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In-Situ Study of the Influence of Paracetamol on the Nucleation behaviour and Accelerated Crystal growth rates of Metastable α Glycine

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Abstract: The influence of the pharmaceutical solid paracetamol at different concentration levels on the nucleation behaviour of the glycine polymorphs is investigated by in-situ micro droplet evaporation. Paracetamol when present in the crystallizing solution over a wide range of concentrations from 0.02 to 0.19 mol% do not inhibit the nucleation of α polymorph, but their presence induces change in the morphology and the growth rate of the nucleated α crystals along both their b and c directions. Even at lower concentration levels, paracetamol cause the inhibition of growth along both the +b and –b directions of α glycine. Accelerated growth rates along both their +c and -c directions is observed leading to lengthy needle like morphology of the crystals even at lower supersaturation levels in the solution. This altered growth behaviour is attributed to the perturbing effect of the paracetamol molecules at the {010} faces along both the b directions by their bulkier side containing the benzene ring core substituted by one hydroxyl group and the nitrogen atom of an amide group in (1,4) para position. This occurs only through the favourable (gly) NH···OC (para) hydrogen bonding interactions at these faces. The nucleation of neither β nor γ was observed at any of the concentrations studied. Form of crystallization and the purity of the nucleated polymorph were confirmed by PXRD.
Keywords: Nucleation; Crystal morphology; Optical microscopy; Growth from solutions.

Introduction and Experimental

Polymorphism is a solid state phenomena due to which the material with same chemical composition packs in different conformations resulting in significant variation in their physical characteristics (1, 2). Glycine, the simplest amino acid exhibits polymorphism with three polymorphs α, β and γ at ambient conditions (3, 4). Reports exist on the influence of several tailor made additives and racemic impurities on glycine polymorphism, but so far no report exist on the influence of pharmaceutical solids on glycine. Hence the main aim of this work is to study for the first time, the influence of the pharmaceutical solid paracetamol at different concentration levels from 0.02 to 0.19 mol% on the nucleation behaviour and habit modification of glycine polymorphs by in-situ micro droplet evaporation.

The glycine solution was saturated at 308 K with different concentrations of paracetamol in a 250 ml airtight round bottom flask (RBF) and stirred at a fixed rate of 120 rpm for 2 h continuously. This setup was kept inside a digitally controlled constant temperature bath (CTB) having the temperature controlling accuracy of ±0. 01°C. Increase in solubility of glycine due to the presence of various concentrations of paracetamol is compensated by adding excess amount of glycine each time along with the additive in order to enable the system to attain the equilibrium concentration every time. Solubility and pH of glycine in presence of different concentrations of paracetamol were measured regularly. The experiments both in the absence and presence of various concentrations of paracetamol were performed at 302 K in a nucleation cell which enables the homogenization of temperature and careful monitoring was done using an Olympus SZX 16 Stereo Zoom microscope attached with a Jenoptik ProgRes CT3 digital camera system. Form of crystallization and purity of the nucleated polymorphs were confirmed by PXRD through Bruker D8 Advance powder x-ray diffractometer.

Results and discussion

In the presence of paracetamol in the concentration range from 0.02 to 0.19 mol%, the solubility of glycine in the aqueous solution at 308 K increases from 6.24 to 6.73 mol% and the pH of the resultant solution decreases from 5.25 to 4.79. The decrease in pH may be due to the presence of the acetyl group in the added paracetamol molecules. During the nucleation study, due to transferring of saturated solution from 308 K to 302 K, a relative supersaturation is generated in the solution and it increases from 0.06 to 0.16 with increasing concentrations of paracetamol. Consequently, the induction period of nucleation decreases from 210 to 54 sec. Over the entire concentration range of paracetamol in the solution corresponding to the supersaturation from σ = 0.06 – 0.16 only α nucleation was observed. The nucleation of neither β nor γ was observed at any of the concentrations studied. This clearly illustrates the dominant existence of dimers in the solution and the inefficiency of the added paracetamol molecules to act as induced charge compensators that would promote the existence of monomers through charge compensation mechanism leading to γ nucleation in the system (5, 6).

The α polymorph nucleated at different concentrations of paracetamol showed variation in the growth rates along both their b and c directions. The microscopic image of α with such varied morphology nucleated in the presence of 0.04 mol% of paracetamol is shown in Fig. 1(a). Schematic of the equilibrium morphology of α and its actual morphology with such accelerated growth rates along both their c directions are shown in Fig. 1 (b) and (c) respectively.

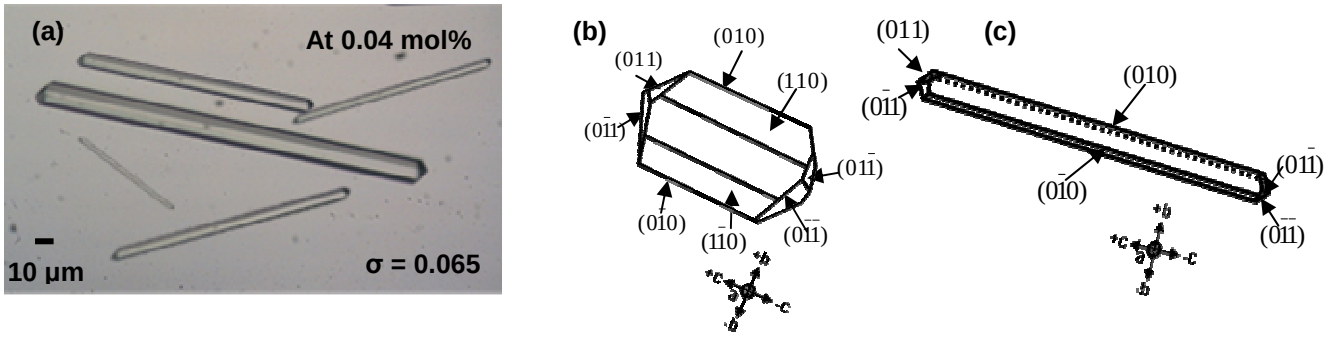

Fig. 1. (a) Microscopic image of the nucleated α with accelerated growth rate along both the c directions, schematic of α (b) equilibrium morphology and (c) actual morphology.

In α glycine, normally the {011} faces are the fast growing faces and the {010} faces are the comparatively slow growing but predominant faces. At the {011} faces, both the amino and the carboxyl groups alternately protrude due to the dimer stacking that exposes two different molecular ends at the same layer. Whereas in the case of {010} faces, only the amino groups are exposed and moreover, the molecules on the (010) face are related to each other by a 2-fold screw symmetry and are related to the molecules on the $(0\bar{1}0)$ face by a centre of inversion as shown in Fig. 2. When the paracetamol molecules are added into the solution, they strongly interact with the {010} faces rather than at the {011} faces of α glycine along both the +b and –b directions through their favourable (glycine) NH···OC (paracetamol) hydrogen bonding interactions. Moreover the bulkier side of the paracetamol molecule containing the benzene ring core substituted by one hydroxyl group and the nitrogen atom of an amide group in (1,4) para position perturbs the further addition of glycine dimers with the protruding unsaturated bonds of the stacked glycine dimers along both the {010} faces.

This in turn accelerates the growth of the {011} faces of α further along both the +c and –c directions leading to lengthy needle like morphology even at lower supersaturation levels in the solution.

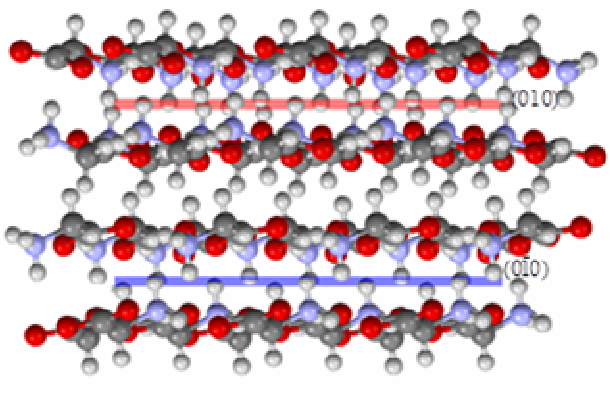

Fig. 2. Molecular packing of {010} faces of α glycine viewed along 'a' direction

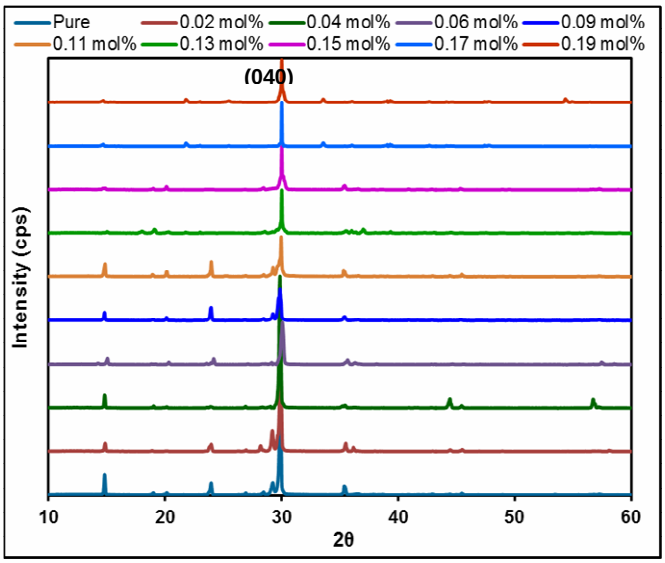

Fig. 3. PXRD patterns recorded for the polymorph nucleated at different concentrations of paracetamol

Though paracetamol is an extensively conjugated system, due to the lone pair on the hydroxyl oxygen, the benzene pi cloud, the nitrogen lone pair, the p orbital on the carbonyl carbon and the lone pair on the carbonyl oxygen, no glycine conjugation has been observed. The purity of the obtained α crystals has been proved further by their PXRD patterns as shown in Fig. 3. All peaks present in the PXRD pattern correspond to α glycine with the characteristic 2θ peak at 29.8º 2θ. No extra peaks were observed and this confirms further that the nucleated polymorphs are α form of glycine without any incorporation of paracetamol into their lattices.

References

1. Bernstein, J. Polymorphism in molecular crystals, Oxford University Press, New York, 2002. pp. 1-4.
2. Bond A. D. Polymorphism in molecular crystals, Curr. Opin. Solid State Mater. Sci. 2009, 13, 91-97.
3. Qi Jiang, Chunhua Hu, and Michael D. Ward, Stereochemical control of polymorph transitions in nanoscale reactors, J. Am. Chem. Soc. 2013, 135, 2144−2147.
4. Marsh, R. E. A refinement of the crystal structure of glycine, Acta Crystallogr. 1958, 11, 654-663.
5. K. Renuka Devi, K. Srinivasan, The role of charge compensation on the nucleation of α and γ polymorphs of glycine from aqueous solution, J. Cryst. Growth, 2013, 364, 88–94.
6. K. Renuka Devi, K. Srinivasan, A novel approach to understand the nucleation kinetics of α and γ polymorphs of glycine from aqueous solution in the presence of a selective additive through charge compensation mechanism, Cryst. Eng. Comm., 2014, 16, 707-722.

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