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Elucidating the Intermolecular Interactions and Crystallographic Structure of Aspirin and Lactose Monohydrate by Synthonic Modelling

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This study is conducted to determine the morphologies of aspirin (ASA) and lactose monohydrate (LM) via molecular modelling tools. The simulations of the crystal morphology of ASA-LM have been made upon geometrical, lattice energy, intermolecular bonding, and interatomic analysis by Accelrys Material Studio and Habit98. The crystalline structure's synthons were calculated using atomistic force fields derived from emipirical data. In this study, synthonic modelling was carried out using optimised molecular structure using Nemethy and Lifson force fields, including morphological prediction. The predicted lattice energies of ASA-LM were in excellent agreement with the previous study, with a percentage deviation of 5.17 % and 10.52 %. The morphology of ASA-LM was predicted to be hexagonal in shape. Furthermore, it was discovered that hydrogen bonds, with intermolecular strengths of -11.46 kJ/mol and -28.91 kJ/mol dominated the lattice energy of both ASA-LM. The findings also showed that ester holds the significant contributions of the functional group in ASA at 76.12 %, whereas hydroxyl functional groups account for most contributions in LM at 58.01 %.

1. Introduction

It is imperative to obtain the desired morphology of a crystal to manage the flow properties, product yield, and downstream processing in the pharmaceutical industry. Powder flowability is determined by the type and extent of interparticle interactions occurring in the molecular crystals. In the pharmaceutical industrial sector, crystalline materials with anisotropic shapes might be a drawback during production (Nguyen et al., 2017). Therefore, it is important to understand the interaction of the crystal surface with the surrounding solution during crystal formation before proceeding to the downstream processing of drugs. Synthonic molecular modeling, such as Material Studio and Habit98 software, can determine a crystal structure's morphology, lattice energy, and intermolecular and interatomic interactions. Nowadays, predicted morphology has become a complementary alternative before experimental works as it may be utilised to provide insight into the relationship between structural characteristics and their physical qualities. it is crucial to comprehend and characterise the bulk crystal. Syntonic molecular modelling can be used to determine the morphology, lattice energy, intermolecular and interatomic interactions of a crystal structure. As it may be utilised to provide insight into the relationship between structural characteristics and their physical qualities. The knowledge of the strengths and contribution of intrinsic synthons (critical bulk) and extrinsic synthons (crystal surface) to crystal growth enables the prediction of the crystallisation effect on crystal morphology. This is actively exploited to reduce the requirement for extensive laboratory studies. Thus, this work focuses on three main goals: *i)* the establishment of an experimental structural and sublimation enthalpy database to serve as a benchmark for the evaluation of force fields; *ii)* the use of molecular modelling tools (Accelrys Material Studio) to predict the crystal structure of ASA and LM and *iii)* determining the morphology and lattice energies and their convergence analysis (limiting radius, intermolecular and interatomic analysis) by Habit98.

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2. Materials

2.1 Crystal structure

The software programme Materials Studio does conventional molecular mechanics (version 3.1, Accelrys). Both the ASA (Shtukenberg et al., 2017) and the LM (Lukman et al., 2020) molecules' structural data were retrieved from the Cambridge Crystallographic Data Centre (CCDC). Based on Figure 1 below, ASA has an aromatic hydrocarbon, carboxylic acid, ester, and methyl group in its structure, whilst LM has two pyranose rings and a water molecule forming a dimer in its structure. Both structures were packed in a monoclinic lattice with space groups of $P_{21/c}$ and P_{21}, which consisted of four ASA molecules and two LM molecules with two water molecules of the same conformation in a unit cell.

(a) (b)

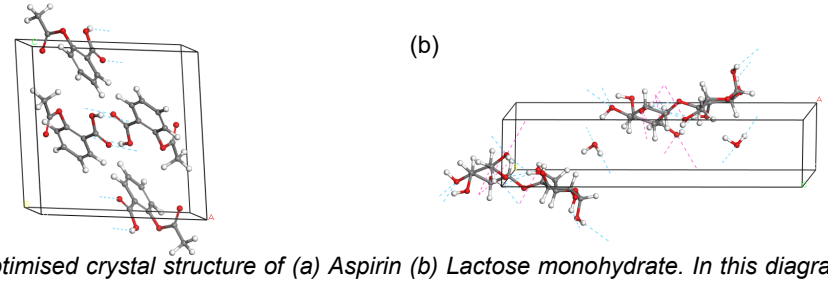

Figure 1: Optimised crystal structure of (a) Aspirin (b) Lactose monohydrate. In this diagram, hydrogen atoms are depicted in white, oxygen atoms are shown in red, and carbon atoms are shown in grey.

3. Method

3.1 Structure conformation analysis

BIOVIA Material Studio 7.0 was used to predict crystal morphology from the atomic structure of ASA and LM crystals, and their structural information was retrieved from the Cambridge Crystallographic Data Centre (CCDC). A Universal force field was used for ASA and PCFF for LM for molecular structure optimisation calculation. The observed morphology of the ASA-LM crystals was compared with three different tools: BFDH, growth morphology (GM) and equilibrium morphology (EM).

3.2 Computation of lattice energy and crystal chemistry

The calculation of lattice energies, intermolecular and interatomic interactions was done by Habit98 program to compute the intermolecular contributions to the energy per mole in a unit cell. The suitable empirical force field methods and calculated atomic charges for morphology simulations were selected prior to synthonic modelling. The calculation of intermolecular interaction energies in ASA and LM were performed by using Nemethy (Nemethy et al., 1983) and Lifson (Lifson et al., 1979) force field, respectively.

4. Results and discussion

4.1 Molecular lattice energy

Table 1 compares lattice energies predicted and literature value and their sublimation enthalpies. A comparison between the predicted and literature value of lattice energies shows that the percentage deviation varies between 5.17 % and 10.52 %. The predicted value, which shows a high deviation of more than 100 % from the reference value, is not suitable to be used for further modeling calculation (Anuar et al., 2012). Hence, the difference between the predicted and reference value was taken as a good approximation.

Table 1: Comparison between the predicted and literature value of lattice energies and its sublimation enthalpy.

Compound	Predicted value	Literature value	
	E_{latt} by Habit98 (kJ/mol)	E_{latt} by Habit98 (kJ/mol)	ΔH_{sub} (kJ/mol)
ASA	-102.59	-114.65[a]	-109.7[a]
LM	-159.87	-168.58[b]	-165.06[b]

[a]Li et al., (2006)
[b]Lukman et al., (2018)

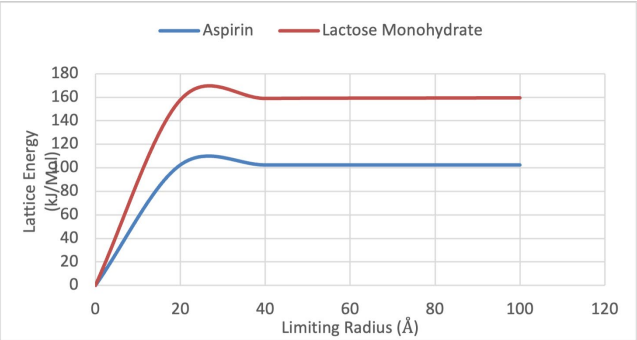

Figure 2: The convergence of the lattice energy with summation radius

To investigate the possibility of a systematic error in lattice minimization energy calculation, the convergence of lattice energies for ASA and LM were plotted against its limiting radius (Figure 2). The fully converged calculated lattice energy of ASA and LM calculated from the sublimation enthalpy of -109.7 kJ/mol and -165.06 kJ/mol, was in good agreement with the literature value. This shows that the synthons within the crystal structures of ASA and LM can be reproduced in Nemethy and Lifson potential in an appropriate manner. The low contribution of coulombic interactions reflects most of the molecules in ASA and LM are apolar in nature. This is because only H-bonding dimers between adjacent carboxylic acids in ASA and alcohol groups in LM molecules contain significantly electronegative atoms to support the molecules' polar nature.

4.2 Morphology simulations

Aspirin

The predicted morphology based on BFDH, GM, and EM of ASA reveals a tabular, roughly hexagonal-shaped morphology, with dominant {100} forms and {011}, {110}, and {002} forms present. Among the three morphology tools used, GM has the simplest prediction of ASA crystal, which contains only 4 crystal facets. The {002} face is expected to show hydrophobic behaviour as the methyl end of the ASA molecule is exposed. As shown in Figure 3 (d), the molecules are aligned alternately parallel and perpendicular to the surface, exposing apart of hydroxyl, ester groups, and benzene ring carbonyl as potential bonding sites.

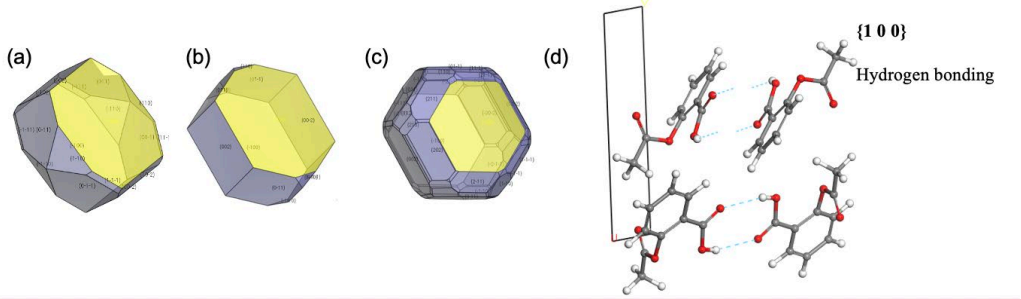

Figure 3: Morphology prediction of LM crystal compound (a) BFDH (b) GM (c) EM (d) Cleaved surface of {100}

Lactose monohydrate

Based on Figure 4 below, the morphology shows a leafy hexagonal and thin elongated shape with a corner angle of about 120° each. The smooth {020} plane was found as the greatest fractional surface area as it has a plate-like morphology compared to other planes. Hence, {020} plane crystal habit was cleaved and analyzed. The exposed faces of {020} are essential in driving the growth rate of the crystallization process as it promotes the formation of a hydrogen bond. The 2 pyranose rings were found perpendicular to the surface, while the water molecule was placed parallel to the surface.

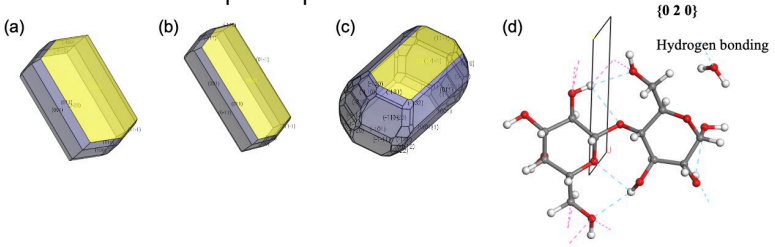

Figure 4: Morphology prediction of LM crystal compound (a) BFDH (b) GM (c) EM (d) Cleaved surface of {020}

4.3 Intermolecular bonding

Aspirin

Table 2 summarises the intermolecular analysis obtained from ASA crystals. As depicted in Figure 5 below, the strongest bond in the intermolecular interaction of ASA was in synthon A, where the hydrogen bond occurs at the shortest distance of 5.40 Å with a bond strength of -11.46 kJ/mol. The strength of the bond was contributed most by the attractive forces between hydrogen and oxygen atom. Most of the intermolecular interactions created were hydrogen bonds due to the molecular structure of ASA itself, where the hydroxyl group is exposed.

Table 2: Summary of intermolecular analysis of ASA crystal by using Habit98

Synthon	Dominating Electronic Forces	Multiplicity	Direction (u v w)	Distance (Å)	Attractive (kJ/mol)	Repulsive (kJ/mol)	Coulombic (kJ/mol)	Total energy (kJ/mol)
A	H-bond	4	(-1 1 -1)	5.40	-22.22	9.50	1.26	-11.46
B	H-bond	4	(2 1 1)	5.91	-23.60	13.26	-0.67	-11.05
C	H-bond	4	(0 -1 0)	27.41	-17.24	9.08	-1.67	-9.83
D	H-bond	4	(0 1 0)	27.41	-16.57	9.08	-1.67	-9.16

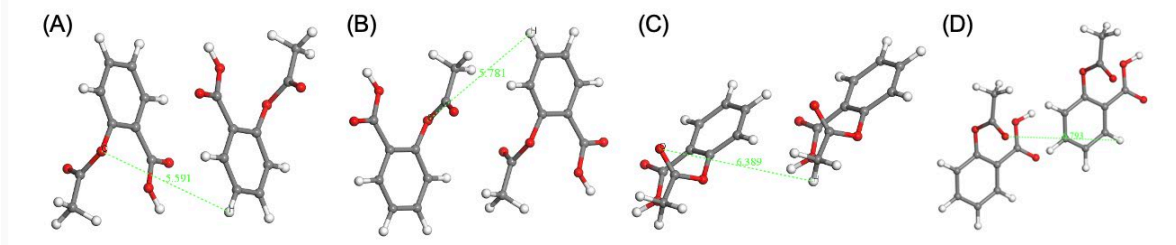

Figure 5: The distance of intermolecular bonding between two atoms of ASA

Lactose monohydrate

A list of the strong intermolecular interactions is presented in Table 3 below. Results from the crystallographic calculations with the limit for zero bond strength is 0.5 kcal/mol revealed four significant intermolecular bonds ranging from -28.91 to -6.40 kJ/mol created within the range of 30 Å limiting radius.

Table 3: Summary of intermolecular analysis of LM crystal by using Habit98

Synthon	Type	Multiplicity	Direction (u v w)	Distance (Å)	Attractive (kJ/mol)	Repulsive (kJ/mol)	Coulombic (kJ/mol)	Total energy (kJ/mol)
A	L-W	4	(1 0 0)	4.78	-48.24	24.56	-5.23	-28.91
B	L-W	4	(1 0 1)	7.92	-20.54	13.89	-4.56	-11.21
C	L-L	4	(0 0 -1)	7.76	-24.81	20.46	-3.55	-7.91
D	L-L	4	(1 -1 2)	11.88	-6.95	5.23	-4.69	-6.40

**L- Lactose Monohydrate, W- Water*

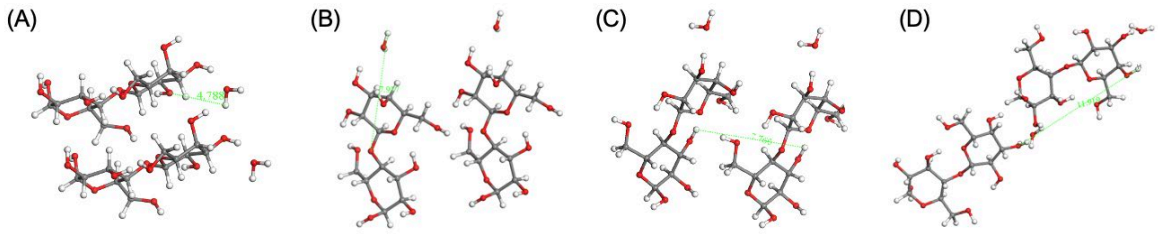

Figure 6: The distance of intermolecular bonding between two atoms of LM

The intermolecular interaction in synthon A was greatest between lactose molecules with hydrogen atoms compared to other synthons, which hold two molecules of LM. Hence, it is suggested that water molecules help to bind the crystal together. Most of the terminating surfaces of LM were monopolised by hydroxyl functional groups, which are believed to act as binding sites for the attachment of other molecules in solution. This occurs due to the presence of H-bond acceptors and H-bond donors on its surface.

4.4 Interatomic analysis

Aspirin

The interatomic analysis of ASA showed that the ASA interatomic stability was driven by aromatic carbon with a significant contribution of 26.26 % towards the total lattice energy. This result was expected due to the aromatic hydrocarbon ring in ASA. Besides aromatic carbon, another major contributor was carbonyl carbon with a total energy of 17.3 %. A specific percentage of each atom's contributor towards the stability of the ASA molecular structure was tabulated in Table 4. Turning now to the main functional group contributions to the lattice energy given in Table 5. It can be concluded that the ester group contributes the highest contributions with 76.12 %. This is because ester consists of a combination of an aromatic ring (43.47 %), carbonyl (16.55 %) and methyl (13.19 %) as depicted in Figure 7.

Table 4: The interatomic analysis in ASA

Atom type	Attractive (kJ/mol)	Repulsive (kJ/mol)	Coulombic (kJ/mol)	Total percentage contribution (%)
Aliphatic carbon	-2.13	1.01	0.66	1.87
Aliphatic hydrogen	-3.42	2.05	-1.23	11.32
Aromatic carbon	-12.28	4.39	1.5	26.36
Aromatic hydrogen	-5.17	3.49	-2.49	17.01
Carbonyl carbon	-5.27	1.98	-0.94	17.3

Table 5: Functional group contribution towards the lattice energy in ASA

Compound	Main functional group	Percentage distribution (%)
ASA	Ester	76.12
	Aromatic hydrocarbon	43.47
	Carboxylic acid	24.32
	Carbonyl	16.55
	Methyl	13.19

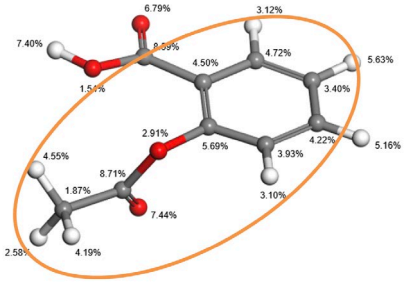

Figure 7: Functional group of ASA. The orange line depicts the major functional group in the crystal structure

Lactose monohydrate

The interatomic analysis of LM showed that the major contributor towards LM lattice energy is aliphatic hydrogen with 43.11 %. The second highest rank is aliphatic carbon with 36.96 %. The individual atomistic contributions can be seen in Figure 8. Taking from the individual atom analysis, the energy contributions of the main functional group of LM exist in the structure can be seen in Table 7. Overall, this concludes that ALM crystal chemistry was driven by hydroxyl functional group. This interaction was supported with the 58.01 % of interatomic contribution was from the hydrogen and oxygen atom in hydroxyl terminal. Second in rank is ether with 50.76 % contributed towards the lattice energy as it holds two pyranose rings of LM and water molecules.

Table 6: The interatomic analysis in LM

Atom type	Attractive (kJ/mol)	Repulsive (kJ/mol)	Coulombic (kJ/mol)	Total percentage contribution (%)
Aliphatic carbon	-58.16	27.61	-5.65	36.96
Aliphatic hydrogen	-35.10	22.13	-29.29	43.11
Carbonyl oxygen	-13.89	3.85	13.64	-3.69
Hydroxyl oxygen	-81.67	64.10	19.75	25.86
Hydroxyl hydrogen	0	0	-25.44	-2.28

Table 7: Functional group contribution towards the lattice energy in LM

Compound	Main functional group	Percentage distribution (%)
	Alcohol	31.69
LM	Ether	50.76
	Hydroxyl	58.01

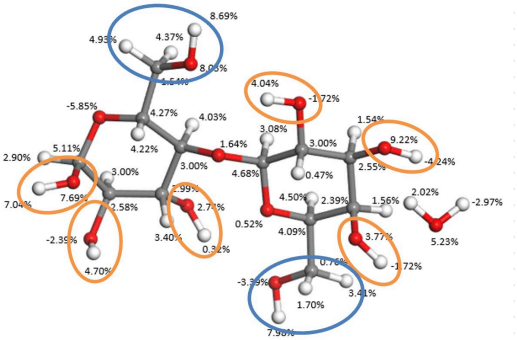

Figure 8: Functional group of LM. The orange line depicts the hydroxyl group, while the blue line indicates the alcohol group

5. Conclusions

The morphological forms and habits of a crystal are important properties in the crystallization process. This paper has presented the initial study of crystal morphology and crystal chemistry of ASA and LM. The main objectives of this work are to determine the potential force field and crystal structure of ASA-LM through molecular modelling tools. Furthermore, to determine the lattice energies and their convergency analysis that includes intermolecular and interatomic analysis of the ASA-LM. The results here gathered, that molecular simulations performed with the software Accelrys Material Studio and Habit98 have successfully predicted the ASA-LM crystal structures. The results of lattice energy and their convergence analysis of ASA-LM have been successfully carried out, along with its limiting radius. There is no correct form in choosing empirical force fields. However, one functional form that is shown to perform better than another is most likely to be opted for. Thus, the chosen potential force field in this study seems to produce reliable values of lattice energy when compared with the sublimation enthalpy of the previous study.

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