Modeling the Impact of Polymer Type on the Long-Term Physical Stability of Amorphous Solid Dispersion Formulations

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Purpose

To predict and compare the impact of polymer type on the long-term physical stability of amorphous solid dispersion (ASD) formulations through modeling and long-term stability studies under standard ICH conditions.

Methods

The thermodynamic model, Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT), and the Gordon-Taylor equation were applied to model the solubility and glass transition temperature (Tg), respectively, for six different API/polymer systems. The combined solubility and Tg curves, commonly referred to as API/polymer phase diagram, was used to predict the physical stability of the ASD formulations under different storage conditions i.e., temperature and relative humidity (RH). Three polymers, namely, hydroxylpropylmethylcellulose acetate succinate (HPMCAS), copovidone (PVPVA 64) and poly(vinyl pyrrolidone) (PVP) were considered with Acetaminophen and Naproxen as model APIs. For validation of the modeling results, ASD formulations with varying API loads (5 - 60 wt%) of amorphous Naproxen and Acetaminophen in the polymers were prepared by hot melt extrusion and stored for up to a year under standard ICH conditions (25 °C/0% RH, 25 °C/60 % RH, 40 °C/75 % RH). To assess the physical stability of the formulations, samples were monitored periodically (2 - 4 weeks) up to 12 months for API recrystallization by powder X-ray diffraction and polarized light microscopy.

Results

Under dry condition (25 °C/0% RH), the PVP based formulations showed the best physical stability, up to 50 wt% Acetaminophen and Naproxen ASDs remained completely amorphous for 12 and 9 months, respectively. PVPVA 64 on the other hand could stabilize up to 30 wt% ASD for both APIs within the same period. At humid conditions (25 °C/60 % RH and 40 °C/75 % RH), the Tg of the formulations significantly reduced due to the plasticizing effect of water. With the influence of moisture, PVP and PVPVA 64 stabilized up to 30 wt% Acetaminophen and 20 wt% Naproxen ASDs for 12 months and 9 months, respectively. Contrarily, 20 wt% Acetaminophen and Naproxen HPMCAS based ASDs recrystallized after only 3 months of storage at 40°C/75% RH. Overall, the stability results agreed quite well with the modeled API/polymer phase diagrams, which reflected the impact of moisture and temperature on the API solubility in the polymer and the Tg of the ASD. It was also observed that favorable interactions between the API and polymer contributed to physical stability. Amongst the three polymers only HPMCAS exhibited unfavorable interactions based on the calculated Flory-Huggins interaction parameter. The ranking ability of the polymers to stabilize the amorphous APIs was found to be PVP>PVPVA 64>HPMCAS which was in complete agreement with the modeled phase diagrams.

Conclusion

The stabilizing ability against recrystallization of amorphous Acetaminophen and Naproxen by three commercial polymers, typically used in ASD formulations, was modeled for different storage conditions. PC-SAFT thermodynamic model and Gordon-Taylor equation were applied to model the API/polymer phase diagrams. Predicted modeling results were validated by long-term physical stability studies. PC-SAFT thermodynamic modeling can potentially be applied as an early tool for polymer selection in the design and manufacturing of ASD formulations for maximum drug load and physical stability.

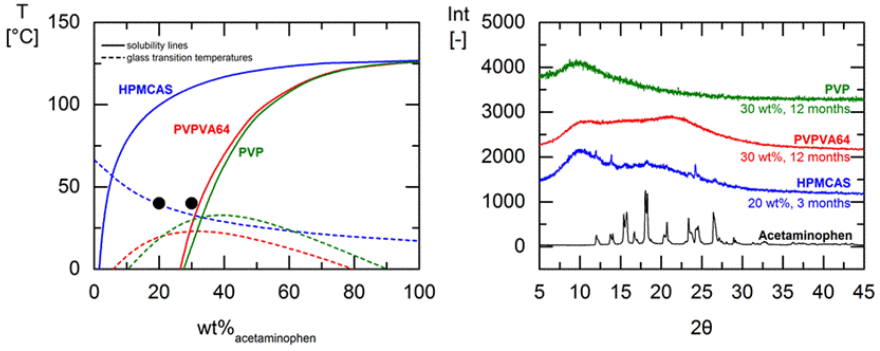

Fig 1. *Left:* Phase behavior of Acetaminophen/PVP, Acetaminophen/PVPVA64, and Acetaminophen/HPMCAS at 40°C/75% RH. The solid and dashed lines show solubility prediction using PC-SAFT and glass transition temperature prediction by Gordon-Taylor equation, respectively. *Right:* XRPD diffractograms of crystalline Acetaminophen and its ASD formulations with the three polymers after storage at 40°C/75% RH.