Solubility of Small-molecule Drugs into Polymer Excipients in Hot Melt Extruded Dosage Forms

Johanna Aho, Magnus Edinger, Johan P. Boetker, Stefania Baldursdottir, and Jukka Rantanen

University of Copenhagen, Department of Pharmacy, Universitetsparken 2, 2100 Copenhagen, Denmark

ABSTRACT

In hot melt extrusion of drug-polymer mixtures, the small-molecule drugs (active pharmaceutical ingredients, APIs) that are soluble and miscible with the polymeric excipients can serve not only in their intended medical use, but also as processing aids by plasticizing the mixture. Ibuprofen (IBU) and paracetamol (PRC) were mixed in hot melt extrusion with polyethylene oxide (PEO) at different ratios to evaluate the maximum API concentration for a full solubility using rheological measurements and thermal analysis.

INTRODUCTION

Hot melt extrusion, a well-established processing method for polymers, has recently gained attention in manufacturing of pharmaceuticals, because it is a solvent-free process that can be tailored for dosage forms of various shapes and sizes, and easily scaled up for mass production[1]. In addition, an efficient melt mixing process with water-soluble polymer carriers (excipients) can help in forming a molecular dispersion from the drug and excipients, which improves the dissolution rate of the poorly water soluble drugs in the aqueous media and therefore increases their bioavailability[2, 3].

Small-molecule drugs (active pharmaceutical ingredients, APIs) are often soluble and miscible with the polymeric excipients used in hot-melt extrusion, and can act as non-traditional plasticizers, by increasing the free volume and inhibiting the intermolecular friction in the mixture, as long as the concentration is below the saturation limit[4]. Traditionally the solubility of the APIs is evaluated from differential scanning calorimetry (DSC) thermograms of the API-polymer mixtures: Plasticizing effect can be seen as a lowering of the glass transition temperature T_g (amorphous polymers) or melting temperature T_m (semi-crystalline polymers) by the addition of the API. Relevant information about the influence of the API on the flow properties of the mixture in the hot melt extrusion process can be achieved by rheological measurements, however they are not carried out routinely in pharmaceutical research.

The purpose of this study was to evaluate the plasticizing effect of model small-molecule APIs in hot melt extruded dosage forms by means of rheology and compare that to the results of the thermal analysis.

MATERIALS

Paracetamol (PRC, T_m= 169 °C) and ibuprofen (IBU, T_m= 76 °C) were used as model small-molecule APIs. Poly ethylene oxide (PEO) with a viscosity average molecular weight M_v= 100.000 g/mol, (T_g = -67 °C and T_m = 65 °C) was used as a model polymer.

METHODS

PRC and IBU were mixed with PEO in ratios of 10:90, 30:70, 50:50, and 70:30. The physical mixtures were melt-mixed using a laboratory scale co-rotating twin-screw extruder/ micro-compounder (Xplore Instruments). The processing temperature for PRC:PEO mixtures was 90 °C and for IBU:PEO mixtures 70 °C, and the screw rotation speed for both was 50 RPM. The mixtures were extruded through a circular die (diameter 1.5 mm), and the extrudates were cooled in ambient conditions and cut into granular samples for both rheological and thermal measurements.

Rheological measurements were carried out using AR-G2 rotational rheometer (TA Instruments) in dynamic oscillation mode using 25 mm parallel-plate geometry. The measurement temperature for IBU:PEO was the same as the extrusion temperature, 70 °C. For PRC:PEO the measurements were conducted at 130 °C due to insufficient melt homogeneity observed at lower temperatures with a high API load. The linear viscoelastic range was determined in a strain sweep at an angular frequency ω= 10 s^{-1}, and a strain amplitude (PRC:PEO γ = 0.3 %, IBU:PEO γ = 0.5 %) within a linear range, was consecutively used for the frequency sweep measurements with ω = 0.01…100 s^{-1}.

Differential scanning calorimetry was carried out using a Discovery DSC (TA Instruments). The thermograms for PRC:PEO mixtures were recorded in heat-cool-heat cycle from -80 °C to 200 °C to -80 °C to 200 °C, keeping the sample in an isotherm for 2 minutes between each step. For IBU:PEO mixtures the same procedure was used, but the heating was carried out only up to 80 °C due to the low melting and degradation temperature of ibuprofen.

RESULTS

Dynamic oscillation rheology

To see the plasticizing effect and the maximum solubility limit of the API, the complex viscosity (η^*) of the API-PEO mixtures obtained from the frequency sweep measurements, was normalized using the same concept as for example by Yang et al[5] and Liu et al[6]:

$$\eta_{norm} = \frac{\eta_{(API:polymer)}}{\eta_{polymer}} \quad (1)$$

The single point η_{norm} values at ω = 0.1, 1, 10, and 100 s^{-1} were plotted against the API content. For PRC:PEO the normalized (complex) viscosity value were lowest at 50:50 concentration, indicating that a higher API load remains as undissolved solid crystals which increase the viscosity of the melt in a similar manner to solid particle fillers (Fig. 1). Such behavior for PRC:PEO has earlier been reported by Yang et al.[5], however, the maximum API solubility in their study was below 50 % even at a higher temperature (140 °C).

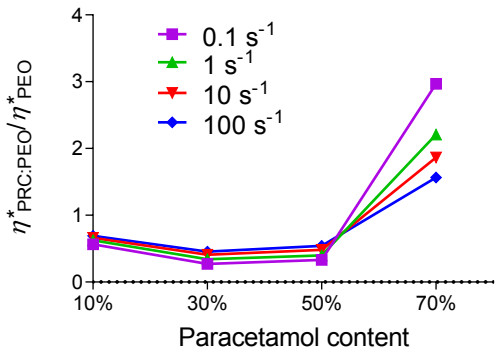

Figure 1. Normalized viscosity of extruded PRC:PEO mixtures at ω= 0.1, 1, 10, and 100 s^{-1}.

Immiscible liquid-liquid systems often show a plateau value in G' at low frequencies in oscillatory shear, which has been related to the interfacial tension between the two phases[7], and similar

behavior has also been reported for systems where one component is in the solid state[8]. According to this, the plateau in *G'* for the PRC:PEO 70:30 mixture (Fig. 2) could be due to the undissolved PRC in PEO melt, which would also agree with the saturation limit estimation by the minimum in the η_{norm} plot.

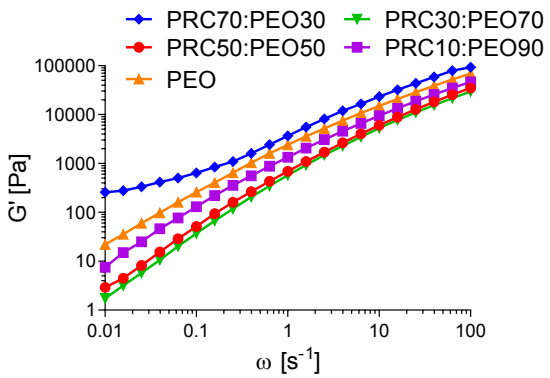

Figure 2. Storage modulus of PRC:PEO mixtures and neat PEO.

The viscosity of PEO was significantly decreased by the addition of IBU, and the lowest viscosity was found at highest IBU content, 70% (Fig. 3). This suggests a full solubility at the tested temperature at all tested concentrations[6]. Ibuprofen has earlier been found to be an efficient plasticizer for ethyl cellulose, that could be extruded even ~45 °C below its T_g by the addition of 60% IBU[9].

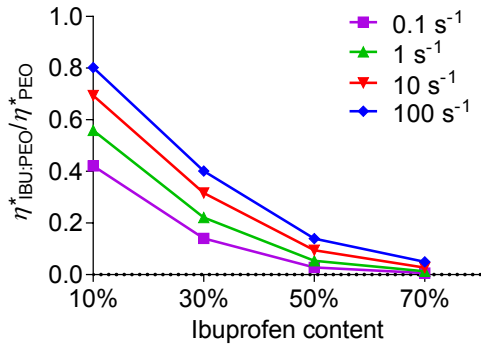

Figure 3. Normalized viscosity of extruded IBU:PEO mixtures at ω = 0.1, 1, 10, and 100 s^{-1}.

Like the complex viscosity, also the storage modulus of the IBU:PEO mixtures decreases as a function of the IBU content (Fig. 4). For the 50:50 and 70:30 concentrations *G'* levels toward a plateau value at low frequency in a similar manner as for PRC-PEO at 70% PRC content. Since the measured torque value at low frequencies for high IBU concentrations is very low and close to the limit of measurement capability of the rheometer, more accurate experimental data is needed to confirm the existence of the plateau.

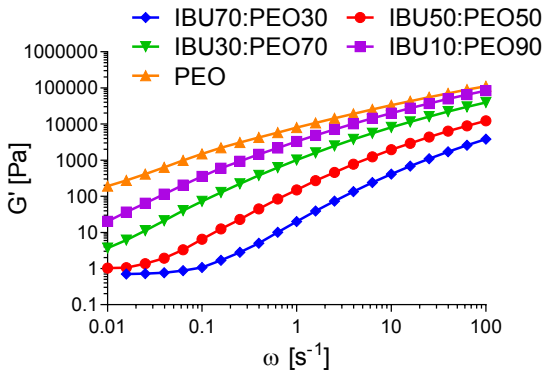

Figure 4. Storage modulus of IBU:PEO mixtures and neat PEO.

Thermal analysis

Melting point depression of the PRC:PEO mixture by the addition of the API is clear until 30% PRC load, whereas at 50% load a slight shift back to higher T_m can be observed (Fig. 5).

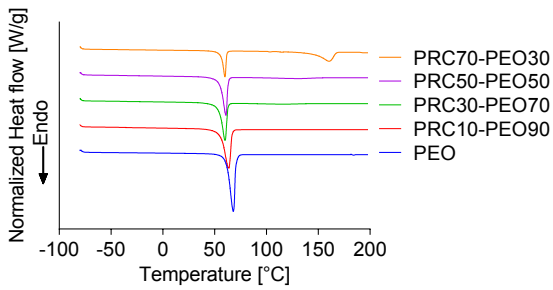

Figure 5. DSC 1st heating cycle for extruded PRC:PEO mixtures (curves are offset to improve the legibility).

Separate melting peaks for PEO and PRC at 70% PRC concentration indicate a solid dispersion with partially undissolved PRC, in agreement with the results from the rheological analyses (Figs. 1 and 2).

Also for IBU:PEO, increasing IBU content decreases the T_m clearly until 30% IBU content after which a shift back towards higher T_m can be seen (Fig. 6).

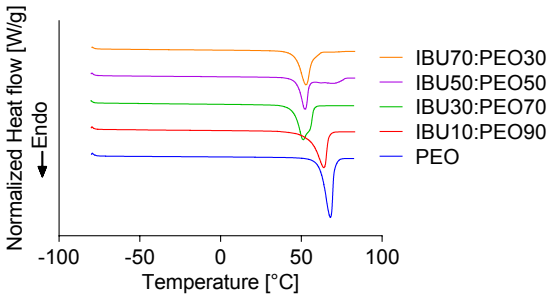

Figure 6. DSC 1st heating cycle for extruded IBU:PEO mixtures (curves are offset to improve the legibility).

In addition, at 30% IBU content the peak broadening suggests an incomplete solubility in contrast to the plasticizing effect seen in the rheological analysis. However, the degree of possible recrystallization of the APIs after extrusion was not evaluated in this study. Therefore it cannot be excluded that the melting endotherms are affected by a recrystallized phase that rapidly dissolves again during the DSC heating run.

CONCLUSIONS

Both IBU and PRC decrease the viscosity of the API:PEO mixture with the increasing API content, until the saturation solubility is reached. For PRC:PEO mixture, 50% API content was found to be the saturation limit, indicated by the increase in η_{norm}, plateau in G', as well as the separate melting endotherms in DSC for the 70% PRC concentration.

For IBU:PEO mixtures the plasticization effect was significant even at the highest concentration tested. It is possible that the broadening of the melting peak at 30% IBU concentration in DSC heating runs is caused by dissolution of a recrystallized IBU phase.

The plasticizing effect enables melt processing of solid dosage forms at lower temperatures which is crucial for many APIs that are prone to thermal degradation. Moreover, enhanced flow properties enable manufacturing of solid dispersions with a high API concentration which can be relevant for some oral dosage forms that require a high dose for providing the therapeutic effect.

ACKNOWLEDGMENTS

We acknowledge the funding from the Danish Council for Independent Research (DFF), Technology and Production Sciences (FTP), project 12-126515/0602-02670B and the Lundbeck Foundation, project R108-A10760.

REFERENCES

1. Crowley, M.M., et al., (2007), "Pharmaceutical applications of hot-melt extrusion: Part I", *Drug Dev Ind Pharm,* **33**(9), 909-926.

2. Sathigari, S.K., et al., (2012), "Amorphous-state characterization of efavirenz-polymer hot-melt extrusion systems for dissolution enhancement", *J Pharm Sci-Us,* **101**(9), 3456-3464.

3. Vo, C.L.-N., C. Park, and B.-J. Lee, (2013), "Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs", *Eur J Pharm Biopharm,* **85**(3, Part B), 799-813.

4. Douroumis, D., ed. *Hot Melt Extrusion – Pharmaceutical Applications*. 2012, John Wiley & Sons Ltd: West Sussex. 364.

5. Yang, M., et al., (2011), "Determination of acetaminophen's solubility in poly(ethylene oxide) by rheological, thermal

and microscopic methods", *Int J Pharmaceut,* **403**(1-2), 83-89.

6. Liu, H., et al., (2012), "Miscibility studies of indomethacin and Eudragit® E PO by thermal, rheological, and spectroscopic analysis", *J Pharm Sci-Us,* **101**(6), 2204-2212.

7. Graebling, D., R. Muller, and J.F. Palierne, (1993), "Linear Viscoelastic Behavior of Some Incompatible Polymer Blends in the Melt - Interpretation of Data with a Model of Emulsion of Viscoelastic Liquids", *Macromolecules,* **26**(2), 320-329.

8. Zheng, Q., et al., (2002), "Polystyrene/Sn-Pb alloy blends. I. Dynamic rheological behavior", *J Appl Polym Sci,* **86**(12), 3166-3172.

9. De Brabander, C., et al., (2002), "Characterization of ibuprofen as a nontraditional plasticizer of ethyl cellulose", *J Pharm Sci-Us,* **91**(7), 1678-1685.