Cocrystals: preparation via resonant acoustic mixing

Active pharmaceutical ingredients (API’s) usually have the disadvantage that their solubility in water is low. This hampers their bioavailability when administering these compounds as a medicine to patients. To improve the bioavailability of these API’s, they can be cocrystallized with a suitable conformer, leading to a so-called cocrystal. Usually cocrystals consist of a 1:1 molar ratio of the two molecules building up the new crystalline structure, but also 2:1 or other molar ratios have been found. Generally these cocrystals have physicochemical properties (like a higher solubility in water) that differ from the API itself. In line with the development of pharmaceutical cocrystals, also energetic cocrystals have been prepared. The goal for energetic cocrystals is higher performance and lower sensitivity.

Several techniques have been developed to prepare cocrystals, e.g. crystallization, grinding but also resonant acoustic mixing (RAM) (am Ende et al.; Anderson et al.). The latter technique is the topic of this MSc graduation project, since the mechanism underlying RAM to prepare cocrystals is not yet completely clear.

The following activities are foreseen:

- Selection of in first instance inert (i.e. non-energetic) model substances from which it is known that they for cocrystals (e.g. API’s);
- Literature search on the physics behind RAM, and how this could explain why this works for the preparation of cocrystals;
- Determine solubility of the selected compounds using the Crystal16; maybe this is already known from literature; moreover, it may not be necessary to have the exact solubility data, since during RAM processing only a relatively small amount of solvent is required which appears sufficient to facilitate the formation of the cocrystal;
- Selection of (range of) process conditions for RAM processing to prepare cocrystals, based on available literature;
- Preparation of cocrystals using RAM; parameters like vibration frequency, amplitude / vibration intensity, residence time, solvent, molar ratios of the two compounds, etc. can be varied; maybe a screening technique can be designed during which different samples (compounds, solvents) can be tested in one trial (see e.g. Nagapudi et al.);
- Characterization of prepared cocrystals using X-ray diffraction (XRD); comparison to literature data;
- Mechanism behind RAM as a processing technique to prepare cocrystals;
- Risk assessment + required safety measures when preparing cocrystals from energetic materials using RAM;
- Small scale trials applying RAM to prepare energetic cocrystals (if time allows).

This project combines activities that can be performed at the TU Delft (theoretical work, literature search, Crystal16 (if necessary)) and at TNO (RAM experiments, characterization).

References:

Contact: Antoine van der Heijden, A.E.D.M.vanderHeijden@tudelft.nl