MPD for the cocrystal of Citric acid and Paracetamol

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Abstract

Cocrystals are important in pharmaceutical development as they enhance drug properties, such as stability and dissolution rate, without altering chemical structure. This study investigates the cocrystal of paracetamol and citric acid, which form through hydrogen bonding. The resulting cocrystal may improve paracetamol bioavailability, a common analgesic. Prior to this research, the melting point phase diagram (MPD) of this cocrystal was previously unknown. Various concentrations of the cocrystal were synthesized, and a heating device was used to establish the MPD. This research presents the MPD, defining the cocrystal's composition and optimal molar ratio.

Introduction

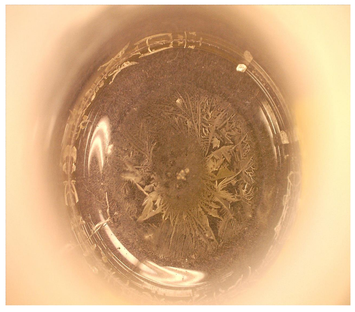
Cocrystals are gaining significant attention in pharmaceutical research for their potential to enhance drug delivery systems. By forming cocrystals, scientists can improve the properties of active pharmaceutical ingredients (APIs), such as stability and solubility, without altering their chemical structure. The synthesis of pharmaceutical cocrystals typically involves combining selected compounds in a suitable solvent, followed by techniques such as slow evaporation or grinding. A key advancement in this field was made by M. A. Elbagerma *et al.*, who identified the cocrystal and its pharmaceutical relevance between citric acid and paracetamol [1].

In this study, a cocrystal of citric acid (CIT) and paracetamol (PA) was synthesized in a 2:1 molar ratio of paracetamol to citric acid in methanol. A critical yet underexplored aspect of cocrystal research is the development and analysis of the melting point phase diagram (MPD). MPDs are crucial as they define the conditions under which cocrystals form and the optimal molar ratios for their formation. Understanding the MPD and behavior of the CIT-PA cocrystal is vital for advancing analgesic development. The aim of this research is to determine the MPD of the CIT-PA cocrystal and establish its optimal molar ratio.

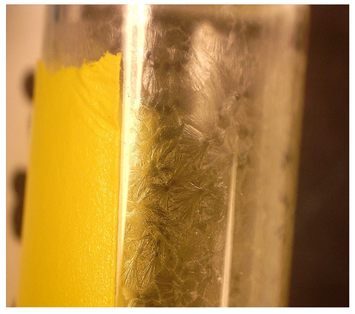
Methods

- Stock solutions of citric acid (CIT) and paracetamol (PA) were prepared by calculating molarities and dissolving the required masses in 5 mL methanol.
- Eleven vials with varying CIT:PA molar ratios (from 100:0 to 0:100) were created by adding precise amounts of each solution, followed by crystallization under a fume hood.
- Crystals were analyzed using a melting point apparatus, and the data were used to generate a Melting Point Phase Diagram (MPD) to determine optimal cocrystal ratios.

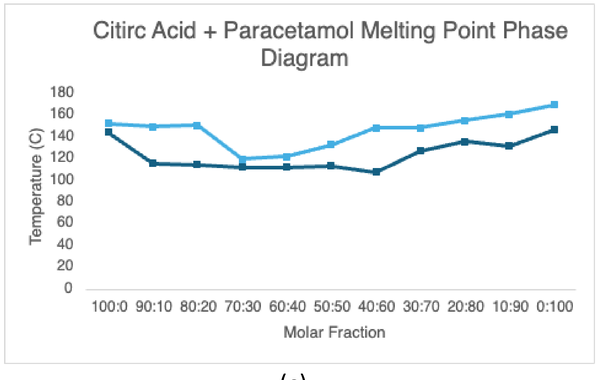
Figures



(a)



(b)



(c)

(a) - 0:100 Citric Acid vial (top)
(b) - 20:80 Citric Acid vial (side)
(c) - MPD of results (obtained by MP apparatus)

Discussion

Molar weights of paracetamol and citric acid were determined, and based on these calculations, eleven vials of specific molar ratios of citric acid (CIT) and paracetamol (PA), ranging from 100:0 to 0:100, were prepared. After the preparation of these mixtures, the vials were left standing so that solvent evaporation could occur and crystallization would be favored. Following this process, crystal fragments were collected carefully, and the melting points of all samples were established. These results of the melting point measurements were subsequently used to construct a Melting Point Diagram (MPD), which provided valuable information regarding co-crystal formation. This diagram effectively defined the range of temperature in which the co-crystals were observable.

Results

- Eleven vials with varying molar ratios of citric acid (CIT) to paracetamol (PA), ranging from 100:0 to 0:100, were prepared.
- After evaporation, crystals were observed, with distinct patterns across several different molar ratios
- MP measurements indicated the variation with changes in the CIT:PA ratio
- The MPD (Figure C) illustrates the temperature range at which co-crystals form, highlighting the molar ratios conducive to co-crystal formation

References

M. A. Elbagerma, H. G. M. Edwards, T. Munshi, and I. J. Scowen. *Identification of a new cocrystal of citric acid and paracetamol of pharmaceutical relevance. 2010, 1-9.*

Anisha Chettri, Ankita Subba, Govind P. Singh, and Partha Pratim Bag. *Pharmaceutical co-crystals: A green way to enhance drug stability and solubility for improved therapeutic efficacy. 2023, 1-4.*