Rheology of co-amorphous drug-drug melts with and without polymeric additives

Lærke Arnfast, Johanna Aho, and Jukka Rantanen

Department of Pharmacy, University of Copenhagen, Copenhagen, Denmark

ABSTRACT

In this paper, results of small amplitude oscillatory shear tests on melts of two small-molecule drugs (1:1 molar ratio) mixed with 20 % polymeric excipient is reported and compared to thermal and physical properties of the polymer. Two drug-drug mixtures and 10 different polymer grades are investigated.

INTRODUCTION

Melt processing is gaining interest in pharmaceutical solid dosage form design[1, 2]. Therefore there is a growing interest in the rheological properties of polymer-drug mixtures, for the determination of suitable formulations, both in terms of desired chemical and physical properties of the final drug product, as well as in terms of acceptable and reliable processability[2, 3]. Melt extrusion has been studied for the production of amorphous solid dispersions (ASD) where the drug and the polymer exist as a single amorphous phase[1]. When selecting polymers for ASD formulations, the drug solubility in the polymer is one of the major criteria[2].

Certain binary mixtures of small organic molecules have been identified to be able to form highly stable amorphous systems with each other, which within the pharmaceutical literature are referred to as co-amorphous formulation[4]. A co-amorphous formulation may be composed of two drug compounds or of a drug compound and a low molecular weight excipient, such as citric acid or amino acids[4]. For the majority of the co-amorphous formulations reported, strong intermolecular forces such as hydrogen bonding and/or π-π interactions have been identified as key stabilizing factors[4]. One example of such system is naproxen-indomethacin, which has been reported to form heterodimers via hydrogen bonding between the carboxylic acid group in naproxen and the carboxylic acid group in indomethacin[5, 6]. The physical mixtures of naproxen and indomethacin have been found to exhibit significant melting point depression typical of that of a eutectic binary mixture, with a maximal depression at 0.55-0.60 naproxen molar fraction[5, 6]. Likewise, a 1:1 molar ratio mixture of naproxen and cimetidine has been found to form an amorphous solid that remains physically stable for extended periods[7]. Raman spectroscopy indicates that this co-amorphous mixture is stabilized through interaction between the carboxylic acid moiety of naproxen and the imidazole ring of cimetidine[7], which is likely salt formation[4].

As these co-amorphous formulations consist of small molecules, one may assume that the viscosity of the melt above the melting temperature of the physical mixtures is low compared to drug-polymer melts typically employed for melt-based processing. However, strong electrostatic interactions and/or formations of ionic bonds within the co-amorphous melt can be

expected to increase the viscosity[8]. In the case of a high-dose immediate release formulation where the polymer is not needed to stabilize the amorphous drug, the role of polymer addition affecting the melt compared to that of the co-amorphous formulation alone should be investigated. The rheological properties of such a mixture may be influenced by a variety of factors; the rheological properties of the medium – which in this case is the drug-drug mixture – as well as those of the polymer. These are influenced by the thermal and physicochemical properties of the compounds, the interactions between polymer and medium, and the external factors, such as temperature and shear [9].

In this study, we have selected a number of linear polymers typically employed in the manufacturing of pharmaceutical dosage forms and tested their effect on the rheological properties of 1:1 molar ratio melts of naproxen-indomethacin and naproxen-cimetidine at the melting temperature of the corresponding drug-drug mixture.

MATERIALS

Cimetidine (CIM), indomethacin (IND) naproxen (NAP), amino-methacrylate copolymer (AMC, Eudragit EPO), polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (PVC-PVA-PEO, Soluplus), vinylpyrrolidone-vinyl acetate copolymer (PVPVA, Kollidon VA64), polyvinylpyrrolidone (PVP, grades Kollidon 12 (PVP K12), Kollidon 17 (PVP K17), Kollidon 30 (PVP K30) and "360.000" (PVP 360.000) and polyethylene oxide (PEO, grades "100.000" (PEO 100.000), "300.000" (PEO 300.000) and "1.000.000" (PEO 1.000.000) were sourced from Hawkins Pharmaceutical Group, USA; Fagron, USA; Evonik, Germany; BASF, Germany and Sigma-Aldrich, USA, respectively.

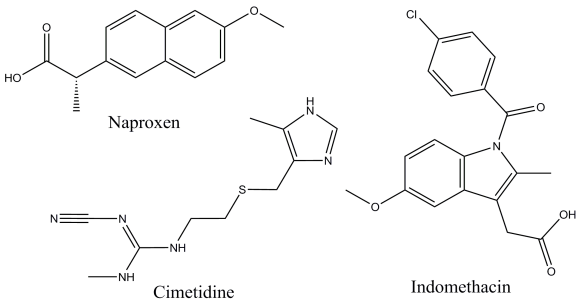

Figure 1. Chemical structures of naproxen, cimetidine and indomethacin.

Glass transition and melting temperatures of the received materials and 1:1 molar drug-drug mixtures were evaluated using a Discovery DSC (TA Instruments, New Castle, DE, USA) at a rate of 2 °C/min (10 °C/min applied for PVC-PVA-PEO, pure drugs, and drug-drug mixtures). Material properties are summarized in Table 1. Structures of the three drugs are displayed in Fig. 1.

Table 1. Molar weight, glass transition temperature (T_g) and melting point (T_m) of drugs and polymers.

Material	M (g/mol)	T_g (°C)	T_m (°C)
CIM	252	36[d]	140
IND	358	45[e]	160
NAP	230	5-6[d,e]	156
NAP-CIM 1:1	241[a]	~35[d]	100
NAP-IND 1:1	294[a]	25-31[e,f]	130
AMC	~47.000[b]	46	-
PVC-PVA-PEO	~118.000[b]	71	-
PVPVA	~45.000[b]	106	-
PVP K12	~2500[b]	103	-
PVP K17	~9000[b]	139	-
PVP K30	~50000[b]	155	-
PVP 360.000	~360000[b]	174	-
PEO 100.000	~100000[c]	-57	63
PEO 300.000	~300000[c]	-56	64
PEO 1.000.000	~1000000[c]	-57	65

[a] calculated average molar mass.
[b] Given as M_w, information from supplier.
[c] Given as M_v information from supplier.
[d]Reported by Allesø et al[7].
[e]Reported by Löbmann et al. [5]
[f]Reported by Beyer et al [6].

METHODS

Samples of 1:1 molar ratio physical mixtures of NAP-IND and NAP-CIM were prepared by mortar and pestle. Physical mixtures of drug-drug mixture and 20 w/w% polymer were prepared in the same manner.

Small Amplitude Oscillatory Shear (SAOS) tests were performed on a AR-G2 stress-controlled rheometer fitted with an Environmental Testing Chamber (both TA Instruments, New Castle, DE, USA) using an 25-mm stainless steel plate-plate geometry, with a gap of 0.5 mm. Samples were applied as powders and pressed directly between the plates. The linear viscoelastic range for each composition was determined separately in strain sweeps at a strain amplitude range from 0.15% to 15% at constant angular frequency, ω = 5 rad/s. Oscillation frequency sweeps were performed at the set temperature with 120 s soak time, 0.5% strain, with increasing angular frequency from 0.1 to 10 rad/s. All frequency sweeps were performed in triplicate.

The temperature was set to 130 °C for samples containing NAP-IND and 100 °C for all samples containing NAP-CIM.

RESULTS AND DISCUSSION

From the results of the frequency sweeps shown in Fig. 2., it is appearent that the two drug-drug mixtures display different behaviour at the melting temperature of the 1:1 molar ratio physical mixture. The viscosity of NAP-IND appears to be at the limit of what can reliably be determined with the 25-mm geometry, in between 0.2-2 Pa·s. The separation of the storage and loss modulus was poor and thus not shown. The NAP-CIM melt displays much higher signals, with better reproducibility. The complex viscosity of NAP-CIM ranges from 800-400 Pa·s in the applied frequency range. The frequency range was kept short due to equipment limitations in the measurement of the very low viscous samples, so no oberservations with regards to shear-dependence could be made.

As the experiment temperature was selected to be as close to the melting (peak) temperature as possible, there is a slight possibility that the two samples are not comparable in the degree of sample uniformity – perhaps there are microcrystalline domains remaining in the NAP-CIM samples at the applied temperature. That possibility aside, the differences would stem from differences in the intermolecular bonding between NAP-IND and NAP-CIM. Difference in the strenght of interaction at the carboxylic moeity of naproxen- hydrogen-bonded with indomethacin versus a possible ionic bond with cimetidine - might be of influence for the viscosity[8]. The NAP-CIM is dominantly viscous, G'' dominating over G', with no cross-over of the moduli within the measurement range.

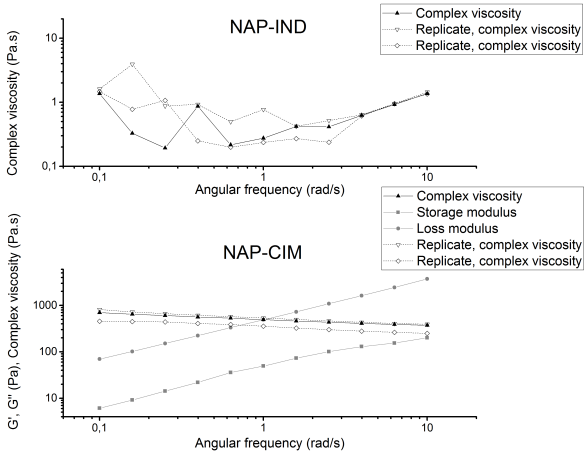

Figure 2. Complex viscosity versus angular frequency from three frequency sweeps of NAP-CIM at 100 °C (top) and NAP-IND at 130 °C (bottom). Additionally, storage and loss moduli of NAP-CIM from one frequency sweep (top).

As seen from Fig. 3, $\eta_{(1\ rad/s)}$ of the 10 NAP-IND-polymer mixtures ranges from app. 2-10.000 Pa·s. While there is no apparent correlation with the polymer T_g (or T_m in the case of PEO), there seems to be a direct and exponential correlation with the polymer

molecular weight, in good agreement with the expected relation between zero-shear viscosity η_0 and molecular weight for monodisperse polymer melts[10].

In the case of NAP-CIM, $\eta_{(1\ rad/s)}$ of the 7 tested polymer mixtures did not show any obvious correlation with polymer weight. PEO 1.000.000, PVP K30 and PVP 360.000 were excluded for this drug-drug mixture as the corresponding samples were too high-viscous to be measured at the temperature applied (100 °C). The $\eta_{(1\ rad/s)}$ range ~400-40.000 Pa·s, and unlike for NAP-IND, the polymers, whose T_g is above the experiment temperature have in general a higher viscosity than those whose T_g is below the experiment temperature.

The majority and also most extreme of the samples in the sample set are different types of PEO and PVP. Vinyl-type polymers generally display highly temperature-dependent melt viscosities when analysed as pure polymers and have narrow temperature processing ranges, with PVP being the most temperature-sensitive, followed by PVPVA and PVC-PVA-PEO[11]. PEO, on the other hand, has a wider processing temperature window and the melt viscosity changes less with temperature[9]. The experiment temperature for the samples containing NAP-CIM is below the T_g of PVP K12, PVP K17 and PVPVA, polymers that at the same

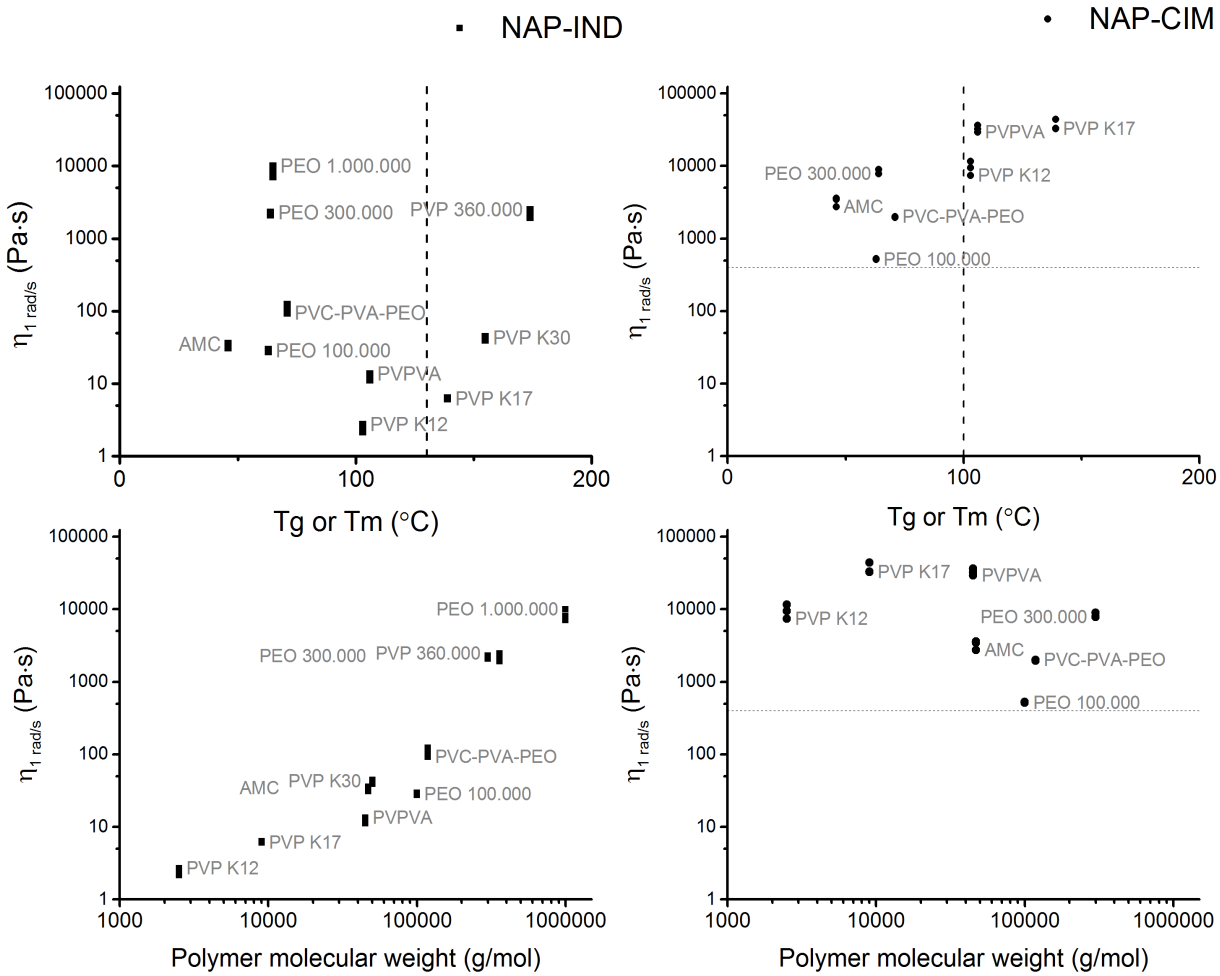

Figure 3. Top: $\eta_{(1\ rad/s)}$ versus polymer T_g or T_m for samples containing NAP-IND-polymer (left, squares), for samples of NAP-CIM-polymer (right, circles). Bottom: $\eta_{(1\ rad/s)}$ versus polymer molecular weight for samples containing NAP-IND-polymer (left, squares), for samples of NAP-CIM-polymer (right, circles). Vertical dashed lines indicate the experiment temperature. Horizontal dashed lines indicates $\eta_{(1\ rad/s)}$ of the pure drug-drug mixture (visible for NAP-CIM alone). Labels indicate polymer grade.

time represent the lowest molecular weights in the sample set. Therefore, the lack of correlation between polymer weight and $\eta_{(1\ rad/s)}$ of the NAP-CIM samples can be explained from the rigidity of the PVP samples at this temperature. On the opposite, despite the experiment temperature being 44 °C below the T_g of PVP 360.000, blends of this polymer and NAP-IND display a $\eta_{(1\ rad/s)}$ closely matching those of NAP-IND+PEO 300.000. A similar observation can be made for PVP K30 (T_g = 155 °C, M_W ~ 50.000 g/mol) and for AMC (T_g = 46 °C, M_W ~ 47.000 g/mol), which are overlapping in the left bottom plot of Fig. 3, despite one having a T_g 16 °C above the experiment temperature and the other 84 °C below. In Fig. 4, the complex viscosity versus angular frequency is shown for a representative sample of all compositions. From this figure, it is noted that the relation between the PVP K12 and PVP K17 samples is similar for both NAP-CIM and NAP-IND-systems, but that their position in comparison to the remaining samples is inverted. Thus, it would seem that while NAP-CIM fails to solubilize/plasticize PVP and PVPVA, NAP-IND is a potent plasticizer/solvent for PVP rendering the T_g of the polymer an irrelevant factor at the

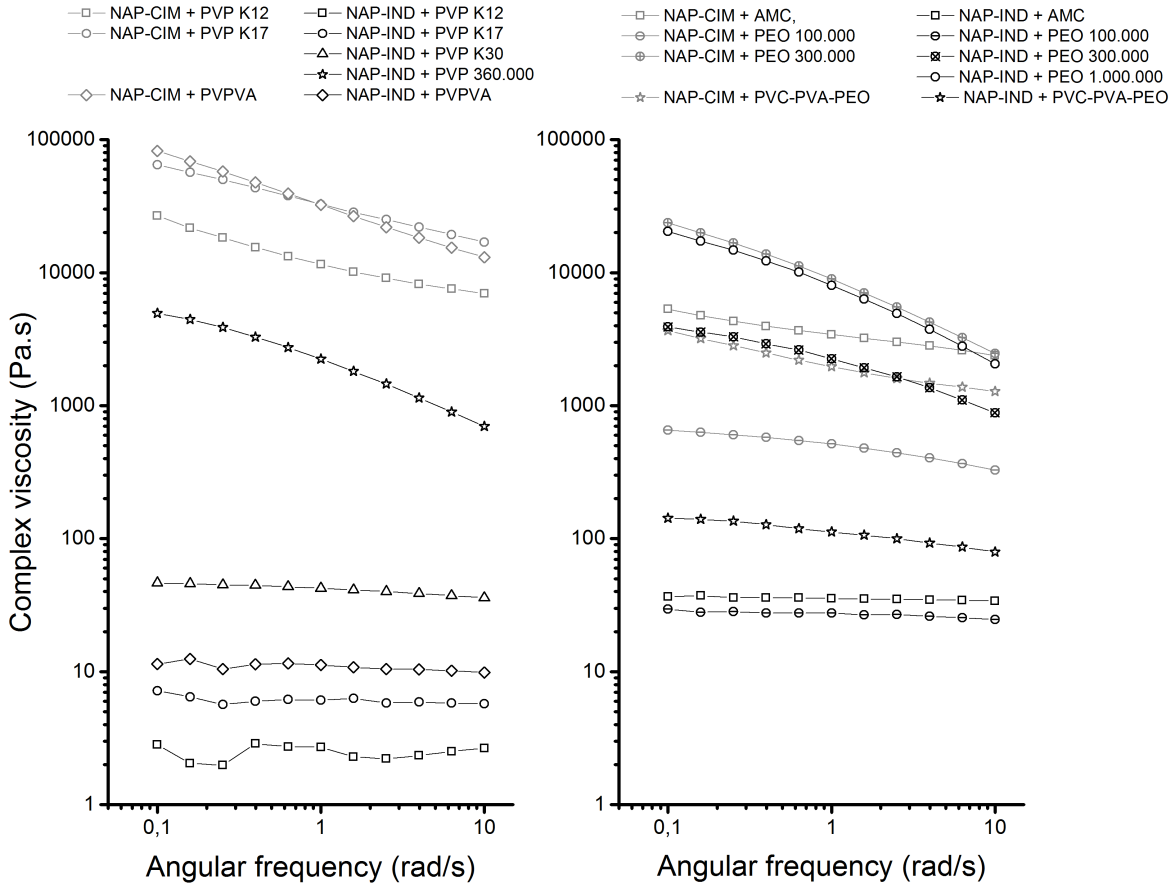

Figure 4. Left: Complex viscosity versus angular frequency of NAP-CIM+-PVP K12 (grey squares), NAP-CIM+-PVP K17 (grey circles), NAP-CIM+-PVPVA (grey diamonds), NAP-IND+-PVP K12 (black squares), NAP-IND+-PVP K17 (black circles), NAP-IND+-PVP K30 (black triangles), NAP-IND+-PVP 360.000 (black stars) and NAP-IND+-PVPVA (black diamonds). Right: Complex viscosity versus angular frequency of NAP-CIM+AMC (grey squares), NAP-CIM+-PEO 100.000 (grey striped circles), NAP-CIM+-PEO 300.000 (grey crossed circles), NAP-CIM+-PVC-PVA-PEO (grey stars), NAP-IND+-AMC (black squares), NAP-IND+-PEO 100.000 (black striped circles), NAP-IND+-PEO 300.000 (black crossed circles), NAP-IND+-PEO 1.000.000 (black open circles) and NAP-IND+-PVC-PVA-PEO (black stars).

concentration studied. Likewise, it is noticed in Fig.3 (right) that the relation between AMC and PVC-PVA-PEO samples is different between the two systems, with the higher molecular weight PVC-PVA-PEO displaying the highest complex viscosity when both are mixed with NAP-IND and the lower molecular weight AMC displaying a higher complex viscosity than PVC-PVA+PEO in the NAP-CIM mixtures. In this case, the polymer with the higher molecular weight also has a higher T_g, so the distance to the experiment temperature cannot be an explanation for this difference. IND is known to be a potent plasticizer of PVP-VA, PVP K30 and AMC [12, 13], while little is published about the interaction between cimetidine and these polymers. Again, NAP-IND is a better solvent for AMC than NAP-CIM. Comparing the samples containing PEO 300.000, the NAP-IND samples have a considerably lower viscosity than those of NAP-IND+PEO 300.000, which is an order of magnitude higher, closely resembling that of NAP-IND-PEO 1.000.000 (Fig. 4 right). As this effect is smaller in relative magnitude than for the lower-weight polymers, the effetc may either be related to the viscosity of the drug-drug mixtures (one being two orders of magnitude higher than the other), an incresead degree of interaction between NAP-IND over NAP-CIM, or simply an effect of the lower temperature.

Naturally, the drug-drug-polymer miscibility is an important factor for processability and satisfactory mechanical properties of the product, but not less importantly, it is known from spray-drying and film casting of drug-polymer systems that solvent-polymer interactions in the solution will have significant effects on the release profile of the drug from the dry product [14, 15].

CONCLUSIONS

1:1 molar ratio NAP-IND and NAP-CIM mixtures display significantly different rheological behaviour at their melting temperatures. The viscosity of samples with 20% w/w polymer was found to be directly correlated with polymer weight in the case of NAP-IND, whereas there was a correlation with T_g in the case of NAP-CIM. The latter effect is argued to be an effect of poor miscibility between vinyl-polymers and NAP-CIM.

ACKNOWLEDGMENTS

The authors acknowledge the funding from the Danish Council for Independent Research (DFF), Technology and Production Sciences (FTP), project 12-126515/0602-02670B.

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