Conference abstract PDD33

Spontaneous Formation of Theophylline–Nicotinamide Cocrystals

T. ERVASTI, J. KETOLAINEN, J. AALTONEN

School of Pharmacy, Pharmaceutical Technology, Faculty of Health Sciences, University of Eastern Finland, Kuopio Campus, Finland

E-mail: Tuomas.Ervasti@uef.fi (T. Ervasti)

Sci Pharm. 2010; 78: 622 doi:10.3797/scipharm.cespt.8.PDD33

In recent years, there has been an increasing interest in cocrystallization of active pharmaceutical ingredients. For example the physical stability can be enhanced by cocrystallizing [1]. Thus, using cocrystals as solid-state forms is an attractive alternative. Theophylline and nicotinamide are known to form cocrystals for example via solid-state grinding [2]. However, in appropriate conditions cocrystals can also form spontaneously [3].

The purpose of this work was to study whether teophylline and nicotinamide form cocrystals spontaneously. Theophylline and nicotinamide powders were gently mixed manually at 1:1 molar ratio and stored at different relative humidity conditions. The solid state of the samples was analysed by differential scanning calorimetry (DSC, Mettler Toledo DSC823) and Raman spectroscopy (Kaiser Rxn1 equipped with a PhAT probe). Three different variations of theophylline were used as starting materials, e. g., two size fractions of theophylline anhydrate (small: sieved through a 355 µm sieve; large: the fraction remaining on the sieve), and monohydrate (recrystallized from water). For reference, pure TP-NCT cocrystals were prepared by solid-state grinding with a Retsch MM400 mixer mill.

TP-NCT cocrystals can form spontaneously from manually mixed physical mixtures of TP and NCT during storage without any mechanical activation. For anhydrous samples, increasing storage humidity has an accelerating effect on the cocrystal formation. Particle size of the starting material was found to affect the cocrystal formation kinetics, especially at high relative humidity conditions. Polymorphism of the starting material (i. e. TP anhydrate vs. monohydrate) leads to complicated solid-state behavaviour during storage, particularly when TP anhydrate containing samples are stored at high humidity and vice versa.

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