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

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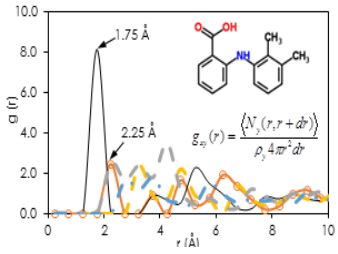
Graphical abstract



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 crystallization 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, which were N-H stretching at 3313cm^{-1}, two endothermic peaks, and significant XPRD peaks at 6.3°, 13.8°, 15.9°, 21.3°, and 26.3°. The molecular dynamics simulations were performed using COMPASS force field available in the Material Studio 5.5 simulation package. The simulations were run for equilibration 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. The trajectory files from the simulation were analyzed for radial distribution function (RDF) to investigate the intermolecular interactions. The simulation results showed strong solute-solute and solute-solvent interactions, which were 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 crystallization with ethyl acetate as a solvent.

Keywords: Crystallization, COMPASS, hydrogen bonding, molecular dynamics simulation, mefenamic acid

1.0 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 on the heating rate employed [9]. The polymorphic Form I and Form II of mefenamic acid are obtained from the crystallization using ethanol or ethyl acetate, and N, N-dimethyl formamide, respectively as a solvent [7, 8]. Meanwhile, the Form III of mefenamic acid is obtained through co-crystal experiments with edinine in N, N-dimethyl formamide/ methanol mixture [6]. The recent works on mefenamic acid are focusing on the production of various mefenamic acid polymorphs and solid-state characterizations [6, 10]. To our knowledge, the mechanisms i.e. molecular interactions that leads to the formation of different polymorphs of mefenamic acid is yet to be reported. These mechanisms can be investigated using computational method namely molecular dynamics simulation [11].

In this work, the crystallization of mefenamic acid using ethyl acetate as a solvent was investigated. A comprehensive characterization of crystals produced was performed using optical microscopy, differential scanning calorimetry, thermal gravimetry, infrared spectroscopy and X-ray diffraction. In addition, a molecular dynamics simulation was performed to understand the solute-solute, solute-solvent and solvent-solvent interactions that control the self-assembly of mefenamic acid molecules in ethyl acetate that consequently leads to the formation of a particular polymorph.

2.0 METHODOLOGY

2.1 Material

The mefenamic acid powder (98% pure, Baoji Tianxin Pharmaceutical Co. Ltd., China) and ethyl acetate (99.5 wt% purity, Fischer Scientific) were used without further purification.

2.2 Preparation of Mefenamic Acid Crystals

A conical flask, consist of 1.59 g of mefenamic acid and 50 mL of ethyl acetate was heated on a hot plate to 60°C until dissolution. The solution was left to cool to room temperature by natural cooling [8]. The amount of mefenamic acid used was obtained from the literature [12]. The crystals produced were filtered and dried in an oven at 50°C. The crystals were periodically dried and weighed until a constant weight was achieved. The dried crystals were stored in a screw cap glass vials for further characterization works.

2.3 Characterization Methods

The optical microscope Leica DM750 with a total magnification of 200x4x/0.10 was used to capture the crystals images. The images were processed using Leica Application Suite Software version 3.6. The melting point analysis of crystals was examined using a Mettler Toledo DSC-1. About 2-10 mg of sample was weighed into a 40 µL standards aluminium pan with a lid and sealed hermetically. The analysis was performed by heating the sample from 25 to 300°C at a heating rate of 10°C/min under constant purging of nitrogen. An empty aluminium pan was used as a reference in all the runs. The results obtained were analysed using Mettler Toledo Stare SW 9.10.

The changes of crystals' weights were examined using TA Instruments (Q500/50). The crystals with a weight range of 4-6 mg were placed in a platinum pan and heated from 25 to 300°C at a constant heating rate of 10 °C/ min. The results obtained were analysed using Thermo-gravimetric Analyzer (TGA) Q500. The structure of crystals was determined using the powder X-Ray diffraction (XPRD) analysis. This analysis was performed using Shimadzu XRD 6000 equipped vertical X-ray goniometer and Cu Ka radiation with angle reproducibility of ±0.001° (2θ). Prior to analysis, the crystals were initially placed in an aluminium holder and gently ground, pressed and flatten softly using spatula and glass plate. The measurement conditions used were: 40 kV of voltage; 30 mA of current; 5-50° (2θ) of scan range; 0.05° of step size and 3°/min of scan mode in a continuous mode. The FTIR spectra of a saturated solution and crystals produced were determined using Perkin Elmer's ATR-FTIR Spectrometer (Frontier) with a wavenumber range of 500 to 4000 cm^{-1}. The analysis was performed using OMNIC software with an average of 16 scans.

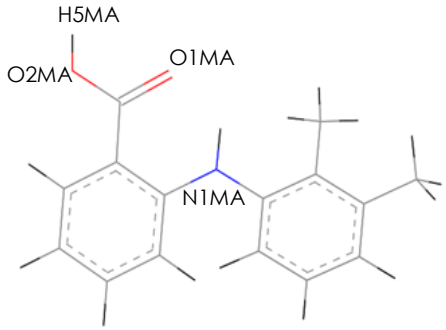
2.4 Molecular Dynamics Simulation

The molecular dynamics simulation works were performed using Material Studio 5.5 (Accelrys, Inc., San Diego, USA). The molecules of mefenamic acid and ethyl acetate shown in Figure 1 was sketched and optimized prior to the energy minimization using Smart minimizer. The number of pure ethyl acetate and the binary mixture of mefenamic acid/ ethyl acetate, as well as the density used in this work, are provided in Table 1. The number of molecules were chosen within the range suggested by vanGusteran and Berendsen, which is from 100 to 10000 atoms [13]. The density of the binary mixture was calculated as follows:

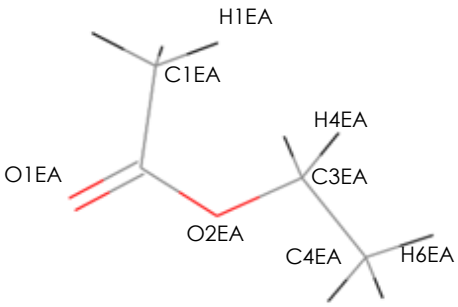
$$\rho_{sol} = \frac{L+S}{L/\rho_L + S/\rho_S} \quad (1)$$

where ρ_{sol} is the density of the solution, L is the mass of solvent, S is the mass of solute, ρ_L is the density of solvent and ρ_S is the density of solute [14]. The density of mefenamic acid used in this calculation was 1.268 gcm^{-3} [15].

The cubical simulation box with the periodic boundary of the targeted molecules was constructed using the Amorphous Cell. The calculation using a periodic boundary system is relatively cheaper and more suitable for simulation of liquid or solid systems [17]. The velocity of molecules in the simulation box were set to follow random configuration. The simulations were performed at 298 K and 1 atm using the COMPASS force field and the Ewald summation technique. Ewald summation was used to address the long-range electrostatic interactions [17].



(a)



(b)

Figure 1 Partial numbering and labeling of (a) Mefenamic acid; and (b) ethyl acetate molecule

Table 1 Summary of simulation parameters

System	Number of Molecules	Density, ρ (gcm^{-3})	Cubic Cell Size *A x B x C* (Å^3)
Ethyl acetate	250	0.894 [16]	34.42x34.43x34.42
Mefenamic acid: Ethyl acetate	25: 250	0.954[a]	36.51x36.51x36.51

[a]This value was calculated using Equation (1).

Each simulation was run in thermodynamic ensemble of NVE (constant number of atoms, volume and energy) for a period of 250 ps and followed by NPT (constant number of atoms, pressure and temperature) for a period of 2000 ps. The temperature of 298 K in the NPT ensemble was maintained using Nose thermostat[18] with a Q ratio of 1.0. The pressure (1 atm), on the other hand, was maintained using Berendsen barostat [19] with a decay constant of 0.1 ps. A time step of 1.0 fs was used during the calculation. At the end of the simulation, various radial distribution functions (RDFs) between each pair of atoms defined in Figure 1 were calculated. These RDFs represent the distances between each pair of atoms which averaged and normalized to the RDF of an ideal gas of the same density [11]. The following equation is used to describe the RDF:

$$g_{xy}(r) = \frac{\langle N_y(r, r+dr) \rangle}{\rho_y 4\pi r^2 dr} \quad (2)$$

where r is a spherical radius from the reference atom, ρ_y is a density of a y atom, $N_y(r, r + dr)$ is the number of y atoms in a shell of width Δr at a distance r and x is the reference atom [2].

3.0 RESULTS AND DISCUSSION

3.1 Characteristics of Mefenamic Acid Polymorph

Shapes or habits are one of the vital characteristics of crystalline pharmaceutical materials as it may influence the bulk density, flowability and mechanical strength of the crystalline materials [20]. Figure 2 shows the shapes of crystals which crystallized using ethyl acetate. As seen, the crystals are needle-like. The shape of the crystals produced in this work are similar with those reported in the literature [7].

Figure 2 Optical microscopy image of mefenamic acid crystals

The DSC and TG curves of mefenamic acid after crystallized using ethyl acetate are shown in Figure 3. The DSC curve has two endothermic peaks, which match the characteristic of mefenamic acid Form I. The first and second endothermic peaks correspond to transition from Form I to Form II at 175.85°C and the melting of Form II at 230.78°C, respectively. These values are concurring with those values of mefenamic acid Form I reported in the literature [21]. The presence of endothermic peak before the melting point shows that the mefenamic acid polymorphs are an enantiotropic, where they can reversibly transformed into one another by cooling or heating process [10, 22].

The derivative TG curves shown in Figure 3 is presented to provide correlation between the weight loss and the calorimetric profile. The curves show a significant weight change between 155°C and 245°C, which is approximately at the second endothermic peak of the DSC curve. The change in the weight is believed due to the decomposition of mefenamic acid crystals during the melting process. In addition, no significant weight loss was detected in the region of 80 to 100°C, whereas in many cases, it may cause the decomposition of the substrate material or volatilization of residual solvents [23].

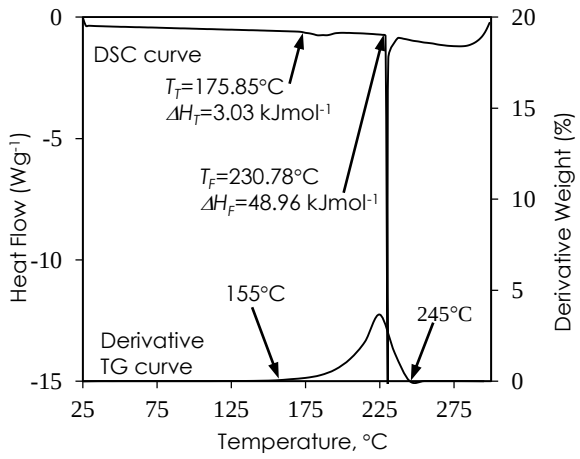


Figure 3 DSC and derivative TGA curves of mefenamic acid crystals after crystallization using ethyl acetate

The XPRD pattern of mefenamic acid crystals obtained in comparison with some major reflections in the reference pattern of Form I which reported by literature is shown in Figure 4. The pattern is concurred with the literature [7, 24]. In addition, any significant peaks at 11.8°, 17.9°, 23.8° and 25.6° as well as 9-12° (2θ) which represent Form II of mefenamic acid were not observed. Thus, confirms pure Form I crystals was successfully produced using ethyl acetate as a solvent.

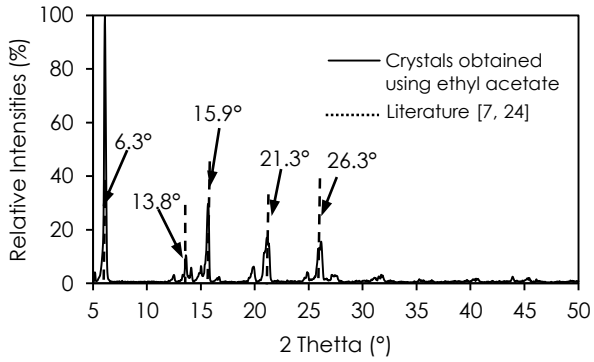


Figure 4 XPRD pattern of crystals growth using ethyl acetate

FTIR analysis was performed to observe the chemical structure of the substance. Romero and co-workers [21] and Gilpin and Zhou [9] highlighted that the N-H stretching band that occurs between 3300 and 3350 cm^{-1} is an important spectral that can be used to distinguish either Form I or Form II of mefenamic acid. Specifically, the N-H stretching frequency that occurs at 3311 to 3313 and 3346 to 3347 cm^{-1} indicate the existence of Form I and Form II, respectively. The N-H stretching within this wavelength arises due to the amine group internal hydrogen bonding with the carbonyl group. Figure 5 shows a full IR spectrum of mefenamic acid that crystallized using ethyl acetate. As presented in Figure. 5, the crystals obtained has N-H stretching band at approximately 3313 cm^{-1}, which corresponds to Form I of mefenamic acid. The N-H stretching at this wavelength suggests a strong hydrogen interaction between N-H and carboxylic group, C=O. The broad band in the range of 3200-2500 cm^{-1} is due to the stretching of O-H that presence in carboxylic group. A very broad peak in this region also indicates the presence of exchangeable protons, typically from alcohol, amide or carboxylic acid groups. While, the peak at 1650 cm^{-1} is due to the presence of C=O stretching [10].

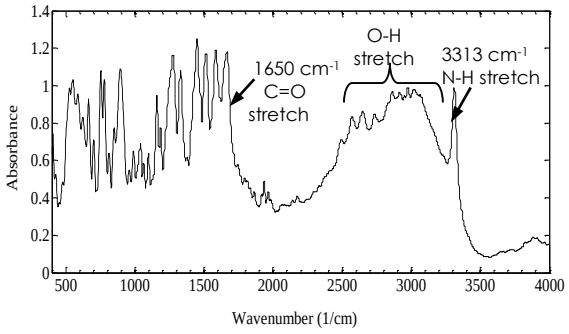


Figure 5 Infrared spectrum of mefenamic acid crystals

3.2 Validation of Simulation Method

Density is an important parameter that can be used as an indicator to validate the simulation method. The density values for each solvent in the periodic boundary system constructed in this work were calculated using the following equation:

$$\rho_{sim} = \left[\frac{M}{0.6022 \times V}\right]\frac{1}{N} \quad (3)$$

where ρ_{sim} is the density in gcm^{-3}, *M is* the molecular weight, 0.6022 is the unit conversion factor, *V* is the calculated volume in Å^3, and *N* is the number of molecules in the periodic box. The simulated density of pure ethyl acetate obtained in this work, which is 0.885 gcm^{-3} shows very good agreement with the literature (0.894 gcm^{-3}) [16]. The deviation is very small, which is 1.01%. The simulated density calculated for binary mixture of mefenamic acid/ ethyl acetate (0.940 gcm^{-3}) also show an excellent agreement with calculated density (0.954 gcm^{-3}). The deviation also very small, which is 1.47%. Other work performed by Sun reported about a 6% difference in the density values during the simulation of 150 organic structures with the COMPASS force field [25]. As the deviation obtained in this work is quite small, it can be suggested that the methods used in this work can produce good simulation results.

3.3 Radial Distribution Analysis in Pure and Binary System

The possible hydrogen bonding formation between atoms in ethyl acetate molecules, which is either O2EA•••H6EA, O2EA•••H1EA, O2EA•••H4EA, O1EA•••H6EA, O1EA•••H1EA, or O1EA•••H4EA are presented in Figure 6 (a) and (b). The RDF for O2•••H1 in Figure 6 (a) shows a shoulder peak at 2.75Å, while O2EA•••H6EA and O2EA•••H4EA at 4.75Å and 5.25Å, respectively. The RDF for O1EA•••H6EA in Figure 6 (b) shows a first peak at a similar distance with O2EA•••H1EA, which is at 2.75Å. However, no peaks were observed for O1EA•••H1EA and O1EA•••H4EA. The first peak observed for O1EA•••H6EA is more intense and nearest than others and thus can be suggested to represent the strength of hydrogen bonding in pure ethyl acetate.

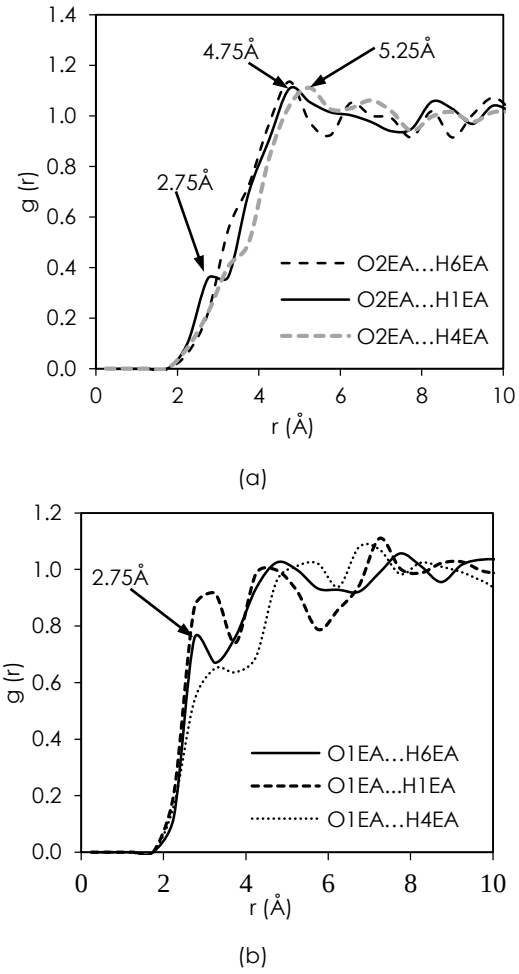


Figure 6 RDFs plots for pure ethyl acetate

The solvent-solvent interaction namely O1EA•••H6EA that presence in mefenamic acid/ ethyl acetate solution is shown in Figure 7. As seen, there are no differences detected between the O1EA•••H6EA interaction pattern calculated in pure solvent simulations with those in a binary mixture. The same RDF pattern indicates that the presence of a mefenamic acid solute in the binary system does not modify the long-range pure solvent structure. However, it can be observed that the probability of this interaction is slightly higher than pure ethyl acetate (Refer Figure 6. (b)). This finding is probably due to the differences in molecular self-assembly of solute-solute and solvent-solvent structures that are present in the solution, but are not present in the pure ethanol. These changes also reflect the start of phase separation between solvent molecules and solute

molecules during dissolution and prior to the formation of solute cluster or nucleation [2].

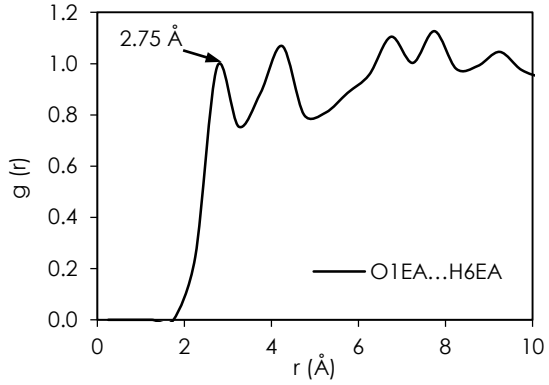


Figure 7 RDF of solvent-solvent interaction that presence in the binary mixture of mefenamic acid/ ethyl acetate

The RDFs for the interaction between mefenamic acid and ethyl acetate solvent are illustrated in Figure 8. As shown in Figure 8, the interactions between atoms of mefenamic acid which are O1MA, O2MA and N1MA with the hydrogen atoms in ethyl acetate are weaker except for O1MA•••H1EA, O1EA•••H15MA, and O1EA•••H15MA. Among these interactions, the RDF of O1EA•••H15MA shows the sharpest peak with the intensity of 3.25 at a radial distance of 1.75 Å. Meanwhile, the second peak of this RDF is observed at a radial distance of 2.75 Å with an intensity of 1.32. At longer radial distances, the RDF approaches one which indicates there is no long-range order interaction. The RDF pattern agrees with Ingebrigtsen and co-workers [26]. Since the O1EA•••H15MA shows the sharpest peak, and, therefore, can be suggested to represent the strength of solute-solvent interactions in mefenamic acid/ ethyl acetate solution. Moreover, this findings implies that the association of mefenamic acid molecules in ethyl acetate solution that leads to high solubility value is primarily through the hydrogen bonds formed by O1EA•••H15MA interactions, where mefenamic acid molecules donates H atom while O1EA in ethyl acetate is hydrogen acceptor.

The formation of specific polymorph is depended on the solute cluster formation in the solution [27]. The formation of the solute cluster, which leads to the nucleation of a targeted polymorph, depends on the hydrogen bonding established between solute-solute molecules. The intermolecular interactions between solute molecules in mefenamic acid/ ethyl acetate are shown Figure 9. As illustrated in this figure, the intermolecular interaction between O1MA•••H15MA shows the sharpest g(r) peak at 1.75Å. Literature reported that the g (r) peaks with a sharp and nearest radial distance will contribute to significant intermolecular interactions during the pre-nucleation event [27]. Therefore, it can be suggested that the intermolecular interaction between O1MA•••H15MA plays an important role during pre-nucleation of Form I of mefenamic acid that crystallized in ethyl acetate.

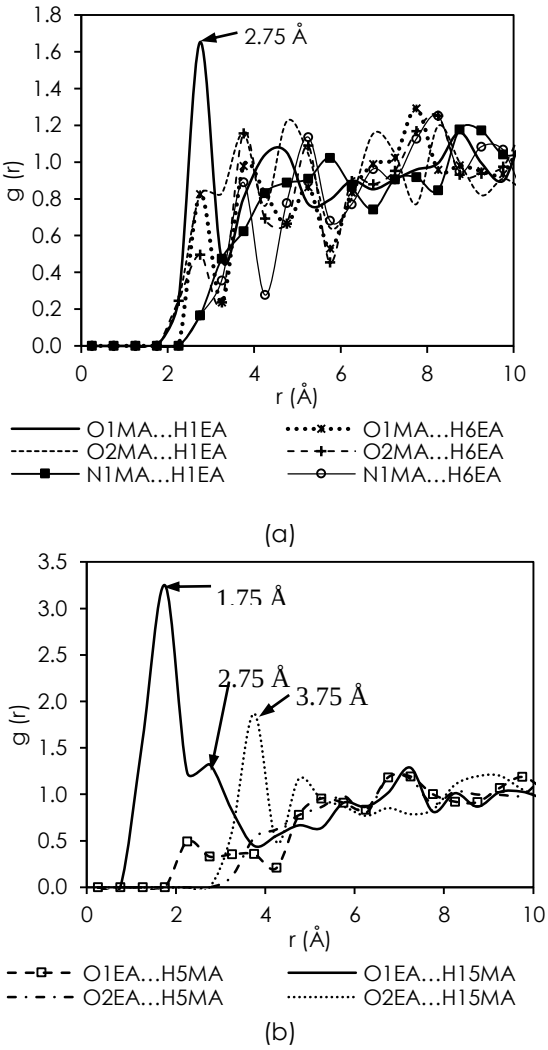


Figure 8 g(r) plots of atoms in mefenamic acid and atoms in ethyl acetate molecules: (a) solute-solvents; and (b) solvent-solute interactions

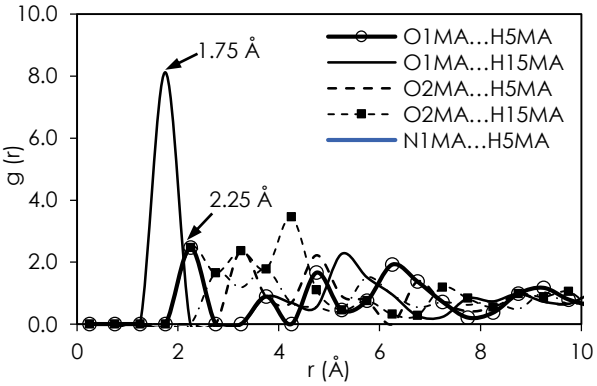


Figure 9 Solute-solute interactions in mefenamic acid/ ethyl acetate

4.0 CONCLUSION

In this contribution, the polymorphic Form I of mefenamic acid has been produced using ethyl acetate as a solvent. The polymorph is needle-like with enantiotropic characteristics. Through the molecular dynamics simulations (MD) studies the molecular recognition of solvation and the polymorphism of mefenamic acid Form I in ethyl acetate have been revealed. The association of mefenamic acid molecules in ethyl acetate solution that leads to high solubility value is primarily through the hydrogen bonds formed by O1EA•••H15MA interactions. The hydrogen bonding between O1MA•••H15MA is identified to be responsible for the formation of hydrogen motif in mefenamic acid Form I.

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References

[1] Brittain, H. G. 2007. Polymorphism and Solvatomorphism. *Journal of Pharmaceutical Science*. 96: 705-728.
[2] Adam, F. 2012. *An Examination into the Influence and Change of Solution Structure on the Polymorphic Behaviour of 2,6-Dihydroxybenzoic Acid.* Institute of Particle Science and Engineering: University of Leeds, Leeds.
[3] Lee, E .H. 2014. A Practical Guide to Pharmaceutical Polymorph Screening & Selection. *Asian Journal of Pharmaceutical Sciences.* 9(4): 163-175.
[4] Heinz, A., C. J. Stracchan, K. C. Gordon, and T. Rades. 2009. Analysis of Solid-State Transformations of Pharmaceutical Compunds Using Vibrational Spectroscopy. *Journal of Pharmaceutical Pharmacology.* 61: 971-988.
[5] Marques, M. P. M., R. Valero, S. F. Parker, J. Tomkinson, and L. A. Batista de Carvalho. 2013. Polymorphism in Cisplatin Anticancer Drug. *The Journal of Physical Chemistry B.* 117(21): 6421-6429.
[6] SeethaLekshmi, S. and T. N. Guru Row. 2012. Conformational Polymorphism in a Non-Steroidal Anti-Inflamatory Drug Mefenamic Acid. *Crystal Growth & Design.* 12: 4283-4289.
[7] Cesur, S. and S. Gokbel. 2008. Crystallization of Mefenamic Acid and Polymorphs. *Crystal Research & Technology*. 43: 720-728.
[8] Panchagnula, R., R. Sundaramurthy, O. Pillai, and S. Agrawal. 2004. Solid-State Characterization of Mefenamic Acid. *Journal of Pharmaceutical Science*. 93: 1019-1029.
[9] Gilpin, R. K. and W. Zhou. 2005. Infrared Studies of the Polymorphic States of the Fenamates. *Journal of Pharmaceutical and Biomedical Analysis*. 37(3): 509-515.
[10] Cunha, V. R., C. M. Izumi. P. A. Petersen, A. Magalhaes, M. L. Temperini, H. M., Petrilli, V. R. Constantino, V. R. 2014. Mefenamic Acid Anti-Inflammatory Drug: Probing Its Polymorphs by Vibrational (IR and Raman) and Solid-State NMR Spectroscopies. *The Journal of Physical Chemistry B.* 118(16): 4333-4344.
[11] Hamad, S., C. Moon, C. R. A. Catlow, A. T. Hulme, and S. L. Price. 2006. Kinetic Insights into the Role of the Solvent in the Polymorphism of 5-Fluorouracil from Molecular Dynamics Simulations. *Journal of Physical Chemistry B.* 110(7): 3323-3329.
[12] Abdul Mudalip, S. K., M. R. Abu Bakar, P. Jamal, and F, Adam. 2013. Solubility and Dissolution Thermodynamic Data of Mefenamic Acid Crystals in Different Classes of Organic Solvents. *Journal of Chemical & Engineering Data.* 58(12): 3447-3452.
[13] vanGunsteren, W. and H. A. Berendsen. 1990. Computer Simulation of Molecular Dynamics: Methodology, Applications, and Perspectives. *Angewandte Chemie International Edition in English.* 29(9): 992-1023.
[14] Mullin, J. W. 2001. *Crystallization.* 4th edition. Oxford: Butterworth-Heinemann.
[15] Surov, A. O., I. V. Terekhova, A. Bauer-Brandl, and G. L. Perlovich. 2009. Thermodynamic and Structural Aspects of Some Fenamate Molecular Crystals. *Crystal Growth & Design*. 9: 3265-3272.
[16] Gonza´lez, B., N. Calvar, E. Go'mez, E. and A. K. Domi'nguez. 2009. Density, Dynamic Viscosity, and Derived Properties of Binary Mixtures of Methanol or Ethanol with Water, Ethyl Acetate, and Methyl Acetate at T = (293.15, 298.15, and 303.15). *Journal of Chemical Thermodynamics.* 39(12): 1578-1588.
[17] Allen, M. P. and D. J. Tildesey. 1991. *Computer Simulation of Liquids*. New York: Oxford University Press.
[18] Nose, A. S. 1984. A Unified Formulation of the Constant Temperature Molecular Dynamics Methods. *Journal of Chemical Physics.* 81(1): 511-519.
[19] Beredsen, H. J. C.1984. Molecular-Dynamics with Coupling to an External Bath. *Journal of Chemical Physics*. 81(8): 3684-3690.
[20] Ho, R., Naderi, M. J. Y. Heng, D. R. Williams, F. Thielmann, P. Bouza, and D. J. Burnett. 2012. Effect of Milling on Particle Shape and Surface Energy Heterogeneity of Needle-Shaped Crystals. *Pharmaceutical Research*. 29(10): 2806-2816.
[21] Romero, S., B. Escalera, and P. Bustamante. 1999. Solubility Behavior of Polymorphs I and II of Mefenamic Acid in Solvent Mixtures. *International Journal of Pharmaceutics.* 178: 193-202.
[22] Park, K., J. M. B. Evans, and A. S. Myerson. 2003. Determination of Solubility of Polymorphs Using Differential Scanning Calorimetry. *Crystal Growth & Design.* 3(6): 991-995.
[23] Craig, D. Q. M. and G. A. K. 2007. *Thermal Ananlysis of Pharmaceuticals.* Boca Raton: CRC Press, Taylor & Francis Group.
[24] Kato, F., M. Otsuka, and Y. Matsud. 2006. Kinetic Study of the Transformation of Mefenamic Acid Polymorphs in Various Solvents and Under High Humidity Conditions. *International Journal of Pharmaceutics.* 321(1): 18-26.
[25] Sun, H. 1998. COMPASS: An ab Initio Force-Field Optimized for Condensed-Phase Applications Overview with Details on Alkane and Benzene Compounds. *The Journal of Physical Chemistry B.* 102(38): 7338-7364.
[26] Ingebrigtsen, T. S., T. B. Schroder, and J. C. Dyre. 2012. What is Simple Liquid? *Physical Review X*. 2(1): 011011.
[27] Davey, R. and J. Garside. 2002. *From Molecules to Crystallizers: An Introduction to Crystallization.* United States: Oxford University Press Inc.