# PREDICTION OF MECHANICAL PROPERTIES OF COCRYSTAL KETOCONAZOLE WITH ADIPIC ACID

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## ABSTRACT

Most pharmaceutical dosage form contain pharmaceutical active ingredients (APIs) in the form of crystals. In the process of drug development, one of the early decisions that should be made is to determine which form or Polymorph crystals to be used. Deformation characteristics of APIs determines the success of pharmaceutical preparations production processes including tabletation, if the BAF is elastic so the resulting tablets will experience capping or lamination. This study aims to predict the mechanical characteristics of API with analyzing crystals by using a software Mercury 3.3. Ketoconazole (KTZ) and cocrystal ketoconazole with adipic acid (KTZ-AD) is used as a model and obtained from crystallography Open Database, then performed an analysis of crystal packing motifs, three-dimensional hydrogen bonding and simulate X-ray diffraction pattern for a single crystal ray powder. Based on the analysis, KTZ have a three-dimensional pattern of hydrogen bonds so that the crystal packing does not have a sliding plane (slip plane) which causes the PCT form I have a poor plasticity properties. In cocrystal KTZ-AD can be seen that the hydrogen bonds in the crystal packing has a flat 2-dimensional pattern. This pattern causes the crystal from cocrystal KTZ-AD is to occur plastic deformation.

**Keywords**: compressibility, deformation, crystal packing

## INTRODUCTION

Most pharmaceutical dosage form contain pharmaceutical active ingredients (APIs) in the form of crystals. In the drug developmentprocess, one of the early decisions that should be made is to determine which form or polymorphto be used. The physical properties of each polymorphs can affect the quality, safety and efficacy of the drug (Aher, 2013).

Crystal structure and morphology of APIs play an important role in determining the physical and mechanical properties of pharmaceutical powders, and hence determine the processing and production behaviour (Carstensen, 2001).

There are several reports showing significant differences in the properties of the material in the same crystal form obtained by different processing conditions or technique. For example, phenytoin crystals when obtained form same solvent but different crystallization condition, behaved differently during compaction (Chattoraj, 2010).

Plasticity is the ability of material to undergo permanent, irreversible deformation upon application stress, and is one of the most critical material properties that directly influence powder tabletability. In this work, we have examined the relationship between crystal structure and crystal plasticity of pure KTZ and cocrystal KTZ-AD P usingMercury software (trial version 3.3).

## MATERIAL AND METHODS

The crystal structure data for KTZ and KTZ-AD were acquired from Crystallographic Open Data Base (COD). Mercury (trial version 3.3) (CCDC, Cambridge, UK) was used to display the crystal packing motifs, to certain the hydrogen bonding dimensionalities, and to generate simulated powder X-Ray diffraction patterns. The crystal slip plane was identified by direct visualization. The direction of slip were computed from Miller indices (h k l) of the identified slip plane.

## RESULT AND DISCUSSION

PCT form I and II were used as a model to analyze the nature of compaction. Crystal structure obtained from Crystallography Open Database (COD). Mercury software (trial version 3.3) (CCDC, Cambridge, UK) was used to display crystal packing motif, to analyze the hydrogen bonding dimensionalities, and to generate simulated powder

X-ray diffraction patterns for form I and II using the single crystal structure data acquired from COD (Carstensen, 2001).

Fig.1 shows the difference between crystal packing KTZ and KTZ-AD. KTZ contains 2 molecules in one packing crystal, whereas KTZ-AD, contains 8 molecules in one packing crystal, 2 molecule KTZ and 2 molecule AD. Table. 1 shows crystallography data for each forms.

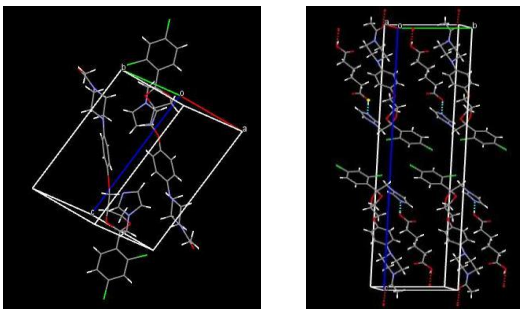

**Fig. 1** Crystal structures of KTZ (a) and KTZ-AD (b)

**Tab. 1.** Crystallographic Data of KTZ and KTZ-AD

| Parameter | KTZ | KTZ-AD |
|---|---|---|
| Crystal system | Triclinic | Triclinic |
| Space Group | P 1 | P -1 |
| a/ Å | 10.3740 | 5.8721 |
| b/ Å | 10.8633 | 8.3797 |
| c/ Å | 13.2251 | 34.4919 |
| α/$^0$ | 67.725 | 92.623 |
| β/$^0$ | 79.262 | 93.859 |
| γ/$^0$ | 65.743 | 103.791 |
| V/ Å$^3$ | 1256.6 | 1641.21 |

Simulated x-ray diffraction pattern of PCT single crystal obtained from Mercury (trial v.3.3) software can be used to differentiate each PCT polymorph. In Fig. 2.we can see a clear distinction between the PCT forms I and II diffraction patterns.Thus confirms both form crystallized in different crystal packing (different internal structure).

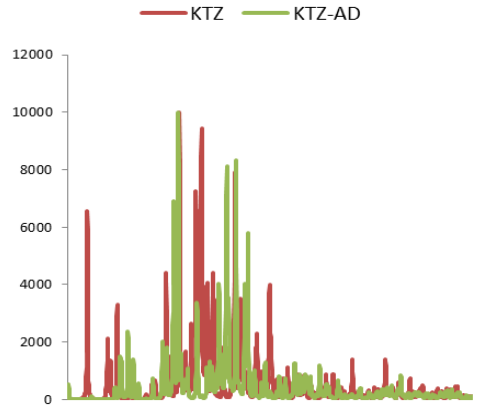


**Fig. 2** PXRD pattern of KTZ and KTZ-AD

Based on Fig. 3 it can be seen that the crystal packing on KTZ have hydrogen bonding pattern in all axis directions a, b and c, or referred to 3-dimensional pattern of hydrogen bonds. Such a network makes this crystal extremely difficult to deform plastically, this is due to the absence of sliding fields (the slip plane) in the crystal packing (Gilmore, 2011). In fact, the existence of such a hydrogen bonded network in KTZ crystal was predicted on the basis of its poor compressibility.

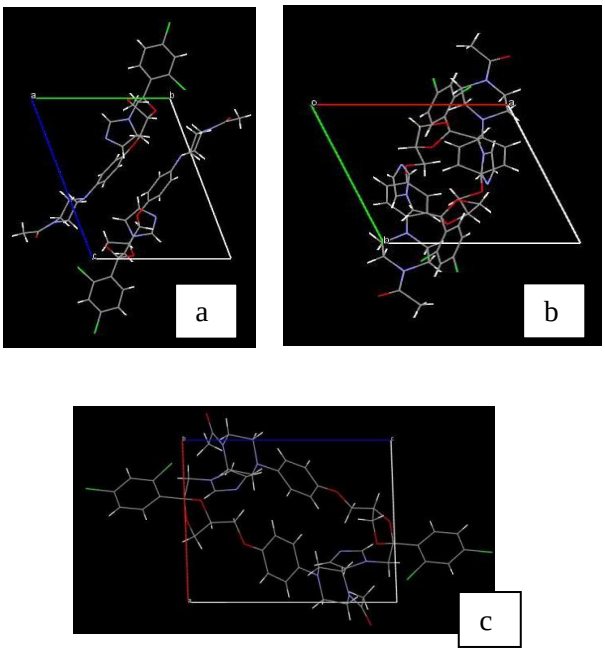


**Fig. 3** KTZ crystal, view along axis a (a), view along axis b (b), and view along axis c (c)

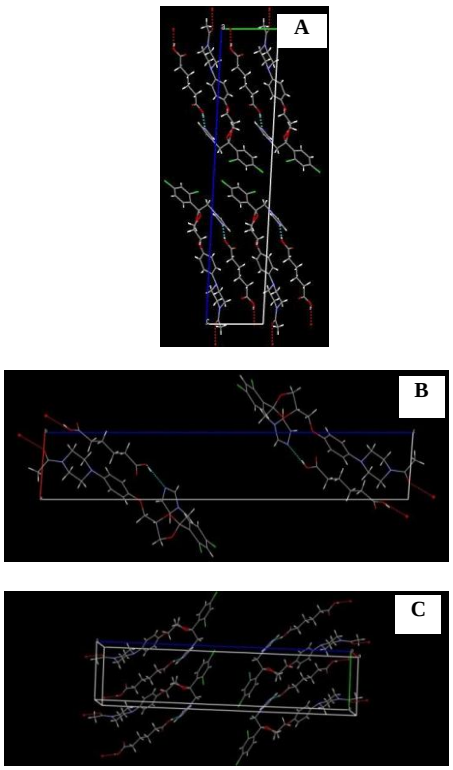


**Fig. 4.** KTZ-AD crystal, view along axis a (a), view along axis b (b), and view along axis c (c)

The hydrogen bonding pattern PCT form II occurred in 2 axis direction a and c (flat-pattern hydrogen bonds). Such a pattern found in graphite crystal, which can increase plastic deformation between crystal plane (Gilmore, 2011). Based on direct visualization of the crystal packing (Fig. 5), the slip plane in the crystal packing of PCT form II was identified as (0 2 0).

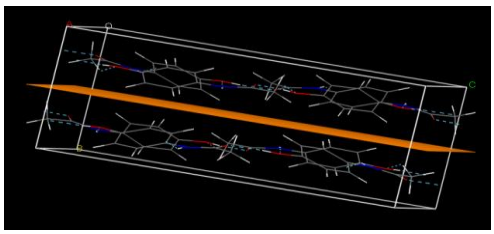

**Fig. 5** KTZ-AD crystal, showing predicted slip plane

## CONCLUSION

Based on the analysis, KTZ have a three-dimensional pattern of hydrogen bonds so that the crystal packing does not have a sliding plane (slip plane) which causes the PCT form I have a poor plasticity properties. In cocrystal KTZ-AD can be seen that the hydrogen bonds in the crystal packing has a flat 2-dimensional pattern. This pattern causes the crystal from cocrystal KTZ-AD is to occur plastic deformation.

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