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Research Article

Molecular insights: Aspirin-lactose monohydrate interactions for 3D-printed tablets via selective laser sintering

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Abstract
Understanding the synthonic and surface energy properties of a drug molecule is essential for optimising the performance of formulated products, particularly in the pharmaceutical industry. However, gaining this insight often requires costly trial-and-error experiments. In this study, advanced surface analysis tools were introduced that provided visualisation and topological information based on crystallographic data. By using functional group analysis, roughness calculations, and statistical interaction data, direct comparisons of crystal surfaces were enabled. Molecular modelling simulations were conducted utilising Material Studio 7.0 software to evaluate the suitability of lactose (as an excipient) and aspirin (as an active pharmaceutical ingredient, API) crystals for the selective laser sintering (SLS) 3D-printing process. The study also examined each crystal’s morphology, lattice energy convergence, and contributions, such as interatomic and intermolecular interactions. These simulations offered preliminary insights into the potential compatibility of the selected compounds. Surface analysis of the aspirin and lactose crystal facets ranked their stability from strongest to weakest. For aspirin, the ranking was (1 0 0), (0 1 1), and (0 0 2), while for lactose, the order was (0 2 0), (0 0 1), and (0 1 1), indicating greater stability in the lactose facets. Theoretically, crystal faces with higher attachment and slice energies grow more rapidly and hold less morphological importance (MI), resulting in smaller surface areas. The stability of lactose monohydrate crystals may be linked to the presence of water molecules in their structure, which enhance the binding between the two substances. The study further demonstrates its practical relevance by correlating the sticking propensity of different aspirin and lactose surfaces with surface and particle descriptors derived from their single crystal structures. Interaction maps and surface roughness characteristics revealed that all three aspirin facets displayed hydrophobic behaviour, while the selected lactose facets exhibited hydrophilic properties, with a strong tendency for hydrogen bonding interactions due to the presence of hydrogen bond donors and acceptors.

Keywords: aspirin, lactose monohydrate, synthonic interaction, surface analysis, simulations

Introduction

The investigation into the molecular interactions between aspirin and lactose monohydrate in the context of 3D-printed tablets using selective laser sintering (SLS) is essential for optimising pharmaceutical formulations. SLS technology offers precise control over dosage forms, making it critical to understand the intermolecular interactions between the active pharmaceutical ingredient (API) and excipient when developing a successful solid dispersion formulation. Understanding these interactions is key to determining compatibility or miscibility, which in turn aids in the rational design and screening of drug formulations, reducing both the costs and risks of drug development. In this study, aspirin and lactose monohydrate were chosen as the API and excipient, respectively. Aspirin or acetylsalicylic acid is composed of an acetyl group attached to a salicylic acid structure, featuring both a carboxyl group (-COOH) and an ester group (-COOR). It is mildly polar and can form hydrogen bonds or hydrophobic interactions depending on its environment. Lactose monohydrate, on the other hand, is a disaccharide comprising glucose and galactose units with a single water molecule bound to the structure. Due to its multiple hydroxyl (-OH) groups, it is highly polar and capable of forming numerous hydrogen bonds. In SLS, aspirin and lactose are fused selectively by a laser to create a solid structure layer by layer. The thermal and molecular interactions between aspirin and lactose during this process are critical in determining the properties of the final printed tablet (printlet). The high temperature from the SLS printer can cause partial or complete melting of the powders, allowing fusion, but it also carries the risk of drug degradation due to laser-induced heat [1]. Thus, this study aimed to assess the compatibility of aspirin and lactose for SLS printing by investigating their synthonic and surface interactions.

Many attempts have been made to link crystal morphology with its internal molecular structure. The Bravais-Friedel-Donnay-Harker (BFDH) method focuses solely on the geometry of crystal lattices, assuming that the relative growth rates (R_{hkl}) of crystal faces are inversely proportional to the interplanar distance (d_{hkl}). However, this method does not take into account the chemical properties or molecular packing arrangement of the crystal. The BFDH model is based on the principle that stronger intermolecular interactions lead to higher slice energy, resulting in larger interplanar lattice spacings. To overcome the limitations of this model, alternative approaches, such as growth and equilibrium morphology have been employed to calculate the attachment and slice energy of specific crystal facets. The attachment and slice energies of a given facet are complementary, and the growth rate is directly related to the attachment energy. Attachment energy (E_{att}) is defined as the energy released per mole of molecules when a new layer with thickness d_{hkl} attaches to the crystal surface. This energy is linked to the growth rate perpendicular to the crystal face; faces with higher attachment energy grow more quickly but have lower morphological importance (MI), leading to smaller surface areas. In contrast, slice energy (E_{sl}) refers to the energy required to remove a slice of the crystal parallel to a particular facet. Lower slice energy suggests that the formation of a slice along that facet is easier, which corresponds to greater stability and a larger surface area. On the other hand, facets with higher slice energy tend to be less stable and have smaller surface areas, as they are more energetically expensive to maintain.

The practical significance of this study is highlighted by establishing a connection between the sticking propensity of aspirin and lactose and the surface and particle descriptors obtained from their single crystal structures. The full interaction map provides valuable insights into the distribution and likelihood of potential binding sites on a crystal surface. These interactions are visualised by highlighting regions with a high probability of forming hydrogen bonds, hydrophobic areas, or polar interactions. Surfaces with hydrophilic regions, often indicated by hydrogen bond donors and acceptors, tend to effectively adsorb polar molecules. In contrast, hydrophobic regions, such as exposed methyl or aromatic groups, may preferentially adsorb nonpolar species [2]. Crystal surfaces with a high density of exposed functional groups, like hydroxyl or carboxyl groups, serve as efficient adsorption sites. For example, surface areas that display strong hydrogen bonding potential (marked as blue or red regions on the interaction maps) are more likely to facilitate adsorption through hydrogen bonding with incoming molecules [3]. Regarding surface roughness, higher rugosity values indicate a larger surface area available for interaction. Rough surfaces, especially those with high skewness and kurtosis, typically feature peaks and valleys, leading to greater adsorption performance compared to smoother surfaces [4].

Materials and Methods

Crystal structure

The crystal structures of aspirin (ref code: ASCALA 12), serving as the active pharmaceutical ingredient (API), and lactose monohydrate (ref code: LACTOS11), acting as the excipient, were sourced from the Cambridge Crystallographic Data Centre (CCDC). Aspirin's structure comprises a benzene ring, along with ester and carboxylic acid functional groups, while lactose features two pyranose rings and a water molecule, forming a dimer in its crystal structure. **Figure 1** and **Figure 2** illustrate the crystal structures of aspirin and lactose monohydrate, respectively, as viewed along the x-, y-, and z-axis directions. The structures are arranged in monoclinic lattices, with aspirin belonging to the space group P21/c and lactose to the space group P21. Both structures exhibit periodic hydrogen bonds extending in all three dimensions, contributing to 3D hydrogen bond dimensionality.

Synthonic interaction analysis

The calculation of intermolecular interactions was done by Habit98 program to compute the intermolecular contributions to the energy per mole in a unit cell. The empirical force field that was deem fit for aspirin and lactose monohydrate was Nemethy [5] and Lifson [6], respectively. The selection was done by choosing values that has the closest value with its sublimation enthalpy of each compound.

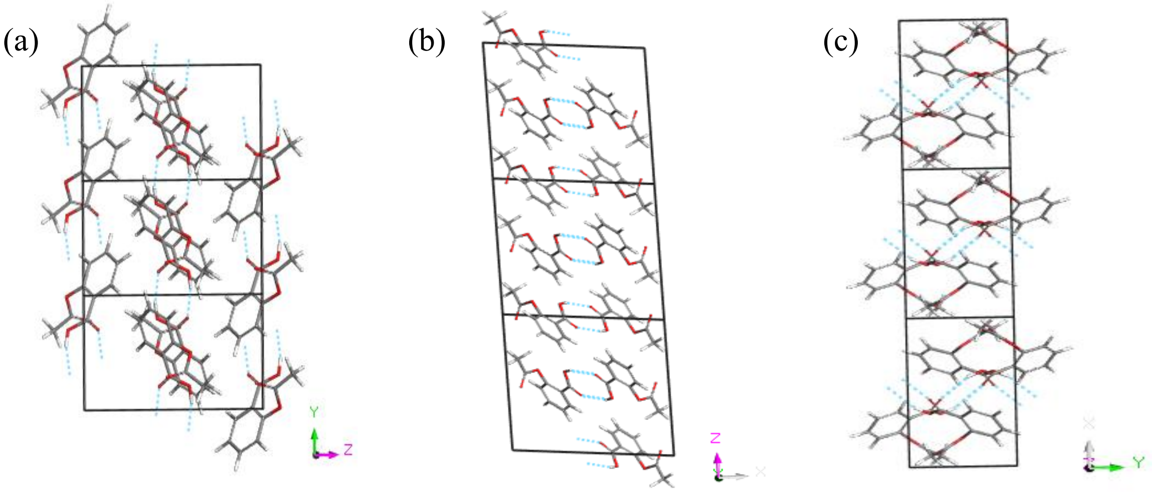


Figure 1. Molecular structure of aspirin within the crystal lattice, viewed from (a) the x-direction, (b) the y-direction, and (c) the z-direction, highlighting the 3D dimensionality of the hydrogen bonding network

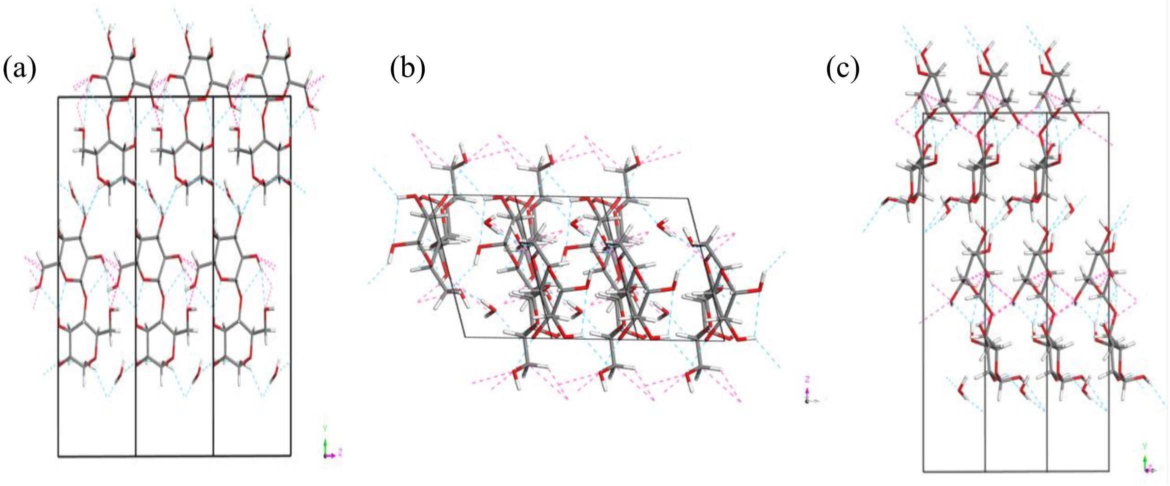


Figure 2. Molecular structure of aspirin within the crystal lattice, viewed from (a) the x-direction, (b) the y-direction, and (c) the z-direction, highlighting the 3D dimensionality of the hydrogen bonding network

Geometry optimisation and morphology prediction

BIOVIA Material Studio 7.0 was utilised for geometry optimisation and morphology prediction. The geometry of aspirin and lactose monohydrate within a unit cell was optimised and minimised by using the universal and polymer consistent force field (PCFF), respectively. Atom charges were computed by using the Gasteiger method. The morphology of the selected compounds was predicted by using the Bravais-Friedel-Donnay-Haker (BFDH), growth morphology (GM), and equilibrium morphology (EM) models. The facets with the largest interplanar spacing, (d_{hkl}), are likely to be significant in terms of morphology. For these facets, the lattice energy (E_{latt}) was divided into slice energy, (E_{sl}), and attachment energy, (E_{att}), as outlined in the equation below:

$$E_{latt} = E_{sl} + E_{att} \qquad [7]$$

Where, the slice energy (E_{sl}), is defined as the sum of all interactions between a central molecule and all other molecules within a growth slice of thickness (d_{hkl}), In contrast, the attachment energy (E_{att}), represents the sum of all interactions between the central molecule and molecules located outside the growth slice.

Surface topological analysis

Mercury software utilises pre-extracted IsoStar interaction data from the CSD to calculate surface regions where chemical probe groups are likely to interact. The process begins by identifying distinct functional groups on the observed surface, as described by Bruno et al. [8]. It then retrieves relevant interaction data from IsoStar, integrates this group-based data, and considers steric exclusion and environmental combinative factors to produce a detailed 3D representation of molecular interaction preferences. The likelihood of interaction is visually represented by the colour chosen for the probe. To identify hotspots for each type of probe, the "generate hotspots in the map" option is selected. Additionally, to explore hydrogen bonding interactions, the H-bond line is double-clicked, revealing interactions between molecules and the surface.

Results and Discussion

Synthonic interaction analysis

To predict crystal morphology, it is essential to understand the intermolecular interactions and the energy involved in the addition of new molecules (attachment) or layers (slices) to growing crystal lattices. These energetic factors are referred to as attachment energy (E_{att}) and slice energy (E_{sl}). A detailed analysis of the intermolecular synthons, ranked by their strength, is summarised in **Table 1**. The three strongest synthons showed that the crystal structures of aspirin and lactose are primarily influenced by hydrogen bonding, except for synthon B in lactose. The growth faces and overall morphology of aspirin and lactose crystals are predicted to be shaped by synthon A, which controls the strongest hydrogen bonding between the -OH groups, functioning as both hydrogen bond donors and acceptors. In both aspirin and lactose crystals, synthon A makes the largest contribution to the lattice energy, with synthonic strengths of -11.46 kJ/mol and -28.9 kJ/mol, respectively. Moreover, these synthons are expected to contribute to the E_{sl} for the top three cleaved facets.

Theoretically, slice energy corresponds to detachment or cutting energy, while attachment energy is associated with growth rates during the crystallisation process. The top three cleaved facets of synthon A in both aspirin and lactose were found to contribute more to E_{sl} than E_{att} (**Figure 3**). This may be due to the atomic packing and surface energy of the crystal facets. The arrangement of surface atoms varies across different crystal facets, influencing their stability and reactivity. Additionally, the high-index facets of both aspirin and lactose exhibit loosely packed atoms, which have more dangling bonds and higher surface energy. As a result, these facets are more susceptible to slice energy, since less energy is required to break the bonds of the loosely packed atoms on these surfaces.

Morphology prediction

The surface energy of different habit faces has been successfully computed, along with the attachment energy calculations. The crystal growth morphology of aspirin and lactose crystals has been modelled based on the computed attachment energies of various habit faces, as shown in **Table 2**. Since the BFDH (Bravais, Friedel, Donnay, and Harker) model closely matches the observed morphology, it will be used for further discussions. However, the attachment energy calculations remain valuable for surface chemistry analysis. The facet with the highest percentage of total surface area and the lowest attachment and slice energies is considered the slowest-growing and therefore the most morphologically important (MI). For aspirin, the (1 0 0) face is the most important, while for lactose, it is the (0 0 1) face.

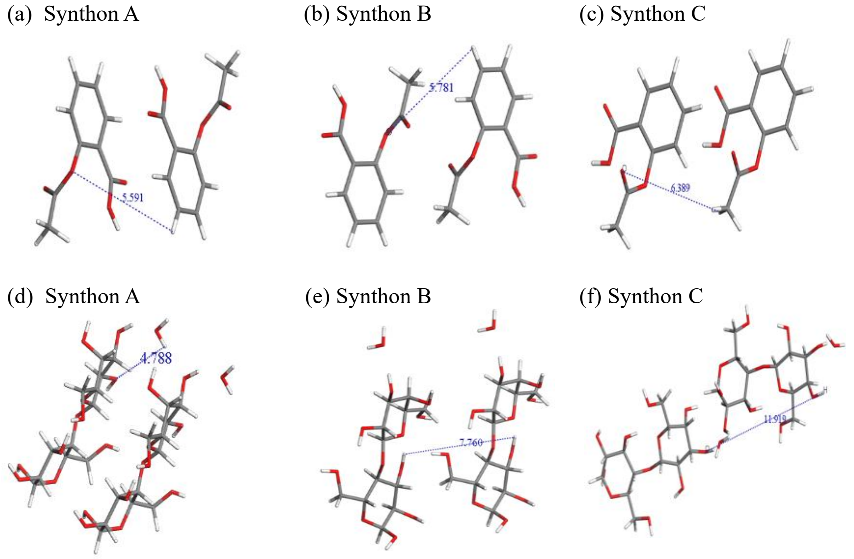
According to the predicted morphology shown in **Figure 4**, the top three dominant facets of aspirin crystals are by rank order (1 0 0), (0 1 1), and (0 0 2). The (1 0 0) facet has the lowest attachment and slice energies, leading to slower growth on this facet and resulting in the largest surface area compared to other facets. The (1 0 0) facet accounts for over 50% of the overall aspirin crystal, followed by the (0 1 1) and (0 0 2) planes, which make up 27.59% and 18.74% of the total facet area, respectively. The (1 0 0) facet covers the largest facet area because of its relatively low suggests slow growth. The moderate E_{sl} (39.36 kcal/mol) indicates that the intermolecular cohesion is not extremely strong, which further contributes to its stability and large surface area.

Table 1. The top three strongest synthons within ASA and LM crystals

Synthon	Intermolecular Synthon Type	Multiplicity	Distance (Å)	Coulombic (kJ/mol)	Synthon Strength (kJ/mol)	(1 0 0)	(0 1 1)	(0 0 2)
Aspirin								
A	H-bond	4	5.40	1.26	-11.46	E_{sl}	E_{sl}	E_{sl}
B	H-bond	4	5.91	-0.67	-11.05	E_{att}	E_{att}	E_{att}
C	H-bond	4	27.41	-1.67	-9.83	E_{sl}	E_{sl}	E_{sl}
Lactose Monohydrate								
A	H-bond	4	4.78	-5.23	-28.91	E_{sl}	E_{sl}	E_{sl}
B	vdW	4	7.76	-3.55	-7.91	E_{sl}	E_{sl}	E_{sl}
C	H-bond	4	11.88	-4.69	-6.40	E_{sl}	E_{sl}	E_{sl}

As for the (0 1 1) facet, which has a smaller facet area than (1 0 0) and slightly higher attachment energy (-42.52 kcal/mol). This suggests faster growth than the (1 0 0) face but still relatively stable. The slice energy is higher (45.35 kcal/mol), suggesting that intermolecular interactions within this facet are stronger. As shown in **Figure 4(c)**, the low attachment energy of the (1 0 0) facet is mainly due to the exposed -OH groups at the surface termination, which promote offset stacking of aspirin molecules. Additionally, higher E_{sl} values indicate stronger cohesion between molecules in the slice and more robust intermolecular bonds, potentially increasing the hydrophobicity of these crystal faces [9]. On the other hand, the (0 0 2) facet has the smallest facet area and the highest E_{sl} value (66.79 kcal/mol), indicating strong intermolecular cohesion. Its attachment energy is also least negative (-21.08 kcal/mol), suggesting faster growth, leading to a smaller facet area.

For lactose crystals, the attachment energy model predicts the (0 2 0) facet to have the highest morphological importance (MI), followed by the (0 0 1) and (0 1 1) facets, which have similar surface areas (**Figure 5**). The smooth (0 2 0) plane, characterised by its plate-like morphology, occupies the largest fractional surface area at 25.79% (according to the BFDH method), followed by 17.09% for the {0 0 1} plane and 9.62% for the {0 1 1} plane. The (0 2 0) face with an E_{att} value of -22.95 kcal/mol, this face grows relatively slowly. Its E_{sl} value of 42.45 kcal/mol suggests moderate molecular cohesion, hence stabilising this face. As for the (0 0 1) facet, this face has a slightly smaller facet area than the (0 2 0) facet. Its E_{att} is similar, indicating a similar growth rate. The E_{sl} value of 43.22 kcal/mol is also similar close to (0 2 0) facet, indicating slightly stronger intermolecular forces. Meanwhile, the (0 1 1) facet has the smallest facet area since it has the highest E_{sl} (45.59 kcal/mol), suggesting strong intermolecular interactions. Its highest attachment energy (-19.81 kcal/mol) implies faster growth as compared to the other two facets, contributing to its smaller surface area. Most of the terminating surfaces of lactose are characterised by hydroxyl functional groups, which act as binding sites for the attachment of other molecules in the solutions. This occurs because these surfaces contain both hydrogen bond acceptors and donors, facilitating strong intermolecular interactions like hydrogen bonding.


(a) Synthon A

(b) Synthon B

(c) Synthon C

(d) Synthon A

(e) Synthon B

(f) Synthon C

Figure 3. The top three intramolecular synthons of (a)-(c) aspirin and (d)-(f) lactose crystals showing their respective distance using Habit98 program

Table 2. The top three morphology importance faces analysis of aspirin and lactose monohydrate using three different tools

Compound	**Aspirin**			**Lactose monohydrate**		
Total E_{latt} (kcal/mol)	-87.87			-65.40		
Face (h k l)	**(1 0 0)**	**(0 1 1)**	**(0 0 2)**	**(0 2 0)**	**(0 0 1)**	**(0 1 1)**
Total Facet Area (%)	51.83	27.59	18.74	25.79	17.09	9.62
Total E_{att} (kcal/mol)	-48.51	-42.52	-21.08	-22.95	-22.18	-19.81
Total E_{sur} (kcal/mol)	0.17	0.15	0.14	0.11	0.15	0.10
Total E_{slice} (kcal/mol)	39.36	45.35	66.79	42.45	43.22	45.59

Surface topological analysis

An understanding of the surface topology on the top three most MI facets of aspirin and lactose crystals is further clarified to better rationalise their particle properties. **Table 3** and **Table 4** below provide descriptions of the surface characteristics for each MI face of aspirin and lactose, while the full interaction maps of these crystal facets are illustrated in **Figure 6** and **Figure 7**. To create interaction maps between the facets and potential surface interactions, each facet was treated as proxy. These maps reveal different interactions sites on the surface. Red regions represent areas with a high likelihood of hydrogen bond acceptors (such as carbonyl oxygen), brown regions highlight hydrophobic preferences (aromatic CH carbon), and blue regions indicate hydrogen bond donors (like uncharged NH nitrogen). Various contour surfaces are employed to demonstrate how much more likely an interaction is at a given point compared to random probabilities. The highest contour levels, which are the most opaque, help visualise all contour surfaces together. Meanwhile, red dashed lines indicate the presence of hydrogen bonding interactions.

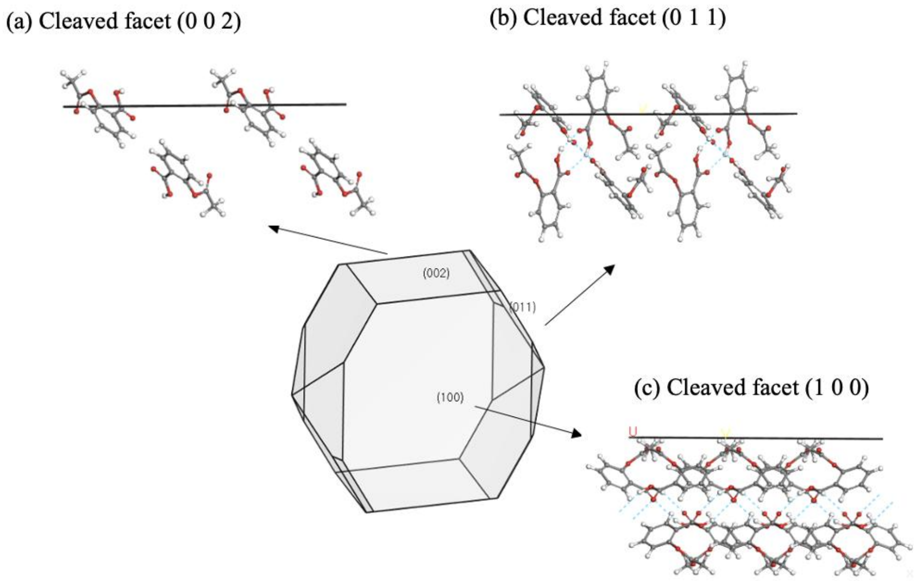

(a) Cleaved facet (0 0 2)
(b) Cleaved facet (0 1 1)
(c) Cleaved facet (1 0 0)

Figure 4. Top 3 cleaved facets of aspirin molecules

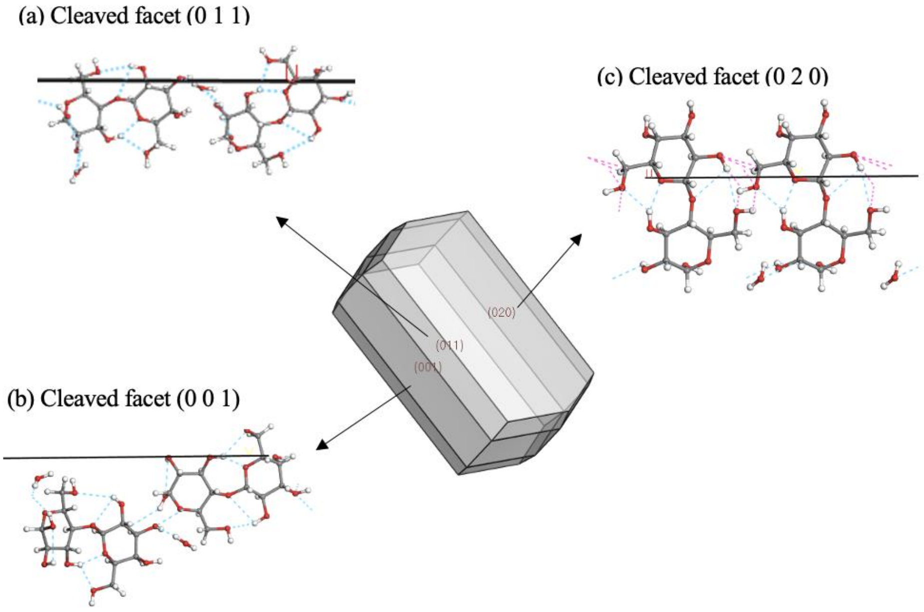

(a) Cleaved facet (0 1 1)
(c) Cleaved facet (0 2 0)
(b) Cleaved facet (0 0 1)

Figure 5. Top 3 cleaved facets of lactose molecules

Table 3. Surface descriptors for the MI faces of aspirin molecules

Density Info (counts/Å^2)			
Face (h k l)	**H-bond Acceptors**	**H-bond Donors**	**Aromatic Bonds**
(1 0 0)	0.054	0.000	0.054
(0 1 1)	0.055	0.014	0.096
(0 0 2)	0.054	0.014	0.109

Topology Info						
Face (h k l)	**Surface Area (Å^2)**	**Projected Area (Å^2)**	**Rugosity**	**RMSD**	**Skewness**	**Kurtosis**
(1 0 0)	200.25	145.436	1.377	1.005	-0.166	2.323
(0 1 1)	96.657	73.509	1.315	0.713	0.133	2.097
(0 0 2)	90.289	73.496	1.228	0.566	-0.138	2.090

When analysing the interaction maps for aspirin crystals facets (**Figure 6 a-c**), it becomes clear that the smooth (0 0 2) face has the largest surface area compared to other faces. Based on the results tabulated in **Table 3** below, the H-bond acceptor density of (1 0 0) face is 0.054, while no H-bond donors are present on this surface. This suggests that the (1 0 0) face is more likely to attract hydrogen bond donors (like -OH or -NH groups) from other molecules due to the presence of acceptor sites but does not contribute to hydrogen bonding as a donor itself. As for the H-bond acceptor density of (0 1 1) face which has almost similar to the (1 0 0) face at 0.055, with a small presence of H-bond donors of 0.014. This means that this facet could engage in both donating and accepting hydrogen bonds, hence contributing to stronger intermolecular forces. The (0 0 2) face however exhibits more aromatic bonds than the other two face (0.109), implying hydrophobic interactions may play a role on this facet. The hydrophilic and carbonyl characteristics of this face promote the formation of hydrogen-bonded dimer pairs. Additionally, since these facets dominate the overall crystal shape, it is expected that the surface's carboxylic acid functional groups will result in a higher sticking propensity. The exposed methyl end of aspirin molecule is predicted to display hydrophobic behaviour on the (0 0 2) face, confirmed by the presence of brown regions in **Figure 6 (c)**, indicating hydrophobicity. This hydrophobic nature could be attributed to aspirin's high crystallinity, which enhances hydrophobicity and, in turn, increases adsorption performance [10].

Next, the nodes characterising the surface topology were used to quantify the surface roughness of each individual facet. Roughness refers to surface periodicity and is measured on the atomistic scale. Rugosity, RMSD (root mean square deviations), skewness, and kurtosis, as listed in **Table 3** and **Table 4**, were used to characterise crystal surfaces. Rugosity is the ratio of the projected area to the surface area, describing the roughness of the crystal facet. A perfectly smooth surface would have a rugosity of 1.0. It was found that all three cleaved facets were moderately rough. The (1 0 0) facets of aspirin experiences molecular inhibition, leading to an enlargement of its surface area, followed by the (0 1 1) and (0 0 2) facets. The rugosity of the (0 1 1) facet was the highest amongst the three, and the RMSD of the node heights was measured at 1.005Å, indicating significant surface variability in terms of height. A rougher surface can lead to a higher likelihood of molecule attachment, which may slow down the crystal growth rate. The (0 0 2) face has a rugosity of 1.228 and RMSD value of 0.566Å, meaning it is smoother than the (1 0 0) face but still somewhat rough and more uniform in its topology. Its lower attachment energy may allow faster growth. Meanwhile, the (0 1 1) face with a rugosity of 1.315 falls between the other two faces in terms of roughness, making it moderately smooth.

Next, the parameters of skewness and kurtosis provide a numerical description of the height distribution across each facet. The negative skewness value of -0.166 for the (1 0 0) and -0.138 for the (0 0 2) facets suggest that the height distribution is skewed below the mean plane, meaning there are more valleys than peaks on the surface. According to Pearson's kurtosis, values greater than 3 indicate extreme surface variations, either with deep valleys or high peaks. For the (1 0 0) surface, a kurtosis value of 2.323 was calculated, which is close to the standard value, indicating a relatively typical distributions of heights with moderate peaks and valleys. These values help illustrate the surface characteristics, where the (0 1 1) facet exhibits the roughest topology with more pronounced variations in height distribution compared to the (1 0 0) and (0 0 2) facets. In conclusion, the (1 0 0) facet has the roughest surface, with high rugosity and RMSD, dominated by hydrogen bond acceptors, and a significant role in crystal inhibition due to surface roughness. As for the moderately rough (0 1 1) facet, comes with its ability to act as both hydrogen bond donor and acceptor, leading to strong interactions. It shows a slightly skewed surface with higher peaks.

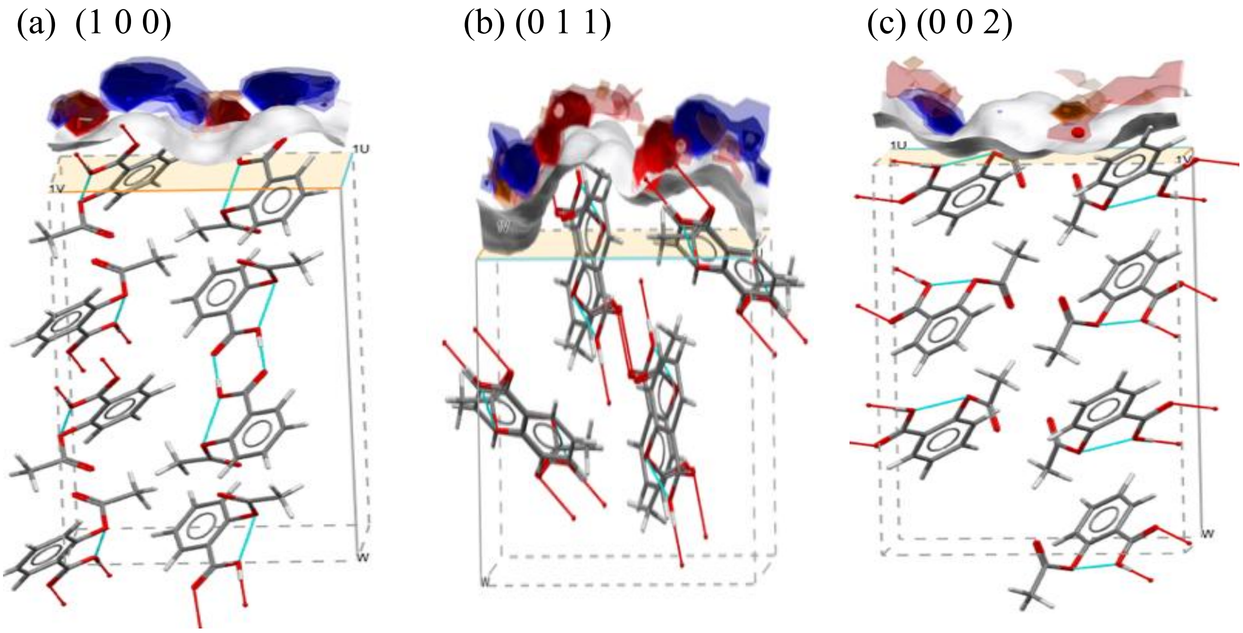


Figure 6. Full interaction maps of aspirin molecules at three different MI facets

Meanwhile, the smoother and more hydrophobic (0 0 2) facet is likely to experience faster growth due to lower attachment energy and less roughness.

The interaction maps for the (0 2 0) facet exhibits strong hydrogen-bonding potential with both hydrogen bond acceptors and donors having the same density of 0.084. This is seen in the regions where the pyranose rings are exposed, facilitating hydrogen bond formation between neighbouring molecules. The absence of aromatic bonds making it more hydrophilic. Similar to the (0 2 0) facet, (0 0 1) facet shows balanced hydrogen bonding with equal densities of hydrogen bond donors and acceptors (0.068). It indicates strong hydrogen-bonding interactions that drive the growth and stability of the facet. The interaction maps and surface roughness characteristics indicate that all three facets are hydrophilic, with a strong tendency for hydrogen bonding interactions due to the presence of hydrogen bond donors and acceptors. Amongst these, the (0 1 1) surface was found to be roughest, with a rugosity value of 1.456 and an RMSD of 1.940 Å. The kurtosis value for this surface, 2.486, is close to Pearson's kurtosis standard, further confirming the moderate roughness of the surface. Given this roughness, the initiation of new layers during growth is expected to be relatively easy. Conversely, new layer formation on smoother surfaces is more challenging, which is often the case for crystal growth from vapour, dilute solutions, and molecular materials during crystallisation processes.

Table 4. Surface descriptors for the MI faces of lactose monohydrate molecules

Density Info			
Face (h k l)	**H-bond acceptors**	**H-bond donors**	**Aromatic bonds**
(0 2 0)	0.084	0.084	0.000
(0 0 1)	0.068	0.068	0.000
(0 1 1)	0.073	0.083	0.000

Topology Info						
Face (h k l)	**Surface Area ($Å^2$)**	**Projected Area ($Å^2$)**	**Rugosity**	**RMSD**	**Skewness**	**Kurtosis**
(0 2 0)	49.483	35.694	1.386	0.824	0.169	2.142
(0 0 1)	146.175	103.026	1.419	1.454	0.203	2.092
(0 1 1)	147.883	109.034	1.456	1.940	0.601	2.486

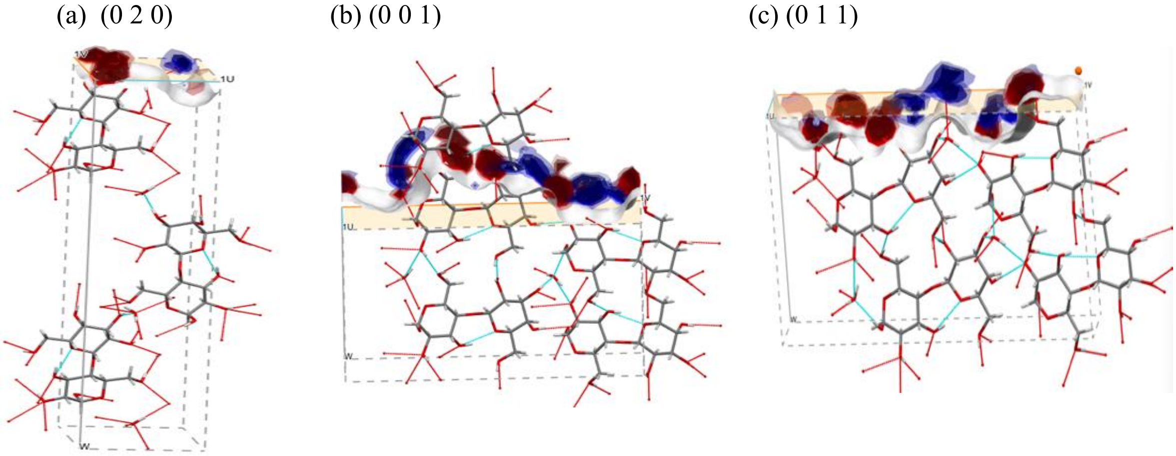

(a) (0 2 0) (b) (0 0 1) (c) (0 1 1)

Figure 7. Full interaction maps of lactose monohydrate molecules at three different MI facets

Conclusion

The interactions between aspirin and lactose monohydrate during 3D printing via SLS are complex but pivotal for the physicochemical characteristics of the printed tablet. Understanding and controlling these molecular interactions can lead to tailored drug delivery systems with improved efficacy and stability. In the present paper of a first principal calculation has been performed to compute the slice and attachment energy for various habit faces of both aspirin and lactose monohydrate crystals. The relationship between the surface area of a crystal facet with its attachment energy, E_{att} and slice energy, E_{sl} is essential for understanding the stability, growth, and morphology of crystals. Both E_{att} and E_{sl} are rooted in how the molecules in a crystal interact with one another, and they directly influence the overall stability and growth rate of specific crystal facets. By analysing the synthonic and surface interactions, the authors conclude that aspirin and lactose monohydrate exhibit moderate compatibility for the SLS printing process. Their ability to form hydrogen bonds and their surface energy characteristics support potential sintering, but the thermal sensitivity of aspirin and the water content in lactose monohydrate are key challenges. Careful optimisation of laser parameters and formulation strategies are essential to ensure efficient sintering and drug stability during the SLS printing process.

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