The Role of Drug – Polymer Hydrogen Bonding Interactions on the Critical Cooling Rate of Amorphous Solid Dispersions

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Purpose: Amorphous solid dispersions (ASDs) have drawn considerable attention due to their potential to enhance the aqueous solubility and therefore the bioavailability of poorly soluble drugs. In ASDs, the drug in the amorphous state, is entrapped and stabilized in a polymeric matrix. Even though a freshly prepared ASD can have all the drug in the amorphous state, an amorphous to crystalline transition can occur during product storage. Once the solubility advantage of the amorphous form is lost, the product bioavailability can be seriously compromised. Generally, a high polymer concentration is used to delay the crystallization and improve the shelf-life of the product. This approach, in addition to leading to processing challenges, cannot be used for high dose drugs. The focus of our work is to understand the impact of processing conditions on the final form of an ASD and develop mitigation strategies to minimize the risk of drug crystallization during product storage. Crystallization occurs through two sequential steps - nucleation followed by the growth of nuclei to larger crystals. Even though analytical techniques allow crystallization in a formulation to be detected, nucleation remains elusive and can be the root cause of formulation instability during storage. Our goal is to investigate the effectiveness of polymers to prepare ASDs that (i) are free from nuclei and (ii) can prevent growth of nuclei if at all they are formed. With this as a basis, we hypothesize that the critical cooling rate required to prepare a stable ASD is a function of the strength of interactions between drug and polymer. A time-temperature-transformation (T-T-T) diagram can serve as a tool to understand the crystallization behavior from melt and identify the potential for crystallization during cooling.

Methods: We investigated drug-polymer systems containing nifedipine (NIF) as the model drug. Polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose acetate succinate (HPMC-AS) and poly(acrylic acid) (PAA) were the model polymers. ASDs containing NIF and each polymer were prepared using the solvent evaporation method. The crystallization onset time was determined using a differential scanning calorimeter (Q2000, TA Instruments). This was used to construct the T-T-T diagrams. The crystallization onset time was also determined using synchrotron radiation. Experiments were performed in the transmission mode in the 17-BM-B beamline at Argonne National Laboratory (Argonne, IL, USA.). A monochromatic X-ray beam (wavelength 0.4485 Å; beam diameter 300 μm) and a two-dimensional (2D) area detector (XRD-1621, PerkinElmer) were used.

Results: The stronger drug-polymer interacting system exhibited longer crystallization onset times and lower critical cooling rates. At 90°C, the onset of crystallization of 'as is' NIF occurred at 4.8 ± 0.7 min. The addition of PVP (4% w/w) increased the onset time to 29.9 ± 3.6 min. On the other hand, PAA (4% w/w) did not have a pronounced effect on the onset. The critical cooling rate decreased from 17.6 ± 2.9°C/min for 'as is' NIF to 2.7 ± 0.3°C/min for ASD containing 4% w/w PVP (Figure 1).

Conclusions: T-T-T diagrams were constructed using the isothermal crystallization method. We concluded that the critical cooling rate required to prepare an ASD is a function of the strength of interaction between drug and polymer. The overall effect depended on both (i) the type of polymer, and (ii) the polymer concentration. High intensity synchrotron radiation helped us to detect the first evidence of crystallization in ASDs. A drug-polymer system with a stronger interaction, can be cooled at a slower rate and will exhibit higher physical stability. The practical usefulness of our work stems from the two-step approach to prepare a drug product by: (i) identifying conditions to avoid nucleation during the manufacture of ASDs, which is the part of future investigation and (ii) if this approach fails, then identifying the excipient to prevent growth of nuclei into larger crystals, i.e., crystal growth inhibitors. A fundamental understanding of the crystallization behavior will enable us to predict the physical stability, which is a critical step in formulation optimization.

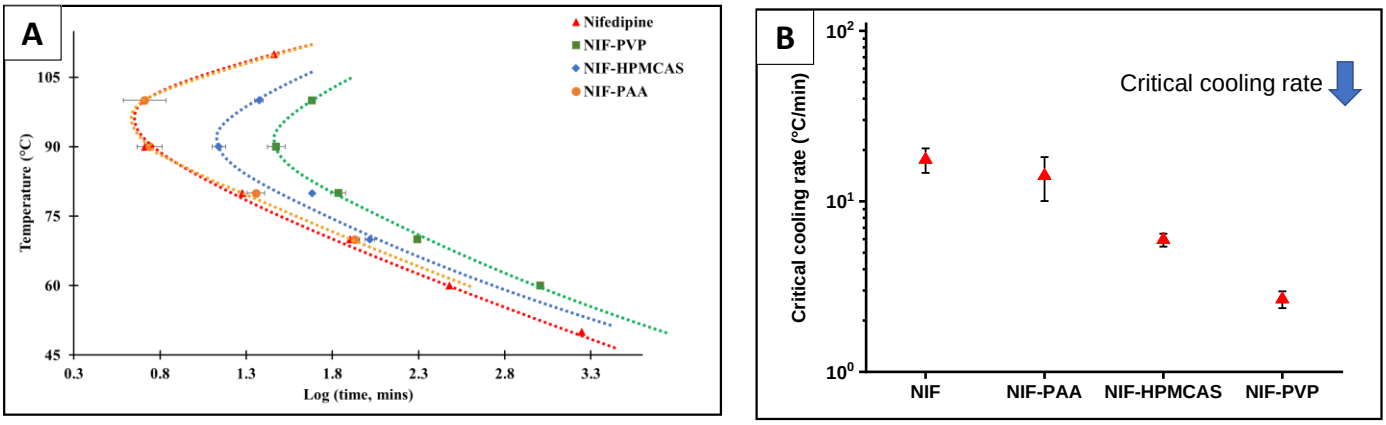

Figure 1 (A). T-T-T diagrams with temperature (°C) on the y-axis and crystallization onset time (min) on the x-axis, for model compound nifedipine (NIF) and ASDs (96% drug load). Each curve represents the phase boundary between the amorphous and crystalline states. **(B)** The critical cooling rate (°C/min) for the ASDs prepared with different polymers. With an increase in the strength of drug-polymer interaction, there is a pronounced decrease in the critical cooling rate.

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