

INVESTIGATING THE ROLE OF MOLECULAR INTERACTIONS IN POLYMORPHISM OF MEFENAMIC ACID IN ETHYL ACETATE SOLUTION

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Abstract

Mefenamic acid, a widely used nonsteroidal anti-inflammatory and analgesic agent, is one of the active pharmaceutical ingredients that exhibit polymorphisms. This study reports a combined experimental and molecular dynamics simulation study of mefenamic acid crystallisation in ethyl acetate. The solid-state characterization of the polymorph produced using Fourier transform infrared spectroscopy (FTIR), X-Ray powder diffractometer (XPRD), and differential scanning calorimetry (DSC) analysis show the characteristic of Form I. The molecular dynamics simulation was performed using COMPASS force field available in the Material Studio 5.5 simulation package. The simulation was run with a time step of 1 fs for a period of 250 ps and 2000 ps simulation in NVE (constant number of atoms, volume and energy) and NPT (constant number of atoms, pressure and temperature) thermodynamic ensemble, respectively for equilibration. The trajectory files from the simulation were analysed for radial distribution function (RDF) to investigate the intermolecular interactions or specifically hydrogen bonding formation between the molecules. The result of the simulation showed strong solute-solute and solute-solvent interactions, which is O1MA•••H15MA and O1EA•••H15MA. These findings revealed the presence of hydrogen bonds that contributes to the solvation and formation of hydrogen motif in polymorphic Form I of mefenamic acid during crystallisation process with ethyl acetate as a solvent.

Keywords: Crystallisation, COMPASS, Hydrogen bonding, Molecular dynamics simulation.

1. Introduction

Polymorphism is a widespread issue observed in the crystallization of active pharmaceutical ingredients (APIs). Polymorphism is defined as the ability of solid materials exists in multiple crystallines forms due to the different molecules arrangements or conformations [1]. In 2014, about 700000 of crystals that exhibit polymorphisms have been deposited in the Crystallographic Cambridge Data Base. This number shows a tremendous increment in comparison with only 250000 crystal structures in 2012 [2]. Polymorphs of a substance are known to show different physicochemical properties such as different melting point, density, morphology, and solubility [3]. Other than that, polymorphs also show significant impact on the product efficacy, stability, bioavailability, and processability during the manufacturing process [4, 5].

Mefenamic acid [2-(2, 3-dimethylphenyl)amino benzoic acid] a widely used nonsteroidal anti-inflammatory and analgesic agent exists in three polymorphic forms namely Form I, Form II, and Form III [6-8]. The mefenamic acid Form I is relatively more stable than Form II and Form III. The solid state transformation of Form, I to Form II or Form III, may occur at a temperature of 160 to 190°C depending