The Optimization of Mefenamic Acid-Nicotinamide Cocrystal Dissolution Performance Using Polymers as Growth Additives

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Nearly 90% of new drug candidates have poor aqueous solubility, leading to low dissolution and bioavailability (Xie et al., 2024). Pharmaceutical cocrystals are of interest as they can improve API solubility without altering its chemical composition. Cocrystals are crystalline materials composed of the active pharmaceutical ingredient (API) and the crystal former (coformer) in a specific ratio within the same crystal lattice. The coformer interacts with the API through noncovalent bonds, altering the crystal structure of the API, resulting in thermodynamic stability and improved dissolution performance of the API (Duggirala et al., 2015). Polymers are introduced to maintain the drug dissolved for a longer period and prevent the drug from recrystallizing as it adsorbs onto cocrystal surfaces – they act a recrystallization inhibitors. (Bhalani et al., 2022).

Mefenamic acid (MFA) is an anti-inflammatory drug used to treat moderate pain, but it has poor aqueous solubility. Nicotinamide (NIC) is a form of vitamin B3 that is highly water-soluble and forms strong hydrogen bonds with MFA. The mefenamic acid-nicotinamide (MFA-NIC) cocrystal was selected for this study due to the poor aqueous solubility exhibited by the API, MFA, as well as the lack of studies on the dissolution of MFA-NIC cocrystals grown in the presence of polymers. Three polymers were selected based on hydrogen-bonding properties: polyvinylpyrrolidone (PVP), poly(ethylene glycol) (PEG), and branched polyethylenimine (PEI). Optimization of both the type of polymer and its concentration is needed for the development of an effective cocrystal formulation (Alinda et al., 2022).

My project aimed to evaluate the dissolution performance of MFA-NIC cocrystals grown with polymer additives by slow cooling using high-performance liquid chromatography (HPLC) with pH buffer. MFA, NIC, and polymer were dissolved and heated in a scintillation vial to 60°C before gradually letting them cool to room temperature. After the growths were left overnight to allow crystal nucleation, the cocrystals were filtered and left to dry on a watch glass overnight. The cocrystal composition was analyzed by Powder X-ray Diffraction (PXRD). Ensuring that there is no MFA recrystallization, the cocrystals were then used for dissolution concentration-time profiles in phosphate buffer solution (PBS) for pH control. To analyze the dissolution time profile of the cocrystals, an excess of cocrystals was added to a vial of 20 mL of PBS. The vials were stirred for 2 hours, collecting 1 mL samples at 5, 15, 30, 60, and 120 minutes. The samples were each filtered and diluted before being analyzed using HPLC. The measurements were complemented by a standard MFA calibration curve to determine the MFA concentration in each sample. The MFA calibration curve was prepared the same way as the cocrystals.

PXRD 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. There was no MFA recrystallization as shown by the absence of the characteristic MFA peak.

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