Understanding crystallization outcomes of metronidazole – gallic acid pharmaceutical polymorphic cocrystal using solvent-mediated phase transformation and mechanochemistry

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Metronidazole (MNZ) is an antibacterial and antiprotozoal drug listed on the WHO (World Health Organization) Model List of Essential Medicines. However, it is slightly soluble in water (approx. 10 mg/mL at 20 °C[1]). Employment of different experimental screening methods (solution crystallization, mechanochemical experiments) and use of solvents with distinct properties allows for selective crystallization of polymorphs of neat components, as well as cocrystal polymorphic forms [2]. Five MNZ cocrystals have been described in the literature up-to-date and among them metronidazole - gallic acid (MNZ:GAL) cocrystal is known to occur in two polymorphic forms [1], [3].

In the presented work, screening for polymorphs of MNZ:GAL cocrystal was conducted using slurry crystallization and grinding experiments, using 18 solvents with different properties. The product phase was analyzed by Powder X-ray Diffraction (PXRD), Fourier-Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC).

The use of non-polar solvents such as n-hexane or toluene resulted in a physical mixture of MNZ and GAL. Form II of MNZ:GAL cocrystal was prepared using low polarity solvents such as diethyl ether, ethyl acetate, dichloromethane and chloroform.

Experiments with higher polarity solvents led to predominantly formation of form I of MNZ:GAL cocrystal. Thermal analysis of polymorphic forms of MNZ:GAL cocrystal indicated that form I is thermodynamically stable form, based on a phase transition visible on a DSC thermogram at 152 °C.

For the selected solvents (toluene, chloroform, acetic acid, methanol, water) grinding experiments were conducted using different weights of the reaction mixture (200 mg or 300 mg). Grinding experiments for toluene and chloroform using 200 mg of the reaction mixture led to a mixture of both forms of MNZ:GAL cocrystal, while applying higher polarity solvents yielded stable form I of MNZ:GAL cocrystal. Use of higher weight of the reaction mixture during grinding experiments produced form II of MNZ:GAL cocrystal regardless of the polarity of the solvent used (except for milling with water which produced form I in every experiment conditions used).

As cocrystal are being considered as promising solid forms for drug development, investigation of cocrystal polymorphism and phase transformation is of growing importance in the field of crystal engineering. Here, we described selective polymorph crystallization of MNZ:GAL cocrystal. The main factors which determine crystallization outcome are the solvent polarity and the milling parameters (grinding time, the mass of the substrates to the amount of solvent ratio [4]).


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