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IMPACT OF SOLVENT FUNCTIONAL GROUPS ON INTERMOLECULAR INTERACTIONS AT CRYSTAL GROWTH SURFACES OF FORM II PARACETAMOL

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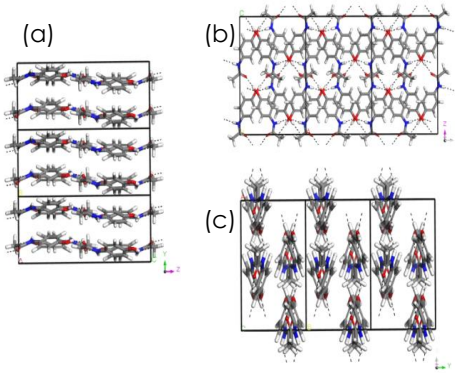
Graphical abstract



Abstract

Desired crystal shapes grown in specific solvents can be achieved by elucidating the interactions between solvent functional groups and the exposed solute molecules on crystal surfaces. This is crucial for the effective design and operation of crystallisation processes, preventing undesired products that cause challenges in downstream processes such as filtration, granulation, and tabletting. This study investigates the influence of solvent functional groups on the morphology of Form II paracetamol polymorph using molecular modelling techniques, focusing on interactions between solvent molecules and various crystal surfaces. The results revealed a strong correlation between the solvent's ability to form hydrogen bonds and the interaction energies. Solvents with strong hydrogen bonding capabilities (carboxylic acids, esters, and ethers) exhibited the strongest non-bonded. Notably, sulfonates displayed the strongest binding energies, exceeding -70 kcal/mol, potentially hindering movement at the surface and influencing crystal growth. This strong binding might have explained the observed shortened growth along the c-axis, suggesting a more stable crystal configuration on this surface. The Electrostatic Potential (ESP) surface contour map revealed the electron density distribution between the solute and solvent molecules, which helped explain the observed binding energies. The correlation between the binding energy ratio of {111}/{200} and {111}/{002} crystal facets in Form II paracetamol and its growth morphology in carboxylic acid solvents suggested that a higher ratio favoured elongated scalenohedral crystals, while a lower ratio led to rod-shaped or plate-like crystals. These findings provide valuable insights into controlling and designing crystallisation processes, specifically paracetamol.

Keywords: Form II paracetamol, crystallisation, functional group, intermolecular interactions, morphology

Abstrak

Rupa bentuk kristal sasaran yang terhasil dalam sesuatu pelarut boleh dicapai dengan memperincikan interaksi di antara kumpulan berfungsi pelarut dan molekul bahan larut yang terdedah pada permukaan kristal. Hal ini merupakan penentu untuk menghasilkan reka bentuk dan operasi proses penghabluran yang berkesan, seterusnya mencegah penghasilan produk yang tidak diingini serta menimbulkan masalah dalam proses hiliran seperti penapisan, granulasi, dan pembuatan tablet. Kajian ini menyelidiki kesan kumpulan berfungsi pelarut terhadap morfologi polimorf parasetamol *Form II* dengan menggunakan teknik pemodelan molekul, yang memberi tumpuan kepada interaksi di antara molekul pelarut dan pelbagai permukaan kristal. Hasil kajian menunjukkan korelasi yang kuat di antara keupayaan pelarut membentuk ikatan hidrogen dengan tenaga interaksi. Pelarut dengan keupayaan ikatan hidrogen yang kuat (asid karboksilik, ester, dan eter) mempamerkan interaksi tak terikat yang paling kukuh. Khususnya, sulfonat menunjukkan tenaga ikatan terkuat melebihi -70 kcal/mol, yang berpotensi menghalang pergerakan

pada permukaan dan mempengaruhi pertumbuhan kristal. Ikatan kuat ini mungkin boleh menjelaskan perihal pemendekan pertumbuhan di sepanjang paksi-c, yang mencadangkan konfigurasi kristal yang lebih stabil pada permukaan tersebut. Peta kontur permukaan Potensi Elektrostatik (ESP) menunjukkan taburan ketumpatan elektron di antara molekul bahan larut dan pelarut, sekali gus menjelaskan tenaga ikatan yang dicerap. Korelasi di antara nisbah tenaga ikatan faset kristal {111}/{200} dan {111}/{002} dengan morfologi pertumbuhannya dalam pelarut asid karboksilik mencadangkan bahawa nisbah yang lebih tinggi cenderung menghasilkan kristal skalenohedral bujur manakala nisbah yang lebih rendah menghasilkan bentuk rod atau plat. Dapatan ini memberikan cerapan berharga dalam mengawal dan mereka bentuk proses pengkristalan untuk mencapai sifat kristal yang diingini.

Kata kunci: Jenis II parasetamol;, penghabluran, kumpulan berfungsi, interaksi antara molekul; morfologi

1.0 INTRODUCTION

Crystallisation is a vital separation technique for purifying active pharmaceutical ingredients (APIs). However, achieving consistent product quality remains a challenge. Empirical approaches, particularly solvent selection, significantly impact crystal properties like solubility, nucleation, growth, morphology, and physicochemical characteristics [1]–[6]. These properties, in turn, affect downstream processing, potentially leading to issues like difficulty in filtration, poor flowability, agglomeration, and "fines" production [7]. While the experimental method lacks precision and predictability, hindering targeted control, computational modelling offers a powerful tool to understand and manipulate crystallisation processes at a molecular level [8]. This approach has been used to investigate crystal-solvent interactions, highlighting the importance of understanding these interactions for optimising the crystallisation process at a molecular level [1], [2], [5], [9]–[13].

Paracetamol, a commonly used pain reliever (analgesic) and fever reducer (antipyretic), exemplifies this challenge. It exhibits polymorphism, a phenomenon where a compound exists in multiple crystal forms (polymorphs) with distinct properties influenced by the crystallisation solvent. Paracetamol exists as monoclinic Form I (stable), orthorhombic Form II (metastable), and unstable Form III [14]. Previous studies have explored paracetamol-solvent interactions for the stable Form I using computational modelling [3], [14]–[17]. Nevertheless, Form II, a metastable form, remains less understood.

This study addresses this gap by utilising computational molecular modelling techniques, particularly the surface-docking method [14], [18]–[21]. This established method investigates specific interactions between various solvents and crucial surfaces of Form II paracetamol. It assesses the likelihood of solvent incorporation at the crystal surface by determining the binding energy (i.e., the strength of interaction) between the solvent and the crystal, where a more negative binding energy value indicates a stronger interaction. The approach provides a foundation for assessing solvent affinity toward different crystal facets but is based on several assumptions. It considers the interaction between a single solvent molecule and a specific crystal surface without accounting for solvent-solvent (cluster-cluster) interactions. Moreover, it does not explicitly incorporate solvent effects on crystal growth, such as differences in surface wetting. It also does not account for variations in solid-solid, solid-liquid, and liquid-liquid intermolecular interactions across different crystal faces. For instance, a previous study successfully predicted how different solvents can modify the crystal morphology of Form I paracetamol. This suggests that solvents with stronger interactions with specific surfaces can hinder the growth of those surfaces, leading to a change in the overall crystal shape [14].

By determining the binding energy of these interactions, we aim to identify how solvent functional groups influence their preferential binding sites at a molecular level. Understanding these interactions in Form II paracetamol is crucial, as they might differ from those observed in Form I paracetamol due to variations in crystal structure and surface properties. Ultimately, this knowledge will aid in the targeted control of Form II paracetamol crystal morphology and open doors to exploring how these interactions influence its thermodynamic stability relative to Form I paracetamol. This research will contribute to developing more targeted approaches for controlling crystal morphology in paracetamol and potentially other pharmaceuticals, improving product quality and efficient manufacturing processes.

2.0 METHODOLOGY

2.1 Materials

This study used Form II paracetamol ($C_8H_9NO_2$, MW = 151.16 g/mol), an understudied drug material. For the crystallisation process, solvents were chosen based on the presence of various functional groups, including hydroxyl (amyl alcohol, benzyl alcohol, and phenol), ester (isobutyl acetate, isoamyl acetate, and phenyl acetate), carboxylic acid (adipic acid, succinic acid, and maleic acid), sulfone (sulfolane), and ether (tert-amyl methyl ether). Herein, the carboxylic acids were employed in their dissolved state.

Form II paracetamol has an amide group, a hydroxyl group, and a benzene ring. The crystal structure of this polymorph (reference code HXACAN37) was obtained from the Cambridge Crystallographic Data Centre (CCDC). It crystallises in an orthorhombic space group of P_{bca} in a unit cell with dimensions a = 11.76 Å, b = 7.14 Å, and c = 17.17 Å. It forms eight molecules in a unit cell with one crystallographically independent molecule within the asymmetric unit.

Figures 1 (a), (b), and (c) illustrate the crystal structure of Form II paracetamol packed in its lattice, viewed from x-, y-, and z-directions. Projection of the structure through the y-direction (Figure 1 (b)) clearly shows the 2D hydrogen bond directionality in which the periodic bonding can be seen extending only into the x- and z-directions. The NH...OH forms the hydrogen bond network between the neighbouring amide groups and a hydroxyl group. The HO···O=C hydrogen bond is between a hydroxyl group and the double-bonded oxygen of the amide group.

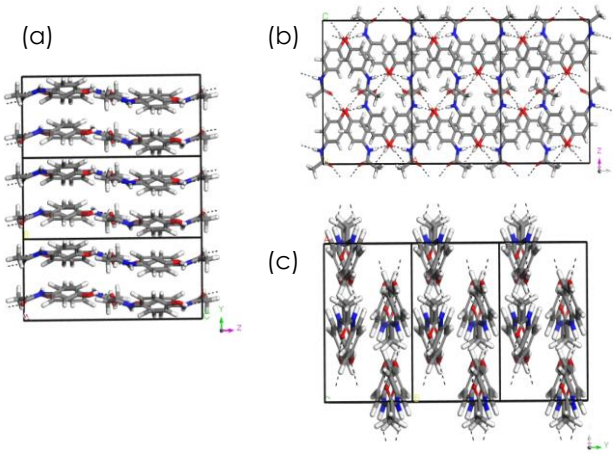


Figure 1 The molecular structure of Form II paracetamol (HXACAN37) viewed from (a) x-direction, (b) y-direction, and (c) z-direction. Atoms are coloured as follows: red for Oxygen (O), grey for Carbon (C), white for Hydrogen (H), and blue for Nitrogen (N)

Figure 2 illustrates the molecular structures of the functional groups of the solvents (hydroxyl (-OH), ester (R-COO-R'), carboxylic acid (R-COOH), sulfone ($R-SO_2-R'$), and ether (R-O-R')).

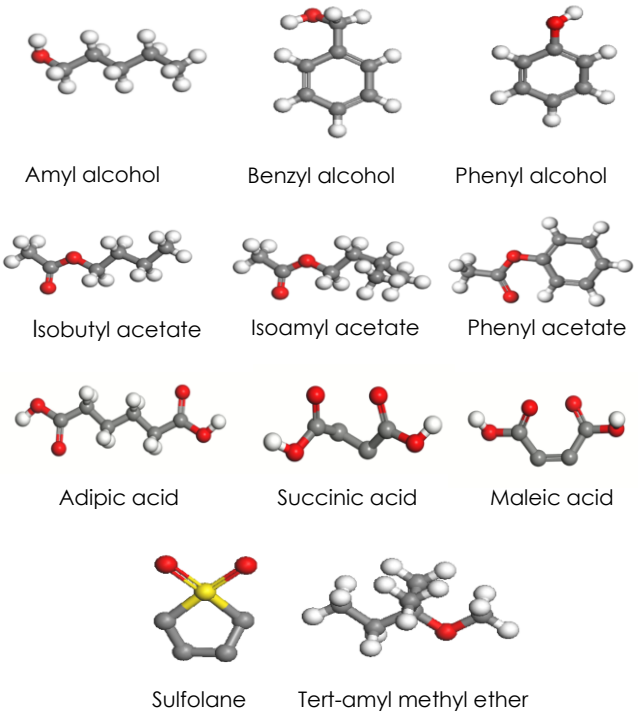


Figure 2 Molecular structures of the functional groups of the solvents (hydroxyl (-OH), ester (R-COO-R'), carboxylic acid (R-COOH), sulfone ($R-SO_2-R'$), and ether (R-O-R')). Herein, the carboxylic acids were employed in their dissolved state. (Row 1: hydroxyl; Row 2: ester; Row 3: carboxylic acid; Row 4: sulfone (left) and ether (right))

Amyl alcohol ($C_5H_{12}O$, MW = 88.15 g/mol) combines a hydroxyl group with a five-carbon chain. Benzyl alcohol (C_7H_8O, MW = 108.14 g/mol) has a hydroxyl group attached to a methylene group (CH_2) directly linked to the benzene ring. Phenol (C_6H_5OH, MW = 94.11 g/mol) is an aromatic compound with a hydroxyl group bonded directly to the benzene ring. Isobutyl acetate ($C_6H_{12}O_2$, MW = 116.16 g/mol) and isoamyl acetate ($C_7H_{14}O_2$, MW = 130.19 g/mol) are carboxylic esters. Isobutyl acetate has a four-carbon branched chain, while isoamyl acetate contains a five-carbon branched chain. Phenyl acetate ($C_8H_8O_2$, MW = 136.15 g/mol) consists of a phenyl group bonded to an acetate ester linkage. Adipic acid ($C_6H_{10}O_4$, MW = 146.14 g/mol) and succinic acid ($C_4H_6O_4$, MW = 118.09 g/mol) are dicarboxylic acids with two carboxylic acid groups. Maleic acid ($C_4H_4O_4$, MW = 116.07 g/mol) is also a dicarboxylic acid. However, it contains a carbon-carbon double bond (cis configuration) between two carbon atoms. Sulfolane ($C_4H_8O_2S$, MW = 120.17 g/mol) has a sulfur atom doubly bonded to two oxygen atoms in a cyclic structure. Tert-amyl methyl ether ($C_6H_{14}O$, MW = 102.17 g/mol) consists of two parts: a tert-amyl group and a methyl group.

2.2 Computational Modelling Techniques

The molecular modelling of Form II paracetamol and various solvents' functional groups was performed using Materials Studio (MS) 2020 (BIOVIA Dassault Systèmes) software (formerly known as Accelrys), with their structures optimised and minimised using embedded protocols in MS's minimisation tools, employing a surface-docking method [14], [18]–[21].

2.2.1 Geometry optimisation and morphology prediction

The crystal structure of Form II paracetamol was optimised in two steps using the Condensed-phase Optimized Molecular Potentials for Atomistic Simulation Studies (COMPASS) forcefield. First, a positional optimisation of the molecules in a unit cell was conducted by assigning the motion group tool. The conformation of the molecules was kept fixed (torsion angles, bond lengths, and bond angles) while allowing the position of the molecules to move to their optimised positions. This prevented excessive atomic movement and distortion of the overall crystal shape. Subsequently, the assigned motion groups were removed, and the structure underwent conformational optimisation. This allows for free atomic movement and variation in packing and molecular conformation. The minimised energy from the optimisation process was noted. The non-bonded interactions were calculated using the Ewald summation method, while the charges of the atoms were calculated using the Gasteiger method. For the crystal morphology prediction, the Bravais-Freidel Donnay-Harker (BFDH) method was employed [22].

2.2.2 Preparation of the Crystal Surface, Solvent, and Vacuum Slab

Specific crystal surfaces, {002}, {111}, and {200}, were cleaved from the crystal structure to create surfaces for solvent interaction. Each surface was assigned a supercell (repeating units of a unit cell surface) with a suitable size for a systematic search to locate the optimal solvent binding position. Table 1 displays the supercell dimensions chosen.

Table 1 Dimensions of the supercell of the cleaved surfaces

Face	Dimensions of Lattices (Å)		
	a	*b*	*c*
{002}	35.27	42.84	78.48
{111}	55.02	37.19	71.56
{200}	42.84	51.51	71.56

A 4 x 2 arrangement of unit cells was employed to create a suitable crystal lattice dimension for the {111} surface. Similarly, the {200} and {002} surfaces were constructed using 6 x 3 and 4 x 6 unit cells, respectively. A vacuum slab of 50Å was added around the crystal to simulate a periodic box. Solvent molecules were optimised using the same forcefield and charges. Subsequently, the optimised solvent molecule was positioned on the minimised crystal surface. The solvent was placed at the midpoint of the supercell surface and preferentially oriented to form a hydrogen bond (set within a distance of 2.5Å) on the crystal surface. A solvent on the crystal surface with a visible hydrogen bond is an essential step and a good starting point for dynamic calculations. For instance, Figure 3 illustrates a solvent (sulfolane) positioned on a {002} surface slab.

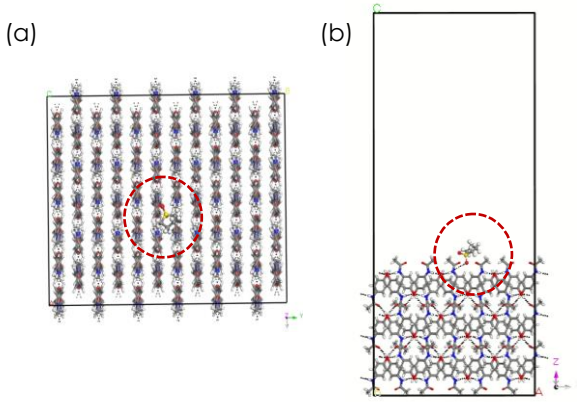


Figure 3 A good initial position of the solvent molecule, i.e., sulfolane, onto the crystal {002} surface with visible hydrogen bonding between the molecules from (a) top view and (b) side view.

2.2.3 Molecular Dynamics (MD) Simulation

The vacuum slab condition was set at a temperature of 300 K with an NVT (constant number of molecules, volume, and temperature) ensemble with a velocity scale thermostat. The number of frame outputs was set at 50 steps for each surface, and the total dynamic simulation time was fixed at 5ps. The crystal surface was set to be in constrained conditions, whilst the solvent was allowed to move freely on the crystal surface to obtain a stable minimum energy orientation. Note that simulations were repeated thrice to identify the system's most negative total energy.

2.2.4 Calculation of Non-bonded and Binding Energies

The system's total energy (E_{total}) was used to measure the interaction between the crystal solvent and the crystal surface constrained. E_{total} was determined by summing the potential energy (E_{pot}), kinetic energy (E_{kin}), and non-bonded energy ($E_{non\text{-}bonded}$) (Equation 1). Non-bonded interactions were calculated using Equation 2. These interactions consisted of van der Waals forces (E_{vdW}), coulombic interactions (E_{coul}), and hydrogen bonding energies (E_{Hbond}).

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

$$En_{on\text{-}bonded} = E_{vdW} + E_{coul} + E_{Hbond} \quad (2)$$

The binding energy ($E_{binding}$) (Equation 3) was calculated as the difference between the minimised total system's energy ($E_{total.min}$) and the sum of the isolated surface ($E_{surface}$) and solvent ($E_{solvent}$) energies. The configuration associated with the most negative binding energy was considered the most stable for solvent binding.

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

The non-bonded and binding energies were calculated considering the system environment. The crystal surface was fixed at its Cartesian position for non-bonded energies, while the solvent molecule was allowed to move freely to search for the most favorable binding sites. Conversely, the surface and solvent molecules were kept unfixed for binding energies at their Cartesian position. Therefore, they were free to move at the minimum structure state. This study focused on the intermolecular interactions between Form II paracetamol and solvent molecules. The interaction energies, i.e., non-bonded and binding energies, were computed based on pairwise calculations between the crystal surface of Form II paracetamol and each solvent molecule, capturing only intermolecular interactions. Intramolecular hydrogen bonding within paracetamol, such as the hydrogen bond between the hydroxyl and amide groups, was already incorporated in the optimised geometry of the molecule. Hence, it did not contribute to the solvent-surface interaction energy.

2.2.5 Density Functional Theory (DFT)

The study used Density Functional Theory (DFT) calculations to examine how electronegative atoms in different solvent functional groups (sulfone, hydroxyl, and ester) affected hydrogen bonding with Form II paracetamol. The solvents were chosen to represent these functional groups and provide a better understanding of their interactions at the molecular level. The calculations were performed using the DMol3 module in BIOVIA MS with Generalized Gradient Approximation (GGA) and Becke, Lee-Yang-Parr (BLYP) correlation functionals and a Double Numerical plus d-functions (DND) basis set. Subsequently, the optimised structures' Electrostatic Potential (ESP) surface maps were computed.

3.0 RESULTS AND DISCUSSION

3.1 Morphology Prediction of Form II Paracetamol Crystal using the BFDH Method

Figure 4 illustrates the morphology of Form II paracetamol, predicted using the BFDH method. Based on the morphological analysis, three predominant crystallographic faces were identified, representing the primary surfaces of the crystal. Note that {111} had the largest total surface area (42.88%), followed by {002} and {200} with 24.28% and 11.07%, respectively. The molecular interactions between solvent molecules and the crystal surfaces were subsequently investigated.

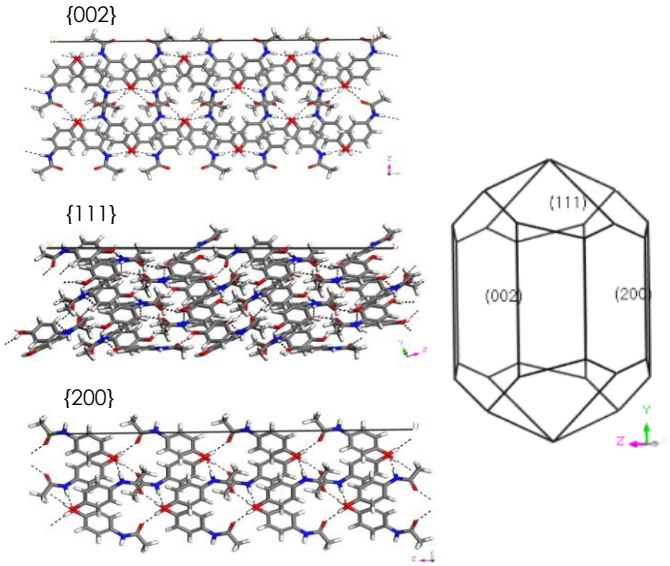


Figure 4 Predicted morphology of a paracetamol Form II crystal, determined using the BFDH method, showing the surface chemistry of the {111}, {002}, {200} surfaces used in this study, exposing similar functional groups like hydroxyl and amide groups

Assessment of the surface chemistry revealed that all the Form II paracetamol crystals' surfaces could attract and retain solvent molecules. This interaction was due to exposed functional groups on the surfaces, which facilitated various non-bonded interactions, such as hydrogen bonding, Coulombic interactions, and van der Waals forces. Form II paracetamol contains functional groups, such as hydroxyl (-OH) and amide ($-CONH_2$), that enable it to bond hydrogen by acting as either a hydrogen bond donor or a hydrogen bond acceptor. For instance, the oxygen atom has lone pairs of electrons in the hydroxyl group. It can act as a hydrogen bond acceptor, while the hydrogen atom bonded to it can act as a donor, forming hydrogen bonds with electronegative atoms (such as oxygen or nitrogen) in other molecules. Similarly, in the amide group, the hydrogen atom attached to the nitrogen also serves as a hydrogen bond donor, while the oxygen atom of the carbonyl group acts as an acceptor due to its lone pairs. Therefore, these interactions allow Form II paracetamol molecules to bond intra- and intermolecular hydrogen bonds.

While the {002}, {111}, and {200} surfaces all exposed similar functional groups like hydroxyl and amide, their hydrogen bonding capabilities vary due to the spatial arrangement and accessibility of these groups. The {002} surface presents both hydroxyl and

amide groups. However, the proximity and orientation of benzene rings at the surface could create steric hindrance within its channels, potentially limiting access to incoming molecules. The {111} surface features the same exposed functional groups within the smaller channels. Nonetheless, the channel dimensions might sterically hinder larger incoming molecules from effectively interacting with the functional groups located within the ridges. Finally, the {200} surface, primarily exposing amide groups alongside benzene rings oriented respectively, suggests potential steric hindrance that could reduce the effective interaction with these functional groups.

3.2 The Non-bonded and Binding Energies between the Crystal Surfaces and the Solvent Molecules

The orientation of solvent molecules that resulted in the lowest non-bonded energy (the most negative energy) corresponded to the most stable binding [23]. This study considered the interactions between the solvent molecule and the assigned surface slab. Figure 5 depicts these interactions, quantified by the sum of van der Waals, coulombic energies, and hydrogen bond energies, for various functional group solvents with Form II paracetamol crystal surfaces {002}, {111}, and {200}.

Figure 5 depicts that surface {002} exhibited the most negative (strongest) non-bonded energies with all solvents, ranging from -3075 to -3117 kcal/mol. This was followed by {200} (-2630 to -2666 kcal/mol) and then {111} (-2440 to -2484 kcal/mol). This trend likely arose from hydrogen bond donors and acceptors on the {002} surface, providing more favourable binding sites for the solvents. While both {002} and {200} possessed either donor and acceptor groups, the surface topography might have influenced solvent conformation and, thus, non-bonded energies. Surface {111}, lacking hydrogen bond donors, exhibited the weakest interactions [24]. Interestingly, the trend in non-bonded energies remained consistent across all surfaces for the different functional groups of the solvents. This aligned with the varying abilities of the functional groups to participate in hydrogen bonding and dipole-dipole interactions, demonstrating the significance of these interactions in determining surface-solvent stability on Form II paracetamol. Even though the {002} surface exhibited the strongest non-bonded energies (compared to other studied surfaces), most of the studied solvents adopted a favourable position on the {002} surface. This was likely due to a dipole-dipole interaction causing a strong attraction between the crystal surface and the solvents.

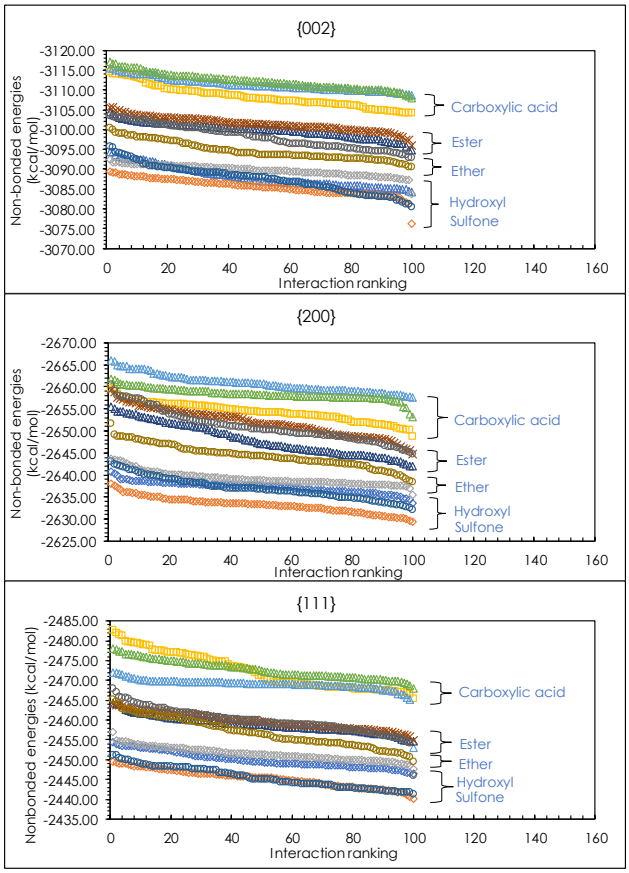


Figure 5 The non-bonded interaction energies of the most stable solvent orientations on the {002}, {200}, and {111} surfaces of Form II paracetamol crystals, calculated using Equation 2.

The order of non-bonded energies for Form II paracetamol in various solvents was carboxylic acids > esters > ethers > sulfones > hydroxyls. This order could be explained by considering the strength of intermolecular interactions between the crystal surface of Form II paracetamol. Carboxylic acids exhibited the strongest non-bonded energies due to their ability to bond hydrogen and dipole-dipole interactions with the Form II paracetamol surface. In particular, the carboxylic acids' hydroxyl and carbonyl groups formed strong hydrogen bonds with the hydroxyl groups exposed on the crystal surfaces of Form II paracetamol, leading to a strong attraction [25]. This was further confirmed by the binding energy results in a later section, where carboxylic acids' exhibited more negative binding energies than other functional groups, indicating stronger interactions. Esters, while capable of dipole-dipole interactions, could not form hydrogen bonds.

This made their interactions with the paracetamol surface weaker than those of carboxylic acids. Ethers, like esters, could only participate in dipole-dipole interactions. However, their interactions were generally weaker than those of esters due to the lower polarity of the ether functional group. As good hydrogen bond acceptors, sulfones relied solely on dipole-dipole forces to interact with the paracetamol surface. This limited their interaction strength compared to carboxylic acids and esters. Hydroxyl groups could participate in hydrogen bonding. However, their intermolecular interactions with the Form II paracetamol surface were generally weaker than those of carboxylic acids. This difference in strength is quantified by the lower (less negative) non-bonded energies observed for hydroxyls, which can be attributed to the lower polarity of the hydroxyl group and the potential for intramolecular hydrogen bonding within the Form II paracetamol molecule, as discussed in previous studies [24].

Crystal morphology was influenced by the interaction energies between solvent molecules and different crystal faces, as most crystals formed in solution. Stronger interactions, indicated by the lowest binding energies (most negative), reflect the more stable binding between the solvent and the crystal surface conformation. This stability corresponds to a greater energetic barrier to separate molecules within the crystal lattice [26]. The present study investigated these interactions by calculating the binding energies, particularly polar interactions, such as non-bonded energies and hydrogen bonds, between the crystal surfaces and the solvent molecules of various solvent functional groups with Form II paracetamol crystal surfaces. Figure 6 depicts the binding energies of the most stable solvent orientations on the {002}, {111}, and {200} surfaces.

Figure 6 reveals that the {002} surface offered the most favourable binding sites for all solvents (indicated by the most negative binding energies). This was followed by the {111} and then the {200} surfaces. Interestingly, the trend in binding energies for individual solvents varied across these crystal surfaces. For instance, the {002} surface exhibited binding energies ranging from -9 to -84 kcal/mol. The {111} and {200} surfaces followed with ranges of -11 to -74 kcal/mol and -10 to -72 kcal/mol, respectively. Despite this variation, most studied solvents exhibited a consistent range of binding energy values.

Conversely, sulfolane, containing a sulfone functional group, exhibited powerful binding energies (exceeding -70 kcal/mol) with all surfaces, notably more negative than those observed for other solvents. This pronounced interaction strength is attributed to sulfolane's high affinity for surface binding, likely due to its strong dipolar character and ability to form favourable interactions with the surface [27], [28]. Consequently, this strong interaction between sulfolane and the surfaces likely hindered the formation of new growth layers, potentially hindering the movement of solvent molecules or crystal units at the surface. This could also explain the shortened growth along the c-axis, implying a more stable binding configuration. The results also suggested that sulfonate, as a small molecule, may have been well-fitted to the cavities of crystal surfaces. The presence of a cyclic ring in sulfolane could have significantly contributed to the interaction energies, hindering the growth of Form II paracetamol. Nevertheless, it is important to note that some solvents within each functional group category might have had weaker (less negative) binding energies depending on the surfaces. For instance, solvents with functional groups like ethers (tert-amyl methyl ether), which exhibited weaker interactions (below -15 kcal/mol), might have had a less pronounced effect on the crystal morphology. This further emphasised the role of hydrogen bonding in binding energy and its influence on crystal growth.

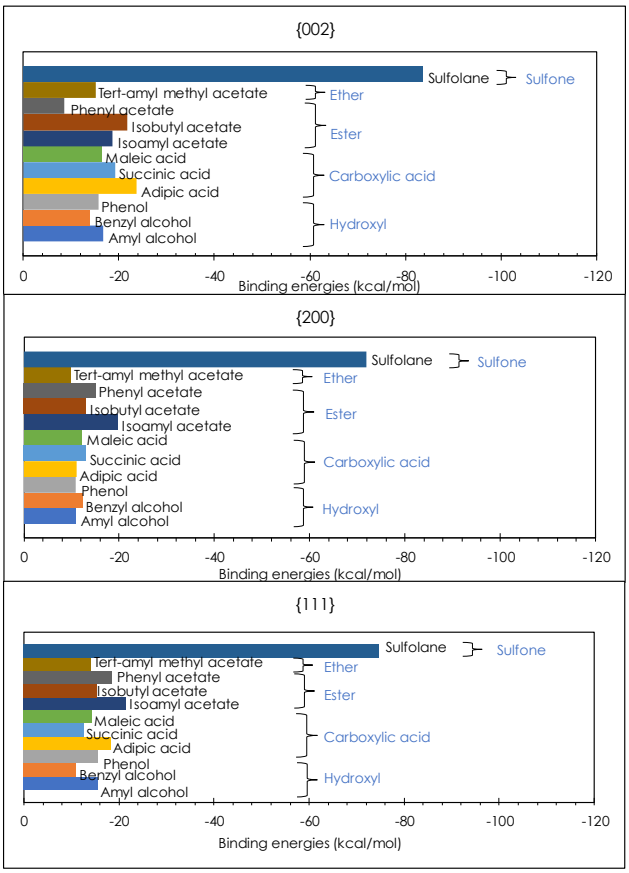


Figure 6 The binding energies of the most stable solvent orientations on the {002}, {200}, and {111} surfaces of Form II paracetamol crystals, calculated using Equation 3

The calculated interaction energies in this study are further supported by previous observations of Form II crystal morphologies in carboxylic acid solvents [29]. Interestingly, they revealed that Form II paracetamol exhibited a remarkable dependence on the solvent used, as evidenced by its ability to form distinctly different morphologies due to solute-solvent interactions, including elongated

scalenohedral, needle-like, and plate-like shapes. This dependence was further illustrated by the observation that carboxylic acids, like adipic and maleic acid, formed scalenohedral and plate-like crystals. In contrast, succinic acid produced a more uniform rod-shaped crystal. This dependence was likely linked to the strength of hydrogen bonding interactions. Surfaces that exhibited stronger hydrogen bonding with the solvent molecules were expected to bind more tightly, hindering their growth rate and influencing the final crystal morphology. Notably, Form II paracetamol crystallised in carboxylic acids often exhibited dominant {002} and {200} surfaces, leading to needle-like morphologies with a reduced {111} surface area.

To gain deeper insights into Form II paracetamol's growth mechanisms, we compared the calculated binding energies of carboxylic acids with reported crystal morphologies [29]. The results revealed a strong correlation, suggesting that the obtained binding energies directly influenced the observed crystal morphologies. In general, the binding energies for these carboxylic acid solvents varied significantly across crystal surfaces, with the {002} surface exhibiting the strongest interactions (-16 to -23 kcal/mol), followed by {111} (-14 to -18 kcal/mol) and {200} (-11 to -13 kcal/mol) surfaces. For both adipic and maleic acid, the results showed the most favourable binding sites, based on the most negative binding energies, followed by this order: {002} surface, then {111}, and finally {200}. However, for succinic acid, the order was {002} > {200} > {111}. This trend aligned well with the observed morphologies. For instance, adipic acid and maleic acid, which exhibited the strongest binding energy, formed elongated scalenohedral and plate-like crystals, as reported in previous studies [29]. This suggested that their molecular conformations may have enhanced binding, leading to stronger interactions with the crystal surfaces. Conversely, succinic acid, having the weakest binding energies, conformed to the observed uniform rod-shaped crystals. Here, steric hindrance from the carboxylic group might have been less pronounced than the other two acids. Nevertheless, the carboxylic group likely contributed to steric hindrance on certain crystal surfaces, influencing the ability of the solvent to inhibit growth on those surfaces.

3.3 Morphology Prediction based on Binding Energy Ratio Modification

As depicted in Figure 7, the experimental and simulated growth morphologies of Form II paracetamol in these carboxylic acid solvents exhibited a strong correlation, further validating the findings of *Yeh et al. (2022)* [29].

Simulations were performed with water excluded from the system to isolate and evaluate the effect of paracetamol-carboxylic acid interactions and to assess their potential impact on Form II paracetamol morphology under hypothetical conditions. The binding energy ratio of {111}/{200} and {111}/{002} was a key factor determining crystal habit and was found to correlate with the observed morphologies.

Adipic acid, with a higher ratio of 1.64:1 ({111}/{200}), exhibited elongated scalenohedral crystals, while succinic acid and maleic acid, with lower ratios of 0.95:1 ({111}/{200}) and 0.87:1 ({111}/{002}), respectively, produced rod-shaped and plate-like crystals. This observation highlighted the significance of intermolecular interactions of solute-solvent molecules in governing the crystal growth process of Form II paracetamol.

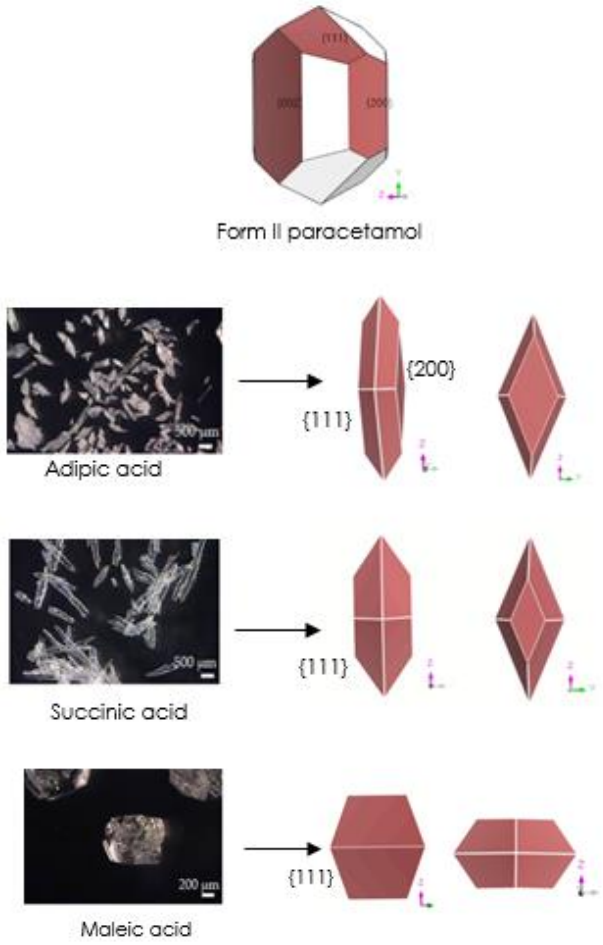


Figure 7 Simulated growth morphology of Form II paracetamol using the BFDH method as a reference and comparison of experimental [29] and modified growth morphologies of Form II paracetamol crystals in carboxylic acid solvents: (a) adipic acid, (b) succinic acid, and (c) maleic acid, based on the binding energy ratio of {111}/{200} and {111}/{002}

To correlate with the other studied solvents, the results might suggest that higher binding energies, such as those observed with sulfolane, tended to hinder crystal growth along specific axes. It was likely due to its strong hydrogen bonding interactions exceeding -70 kcal/mol, leading to more stable configurations like shortened growth along the c-axis. In contrast, weaker binding energies, like those

exhibited by ethers below -15 kcal/mol, likely had a minimal impact on crystal morphology. This reinforced the crucial role of hydrogen bonding in determining binding energy and its direct influence on crystal growth mechanisms.

For better understanding, we have categorised the solvents based on the atoms present in their functional groups. For example, carboxylic acids contain both -OH and C=O groups, hydroxyl compounds contain -OH, esters contain C=O and -O- groups, ethers contain C-O-C, and sulfones are distinguished by S(=O)2.. Regarding non-bonded interactions, carboxylic acids exhibited the most negative interactions due to their C=O and groups, while esters showed significant negative interactions attributed to their C=O and -O- groups. On the other hand, sulfones consistently displayed the least negative non-bonded energies across all surfaces. A similar trend was observed for binding energies with carboxylic acids, esters, and sulfones. Notably, sulfones consistently exceeded the other two solvents in terms of binding energies on all surfaces studied.

The observed trends in non-bonded and binding energies among these solvents can be attributed to several factors, such as intermolecular interactions. Carboxylic acids' ability to form strong hydrogen bonds due to the more electronegative oxygen atom and favourable molecular geometry contributed to stronger intermolecular interactions than those formed by hydroxyl groups. Esters exhibited higher energy than ethers due to their enhanced polarity, facilitating stronger dipole-dipole interactions and indirectly influencing hydrogen bonding. Additionally, the molecular geometry of esters allowed for more favourable packing arrangements in the crystal lattice, resulting in stronger intermolecular interactions and, ultimately, lower overall energy. Sulfones, highly polar functional groups containing two oxygen atoms double-bonded to a sulphur atom, could exhibit even higher energy due to their strong dipole-dipole interactions and favourable molecular geometry.

3.4 Density Functional Theory (DFT) Analysis

Figure 8 illustrates the ESP surface map for Form II paracetamol interacting with different solvents: sulfolane (a sulfone), benzyl alcohol (a hydroxyl), and isoamyl acetate (an ester), computed using DFT. The ESP map provided visual information about the electron density distribution on the molecule's surface. By analysing the colour coding (blue for low electron density, red for high), we inferred the atomic charge distribution and predicted the strength of interactions between paracetamol and the solvents. The structure and charge density of the molecule influenced the shape and intensity of the ESP contours.

The amide group of Form II paracetamol generated the most negative ESP due to the high electron density surrounding the oxygen atom of the solvents, as shown in Figure 8. Conversely, the most positive ESP was localised around the hydrogen atoms of the methyl groups.

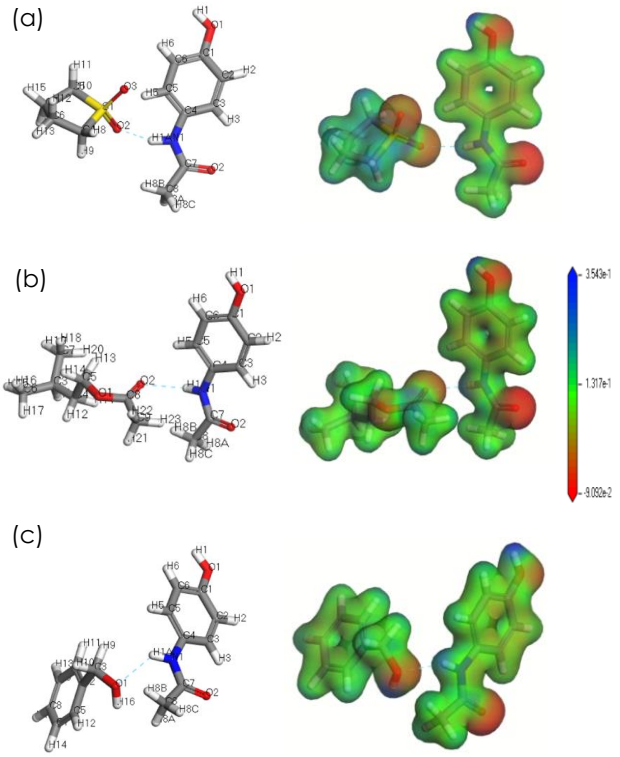


Figure 8 Computed Electrostatic Potential (ESP) surface maps of the structure of Form II paracetamol crystal interaction with (a) sulfolane, (b) isoamyl acetate, and (c) benzyl alcohol on the {200} surface

Figure 8 (a) depicts the ESP map illustrating the interaction between sulfolane and Form II paracetamol at the position most favoured by sulfolane on the {200} surface. This position yielded the most negative non-bonded energy. The orientation resulted in strong hydrogen bond interactions between the sulfone group of sulfolane and the amide group of Form II paracetamol, with corresponding bond lengths and angles of 2.37 Å and 137.09°, respectively. This interaction was deemed the strongest hydrogen bonding interaction due to its shorter bond length and angle closer to 180°. The blue region on the ESP map between sulfolane and Form II paracetamol represents the lowest electron density due to the orientation of the sulfolane molecule, where the cyclic compound positions itself accordingly. Consequently, repulsive forces dominated attractive forces between the hydrogen bonds.

Figures 8 (b) and (c) depict the interactions between isoamyl acetate and benzyl alcohol with Form II paracetamol. The hydrogen bond lengths and angles between isoamyl acetate – Form II paracetamol and benzyl alcohol – Form II paracetamol were 2.38 Å and 119.73°, and 2.47 Å

and 109.93°, respectively. The amide group of Form II paracetamol exhibited the highest electron density due to the electronegativity of the nitrogen atom. Without solvent molecule interactions, the interactions between Form II paracetamol molecules were primarily attributed to intramolecular interactions. Consequently, the charge distribution was influenced solely by the electronegativity of the nitrogen atoms within the Form II paracetamol molecules. The order of hydrogen bond strength from strongest to weakest was sulfolane – Form II paracetamol > isoamyl acetate – Form II paracetamol > benzyl alcohol – Form II paracetamol.

DFT calculations for Form II paracetamol on the {200} surface with sulfolane, isoamyl acetate, and benzyl alcohol yielded binding energies that differed from those obtained via surface docking. The most negative binding energies were calculated for isoamyl acetate (-2.83 kcal/mol), followed by benzyl alcohol (-1.13 kcal/mol) and sulfolane (4.07 kcal/mol). This suggests a stronger interaction between isoamyl acetate and Form II paracetamol. While sulfolane exhibited a shorter hydrogen bond with Form II paracetamol and a more favourable hydrogen bond angle, its positive binding energy indicates an unfavourable overall interaction. This could be due to electrostatic repulsion between specific regions of sulfolane and Form II paracetamol, overriding the favourable hydrogen bonding interaction, or unfavourable molecular orientations that hindered the formation of a stable complex, leading to a positive binding energy. Despite these differences, the amide group of Form II paracetamol consistently formed hydrogen bonds with the oxygen atoms of all three solvents.

3.5 Comparative Study of Interaction Energies in Form I and Form II Paracetamol

Previously, we investigated the interaction energies of Form I paracetamol with solvents containing hydroxyl functional groups, such as amyl alcohol, benzyl alcohol, and phenol [15]. To further elucidate these interactions, this study compared the interaction energies of Forms I and II paracetamol with the same functional groups of solvents, i.e., hydroxyl. The results showed that the interaction energies differed between Forms I and II due to the distinct crystal surface chemistry exposed in each predicted morphology. Despite these variations, coulombic interactions, rather than van der Waals forces, were the predominant non-bonded interactions between the crystal surfaces and the solvents. Among the solvents studied, benzyl alcohol and phenol were favoured by Form I, particularly for certain facets. In contrast, phenol consistently exhibited the most negative non-bonded interactions with Form II paracetamol.

Form I paracetamol exhibited different binding energies for amyl and benzyl alcohols across its crystal surfaces due to variations in surface chemistry. The {002} surface showed the strongest binding, which might expose a higher density of functional groups favourable for interaction (e.g., oxygen atoms for hydrogen bonding). This strong binding primarily resulted from hydrogen bonding interactions between the oxygen atoms on the surface, the hydrogen donor groups in the solvent molecules, and potential dipole-dipole interactions. This was followed by {110} and {011}, likely due to differences in the arrangement of atoms on these surfaces. Interestingly, phenol interacted differently. Its bulkier aromatic ring and additional hydroxyl group compared to the alcohols might influence its interaction with the surfaces. The {002} surface again had the strongest binding, potentially because it offered a better fit for the phenol molecule.

In contrast, paracetamol Form II behaved differently. For the {002} and {111} surfaces, amyl alcohol likely experienced the strongest interaction due to its size and functional groups that complemented the surface chemistry. Phenol and benzyl alcohol might bind less strongly due to their size or the lack of optimal functional group alignment with the surface. However, the trend reverses for the {200} surface. Here, the shape of benzyl alcohol might allow it to fit more effectively compared to the larger amyl alcohol molecule. Overall, the morphology of Form I and Form II paracetamol could be controlled by its growth intermolecular interactions.

4.0 CONCLUSION

This study employed molecular modelling techniques to quantify the intermolecular interaction energies between Form II paracetamol and various solvent functional groups for the investigated surfaces ({002}, {111}, and {200}). The results demonstrated a clear trend that solvents capable of hydrogen bonding (carboxylic acids, esters, and ethers) exhibited the strongest non-bonded interactions due to dipole-dipole interactions and hydrogen bond formation. This is followed by solvents with sulfone groups and hydroxyls with weaker non-bonded interactions. Notably, sulfonates displayed the strongest binding energies, exceeding -70 kcal/mol, potentially hindering the incoming solute molecule at the surface of the crystal. This strong binding might have explained the observed shortened growth along the c-axis, suggesting a more stable configuration on this surface.

Conversely, ethers exhibited the weakest binding energies. The ESP surface contour map revealed the electron density distribution between the solute and solvent molecules, which helped explain the observed binding energies. The binding energy ratio between the {111}/{200} and {111}/{002} crystal facets of Form II paracetamol correlated with its growth morphology in carboxylic acid solvents, with a higher ratio leading to elongated scalenohedral crystals and a lower ratio resulting in rod-shaped or plate-like crystals. The significant differences in

interaction energies between Form I and Form II paracetamol highlighted the influence of the exposed surface chemistry on these interactions. It impacts crystal morphology, with coulombic interactions dominating van der Waals forces.

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Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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