

## SINGLE CRYSTAL STUDIES OF MEFENAMIC ACID AS A TOOL TO UNDERSTAND POLYMORPHISM

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Mefenamic acid (MA) is a high dose anti-inflammatory drug, which poses bioavailability and processing problems. The drug is reported to exhibit polymorphism and two polymorphs have been reported (Form I and Form II). The present work is a pioneer attempt to understand packing arrangement of mefenamic acid in unit cell and appreciate polymorphism by single crystal XRD studies.

Single crystal was isolated from tetrahydrofuran by vapor diffusion technique, using acetone as a second solvent. The Mo K<sub>α</sub> radiation was utilized for single crystal studies.

MA single crystal data revealed that the drug exhibited both intra and inter molecular hydrogen bonding, the suspected reason behind its ability to form polymorphs. Molecule shows presence of intra molecular hydrogen bonding as the carbonyl oxygen and the hydrogen of –NH are in proximity (H1N ...O2 =1.935 Å), being able to interact and form hydrogen bond. Similarly in intermolecular hydrogen bonding, carbonyl oxygen of one molecule interacted with, hydrogen of the carbonyl -OH of the other molecule (O1-H1O...O2 =177.29 Å and H1O...O2 =1.700 Å). The ORTEP structural elucidation was created to illustrate the molecule in three dimensions. The data was supplemented by a molecular modeling study, using AM1 (Austin Model 1; a semi-empirical quantum chemical method based on Schrodinger equation) that depicted a possibility of two polymorphs of minimal energy. However, there is one structure that has global energy minima, which can be assumed to be Form I, the most stable form of MA. The modeling studies also predicted a possible dimerization of the molecule and expected tautomeric barrier is supposed to be 36.98 k cal/mol.

Contrary to solid-state pharmaceutics that depends on all techniques in concert, single crystal XRD as a lone technique is certainly useful to understand the dimensions and packing arrangements of the molecules in unit cell. Different arrangements and the appearance of hydrophobic groups on the outward side may be responsible for polymorphism, cohesivity and poor flow properties of the drug.