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Oscillatory Shear Rheology in Examining the Drug-Polymer Interactions Relevant in Hot Melt Extrusion

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ABSTRACT

The flow properties of drug-polymer mixtures have a significant influence on their processability when using techniques such as hot melt extrusion (HME). Suitable extrusion temperature and screw speed to be used in laboratory scale HME were evaluated for mixtures containing 30% of paracetamol (PRC), ibuprofen (IBU), or indomethacin (IND), and 70% of polyethylene oxide, by using small amplitude oscillatory shear rheology. The initial evaluation of the drug:polyethylene oxide solubility was estimated by differential scanning calorimetry of the physical mixtures containing a wide range of weight fractions of the drug substances. Consecutively, the mixtures were extruded, and the maximum plasticizing weight fraction of each drug was determined by means of rheological measurements. IBU was found to have an efficient plasticizing functionality, decreasing the viscosity of the mixtures even above its apparent saturation solubility, whereas IND and PRC initially lowered the viscosity of the mixture slightly but increased it significantly with increasing drug load. The main reason for the enhanced plasticization effect seems to be the lower melting temperature of IBU, which is closer to the used HME temperature, compared to PRC and IND. This study highlights the importance of rheological investigation in understanding the drug-polymer interactions in melt processing.

Introduction

Hot melt extrusion (HME) is a solvent-free process that can easily be scaled up for mass production that enables continuous manufacturing of solid dosage forms having various shapes and sizes.[1] In addition, the efficient mixing provided by the screws of a twin-screw extruder can enhance the dispersion of the drug in the carrier materials (excipients), which improves the dissolution rate of the poorly water-soluble drugs (from hydrophilic excipients) in the aqueous media, thereby increasing their bioavailability.[2,3]

Different microstructures can be present in extruded solid dispersions formed by the drug substances and the matrix of excipients: in a glassy suspension, the drug forms amorphous domains in the matrix, in a crystalline suspension the drug remains in crystal domains, and in a glassy solution ("solid solution") the drug is amorphous and molecularly dispersed in the matrix. Glassy solutions are usually preferred to increase the bioavailability of poorly water-soluble drugs.[4,5] Also, combinations of the previously mentioned are possible. For example, when the saturation solubility is exceeded or recrystallization of the drug after initial dispersion occurs, the drug can be present both molecularly dispersed, and in crystalline suspension.[6,7]

Many small-molecule drugs that are soluble in the polymeric excipients used in HME can act as plasticizers, by increasing the free volume and decreasing the friction between the polymer molecules.[8] In general, plasticizers are often used in the polymer industry to improve the processability and to decrease the brittleness of the finished products. In thermal analysis, the plasticization effect is seen as a decrease in the glass transition temperature T_g and changes in the crystallinity and melting temperature T_m (for semicrystalline polymers).[9-11]

The plasticizing ability of some drugs may enable lowering the processing temperature in HME, which can be beneficial for drugs that are prone to thermal degradation. A significant plasticizing effect has been reported, for example, for ibuprofen in ethylcellulose,[12] vitamin E in hydroxypropyl cellulose and polyethylene oxide (PEO) films,[13] and ibuprofen and chlorpheniramine maleate in Eudragit® RS 30D.[14] Additionally, paracetamol (PRC) has been found to have a moderate plasticizing effect on PEO, however, it was only seen up to the saturation concentration, after which the remaining solids content increased the viscosity of the PRC-PEO mixture similarly to solid insoluble fillers.[15]

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Rheology of a suspension is influenced by the volume fraction of the suspended particles, their size, size distribution, and shape.[16] In a dilute suspension only the Brownian (thermal) motions are significant. This is the case when the particle volume fraction (volume of the space occupied by the particles in relation to the total volume, ϕ) is below 0.01. At $\phi > 0.01$, the hydrodynamic interactions between the particles become important. When $\phi > 0.2$, the suspension is concentrated and starts to exhibit complex flow behavior.[17] In addition, the interaction (repulsive or attractive) between the particles plays a role: hard sphere particles exhibit neither repulsion nor attractive forces, and the rheology of such a system is determined by the balance between Brownian diffusion and hydrodynamic interaction. On the other hand, for the particles with soft or electrostatic interactions the rheological behavior is defined by double-layer repulsion, and for particles with steric interactions the rheology is defined by the steric repulsion. Systems with attractive net interactions show either weak or strong flocculation depending on the attractive forces.[17]

The interactions between closely packed particles in concentrated suspensions can cause formation of a reversible structural network. Breaking down this network requires extra energy and in the flow behavior of such suspensions this can be seen as a yield stress at low deformation rates: the yield stress is the limiting shear stress value which needs to be exceeded for any flow to occur.[18] However, the implications of yield stress may be a matter of chosen experimental conditions, or due to the limitations of the measurement device,[19] thus the term "apparent yield stress" will be used in the current study. All the previously mentioned factors can have a significant impact on the processability of solid suspensions,[20,21] such as HME of drug-polymer mixtures.

From the discussion mentioned previously, it is evident that understanding the nature of the dispersed systems and the influence of the drug substances on the flow behavior supports the successful extrusion of solid dosage forms. Optimally, the dosage form size should be kept at a minimum, thus the highest possible drug-to-excipient ratio is usually desired. Moreover, the degree at which the drug dissolves into the polymeric excipient and plasticizes the mixture, or remains as solid matter (amorphous or crystalline), may have a major effect on the properties of the end product—both for the bioavailability[5] as well as for other quality attributes, such as mechanical properties and visual appearance. The previously discussed drug-polymer interactions and their consequences on the processability are summarized illustratively in Figure 1: different polymeric excipients have different degrees of shear thinning, temperature dependence of the viscosity, and thermal stability. These are affected in different ways by the added drug, and depending on the solubility and the drug load, can result in lowering viscosity (plasticization) or apparent yield stress and/or shear thickening (concentrated suspensions). All of this has an effect on the required operating conditions and equipment design used for melt processing.

The solubility of the drug substances can be evaluated, for example, from differential scanning calorimetry (DSC) thermograms of the drug-polymer mixtures.[22,23] However, thermal analysis alone does not provide sufficient information on the processability of pharmaceuticals by HME.[24] On the other hand, small amplitude oscillatory shear (SAOS) rheometry enables evaluation of the flow behavior as a function of time, temperature, and deformation rate, and can provide insight to the material microstructure and changes thereof, such as interactions between the

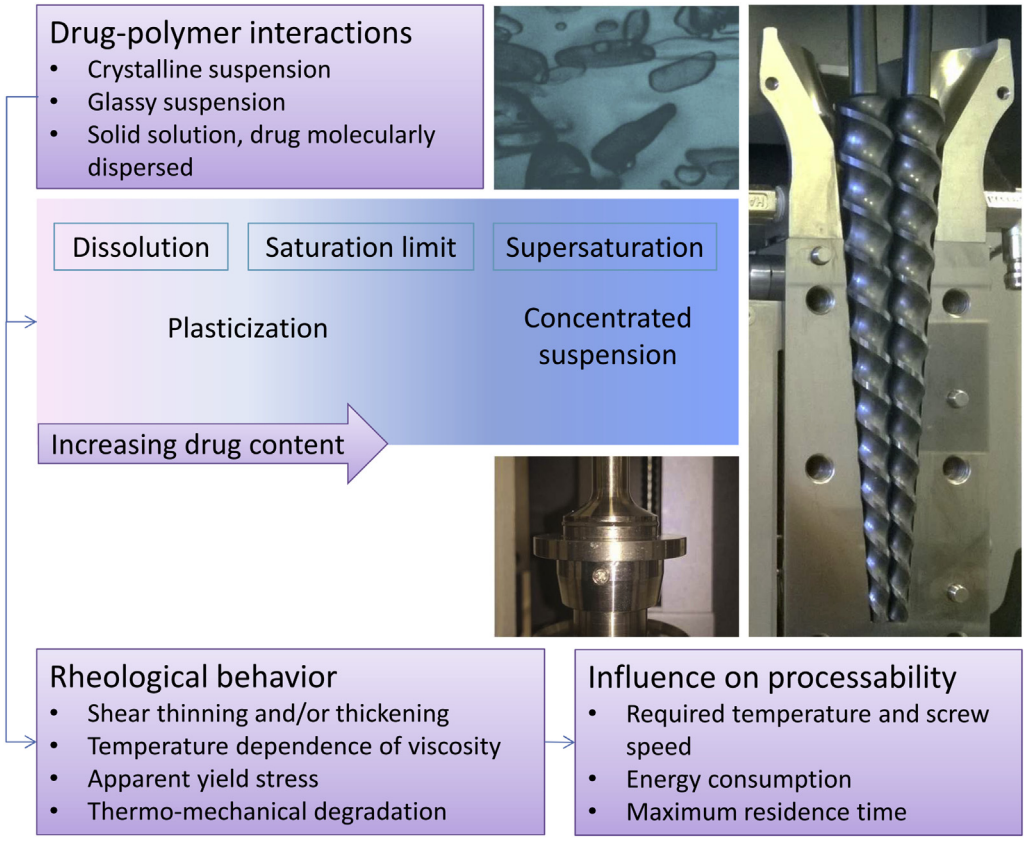

Figure 1. Illustration of possible interactions in drug-polymer systems containing molten and solid phases (microscopy image: paracetamol particles in PEO melt under flow), their potential manifestations in rheology, and the related effect in their processability in melt processes such as HME.

particles in a dispersion.[18] For a better understanding of the dynamics of the transformation from the mixture of powders into a melt with suspended drug particles, and to their (potential) dissolution during the extrusion process, a possibility to monitor the linear viscoelastic properties on-line with direct sampling at different stages of the screw could provide a helpful insight.[25,26] However, such techniques are not widely available, and in this study the drug-polymer interactions and processability were evaluated using conventional off-line SAOS rheometry as the main analytical tool. The rheological behavior was related to the thermal analysis of the mixtures performed by DSC.

Materials

Three poorly water soluble drugs, according to the Biopharmaceutics Classification System (BCS): paracetamol (PRC, T_m = 169°C, Fagron, BCS class II), indomethacin γ form (IND, T_m = 160°C, BCS class II), and ibuprofen (IBU, T_m = 76°C, Fagron, BCS class IV) were used as model drugs. Polyethylene oxide (PEO, viscosity average molecular weight M_v= 100.000 g/mol, T_g = −67°C and T_m = 65°C, data reported by the supplier Sigma-Aldrich) was used as a model polymer. PRC, IND, and IBU were mixed with PEO in weight ratios of 10:90, 30:70, 50:50, and 70:30.

Methods

Rheological Characterization

An AR-G2 rotational rheometer (TA Instruments) with 25-mm parallel-plate geometry and environmental test chamber with a heating capacity up to T = 600°C was used. The samples were pressed directly between the plates either from the physical mixtures or the granulated extrudates. The environmental test chamber was flushed with nitrogen during the test to minimize the potential oxidation at higher temperatures. Temperature sweep measurements in SAOS were run at constant strain amplitude γ = 0.5% and constant ω of 1, 10, and 100 rad/s. The linear viscoelastic range (LVE), which is a prerequisite for reliable SAOS measurements, was determined separately for each composition in strain sweeps at strain amplitude range γ = 0.01…10% at constant angular frequency ω = 10 rad/s. In the SAOS frequency sweeps, all the tests were run at a decreasing angular frequency, from 100 to 0.01 rad/s. A minimum of 2 repetitions with a fresh sample were performed for verification of the data consistency.

Thermal Analysis

DSC was carried out using a Discovery DSC (TA Instruments). The thermograms were recorded in heat-cool-heat cycle at 10°C per min keeping the sample in an isotherm for 2 min between each step. The cycle was started at 25°C, and heating was carried out up to 200°C for the pure PEO, 170°C for pure IND, 200°C for pure PRC, and 85°C for pure IBU. To minimize any degradation of the drug substances, the drug-polymer mixtures were heated up to 175°C (PRC:PEO), 165°C (IND:PEO), or 85°C (IBU:PEO) in the consecutive DSC runs.

Hot Melt Extrusion

The physical drug:PEO mixtures were extruded using a laboratory scale corotating twin-screw extruder (Xplore Instruments, Geleen, the Netherlands) with a volume of 5 mL. The processing temperatures and screw speed were chosen on the basis of the rheological measurements of physical mixtures as will be described in the following section. The mixtures were extruded through a circular die (diameter 1.5 mm), and the extrudates were cooled at ambient conditions and cut into granular samples for the further rheological analyses.

Results and Discussion

Determination of Extrusion Parameters

Extrusion Temperature Range

The initial rough evaluation of the processability was tested with 30% drug content that was estimated to dissolve in the PEO matrix based on the analysis of preliminary DSC thermograms (reported later).

The suitable extrusion temperature range was estimated by temperature sweep tests of the physical mixtures in SAOS. This was done to enable a broader measurement range because the polymer melts typically experience edge fracture instability in parallel-plate or cone-plate configurations at high deformation rates and large strains (see e.g., Tanner and Keentok[27] and Mattes et al.[28]) in steady rotational shear. Depending on the material, this can occur already at a shear rate ($\dot{\gamma}$) of 5–10 s^{-1}. In addition, the temperature sweep in SAOS with the applied small strain enables the measurement down to lower temperatures than in the rotational mode. Thereby, neither the rheometer torque limits are exceeded nor does the sample detach from one of the plate surfaces on cooling and excess stress.

To be able to relate the oscillatory flow to the steady shear flow, one must presume that the Cox-Merz rule[29] is valid. The relationship was originally discovered for linear homopolymers, and it relates the shear viscosity as a function of shear rate to the complex viscosity as a function of angular frequency, $\eta(\dot{\gamma}) = |\eta^*(\omega)|$, when $\dot{\gamma} = \omega$. In characterization of polymers with particulate fillers, the Cox-Merz rule has been found to be valid in some cases, for example, for a model suspension containing 30% glass beads in a Newtonian hydroxyl-terminated polybutadiene fluid[30] and for polydimethylsiloxane suspensions with nearly up to 40% calcium carbonate.[31] The applicability is obviously highly dependent on the nature of the particle-particle interactions and, therefore, varies from one system to another. For the materials exhibiting apparent yield stress, a modified Cox-Merz rule has been proposed.[32] In this study, no apparent yield stress behavior was observed for the mixtures at 30% drug load, of which a large part is expected to be dissolved in PEO at the HME temperature. Thus, in this study the original Cox-Merz rule is assumed to be applicable with sufficient accuracy.

The temperature sweeps were performed in cooling mode, starting at a temperature clearly below the T_m of each drug. The starting temperature of 140°C was chosen for IND:PEO and PRC:PEO mixtures, whereas 65°C was used for IBU:PEO mixture. Complex viscosity ($|\eta^*|$) as a function of temperature for all 3 mixtures is presented in Figure 2a. The shaded area in the figures indicates the generally accepted “rule-of-thumb viscosity range,” 800-10,000 Pa s for small-scale extrusion.[33] It must be noted that this range is only informative and depends on the capacity and other characteristics of the extruder. In general, it is desirable to keep the processing temperature as low as possible to avoid thermal degradation of thermosensitive drugs, as well as for minimizing the energy consumption. For the following extrusion experiments, T = 90°C was chosen for IND:PEO and PRC:PEO mixtures and T = 60°C for IBU:PEO mixtures. SAOS frequency sweep of each mixture at their selected HME temperature was also measured, and the resulting viscoelastic functions, storage modulus $G'(\omega)$, loss modulus $G''(\omega)$, and $|\eta^*(\omega)|$ are presented in Figure 2b. The figures clearly indicate that the viscosity of the IBU:PEO mixture is lowest at its selected extrusion temperature, even though it is 30°C lower than the temperature selected for PRC:PEO and IND:PEO mixtures. The difference between these 2 is less significant, IND:PEO mixture being somewhat less viscous.

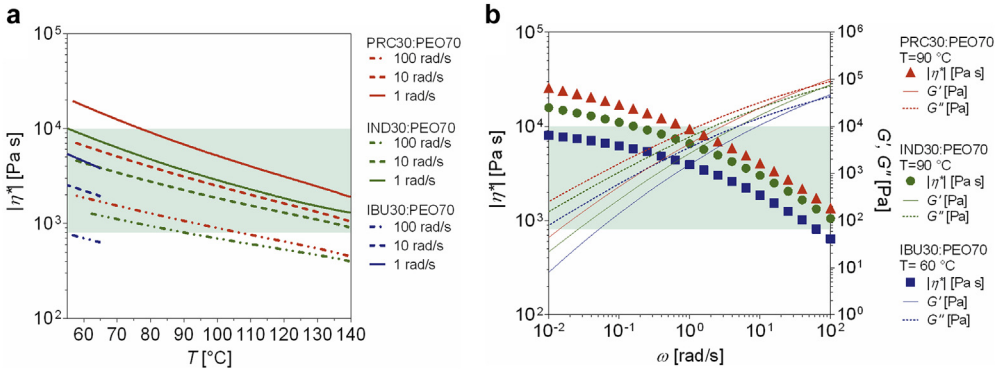

Figure 2. (a) Complex viscosity versus temperature for physical mixtures of PRC30:PEO70 (red), IND30:PEO70 (green), and IBU30:PEO70 (blue) in oscillatory shear at 1, 10, and 100 rad/s (from top to bottom). (b) Storage and loss moduli and complex viscosity versus angular frequency for the same mixtures measured at their respective HME temperatures, $\omega = 100\ldots 0.01$ rad/s.

Screw Speed and Average Shear Rate in a Small-Scale Extruder

A simplified estimation of the radial shear rate in the extruder screw can be calculated using the rotation speed (N), barrel diameter (D), and screw channel depth (h)[34,35]:

$$\dot{\gamma}_{ave} = \frac{\pi ND}{h} \quad (1)$$

The maximum shear rate the material experiences occurs at the narrowest flow gap, which is normally the screw overflight (the clearance between screw flight and the barrel wall) and can naturally be many orders of magnitude higher. The corotating twin-screw extruder used in this study has a conical screw design, where both the diameter and the channel depth vary across the screw length. The approximate upper diameter of the barrel = 17 mm, upper channel depth = 4 mm, the lower diameter = 5.6 mm, and the lower channel depth = 1.4 mm (Fig. 3). With an approximately constant D/h ratio across the screw length, the screw speed of 50 revolutions per minute produces the average shear rate roughly around 10 s^{-1} between the screw channel and the barrel wall.

Figure 2b shows (applying the Cox-Merz rule) that at a shear rate of 10 s^{-1} all the mixtures are within a viscosity range suitable for HME, thus, 50 revolutions per minute was chosen as a screw speed for extrusion. In these experiments, the evaluation of processing conditions is limited to the average shear rate. However, a rigorous process optimization of an extrusion process includes evaluation of other operating conditions such as melt pressure, conveying of solids and melt, feeding rate, and residence times, as well as the geometrical factors, such as different screw elements and the die characteristics.[36] In addition, viscous (frictional) heating due to the shear forces can raise the actual temperature significantly from the preset value[34,37] and should be considered when processing thermosensitive materials. Detailed calculations of viscous heating in a corotating twin-screw extruder for the simulation of the HME process have been conducted, for example, by Eitzlmayr et al.[37]

Thermal Analysis

DSC of the physical mixtures provides information on the solubility of the drug substances in PEO and can also give an initial indication of the plasticization ability in the melt processing, such as HME. Various methods based on the thermal analysis can be used to evaluate the drug-polymer solubility, as recently thoroughly discussed by Knopp et al.[23] Here, a preliminary evaluation is done by observing the thermal events in the DSC of the physical drug-polymer mixtures (Fig. 4).

For both IND and PRC mixtures, a second endotherm could be seen for the 2 highest drug loads right below the melting temperature of the drug (Figs. 4a and 4b), albeit for 50% mixtures the peak is so weak that it is hard to distinguish it from the baseline. For IBU:PEO (Fig. 4c), the interpretation of the thermal analysis is more difficult due to the fact that T_m of IBU and PEO are much closer to each other than for the other mixtures. Broadening of the melting peak of PEO can be seen already at 10% IBU content, and clear signs of 2 separate endotherms can be seen at 50% and 70% concentrations, albeit for 50% one broadened endotherm, rather than

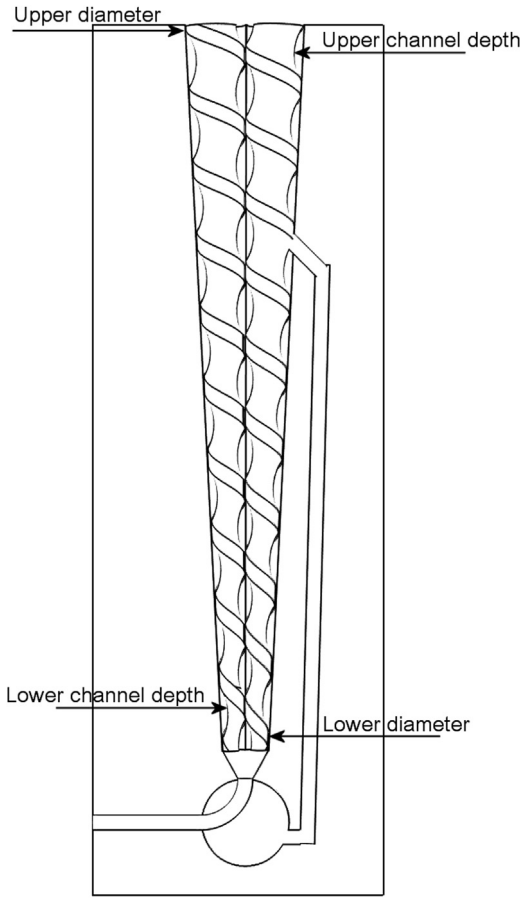

Figure 3. Schematic drawing of a lab-scale corotating twin-screw extruder with a recirculation channel. The positions for the dimensions used in the calculation of the average shear rate using Equation 1 are indicated.

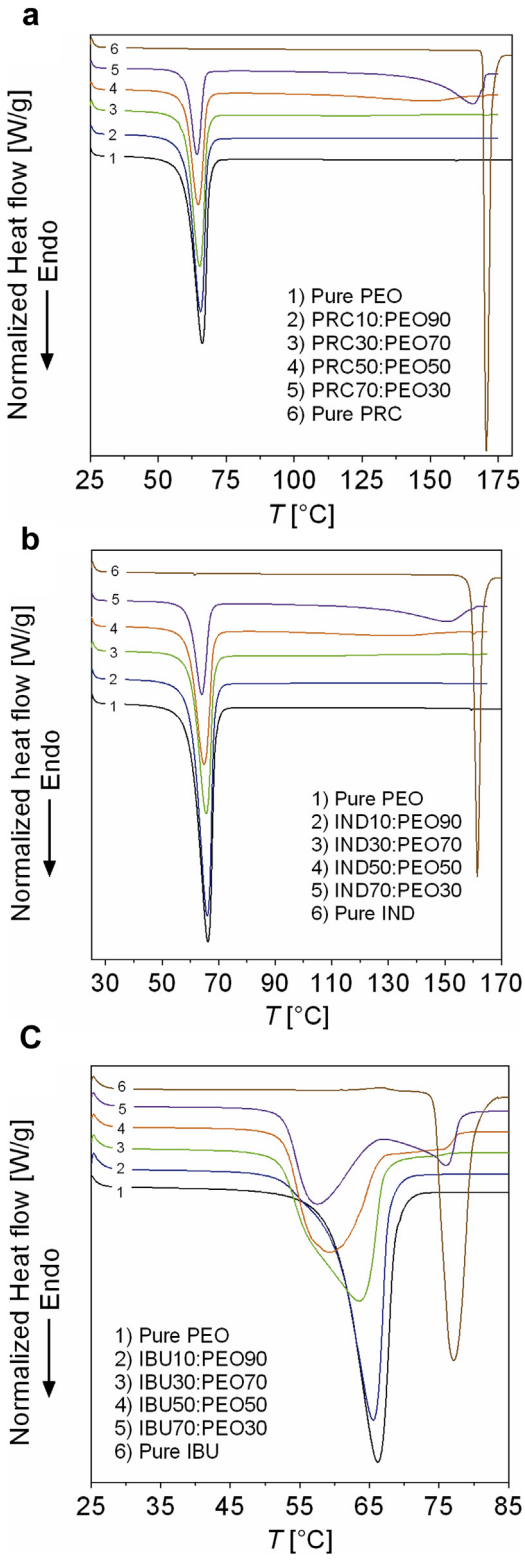

Figure 4. First heating (10°C/min) of the drug:PEO physical mixtures, pure drug, and pure PEO: (a) PRC:PEO (b) IND:PEO, and (c) IBU:PEO (endotherm down). Curves are shifted for legibility.

2 separate thermal events, was observed. The indication of a second endotherm visible for the drug:PEO mixtures at 50% and 70% below the T_m of the pure drug occurs due to the undissolved drug that is either melting at the lower temperature due to the presence of PEO or dissolving in PEO melt.[38-40]

Evaluation of Plasticization by Rheology

Linear Viscoelasticity

The SAOS measurements for the evaluation of plasticization were performed at the temperature that was used for the extrusion of each mixture. However, in the case of IBU:PEO mixtures the extrusion was performed below the T_m of PEO, thus, the sample loading and trimming of pure PEO, IBU10:PEO90, and IBU30:PEO70 was performed at 65-68°C, after which the sample was cooled down to the measurement temperature, 60°C.

First, the LVE for all the mixtures was determined in a strain sweep at an angular frequency $\omega = 10$ rad/s. When the LVE is exceeded, the (elastic) storage modulus G' and (viscous) loss modulus G'' become a function of the strain amplitude, usually decreasing with increasing strain amplitude. However, in some cases for suspensions, G'' may begin to rise and G' fall beyond the LVE. The structural changes leading to the nonlinearity can usually be seen in the elastic properties first, thus, only G' is presented here. At 70% drug load, the G' starts to decrease practically from the beginning of the test (Figs. 5a-5c).

For the consecutive SAOS measurements within the frequency range $\omega = 0.01 \ldots 100$ rad/s, a strain amplitude of $\gamma = 0.5\%$ was selected for all the mixtures at 10% and 30%, and for IBU:PEO and INDO:PEO at 50% drug load. Because of the narrowing down of the LVE at high particle concentration (Fig. 5a), $\gamma = 0.03\%$ was used for PRC:PEO at 50% PRC load, and for all the mixtures at the 70% drug load (Figs. 5a-5c). Typically, increasing the solid particle content narrows down the LVE range. Highly concentrated suspensions have a narrow, sometimes nearly inexistent LVE, which makes their fundamental SAOS analysis difficult.[41,42] The mixtures with 70% drug load have a practically inexistent LVE, which suggests that they form a concentrated solid suspension at the current measurement temperature.

Normalized Viscosity and Plasticizing Effect

To see the maximum plasticizing effect of the given drug loads and temperatures, the absolute values of complex viscosity $|\eta^*|$ of the drug:PEO mixtures were normalized with the pure PEO viscosity:

$$\eta_{\text{norm}} = \frac{\eta_{(\text{drug:PEO})}}{\eta_{(\text{PEO})}} \quad (2)$$

The same concept has been used, for example, by Yang et al.[15] The single point η_{norm} values at $\omega = 0.01$, 0.1, 1, 10, and 100 rad/s were plotted against the drug content and are presented in Figures 6a-6c for all the drug:PEO mixtures at the extrusion temperature of each mixture.

For PRC:PEO, the maximum plasticization at 90°C was reached at 30% for 0.01, 0.1, and 1 rad/s, and at 10% PRC load for 10 and 100 rad/s, beyond which the undissolved drug particles increased the viscosity. With 30% PRC, the viscosity was decreased to approximately 35% of the viscosity of pure PEO at $\omega = 0.01$ rad/s. The effect is less significant at higher deformation rates: At $\omega = 10$ rad/s (corresponding to the average shear rate of 10 s^{-1} in extrusion performed in this study), the viscosity of PRC30:PEO70 is approximately 80% of the pure PEO viscosity. Yang et al.[15] used the minimum of a fourth degree polynomial fitted on the normalized viscosity data as an indicator of a full solubility at tested concentrations for PRC in PEO with the same molecular weight as the one used in the present study. Because this does not describe the actual physical phenomenon of solubility, no fitting procedures were used in the present study. Instead, the minimum normalized viscosity found at the tested concentrations is merely referred to as a "maximum plasticization effect."

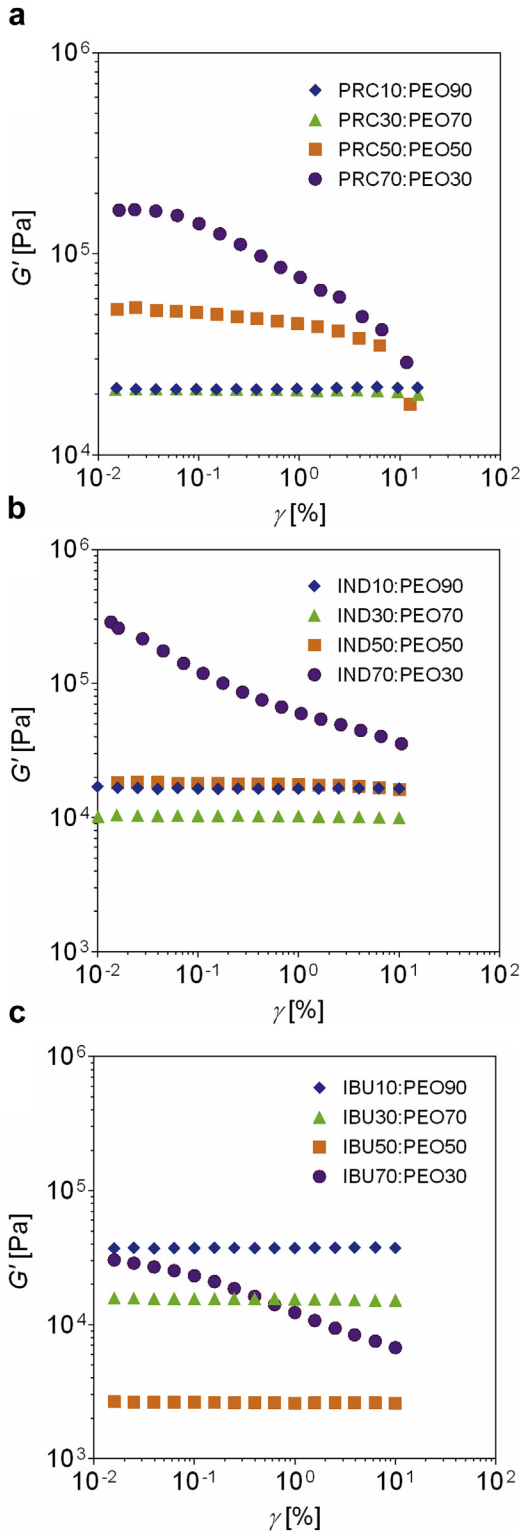

Figure 5. Storage modulus versus strain amplitude at ω = 10 rad/s for (a) PRC:PEO (T = 90°C), (b) IND:PEO (T = 90°C), and (c) IBU:PEO (T = 60°C).

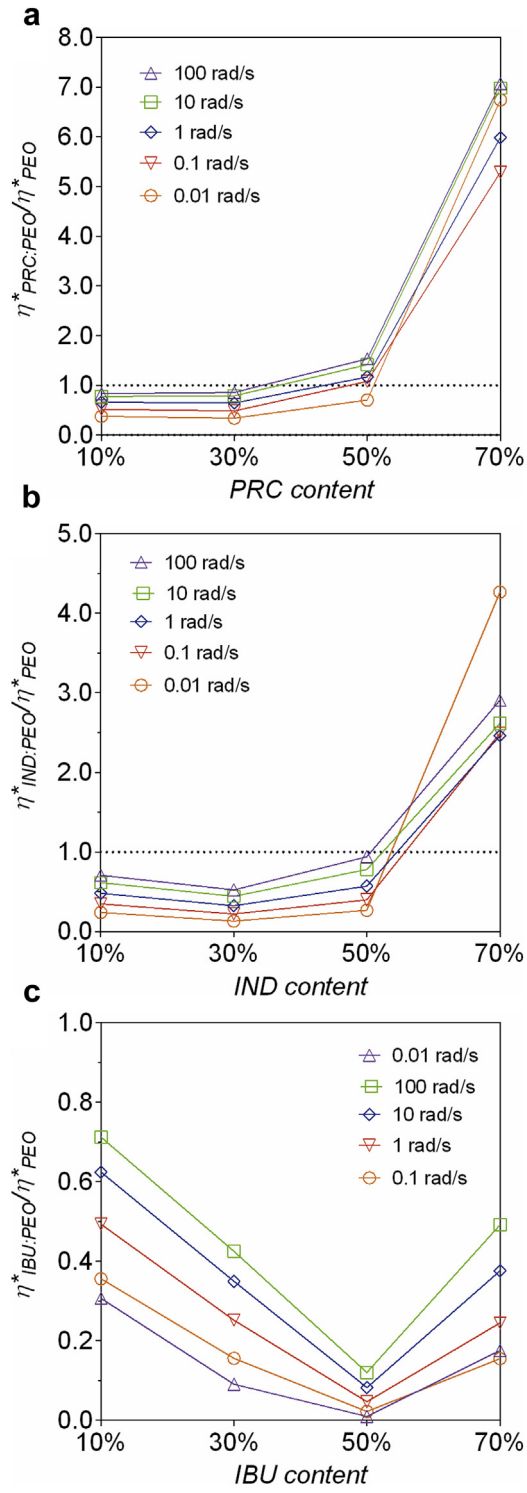

Figure 6. The normalized viscosity at the HME temperatures for (a) PRC:PEO (T = 90°C), (b) IND:PEO (T = 90°C), and (c) IBU:PEO (T = 60°C).

For IND:PEO mixtures, the maximum plasticization throughout the measured frequency range was found at 30% IND load. The viscosity decrease was more pronounced than with PRC, the lowest values being around 13% (0.01 rad/s) and 44% (10 rad/s) of the PEO viscosity. With 50% drug load for IND:PEO (and also for PRC:PEO at ω = 0.01 rad/s) the plasticizing effect is still dominating over the presence of undissolved particles ($\eta_{norm} < 1$, Figs. 6a and 6b). Minimum normalized viscosity at 10%-30% drug load for PRC:PEO and 30% for IND:PEO seems to correlate well with the DSC findings, that showed 2 separate endotherms at 50% and 70% drug loads.

IBU:PEO mixtures had the maximum plasticization at 50% IBU load (Fig. 6c), with the viscosity being as low as 1% (at 0.01 rad/s) and 8% (at 10 rad/s) of the pure PEO. This is a significant reduction with practical significance for melt processing: indeed, even with

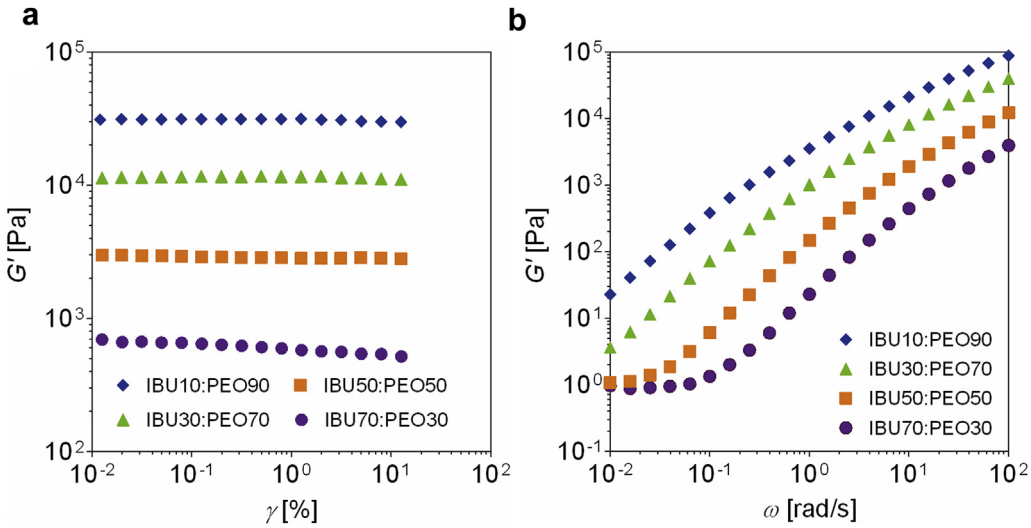

Figure 7. Storage modulus versus strain amplitude (a) and storage modulus versus angular frequency (b) for IBU:PEO mixtures at T = 70°C.

the addition of 10% of IBU the extrusion could be done below the T_m of the pure PEO. An optical microscopy study of the IBU50:PEO50 physical mixture under flow at 60°C (results not shown) exhibited very few solid particles.

The results discussed previously lead us to conclude that the plasticization ability gives an indication of solubility but does not necessarily imply that the drug is fully dissolved in the polymer carrier.

Effect of Temperature (IBU:PEO)

The increase of temperature is generally known to enhance the solubility. Therefore, it is relevant to compare the proximity of the current measurement and extrusion temperatures to the melting temperatures of each drug. According to the T_m reported by the suppliers, the difference, $T_{m(drug)}-T_{HME}$, yields 79°C for PRC, 70°C for IND, and 16°C for IBU. The plasticization ability of the studied drug substances seems to follow the same trend; the closer the melting temperature of the drug is to the processing temperature, the more efficient is the plasticization effect (due to the enhanced solubility). Therefore, it seems obvious that the drugs with lower T_m possess better plasticizing capability. IBU has an exceptionally low T_m among the common small-molecule drugs,[43] and processing close to this temperature can enhance the solubility significantly, therefore causing the enhanced plasticizing effect. IBU has previously been found to be an efficient plasticizer for ethyl cellulose, which could be extruded even ~45°C below its T_g when 60% IBU was added.[12] In addition, indomethacin-Eudragit® E PO mixture showed a decreasing zero-shear viscosity as a function of increasing indomethacin content when the measurements were run at 145°C, only 17°C below the melting temperature reported for the drug used in the study.[44] Similar results have been obtained with lidocaine HCl that was found to plasticize Eudragit® E100 efficiently, when the extrusion was carried out at 80°C-130°C, which is above the melting point of the lidocaine HCl (T_m= 77°C-79°C).[45]

To test the role of temperature in the plasticizing efficiency of IBU, SAOS tests were also performed at 70°C. At this temperature the strain sweeps of IBU:PEO mixtures exhibited an extended linear region even at 70% drug load, and the magnitude of G' decreased with increasing IBU content, as opposed to the results at 60°C, where the minimum values were achieved at 50% IBU content (Fig. 7a). This suggests that a 10°C increase in temperature reduced the solid particle content, indicated by the higher level of G′ and the narrow LVE at 60°C.

For linear polymers, $G'' \propto \omega$ and $G' \propto \omega^2$ at the terminal zone (very low frequency and thus long time scale), as predicted by the linear viscoelastic models.[46] Deviations from this can give clues about the microstructure of the material: for concentrated dispersions, bending of G' toward a plateau or a shoulder at low frequencies has been associated with a buildup of a reversible network.[47] A similar pattern can also be seen in oscillatory shear of immiscible liquid-liquid systems (emulsions), where the plateau of G' at low frequencies is related to the additional elasticity due to the interfacial tension between the 2 phases.[48] Finally, an apparent plateau in G' can also be observed in samples that contain air bubbles, for instance due to moisture, thus, care must be taken not to make false conclusions about the microstucture.[49]

IBU50:PEO50 and IBU70:PEO30 show clear plateaus in G' (Fig. 7b) indicating that 2 phases in the system may exist according to the previously presented mechanisms. The fact that the moduli decrease as a function of increasing IBU load, does not match the description of solid concentrated dispersion but rather to an emulsion formed of 2 immiscible liquid phases. Therefore, it may be postulated that the IBU turned amorphous in the mixture with PEO but due to the supersaturation remained in separate domains in the molten polymer, in a similar way as suggested by Qi et al.[6,7]

The temperature dependence of the SAOS parameters presented here suggests that the plasticizing efficiency of IBU was mainly due to the vicinity of its T_m to the used processing temperature, and the IBU could significantly plasticize the mixture both in solution, and in emulsion-like 2-phase system (phase-separated amorphous dispersion) with PEO melt.

The effects of the thermomechanical treatment that the materials undergo in the process, such as the viscous heating on the shearing and its influence on both the overall flowability and potential thermal degradation of the drug and the excipients, are worth further investigation. In addition, the investigation of the influence of the particle shape, size, and size distribution of the drug substance may be of interest for melt processing of products containing drug substances with varying crystal structures.

Conclusions

The processability of the drug-polymer mixtures is highly dependent on their rheological properties, which depend on whether the drug is dissolved in the polymer or forms a 2-phase system with it. The investigated small-molecule drugs dissolved

partially in the PEO melt in the extrusion process, causing plasticization of the melt. The maximum plasticization effect was found to be 10%-30% for PRC:PEO and 30% IND:PEO mixtures, both studied at T = 90°C. For IBU:PEO, the maximum plasticization was achieved at 50% drug content at T = 60°C. Increasing the temperature in the rheological tests of IBU:PEO mixtures to 70°C increased the plasticizing effect: even the mixture with 70% IBU decreased the viscosity significantly. However, the bending of the G' at low frequencies suggested that at 50% and 70% IBU:PEO was a phase-separated system comparable to an emulsion in regard to its rheological behavior.

Thus, the results suggest that plasticizing can also occur in a 2-phase system with a drug supersaturation when the temperature is approaching the T_m of the drug. In such a case the viscosity of the mixture decreases with increasing drug content, even if the DSC thermograms might show multiple endotherms. Therefore, the DSC analysis of physical mixtures alone cannot give a full picture of the plasticization ability of the drug in terms of decrease of the overall viscosity, which is important for melt processes such as HME.

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