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Original Article

Role of Weak Intermolecular Interaction in Plastic bending Behavior of Flufenamic Acid Polymorph

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Abstract: In recent times, the study of flexible crystals gaining considerable attention from crystal engineers. In this work, the plastic bending of flufenamic acid polymorph has been identified, and the mechanism of plastic bending is explored. Plastic bending is correlated with the presence of a slip plane in the crystal lattice andof different intermolecular interactions present in the crystal using analyzed by Hirshfeld surfaces.

Keywords: Plastic bending; polymorph; Hirshfeld surfaces; Flufenamic acid

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1. Introduction

It is a common perception that crystals of organic compounds are brittle.[1-4] However, in recent times, the perception is changed because of the discovery of plastic and elastic crystals.[1-2] The differentiation of organic elastic and bending crystals are elastic or plastic, describe based on the primary macroscopic behavior of the crystal. The bendable crystals are commonly designated in two categories, *i.e.* elastic crystals, which restore their original shape upon removing the external stimuli, and plastic bend crystals, which shows bending upon applying external stimuli and attain permanent deformation as the stimulus has been removed. For instance, copper(II) acetylacetonate [$Cu(acac)_2$] crystals shows elastic bending.[4] Prediction of bending behavior of crystals is not easy and there are no general rules for such kind of prediction. The elastic bending behavior of caffeine and 4-chloro-3-nitrobenzoic acid cocrystal was described based on the weak interlocking interactions between 2D sheets of molecules and dispersive interactions in three mutually orthogonal directions.[3] In another case, the elastic behavior of 4-bromo-3-chlorophenol was rationalized by the hydrogen bonding and halogen bonding in its crystal packing.[5] Polymorphism is the capability of a molecule to be in more than one crystalline form is an important property of crystalline material.[6-8] Different polymorphs of the same drug molecule can show entirely different properties like solubility, dissolution rate, stability,

hygroscopicity, tablability etc., properties that are crucial in final drug product development.[6, 9-10] Herein, we reported the plastic crystal of polymorphic form **III** of the anti-inflammatory drug, flufenamic acid (FA, Figure. 1). Several polymorphic forms of as well as multi-component crystalline forms of FA are reported elsewhere. In this work, the mechanism of bending of FA polymorphic form is explored.

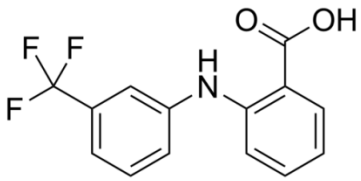

Figure 1: Molecular structure of drug flufenamic acid (FA).

2. Materials and methods

Flufenamic acid (> 99%) was obtained from TCI. Ltd. All solvents were purchased from Merck. All chemicals were used without further purification. Single crystal of polymorph form **I** and **III** of FA was obtained by slow evaporation from dichloromethane and nitromethane respectively. FT-IR spectra of the obtained polymorphic form were recorded in the frequency range of 600–4000 cm^{-1} in a PerkinElmer Spectrum 100 ATR instrument. Powder diffraction patterns were recorded on a PANalytical Empyrean diffractometer using Cu K_α radiation (λ = 1.54 Å), tube voltage of 40 kV, and 40 mA current. The 2D fingerprint plot with unique colors generated from the Hirshfeld provides a 'fingerprint' of the different intermolecular interactions in the crystal and provides an understanding of various interactions. The analysis was carried out using the software Crystal Explorer 3.0.

3. Results and discussion

FA has nine reported polymorphic forms and many multi-component systems of it are also reported. Careful analysis of FA form **III** crystal structure shows that FA molecules interact through strong carboxylic acid homosynton formation (see Figure 2). C–H··π interactions and aromatic stacking also help to expand the dimer along the b axis. However, the interaction between the dimer columns are weak and a slip plane can observe parallel along the a-axis. The $–CF_3$ groups are participating through C–F···H interaction. It has been reported that the presence of a slip plan in the crystal could aid plastic bending. Based on the crystal packing of it is predicted that the form III crystal will show bending (see Figure 3).

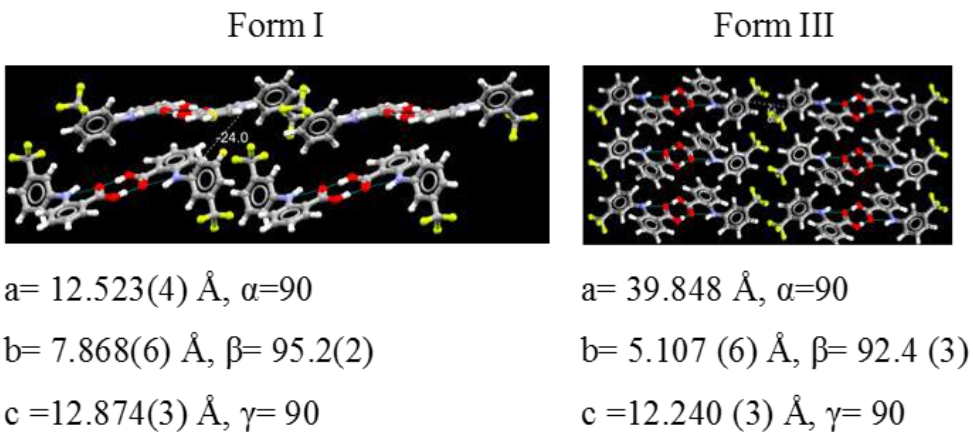

Figure 2. Acid···acid heterosynthon via O–H···O hydrogen bonds in the crystal structure of form **I** and form **III**, layered structure guided by weak C–H···π interaction in form **I**. A slip-plan along **c**-axis is prevalent in form **III**.

As predicted, in the case of FA form **III** crystal because of the presence of the slip plan, the crystal bending behavior is observed. Moreover, a face indexing experiment (see Figure 4) of polymorph **III** crystal also confirms the bending behavior of it along the a–axis. Form **I** does not show bending behavior as the slip plane is absent in its crystal packing (see Figure 2).

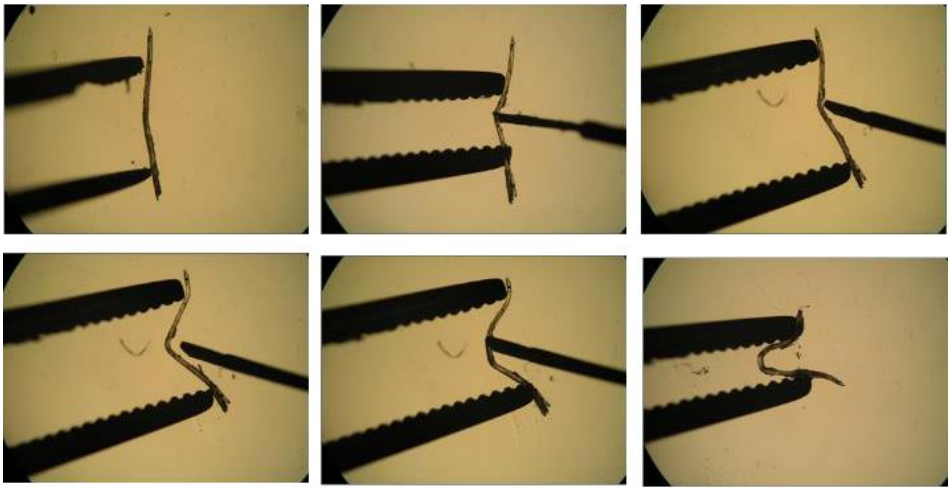

Figure 3: Microscopic images (scale bar 200 μm) demonstrate the plastic bending of polymorph **III** crystals of FA.

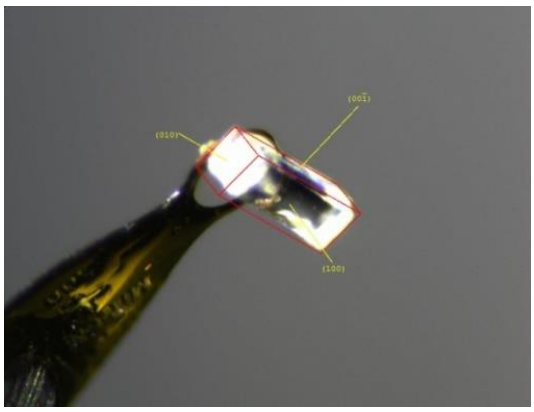

Figure 4: Face indexing of polymorph **III** crystal.

Furthermore, the crystal structures of forms **I** and **III** were considered for quantitative analysis of different intermolecular interactions present in the crystal using Hirshfeld surfaces. The 2D fingerprint plots resulting from the Hirshfeld surfaces, are unique for each polymorph and presented in Figure 5.

The contribution of the O···H and F···H interaction in Form **I** (14.7 % and 26.2% respectively) in comparison with form **III** (12.3 % and 18.0 % respectively) suggests a lower degree of interactions within the crystal of form **III**. The higher contribution of O···H and F···H interactions in form **I** suggests a better interaction property and thus this crystal is more compact. Thus, brittle nature for form **I** can be anticipated. Differences in bonding contribution in crystal structures ensured the mechanical behavior of the crystal.

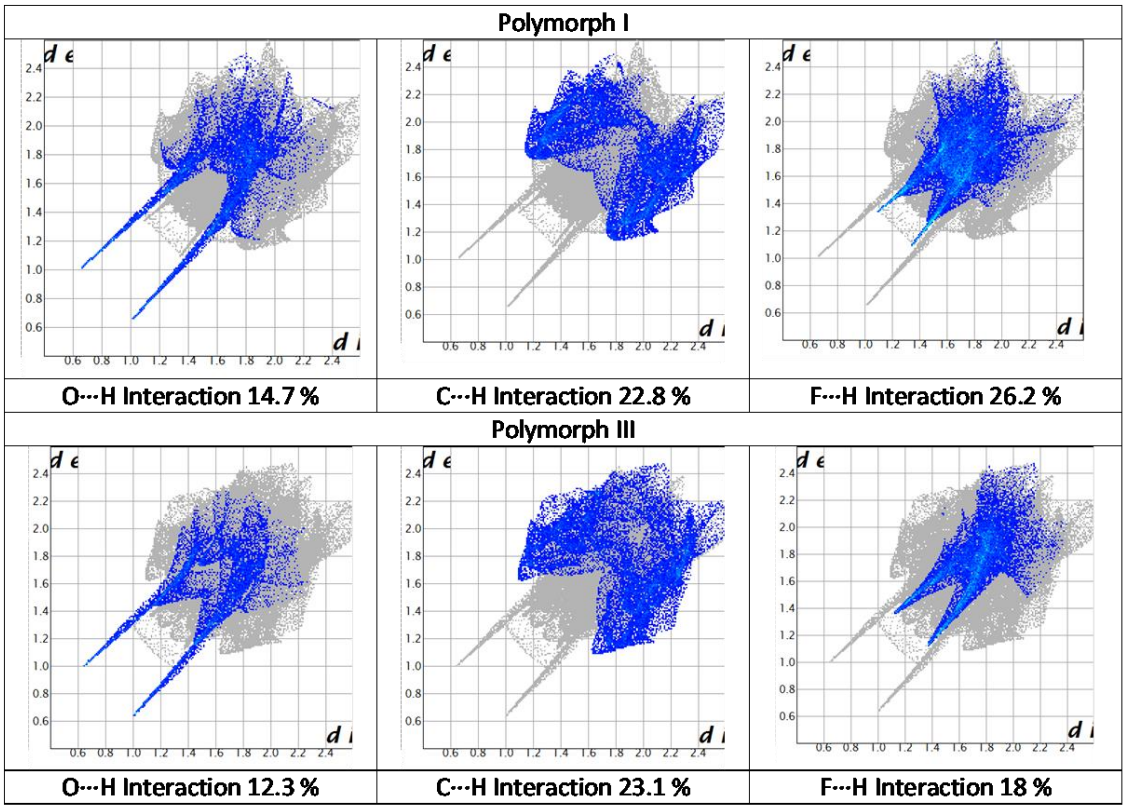

Figure 5. Hirshfeld surfaces show high F···H interaction contributions in polymorph **I** compared to polymorph **III** leading to brittle behaviour.

4. Conclusion

Different polymorphic forms of the same molecule can have different mechanical property and in this work, we have demonstrated it with an example of the flufenamic acid system. In summary, we report the crystal bending behavior of flufenamic acid polymorphs. The crystal structures analysis suggests that the crystal packing and presence of different weak interaction plays a major role in the bending behavior. The presence of slip plan and lower contribution of the C–F···H interaction is dominant to the elastic bending process. This work paves the way for the prediction of mechanical properties of crystalline materials based on crystal packing.

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