Exploring Synthesis Conditions of Mefenamic Acid Cocrystals

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Crystals are all around us, from the salt on our dinner tables to the many components inside electronic devices. They also play a critical role in manufacturing, particularly in pharmaceuticals. By controlling how crystals form and grow, a drug's safety and effectiveness can be drastically improved.[1] A crystal is a solid in which atoms or molecules are arranged in a repeating three-dimensional pattern called a lattice. This ordered structure influences a crystal's physical and chemical properties—not only through the crystal's chemical make-up (composition) but also through the internal arrangement of molecules within the crystal and the crystal's external shape (morphology).[2] Understanding how crystals behave in different conditions is especially important in medicine, where drugs encounter varying temperatures, pH levels, and dissolution environments inside the human body.

This project focused on a type of crystal called a cocrystal, which contains two different molecules in the same lattice: an active pharmaceutical ingredient (API) and a coformer. The API is the biologically active part of a medication that produces its therapeutic effect, while the coformer is a compound that crystallizes with the API to change its properties.[1,2] Cocrystallization offers a way to improve drug characteristics such as solubility, dissolution rate, stability, and bioavailability—key factors for medicines with poor water solubility that would otherwise dissolve too slowly to be effective.[3] The system of interest in this study is mefenamic acid (MFA), a nonsteroidal anti-inflammatory drug (NSAID) with low aqueous solubility, and nicotinamide (NIC), a water-soluble form of vitamin B3. While MFA–NIC cocrystals have shown potential benefits, they have not been widely studied, partly because of synthesis challenges. Previous research suggests that adding polymers during cocrystallization can improve dissolution performance.[3,4] In particular, polymers can slow down drug precipitation, keeping a solution in a supersaturated state longer—meaning more of the drug stays dissolved than would normally be possible under equilibrium (solubility) conditions.

This study investigated how varying concentrations of two polymers—hydroxypropyl cellulose (HPC) and polyethylene glycol (PEG)—affected the morphology of synthesized MFA–NIC cocrystals when used as growth additives. By systematically adjusting polymer identity and concentration during cocrystallization, we aimed to identify trends in crystal size, morphology, and surface features as determined by scanning electron microscopy (SEM) and to identify accurate synthesis of the proposed cocrystal using powder x-ray diffraction (PXRD). MFA–NIC cocrystals were synthesized utilizing a slow-cooling method: dissolving the API, coformer, and polymer in acetone at an elevated temperature, and then slowly cooling the solution to form cocrystals.

The results indicated that cocrystals were successfully grown with polymer (both HPC and PEG) concentrations ranging from 0 mg/mL to 24 mg/mL, highlighting the ability to control cocrystal synthesis under varying growth conditions. Similar PXRD peaks across the diffraction patterns of the cocrystals grown under varying polymer concentrations were used to confirm the correct structure (phase) of cocrystals. Furthermore, SEM imaging confirmed distinct morphologies between select cocrystals of HPC and PEG grown with polymer concentrations of 6 mg/mL. Future steps include continuing SEM of the synthesized cocrystals to explore potential morphology differences of cocrystals grown under higher polymer concentrations, such as 24 mg/mL. Additionally, upon identifying the morphologies of these cocrystals, high performance liquid chromatography (HPLC) will be used to identify the dissolution profiles of cocrystals in a pH buffer - a similar condition to that of the gastrointestinal environment. This work would allow us to further elucidate the effect of cocrystallization in improving the pharmaceutical efficacy of MFA cocrystals.

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References

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