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# Assessment of intermolecular interaction of mefenamic acid (Form II) in acetone and dimethylformamide (DMF) solution using molecular modelling technique

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**Abstract**

Solvent plays an important role in the solute-solvent intermolecular interactions of crystal morphology to regulate the crystal shape. Therefore, this work aims to assess the role of functional groups of solvents on the preferential sites on mefenamic acid (Form II) crystal surfaces, namely {001}, {011}, and {010} using the computational molecular modelling interactions techniques. The crystal morphology was successfully predicted as a plate-like crystal morphology using the BFDH method, and the molecular interactions of solute-solvent were assessed using the surface-docking method via Biovia Materials Studio software. The solute and solvent interactions along with surfaces used in this study disclosed that the {001} surfaces had the most negative non-bonded energy, followed by the {010} and {011} surfaces, ranging from −2036 to −2994 kcal/mol. Meanwhile, the binding energy values of acetone on all facets of interest were stronger compared to the binding energy of DMF, which possessed the binding energy of only less than −10 kcal/mol. Nevertheless, the results showed that acetone as a small molecule interacted most strongly with all facets of mefenamic acid (Form II) crystals because it could form stronger hydrogen bonds due to its ketone functional group, hence inhibited the growth of the mefenamic acid (Form II) crystal facets.

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## 1.0 Introduction

Crystallisation is a separation process that converts a liquid solution into a crystalline solid (Gao et al., 2017). It modifies molecular interactions to improve medicinal properties (Cui et al., 2020). This process is an important separation technique in the pharmaceutical industry to obtain purity for product quality demands, for example, in a polymorphic compound's bioavailability, stability, solubility and morphology (Yan et al., 2020). The intermolecular interactions within the structure and those produced between solute or solvent molecules and the crystalline surface can significantly impact the crystal development of the material from the solution. Therefore, producing a correct polymorph during the crystallisation process is critical. Crystal morphology needs to be modified and controlled as different solvents that act as inhibitors produce different morphology, where in-depth research needs to be done to identify the effect of solvent on the growth of crystal shape (Li et al., 2019). The solvent effect is an important factor in crystal formation, the type of polymorphic forms and the crystal shape, which results in a wide range of physical and chemical properties in pharmaceutical products (Zhou et al., 2021). The crystal's habit can be changed by adding additives or solvents (Zhou et al., 2021). Other factors such as supersaturation, temperature, pH, impurity, or cooling rate can also significantly change crystal properties. The changes include particle size, shape, purity, and crystals with some defects, as well as less pronounced but significant changes in thermodynamic and mechanical properties (Nugrahani & Parwati, 2021). Modifying crystal shape with certain solvents has shown that incorporating a solvent enhances the crystal-free energy and entropy, reduces the enthalpy of fusion, and increases the dissolution rate (Rosbottom et al., 2017).

Molecular modelling techniques have been widely used to uncover the critical areas in the molecular interactions between solute-solvent at the molecular level. Among the common molecular modelling techniques, the surface-docking method is one of the methods that can be used to assess the likelihood of

solvent attachment to a specific crystal facet. This is based on the binding energies between the solvent and the crystal facet, where it is postulated that the more negative the binding energy, the more solvent can effectively interact with the crystal facet. For example, the effect of solvents that contains hydroxyl functional groups on paracetamol Form I crystal surfaces carried out using this technique has shown that the most favourable solvent binding on the {002} facet delayed the growth of an elongated hexagonal morphology along the c-axis, forming a prism-like morphology (Shahrir et al., 2022). In their other work, they reported the influence of polar protic solvents on urea crystal morphology, which resulted in {111} and {001} capping facets as the most negative binding energy and {110} as the lowest negative binding energy, hence affecting the overall crystal morphology from an elongated cuboid to a prismoidal shape (Shahrir et al., 2023).

Mefenamic acid (Form II) is a non-steroidal anti-inflammatory medication commonly utilised in clinical supplication. This compound appears in three polymorphic forms: Forms I, II, and III. The polymorphs of mefenamic acid differ according to the relative conformation of the carboxylic group in the molecular structure (SeethaLekshmi & Guru Row, 2012), highlighted by a rectangular shape. The polymorphs are formed when the mefenamic acid with the same chemical composition crystallises into more than one crystal structure or form depending on several factors (Panchagnula et al., 2004). Among the factors affecting the polymorphism of mefenamic acid are the choice of solvent, temperature, supersaturation, stirring, and the presence of interfaces or impurities during the crystallisation process (Abdul Mudalip et al., 2018). This work aims to investigate the nature of the solute-solvent interactions between mefenamic acid (Form II) and acetone or dimethylformamide (DMF) at the molecular level using the surface docking method as described by previous researchers (Shahrir et al., 2022; Shahrir et al., 2023). The method involves the docking of the solvent molecule on top of the crystal surfaces of interest, e.g., {001}, {010}, and {011} facets. The role of solvent as an inhibitor to the crystal facet growth is assessed based on the solvent's functional groups on the preferential sites on crystal surfaces in the solution. Hence, the solute-solvent interactions can be explained in depth to uncover critical areas and their overall impact on the solute-solvent interactions at the molecular level.

## 2.0 Methodology

### *2.1 Materials*

Mefenamic acid (Form II) ($C_{15}H_{15}NO_2$, MW = 241.29g/mol) was utilised as a crystallised material, while acetone ($(CH_3)_2CO$, MW = 58.08g/mol) and dimethylformamide (DMF) ($C_3H_7NO$, MW = 73.09g/mol) solution were used as solvents. Mefenamic acid (Form II) contains one of the hydrogens attached to the nitrogen being substituted with a 2,3-dimethylphenyl group, while acetone and dimethylformamide (DMF) comprise the functional groups of ketone and amide, respectively. The double-bonded oxygen of the amide group possessed the ability to accept the H-bond, while the N–H group of the amide acted as an H-bond donor. However, ketones cannot donate hydrogen since they acquired no hydrogens bonded to oxygen or nitrogen but can accept H-bond (Johansson et al., 1974). The crystal structure of the mefenamic acid (Form II) was obtained from the Cambridge Crystallographic Data Centre (CCDC) database (CCDC Ref. code: XYANAC07). Mefenamic acid (Form II) crystallises in a triclinic lattice with P-1 space group with cell parameters of $a$ = 7.6969, $b$ = 9.1234 and $c$ = 9.4535. Fig. 1 (a) and (b) show the crystal structure of mefenamic acid (Form II) in its lattice view from x- and y-directions. The crystal view from the y-direction shows the zero-dimensional (0D) hydrogen bond direction, where the H-bonds formed between the pair of the dimers are not stoichiometric (Anuar, et al., 2022). The 3D structure of the solvents i.e., acetone (National Center for Biotechnology Information, 2023a) and DMF (National Center for Biotechnology Information, 2023b) was obtained from the PubChem websites. The optimised acetone and DMF are also shown in Fig. 1 (c) and Fig. 1 (d). All the structures were refined using an embedded tool in Biovia Materials Studio.

### *2.2 Computational modelling method*

The molecular modelling was carried out using Biovia Materials Studio (MS) software. The mefenamic acid (Form II), acetone and DMF were optimised and minimised using protocols embedded in the minimisation tools in MS.

#### *2.2.1 Geometry optimisation and morphology prediction*

The structures within the unit cell of mefenamic acid (Form II) were optimised in rigid conditions by applying motion constraints to the structures to

prevent the atoms from moving too much, and the structural energy was further minimised in unrigid conditions without motion constraints to allow the atoms to move more freely and find their lowest energy positions, using the COMPASS force field. The non-bonded interactions were calculated using the Ewald summation method, while the charges of the atoms were calculated using the Gasteiger method. The crystal morphology was predicted using the Bravais-Freidel Donnay-Harker (BFDH) method (Docherty et al. 1991).

### 2.2.2 *Preparation of crystal surface, solvent, and vacuum slab*

The crystal surfaces of facets {001}, {011} and {010} were cleaved from the crystal structure as perfect termination surfaces, where a supercell was created for each facet at a suitable size to determine the best position of binding energy. The supercell dimension for each facet is displayed in Table 1.

The vacuum slab was built on top of the supercell that had been cleaved. Then, the optimised (using COMPASS forcefield) solvent molecule was positioned on the minimised crystal surface. The solvent was positioned at the midpoint of the supercell surface using the surface attachment technique, forming an H-bond with the mefenamic acid molecule (Orehek et al., 2020). The H-bond distance between crystal facets and the solvent molecule was set to be ≤ 2.0 Å as a starting point before running the dynamic simulation. The final crystal conformation in the chosen solvent was produced after the molecular dynamic calculation reached equilibrium.

### 2.2.3 *Dynamic simulation*

The vacuum slab condition was set at a temperature of 300 K with constant NVT (constant number of molecules, volume, and temperature) ensemble. The number of frame outputs was set at 50 steps for each facet, and the total dynamic simulation time was fixed at 5 ps. Before the dynamic simulations, the crystal surface was in constrained conditions, whilst the solvent was allowed to explore the crystal surface to obtain a stable minimum energy conformation. The final crystal conformation in the chosen solvent was produced after the molecular dynamic calculation reached equilibrium.

### 2.2.4 *Non-bonded energy and binding energy calculations*

Prior to the non-bonded energy calculations, the non-bonded energy was computed from the total

**Table 1**: Supercell dimensions of the cleaved surfaces for the dynamic simulation

| Facet | Lattice dimensions, (Å) | | |
|---|---|---|---|
| | *a* | *b* | *c* |
| **{001}** | 46.740 | 45.945 | 68.097 |
| **{011}** | 46.740 | 59.716 | 63.261 |
| **{010}** | 47.060 | 38.950 | 66.556 |

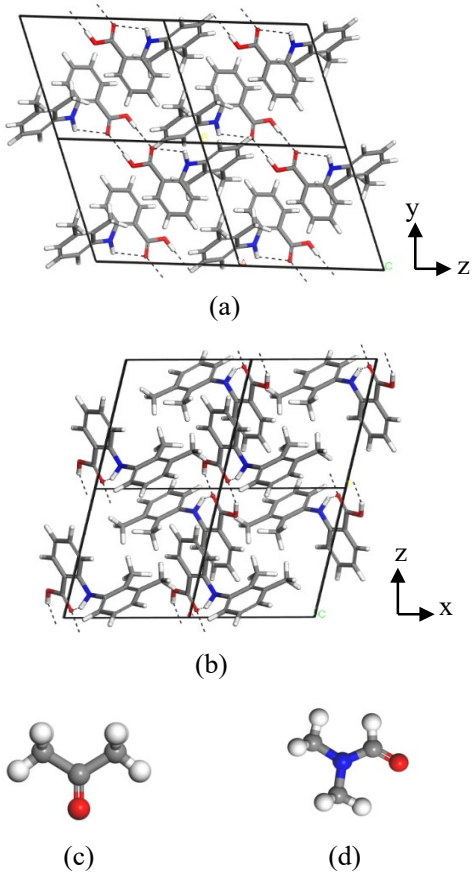



**Fig. 1** Molecular structure of mefenamic acid (Form II) in crystal lattice view from (a) x-direction, and (b) y-direction showing a zero-dimensional (0D) hydrogen bond network. The molecular structure of (c) acetone and (d) DMF in a ball and stick form

energy ($E_{total}$) of the system from the constrained crystal surface. $E_{total}$ was the sum of the potential energy ($E_{pot}$), kinetic energy ($E_{kin}$) and non-bonded energy ($E_{non\text{-}bonded}$), where it consisted of $E_{vdW}$ (the summation of repulsion/attraction van der Waals forces), $E_{coul}$ (ion-ion interactions between the partial charges) and $E_{H\text{-}bond}$ (the interacting energy between the attachment of the molecule) as shown in Eq. (1) and (2).

$$E_{total} = E_{pot} + E_{kin} + E_{non\text{-}bonded} \quad (1)$$

$$E_{non\text{-}bonded} = E_{vdW} + E_{coul} + E_{H\text{-}bond} \quad (2)$$

Then, the binding energy was calculated using Eq. (3). $E_{total.min}$ is the system's total energy after the surface and solvent molecules are relaxed and minimised. The energies of the crystal surfaces ($E_{surface}$) and solvent ($E_{solvent}$) were also calculated. The pure crystal binding energies were then determined using Eq. (3):

$$E_{binding} = E_{total.min} - (E_{surface} + E_{solvent}) \quad (3)$$

## 3.0 Results and discussion

### *3.1 Morphology prediction of mefenamic acid (Form II) crystal using BFDH method*

Fig. 2 shows the predicted morphology of mefenamic acid (Form II) crystals, as well as the crystal facets {001}, {011}, and {010} that were used to determine the potential energy bond of solvent molecules on their surfaces in this study.

The results showed that the mefenamic acid (Form II) morphology produced using BFDH method was predicted as a plate-like crystal morphology with the {001} facet has an exposed OH, and hydrogen of $–C_6H_5$ functional groups at the surface, the {011} facet possesses OH, –C=O, and $–C_6H_5$ functional groups at the surface, and the {010} facet only has $–C_6H_5$ functional groups at the surface. These three important facets were chosen because they were the dominant facets of mefenamic acid (Form II) crystals. Therefore, they were used to further assess the role of functional groups of solvents on the preferential sites on mefenamic acid (Form II) crystal surfaces at the molecular level.

### *3.2 The non-bonded energy and binding energy of the crystal surfaces and the solvent molecules*

Table 2 shows the non-bonded energy values for each facet, {001}, {011} and {010} for acetone and DMF solvents. The result was obtained from the dynamic simulation between crystal surfaces and solvents, with the crystal surfaces being constrained. This showed that the crystal solute had non-bonded energy interactions with the solvent as an additive. In general, the non-bonded interaction is the interaction between atoms in the same molecule and other molecules (Fomin & Alemasov, 2009). Theoretically, the lowest non-bonded energy indicated the most stable binding energy orientation between the solvent molecules and crystal surfaces (Docherty et al., 1991).

From the results, it can be observed that the trend of the non-bonded energy of both acetone and DMF solvents was similar, with the most negative non-bonded energy obtained from the dynamic calculation in the order of {001} facet, followed by {010} facet, and {011} facet. It can also be observed that the most negative to the least negative orders of non-bonded energy between the solvent on the surface were in the following order: acetone > DMF for {001} facet and DMF > acetone for both {011} and {010} facets.

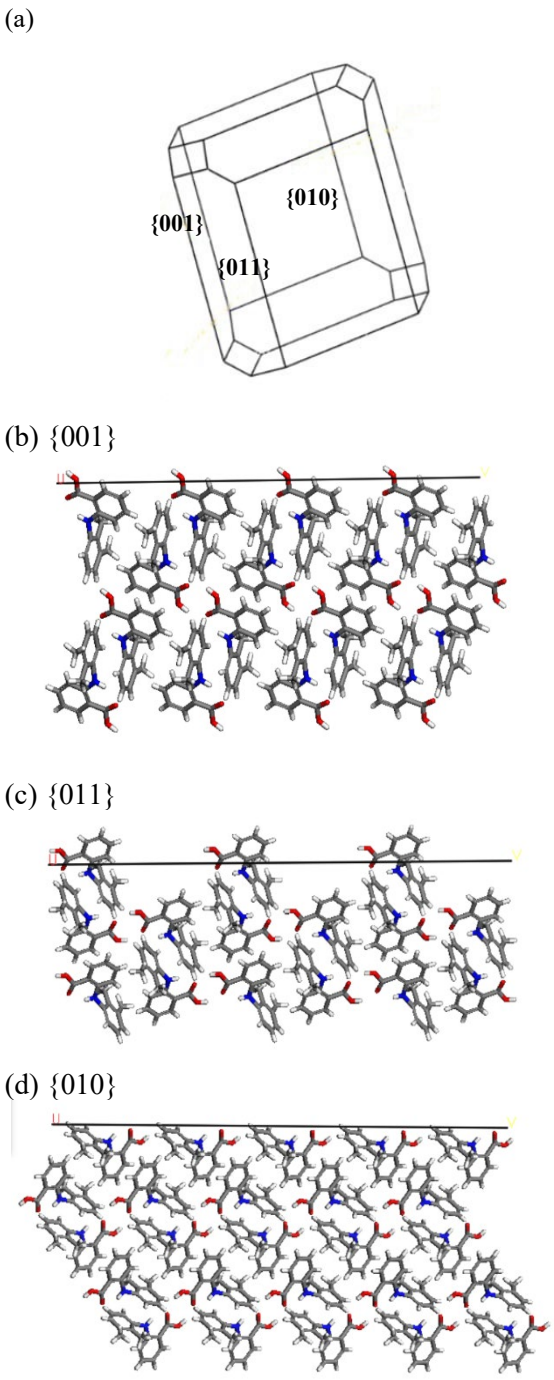



**Fig. 2** (a) Crystal morphology of a mefenamic acid (Form II) obtained using Bravais-Friedel-Donnay-Harker (BFDH) method showing the surfaces chemistry of different facets of (b) {001}, (c) {011} and (d) {010} used in this study

The same trend can also be seen in the total energy results, where the most negative total energy specified the most stable position between the surface and the solvent. Nonetheless, it can be concluded that the position on the {001} surfaces gave the most stable configuration for both solvents based on the most negative values of the non-bonded energy recorded in Table 2.

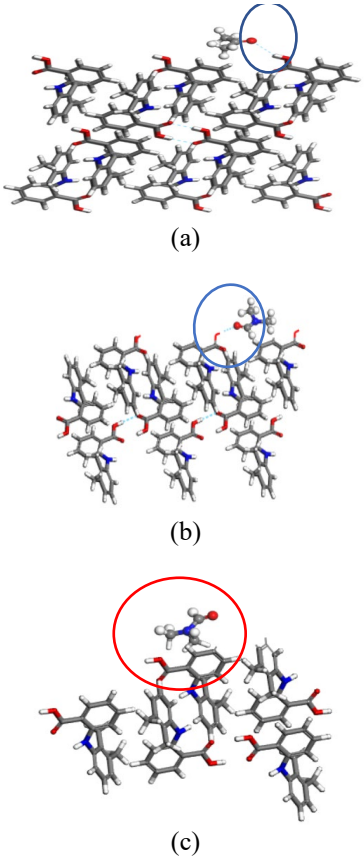
Generally, the solvent molecule was positioned on the crystal surface to identify the most favoured position for final interaction before running the dynamic simulation. For instance, Fig. 3 (a) shows the most favoured position was between the oxygen of the ketones and hydrogen of the carboxyl group for the interaction between {001} surface and acetone solvent. To compare, the most favoured position on the same surface {001} using DMF solvent, was between the hydrogen of the carboxyl group and the oxygen of the amide group, as shown in Fig. 3 (b).

From the results in Fig. 3 (c), the {011} surface using DMF solvent showed that the arrangement was less favourable since the solvent molecule was in close contact with the crystal surface of mefenamic acid (Form II). This was maybe due to an induced-induced dipole interaction that caused a weak attraction between the DMF solvent and crystal surface. Weak attraction occurs when a polar molecule disrupts the arrangement of electrons in a nonpolar atom to cause a dipole in the nonpolar molecule (Shibata & Kuntzleman, 2009).

Meanwhile, Fig. 4 shows the non-bonded energy interaction between solvents and crystal facets based on the best searching position of the solvent. The non-bonded energy interaction calculated for the most stable position of the solvents onto the (a) {001}, (b) {011} and (c) {010} surfaces molecules onto the crystal surfaces of the mefenamic acid (Form II). The results from the search were ranked among the top 100 interaction energies, from the most negative to the least negative values, indicating the most favourable interactions. As can be seen in Fig. 4, the results showed that the strongest to the weakest non-bonded energies were in the following order: {001} > {010} > {011} facets which corresponded to the values obtained in Table 2. To summarise, the highest non-bonded energy interaction was shown by surface {001} between acetone and DMF solvents, compared to the {010} and {011} surfaces based on Fig. 4. Hence, this indicated that surface {001} possessed the strongest interactions energy with the most stable position,

**Table 2**. The most stable non-bonded interactions between solvent and crystal facets

| Solvents | Facet (hkl) | Non-bonded Energy (kcal/mol) | Total Energy (kcal/mol) |
|---|---|---|---|
| **Acetone** | {001} | −2994.81 | −2984.30 |
| | {011} | −2036.12 | −2024.55 |
| | {010} | −2578.404 | −2566.89 |
| **Dimethylformamite (DMF)** | {001} | −2852.78 | −2847.05 |
| | {011} | −2613.74 | −2595.12 |
| | {010} | −2751.19 | −2731.94 |



(a)

(b)

(c)

**Fig. 3** The most favourable position of the solvents: (a) acetone and (b) DMF on the {001} surface of the mefenamic acid. The example of unfavored interaction on the (c) {011} surfaces of the DMF solvent is shown in the red circle. The blue circle is the most favourable position of the solvent. The red circle is the unfavoured interaction of the DMF solvent onto the {011} surface

followed by {010} and {011} surfaces.

Binding energies mainly describe the intermolecular interaction between crystal facets and solvent molecules by forming hydrogen bonds and non-bonded energies. Table 3 shows the total binding energy calculated using Equation (3). From the results in Table 3, it can be determined that the most favoured binding sites for acetone were in the following order: the {001}, followed by the {010}, and the {011} facets.

**Table 3**: Binding energy calculation of the solvent molecules and crystal surfaces

| Solvent | Facet (*hkl*) | Total energy (kcal/mol) | Surface energy (kcal/mol) | Solvent energy (kcal/mol) | Binding energy (kcal/mol) |
|---|---|---|---|---|---|
| **Acetone** | {001} | −4830.71 | −4812.94 | −5.40 | −12.37 |
| | {011} | −3368.66 | −3352.72 | −5.67 | −10.26 |
| | {010} | −3965.54 | −3949.48 | −5.68 | −10.39 |
| **DMF** | {001} | −8745.67 | −8752.29 | 9.92 | −3.30 |
| | {011} | −8898.21 | −8902.94 | 13.93 | −9.20 |
| | {010} | −8181.69 | −8187.86 | 10.27 | −4.10 |

Meanwhile, the DMF was preferred to bind the strongest on the {011}, followed by the {010} and the {001} facets. However, the binding energy value of acetone solvent on all facets of interest was stronger compared to the binding energy of DMF, which possessed a binding energy of only less than −10 kcal/mol. It was postulated that the results of DMF might be due to unfavoured binding, which indicated the unstable solute-solvent interaction of mefenamic acid (Form II).

Nonetheless, the strongest binding energy between DMF and surface {011} was among all the facets. This could indicate that the position was stable with the favoured binding position, which can prevent the growth of solute molecules on the surfaces (Chen et al., 2019). Overall, it can be concluded that acetone showed the most significant interaction of binding energy on all facets of mefenamic acid (Form II) crystals.

### *3.3 The effects of functional groups of solvents on interactions energy*

The results obtained in previous sections can be further assessed by explaining how the functional groups of the solvents affect the solute-solvent interactions in the mefenamic acid crystals at the molecular level in more depth. For instance, the {001} facet showed the strongest interactions between solute-solvent among all the understudied facets. The stable orientations of acetone and DMF on the {001} facet (Fig. 3(a) and (b)) were such that the oxygen atom of acetone and DMF was aligned with the hydrogen atom of the carboxyl group of mefenamic acid. This orientation was suggested to be preferable because it created strong solute-solvent interactions, with the methyl groups of the acetone and DMF molecules pointing towards the $–C_6H_5$ group of mefenamic acid, thus allowing the interactions between solute-solvent to occur. In this case, acetone (ketone functional group) and DMF (amide functional group) were polar aprotic solvents, which could only act as electron acceptors and not donors. This is because the oxygen atom in

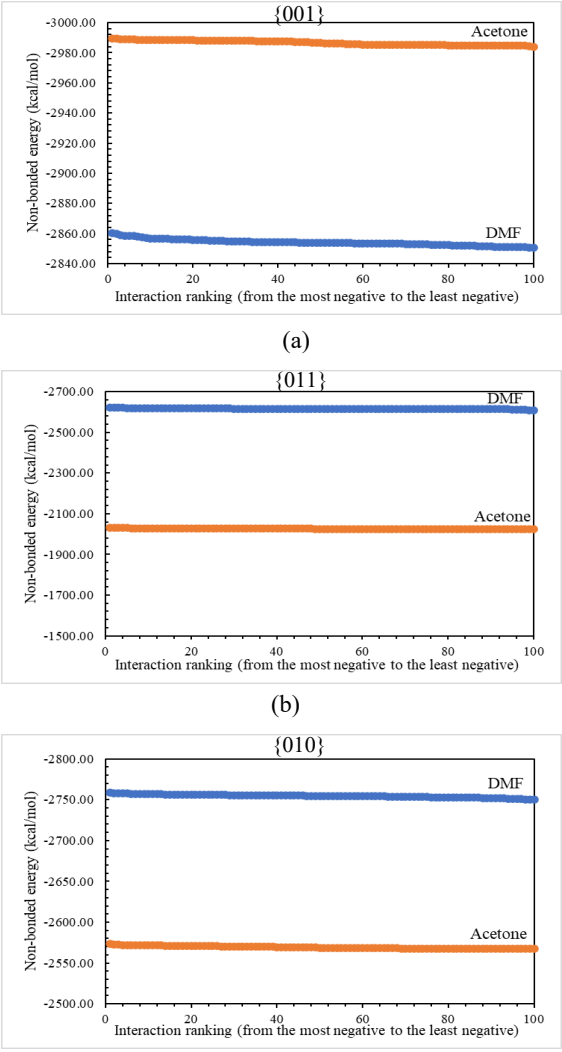



**Fig. 4**: The non-bonded energy interaction calculated for the most stable position of the solvents onto the (a) {001}, (b) {011} and (c) {010} surfaces

both solvents was not covalently bonded to any hydrogen atom, and therefore could not be a hydrogen bond donor. Therefore, the hydrogen bonding occurred between the oxygen of the solvent molecule and the hydrogen of the carboxyl group of the mefenamic acid molecule. In addition, the {001} facet possesses significant hydrogen bonding ability with –OH and $–C_6H_5$ functional groups exposed at the surface, therefore it may permit strong hydrogen bonding between the facet and the solvents, and eventually inhibited the growth of the facet.

Nonetheless, the overall results showed that the interactions energy between acetone and mefenamic acid (Form II) crystals were much stronger than DMF. This indicates that the influence of acetone in modifying the mefenamic acid morphology was more significant than DMF. It was expected because acetone as a ketone functional group was a stronger hydrogen bond acceptor, where the carbonyl oxygen in acetone was more electronegative than the amide oxygen in DMF. Therefore, the presence of carbonyl functional group in acetone could significantly contribute more to the interaction energy compared to DMF. Hence, it could have a higher degree of impact on the interaction's energy compared to DMF having a structure with less electronegativity. The results also suggested that acetone as a small molecule may be well fitted to the cavities of crystal surfaces, thereby able to stop or block the growth of the mefenamic acids along their respective growths. However, DMF was a big molecule so it may not be well fitted to the cavities of crystal surfaces, hence the steric hindrance effects of the solvent were lesser, therefore it may contribute to the weak interactions between solute-solvent. Hence, explaining why acetone could have a better impact on the habit modification of the mefenamic acid crystal (Form II) than DMF.

## 4.0 Conclusions

In conclusion, the crystal morphology of mefenamic acid Form II was successfully predicted as a plate-like crystal morphology by using a computational molecular modelling method for different types of facets such as {001}, {011}, and {010}. This study used two different polar aprotic solvents, acetone and dimethylformamite (DMF). From the molecular interaction between the solvents and the crystal surfaces used in this study, it can be concluded that the most negative non-bonded energies were recorded by the surface {001}, followed by {010} and {011} surfaces for both solvents, ranging from −2036 to −2994 kcal/mol. For the binding energy calculations, acetone's interactions with all facets of interest showed stronger binding energy than DMF, which had a binding energy of less than −10kcal/mol. Therefore, acetone solvent showed the most significant interaction of binding energy on all facets of mefenamic acid (Form II) crystals with its ability to permit stronger hydrogen bonding due to the ketone functional group in its small structure, hence inhibited the growth of the crystal facets.

## Contribution statement

**Nur Syazwina Mohd Aizuddin, Muhammad Syahir Syazwan Supian, Nornizar Anuar**: Methodology, software analysis, investigation, data curation and writing original draft; **Nornizar Anuar, Nurshahzanani Shahrir**: Writing-review & editing, conceptualisation, supervision, project administration.

## Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## References

Abdul Mudalip, S. K., Abu Bakar, M. R., Jamal, P., Adam, F., Che Man, R., Sulaiman, S. Z., Mohd Arshad, Z. I., & Md Shaarani, S. (2018). Effects of solvents on polymorphism and shape of mefenamic acid crystals. *MATEC Web of Conferences,* 150. https://doi.org/10.1051/matecconf/20181500200

Anuar, N., Yusop, S.N., & Roberts, K.J. (2022) Crystallisation of organic materials from the solution phase: A molecular, synthonic, and crystallographic perspective. *Crystallography Reviews, 28* (2–3), 97–215. https://doi.org/10.1080/0889311X.2022.2123916.

Chen, F., Zhou, T., Li, J., Wang, X., Cao, D., Wang, J., & Yang, Z. (2019). Crystal morphology of dihydroxylammonium 5,5′-bistetrazole-1,1′-diolate (TKX-50) under solvents system with different polarity using molecular dynamics. *Computational Materials Science*, *168*, 48–57. https://doi.org/10.1016/j.commatsci.2019.05.060

Cui, P., Yin, Q., Zhang, S., Cheng, X., Dai, J., Zhang, Z., Zhou, L., & Xie, C. (2020). The effect of solvents on crystal morphology of sucralose: Experiments and molecular dynamics simulation studies. *Journal of Crystal Growth*, *532*, 125398. https://doi.org/10.1016/j.jcrysgro.2019.125398

Docherty, R., Clydesdale, G., Roberts, K. J., & Bennema, P. (1991). Application of Bravais-Friedel-Donnay-Harker, attachment energy and Ising models to predicting and understanding the morphology of molecular crystals. *Journal of Physics D: Applied Physics*, *24*(2), 89–99. https://doi.org/10.1088/0022-3727/24/2/001

Fomin, E., & Alemasov, N. (2009). Implementation of a non-bonded interaction calculation algorithm for the cell architecture. *Lecture Notes in Computer Science*, 399–405. https://doi.org/10.1007/978-3-642-03275-2_39

Gao, Z., Rohani, S., Gong, J., & Wang, J. (2017). Recent developments in the crystallisation process: Toward the pharmaceutical industry. *Engineering*, *3*(3), 343–353. https://doi.org/10.1016/j.eng.2017.03.022

Johansson, A., Kollman, P., Rothenberg, S., & McKelvey, J. (1974). Hydrogen bonding ability of the amide group. *Journal of the American Chemical Society*, *96*(12), 3794–3800. https://doi.org/10.1021/ja00819a013

Li, Z., Jia, S., Gao, Y., Wang, M., Hong, W., Gao, Z., & Gong, J. (2021). Solid-liquid equilibrium behavior and thermodynamic analysis of p-aminobenzoic acid using experimental measurement and molecular dynamic simulation. *Journal of Molecular Liquids*, *323*, 114964. https://doi.org/10.1016/j.molliq.2020.114964

National Center for Biotechnology Information (2023a). PubChem Compound Summary for CID 180, Acetone. Retrieved October 23, 2023, from https://pubchem.ncbi.nlm.nih.gov/compound/Acetone

National Center for Biotechnology Information (2023b). PubChem Compound Summary for CID 17824068, DMF dimethylformamide. Retrieved October 23, 2023, from https://pubchem.ncbi.nlm.nih.gov/compound/DMF-dimethylformide

Nugrahani, I., & Parwati, R. D. (2021). Challenges and progress in nonsteroidal anti-inflammatory drugs co-crystal development. *Molecules, 26*(14), 4185. https://doi.org/10.3390/molecules26144185

Orehek, J., Teslić, D., & Likozar, B. (2020). Continuous crystallisation processes in pharmaceutical manufacturing: A review. *Organic Process Research & Development*, *25*(1), 16–42. https://doi.org/10.1021/acs.oprd.0c00398

Panchagnula, R., Sundaramurthy, P., Pillai, O., Agrawal, S., & Raj, Y. A. (2004). Solid-state characterisation of mefenamic acid. *Journal of Pharmaceutical Sciences, 93*(4), 1019–1029. https://doi.org/10.1002/jps.20008

Rosbottom, I., Ma, C. Y., Turner, T. D., O'Connell, R. A., Loughrey, J., Sadiq, G., Davey, R. J., & Roberts, K. J. (2017). Influence of solvent composition on the crystal morphology and structure of p-aminobenzoic acid crystallised from mixed ethanol and nitromethane solutions. *Crystal Growth & Design*, *17*(8), 415. https://doi.org/10.1021/acs.cgd.7b00425

Shahrir, N., Anuar, N., Muttalib, N.A.A., Yusop, S.N., Bakar, M.R.A., Adam, F., & Ibrahim, S.F. (2022). The role of solvent hydroxyl functional groups on the interaction energy and growth of Form I paracetamol crystal facets. *Organic Process Research & Development, 26(12),* 3226-3235. https://doi.org/10.1021/acs.oprd.2c00151

Shahrir, N., Anuar, N., Yusop, S.N., Zaki, H.M., & Tominaga, Y. (2023). Influence of polar protic solvents on urea morphology : A combination of experimental and molecular modeling. *Crystal Growth & Design*, *23*(6), 4240–4254. https://doi.org/10.1021/acs.cgd.3c00060

SeethaLekshmi, S., & Guru Row, T. N. (2012). Conformational polymorphism in a non-steroidal anti-inflammatory drug, mefenamic acid. *Crystal Growth & Design, 12*(8), 4283–4289. https://doi.org/10.1021/cg300812v

Shibata, M., & Kuntzleman, T. S. (2009). Intermolecular interactions: dipole–dipole, dipole–induced dipole, and London dispersion forces. *Journal of Chemical Education*, *86*(12), 1469. https://doi.org/10.1021/ed086p1469.1

Yan, Y., Li, A., Si, Z., & Zhang, X. (2020). Solubility measurement, correlation, and molecular simulation of dabigatran etexilate mesylate polymorphs in five mono-solvents. *Journal of Molecular Liquids*, *314*, 113676. https://doi.org/10.1016/j.molliq.2020.113676

Zhou, J., Jiao, Z., Zhang, J., & Zhong, Z. (2021). Nanoindentation of single-crystal and polycrystalline yttria-stabilised zirconia: A comparative study by experiments and molecular dynamics simulations. *Journal of Alloys and Compounds*, *878*, 160336. https://doi.org/10.1016/j.jallcom.2021.160336