Characterization and Prediction of the Non-Bonded Molecular Interactions between Racemic Ibuprofen and α-Lactose Monohydrate Crystals Produced from Melt Granulation and Slow Evaporation Crystallization

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Abstract: *Granulation of racemic ibuprofen (±IBP) and α-lactose monohydrate (ALM) at a slightly lower (±IBP) melting point is an efficient method of binding the active pharmaceutical ingredients (API) and excipient in a binderless condition. However, the co-crystals may be formed from recrystallization of ±IBP on ALM. The objective of this study is to evaluate the tendency of co-crystal formation of granules (3:7 w/w ratio of ±IBP:ALM) by melt granulation process. Second, investigate the recovery of crystals from polyethylene glycol (PEG) 300 solutions containing ±IBP-ALM mixtures. Characterizations of the samples were performed using Fourier Transform Infrared (FTIR) spectroscopy, Differential Scanning Calorimetry (DSC) and Powder X-Ray Diffraction (PXRD) system of the ±IBP-ALM granules produced from melt crystallization and harvested crystals from PEG 300 solution which is produced using slow evaporation crystallization. Crystal analysis of solution containing ±IBP-ALM mixtures revealed that the crystals formed were not co-crystals. Molecular interactions assessment through binding prediction between ±IBP and ALM terminating surfaces was conducted using molecular modelling technique. The result showed that the favorable binding sites of ±IBP molecules were on the surfaces of (0-20), (1-10), (001) and (011) ALM crystals. Successful binding prediction by the attachment energy method has proven that the co-crystal formation between these molecules is theoretically possible.*

Keywords: *surface chemistry; hydrogen bond; lattice energy; melt crystallization; binding prediction*

■ INTRODUCTION

In recent years, there has been increasing interest in melt granulation [1-4], apart from dry granulation and wet granulation. Melt granulation employs molten binder such as PEG and Gelucire [2-6]. The process skips the drying stage which is a part of routine stages in wet granulation. Drying stage in wet granulation consumes a lot of time and energy to dry the solvent (such as water) and volatile solvents, such as ethanol and isopropanol [3,5,7]. This becomes compelling when melt granulation involves racemic ibuprofen (±IBP) and a widely used excipient, α-lactose monohydrate (ALM). Ibuprofen is a highly potential active pharmaceutical ingredients (API) of non-steroidal anti-inflammatory drugs (NSAIDs) [8] and cannot afford to have residual solvents in the formulations [9]. However, there are limited reports focusing on racemic ibuprofen in melt granulation [5,10].

Melt spherical granules of α-lactose monohydrate and racemic ibuprofen can be prepared using a pressure swing granulation (PSG) technique in a fluidized bed [4,10]. Three types of granule products can be produced namely core, coated and heated granules. It has been proven that racemic ibuprofen can be acted as an API and binder simultaneously. The granule products have enough strength to handle processes before tableting. Enhanced strength was recorded for both coated and heated granules due to solidification of melting ibuprofen, which binds α-lactose monohydrate particles in the granules and results in no requirement for any

other type of binders [10]. Application of this technique also solved the tendency of high sublimation of racemic ibuprofen [10-11] by blocking the diffusion of racemic ibuprofen out of the granules through the coating with 2 wt.% α-lactose monohydrate layer. Coating naked tablets of ibuprofen mixture with cooling crystallization sucrose produces uniform and crystalline coating, but analysis of sublimation of ibuprofen was not carried out yet [12]. However, Abu Bakar and co-workers [10] characterized only physical properties of the granules. Walker et al. investigate racemic ibuprofen-α-lactose monohydrate-PVP-PEG 600 granules determined the nature of the crystals formed during the process [5-6]. The granules were produced by fluidized hot melt granulation method. A mixture of 300 g of granulated racemic ibuprofen, α-lactose monohydrate, PVP and PEG 600 was heated at 100 °C for predetermined period, before cooling to ambient air for 30 sec [5]. However, the properties of solidified ibuprofen in the granules form remain unclear [10]. It is postulated that the ±IBP recrystallizes on α-lactose monohydrate particles, especially when the melt granulation approximately has the same principle with melt crystallization [13], which can form co-crystal [14]. Thus, formation co-crystal of racemic ibuprofen-α-lactose monohydrate is possible. Co-crystal is a molecular complex which contains two or more different molecules in the same crystal lattice [15]. Ibuprofen co-crystal is desired because it has shown significant improvement in dissolution, compactability and compressibility of the co-crystals [16] compared to pure ibuprofen crystals. The pure racemic ibuprofen crystals are undesired because it has high cohesivity, adhesivity and hydrophobicity in nature [17]. Various attempts were made to produce co-crystals, such as racemic ibuprofen-2-aminopyrimidine by solvent-free grinding and slow evaporation of acetonitrile solution [18]. Meanwhile, racemic ibuprofen-nicotinamide co-crystal was produced by Kofler mixed fusion and slow evaporation of methanol or ethanol solution [19]. An alternative proposed technique to produce the racemic ibuprofen-nicotinamide co-crystal is by simultaneous agglomeration via hot melt extrusion [16]. Only fusion method forms amorphous granule of racemic ibuprofen-gelucire [20]. Measurement using Fourier Transform Infrared Spectroscopy (FT-IR) showed that the racemic ibuprofen has the tendency to produce co-crystal with PEG via hydrogen bonding interactions [21]. The attempts showed that different racemic ibuprofen recrystallized methods from racemic ibuprofen mixtures will differ in final product of recrystallization. Therefore, the investigation of properties of racemic ibuprofen crystals in granules subjected to the granulation conditions is imperative.

The interactions between crystal surfaces and molecules in the bulk solution have been predicted using molecular modelling technique in previously reports [22-25]. Some of computational techniques such as docking/grid search are commonly used to assess the wettability of the crystal surface. These methods rely on the finding a suitable attachment site between a free molecule in the solution to the surface. Another application of grid search is to calculate solvent-dependent morphologies of organic material. For example; the grid-based search for crystal surface of racemic ibuprofen terminating surfaces of (100), (001) and (011) and the solvents (ethanol, ethyl acetate, acetonitrile and toluene) showed that the solute racemic ibuprofen molecules has the strongest interaction with the capping (011) morphology, followed by the side (0 0 1) and the weakest with the top (1 0 0) crystal surface [26]. The molecular modelling study on the effect of additives on the crystal growth of methyl paraben has shown that acetaminophen, *p*-methyl acetanilide and acetanilide selectively adsorbed on the growth surfaces of methyl paraben and induced the change in methyl paraben crystal habit [27]. The work on assessment of additives on the *p*-toluamide crystal surface also has showed that additive molecule was capable to promote the growth of specific crystal faces by repelling the solvent molecules and eliminating the negative influence of the solvent on the surface diffusion of *p*-toluamide [28].

In this article, the tendency of co-crystal formation of racemic ibuprofen-ALM in granules produced through melt crystallization; and in crystals produced from PEG 300 solutions through slow evaporation crystallization are studied.

Assessment of co-crystal formation was carried out using an X-Ray Powder Diffraction (XRPD), Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared (FTIR) spectroscopy. A molecular modelling work was conducted to predict first the binding preference of racemic ibuprofen on the α-lactose monohydrate surfaces and second to predict the possibility on the co-crystal formation.

■ EXPERIMENTAL SECTION

Materials

Form I polymorphic form of racemic ibuprofen, (±)-IBP, (±)-2-(4-isobutylphenyl) propanoic acid, $C_{13}H_{18}O_2$ (PhEur) of 99.9% purity CAS 15687-27-1 were obtained from Shasun Pharmaceutical Limited, India. (±)-IBP is a white, crystalline powder and has a characteristic odor. The compound is insoluble in water, but soluble in most organic solvents. Its molecular weight is 206.29 g/mol and conforms to Ph.Eur. The α-lactose monohydrate (ALM) ($C_{12}H_{22}O_{11}$) powder (Pharmatose 450M, DMV) with 99.99% of purity, was purchased from Sigma Aldrich. The white or almost white α-lactose monohydrate crystalline powder is soluble in water, but insoluble in ethanol and non-polar solvents. Its molecular weight is 342.30 g/mol. Polyethylene glycol 300 ($C_{2n}H_{4n+2}O_{n+1}$) (PEG 300) of CAS 25322-68-3, Ph.Eur was obtained from Sigma-Aldrich, Germany. The viscous, clear solvent is soluble in water with an average molecular weight of 300 g/mol.

Crystal Structure

The molecular structures of racemic ibuprofen and α-lactose monohydrate were shown in Fig. 1(a) and (b), respectively. Ibuprofen has an aromatic ring, a methyl, and a carboxyl functional group in its structure, whilst α-lactose monohydrate has two pyranose rings and a water molecule, forming a dimer in its structure. An α-lactose monohydrate is built from a moiety of β-D-galactose and α-D-galactose, joined by a 1,4 glycosidic bond between C1 of galactose and C4' of the glucose unit [29,31-33]. Fig. 2(ai–aiii) showed the α-lactose monohydrate structure in its crystal lattice, viewed from x-, y- and z-axis direction. The structure was packed in monoclinic lattice with space group P_{21}, in which consisted of two α-lactose monohydrate molecules of the same conformation and two water molecules in a unit cell. One asymmetric unit of α-lactose monohydrate consisted of a pair of α-lactose monohydrate and water molecule. The cell parameters were a = 4.7830, b = 21.540, c = 7.7599 Å, and α = γ = 90°, β = 105.911°. The packing involved a complex 3D hydrogen bond network, in which each α-lactose was intermolecularly bonded with its neighboring atoms with 14 hydrogen bonds. Meanwhile, each water molecule was hydrogen-bonded to four different α-lactose molecules [29,34]. Fig. 2(b) showed the α-lactose monohydrate crystals grown in PEG 300 solution and Fig. 2(c) showed the predicted morphology of α-lactose monohydrate crystals in vacuum using PCFF force field and Hirshfield atomic charges. The calculated lattice energy was -41.9 kcal/mol [30]. Most of the terminating surfaces of α-lactose monohydrate were monopolized by the hydroxyl functional groups, which can act as binding sites for attachment of other molecules in solution, due to the presence of H-bond acceptors and H-bond donors on the surfaces.

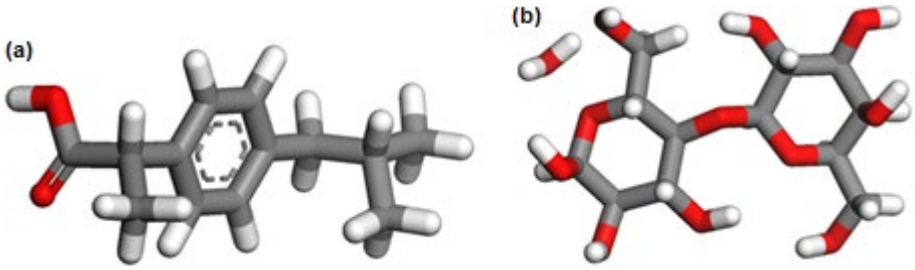

Fig 1. (a) A racemic ibuprofen molecule, and (b) An α-lactose monohydrate molecule

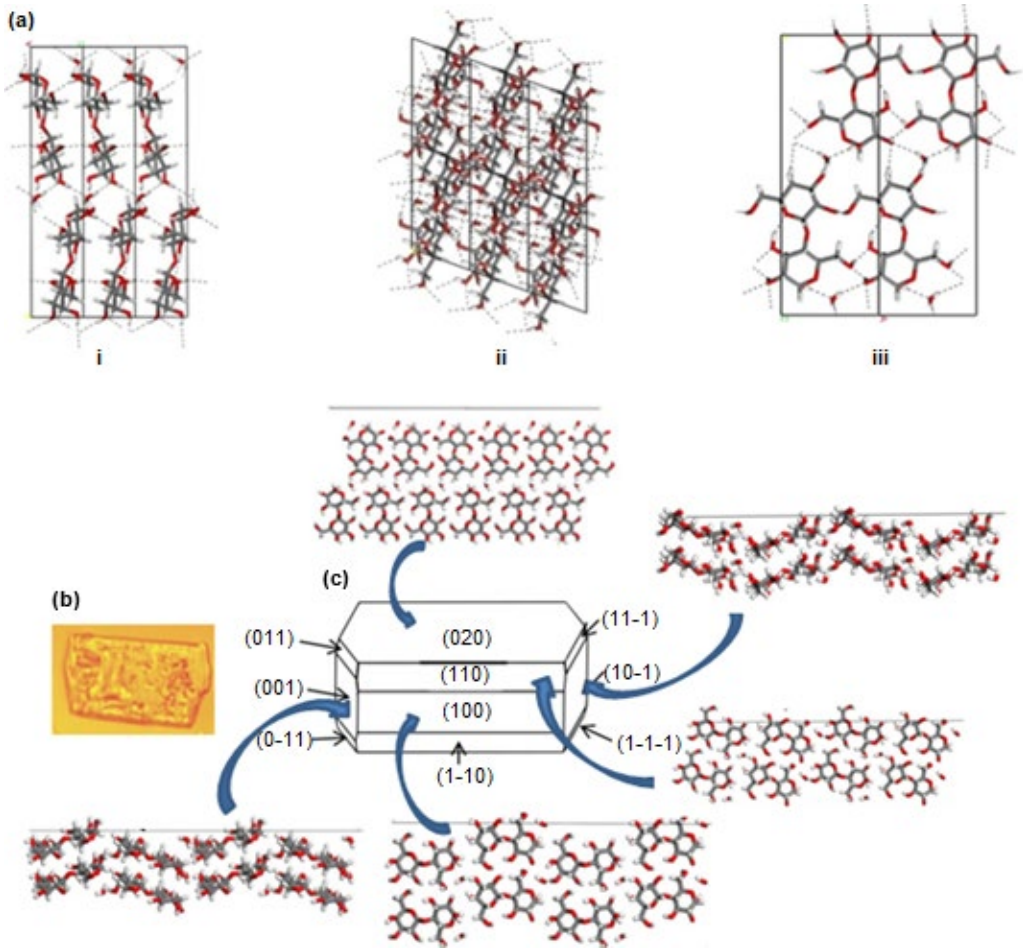

Fig 2. (a) The α-lactose monohydrate crystal lattice, showing the hydrogen bond network, in the order of: (i) view from x-direction, (ii) view from y-direction and (iii) view from z-direction [29], (b) α-lactose monohydrate crystal grown in PEG 300 solution (top view); and (c) morphology prediction of α-lactose monohydrate in vacuum, showing an elongated hexagonal crystal shape and selected surfaces of the crystal. Images were adopted from [30]

Procedure

Granules produced from pressure swing granulation (PSG) technique

Detail description of the employed pressure swing granulation (PSG) technique were detailed out by Ab Ghani et al. [4]. Granules of (±)-IBP-ALM was produced according to methods and conditions underlined by Abu Bakar et al. [10]. A 70 wt.% milled lactose and 30 wt.% milled ibuprofen were fed to the PSG at the ambient temperature for the production of core granules. A batch size of 120 g of well mixed (±)-IBP-ALM sample was fed into the PSG fluidized bed through a rotating sieve with aperture size of 840 μm. The gas velocity used to produce the granules was 0.364 m/s. The duration of fluidization was 15 sec and the duration for compaction was 1 sec. The compaction pressure used was 0.03 MPa and with the vibration frequency of 40 Hz. The total granulation time was 240 min. The granules then further coated with 2 wt.% of fine lactose particles in the fluidized bed at 70 °C for 1 h.

Crystals produced from slow evaporation crystallization

Crystallization experiments involved three separate systems, namely α-lactose monohydrate, ibuprofen and (±)-IBP-ALM mixtures, crystallized in PEG 300 solution. Crystallization experiment was conducted by trial and error method in which substrates and water were added successively into PEG 300

solutions to produce supersaturated solution in a 100 mL beaker. The methods used to prepare the supersaturated solution were as follow: (1) for α-lactose monohydrate supersaturation: A 0.2 g of α-lactose monohydrate and a 2 mL of water were added successively to a 5 mL PEG 300, (2) for Ibuprofen supersaturation: 6.48 g of ibuprofen were added to a 5 mL of PEG 300 solution, and (3) for (±)-IBP-ALM supersaturation: A mixture of 0.123 g ibuprofen and 0.2 g α-lactose monohydrate (1:1 molar ratio, 1:1.62 w/w ratio of (±)-IBP-ALM) were added successively to a 5 mL of PEG 300 solution. The solutions were heated at 70 °C and mixed at 1100 rpm using a magnetic stirrer on a hot plate. The solutions were cooled to the ambient temperature, with the top of the beakers capped with an aluminium foil with punctured holes, so that water vapor could escape from the solution. The crystals were harvested from the solution when the crystals have grown in the solution (after being left to stand for 3 days). The crystals were filtered from the solution using a filter paper. Then, the crystals were dried in a dryer at 40 °C for 4 days.

Solid state characterization of granules and crystals of (±)-IBP-ALM

The granules and crystals produced in this work were characterized using a Fourier Transform Infrared (FTIR) spectroscopy, X-Ray Powder Diffraction (XRPD) system and Differential Scanning Calorimetry (DSC). Transmission from the FTIR spectroscopy was recorded on a Perkin-Elmer Spectrum One spectrometer (Perkin-Elmer Instruments, USA). The Attenuated Total Reflection (ATR) samples disk was scanned four times from 400 to 4000 cm^{-1} with a resolution 4 cm^{-1}. The XRPD diffractograms at 25 °C were collected by Rigaku D/Max-2000 (Rigaku, Japan) to provide information for the identification and crystallinity of materials. The source of XRPD was Cu Kα (λ = 1.542 Å). The diffractometer was operated at 40 kV, 40 mA with scan speed 0.6°/min, sampling step 0.02° and the range at 2θ between 3 and 40°. The DSC was used to analyze solid transformation and to identify melting temperatures in the materials. Indium standard of high purity was used to calibrate the DSC temperature and enthalpy scale. Thermal analytical data of the samples (between 2–4 mg) in a 40 μL perforated aluminium crucible were collected by a Mettler Toledo DSC 1 (Mettler-Toledo, Germany). The heating rate used was 10 °C/min, heated from 25 to 300 °C, under a constant flow rate of 50 mL/min nitrogen gas purge.

Molecular computational technique details

In this work, molecular modelling software, Material Studio 4.4 from Accelrys was used for the prediction of the α-lactose monohydrate morphology. Crystal structures of α-lactose monohydrate molecules (CCDC ID: LACTOS10) and racemic ibuprofen (CCDC ID: IBPRAC03) were obtained from Cambridge Crystallographic Data Centre. The simulation was carried out in a vacuum environment. The lattice energy and the attachment energy of each facets of α-lactose monohydrate were obtained from Lukman et al. [30]. In their work, the predicted lattice energies (obtained from the morphology prediction) were compared to the experimental data which was calculated by using Eq. (1).

$$E_{latt} = \Delta H_{sub} - 2RT \quad (1)$$

Where ΔH_{sub} is the sublimation energy of α-lactose monohydrate and the 2RT represents a correction factor, for the difference between the gas enthalpy and the vibrational contribution to the crystal enthalpy [35-37]. The attachment energy, E_{att} used as a reference in this work, was obtained as the difference between the lattice energy and the slice energies, E_{slice} of each habit facet, and as shown by the Eq. (2);

$$E_{att} = E_{latt} - E_{slice} \quad (2)$$

The values of E_{att} for the terminating surfaces tested in this work were also obtained from Lukman et al. [30].

Binding prediction

All visible surfaces of the facetted morphology of α-lactose monohydrate were cleaved to a depth of 323 Å and a periodic superstructure was constructed from a unit cell. A 60-Å thick vacuum slab was built above the crystal slice. Attachment method was used between a guest molecule (either (±)-IBP or ALM) and a host surface (ALM) for the binding prediction work. Binding prediction between ibuprofen and α-lactose monohydrate was first conducted as it gave a preliminary indication on the facet suitability for (±)-IBP binding. Only then the appropriate facets were

selected for self-binding simulation between an α-lactose monohydrate molecule and an α-lactose monohydrate surface (as a host facet). The selected ALM surface molecules were locked to its Cartesian coordinates while a relaxed guest molecule was given a reasonable initial position, so that the molecule possibly formed hydrogen bond with the layers of α-lactose monohydrate.

The guest molecule was relaxed, which allows flexibility of molecular structure to interact with the rigid hkl surface. The molecular dynamics calculation allows the simulation of a relaxed guest molecule to move under the influence of computed forces. Hence, the calculation determines the best orientation of guest molecule on the rigid host slice. Both molecule and the rigid layers were then relaxed to achieve the minimum energies in optimization stage. Ewald summation method was used to compute electrostatics and van der Waals forces. Modified attachment energy, E_{att}^{mod} was calculated by using Eq. (3) [36];

$$E_{att}^{mod} = E_{att} - \frac{E_{att} \cdot \Delta b}{E_b^{host}} \quad (3)$$

Attachment energy, E_{att} for each facet of α-lactose monohydrate was obtained from Lukman et al. [30]. Binding energy difference, Δb was calculated for both host and guest molecule. In cases where $\Delta b < 0$ (preferred interaction with guest molecule), E_{att}^{mod} will be smaller and growth rate becomes slower, contributing to morphological important face, and vice versa [36].

■ RESULTS AND DISCUSSION

Characterization of Solid Granules from Melt Crystallization

Both α-lactose monohydrate and ibuprofen (polymorph I) were used as received from the manufacturer and used to compare the characteristic of feed materials with the granules produced using the PSG. The FTIR spectra of ibuprofen, the (±)-IBP-ALM granules and α-lactose monohydrate are shown in Fig. 3.

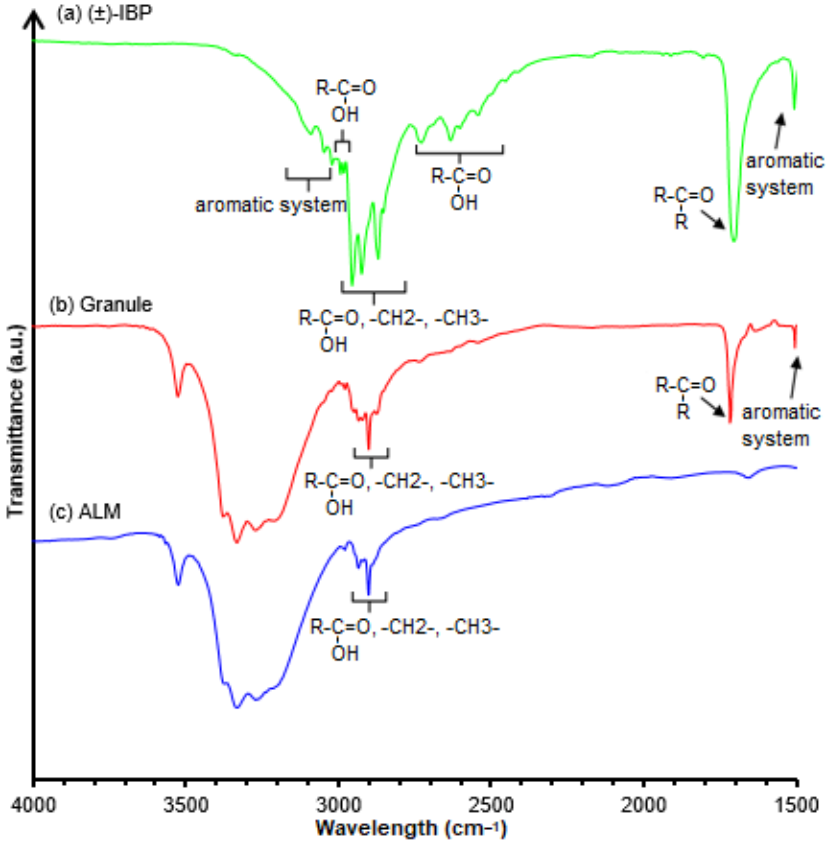

Fig 3. FTIR spectra of (a) pure ibuprofen, (b) granules of (±)-IBP-ALM produced from melt crystallization, and (c) pure α-lactose monohydrate

Based on the FTIR analysis, due to H-bridge and crystal water band are observed, it can be concluded that the pressure swing fluidization procedure did not produce anhydrous α-lactose monohydrate granules to become anhydrous, proven by the H-bridge and crystal water band present in the FTIR spectra.

The FTIR spectrum of the (±)-IBP-ALM granules is dominated by α-lactose monohydrate, except for the carboxylic group and aromatic system bands which are the identifying bands for ibuprofen. The carbonyl absorptions were observed at 1714 cm^{-1} for granules, whilst at 1705 cm^{-1} for ibuprofen (Fig. 3(a) and (b)). From the work of Chan and Kazarian [21], the shift of carbonyl stretching at 22 °C from 1705 (ibuprofen) to 1732 cm^{-1} (pure ibuprofen dispersed in PEG 1500) is due to H-bonding of PEG 1500 (hydroxyl group) and pure (±)-IBP (carbonyl and hydroxyl groups). In this work, the shift of band (1714 cm^{-1}) for the granules from the ibuprofen of 1705 cm^{-1} probably indicates that the interaction between the carbonyl of ibuprofen and the hydroxyl groups of the α-lactose monohydrate. This band could be an indicator of the presence of a new phase, i.e. the co-crystals formed in the granules.

Differential scanning calorimetry (DSC) analysis shows that the melting points at notation 1 (78 °C, (±)-IBP) and notation 2 (76 °C, granules) indicate the presence of (±)-IBP in granules (Fig. 4). Both melting points of ibuprofen sample and granules are within the range as reported by previous researchers, from 71 to 78 °C [10-11,38-41]. The wide range of the melting points reported for ibuprofen could be due to the degree of crystallinity and nature of employed solvents in crystallization process [42]. The endotherm at notation (3) (131 °C, granules) and notation (4) (144 and 148 °C, ALM) are believed due to the dehydration of crystalline water. These values are within and over the range of 120

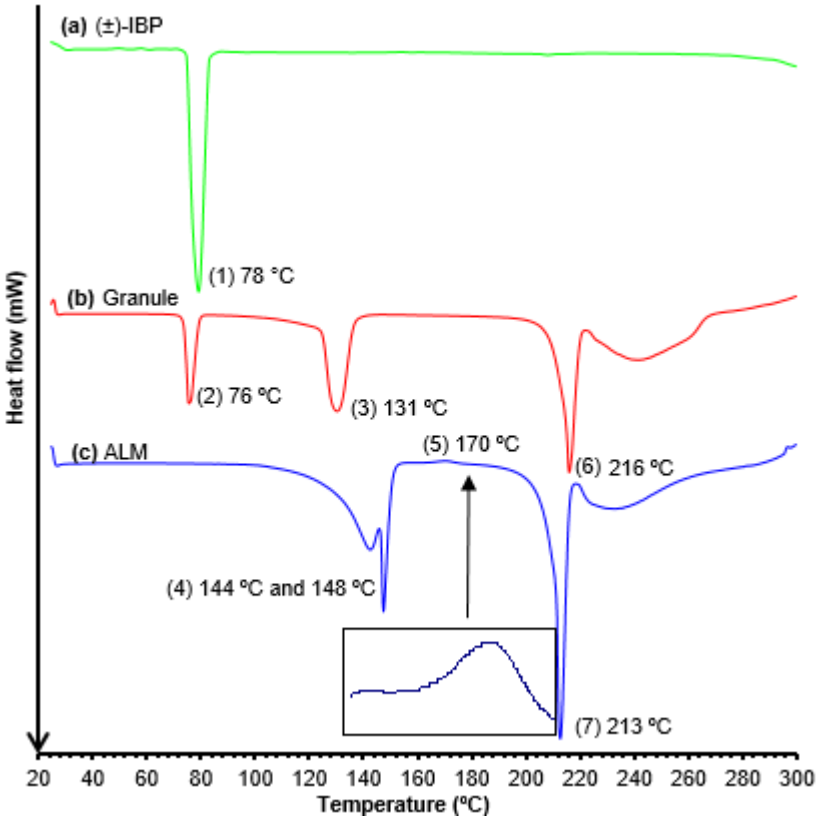

Fig 4. Comparison of DSC patterns between: (a) racemic ibuprofen (b) the granules, and (c) milled ALM. The notations are as follows: (1) 78 °C – melting temperature of racemic ibuprofen. (2) 76 °C – melting temperature of racemic ibuprofen. (3) 131 °C – loss of water. (4) 144 and 148 °C – loss of water, (5) 170 °C. (6) 216 °C – melting temperature of α-lactose monohydrate, and (7) 213 °C – melting temperature of α-lactose monohydrate

and 140 °C which were reported by previous researchers [43-48]. The lower value of 131 °C (notation 3, granules) relative to 144 and 148 °C (notation 4, ALM) might be due to partial water evaporation during heat treatment at 70 °C during granulation process by PSG [49]. The α-lactose monohydrate sample (Fig. 4(c)) and α-lactose monohydrate in granules sample (Fig. 4(b) become anhydrous due to the dehydration of α-lactose monohydrate. This is supported by Garnier et al. [34], who reported that α-lactose monohydrate could become anhydrous α-lactose by losing its water molecule after 100 °C. The small exotherm at notation 5 (170 °C, ALM) is similarly found in α-lactose monohydrate by Gombás et al. [44] and Garnier et al. [34]. However, the close-up (the small insertion of notation 5) shows that it is not preceded by a small endotherm [50]. This exotherm might be the recrystallization of anhydrous α-lactose to β-lactose. This recrystallization is proved by temperature-resolved XRPD which revealed that, at 170 °C, α-lactose monohydrate composed of both anhydrous α-lactose and β-lactose [50]. In fact, the presence of β-lactose in α-lactose monohydrate was also detected at 100 °C [50]. However, the granules do not show the same exotherm (notation 5), even though the granules are composed of mixtures of both α-lactose monohydrate and ibuprofen. The endotherms at notation (6) (216 °C, granules) and notation (7) (213 °C, ALM) correspond to the melting point of α-lactose monohydrate. These values are slightly lower than those reported by the researchers [39,46] which were in between 217 and 218 °C. The presence of an endothermic peak at 213 °C (notation (7)) indicates that the samples (Fig. 4(b)) contains α-lactose monohydrate only [47] which contradicts the finding by Garnier et al. [50]. α-Lactose monohydrate starts to degenerate at a temperature higher than 220 °C [45,47,51]. The presence of a co-crystal normally can be detected from the presence of a new melting peak in the DSC endotherm [52-53]. In this work, no new peak was detected, which could indicate that the granulation of (±)-IBP-ALM mixture in PSG does not produce a co-crystal.

The XRPD patterns shown in Fig. 5 are for ibuprofen, granule, and α-lactose monohydrate. The result

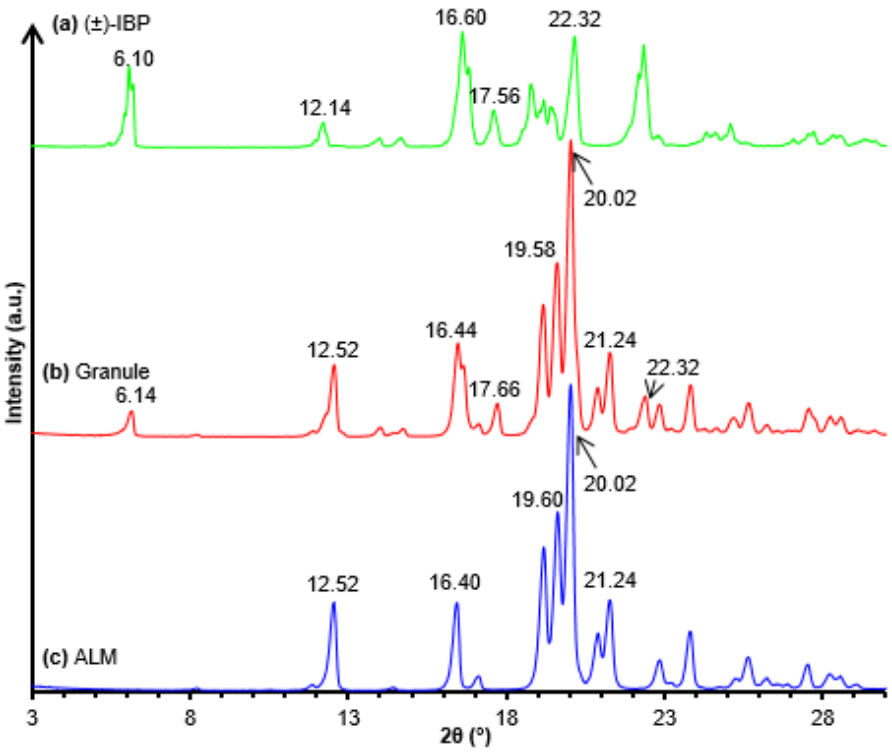

Fig 5. Comparison of XRPD patterns between (a) racemic ibuprofen (b) granules, and (c) α-lactose monohydrate, showing the important diffraction angle peaks which indicate that the granules produced using the PSG method contains mixtures of ibuprofen and α-lactose monohydrate only, and no co-crystal was produced

shows that the granule contains a mixture of peaks from both ibuprofen (polymorph I) and α-lactose monohydrate. However, there was no new peak observed for the granules, which indicates that no co-crystal was formed in the granules produced from the PSG process. The absence of new crystalline phase in granule might be due to structural difference between the ibuprofen and α-lactose monohydrate molecules. Nevertheless, high structural similarity between the host molecule and additive does not guarantee co-crystal formation. These are consistent with the finding that there was no incorporation of structurally related additives (SRAs) in ALM layers based on HPLC analyses although strong morphological changes were observed [34].

Characterization of Racemic Ibuprofen-Alpha Lactose Monohydrate Crystals Grown in PEG 300 Solutions

In this work, all the crystals (ibuprofen, α-lactose monohydrate, and crystals from (±)-IBP-ALM mixtures) were grown in PEG 300 solution. Both the ibuprofen and α-lactose monohydrate produced from PEG 300 were compared with the pure form of these components (feed materials) using the XRPD. The results show that both ibuprofen and α-lactose monohydrate crystallized from PEG 300 are of the same polymorphs as the feed materials. Comparison of FTIR spectra of the crystals grown in the PEG 300 solution using slow evaporation method are shown in Fig. 6. The spectrum of (±)-IBP-ALM (Fig. 6(b)) is composed of moieties of (±)-IBP (carboxyl) and ALM (hydroxyl). This indicates that both compounds are present in (±)-IBP-ALM crystal sample. The carbonyl band at 1651 cm^{-1} was recorded by both α-lactose monohydrate (Fig. 6(c)) and (±)-IBP-ALM (Fig. 6(b)). Nevertheless, ibuprofen recovered from PEG 300 solution in Fig. 6(a) recorded higher carbonyl stretching, 1713–1651 cm^{-1} which is similarly to the band recorded for granule in Fig. 3(b). This shift of carbonyl stretching from 1705–1651 cm^{-1} of pure ibuprofen (Fig. 3(a)) to 1713–1651 cm^{-1} (Fig. 6(a)) might indicate that the ibuprofen is in a monomer state and could interact with carboxyl moiety of PEG 300 [21,53]. However, the shift of peak could also indicate that a new crystalline phase (such as a co-crystal) has formed [52-53].

The showed ibuprofen crystal in Fig. 7(a) was grown in PEG 300 solution, and the melting temperature recorded by the DSC has shown that the ibuprofen has a

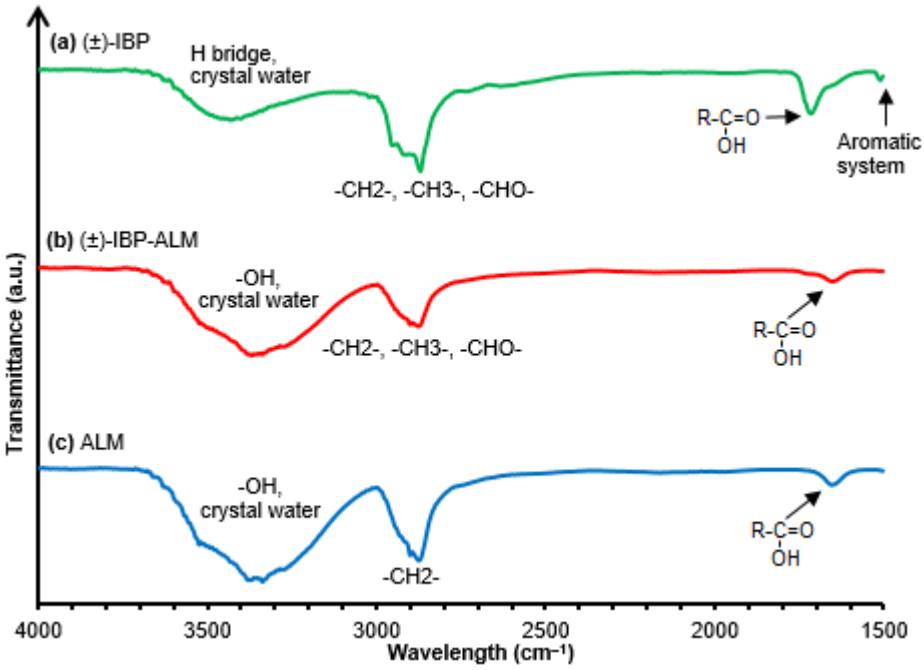

Fig 6. FTIR spectra of crystals grown in PEG 300 solution: (a) ibuprofen, (b) crystals from (±)-IBP-ALM mixtures, and (c) α-lactose monohydrate

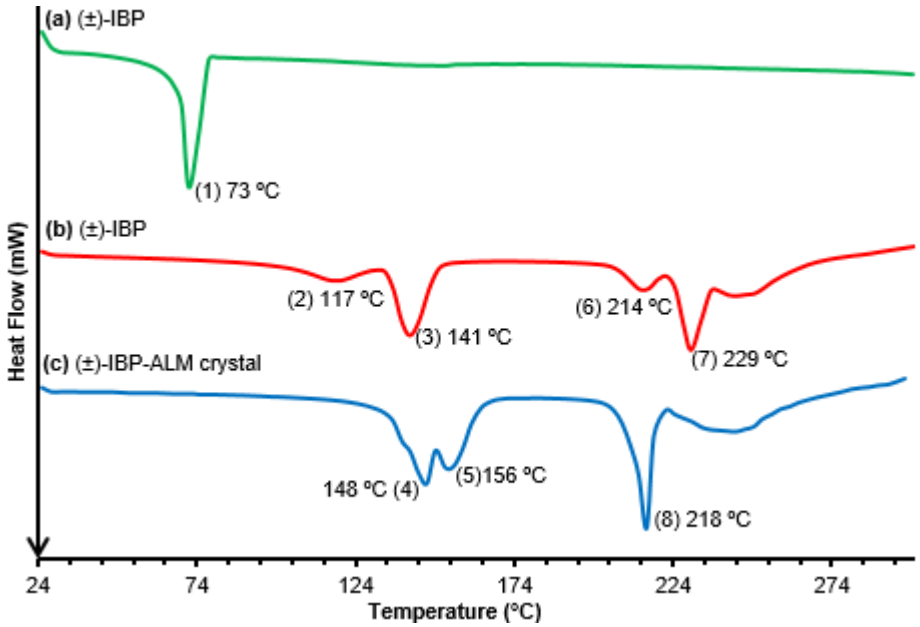

Fig 7. Comparison of DSC patterns of product crystals recovered from PEG 300 solutions between (a) ibuprofen (b) crystals from (±)-IBP-ALM mixtures (c) α-lactose monohydrate. The notations are as follow: (1) 73 °C – melting of (±)-IBP. (2) 117 °C – loss of water. (3) 141 °C – loss of water. (4) 148 °C – loss of water. (5) 156 °C – loss of water. (6) 214 °C – melting of α-lactose monohydrate. (7) 229 °C and (8) 218 °C – melting of α-lactose monohydrate

lower melting point, at 73 °C (notation 1) than that of ibuprofen (78 °C) in Fig. 4(a), but within the range of values recorded by other researchers from 71 to 78 °C [10-11,38-41]. Both patterns of the crystals recovered from the solution containing (±)-IBP-ALM (Fig. 7(b)) and α-lactose monohydrate (Fig. 7(c)) are similar, with no endotherm of ibuprofen detected in the crystal. This result shows that crystallization of (±)-IBP-ALM mixture in PEG 300 solution yields only α-lactose monohydrate. The endotherms at notation (2) 117 °C, (3) 141 °C and notation (4) 148 °C, (5) 156 °C are believed due to the dehydration of crystalline water. These values are within and over the range of 120–140 °C, as previously reported by researchers [43-48]. The endotherms at notation (6) 214 °C, (7) 229 °C and (8) 218 °C are believed correspond to the melting point of α-lactose monohydrate, which are somewhat higher than reported by the previous researchers [46-47], i.e., between ~217 °C and 218 °C. α-Lactose monohydrate starts to degenerate after 220 °C [45,47,51], nevertheless, in this work, the (±)-IBP-ALM crystals (Fig. 7(b)) start to degenerate at a temperature higher than 229 °C. As there is no new endotherm in (±)-IBP–ALM, and the peaks are identical to the peaks of pure ALM and (±)-IBP, this might indicate no co-crystal is formed.

Fig. 8 depicts the XRPD diffractogram of the crystal of (±)-IBP-ALM mixtures grown in PEG 300 solution and the result shows that the 2-theta peaks (Fig. 8(b)) resembles that of α-lactose monohydrate (Fig. 8(c)). This phenomenon indicates that only α-lactose monohydrate crystallized from (±)-IBP-ALM mixtures, and this result confirms that no co-crystal has been successfully formed from the slow evaporation method adopted in this work.

In other similar work, Mohammad et al. [54] found that a mixture of sucrose-indomethacin analyzed using a DSC to have two distinct endotherms, which belong to melting endotherms of sucrose and indomethacin; respectively, due to a lack of miscibility and no co-crystal formation. The same phenomena were also observed in this work (Fig. 7 and 4), which have separate melting endotherms for both ibuprofen and α-lactose monohydrate. Sucrose and maltose were found to not co-crystallize with ibuprofen through co-evaporation of ethanol solutions at 65 °C ((±)-IBP:sugar 4:1 w/w [55]). Through XRPD analysis, the co-evaporated crystals have

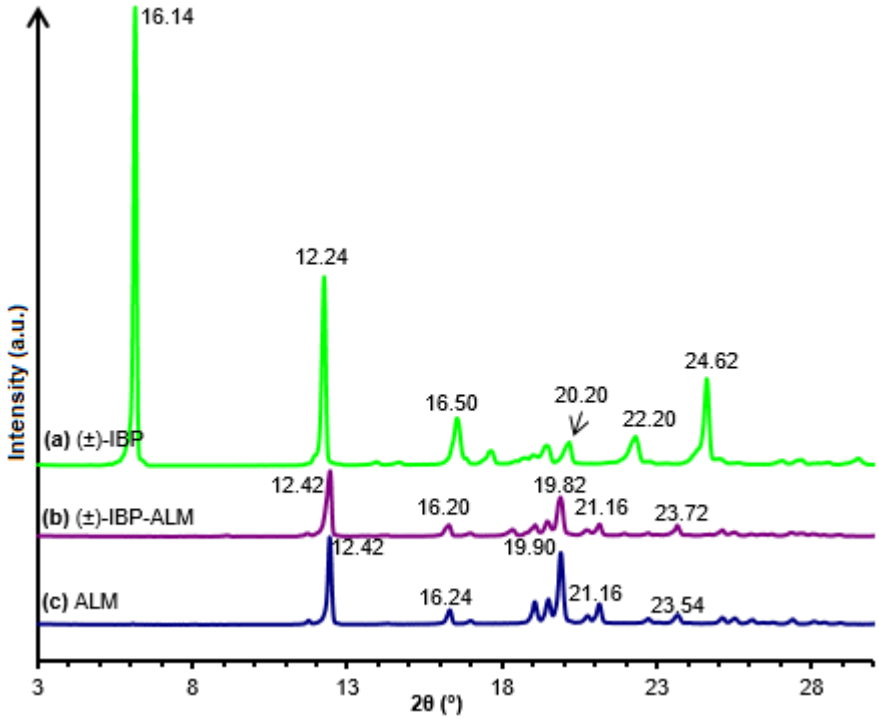

Fig 8. Comparison of powder XRD diffractogram between product crystals recovered from PEG 300 solution: (a) ibuprofen (b) (±)-IBP - ALM and (c) α-lactose monohydrate

patterns which are almost identical to that of ibuprofen. This trend was also observed in Fig. 5 and 8, in which XRPD pattern of crystals produced from the (±)-IBP-ALM mixtures resembles that of α-lactose monohydrate. This might be due to the separate crystallization of (±)-IBP and sugar [55], or (±)-IBP, and in this case the α-lactose monohydrate molecules.

Binding Process Analysis

In this work, cleaved surfaces, and corresponding attachment energy, E_{att} of the predicted facetted morphology of α-lactose monohydrate from Lukman et al. [30] was calculated using PCFF potential function and Hirshfeld charge set. Table 1 shows the changes in the differential binding energy, Δb between guest molecules of α-lactose monohydrate and ibuprofen attached to different habit facet of α-lactose monohydrate and the corresponding modified attachment energy, E_{att}^{mod} calculated using Eq. (3). Table 1 also shows the distribution of E_{att} due to the van der Waals interaction and E_{att} due to the Coulombic interaction, which indicate that the Coulombic interaction comprise only about 5% to 18% of the total attachment energy for the respective crystal facets, and the interactions were dominated by the van der Waals interactions. According to Dressler et al. [36] favorable binding (forming co-crystal) with the additive (i.e., racemic ibuprofen) for a given facet occurs when $\Delta b < 0$, in which the binding predicted between ibuprofen molecule and the α-lactose monohydrate surface is more negative compared to the binding energy between the α-lactose monohydrate molecule with its self-crystal surface. In other words, the presence of ibuprofen on the α-lactose monohydrate surface prevents the binding of the α-lactose monohydrate molecule as a growth unit to the surface and suppresses the growth of that facet. This results in E_{att}^{mod} becomes less negative to that of attachment energy, E_{att} of pure habit facet (i.e., α-lactose monohydrate). From Table 1, there are four habit facets ((0 -2 0), (1 -1 0), (0 0 1), and (0 1 1)) which were predicted to have favorable binding with ibuprofen as it fulfilled the condition set by Dressler et al. [36]. These results are agreeing well with the prediction on the possibility of binding sites based on the premise of low electrostatic energy, E_{stat} carried out by Lukman et al. [30].

Table 1. Binding energy difference, Δb and modified attachment energy, E_{att}^{mod} between α-lactose monohydrate and ibuprofen with the corresponding attachment energy, E_{att} of pure α-lactose monohydrate surfaces. The recorded lattice energy for α-lactose monohydrate was -41.9 kcal/mol [30]. All energies are in kcal/mol

ALM facets	E_{att}	E_{att} (vdW)	$E_{att(Est)}$	Δb_{total}		$\Delta b_{non\text{-}bonded}$	
						Δb (vdW)	Δb (E_{stat})
(0 2 0)	-12.09	-11.49	-0.60	-	-	-	-
(0 -2 0)	-12.09	-11.49	-0.60	-2590.41	-4.36	3.59	-2608.78
(1 0 0)	-17.38	-13.68	-3.71	460.90	-18.76	-	-
(1 1 0)	-18.25	-15.00	-3.24	106.81	-18.67	-	-
(1 -1 0)	-18.25	-15.00	-3.24	-884.32	-12.82	-1.70	-882.06
(1 0 -1)	-27.9	-26.30	-1.60	254.46	-29.73	-	-
(0 0 1)	-29.4	-26.90	-2.50	-236.83	-28.09	5.02	-241.70
(1 1 -1)	-29.2	-27.40	-1.80	296.75	-29.22	-	-
(1 -1 -1)	-29.2	-27.40	-1.80	-1876.25	-29.22	-	-
(0 1 1)	-30.5	-28.00	-2.50	-185.66	-29.43	9.58	3169.19
(0 -1 1)	-30.5	-28.00	-2.50	566.89	-35.18	-	-

This work helps to pinpoint the specific habit facet favoring binding with ibuprofen, which possibly is an indication that the co-crystal formation could form. Prediction of successful binding is illustrated in Fig. 9 which shows that ibuprofen becomes either both H-bond donor and acceptor or just H-acceptor. In this work, ibuprofen is represented by carboxyl (COOH) and carbonyl (CO) moieties which make up the carboxylic acid dimer (COOH·COOH) while hydroxyl (OH) is represented by α-lactose monohydrate. The working binding prediction as illustrated in Fig. 9 clearly shows that either carboxyl or carbonyl moieties must be complemented by hydroxyl via H-bond, forming a hetero-synthon. The attachment preserves the complex

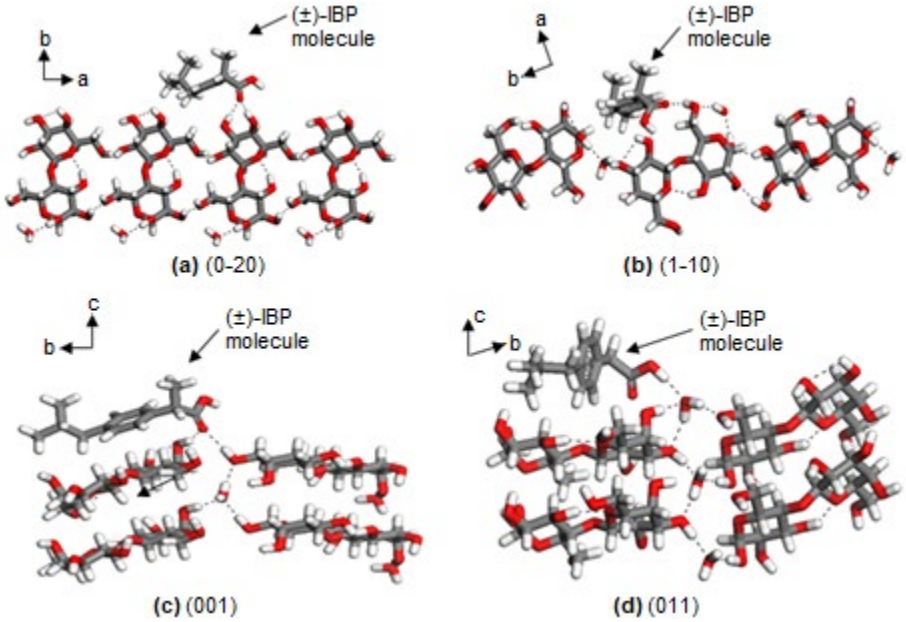

Fig 9. The most favorable position of the ibuprofen molecule on the host slice of α-lactose monohydrate for the respective crystal surfaces from the molecular dynamics simulation; illustrating possible interaction of ibuprofen molecule with the crystal surface that can suppress the growth of α-lactose monohydrate surface. These also can be taken as a possible interaction between the two compounds for the formation of the cocrystal

3D hydrogen bond network of α-lactose monohydrate by comparing with corresponding surfaces in Lukman et al. [30]. It was observed from facets in Fig. 9(a–c) that ibuprofen molecule is positioned with its phenyl group facing downward towards the α-lactose monohydrate surface while its isobutyl and methyl group projected upwards. This is probably due to high repulsive van der Waals forces compared to other facets in Fig. 9(d) to ensure that the position of the concerned groups can fully minimize van der Waals repulsive effects. Furthermore, the hydrocarbon part of ibuprofen cannot be fitted into the gap between the α-lactose monohydrate molecules because of the presence of carbon and hydrogen atoms of α-lactose monohydrate on both sides which interact via van der Waals forces and steric effects. Interestingly, the phenyl, isobutyl and methyl groups recede downward to the (0 1 1) facets (Fig. 9(d)). This might be the case due to the van der Waals forces dominating the facets. For (0 -2 0), (1 -1 0) and (0 0 1) surfaces, (Fig. 9(a–c)), the phenyl ring is oriented parallel with the α-lactose monohydrate surfaces, probably so that it can maximize van der Waals attractive forces. This favorable binding prediction is consistent with prediction using superimposition method, reported by Garnier et al. [34]. Four (α-glucosamine hydrochloride, maltitol, α-galactose and β-cellobiose) out of six structurally related additives (SRAs) (including sucrose and β-glucuronamide) are predicted to be incorporated successfully into α-lactose monohydrate layers, either disrupting or preserving H-bonds formation.

This successful binding could also be contributed by the geometrically optimized ibuprofen and α-lactose monohydrate individual structures, in which minimum energies were achieved for stabilization. Furthermore, it also depends on exact orientations of (±)-IBP positioned centrally on the exact surface sites of the α-lactose monohydrate facets during the stage of molecular dynamics and geometrical optimization of (±)-IBP-ALM [13].

■ CONCLUSION

The evaluation of cocrystal tendency in this work has shown that ALM-(±)-IBP cocrystals has not been successfully formed in both solid granules from melt granulation and in crystals formed from through slow evaporation technique. Analysis of the crystals has revealed that the crystals formed in the granules were a mixture of pure components of ibuprofen and α-lactose monohydrate, even though the mixtures have been granulated and heated in the pressure wing granulator. In the case of the mixture of ibuprofen and α-lactose monohydrate crystallized in PEG 300 solution, the crystals harvested was of α-lactose monohydrate only, with ibuprofen remained dissolved in the solution. Molecular modelling work undertaken in this study reflected the phenomenon in melt crystallization of the (±)-IBP-ALM, and has shown that ibuprofen is capable to form favorable interactions with the (0 -2 0), (1 -1 0), (0 0 1), and (0 1 1) terminating surfaces of α-lactose monohydrate crystals, reflecting that the co-crystal formation between these molecules is theoretically possible.

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