Poster

Cocrystalline and co-amorphous systems of metformin with nonsteroidal anti-inflammatory drug meloxicam – synthesis, crystal structure and thermal properties

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Metformin is a biguanide compound for treating type II diabetes. It is assumed to be an antihyperglycemic due to lowering glucose levels in the blood, not causing hypoglycemia [1]. Recent studies showed the potential use of metformin as an analgesic agent. However, high doses needed to achieve the effect might potentiate dose-dependent gastrointestinal side effects [2-4]. Synthesis of multicomponent formulation is one avenue to overcome the issue. The synergistic mode of action in the modulation of pain mechanism was shown for a combination of metformin and curcumin [4]. Here, we present metformin systems' synthesis and physicochemical analysis with the nonsteroidal anti-inflammatory drug meloxicam.

The binary formulation of metformin and meloxicam was synthesised in the solid state by neat grinding using a ball mill or microwave and from ethanolic solution on small (20 mg) and larger scales (300 mg, Fig. 1). Microwave-assisted grinding led to the physical mixture of the substrates, while one performed in a ball mill led to the amorphous phase. The DSC analysis of the latter showed that the obtained powder has a glass transition (Tg) of about 87.8 °C. This Tg temperature differs from neat metformin and meloxicam; thus, the formulation is co-amorphous. During heating, after the vitrification process, cold crystallisation at 151.7 °C occurs. The newly raised crystalline phase was identified as cocrystals based on powder X-ray analysis. The same cocrystalline product was formed during the reaction in the solution made on a bigger scale. The ethanol was quickly removed using a vacuum evaporator during this synthesis, so the crystallisation process was rapid. Thermogravimetric analysis indicated no ethanol molecules in this formulation, and a coformer molar ratio was established to 1:1.

On the contrary, the ethanol evaporated slowly on a small scale, and the single crystals suitable for X-ray analysis were grown. The asymmetric unit of elucidated crystal structure comprises metformin, meloxicam and ethanol molecules in a 1:1:1 ratio, so the product differs from that obtained after fast crystallisation.

The details about different synthesis approaches and relations between cocrystalline phases will be presented.

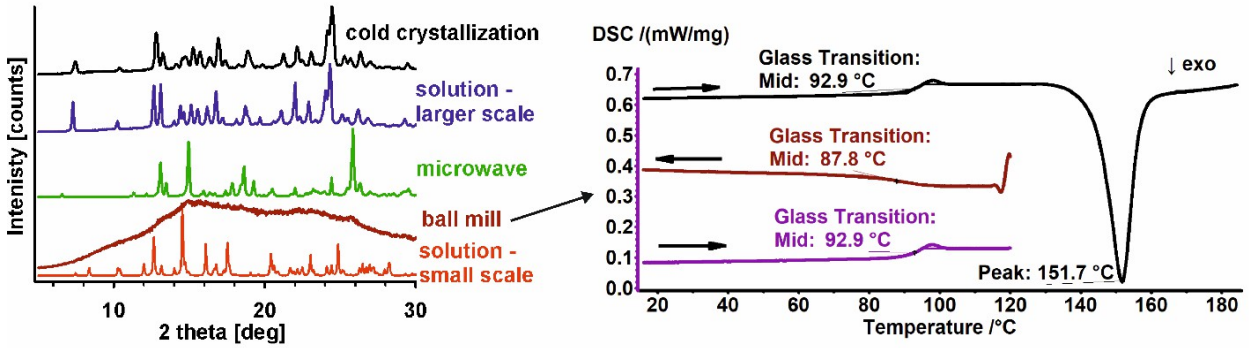

Figure 1. Powder X-ray diffraction patterns of metformin-meloxicam systems (left). DSC thermograms of heating-cooling-heating cycles (from bottom to top) of the amorphous metformin-meloxicam system (right).

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