating tablets	(Alshehri et al., 2015)

## CONCLUSION

Solid self-emulsifying drug delivery systems (S-SEDDS) combine the benefits of solid dosage forms with liquid lipid formulations, including greater stability, the preservation of drug crystallization and precipitation post emulsification at the GIT, and a longer time of storage. When developing solid self-emulsifying drug delivery systems, HME has surpassed more conventional methods as a preferred technology in the pharmaceutical research field. The method is free of solvents, simple to scale up, and suitable for continuous manufacturing. It is an intriguing alternative for the development of S-SEDDS because it requires less time than many of the other technologies utilized for S-SEDDS preparation. A HME's capacity to produce a product dispersion of nanoparticles seems to be a potential platform technology for enhancing drug solubility and bioavailability while also boosting patient compliance.

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