International Journal of ChemTech Research
CODEN (USA): IJCRGG ISSN : 0974-4290
Vol.6, No.3, pp 1630-1632, May-June 2014

ICMCT-2014 [10th – 12th March 2014]
International Conference on Materials and Characterization Techniques

Crystallization of Metastable Orthorhombic Paracetamol by Specially Designed Seeding Technique

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Abstract: Elusive metastable orthorhombic paracetamol single crystals were obtained by specially designed seeding technique from conventional slow evaporation method. Seeds were prepared at optimized conditions under different cooling rates from seed preparation unit and Powder x-ray diffraction (PXRD) was performed to ensure the polymorphic form of seeds. Saturated paracetamol solutions with three different selected polar protic water, ethanol and aprotic cyclohexanone solvents were examined with and without seeding. All the three unseeded solutions and the seeded solution of polar protic water and ethanol yielded only stable monoclinic paracetamol whereas the seeded aprotic solvent cyclohexanone yielded metastable orthorhombic paracetamol single crystals. The effect of crystallization of polymorph is mainly attributed by the efficiency of seeding, metastable zone width of desired polymorphic region and by different types of intermolecular interaction of solute-solvent through hydrogen bonding. Morphology of the grown paracetamol single crystals was studied by optical goniometry. The difference in the stretching of specific bonding of few functional groups of the paracetamol molecule when it is stacked in mono and ortho crystallographic structures is evidently noticed from recorded FTIR spectra of both the polymorphs. Polymorphic transformation from ortho to mono at 89.44 °C was confirmed by DSC analysis.
Keywords: paracetamol, nucleation, solution growth, morphology, PXRD.

Introduction and Experimental

The need to control polymorph and to ensure reproducible production of desired polymorph of the drug material is very much essential in pharmaceutical applications (1). Paracetamol, an analgesic and antipyretic drug crystallizes in three polymorphic forms monoclinic form I (stable) needs capping for tabletability, orthorhombic form II (metastable) the most wanted form in pharmaceutical industries and unstable form III. Under laboratory conditions, several methods have been tried to selectively crystallize the orthorhombic polymorph and had only limited success, difficult to control precisely and hence remain as a formidable challenge (2).

Seeding technique is one of the well-established method that has been adopted in the present work and three solvents such as polar protic water, ethanol and aprotic cyclohexanone were chosen based on the solvent polarity and hydrogen bonding characteristics. Seeds were prepared by melting the commercial paracetamol powder form I in our designed seed preparation unit. After melting, the ampoule was gradually lifted at

different translational movement using 1, 3, 15, 30, 45, 60, 120, 150 and 200 rpms. The variation in translational rate enables the melted sample to crystallize at different cooling rates. PXRD was performed for the prepared seeds A-I to ascertain their polymorphic forms.

Solutions to be crystallized were prepared with selected solvents at saturation temperature 32 °C according to the solubility by dissolving appropriate amount of paracetamol in 500 mL of water, ethanol and cyclohexanone separately. Saturated solution was filtered and equally distributed in ten crystallizing vessels totally 30 solutions for crystallization. Immediately after transferring the solution, seeds of weighed mass 14 mg with size 250 µm were selected. Among thirty crystallizing vessels, three vessels containing the solution with three different selected solvent were left unseeded and remaining solutions were seeded separately with the prepared seeds A-I. Then the vessels were covered with perforated polythene sheets and kept in controlled slow evaporation chamber. Nucleation time was monitored carefully and the nucleated small crystals were allowed for further growth for two weeks until they attained a desired size.

Results and Discussion

Crystallization under different cooling rates favours the formation of different polymorphic seeds. The designed seed preparation unit and polymorphic form of seeds confirmed by PXRD was shown in Fig. 1a and 1 b. PXRD pattern reveals that the prepared seeds A and D are the stable polymorphic seeds of monoclinic form I. The prepared seeds B, E, F, G, H and I shows the mixture of monoclinic and orthorhombic polymorphic form whereas seed C confirms the metastable orthorhombic polymorph. The experimentally grown paracetamol single crystals exhibit with different morphology with three different selected solvents from slow evaporation. The growth rate of a crystal varies probably due to the variation in the degree of supersaturation with respect to each of unseeded and seeded solution depending on the evaporation of the solvent. It was observed that in unseeded solution, all the three different selected solvents yielded monoclinic paracetamol crystals with columnar and prismatic morphology. In the case of seeded solution of water and ethanol, also exhibit similar morphology as observed in unseeded solution and the crystals obtained were confirmed by PXRD as monoclinic form I with ICDD standard files (00-039-1503 for mono).

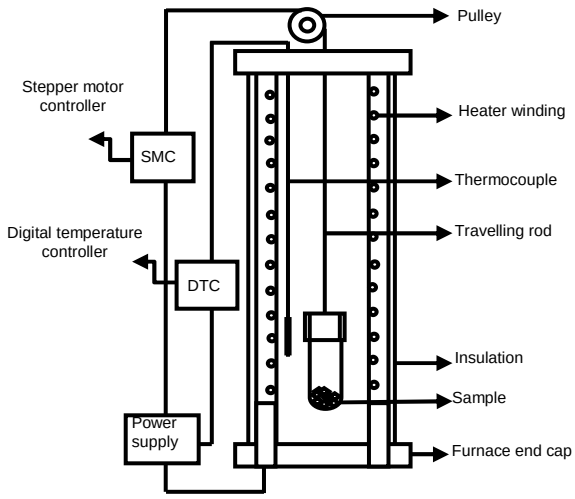

Fig. 1a. Seed preparation unit

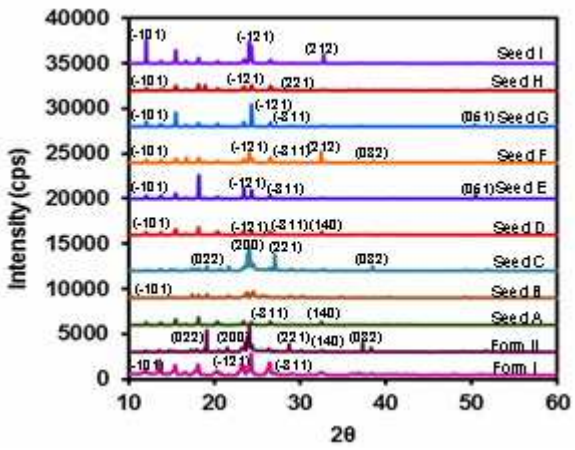

Fig. 1b. PXRD pattern of paracetamol crystals

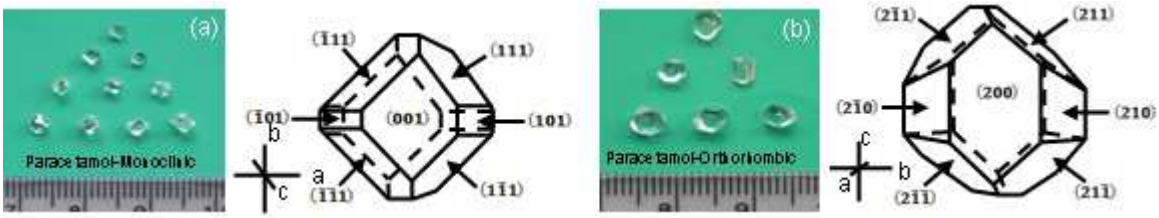

Fig. 2. Grown monoclinic and orthorhombic paracetamol single crystals in cyclohexanone with (a) seed A (b) seed C.

In the case of cyclohexanone as a solvent except the solution seeded with seed C, all other crystals grown from cyclohexanone with seeds A, B, D, E, F, G, H and I yielded prismatic morphology. It has {001} faces as the greatest morphological importance as the prominent faces comprising {110}, {101}, {011} and {111} as the smallest end faces which are monoclinic form I. The crystals obtained from the seeded solution of seed C in cyclohexanone shows a equant, squat prismatic habit of orthorhombic form II showing {211}, {200} and {210} faces as the dominant. The obtained crystals were confirmed by PXRD with ICDD standard files (00-087-9505 for ortho). Fig.2 shows the photograph of the grown monoclinic from seed A and orthorhombic paracetamol crystals from seed C and their respective morphology. The dissimilarity showed by form II from form I could be the effect of seed crystals of desired form as well as by the effect of solvent in the solution.

Generally in the presence of seeding, metastable zone width (MSZW) of the solution decreases when compared to the unseeded solution (3). As a result, seeding with the stable polymorphic seeds, the generation of supersaturation in the solution on evaporation favours the formation of stable secondary nuclei and enables the growth of stable monoclinic paracetamol crystals. It can be noted that when water and ethanol used as a solvent, seeding has no effect on the polymorph of the desired orthorhombic crystal by slow evaporation. However the solution seeded with metastable polymorphic seed C in cyclohexanone favours the necessary supersaturation for the formation of metastable orthorhombic paracetamol single crystals by slow evaporation. These results lead to the conclusion that the metastable seed C present in the solution of cyclohexanone reduces the MSZW favourable for the desired polymorph or it may acts as a substrate for the metastable secondary nuclei and accelerates the growth of metastable orthorhombic crystals. Besides seeding, it is clear that the cyclohexanone solvent has specific solute-solvent interaction effect compared to water and ethanol in polymorph formation during crystallization.

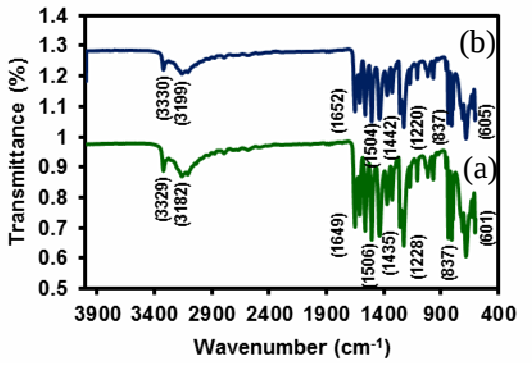

Fig. 3. FTIR spectra (a) form I (b) form II

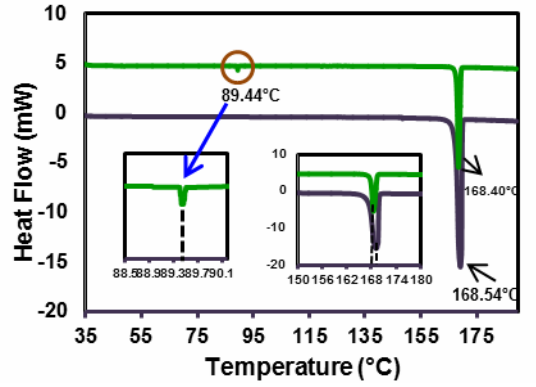

Fig. 4. DSC thermogram (a) form I (b) form II

The frequencies of the mode of vibrations attributed to the paracetamol molecules were identified for two polymorphs from the recorded FTIR spectra; a small shift in the vibrational frequency of ortho polymorph was recognized (4). DSC analysis reveals the polymorphic transformation from ortho to mono at 89.44 °C and its melting point at 168.40 °C (5).

References

1. Brittain H.G., Polymorphism in Pharmaceutical Solids, Marcel Dekker, New York, 1999.
2. Mikhailenko M.A., Growth of large single crystals of the orthorhombic paracetamol, J. Cryst. Growth., 2004, 265, 616-618.
3. Beckmann W., Seeding the desired polymorphs, Org. Process Res. Dev.,2000, 4, 372-374.
4. Moynihan H.A. O' Hare I.P., Spectroscopic characterisation of the monoclinic and orthorhombic forms of paracetamol, Int. J. Pharm. 2002, 247, 179-185.
5. Boldyreva E.V, Drebushchak V.A, Paukov I.E, Kovalevskaya Y.A, Drebushchak T.N., DSC and Adiabatic Calorimetry study of the polymorphs of paracetamol, J. Therm. Anal. Calorim. 2004, 77, 607-623.

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