# Melting and Twin Screw Extrusion Laminar Dispersive and Distributive Mixing with Dissolution and Applications to Hot Melt Extrusion

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## Abstract

Hot Melt Extrusion (HME), a novel and potentially disruptive process for manufacturing oral dosage pharmaceutical products, has been explored and studied in recent times, by both industrial and academic investigators, because of its potential of rendering poorly water-soluble active pharmaceutical ingredients (APIs) readily bioavailable to patients through oral dosages. This article presents a brief review of HME from the "elementary steps of polymer processing" perspective: handling of particulate solids, melting, mixing, devolatilization and stripping, pressurization, pumping, as well as *dissolution* of the API in molten polymeric excipient processed stream. In contrast to traditional polymer processing, the dissolution of the API in the molten excipient during HME is the most important, key, elementary step. The main focus of this article is to discuss the physico-chemical and transport phenomena involved in dissolution and the material, equipment design, and HME process variables which affect it. The main task of the dissolution is to *completely dissolve* APIs in polymeric melt within the shortest possible residence time, without raising the processed stream melt temperature, and eliminating the possibility of degradation of heat sensitive APIs. We concluded from our work that *the dissolution process is a laminar forced convective diffusion process*. We will also present results on how to promote the dissolution rate through three categories of variables: process variables (screw speed, feeding rate, barrel temperature,), equipment variables (screw elements and configurations) and material variables (viscosity ratio, solubility parameters and particle sizes of API and excipient particulates). A novel viscometric method for the determination of the solubility of APIs in polymeric melts will also be discussed.

**Keywords:** hot melt extrusion, dissolution, mixing, solid dispersions

## 1. Introduction

Pharmaceutical hot-melt extrusion (HME) has been explored and studied in the last few decades, by both industrial and academic investigators, because of its potential of rendering poorly water-soluble active pharmaceutical ingredients (APIs) readily bioavailable to patients through oral dosages. The HME field is currently being investigated even more intensively because of recent discoveries of large families of potent and promising, but essentially water-insoluble, APIs.

HME is a term that the pharmaceutical sector adopted to differentiate it from traditional oral dosage producing techniques, such as direct compression and tableting. It involves the use of single- or twin-rotor extruders for the processing of usually water-soluble polymeric excipients, mixing them while molten with APIs to affect partial or total API dissolution and pumping the homogeneous mixture through a die to form an extrudate, where the API exists in a totally or partially dissolved but (in both cases) stable form. Compared to the traditional drug production processes, HME is a solvent-free continuous process and it may lead to fewer required processing steps.

However, degradation of the drug (API) and excipient may occur during HME due to the relatively high processing temperatures needed to melt the excipient and viscous energy dissipation. This may limit universal application of HME for all excipient/API pairs. Informative accounts and information regarding equipment, formulation principles and process conditions and parameters used in HME can be found in several review articles and a recently edited book [1–6].

Extrusion processing has been used in the polymer, as well as the food industries for over a century, and a great wealth of knowledge has been generated and accumulated both in theory and practice. From a processing point of view, it involves five elementary steps: handling of particulate solids, melting, mixing, devolatilization and stripping, pressurization and pumping [7], as shown schematically in Figure 1, for the case of processing a polymer with solid particulate functional additive(s) to form compounded (or filled) plastic pellets, or, as is the case with in-line compounding processes [7a], compounded plastic products. As noted the two most important elementary steps for plastics compounding are melting and dispersive and distributive mixing of the additives in the polymer matrix. On the other hand, as shown conceptually in Figure 2, for HME pharmaceutical processing, *dissolution of the API in the molten excipient is an additional and most important elementary step*, along with *melting* which precedes it and *mixing,* which assists and speeds up dissolution. Thus, such elementary steps may interact with each other as well as occur simultaneously (i.e., be *coupled*). Although *any* of the elementary steps may be critically important to a particular HME process, this article will deal with mixing with laminar dispersive and distributive mixing of API particulates in the molten excipient as they occur simultaneously with the desired dissolution of the API.

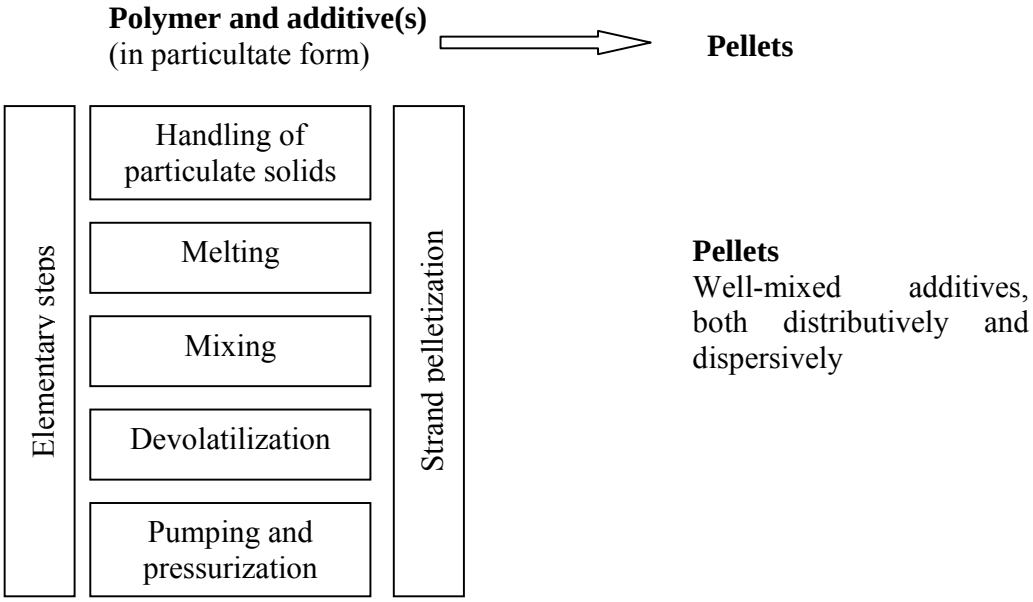



**Figure 1** Conceptual structural breakdown of polymer compounding processes.

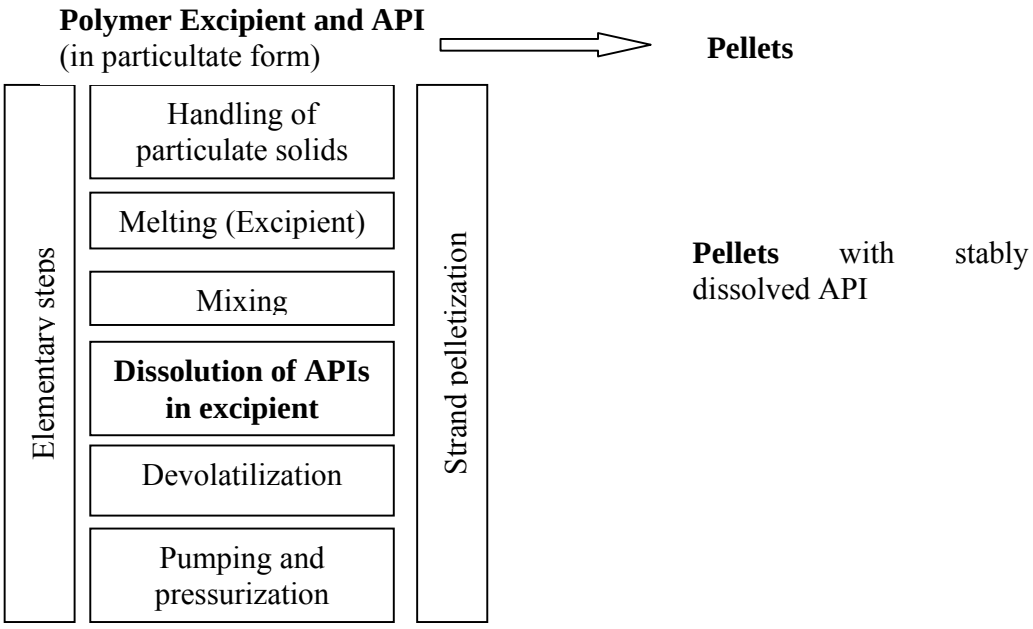



**Figure 2** Conceptual structural breakdown of pharmaceutical Hot Melt Extrusion processes.

## 2. Elementary Steps in HME

While briefly reviewing the features of the elementary steps which are relevant to HME processes and products, the following are worth considering.

### *2.1 Particulate Solids Handling (PSH)*

Single-screw extruders (SSEs) are 'flood fed' through hoppers, the feed being a mixture of the excipient and API in particulate form. The fact that the barrel surface is rougher than that of the single screw allows for drag-induced packing of the particulates bed, as well as downstream movement and pressurization. In co-rotating twin-screw extruders (co-TSEs), which are commonly used in HME process development, the PS ingredients are fed gravimetrically or volumetrically controlled at constant rates. These rates are smaller than those needed to fully fill the parallel channels of the co-TSE, resulting in 'starve-fed' processing. PSH in co-TSEs may result in spatial particle segregation if the relative sizes or shapes of the API and the excipient are very different, due to different air resistive forces and different particle/wall kinematic friction coefficients. It is also worth noting that polymer excipients are commonly hygroscopic, so they may have to be dried prior to dry mixing with the API particulates [7b].

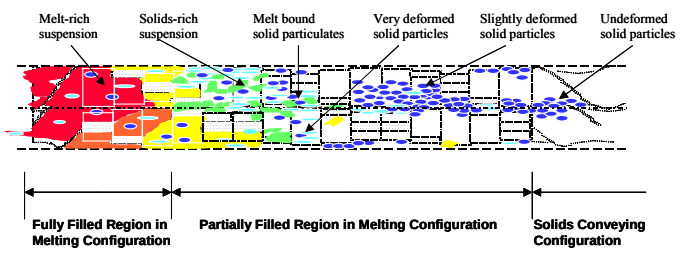
### *2.2 Melting*

The physical mechanisms available for melting polymer systems in polymer processing equipment are as follows.

For SSEs, the important melting mechanisms are the *conductive melting* of the packed particulate bed surface by and next to the hot barrel surface and *viscous energy dissipation* during the drag flow causing the removal of the melt generated to the trailing end of the bed. Melting is localized at the barrel surface and is gradual, requiring much of the extruder length to complete. Consequently, the age distribution of the melt generated in a typical SSE is of the order of its average residence time. This fact may result in adverse consequences for HME processing. First, since dissolution and mixing takes place only when the excipient is molten, there will be only limited dissolution of the API in that fraction of the excipient which melted late, potentially resulting in a wide distribution of the percentage of API dissolved. Second, the portion of the excipient which melted early will be more susceptible to thermal degradation [7c].

For co-TSEs, the available melting mechanisms are again *conductive melting* of the starve-fed loose particulates by the hot barrel. This mechanism is significant for the small co-TSEs used in HME development, where the TSE equipment surface-to-volume ratio is large. However, for both smaller and larger-diameter co-TSEs, reverse-screw or reverse-kneading elements are used to create a filled section in which the packed particulates undergo repeated volume-wide deformations before exiting the fully filled region. During this process, the very powerful melting mechanism of *plastic energy dissipation* (*PED*) is important. It is also worth pointing out that the repeated large compressive deformations taking place in full kneading blocks induce particulate-to-particulate frictional heating and localized melting because of *frictional energy dissipation* (*FED*) [7d, 8]. The melting mechanisms for co-TSEs are summarized in Figure 3. In

our view, it is primarily FED, along with PED, which cause the fast melting of the particulates involved, allowing the dissolution of the API in polymeric excipients for KinetiSol [9，10] in extremely short time periods and the formation of co-crystals [11] in a co-TSE.




| | | | | |
|---|---|---|---|---|
| | | | | "States" of the Stream<br>Schematic Representation<br>Co-TSE Screw Configuration |
| VED | PED<br>VED<br>(DMM) | PED | Conduction | Melting Mechanisms (Pellets) |
| VED | PED<br>VED<br>(DMM) | PED | Conduction | Melting Mechanisms (Powder) |

**Figure 3** Schematic representation of the evolution of melting of plastic pellets or powder in a co-TSE [7].

## *2.3 Devolatilization*

This elementary step refers to the removal of low levels of volatiles of the order of 1000 ppm, dissolved in the molten matrix. Devolatilization is carried out in vented two-stage SSEs and co-TSEs in partially filled sections isolated from both the upstream and downstream sections by 'melt seals' so that vacuum can be applied. Under vacuum conditions, the dissolved molecules cause bubbles to be formed in the flowing melt stream (much like the bubbles formed by opening a carbonated refreshment container) which, when they reach the melt–vacuum interface, burst and are removed [7e]. Although there does not appear to be much work on devolatilizing HME extruders, the subject will receive attention because of FDA regulations.

## *2.4 Pumping and Pressurization*

After the accomplishment of all the other elementary steps, extruders are required to pump ('meter') the molten charge through a die which shapes the exiting stream in operations such as pelletization and sheet, film, tube or profiled cross-sectioned products. *Drag-induced* pumping and pressurization is the mechanism enabling both co-TSEs and SSEs to be the pumps of choice for viscous fluids. SSEs can generate higher pressures under closed discharge conditions because their flight heights can be small in the metering section upstream of the die. On the other hand, because co-TSEs are fully intermeshing (and self-wiping, which is an advantage for HME operations) they are 'locked in' with wide channels which are incapable of generating high pumping pressures; in cases of very viscous extrudates, this limits the extrusion rate [7f]. Since

excipients are water soluble care has to be taken in cooling strand extrudates, using chill rolls for conductive cooling and/or cold air for forced convective cooling.

## 3. Dispersive and Distributive Mixing

The mixing processes in single- and twin-screw extruders are generally categorized into two types: dispersive mixing and distributive mixing [7g].

*Dispersive mixing* refers to the process involving the particle size reduction of cohesive components such as solid fillers (by de-agglomeration), or for liquid droplets by droplet deformation and break-up. *Distributive mixing* refers to distributing de-agglomerated particulates uniformly throughout space, or stretching the interfacial area between the components lacking a cohesive resistance and distributing them uniformly throughout the product volume. Dispersive mixing requires high flow stresses (either through high viscosity of high shear or elongational rates) in order to provide the dispersive forces to overcome the cohesive forces of the agglomerates or immiscible droplets; distributive mixing is dictated only by the flow-generated strain and does not require high stresses.

According to these definitions, the mixing of miscible liquids is regarded as distributive mixing; mixing of hard solid agglomerates, immiscible liquids and soft agglomerates is regarded as dispersive mixing [7g]. For illustrative purposes, the dispersive and distributive mixing of solid agglomerates is shown schematically in Figure 4.

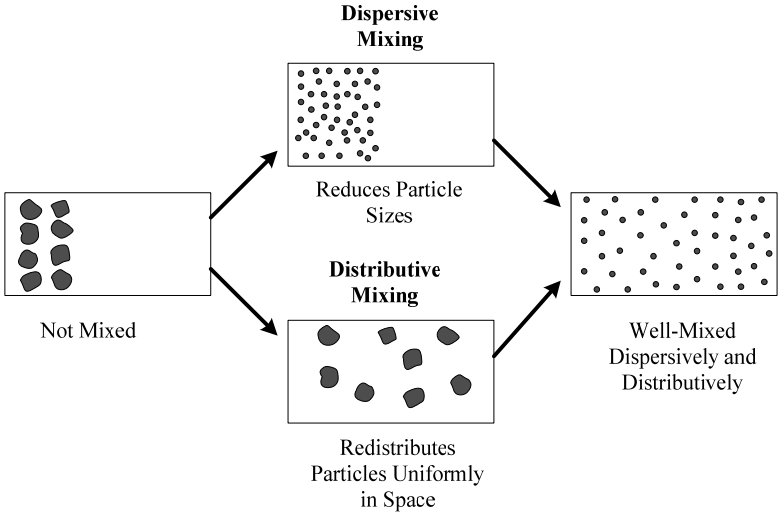



**Figure 4** Dispersive and distributive mixing of solid agglomerates and immiscible liquid droplets [7].

## 4. HME Processes: Cases I and II

HME processes can be classified into two categories:

- Case I: in which the processing temperature is above the melting temperature of asemi-crystalline polymer, or the softening temperature of an amorphous polymer ($T_g$ > 50–100ºC) but *below* the melting point of a crystalline API.

- Case II: in which the processing temperature is above both the melting or softening temperature of semi-crystalline or amorphous polymer excipient, respectively, and *above* the melting point of the API.

'Processing temperature' refers to the melt temperature rather than barrel set temperature. Case I is more common, simply because it is carried out at temperatures which are safer from an API degradation point of view (since that temperature is below its melting point). On the other hand, dissolution rates and solubility are expected to be higher if the process is carried out at higher temperatures.

### *4.1 Case I*

The process represented by Case I provides a viable dissolution path which minimizes or circumvents the thermal degradation issue of drugs. The API is processed below its melting point and mixed with a polymer melt and the solid drug particles gradually dissolve into the polymer excipient melt, resulting in a desirable polymer–drug solid dispersion or solid solution. In this case, the solid API and the polymeric melt act as a solute and a highly viscous solvent, respectively, during HME. A physical model ("cartoon") for Case I is schematically shown in Figure 5.

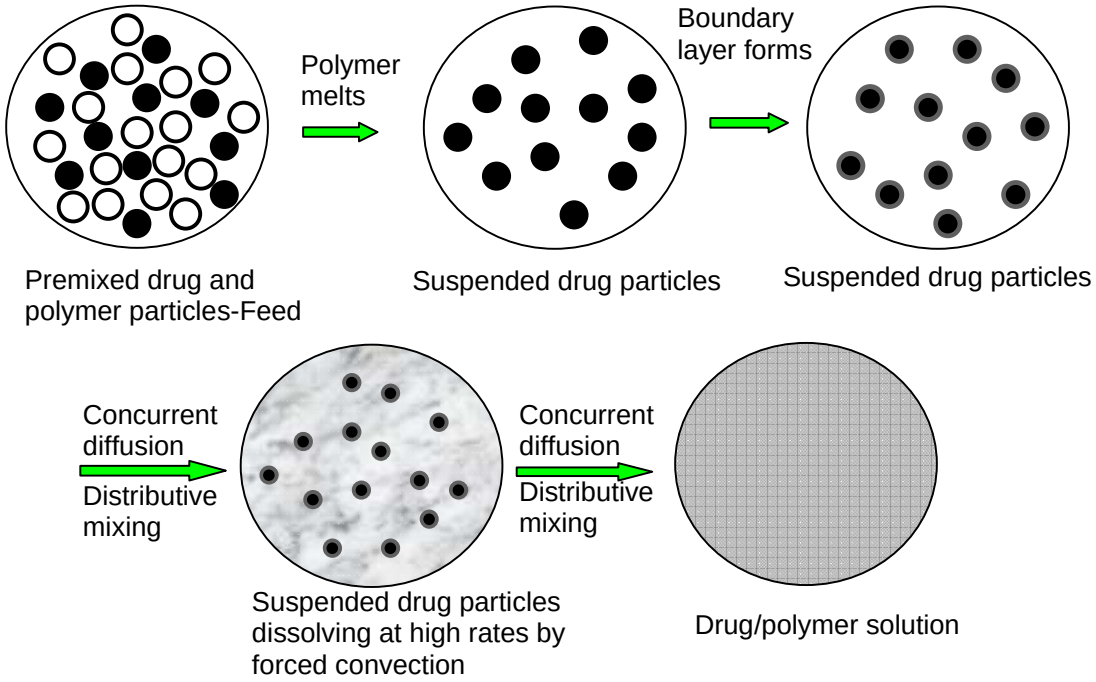



**Figure 5** Schematic representation of the morphological changes of the drug and polymer system in the solution formation process.

Firstly, the premixed drug (black) and polymer particles (white) are fed into an extruder. The polymer particles then start melting due to the conductive heat from the extruder barrel and frictional and plastic energy dissipation for co-TSEs, leading to the solid drug particles being

suspended in a continuous polymer melt matrix. While suspended at the processing temperature, which favors dissolution assuming intermolecular forces compatibility between the API and the excipient (i.e. miscibility), the drug molecules start dissolving and create a mass-transfer boundary layer around each drug particle. This layer is continuously wiped away and replaced by fresh polymer melt around each API particulate by the laminar distributive flow of the mixer. The same laminar mixing flow helps the drug molecules to diffuse and mix distributively into the molten excipient. The size of suspended drug particles diminishes as the diffusion continues until the particles disappear and a homogeneous solution is formed or until the limit of API solubility at the processing temperature is reached. In the latter case, they reach a minimum average size and remain suspended.

*The dissolution of the drug in the polymer melt in an extruder is achieved by laminar forced convective mass transfer involving the dissolving and dissolved API molecules*. Both dispersive and distributive mixing may play key roles on the dissolution of the drug into the polymeric excipient melt. Dispersive mixing may break up the drug agglomerates or even particulates due to high laminar flow forces generated by either material properties such as excipient viscosity, operating variables such as screw speed or extruder design variables such as the width of kneading elements in co-TSEs of Maddock 'barrier' mixing elements in SSEs. The total surface area of the drug particles exposed to the polymeric melt will therefore be increased and the dissolution rate will be increased. Distributive mixing can homogenize the drug concentration in the polymeric melt through shear or extensional flow or reorientation and bring more polymer melt into contact with the suspended drug particles, thus leading to dissolution rate enhancement.

Case I, the dissolution of APIs into polymer matrix, is of cardinal importance in practical HME because many APIs are heat sensitive, especially at temperatures above their melting point. In traditional polymer processing, only few examples involving dissolution of small molecule additives into molten polymer matrices can be found (e.g. physical blowing agents and certain process stabilizers). Additionally, these examples involve dissolving additives at much lower concentrations (>1%) than those used in typical API formulations. The main task of Case I is to completely dissolve drugs in polymeric melt within the shortest possible residence time without raising the processed stream melt temperature.

## *4.2 Case II*

Case II, relevant at processing temperatures above the melting point of the crystalline API, involves liquid–liquid mixing between miscible or partially miscible components. The criterion that the solubility parameter difference $\Delta\delta$ between the drug and excipient be less than 7 $MPa^{1/2}$ is generally accepted during HME API/Excipient formulation screening, implying the need of at least partial miscibility [12, 13]. Additionally, such systems possess dynamic surface tension. The morphological evolution of mixing such partially miscible systems will therefore involve liquid phase break-up of the minor phase, and may follow the Scott/Macosko lacing/sheeting blend morphology evolution mechanism in the softening/melting region [14]. The minor phase break-up may actually be more complex, since the API viscosity is many orders of magnitude smaller than that of the polymer excipient [7h].

Schematically, the morphology changes for Case II may follow the sequence shown in Figure 6. At the beginning, the premixed drug (black) and polymer (white) particles are fed into an extruder and conveyed by the conveying elements. The polymer particles melt first due to the energy input from the barrel and frictional and plastic dissipation. After the polymer particles totally or partially melt, the drug particles suspended in the molten polymer begin to melt rapidly, and the drug droplets begin to be deformed by the mixing laminar flows of the polymer melt. After that, the drug liquid phase breaks up into much smaller droplets due to the competition of surface tension and surface flow stress. The small droplets are deformed along the shear direction. With numerous very small droplets, which have an enormous surface, diffusion between the droplets and the polymer predominates causing the droplets to disappear, creating a drug–polymer solution. Diffusion also occurs during the break-up of the large drug droplets. Note that the 'characteristic diffusion time' $t_D$ in Figure 6 is proportional to the square of the API phase droplet or ligament radius or the thin dimension of a sheet. Thus, for a molten excipient-API system with a diffusivity $D = 10\times10^{-11}$ m$^2$/s and where the API exists in 20 μm diameter droplets, the diffusion characteristic time is of the order of 10 seconds. It is worth emphasizing that all of the elementary steps described in Section 2 , including polymer melting, drug melting, the break-up of drug droplets and even diffusion between drug droplets and polymer melt may occur simultaneously in the span of several seconds (especially with co-TSEs), so that direct experimental evidence of the individual phenomena may not be easily obtainable.

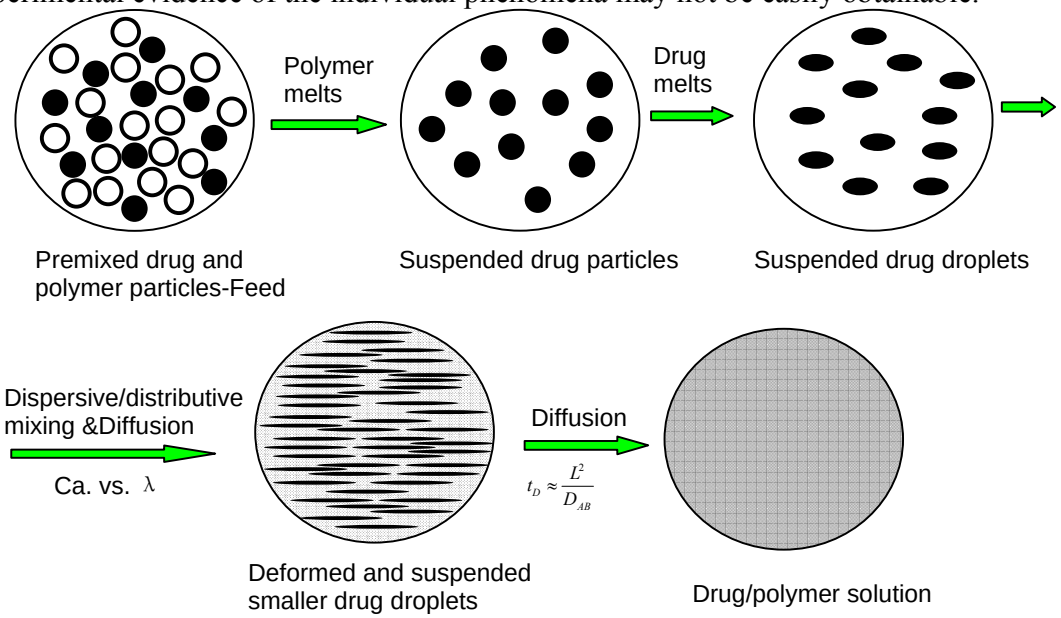



**Figure 6** Morphological changes in drug/polymer system for Case II.

Similarly to Case I, both dispersive and distributive mixing play key roles on the break-up of drug droplets in Case II. Droplet break-up for partially miscible systems during both simple shear and 2D extensional (elongational) flows is shown in Figure 7, where the critical capillary number $Ca_{crit}$ is plotted against the viscosity ratio λ for Newtonian fluids. $Ca_{crit}$ is defined as the

ratio of viscous (dispersive) to the interfacial (cohesive) stresses [15]. The viscosity ratio is defined as the ratio of the dispersed phase to the continuous phase viscosities.

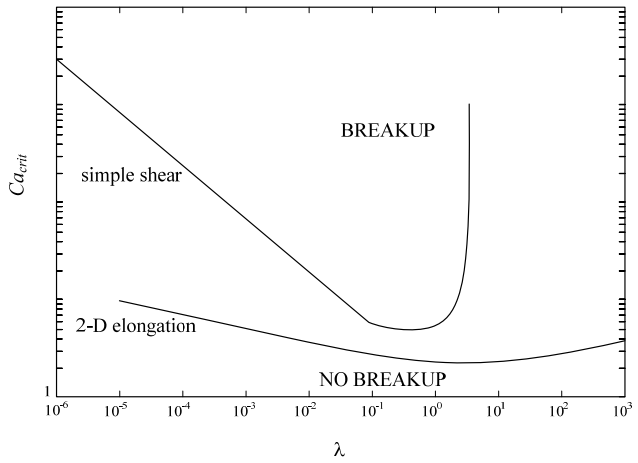



**Figure 7** Critical capillary number versus the viscosity ratio λ [15].

As seen in Figure 7, the 2-D elongational (squeezing) flow is more efficient for droplet break-up than shear flow with much lower $Ca_{crit}$ for the physically very broad region where $\lambda > 4$ and $\lambda < 10^{-3}$ (the latter being relevant to case II of HME). It should be noted that extensional flows are also more efficient than shear flows for distributive mixing because they are capable of increasing the resulting strain and interfacial area *exponentially*. In contrast, shear flows increase shear strain linearly and are therefore less efficient [7g]. Since fully filled co-TSE kneading element sections generate compressive extensional flows, they are well suited to mixing and dispersing the rheologically mis-matched fluids involved in HME.

## 5. Dissolution of Drug Particulates in Polymeric Melts

The dissolution rate of a pure substance depends on the total resistance of two sequential stages: the transition of dissolved substances from solid to solute state immediately due to interface molecular interaction and the transport of solute from the surface to the bulk of solvent by diffusion or convective diffusion [16, 17]. Similarly to the dissolution of drugs in an aqueous medium, the dissolution of drug particulates in molten polymeric excipients during HME can also be described by the Noyes–Whitney equation [18, 19]

$$\frac{dC}{dt} = \frac{D \times A \times (C_S - C)}{h \times V} \tag{1}$$

where $D$ is the diffusion coefficient; $A$ is the total surface area of the drug exposed to the dissolution media; $C_s$ is the saturation solubility of the drug in the liquid which (for HME) is the excipient melt; $C$ describes the concentration of the dissolved solid phase in the bulk at time $t$; $h$ represents the diffusion boundary layer at the solid-liquid interface; and $V$ is the volume of the dissolution medium.

The *variables influencing the dissolution rate of drug particulates* in the excipient melt can be grouped into three categories: *process, equipment and material*.

## *5.1 Process Variables*

Process parameters have an important impact on the dissolution rate of drug particulates in polymeric melts. For co-TSEs, the most important process parameters are the barrel set temperature, the screw speed and the feeding rate. Screw speed and feeding rate can be used to calculate the *characteristic* channel *shear rate*, *shear stress*, *specific mechanical energy* [5, 20] and the *mean residence time* [21, 22]:

$$\dot{\gamma} = \frac{\pi \times D \times n}{h \times 60} \tag{2}$$

$$\tau = \dot{\gamma} \times \eta \tag{3}$$

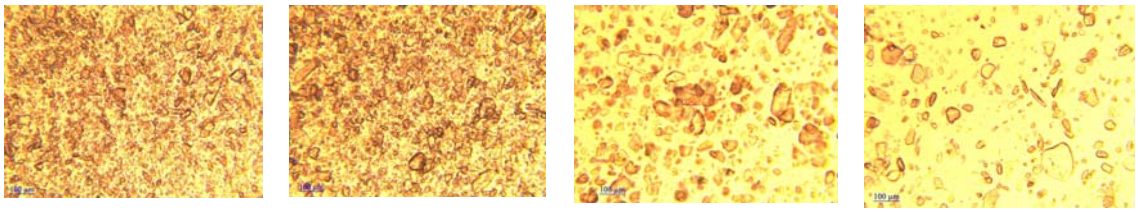
$$\text{SME} = \frac{\text{consumed motor power}}{Q} = \frac{n \times (\%\text{torque}) \times \text{motor rating} \times 0.97}{\text{max rpm} \times Q} \tag{4}$$

$$t_m = \frac{A}{Q} + \frac{B}{n} \tag{5}$$

where $\dot{\gamma}$ is shear rate in $\text{sec}^{-1}$; $D$ is the screw diameter in mm; $n$ is the screw speed in rpm; $h$ is the over-flight clearance in mm; $\tau$ is shear stress in kPa; $\eta$ is the melt viscosity in Pa s; SME is the specific mechanical energy (kW h/kg); $Q$ is the feeding rate in kg/h; % torque is the percentage used of the maximum allowable torque; the motor rating is in kW; 0.97 is the gear box efficiency; max rpm is the maximum number of attainable screws rotations per minute; $t_m$ is the mean residence time in seconds; and $A$ and $B$ are constants.

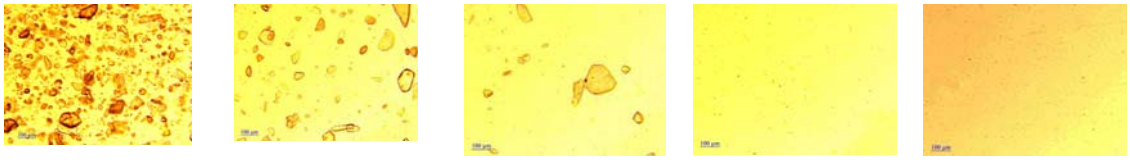
Many studies have been published concerning the effect of process variables on the final dissolution characteristics of drugs in aqueous media [23, 24], and the significance of process variables has been widely recognized [25, 26]. Liu et al. investigated the effects of batch hot melt mixing process parameters on the dissolution behavior of indomethacin (melting point=162 ºC) in Eudragit® E PO ($T_g$=48 ºC) matrix using a batch mixer. The barrel temperature was set at 100, 110 and 140 ºC; the screw speed was set at 20 and 100 rpm for each temperature, and samples were taken at 50, 95, 140, 280 and 420 seconds for each run. In all runs, the actual melt temperature was below the melting point of indomethacin. The weight ratio of Eudragit® E PO to indomethacin was kept at 70:30 [27].

Figure 8 and Figure 9 show optical micrographs of samples processed at 100 ºC 20 rpm and 110ºC 100rpm. The amount of the solid drug particles decreases with increasing mixing/processing time. For the run at 100 ºC 20 rpm, both optical micrographs and SEM pictures (not shown) show that there are still considerate amounts of drug particulates which were not dissolved after 420s of mixing, whereas for the run at 110 ºC 100 rpm, both optical micrographs and SEM pictures (not shown) show that essentially no drug particulates can be found in the 285s sample. This morphological observation was also supported by DSC and XRD results.



(a) (b) (c) (d)

**Figure 8** Optical micrographs of run at 100ºC 20rpm: (a) 100 s; (b) 145 s; (c) 285 s; (d) 420 s [27].



(a) (b) (c) (d) (e)

**Figure 9** Optical micrographs of run at 110ºC 100rpm: (a) 55 s; (b) 100 s; (c) 145 s; (d) 285 s; (e) 420 s [27].

The evolution of the specific enthalpy (integration DSC-obtained enthalpy of the broad peak/total drug mass) with mixing time, at different processing conditions, is presented in Figure10. All three processing variables, namely the barrel set temperature, screw speed, and residence time, are found to influence the indomethacin's dissolution into the E PO melt. Given the same rotor speed of 20 rpm, all indomethacin particles are dissolved into the matrix within three minutes at the highest set temperature of 140ºC employed in this study. At the set temperatures of 100 ºC and 110 ºC, the drug particulates are not fully dissolved after 420 seconds at the lowest rotor screw speed used; increasing the screw speed to 100 rpm allows a full dissolution of drug particulates within 300 seconds. Obviously, both the barrel set temperature and screw speed can increase the dissolution rate appreciably.

The effects of barrel set temperature and rotor speed can be explained by the Noyes-Whitney equation. On one hand, if the mixer set temperature increases, the diffusion coefficient will increase due to the increased temperature and resultant decreased matrix viscosity; on the other hand, $C_s$ also will increase. Both of these factors contribute to an increase of the API dissolution rate in the molten polymer excipient. When the *mixer rotor speed increases*, the *distributive mixing is improved* within the chamber, and thus a higher concentration gradient in the region of the particulate surface is available. Moreover, the *thickness of mass transfer boundary layer decreases, as forced convective mass transfer prevails*. Both effects lead to an increased dissolution rate.

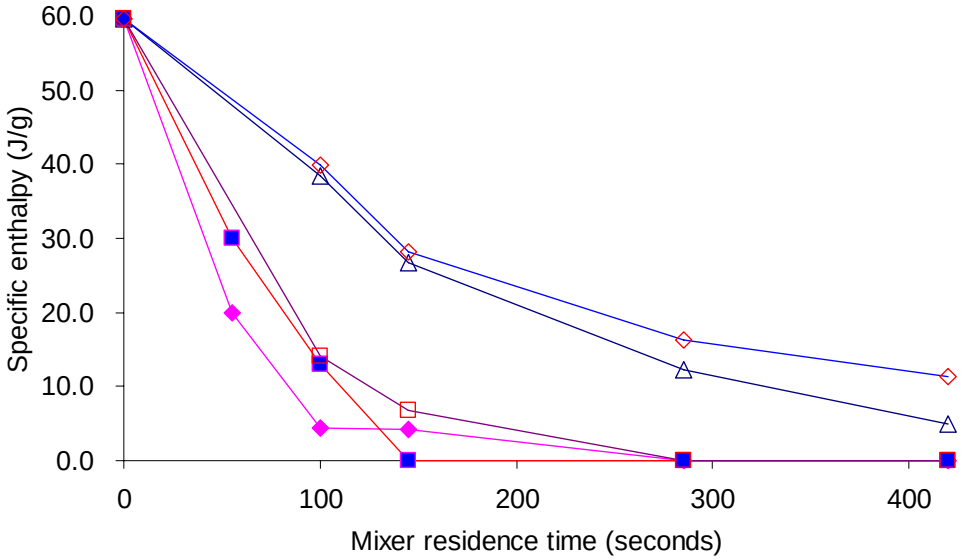



**Figure 10** The evolution of the specific enthalpy with residence time, screw speed and setting temperature: (◇) 100ºC 20rpm (△) 110ºC 20rpm (□) 100ºC 100rpm (◆) 110ºC 100rpm (■) 140ºC 20rpm[27].

As discussed in the introduction section and above, both dispersive mixing and distributive mixing may significantly enhance the dissolution rate. However, in this study, there was no evidence that dispersive mixing was involved because the size reduction of drug particles was due to the diffusion of the drug molecules to the polymeric melt rather than shear forces [27]. Furthermore, the drug particles of the system used do not form agglomerates in the mixture based on the SEM pictures (not shown) of tumble mixed solid before hot melt processing. Thus, dispersive mixing is *not needed* in the system studied. Nevertheless, it should be mentioned that, in other drug and polymer systems, dispersive mixing may break up existing drug agglomerates or even individual particles due to the high laminar flow forces. Then, the total surface area of the drug particles exposed to the polymeric melt will be increased, thus increasing the dissolution rate. Miller et al. demonstrated that HME processes can de-agglomerate and disperse "engineered" drug particulates into an excipient matrix without altering their drug properties, and achieving enhanced dissolution properties [28].

The experimental results also lead to an important finding which has been overlooked before [27]: the times needed for the drug to dissolve inside the polymer melt and the typical residence time for an extrusion process *have to be comparable*, under appropriate processing conditions. Depending on the barrel set temperature and the screw speed, the drug dissolution process may take from one up to a few minutes. The residence time of a typical continuous manufacturing extrusion process falls in the same range [21]. On the other hand, one has to be careful when optimizing the HME process parameters such as screw speed, feeding rate and barrel temperature, because changes in those parameters may lead to a change of the processing stream's residence

time, as equation 5 shows. Furthermore, the implication of the finding is that not only specific mechanical energy but also residence time should be matched for HME scale-up.

## *5.2 Equipment Variables*

Equipment or design variables concern mainly screw design. There are primarily three kinds of co-TSE screw elements: *conveying screw* elements, *kneading* elements and *toothed screw* elements. Comprehensive discussion on these can be found in several books [3, 7, 20]. Screw design plays an important role for both distributive mixing and dispersive mixing. In co-TSEs, for example, the wider the kneading blocks (KB), the more intensive the dispersive mixing; the narrower the KBs, the more intensive the distributive mixing. Toothed screw elements, such as Coperion's *SME* (screw mixing element), *TME* (turbine mixing element) and *ZME* (Zahnmishelement), can generally offer more distributive mixing while inputting less mechanical viscous energy [20].

Although the importance of screw configuration has been mentioned in several review articles [1, 4], there are only a few publications specifically addressing the effect of screw configuration on preparing solid dispersions using twin-screw extruders.

Nakamichi et al. reported that kneading blocks play a key role in transforming the crystalline nifedipine (melting point = 175ºC) to an amorphous form inhydroxypropylmethylcellulose phthalate (HPMCP, $T_g$ ~ 160–170ºC). The barrel temperature in all experiments was set at 100ºC [23]. Verhoeven et al. studied the system of metoprolol tartrate (melting point = 120ºC) and ethylcellulose ($T_g$ ~ 123ºC) mini-matrices using a twin-screw extruder. The barrel temperature in all experiments was set at 60ºC. They found that the release rate of metoprolol tartrate in ethylcellulose and the homogeneity of the drug component were not affected by the number of kneading mixing zones or their position along the extruder barrel, as long as one kneading mixing zone was present [29]. The importance of using one fully filled kneading element zone is clearly demonstrated in the results of Liu's work [30].

It should be emphasized that the melting of polymer excipient and the dissolution of API into polymeric melt may simultaneously occur and be complete in a single kneading block, resulting in a much narrower 'melt age' distribution. One of the breakthroughs in the polymer processing field during the last two decades was polymer–polymer blend morphology evolution studies; it was found that a major reduction in phase domain size takes place in conjunction with the melting or softening of the components in a melting zone, usually consisting of kneading blocks [32]. Similarly to polymer–polymer blends preparation, the melting of polymer excipients and the dissolution of drugs can simultaneously take place and may be complete once passing through a kneading block, although no publications have explicitly presented this phenomenon to the date.

## *5.3 Material Variables*

From a thermodynamic aspect, mixing a drug with a polymer is not so much different from mixing a plasticizer with a polymer. Two strategies have been applied to predict/estimate the

drug-polymer miscibility. The first strategy is based on a simple assumption: the solubility parameters of two miscible chemicals should be smaller than a critical value. The solubility parameter $\delta$ is defined as follows:

$$\delta = \sqrt{\frac{\Delta E}{v}} \tag{6}$$

where $\Delta E$ is the molar change in internal energy on vaporization and $v$ is the molar volume of liquid.

As mentioned Section 4.2, Forster et al. proposed an empirical criterion for miscibility prediction: a drug and a polymer can form a solution if their difference in solubility parameter is less than 7.0 $MPa^{1/2}$. If the difference is larger than 10 $MPa^{1/2}$, then the two are immiscible [12, 13]. This criterion has been widely applied for a rough estimation of drug–polymer miscibility. It should be pointed out that the polymer engineering and industry has been using 1.3–2.1 $MPa^{1/2}$ as the critical difference in solubility parameter to estimate the miscibility of two polymers [33]. Considering that the entropy of mixing is much smaller for a polymer–polymer system than that of a drug–polymer system, it is understandable that the critical solubility parameter difference is larger for a drug–polymer system.

Another material variable is related to API's particle size. Based on the Noyes–Whitney equation, the dissolution rate of drug particulates in polymer melt will increase if the total surface area of the drug particulates exposed to the dissolution media increases. Therefore, after drug loading is fixed in formulation development, the micronization of drug particulates is beneficial for enhancing the dissolution rate of drug particulates in polymer melt. Furthermore, the narrower the drug particle size distribution, the more uniform the total dissolution time distribution needed for complete dissolution of drugs in polymer melt will be. There are many commercialized mills available such as fluid energy mills (FEM) [34, 35].

## 6. Solubility Determination

The solubility of drugs in polymer matrices, $C_s$, is an important thermodynamic property affecting both the feasibility of the HME process as well as the product quality. If the drug loading is above the solubility at processing temperature of melt extrusion, no matter what are the extruder type, mixing elements or process parameters, the drug can not be fully dissolved and/or diffused into the matrices. In other words, the solubility of drugs in polymer matrices at the processing temperature defines the upper limit of drug loading for formulation design. Unfortunately, no standard technique has been developed for the measurement of drug solubility in excipient melts.

The DSC dissolution-endpoint method was developed by Tao et al. [36, 37]. The method involves heating a drug/polymer particulate system of known composition ($x$) to slowly dissolve the drug in the polymer melt. If phase equilibrium is reached during heating, the solubility of the drug in the polymer is x at the final temperature of drug dissolution, $T_{end}$. The $T_{end}$ should not be dependent on the heating rate, that is, the dissolution process is not limited by diffusive mixing. Therefore, the particle size should be very small. The authors utilized cryomilling to reduce the

drug particle size and make the drug partially amorphous. The $T_{end}$ can be extrapolated to around $T_g$.

Our group developed a *rheological method to determine the solubility* of drugs in polymeric melt [38, 39]: mixtures are directly equilibrated at the temperature of interest, followed by measuring directly the mixture's viscosity and the glass transition temperature. Figure 11 shows the relationship between the *reduced viscosity*, i.e. the viscosity of the acetaminophen (APAP) and polyethylene oxide (PEO) mixture divided by that of a pure PEO, and the drug loading. Each curve corresponds to one temperature. Four curves at different temperature exhibit the same trend, namely, the reduced viscosity value drops first with increasing the drug loading, and then increases after reaching a concentration characteristic of each of the temperatures used. The initial decrease of viscosity indicates an increase of the mixture's polymer structure mobility, due to the drug dissolution. The dissolved drug acts as a plasticizer at small drug loadings, which leads to decrease of the viscosity with the increase of drug concentration. On the other hand, the rise of the viscosity at higher drug concentrations occurs when the drug solubility is exceeded and undissolved solid drug particles act as suspended filler particulates, increasing the mixture's viscosity. The APAP loading at the critical point, where the reduced viscosity reaches a minimum, gives us APAP's solubility in PEO at that temperature. These data were further confirmed by the results from measurements of the glass transition temperature and a direct observation using a polarized optical microscope.

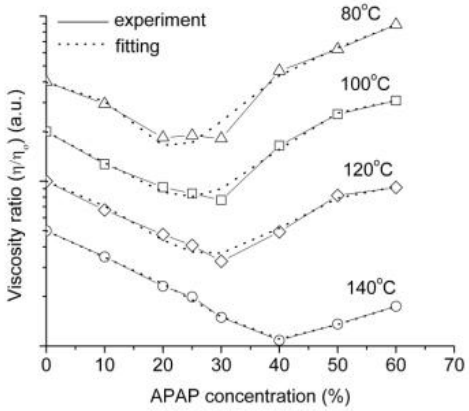



**Figure 11** Experimental and polynomial fitted reduced viscosity of the PEO-APAP mixture with different acetaminophen loading at different temperature: 80ºC (△), 100ºC (□), 120ºC (◇) and 140ºC (○) [38].

## 7. **Concluding Remarks**

In this review article the authors take the position that the relatively new field of pharmaceutical oral dosage processing method of HME can be analyzed in a rational and orderly manner in terms of the Elementary Steps of Polymer Processing polymer processing, which for HME *have to include the additional Step of Dissolution of monomeric APIs in the water soluble molten polymer excipient.*

They propose specific physical mechanisms for the dissolution of APIs for the two Cases (types) of HME processes: Case I, where the processing temperature is below the crystalline melting point of the API, and Case II, where it is above. In both Cases, they maintain, *forced convective mass transfer with diffusion* is the operative dissolution mechanism. When prevailing laminar flows imposed by the Co-TSE equipment are extensional in character, then the forced convective mass transfer is accelerated and dissolution rates become smaller.

The authors point to the reasons on why uniform (i.e., volume-wise) and rapid melting of the polymer excipient is crucial to the product quality of HME, which necessitates the use of reversed kneading elements after particulates solids conveying. The later design feature accomplishes complete volume-wise polymer excipient melting in 1-3 diameters.

Finally, it is the informed belief of the authors that, in order to fully understand, successfully simulate, and be able to scale-up the HME process, the *dissolution kinetics has to be measured and understood at processing temperatures.* In this sense, this is the area requiring immediate attention and work by those involved in HME in order to advance both the understanding and practice of pharmaceutical HME .

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