Investigating Drug–Polymer Interactions to Tune the Dissolution Performance of Poorly Water-Soluble Drugs: A Case Study on the Mefenamic Acid-Nicotinamide Cocrystal

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Poor solubility in water is a serious problem affecting more than 70% of active pharmaceutical ingredients (APIs), reducing their effectiveness in the body.[1, 2] Pharmaceutical cocrystals are of particular interest to improve the dissolution rate and solubility of APIs.[3, 4] Polymers have been applied as potential recrystallization or precipitation inhibitors for pharmaceutical cocrystals to further ameliorate solubility performance.[5-7] However, the mechanisms by which polymers stabilize solutions with a high API concentration are not yet fully understood. This study aimed to investigate cocrystal dissolution performance and solution-phase interactions between cocrystal components and polymers as a function of polymer identity. The mefenamic acid-nicotinamide (MFA-NIC) cocrystal has been selected for this study due to the poor aqueous solubility exhibited by the API, mefenamic acid (MFA), as well as the lack of studies on MFA-NIC cocrystal dissolution in the presence of polymers. Three polymers - polyvinylpyrrolidone (PVP), poly(ethylene glycol) (PEG), and branched polyethylenimine (PEI) were selected based on hydrogen-bonding properties.

MFA-NIC cocrystals were grown by solvent evaporation. MFA and NIC were dissolved together in acetone before leaving the solution to evaporate in a glass dish. After a few hours, MFA-NIC cocrystals were collected from the dish and analyzed by X-ray diffraction (XRD) and Fourier-transform infrared (FTIR) spectroscopy, along with MFA and NIC starting materials. Cocrystals were then used for dissolution concentration-time profiles. For these experiments, we prepared vials containing 20 mL of pure H_2O or H_2O containing a selected concentration of each of our three selected polymers (PVP, PEG, and PEI). After adding an excess of cocrystals, we stirred our vials at 400 rpm over the course of 2 hours, collecting 1 mL samples at 5, 15, 30, 60, and 120 minutes. These samples were each filtered and diluted before being analyzed. High-performance liquid chromatography (HPLC) was employed to monitor the MFA concentration of each sample. These measurements were complemented by nuclear magnetic resonance (NMR) spectroscopy measurements to elucidate solution interactions between the cocrystal components and polymers, but in this this summary, I will detail results from XRD, FTIR, and HPLC.

XRD and FTIR confirmed that MFA-NIC cocrystals were successfully synthesized, exhibiting characteristic peaks of a new crystal phase distinct from that of MFA and NIC starting materials.[8-10] HPLC data, shown in Figure 1, demonstrated that PVP and PEG did not greatly alter the dissolution performance of MFA-NIC cocrystals, but PEI caused a great increase in concentration compared to when the cocrystals were dissolved in pure H_2O. PEI also greatly changed the pH of the H_2O from 5.52 to 9.00, making it much more basic. This caused deprotonation of MFA, allowing it to dissolve to a higher concentration. It is also believed that PEI has the strongest intermolecular interactions with MFA out of the 3 polymers.

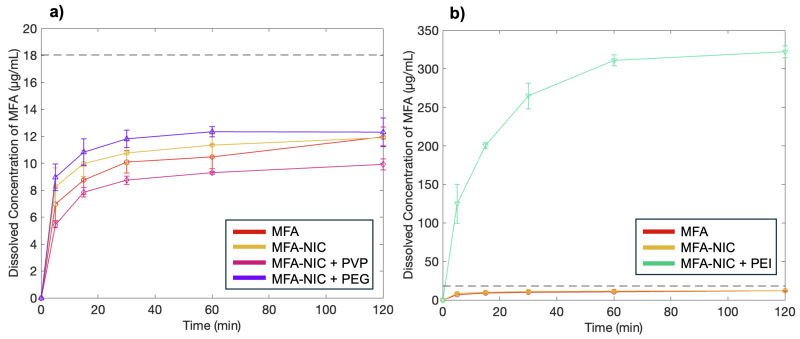

Figure 1. Dissolution concentration-time profiles of a) MFA, MFA-NIC, MFA-NIC with pre-dissolved PVP, MFA-NIC with pre-dissolved PEG; b) MFA, MFA-NIC, and MFA-NIC with pre-dissolved PEI.

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