Viscosity of Amorphous Solid Dispersions at Humid Conditions

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Amorphous solid dispersions (ASDs) are mixtures of active pharmaceutical ingredients (APIs) and polymers. They are e.g. used as medical tablets. If the concentration of the API exceeds its equilibrium solubility in the polymer, it tends to crystallize. This should be avoided during the shelf life of the ASD as it decreases the bioavailability of the API in the human body. One factor influencing the ASD shelf life is the molecular mobility of the API in the polymer. Since these molecular motions are physically related to viscosity, the molecular mobility can be evaluated based on viscosity. We proposed an approach to predict the viscosity of ASDs only based on the temperature dependence of the viscosity of the neat polymer as well as the predicted water content in the ASD at certain relative humidity (RH) using the Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT). This approach helps to remarkably reduce the experimental effort for identifying suitable polymers to be used in ASDs.

Rheological investigations of ASDs are often performed to design hot-melt-extrusion processes and thus only data at high temperatures (above the melting temperature) and high shear rates are available in literature. The focus of this work was to investigate the viscosity at storage-relevant temperatures (far below the HME-process window) and no-shear conditions (zero-shear viscosity, ZSV η_0). The ZSV of the pure polymers poly(vinyl acetate) (PVAc) and poly(vinyl pyrrolidone-co-vinyl acetate) (PVPVA) as well as of ASDs containing the API ibuprofen and either PVAc or PVPVA were measured at dry and humid conditions.

It was found that temperature, API content, as well as RH, have a significant influence on the ZSV. E.g., the addition of 20 % ibuprofen to PVAc led to a ZSV reduction by 97 %. The absorption of only 4.4 wt.% water at 75 % RH and 70 °C led to a ZSV reduction by even 99 %. Water has a much stronger plasticizing effect than ibuprofen, which can be explained by the much lower glass-transition temperature (Tg) of water (-135.15 °C) compared to the one of ibuprofen (- 42.30 °C).

The Williams-Landel-Ferry (WLF) equation was used to model the temperature dependence of the ZSV of the pure polymers. To account for the influence of ibuprofen and water on the ZSV the system temperature used in the WLF equation was replaced by an apparent temperature. This apparent temperature accounts for the fact that due to the presence of API and water, the Tg of the ASD is reduced compared to the Tg of the pure polymer. Thus, different systems are considered at the same distance to their own Tg. Using the apparent temperature, the influence of ibuprofen on the ZSV of ASDs composed of ibuprofen/PVAc and ibuprofen/PVPVA could be described very well with the same WLF parameters as for the pure polymer. Also, the plasticizing effect of absorbed water on the ZSV could be fully explained by the reduced Tg of the wet polymer or wet ASD compared to the one of the pure polymer (Figure 1).

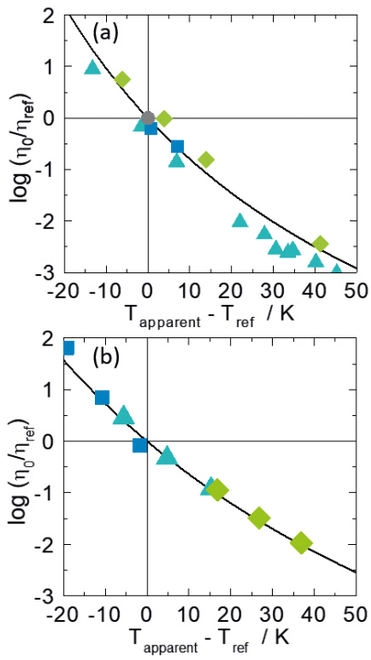

Figure 1: log(η_0/η_{ref}) as function of the temperature difference $T_{apparent}$ - T_{ref} for (a) PVAc at different RHs (squares) and ibuprofen/PVAc ASDs at 0 % RH (diamonds) and ibuprofen/PVAc ASDs at different RHs (triangles).The circle denotes the reference point (70 °C, 0 % RH, 0% API) and the solid line is the WLF modeling using c_1 = 8.86, c_2 = 101.60 K. (b) PVPVA at 60 % RH and different temperatures (squares) and ibuprofen/PVPVA ADS with 10.5 wt.% ibuprofen at 0 % RH at different temperatures (diamonds) and an ibuprofen/PVPVA ASD with 20 wt.% ibuprofen (triangles).The solid line is the WLF modeling using c_1 = 10.04, c_2 = 147.4 K and T_{ref} = 150 °C.

This means that ASDs stored at the same temperature distance from their Tg have the same viscosity regardless of whether the Tg distance is generated by temperature, API loading, RH increase, or a combination thereof. Thus, the ZSV of an ASD can be predicted without any additional viscosity measurements once the temperature dependence of the ZSV of the pure polymer and the Tg of the ASD is known. Together with the crystallization driving force in a metastable ASD, this approach allows estimating the API crystallization kinetics and thus the shelf life of ASDs.

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