ENHANCEMENT OF THE WATER SOLUBILITY AND PHOTOSTABILITY OF ACETAMINOPHEN BY CO-CRYSTAL FORMATION

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Introduction

The rapidly evolving field of pharmaceutical crystal engineering is set for a prominent position in the development and improvement of pharmaceutical products.Crystal engineering mainly relies on non-covalent bonding to achieve the organization of molecules and ions in the solid state. Because the physical properties that influence the performance of pharmaceutical solids are reasonably well appreciated, there is a unique opportunity to apply crystal engineering techniques and the appropriate follow-up studies to solve problems, such as poor physical and chemical stability or inadequate dissolution for appropriate biopharmaceutical performance of an oral drug. In this research, the aim was to enhance the water solubility and photostability of a commonly used analgesic drug, Acetaminophen (paracetamol) via co-crystal formation. Pharmaceutical co-crystals can be defined as crystalline materials comprised of an active pharmaceutical ingredient (API) and one or more unique co-crystal formers, which are solids at room temperature.

Materials and Methods

The methodology includes four major experimental steps. First evaluation of physico-chemical properties of free API: Acetaminophen and co-crystal former: Maleic acid was carried out by checking the melting points, PXRD study and solubility test. Then the selection of the suitable solvent system and molar ratio for the formation of co-crystal were determined via trial and error method and the product was obtained by slow solvent evaporation. Next, co-crystals were characterized by checking the melting point, and using TLC, PXRD, NMR, IR and UV-visible spectroscopic methods. Finally the photo-stability and water solubility of co-crystals were checked and compared with pure compounds.

Results and Discussion

Co-crystal formation and preliminary characterization

When Acetaminophen (0.0755 g) and Maleic acid (0.0580 g) (in 1:2 molar ratio) were dissolved in 5:1 solvent mixture of Acetone and Ethyl acetate (4.50 cm^3), yellow colored needle shaped crystals different from the twopure compounds (Acetaminophen – colourless elongated hexagons, Maleic acid – colourless tiny plates) were obtained. The product gave a sharp melting point which was different from pure compounds (Acetaminophen – 169-172 ^0C , Maleic acid - 131-139 ^0C, product 107-112 ^0C) and this is a first-rate indication for changes in supramolecular level arrangements and intermolecular interactions.TLC

analysis confirmed that the newly formed crystals consist only of pure compounds and there are no by-products.

Secondary investigations for co-crystal

When considering Powder X-Ray Diffraction (PXRD) patterns, it was found that the diffraction patterns of co-crystal differ from those of two pure compounds. This reflects the formation of a new crystal lattice different from both parent lattices and that may be due to the assembly of API and co-crystal formation via intermolecular interactions. In addition to that, solid state IR absorbance spectroscopy of the co-crystal exhibited a broad absorbance peak in the range of 1700-1900 cm^{-1} which is a characteristic of H-bonding in co-crystals (Blagden *et al.*, 2007). Furthermore ^{1}H NMR, ^{13}C NMR and UV visible spectroscopy confirmed the presence of pure API and co-crystal former with no by-products in the co-crystals.

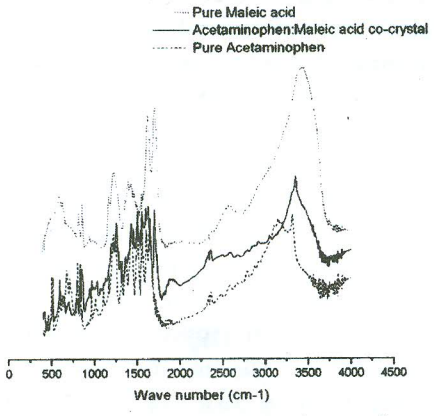

Figure 1. FT-IR comparison of pure Acetaminophen, Pure Maleic acid and the co-crystal

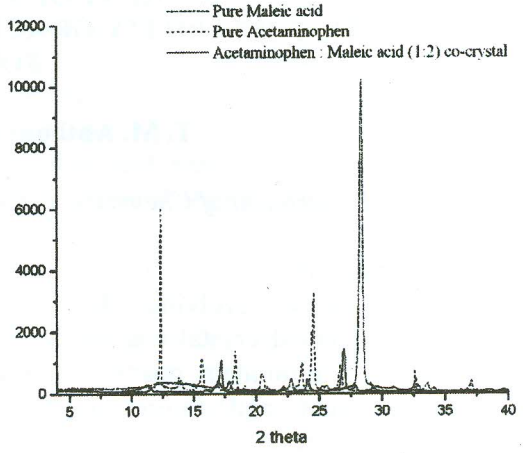

Figure 2. PXRD comparison of pure Acetaminophen, Pure Maleic acid and the co-crystal

Water solubility and photo-stability of the co-crystal

Table 1. Solubility comparison of pure compounds and co-crystal

Compound	Average Solubility / 10^3 $g^{-1}cm^3$
Acetaminophen	7.402
Maleic acid	40.00
Co-crystal	13.33

The solubility test result shows that at ambient temperature, the co-crystal shows greater water solubility than that of pure API. Moreover when the co-crystal was irradiated with UV radiation of wavelength 350 nm (Current = 8.6 mA) the PXRD pattern of the co-crystal has shown a significant change in intensities of peaks with 2θ values 26.918, 24.140 and 17.226 (percent conversion of 37.76 %, 33.75 % and 18.70 % respectively). However, when considering pure Acetaminophen,

peaks with 2θ values 24.251, 16.582 and 26.403 gave a percent conversion of 112.59 %, 80.59 % and 42.77 % respectively, which was a far greater difference than the co-crystal.

Conclusion

There by, Acetaminophen: Maleic acid (molar ratio 1:2) in solvent system acetone: ethyl acetate (5:1) forms a co-crystal by slow solvent evaporation. Furthermore it shows a greater water solubility and solid state photo-stability than pure Acetaminophen.

Reference

Blagden N., de Matas M., Gavan P.T, York P. (2007) Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Advance Drug Delivery Review, 59: 617–630.