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PXRD Structure Analysis of Polymorphic Transformation of Metoclopramide Crystals

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1 Introduction

Active pharmaceutical ingredients (APIs) often exist in various crystalline forms such as polymorph, hydrates, and solvates. Understanding these crystalline forms are very important because they commonly have different physicochemical properties such as stability, compaction properties, solubility, dissolution rate, and therefore bioavailability. Furthermore, transformations between different crystalline forms may occur during drug manufacturing process or during storage of the final dosage form. Hence, characterization of the structural features of each crystal form, their thermodynamic relationship and physicochemical properties is essential for pharmaceutical industry.

Single crystal X-ray diffraction is the most powerful technique to reveal the structural properties in order to understand the mechanistic aspect of polymorphic transformation. However, in many cases, single crystals of the parent compound tend to lose their integrity during solid-solid transformations, yielding a polycrystalline product. Techniques to determine the crystal structure directly from powder X-ray diffraction data have been developed for organic materials in the last decades. These techniques have been proved to be useful for establishing the mechanism of polymorphic transformation.

Metoclopramide (MCP) is a substituted benzamide medication mostly used for treatment of nausea and vomiting, gastroparesis, and gastroesophageal reflux disease. MCP undergo transformation from the stable form I into the metastable form II by heating. Crystal structure of form I of MCP has been reported. [1] In our present work, we determined the crystal structure of form II of MCP from high-resolution powder x-ray diffraction data to understand the transformation process of MCP.

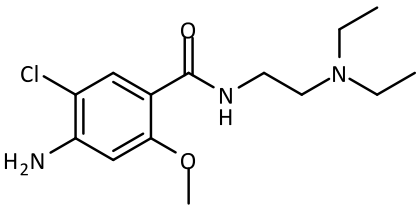

Fig. 1: Chemical Structure of Metoclopramide.

2 Experiment

Powder x-ray diffraction data of MCP form II were recorded under ambient condition at Photon Factory BL-4B2 multiple detector system (MDS) diffractometer (λ=1.197459(11) Å). Form II sample was prepared by heating the powder crystals of form I and packed into 2 mm diameter borosilicate glass capillary tube. The data collection time was ~2h. The PXRD pattern of MCP form II was indexed using X-Cell in Materials Studio 7.0 (BIOVIA) and the space group was determined by DICVOL06 in DASH package followed by the structure solution. Rietveld refinement was performed in GSAS.

3 Results and Discussion

The profile fitting after final Rietveld refinement is shown in Figure 2.

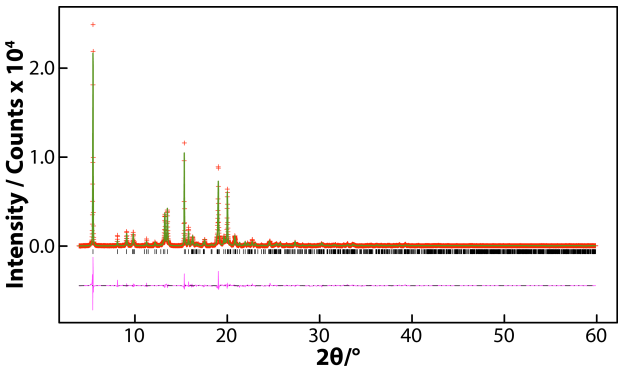

Fig. 2: Profile fit of powder pattern after final Rietveld refinement of form II of MCP.

The final Rietveld refinement gave the following parameters: a=25.5766(11) Å, b=8.91631(19) Å, c=14.4337(3) Å, β=104.392(3)°, V=3188.3(2) Å^3, $C2/c$, Z=8, and R_{wp}=0.0924.

From the crystal structure, form II of MCP has identical hydrogen bond chain with those observed in form I leading to a similar packing arrangement along b-axis. These similar crystal packing is responsible for the ease of the transformation of form II to the more stable form I in ambient condition.

References

[1] M. Cesario *et al.*, *Eur. J. Med. Chem.* **16**, 13 (1981).

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