Unravelling the Drug-Polymer Interaction: A Case Study of Mefenamic Acid-Nicotinamide Cocrystal

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In the pharmaceutical industry, over 70% of newly developed drugs, or active pharmaceutical ingredients (APIs), suffer from poor aqueous solubility, leading to low dissolution rate and bioavailability.[1] Pharmaceutical cocrystals are crystalline materials composed of APIs and cocrystal formers ('coformers') in the same crystal lattice, typically held together by H-bonds.[2] Cocrystals are of interest due to their thermodynamic stability while improving the dissolution performance of the API.[3] The improvement was believed to come from the achievement of supersaturation state of the API during the dissolution of the cocrystal, a thermodynamically highly unstable state above the solubility of the drug. To keep the drug dissolved for longer time, polymers are introduced in the dissolution medium to inhibit the precipitation of the drug either on the surface of the cocrystal or in the bulk.[4] Polymers can interact with the API and coformer through their hydrocarbon chains (hydrophobic groups) or via specific H-bond donating/accepting groups (hydrophilic groups) in solution.[5]

In this study, the mefenamic acid-nicotinamide (MFA-NIC) cocrystal was selected due to the problematic solubility exhibited by the API. Mefenamic acid (MFA) is a non-steroidal anti-inflammatory drug (NSAID) with poor aqueous solubility, and nicotinamide (NIC) is a common coformer on the generally recognized as safe (GRAS) list chosen due to its high solubility. Three polymers – polyvinylpyrrolidone (PVP), poly(ethylene glycol) (PEG), and branched polyethylenimine (PEI) – were selected in the order of increasing capacity of H-bond donation. While my lab partner Brendan Hill focused on the dissolution performances of MFA, unravelling the drug-polymer interactions during cocrystal dissolution was central to my study.

The MFA-NIC cocrystal was grown by solvent evaporation in acetone and characterized by X-ray diffraction (XRD). The appearances of new XRD peaks confirmed the successful growth of the MFA-NIC cocrystal. The drug-polymer interactions were then investigated by solution-phase nuclear magnetic resonance (NMR) spectroscopy. The three polymers demonstrated varying degrees of H-bond interactions with MFA in ^{1}H NMR. These effects showed up as either broadening or shift of the amine (H-bond donor) peak of MFA in the NMR spectra. Moreover, the spectrum of cocrystal with pre-dissolved PEI showed shifts of most of MFA peaks while all NIC peaks remained in place. These NMR results were supported by nuclear Overhauser effect spectroscopy (NOESY), which shows cross peaks when two protons are in spatial proximity. The appearances of cross peaks in the spectrum of cocrystal with PEI between the polymer and all MFA protons confirmed both the hydrophobic and hydrophilic interactions. Similar peaks were observed between PVP and methyl groups of MFA (hydrophobic). This work helps elucidate the molecular mechanisms by which polymers help improve the dissolution performance of poorly soluble APIs from cocrystals.

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References

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