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An update on the contribution of hot-melt extrusion technology to advance drug delivery in the 21st century: Part II

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Abstract

Introduction: Interest in hot melt extrusion (HME) technology for novel applications is growing day by day, which is evident from several hundred publications within the last five years. HME is a cost-effective, solvent free, “green” technology utilized for various formulations with low investment costs compared to conventional technologies. HME has also earned the attention of the pharmaceutical industry by the transformation of this technology for application in continuous manufacturing.

Areas covered: Part II of the review focuses on various novel opportunities or innovations of HME such as multiple component systems (co-crystals, co-amorphous systems and salts), twin-screw granulation, semi-solids, co-extrusion, abuse deterrent formulations, solid self-emulsifying drug delivery systems, chronotherapeutic drug delivery systems and miscellaneous applications.

Expert opinion: HME is being investigated as an alternative technology for preparation of multi-component systems such as co-crystals and co-amorphous techniques. Twin-screw granulation has gained increased interest in preparation of granules via twin-screw melt granulation or twin-screw *dry* granulation. This novel application of the HME process provides a promising alternate approach in the formulation of granules and solid dosage forms. However, this technology may need to be further investigated for scalability aspects of these novel applications for industrial production.

Keywords

Abuse deterrent formulations; Co-extrusion; Hot Melt Extrusion; Pharmaceutical Co-crystals; Semi-solid formulations; Twin-Screw granulation

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1. Introduction

Hot-melt extrusion (HME) has become one of the widely used processing techniques within the pharmaceutical industry over the past 30 years [1, 2]. Hot-melt extrusion is the process of pumping raw materials into an extruder with counter rotating or co-rotating screw elements at high temperatures to melt and mix the components within the instrument to ultimately produce extrudates via an appropriate die, thus obtaining desired products [1, 2, 3, 4]. The increasing number of publications on HME for various novel applications/opportunities confirms its wide applicability in pharmaceutical research. The characteristic features of HME, such as its solvent free nature, easily scalable and cost-effective process, low investments and continuous manufacturing capability make it a boundless opportunity for the development of novel drug delivery systems. However, the challenges such as high processing temperatures, high energy input, non-availability of HME grade polymers may have inhibited broader use of HME. Nevertheless, these issues have been overcome over years of research by input of new techniques and equipment modifications, using suitable additives, and availability of HME grade polymers.

Part I of this review described the update on solubility enhancement of poorly soluble drugs, SWOT analysis, process analytical tools such as UV/Visible spectrophotometry, Near InfraRed spectroscopy, Raman Spectroscopy and Rheometry for continuous manufacturing. Further the review addressed special emphasis on HME coupled 3D printing and its applications. The opportunities or applicability of HME for development of novel drug delivery systems is evident from recent publications. In this Review article (Part II) authors focus on various novel opportunities or innovations of HME such as multiple component systems (co-crystals, co-amorphous systems (CAMs), salts) [5], twin-screw granulation [6], semi solids [7], co-extrusion [8], abuse deterrent formulations [9], solid self-emulsifying drug delivery systems [10], targeted drug delivery (chronotherapeutic systems, gastroretentive drug delivery systems) [11, 12] and miscellaneous applications of HME with detailed case studies [1, 2, 4, 13, 14].

2. Opportunities of HME

Versatility of HME has been exemplified with various novel applications or opportunities reported in the literature for production of different drug delivery systems (Figure 1).

2.1. HME in pharmaceutical multicomponent systems

Most of the newly approved drug molecules exhibit poor aqueous solubility due to either increased size or lipophilicity. Several techniques were being used to overcome this challenge; however, in the last decade, pharmaceutical multicomponent systems have gained increasing interest, including pharmaceutical co-crystals, salts, and more recently, CAMs [15]. Fernandes et al. [16] emphasized the potential of co-crystals and CAMs in general and particularly for solubility enhancement of neutral molecules such as carvedilol. Various techniques are available for preparing pharmaceutical co-crystals, salts, and CAMs, some of which are solvent-based, whereas the others are solvent-free. Figure 2 shows a schematic representation of pharmaceutical multicomponent systems.

Karimi-Jafari et al. [17] classified co-crystal preparation techniques as solvent-free solid-state methods that include HME and mechanochemical grinding where very little or no solvent is used. Solvent-based, liquid-assisted cocrystallization methods include liquid-assisted grinding, high-shear granulation, spray-drying, antisolvent cocrystallization, supercritical carbon dioxide processing, freeze-drying, microfluidic and jet dispensing approaches, and ultrasound crystallization techniques. Quench cooling, ball milling, solvent evaporation, and HME are some of the methods reported for the preparation of CAMs. There is a definite need for a solvent-free, scalable, continuous manufacturing (CM) technique such as HME for the preparation of this novel pharmaceutical multicomponent systems [18]. In the last few years, HME has been among the techniques highly explored for the preparation of this pharmaceutical multicomponent systems. The different multicomponent systems discussed in this review are summarized in table 1.

2.1.1. Cocrystallization by HME—Co-crystals are single phase solid neutral crystalline materials comprising of two or more different molecular/ionic compounds in a stoichiometric ratio held together by noncovalent forces [15, 19]. In pharmaceutical co-crystals, one of the components is an active pharmaceutical ingredient (API) and the other is a co-former. The API and co-former interact via non-covalent bonds, such as ionic interactions, hydrogen bonds, and Van der Waals bonds. Co-crystals are generally aimed to provide superior solubility, stability, and drug release, which thereby enhance drug bioavailability without affecting the physiological action of the drug. Co-crystals are also proved to help in improving mechanical properties of API, which ultimately help in dosage form preparation [20].

Interaction of the API and co-former results in various melting point of the product, which might be intermediate, high, or low melting point compared to that of either pure component. Schultheiss and Newman [21] reported that 51% of co-crystals had a melting point between those of the starting components, whereas 39% has less than those of either component, 6% has higher than that of either, and 4% has the same melting point. Melting point is one of the key factors for techniques such as HME to ensure proper processing. The reported techniques involving melt extruders include twin screw extrusion (TSE), HME, and matrix-assisted cocrystallization (MAC).

HME offers high shear and intense mixing that improves the contact between an API and co-former, resulting in the formation of co-crystals in a solvent-free process [5]. Medina et al. [22] for the first time applied TSE as a solvent free scalable process for the co-crystallization of 2:1 caffeine-oxalic acid and 1:1 AMG 517-sorbic acid. The authors have reported that co-crystallization was observed only with high mixing screw design, whereas the control design consisting of only conveying elements did not result in co-crystal formation. This shows that TSE can provide efficient mixing and surface contact, facilitating co-crystal formation.

Boksa et al. [23] introduced MAC as a novel method of co-crystal production. The authors have successfully prepared matrix-assisted co-crystals of 1:1 carbamazepine-nicotinamide with 20% (w/w) Soluplus® as a matrix former. The processing temperatures were set to melt the polymer or matrix wherein the co-crystals are embedded. The obtained matrix-assisted co-crystals showed similar quality characteristics to those of the reference co-crystals

prepared through solvent evaporation technique. Incorporation of Soluplus® in the matrix has greatly improved the *in vitro* dissolution profile.

Gajda et al. [24] investigated semicrystalline (poloxamer P407, PEG-PVA copolymer) and amorphous (Soluplus®, PVPVA64, and HPMCAS) polymers exhibiting different structural and physicochemical properties as functional matrices for 1:1 flufenamic acid-nicotinamide (FFA:NA) co-crystals using HME. Polymers, compared to pure components, improved the processability of MAC by reducing the process torque. FFA:NA cocrystal encapsulated in the polymer matrix was successfully formed in all the investigated FFA:NA/polymer ratios of the semi-crystalline polymer, regardless of their melting temperatures. In addition, partly crystalline or amorphous composites were synthesized with the amorphous polymers with T_g values 30-60°C below the processing temperature, whereas with HPMCAS polymer whose T_g was close to the HME processing temperature, co-crystals embedded in the polymer matrix were observed. In general, the polymers effectively reduced the torque values, which increased throughput and dissolution profile.

Li et al. [25] investigated polymeric carriers (Eudragit® EPO, Soluplus®) and small molecular polyol (xylitol) as matrix formers in the preparation of ibuprofen and isonicotinamide co-crystals using HME. They successfully prepared cocrystal particulates of ibuprofen and isonicotinamide physically suspended in xylitol, whereas with the polymeric carriers, there was no evidence of cocrystal formation. This study established that a right carrier with no or limited interaction with the reagent pair, processing temperatures lower than the melting onset of co-crystals, as well as low melt viscosity and rapid solidification on cooling are important factors in the preparation of co-crystals by HME. The same research group in 2017 [26] for the first time applied the concepts of Hansen solubility parameter and Flory-Huggins solution theory to understand the importance of miscibility between co-crystal reagents and the solubility/miscibility of co-crystal reagents and co-crystals in matrix carriers. It was found that the F-H solution theory was more relevant to extrusion co-crystallization, in which temperatures that promote solubilization of co-crystal reagents and later precipitation of the formed co-crystals in the carrier matrix were necessary in generating high co-crystal yields. Construction of phase diagram served as a guide to select the HME process temperatures, and introduction of kneading/mixing elements in the screw configuration improved co-crystal yield.

Pharmaceutical co-crystals are formed when a drug and a co-former interact in a stoichiometric ratio, and reproducible control of stoichiometry is a challenge in the commercial scale-up of co-crystals. Kulkarni et al. [27] studied melt extrusion as a solvent-free co-crystallization technique to control stoichiometry in caffeine-maleic acid co-crystals with controlled feed stock composition and process conditions. In this study, the authors prepared caffeine-maleic acid co-crystals in two stoichiometric ratios: 1:1 and 2:1, and even a 1:1 cocrystal can be converted to 2:1 and vice versa when fed with excess caffeine and maleic acid. This study showed the possibility of different cocrystal formation with controlled stoichiometry ratios using HME.

Moradiya et al. [28] designed a continuous process assembled with 6 unit operations in a small footprint, by applying QbD (quality by design), the process was optimized and scaled

up to produce 3000 capsules/h. In the continuous manufacture scheme, indomethacin (IND) and saccharin in equimolar amounts were mixed in a Turbula mixer, and then the powder was placed in a twin-screw extruder operated without a die. Following extruder is a cutter mill for size reduction, a convective twin-screw blender was placed underneath the cutter mill to perform uniform powder blending, and the blended powders was then fed into the Mini-Cap capsule filler. In-line process monitoring was carried out using Fourier-Transform Antaris MX NIR analyzers (NIR spectra) for extrusion co-crystallization and with two Parsum probe particle size probes, with one probe at the extruder and the other probe underneath the 250 mesh of the cutter mill to measure micronized co-crystals. Melt extrusion was also successfully applied to enhance the physicochemical stability of co-crystals by co-processing the 1:1 IND-saccharin co-crystals with the inert excipients PEG 6000 (crystalline hydrophilic polymer), HPMC (amorphous hydrophilic polymer), and Neusilin (aluminometasilicate) during melt extrusion [29]. Recently Fernandes et al. [30] showed successful utilization of HME as a solvent-free CM for preparing 2:1 IND-carvedilol co-crystals with improved characteristics. The above studies confirmed HME as a potential alternative method for formulating pharmaceutical co-crystals.

2.1.2. Co-amorphous systems—Polymeric amorphous solid dispersions (PASDs) reasonably addressed the solubility issue associated with the majority of New chemical entities (NCEs). The term co-amorphous was coined to differentiate an amorphous mixture containing two small molecules from PASDs. In recent years, co-amorphous systems (CAM) gained greater attention in overcoming the stability issues associated with PASDs. These PASDs are associated with problems such as poor drug solubility/miscibility with polymers resulting in increased incorporation of polymer thus increasing the volume of the final dosage form, especially for high-dose drugs. Further these PASDs are associated with phase separation, recrystallization resulted due to hygroscopic nature of the polymer. All these factors can potentially affect the dissolution/solubility advantage of polymeric amorphous solid dispersions. Guo et al. [38] reported that most of FDA product recalls on January 2011 to January 2013 were either due to physical instability or failure to meet dissolution specification. In the last few years, CAMs are established as an alternative for PASD. In CAM, a drug is incorporated with small molecules instead of polymers, and the small molecules can be a drug (drug-drug for combination therapy) or excipients, such as amino acids or saccharine [39]. CAMs have been reported to provide both dissolution enhancement and stability advantages. Literature reveals the use of NSAIDs, anti-hypertensives, proton pump inhibitors and statins as model drugs and low molecular weight excipients (co-formers) such as citric acid, saccharine, amino acids, meglumine, nicotinamide for the preparation of CAM [40, 41]. Ball milling, cryo milling, solvent evaporation and spray drying are the commonly used techniques for the preparation of CAM. These currently used preparation methods have demonstrated lab scale success; however a major challenge is in scale up and commercialization [18].

Suresh et al. [42] defined CAM as a multicomponent, single-phase, amorphous solid system lacking periodicity in the lattice, and it is associated by weak and discrete intermolecular forces of interaction, such as hydrogen bond between the components. This system primarily differs from co-crystals, salts, and eutectics in its amorphous nature. Chavan et al. [18]

mentioned the need for a continuous and solvent-free manufacturing technique such as HME for the preparation of CAM. This offers several advantages, such as easy scale-up, because of the availability of equipment with different capacities, which are suitable for in-line monitoring of intermolecular interactions between drugs and co-formers, mixing efficiency, particle size, and in-process degradation.

Amorphous systems with small molecules are not new; urea was used in the preparation of solid dispersions through melt granulation and melt quenching methods [43, 44]. However, the term “co-amorphous system” was coined by Cheing et al. [45] in 2009. After 2009, there are several reports on drug-drug and drug-excipient CAMs. Chavan et al. [18] reported a list of drug-drug and drug-excipient CAMs prepared using different techniques. For the first time, Lenz et al. [41] evaluated the suitability of HME as a CM technique in the development of IND-ARG (indomethacin-arginine) CAMs with and without copovidone as a polymer. Because ARG cannot be converted to the amorphous state by hot melt approach, the authors used a melting-solvent approach to successfully prepare IND-ARG CAMs. In this approach, amino acid dissolved in water at 23% (w/w) is fed separately into an extruder after the first kneading zone, whereas a drug and polymer are fed at the feeding zone. A yellow transparent liquid product was obtained, indicating the amorphization of IND and ARG, and was later dried under reduced pressure. The combination of co-amorphous formulation with the polymer improves the non-sink dissolution behavior of IND.

Arnfast et al. [46] from the same research group investigated the processability of a model drug-drug combination of IND-cimetidine (CIM) with and without polymer [5% (w/w) polyethylene oxide (PEO)] for the preparation of CAM using HME. Results of DSC studies of the IND-CIM physical mixture showed a melting onset at 110°C, which is 30-50°C below the melting temperature of the individual components, suggesting a eutectic behavior. Thus, the processing temperature for melt extrusion was set at 120°C. Surprisingly, at a processing temperature of 120°C, the drug-drug mixture showed high melt viscosities. To improve processability, 5% PEO was used, and the mixtures with polymer showed low melt viscosity and elastic-like behavior, favoring the extrusion process. Addition of small amounts of polymer hindered the amorphous phase separation in the co-amorphous extrudates. This development of CAMs using HME is an interesting research area to further explore the effect of polymers on HME processability. Very recently, Mizoguchi et al. [47] reported the conditions required for formation of CAM and the mechanisms responsible for the stabilization of the amorphous state in CAM. In this study, the authors screened different combinations for the CAM formation using a melting method. A relationship was established between the formation of CAM, H_{mix} and $\log P$. The compounds that have negative H_{mix} and similar lipophilicity are likely to form CAM. H_{mix} was also found to contribute towards the stabilization of an amorphous state, with a greater negative H_{mix} indicating a more stable CAM.

2.1.3. Salts by HME—Pharmaceutical salts comprise of either a cationic or anionic molecule and a counter ion, which might be molecular or monatomic. A salt must have a definite stoichiometry for charge balance. In the last few years, researchers have reported the suitability of HME for preparation of salts. Salts are generally prepared by an acid-base reaction in organic solvents, followed by crystallization.

Liu et al. [48] investigated the reactive melt extrusion of naproxen (NPX)-meglumine (MEG) using Leistritz Nano 16 extruder (Leistritz Corporation, Allendale, NJ). The authors prepared NPX amorphous solid dispersions with and without MEG using 3 different polymers: Soluplus[®], PVPVA64, and PVPK30. The polymer was used at 10% (w/w) in NPX-MEG formulations and at 51.3% (w/w) in formulations without MEG. The processing temperature was set well above the melting temperature of individual components. An extensive characterization of the prepared formulations showed *in situ* salt formation between NPX and MEG during the reactive melt extrusion process. Proton transfer from NPX to MEG was confirmed by FTIR and X-ray photoelectron spectroscopy, and polymers did not interfere with the proton transfer reaction. Non-sink dissolution and stability studies indicated improved dissolution profiles and stability, suggesting that *in situ* salt formation was an effective approach to improve NPX solubility and stability.

Lee et al. [49] investigated TSE as a solvent-free CM technique for preparation of haloperidol and maleic acid salt. Extrusion of a 1:1 mixture at 60°C resulted in formation of highly crystalline salts, as observed using DSC, powder X-ray diffraction (PXRD), FTIR, and optical microscopy. When processed at 80°C, which is close to the melting temperature of salt (110°C), less crystalline salt was obtained. Two different screw designs were used for TSE, and the one with six high-shear mixing zones resulted in complete conversion to salt, whereas the one with three low-shear mixing zones resulted in partial conversion to salt. TSE allows easy, continuous production of haloperidol-maleic acid salt at low temperature.

Bookwala et al. [50] for the first investigated preparation of a highly crystalline salt of a weakly acidic drug by HME. A 1:1 mixture of Indomethacin(IND) and tromethamine was extruded using 11-mm co-rotating twin-screw extruder with all zones heated to 135°C, with a screw speed of 150 rpm. FTIR and NMR studies confirmed *in situ* salt formation with proton transfer, whereas crystallinity was confirmed with DSC and PXRD studies. Salt formation increased the dissolution of IND in aqueous medium, thus proving HME as a promising alternative for the preparation of crystalline salts. The above studies confirm the potential of HME as a solvent free process for production of pharmaceutical multicomponent systems.

2.2. Twin-screw granulation

In recent years, twin screw granulation, as twin-screw melt granulation (TSMG) or twin-screw dry granulation, has gained increasing interest in the preparation of granules. This novel application of HME provides an alternative, promising approach in the formulation of granules and solid dosage forms. In this section, we discuss recent studies on twin screw granulation separately.

2.2.1. Twin-screw melt granulation—Granulation is a vital step in the manufacturing of solid dosage forms because it guarantees the flowability, processability, and compactibility of raw materials to be converted into a final dosage form [51]. Twin screw granulation (TSG) can be a good alternative to the batch processes that are conventionally employed by industries [52]. Recently, Thompson et al. [53] emphasized the influence of

various formulation and process parameters on the granulation process. According to the reports, better knowledge and understanding of scale-up of extrusion granulation are needed.

Inorganic excipients were investigated as solubilizing carriers in twin screw granulation. Maniruzzaman et al. [54] employed a QbD approach to manufacture ibuprofen-loaded granules via hot melt granulation. Particle morphology observed using SEM, showed ibuprofen as small micro-agglomerations in granules, which may aid the dissolution rate of poorly soluble drugs. In another study by Maniruzzaman et al. [55] Neusilin® US2 alone was used in a one-step continuous extrusion process to successfully prepare solid dispersions of indomethacin with enhanced dissolution rates. The solid dispersions were obtained in the form of granules, with indomethacin molecularly dispersed in the porous network of the carrier.

Patil et al. [56] successfully developed a pH-dependent/independent tablets of ondansetron HCl using Klucel™ EF as a binder, Ethocel™ 10 premium as a sustained-release agent, and fumaric acid as a pH modifier by twin-screw melt granulation (TSMG). The presence of fumaric acid enhanced the drug release of ondansetron HCl owing to the micro-environment created inside the tablet, and 90% drug release was observed at 24 h. The tablets without fumaric acid showed slower drug release in pH 6.8 buffer, compared to the formulations with fumaric acid.

Keen et al. [57] developed a Compritol® 888 ATO-based, sustained-release tablets and studied the effect of different formulations and processing conditions on granule formation and drug release characteristics. In the preliminary studies, it was confirmed that a 15% drug load could produce granules that can be compressed into tablet matrices with a controlled release profile over 16 h. The process temperature was 80°C, and from the results it was obvious that if Compritol® 888 is completely molten, it does not affect particle size distribution in the granules. A decreased temperature at discharge point (below the M.P of Compritol® 888) resulted in granules with the desired particle size distribution, because completely molten Compritol® 888 contributed a sticky mass. This suggests the selection of appropriate processing conditions for the development of granules with the desired properties.

Verstraete et al. [58] investigated three techniques (twin-screw melt granulation/compression, HME, and injection molding) to manufacture [metformin hydrochloride](#) sustained-release matrices using thermoplastic [polyurethane](#) (TPU) material. The matrices obtained using HME and injection molding showed sustained release for 24 h, whereas TPU-based TSMG matrices released complete drug in 6 h. By altering the ratio of the hydrophilic and hydrophobic portions of TPUs, *in vitro* release kinetics can be adjusted.

Monteyne et al. [59] developed metoprolol tartrate (MPT) granules via TSMG by employing stearic acid (SA) and SentryPolyox® WSR N12K (PEO; M.W 1,000,000 g). The TSMG process was carried at 60°C, except for the last segment, at a screw speed of 150 RPM. This study investigated the effect of stearic acid/PEO on the dissolution rate of highly soluble MPT. The preferential interaction of MPT with SA hindered PEO to form hydrogen bonding with SA, thus allowing free PEO to recrystallize in the stearic acid matrix granules and

increasing the sustained release characteristics of MPT in the formulation. This study showed the use of SA and PEO as matrix-formers for TSMG.

Kallakunta et al. [6] investigated the effect of manufacturing techniques on lipid-based sustained release tablets prepared via direct compression (DC), wet granulation (WG) and TSMG. This study conducted employing 3 lipids (Compritol® 888 ATO, Precirol® ATO5, Geleol™) of different chemical compositions and HLBs revealed the successful granulation by TSMG technique. The temperature conditions employed only melted the lipid, the shear of TSMG process aided the distribution of lipid in the blend which was revealed by the presence of recrystallized stable polymorphic form of lipids in XRD and DSC studies. The in-vitro drug release studies showed fast release for DC formulations, hindered release in WG formulations whereas TSMG formulations showed the sustained drug release up to 24h. This suggests suitability of HME technology in granulation for sustained release tablets.

Batra et al. [60] did a systematic screening of polymers (binders) for their suitability in the melt granulation of metformin hydrochloride and acetaminophen. Granules prepared from different polymers of different chemical classes, namely PVP, HPMC, HPC (hydroxyl propyl cellulose), and methacrylate, provided an acceptable compactibility of metformin hydrochloride granules at 180°C with only 10% (w/w) binder. Owing to the lower M.P of acetaminophen (169-170°C), the process was carried out at 130°C. At that temperature, the polymers Klucel™ EXF, Klucel™ JXF, Soluplus®, Eudragit® L100-55, Eudragit® EPO, and Soluplus® resulted in tablets with acceptable compatibility (>2 MPa) and with enough mechanical strength to withstand mechanical shocks during manufacturing and processing. From this study, it is evident that a wide range of polymers are suitable with APIs with different M.P for TSMG.

The above reports confirm the use of HME as an alternate option for granulation with appropriate processing conditions based on the type of drugs and materials employed in the formulations.

2.2.2. Twin-screw dry granulation—Dry granulation techniques offer additional advantages compared to conventional granulation techniques (wet granulation, fluidized bed granulation, and melt granulation), primarily due to the fact that it involves no solvent and no drying process [61]. Dry granulation is particularly useful for formulations with heat-sensitive components and for those prone to hydrolysis [62]. The main pitfall of the conventional dry granulation techniques is loss of strength after the re-compression step, which is a result of opposing phenomenon to permanent plastic deformation due to particular level complexities, which was explained by Malkowska et al. [63] as the phenomenon called “work hardening”. Similarly, wet granulation and melt granulation can pose serious problems for product stability owing to usage of solvent and molecular level interactions. Wet granulation involves a drying step, which is not economic, although hot melt granulation is held back by relatively high process temperatures [64]. Therefore, twin-screw dry granulation technique can be an excellent option in the development of quality products. The absence of solvents and excess heat energy will overcome stability issues, such as hydrolysis and product degradation due to high temperatures. Additionally, the shear

associated with granulation aids the distribution of binders throughout the blend, improving granule properties and compression properties of the granules [65].

Upadhye et al. [66] for the first time successfully performed dry granulation through twin-screw technology. A physical mixture was kneaded to granules under the operated processing conditions. Dry granulation was performed for 2 APIs, sildenafil citrate and ondansetron, to formulate extended-release formulations. The polymers used for granulation were Klucel™ HF (HPC), Natrasol® (HEC), and Ethocel™ standard 10 (ethyl cellulose). The process was carried out at a steady temperature of 65°C and at a screw speed of 100-200 rpm with various screw configurations. The granules obtained were successfully compressed into tablets.

Liu et al. [67] investigated the effect of the molecular weight of polymeric binders and non-binder ingredients on formulations via heat-assisted dry granulation. Anhydrous caffeine was used as a model drug in this study, and Affinisol™, HPMC HME 100LV, and HPMC HME 4M were used as binders. The diluents used were Flowlac® (lactose α -monohydrate) and Avicel® PH 101 (microcrystalline cellulose). Both dry and melt granulation batches were performed. In melt granulation, all the zones were maintained at 160°C to melt the binder and flow, whereas in dry granulation, only zone 2 was maintained at that temperature. Lower feed rate was found to increase the residence time of blend in the extruder and improve the possibility of granulation. The presence of caffeine and microcrystalline cellulose decreased the particle size of granules, indicating the inherent nature of the ingredients in the formulations. With Affinisol™ 100 LV, particle agglomeration was greater than with Affinisol™ 4M at lower screw speed and at higher binder content owing to the high sintering rate of the binder. With Affinisol™ 4M, higher molecular weight and viscosity of binder resulted in larger granules under processing conditions where binder softening was not interfered or hindered. This study showed the effect of the properties of ingredients and process conditions, such as screw speed and feed rate, on successful granulation within safe processing limits. Considering the transitions observed in melt granulation trials, it can be concluded that twin-screw dry granulation is an effective and relatively safe process to produce quality products. Majumder et al. [68] demonstrated Neusilin® US2 as an alternative carrier in development of amorphous granules with enhanced dissolution for the model drug benzoyl-methoxy-methylindol-acetic acid (BMA) by means of a continuous dry granulation approach.

Recently, Kallakunta et al. [65] successfully achieved dry granulation using 3 APIs with different M.P, namely theophylline (273°C), APAP (169°C), and lidocaine HCl H₂O (82°C). The binders HPC SSL, Klucel™ EF and the sustained-release agents Aqualon® T10 (ethyl cellulose), Klucel™ MF, and Eudragit® RSPO were used based on the M.P of the API. The process temperature in all zones of extruder was maintained below the M.P/Tg of the formulation ingredients. The binder was subjected to shear associated with thermal energy of the twin-screw process, which aided the granulation process. The effects of feed rate and number of mixing zones on the possibility of granulation and tablet compression were investigated. Crystallinity of API affected the maximum possible drug load, whereas higher polymer viscosity aided the granulation process and resulted in bigger/stronger granules. DSC and XRD studies proved the crystalline nature of the formulations, indicating that

granulation was achieved under dry conditions. Drug-release profiles revealed that release pattern is affected by not only sustained-release polymers but also the nature of API. The formulations prepared were stable for up to 6 months at 25°C/60% RH (relative humidity) studied.

Thus, the above studies suggested the suitability of twin-screw dry granulation as an alternative to the current conventional dry granulation techniques. The schematic diagram and parameters to be considered in twin-screw granulation are presented in Figure 3. Twin-screw dry granulation can be a potential option to improve tabletability and stability. This continuous process can reduce processing steps and produce stable products. However, this process needs to be further investigated with various materials and processing conditions.

2.3. Self-emulsifying drug delivery systems and HME

Self-emulsifying drug delivery systems (SED DS) are designed to improve oral bioavailability by enhancing the solubility of poorly soluble drugs and keeping them in a soluble form by dispersing them all over their transit in the gastrointestinal tract [69]. Solid SED DS is a convenient option to improve stability, ease of manufacturing, and accuracy of dose. This modification of liquid SED DS form presents combined advantages of SED DS and solid dosage forms. The conventional method to prepare solid SED DS involves the adsorption of liquid SED DS onto solid carriers to produce free-flowing powders [70]. HME serves as an option for CM of dosage forms with commercial scalability [71].

Very recently, Silva et al. [10] reported the development of carvedilol solid SED DS by employing Velsan® CCT (capric/caprylic triglycerides) as an oil phase, Plurol Isostearique® (polyglyceryl-6-isostearate, Plurol) as a surfactant, and Transcutol HP® (diethylene glycol monoethyl ether) as a co-surfactant with the aid of an extruder. Liquid SED DS was prepared in a conventional way by using a magnetic stirrer. The formulations with successful emulsifying characteristics were converted into solid SED DS by employing solid carriers HPMCAS/HPC and microcrystalline cellulose in a mortar. Next, the mixture was extruded using a twin-screw hot melt extruder, and the extrudates were processed for a downstream process. PXRD studies confirmed the amorphous nature of the API in the prepared solid SED DS. The extrudates manufactured with the lowest drug load at the highest processing temperature and recirculation time showed fast drug release in pH 6.8 media. This recent report on the application of HME in the formulation of solid SED DS is a novel opportunity of HME in development of diverse pharmaceutical drug delivery systems.

2.4. HME for semisolid formulations

HME has been explored for developing topical semi-solids such as ointments, gels, nanostructured lipid carrier gels, and creams. In this part of the review, we summarize case studies of HME-based topical semi-solids. HME, which drives the physical blend of drugs and inactive excipients by uniform mixing at a desired temperature, offers many advantages over conventional methods for semi-solid preparations. HME offers reduced processing time because in this method, both the melting and mixing of components are performed in one step, and it requires no additional agitators because the mixing process is facilitated by screw elements within the barrel. Moreover, the processing conditions for various semi-

solids could be customized to obtain the desired products, and different phases of formulation ingredients can be mixed separately into the extruder. The schematic representation of semi-solid preparation employing HME is depicted in Figure 4.

Bhagurkar et al. [7] investigated and demonstrated the application of HME for the development of PEG-based ointment using lidocaine as a model drug. A modified screw design was employed in HME to produce a uniform ointment product. The quality of the HME-based ointment, with respect to rheology, texture, and drug release, was comparable to that of conventionally prepared ointment. Similarly, the same group studied and prepared nanostructured lipid carrier (NLC) using HME coupled with probe sonication. The parameters for the HME and sonication processes were optimized, and a modified screw configuration was employed during extrusion to prepare lidocaine-loaded NLCs, which were then added to carbopol gels to obtain NLC gels. Permeation studies confirmed the sustained-release characteristics of the prepared gels; thus, the conventional HME process was modified for CM of NLCs [72]. Pawar et al. [73] developed HME technology for CM of topical diclofenac sodium gels using Kolliphor® P407 and Kollisolv® PEG400 as gel bases. A central composite design was utilized to optimize formulation parameters. Uniform gels were successfully obtained using a modified screw design. The obtained gels were characterized for physicochemical properties, such as DSC and XRD, and the drug was shown in the amorphous state. Further, results of pH, rheology, surface tension, and texture profile analyses showed homogeneity with consistent viscoelastic properties, suggesting excellent gel preparation using HME. Similarly, Mendonsa et al. [74] developed polaxomer gel formulations using ketoprofen as a model drug by HME and conventional method. The obtained 30% polaxomer gels were reported to be more ideal than 40% polaxomer gels. The drug was in the amorphous state in the polaxomer gels prepared by extrusion and conventional method. Furthermore, the texture analysis and rheology studies data were similar and comparable for each gel preparation.

Bagde et al. [75] successfully prepared solid lipid nanoparticles of Ibuprofen using HME, which was later prepared as a gel using 1% Carbopol 981 A. In the preparation of SLNs, the lipids and drug were fed into the extruder and the surfactant solution was preheated to 70°C, which was injected at the mixing zone. The barrel temperature for all the zones was maintained at 110°C. The product was reintroduced in to the extruder and processed at a higher screw speed of 800 rpm, which resulted in the size reduction. The globule size reduced emulsion, when cooled to room temperature, resulted in SLNs. The effect of formulation variables was optimized using a DoE approach.

The above reports suggested the applicability of HME technology as a continuous process with short processing times, uniform mixing, and cost efficiency in the development of topical semisolid products. However, this technology may need to be investigated further for scalability aspects of these semisolid products for industrial production.

2.5. Co-extrusion

Co-extrusion is the concurrent extrusion of two or more materials to obtain a multi-layered extrudate. This offers advantages such as coating of the inner layer by an external layer to modify release or protect the inner component, as well as simultaneous administration of

two incompatible drugs as separate layers. Hot melt co-extrusion was reported for development and characterization of stearic acid-based, sustained-release devices. In a study, stearic acid and PEG were used as hydrophobic and hydrophilic components, respectively, with acetaminophen and theophylline as model drugs, and co-extrusion length and configuration were found to sensibly affect release kinetics [76]. Further, the same group has studied the *in vivo* performance of co-extrudates of sustained-release devices, and they achieved the desired release of theophylline and confirmed the viability of HME in the development of sustained-release devices as co-extrudates [77].

An additional advantage of this hot melt co-extrusion process is the development of fixed-dose combination products in a single-step CM. Dierickx et al. [78] studied co-extrusion as a manufacturing technique for the development of a multi-layered, fixed-dose combination product of MPT and hydrochlorothiazide (HCT) as sustained- and immediate-release drugs. Using polycaprolactone as a core and PEO as a coat layer, the extrusion process was successful. HCT was completely released from the coat within 30 min, and MPT release was sustained over 24 h. Thus, the *in vitro* and *in vivo* performances of this co-extruded, fixed-dose combination product were comparable and similar to those of the reference tablet. Similarly, Dierickx et al. [79, 80] further developed multilayer mini-matrices for dual release of diclofenac sodium and co-extruded solid solutions as immediate-release, fixed-dose combination product of acetylsalicylic acid and fenofibrate. To produce the dual-release, mini matrices of diclofenac sodium, a combination of ethyl cellulose, Soluplus®, polycaprolactone, and PEO polymers was used, whereas to produce immediate-release FDC product, a combination of Kollidon® PF 12 and Kollidon® VA 64 was used for ASA (core), while Soluplus®, Kollidon® VA 64 and Kollidon® 30 were useful for fenofibrate (coat). These studies confirmed the availability of pharmaceutical polymers and viability of co-extrusion method to produce multilayer dosage forms or fixed-dose combination products. Following these studies, there are reports on the development of fixed-dose combination products using co-extrusion.

Laukamp et al. [81] developed sustained- and dual-release formulations of carbamazepine for use in a solid dosage pen. The Solid dosage pen (SDP) is a device consisting of a screw that can be adjusted for a specific dose, and this device cuts cylindrical extruded rods placed in it into slices to produce individual dosing [82, 83]. Vynckier et al. [8] developed a dual sustained release, co-extruded, fixed-dose combination product of both poorly water-soluble (gliclazide) and freely soluble (metformin HCl) drugs using polycaprolactone (CAPA 6506; as a hydrophobic polymer) and Kollidon® VA for treating diabetes mellitus. Jamroz et al. [84] studied and evaluated the effect of dual co-extrusion processes on the characteristics of aripiprazole 3D-printed tablets.

2.5.1. Challenges in co-extrusion—The biggest challenge in the co-extrusion process is selection of suitable polymers for a desired pharmaceutical application considering the extrusion temperature, melt viscosity, adhesion of polymer layers, inter-diffusion of polymers, and suitable die design. These factors are all crucial in the successful production of co-extrusion dosage forms [85]. Co-extrusion has an advantage of simultaneous administration of two incompatible drugs, however this is not always feasible in all combinations. Vynckier et al. [86] developed a fixed-dose combination product for enteric

protection with naproxen as a core layer as well as an HPMC AS LF polymer and esomeprazole magnesium as coat layers, using PEO and PEG. The co-extrusion process was not an appropriate solution to overcome the interaction between naproxen and esomeprazole in this fixed-dose combination. However, this interaction can be potentially addressed by incorporating a third polymer layer between the two drugs studied. Although co-extrusion is reported to have multiple advantages considering the above issues, the applicability of co-extrusion seems to be limited, as evident from the small number of publications in the recent past. Nevertheless, co-extrusion may be a promising HME application with significant number of studies on pharmaceutical polymers, appropriate feeder, and die modifications.

2.6. Targeted drug delivery/chronotherapeutic systems

Targeted drug delivery systems are intended to deliver drugs to the site of action, thereby improving drug availability at the site of action. This leads to more efficient treatment for patients and fewer possible side effects compared to those of conventional drug delivery systems. Advantages of targeted drug delivery systems include reduced or avoidance of first-pass metabolism, lower dose, and reduced toxicity [71]. HME technology has multiple applications tailored for specific purposes such as sustained-release dosage forms [87], drug-loaded devices [88], chronotherapeutic systems [11], and delayed-release dosage forms [89].

Recently, Dumpa et al. [11] developed a chronotherapeutic delivery system for arthritis patients with early morning stiffness. This study investigated two APIs, ibuprofen and ketoprofen, and the polymers Eudragit® S 100 and ethyl cellulose, to develop a time-dependent release system. The obtained extrudates were proven to be amorphous in nature by DSC and XRD studies, and were cut into pellets of sizes ranging from 1-3 mm. Results of *in vitro* studies demonstrated a lag of 6 h (with <20% drug release) to meet the criterion for early morning release, and drug release was observed to be affected by the size and surface area of pellets. Results of SEM studies inferred that the surface of pellets was intact in 1.2 pH media and very low drug release was observed in 6.8 pH media with slight cracks on the pellet surface. At 7.4 pH, as the Eudragit® S100 polymer dissolves, the release was completed within study period.

Gately et al. [90] developed shellac-based delivery systems for colon-specific delivery. The process employed pharmaceutical-grade shellac (SSB® 55) as a melt-extrudable polymer to encapsulate freeze-dried probiotic powder (Biocare® Bifidobacterium). FTIR spectra proved that there is no interaction between the carrier and the probiotic. The melt viscosity of the formulation was reduced when % of probiotic powder was increased, indicating the plasticizing effect of probiotic powder on shellac. A higher drug load of 50% was possible, and results of *in vitro* degradation studies showed <5% degradation at pH 1.2 and 6.8, thus proving successful colonic delivery of the probiotic.

Balogh et al. [91] developed a Eudragit® FS 100-based controlled release drug delivery system of spironolactone by using HME and electro-spinning techniques. The processing temperature was set at 120°C to establish a safe extrusion process because this temperature is below the M.P of the API (210°C). *In vitro* drug release studies were conducted for 2 h in 0.1 N HCl and in pH 7.4 buffer for next 6 h. The formulations prepared by melt extrusion process relatively showed lower (<5%) release than the electro-spun formulations at the first

2 h, irrespective of drug load, showing the control of the process over drug release. In pH 7.4 buffer media, immediate release was observed and % drug load inversely affected drug release rate.

Vo et al. [12] designed a floating delivery system via HME technology using a solvent-based mechanism. The escape of solvent (ethanol) from the extrudate made a uniform vacuous region in the extrudates, which aided the floating behavior of the pellets without any lag time. Owing to reverse-flow of solvent with standard screw configuration, an altered configuration was employed for process feasibility. The temperature was controlled in such a way to avoid high torque and ensure uniformity of the strands. Thus, due to the lower process temperature requirement, the API was observed to be in the crystalline state, which was confirmed by XRD studies. Drug release profiles over 24 h were influenced by HPMC K15M content. Simons et al. [92] formulated hallow tubes of metformin embedded in inert polymer matrices of Eudragit® RS PO and Eudragit® E PO using hot melt extrusion and the tubes produced served as a floating devices. Sustained release profiles were obtained at very high drug loadings of up to 80% (w/w) without exhibiting a burst release. It is observed that release rates and buoyancy can be controlled by monitoring the outer to inner diameter. Thus the wall thickness and surface mass ratios are the main factors influencing the release properties. The diffusion-controlled matrices allowed alterations in dose without affecting release profiles.

Zhang et al. [93] developed colon-specific drug delivery system using Eudragit® FS polymer. The model APIs selected were 5-aminosalicylic acid (5-ASA), diclofenac sodium, and theophylline. Owing to the lower T_g of Eudragit® FS (53°C), the maximum temperature for the extrusion process was 75°C; moreover, because of the operated conditions, the APIs in the obtained granules were dispersed in the crystalline form. The prepared formulations showed lower drug release in pH 1.2 and 6.8 media, and showed complete release in pH 7.4 medium owing to complete dissolution of Eudragit® FS. Drug release (%) was observed to be dependent on the physicochemical properties of the APIs studied. These reports yet again confirmed the ability of HME in targeted delivery; however, the development of chronotherapeutic pulsatile or modified-release systems, floating drug delivery systems for treatment of specific diseases using HME needs to be further investigated *in vivo*.

2.7. Abuse-deterrent formulations

The term abuse is defined as the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect. Misuse, refers to the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse [94]. Abuse is the use of a medication without a prescription, in a way other than as prescribed, or for the experience of feeling elicited. Substance abuse refers to the harmful, hazardous use of psychoactive substances, including alcohol and illicit drugs, or misuse of prescription or over-the-counter drugs with negative consequences [95]. Opioids and psychiatric drugs are the most commonly abused legal drugs. Oxycodone (OxyContin®), hydrocodone (Vicodin®), codeine, morphine, and fentanyl are some of the examples of opioid drugs that are abused, and these compounds are available as prescription drugs on the US market. Ingestion (chewing), inhalation (snorting), injection,

and vaping are primary routes of prescription opioid drug abuse [96]. The last decade has witnessed a parallel increase in the number of opioid prescriptions dispensed and the number of deaths due to prescription opioids [97, 98].

Various technologies have been developed to deter drug abuse or to make manipulation more difficult. Currently, OxyContin[®], Targiniq[™] ER, Embeda[®], Hysingla[®] ER, MorphaBond ER[™], Xtampza[®] ER, Arymo[®] ER, and RoxyBond[™] are the 8 products approved by the FDA with abuse-deterrent labelling [99]. Opana[®] ER and Nucynta[®] ER are manufactured using the INTAC[™] platform technology (melt extrusion and cold milling manufacturing processes). Opana[®] ER was approved by the FDA with abuse-deterrent labelling in 2012, but later in June 2017, the FDA issued market removal of the product due to issues related to drug abuse. Few other approved products are manufactured using proprietary thermal processing [95]. HME, a thermal processing technique, is being explored for the preparation of abuse-deterrent formulations.

HME has been used to prepare extended-release, abuse-deterrent formulations. Wening et al. [9] has formulated an IR abuse-deterrent formulation consisting of hydrocodone 10 mg/acetaminophen 325 mg by HME. The prepared formulation, when manipulated, is resistant to syringing, and it has a particle size of >500 µm, thus not suitable for intranasal abuse.

Baronsky-Probst et al. [100] evaluated the suitability of the HME process for preparation of tamper-resistant formulations. PEO 7,000,000 and PEG were used as matrix polymers, whereas the API concentration ranged from 7-28%. Parameters such as specific mechanical energy input and melt pressure are considered as CQAs. The use of design of experiments (DOE) provided a design space for robust tablet production.

Jedinger et al. [101] developed an abuse-deterrent formulation product based on HME and film coating. In this approach, first, crush-resistant pellets of codeine phosphate and antipyrine were prepared using HME. Selected pellet formulations were later film-coated with Aquacoat[®] ECD 30 plasticized with 25% triethyl citrate (TEC) and guar gum at a ratio of 93:7 using fluidized bed coater. The pellets were characterized for *in vitro* dissolution, pellet compression strength, and DSC before and after coating. The matrix system helped in preparing tamper-resistant formulation, and film coating helped to prevent alcohol dose dumping.

Recently, researchers have extended the application of 3D printing technology to prepare abuse deterrent formulations. Nukala et al. [102] reported application of 3D printing for the preparation of abuse deterrent formulations as an egg-shaped tablet (egglet) using fused deposition modelling 3D printing technology. Based on printability and hardness results, polyvinyl alcohol (PVA) with 10% w/w sorbitol was found to be the most suitable polymer matrix for the preparation of the egglets. Extrusion was conducted at 170°C and 3D printed at 200°C. The egglets prepared with 45% infill density and 15% drug load passed the majority of tests described in the FDA guidance for the abuse deterrent opioids.

2.8. Miscellaneous

HME was also used in the preparation of films meant for topical delivery of pharmaceuticals. Qi et al. [103] developed Eudragit® RS PO-based transdermal films alone and in combination with different hydrophilic additives where drug release is triggered by hydration from the skin itself. Nasr et al. [14] have compared the skin deposition and clinical efficacy of nicotinamide-Soluplus® extrudates prepared through HME to those of nicotinamide gels. Nicotinamide extrudates have displayed increased skin deposition via enhanced adhesion and better clinical efficacy.

Owing to the potential of HME to prepare co-crystals and salts, this technique was also investigated for organic synthesis [104], for modification of polymer matrix using small molecular additives as co-formers [105]. Parikh et al. [106] prepared physically stable, amorphous, solid dispersions of the weakly basic drug itraconazole by interaction with a weak acid glutaric acid at high drug loads using HME, in which the presence of the polymer Kollidon® VA 64 further increased the supersaturation of the dissolution media. The day-to-day increase in pharmaceutical applications of HME technology and its ability to be adopted for CM make it a promising technology in the pharmaceutical industry.

For the benefit of the readers, this miscellaneous subsection was added to include additional 2019 articles:

Nukala et al. [107] investigated the effect of 3D printing patterns on disintegration and dissolution of hydrochlorthiazide-loaded PVA filaments. The diamond printing pattern (dicaps) exhibited higher hardness, slow disintegration and dissolution profiles compared to the hexagonal printing pattern (hexcaps). These findings aid in development of patient centric dosage forms. Marilena et al. [108] performed a systematic study on effect of particle size of the polymer (poly vinyl alcohol) on drug loading and efficiency of extrusion processes via fused 3D printing. Ciprofloxacin hydrochloride was selected as an active and finer particle size of the polymer showed good process feasibility with less drug loss. Kinga et al. [109] investigated the applicability of pharmaceutical blends towards fused deposition modelling 3D techniques. The results demonstrated that melt viscosity and brittleness are the main limitations of the process, in that temperature and humidity of the storage conditions affect the product quality. Shi et al. [110] prepared self-micellizing solid dispersions (SmSD) of indomethacin and fenofibrate using different techniques (HME, solvent evaporation, freeze-drying, microwave radiation and quench cooling). The SmSDs prepared by HME noticeably improved drug solubility and dissolution compared to other techniques. This study highlights the use of HME technology for improving drug delivery systems for poorly soluble drugs. Ma et al. [111] investigated the effect of mechanical and thermal energy input on nifedipine ASDs prepared by HME. A model system containing nifedipine and polyvinylpyrrolidone vinyl acetate (PVP/VA 64) was used to assess the effect of screw design, screw speed, barrel temperature and feed rate on amorphous conversion of nifedipine in the solid dispersions.

3. Conclusion

HME has become one of the preferred technologies over traditional techniques in pharmaceutical research for development of novel drug delivery systems. These various drug delivery approaches investigated using HME range from oral, topical and parenteral routes. The multi-component systems such as pharmaceutical co-crystals, co-amorphous systems, twin-screw granulation, co-extrusion, semi-solids, abuse deterrent formulations and other miscellaneous applications in the literature were presented. The availability of broad spectrum HME polymers and functional excipients facilitated the development of these novel drug delivery systems.

The use of pH sensitive polymers investigated proved yet again the ability of HME applications for targeted delivery as chronotherapeutic pulsatile or modified release systems for improved treatment of time dependent diseases. However, these drug delivery techniques need to be further investigated in vivo to optimize the therapies. Finally, the novel applications such as development of solid self-emulsifying drug delivery systems using HME need to be further validated.

4. Expert opinion

As discussed in detail in Part I of the review, HME has been widely employed for solubility enhancement, continuous manufacturing, and process analytical technology (PAT) tools. In addition, this cost-effective, solvent-free, “green” technology coupled with Fused Deposition Modeling (FDM) 3D printing applications were also presented and examined for product feasibility. However, recently, (and explored in Part II), HME has been utilized as an alternative approach in the development of multi-component systems (pharmaceutical co-crystals, co-amorphous systems and salts). In addition, fixed dose combinations by co-extrusion, chronotherapeutic systems, self-emulsifying drug delivery systems, and semi-solid dosage forms have been explored and developed. Twin-screw granulation has gained increased interest in preparation of granules via twin-screw melt granulation or twin-screw dry granulation. These novel applications of the HME process provides promising alternate approaches in the formulation of granules and solid dosage forms. Notably, the suitability of twin screw *dry* granulation as an alternative to the current conventional dry granulation techniques can improve tableability and stability of products. However, this technology may need to be further investigated for scalability aspects of these applications for industrial production. Regardless, dry granulation is a promising use of HME applications.

Floating drug delivery systems (FDDS) via this technology will be valuable for improved delivery of low absorption window drugs, which are specifically absorbed from the upper part of the small intestine. These FDDS provide a unique opportunity to solve the problem as described above. Proactively, HME has also been employed in the development of abuse deterrent formulations, *earmarked for opioid abuse* as solicited by agencies such as the National Institutes of Health and the US Food and Drug Administration. These initiatives provide an invaluable opportunity for HME techniques. As co-extrusion processing gains popularity and industry interest, its biggest challenge is selection of suitable polymers for desired pharmaceutical applications and appropriate extruder die design. The advantage of

simultaneous administration of two incompatible drugs as a fixed dose combination product is, and has been, limited. However, this incompatibility may be addressed by incorporating a third polymer layer between the two drug matrices. This is only one approach that pharmaceutical scientists are exploring to solve these issues. In addition, a huge opportunity via HME is semi-solid production. This technology drives the physical blend of drugs and inactive excipients by uniform mixing at a desired temperature, therefore offering many advantages over conventional methods for semi-solid preparations. HME offers reduced processing time because in this method, both the melting and mixing of components are performed in *one step*, and it requires no additional agitators because the mixing process is facilitated by screw elements in the barrel (which designs can be customized for the semi-solid product). Moreover, additional processing conditions for various semi-solids can be customized to obtain the desired products, and different phases of formulation ingredients can be mixed separately into the extruder. Similarly, the applicability of HME for semi-solid dosage forms, self-emulsifying drug delivery systems, and matrix assisted multi component systems should be studied further to achieve scalability in continuous industrial production. In summary, Part I and Part II of this review compliment hot-melt extrusion (from solubility enhancement to 3D printing, as well as a focus on multi-component systems to semi-solid opportunities). As is evident from these reviews, HME advancement has accelerated, just over the last four to five years. It appears that this phenomenon is, and will be, a *continuous process*.

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Article highlights

- This Part II of the review focuses on various novel opportunities or innovations of HME in pharmaceutical research.
- HME is being investigated as an alternative technology for production of multiple component systems like co-crystals and co-amorphous systems.
- HME is an established platform for targeted drug delivery to treat specific disease conditions.
- Twin screw melt granulation or twin-screw dry granulation is a novel application of HME, which may be a promising approach in the preparation of granules and solid dosage forms.
- The applicability of HME in novel applications needs to be further investigated for scalability in industrial production.

This box summarizes key points contained in the Review article.

Figure 1.
HME as an effective manufacturing technology for production of various drug delivery system

Figure 2.
Schematic representation of pharmaceutical small molecular multicomponent systems

Figure 3.
Illustration of formulation and process parameters in twin-screw granulation by HME.

Figure 4.
Representation of HME technology for preparation of semisolid products

Table -1.

Examples of multicomponent systems prepared using HME

S.No	Drug	Co-former	Matrix	Description	Reference
1	Ibuprofen	Nicotinamide	NA	Demonstrated co-crystallization and simultaneous agglomeration using HME	[31] dhumal et al., 2010
2	AMG 517	Sorbic acid	NA	Demonstrated twin screw extrusion can provide efficient mixing and surface contact facilitating cocrystal formation	[22] Medina et al., 2010
3	Caffeine, nicotinamide, carbamazepine, theophylline	Oxalic acid, cinnamic acid, saccharin, citric acid	NA	Identified that temperature and extent of mixing were critical in preparation of co-crystals by HME	[33] Daurio et al., 2011
4	Ibuprofen	Nicotinamide	NA	Demonstrated NIR as a PAT tool to monitor formation of co-crystals by Solvent free co-crystallization (SFCC)	[32] Kelly et al., 2012
5	Carbamazepine	Nicotinamide	NA	Amorphous solid dispersion with cocrystal technique by HME and improved chemical stability	[34] Liu et al., 2012
6	Carbamazepine	Saccharin	NA	Demonstrated effect of feed rate, screw speed, extrusion temperature on carbamazepine	[35] Moradiya et al., 2013
7	AMG 517	Sorbic Acid	NA	The cocrystal yield was more dependent on extrusion processing temperatures than screw speed and feed rate	[36] Daurio et al., 2014
8	Carbamazepine	Trans-Cinnamic Acid	NA	Monitoring continuous co-crystallization of carbamazepine and trans-cinnamic acid via melt extrusion processing using NIR	[37] Moradiya et al., 2014
9	Carbamazepine	Nicotinamide	Soluplus	Matrix-assisted co-crystallization (MAC)	[23] Boksa et al., 2014
10	Caffeine-Maleic Acid	Maleic acid	NA	Stoichiometric control of co-crystal formation by solvent free continuous co-crystallization (SFCC)	[27] Kulkarni et al., 2015
11	Ibuprofen	Isonicotinamide	Xylitol	Synthesis of pharmaceutical co-crystals suspended in a meltable matrix	[25] Li et al., 2016
12	Carbamazepine	Saccharin	NA	Integration of PAT tools for preparation and monitoring of high quality co-crystals	[28] Moradiya et al., 2016
13	Ibuprofen	Isonicotinamide	Xylitol	Applied concept of Hansen solubility parameter and Flory-Huggin's solution theory to optimize the extrusion processing conditions to improve/increase co-crystal yield.	[26] Li et al., 2017
14	Flufenamic acid	Nicotinamide	Polaxamer P407, PVPVA 64, HPMCAS, PEG-PVA copolymer	To determine the role of polymers (poloxamer P407, PEG-PVA copolymer), amorphous (Soluplus®, PVPVA64, and HPMCAS) in synthesis of pharmaceutical co-crystals	[24] Gajda et al., 2018
15	Carvedilol	Indomethacin	NA	Synthesis of co-crystals to improve solubility and stability of carvedilol	[30] Fernandes et al., 2018
16	Indomethacin	Saccharin	PEG 6000, HPMC and Neusilin	Co-processing of pharmaceutical co-crystals with excipients to improve physicochemical stability.	[29] Ross et al., 2018
17	Indomethacin	Arginine	Copovidone	Melting-solvent approach was used to successfully prepare IND-ARG CAM. Addition of copovidone improved non-sink dissolution behavior of IND.	[41] Lenz et al., 2017

S.No	Drug	Co-former	Matrix	Description	Reference
18	Indomethacin	Cimetidine	PEO	Processed at 120°C, which is 20-30°C below the melting temperature of both the drugs.	[40] Amfast et al., 2017
19	Naproxen	Meglumine	Soluplus® PVPVA64 PVPK30	Demonstrated <i>in situ</i> salt formation between Naproxen and meglumine using reactive melt extrusion technique. The extrusion processing temperatures was set well above the melting points of individual components. NPX-MEG ASDs have shown better solubility and stability	[48] Liu et al., 2017
20	Haloperidol	Maleic acid	NA	Investigated the effect of operating temperature and screw configuration on salt formation. Operating at temperatures closer to the melting temperature of salt resulted in less crystalline salt, incorporation of high shear mixing zones resulted in complete conversion to salt compared to partial conversion at lower processing temperatures	[49] Lee et al., 2017
21	Indomethacin	Tronethamine	NA	The binary mixture demonstrated a eutectic like behavior with melting point of 136°C, 1:1 mixtures of IND and tronethamine was extruded at 135°C. FTIR and NMR studies confirmed the <i>in situ</i> salt formation	[50] Bookwala et al., 2017