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Effect of HPMC concentration on crystal habit of Nifedipine

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Abstract

Crystal habit can have profound influence on the pharmaceutical properties. A study of the underlying mechanisms of interaction is crucial for understanding the foremost reasons responsible for alteration of crystal habit by additives. The effect of different concentrations of hydroxyl propyl methyl cellulose (HPMC) on nifedipine (Nif) crystal growth was studied wherein, an enhancement in aspect ratio was observed with an increase in concentration of HPMC. Similar pattern in aspect ratio was also observed using molecular dynamics (MD) simulation. The increase in the area of specific facet was observed along with an increase in HPMC concentration, resulting in modification of habit from near cubical (without HPMC) to plate shape (0.6% w/v HPMC). The dissolution rate of the re-crystallized Nif habits (dissolution medium 0.05% v/v Tween 20) was in order of; Nif-0 (Nif without HPMC) > Nif-2 (Nif from 0.2% w/v HPMC) > Nif-4 (Nif from 0.4% w/v HPMC) > Nif-6 (Nif from 0.6% w/v HPMC). The reduction in dissolution rate of Nif-6 was statistically significant ($p < 0.05$) when compared with Nif-0. Contact angle values (wetting property) and surface free energy values in three solvents of different nature successfully supported the habit modification and order of dissolution rate. Liquid chromatography-mass spectroscopy (LC-MS) was used to confirm the absence of HPMC incorporated in crystals or deposited on surface. It was observed from the facet specific surface area values, that HPMC induced a remarkable reduction in the growth on all crystal faces except $\{1\ 1\ 0\}$. The facet $\{1\ 1\ 0\}$ was non-polar in nature as concluded from surface chemistry study and resulted in decrease in dissolution rate of crystal grown with higher HPMC concentration, where $\{1\ 1\ 0\}$ occupied the crystal as a major facet.

KEY WORDS: Polymer, HPMC, molecular dynamics study, crystal habit modification, contact angle, nifedipine, surface free energy, dissolution rate

1. Introduction

Crystal habit can significantly affect properties of an API (active pharmaceutical ingredient) such as wettability, dissolution rate, flow rate and compressibility.¹⁻⁴ Crystal habit modification can be induced by changing crystallizing conditions such as solvent, agitating speed, temperature and degree of supersaturation.⁵ In recent times, advanced strategies have been employed to modify crystal habits by addition of additives such as surfactants and polymers.⁶⁻⁸ The presence of these additives, even at very low concentrations affects the crystallization mechanism and varies the habit.⁹ Thus, it is feasible to design the habit as these additives direct the crystal growth rate to different extents.¹⁰ Solvents and additives can impact growth of crystals thus causing a change in habit.^{11,12} The additive may inhibit the interaction of API molecules from solution onto the API crystal lattice by preferentially occupying growth spots and thus acting as a mechanical obstruction.¹³ The interactions accountable for adsorption can be physical or chemical. Physical interaction like van der Waals interactions and electrostatic interactions are reversible in nature. In contrast, chemical interaction occurs through covalent bonds and is relatively stronger and irreversible.⁹ Numerous factors like hydrophobic, electrostatic and Hydrogen bonding also contribute to the adsorption process.^{9, 14-16}

Various reported crystal growth modifiers include surfactants (Spans, Tweens)¹⁷, cellulose derivatives like HPMC,^{6, 9} polyethylene glycols (PEGs) and salts. The inclusion of polymeric materials as crystal habit modifiers of APIs can be valuable for improving pharmaceutical and biopharmaceutical properties.² HPMC is a commonly used polymer in pharmaceutical formulations and many researchers have studied its impact on crystal habit modification.^{3, 9, 11, 18} Femi-Oyewo and Spring have reported crystal growth inhibitory action of HPMC on paracetamol crystals.² Hecq *et al.*, had used crystal growth inhibition property of HPMC on Nif crystals to stabilize the Nif nanosuspensions.¹⁹ Interaction of polymeric additives with crystal facets is heterogeneous because of the anisotropic nature of the majority of molecular crystals.²⁰⁻²² Salvalaglio *et al.*, has studied effect of biuret on urea crystals where the most important facets are the $\{0\ 0\ 1\}$ and the $\{1\ 1\ 0\}$, which are known to grow fast and slow, respectively.¹³ The relative growth rate difference between $\{0\ 0\ 1\}$ and $\{1\ 1\ 0\}$ crystal facets was responsible for the needle crystals grown in aqueous

medium. To avoid this effect, biuret was used to slow down the growth of one facet relative to another, hence controlling the shape of the urea crystal. Hence there is a need to assess the impact of polymeric additives on anisotropic crystal surfaces. Till date focus has been to merely study the overall impact of HPMC on crystal growth. Efforts to study its role on surface anisotropy have been lacking.¹⁻³ Besides this, none of previous studies have correlated the surface chemistry with pharmaceutical properties like wetting and dissolution rate. Molecular dynamics studies can be used to simulate and predict the effect of additives on crystal growth.²³ Hence, a combined modeling and experimental strategy can be useful in obtaining crystals of desired architecture.^{13, 24-26}

The main objective of the present research work was to study mechanisms responsible for crystal habit altering property of HPMC. Nifedipine (Nif), (3,5-dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate) a potent calcium channel blocker (Fig 1a), was chosen as the model drug. The reason behind choosing Nif as a model drug was its poor aqueous solubility and good crystalline property (defined crystal shape) which makes it an ideal molecule for studies related to crystal habit modification. The secondary objective of this research work was to study the impact of HPMC concentration on crystal habit of Nif and correlate important biopharmaceutical properties like wetting and dissolution on the experimentally generated crystal habits.

Surface docking model was used to simulate the conditions used for laboratory grown crystals. Various solid state characterizations tools like P-XRD (powder X-ray diffraction), DSC (differential scanning calorimetry) and TGA (thermogravimetric analysis) were utilized to examine any solid form change during re-crystallization. Liquid chromatography-mass spectroscopy (LC-MS) was successfully used for establishing the absence of HPMC incorporated in crystals or deposited on surface. Dissolution behavior of the modified crystals investigated in dissolution medium 0.05% v/v Tween 20. Contact angle experiments were employed to understand the chemical nature of different crystals whereas *in-silico* surface chemistry studies helped in understanding the chemical nature of each crystal facet.

2. Experimental section

2.1 Materials

Nif was received as a gift sample from Mylan Labs (Hyderabad, India). HPMC E5 (Fig 1b) was purchased from Finar, India. Ethylene Glycol (EG) was obtained from Merck, India whereas Di-iodomethane (DIM) was purchased from Sigma Aldrich, Germany. Methanol (HPLC grade) was purchased from Merck, India. All other chemicals used were of analytical grade. In-house ultra-pure water from Millipore[®] was used for all experiments. Amber coloured glassware was used for all experiments and storage.

2.2 High-Performance Liquid Chromatography (HPLC)

All samples were analyzed for drug content using a previously reported HPLC method with slight modifications.²⁷ The HPLC system (e2695 Waters) consisted of an HPLC pump, automated injector equipped with a UV detector (2998 PDA). Methanol: water was used as mobile phase in 60:40 (v/v) ratios with a flow rate of 1ml/min. A 20 μ L sample was injected and the absorbance of elute was recorded at 238 nm.

2.3 Re-crystallization experiments

A crystallization protocol was developed based on Nif solubility data. DCM was selected as a solvent for re-crystallization in which Nif shows a solubility of \sim 150 mg/ml. The solvent was maintained at boiling temperature. Slight excess amount of Nif (as determined by solubility studies) was dissolved in 4 ml of solvent. Different selected concentrations (0.2%, 0.4%, and 0.6% w/v) of HPMC were added. Stickiness of the solution prohibited the inclusion of higher concentrations of HPMC. The solutions were filtered into a crystallization vessel and allowed to cool to achieve super-saturation. The evaporation rate was controlled using an inverted cotton plugged funnel. After 48 hrs, crystals were collected, washed with cold hexane, dried, weighed and stored in amber colored bottles. These crystals were then used for further characterization. Nif re-crystallized in 0%, 0.2% 0.4% and 0.6% w/v HPMC were referred as Nif-0, Nif-2, Nif-4 and Nif-6 respectively.

2.4 Characterization of crystallized solid forms

2.4.1 Microscopy

Modified crystals were analyzed at different magnifications by inverted microscope operating with NIE software (Nikone TiU). Their aspect ratios and crystal sizes were also determined (n=200).

2.4.2 Differential Scanning Calorimetry (DSC)

DSC analysis was carried out to determine the melting point and enthalpy values using Mettler Toledo DSC system operating with STAR^e software. Indium was used for calibration. The sample cell was purged with dry nitrogen at a flow rate of 80 mL/min. Accurately weighed samples (5–10 mg) in aluminum-crimped pans with a pinhole were scanned at a heating rate of 10 °C/min over a temperature range of 25–220 °C.

2.4.3 Thermo-gravimetric Analysis (TGA)

Presence of solvent or any degradation during heating was examined using TGA (Mettler Toledo) operating with Star SW 9.01 software. Accurately weighed (5–10 mg) samples were loaded in alumina crucibles and heated at a rate of 10 °C/min over a temperature range of 25 to 300 °C under a nitrogen purge of 60 mL/min.

2.4.4 Powder X-ray diffraction (P-XRD)

P-XRD patterns of samples were recorded at room temperature on X-ray powder diffractometer (X'Pert Pro PANalytical), using Ni-filtered Cu K_a radiation (wavelength = 1.5406 Å). The data was recorded over a scanning range of 2 to 50 at step time of 0.045 steps/0.5 sec.

2.4.5 *In vitro* dissolution studies

All crystal samples were passed through BSS sieve no. 10 and 12. The crystals passed through sieve no. 10 but retained on sieve no. 12 (10/12) were weighed and particle size measurement was conducted. The particle size was reported in terms of D₁₀, D₅₀ and D₉₀

where D_{10} , D_{50} , and D_{90} are the respective particle sizes at 10, 50 and 90% cumulative percentage undersize.²⁸ Particles of size 10/12 were used for dissolution study to exclude the impact of particle size on dissolution rate. Dissolution testing was carried out in USP Apparatus II with rotational speed of 50 rpm ($n=3$). Weighed quantity of samples (20 mg) was added to 900 ml of dissolution medium (0.05% v/v Tween 20 in distilled water maintained at 37 ± 0.5 °C).²⁹ Samples were withdrawn at regular intervals through a syringe connected to membrane filter (0.45 μm). Equal quantity of fresh dissolution medium was replaced. These samples were then evaluated for Nif concentration using the HPLC method.

2.4.6 Determination of contact angle, wettability and surface free energy

Contact angle measurements were carried out using compacted disc technique. The crystals were compacted in a hydraulic press (1000 psi) with one-minute dwell time. Contact angles made by double distilled water, EG and DIM on the compacted samples were measured using sessile drop method on a Drop Shape analyzer (FTA 1000, First Ten Angstrom, Virginia, USA). The compacts were mounted on to a glass slide and a drop of liquid medium was dispensed on them. From the captured video, the contact angle was calculated as a function of time by fitting a mathematical expression to the shape of the drop and then calculating the slope of the tangent to the drop, at the liquid–solid–vapor interface line. All measurements were performed under ambient conditions of 25 ± 2 °C and $55 \pm 5\%$ RH, with the reported values being an average of six measurements.

The evaluated contact angle values were employed to determine the total surface energy (γ^S), dispersive surface energy (γ^{LW}) and polar surface energy (γ^{AB}) components of solids using van Oss-Chaudhury-Good theory.³⁰ This theory subdivides the polar element of surface energy of solids and liquids into two definite constituents: the surface energy related to acidic interactions (γ^A) and surface energy related to basic interactions (γ^B). The acidic part theoretically explains tendency of a surface to have more polar interactions with another surface that has higher basic characteristics by donating electrons. On the other hand, the basic component of the surface energy explains the tendency of a surface to have

more polar interactions with a surface that has higher acidic characteristic by accepting electrons. The principle equation for this theory is as follows.

$$(1 + \cos \Theta) \gamma_{LV} = 2 \left[\sqrt{\gamma_S^{LW} \gamma_L^{LW}} + \sqrt{\gamma_S^A \gamma_L^B} + \sqrt{\gamma_L^A \gamma_S^B} \right] \quad (1)$$

In the given equation, γ_{LV} represents surface tension, γ_S^{LW} represents dispersive surface energy of solid and γ_L^{LW} stands for dispersive surface energy of liquid.¹⁵ The method involved use of minimum three liquids: (a) liquid with only a dispersive element to its surface energy (DIM), (b) liquid with a dispersive and an acidic/basic component (water), and (c) liquid with either a dispersive and a basic/acidic component (different from second probe liquid) (EG) or a liquid with all three discussed components.

2.5 Computer simulation studies

Nif Crystal structure (CSD code BICCIZ) was taken from Cambridge Structure Database. All molecular dynamics and morphology simulations were executed using Materials Studio 6.1. Geometry optimization was carried out using COMPASS force field of forcite algorithm. Face list was created using morphology simulation, which gave hkl values of all important faces with their respective d_{hkl} values. Modeling protocol for crystal morphology prediction in vacuum and in presence of solvents/additives is provided as a supplementary material.

3. Results and discussion

3.1 Crystallization experiments and computational simulation

The images of experimentally re-crystallized Nif in the presence of the additive (Fig 2a, 2c, 2e) clearly showed that the crystal morphology changes as a function of HPMC concentration. Results also indicated that HPMC altered the Nif crystal facets differently, resulting in concentration dependent enhancement of aspect ratio of Nif crystals. Vacuum morphology of Nif simulated by BFDH method gave six important facets with their respective percentage surface areas (Supplementary table 1). The calculated aspect ratio of 1.83 was significantly different from the experimentally observed aspect ratio at different

concentrations of HPMC. The noteworthy difference between the simulated and the experimental morphology could be due to the absence of actual conditions provided during crystallization. Therefore, DCM solvent molecules were included with HPMC to generate conditions during simulation that would be comparable to experimental conditions.

The orientation of molecules on the exterior of each facet of a crystal is diverse because of its structural dissimilarity.⁵ The dissimilar relative abundance of functional groups on the facets of crystal habits confers different surface properties. It has been observed that polar moieties are preferentially adsorbed by the polar facets and non-polar moieties by the non-polar facets and this determines the crystal morphology.²³ Relative presence of functional groups of different nature was examined on facets of simulated Nif crystal habit (Fig. 3). This allowed correlation of crystal surface property with properties of crystal growth medium. Similarly, this study also helped in classifying facets according to their surface chemistry (Fig 3). Detailed description of each facet is provided as the supplementary material.

Morphological effects are mostly structure driven and for this reason are specific to the crystallizing system. In presence of HPMC, the aspect ratio of the Nif crystals changed significantly. Columnar shape crystal habit with an aspect ratio 1.62 ± 0.22 (n=200) was obtained experimentally for Nif-2 (Fig 2a, table 1); while a columnar habit with an aspect ratio 1.88 was simulated by computational technique when provided with similar crystallization environment (Fig 2b, table 1). The most important crystal facets were $\{1\ 1\ 0\}$, $\{0\ 0\ 2\}$ and $\{1\ 1\ 1\}$ with a surface area of 44%, 15% and 13% respectively (Fig. 4). Octagonal crystal habit with an aspect ratio 1.91 ± 0.27 (n=200) was observed for Nif-4 (Fig 2c, table 1), while the simulated habit was also almost octagonal with an aspect ratio of 1.89 (Fig 2d). The most important facets were $\{1\ 1\ 0\}$, $\{0\ 0\ 2\}$ and $\{1\ 1\ 1\}$ with their respective surface area of 50%, 19% and 14% (Fig 4). Platy crystal habit with an aspect ratio 2.12 ± 0.31 (n=200) was obtained for Nif-6 (Fig 2e, table 1), while the simulated habit was also plate like with a calculated aspect ratio of 2.19 (Fig 2f). Figure 2f illustrated that the important crystal facets consisted of $\{1\ 1\ 0\}$ and $\{0\ 0\ 2\}$ with their respective surface area of 67% and 22% (Fig 4).

From the above study, statistically no significant variation was observed for aspect ratio of experimental and simulated habits ($p > 0.05$), the findings of which were also supported on microscopic evaluations (Fig 2a, 2c, 2e and supplementary figure 1). The facet area of $\{1\ 1\ 0\}$ is $\sim 22\%$ in Nif-0, $\sim 44\%$ in Nif-2, $\sim 50\%$ in Nif-4 and $\sim 67\%$ in Nif-6. The facet area of $\{0\ 0\ 2\}$ is $\sim 11\%$ in Nif-0, $\sim 15\%$ in Nif-2, $\sim 19\%$ in Nif-4 and $\sim 22\%$ in Nif-6. Thus, it was clearly visible from the facet specific surface area values (Fig 4) that HPMC induced a remarkable reduction of growth on various facets except $\{1\ 1\ 0\}$ and $\{0\ 0\ 2\}$. This effect was more obvious at higher concentrations of HPMC. It was presumed that HPMC molecules might show differential adsorption onto a crystal face and influence the crystal growth in terms of its dimensions. At moderately low concentrations of the HPMC (0.2-0.4% w/v), its suppressing consequence on the crystal growth was not significant because of inadequate polymer molecules. However, at higher HPMC concentration (0.6% w/v), with more numbers of polymer molecules, the chance of the drug-polymer interactions were high. Under these circumstances, the preferred interaction of HPMC at the different crystal faces led to different crystal growth, the outcome of which was macroscopically manifested with 0.6% w/v HPMC as platy Nif crystals. However, in the present study, it was observed from molecular dynamics that HPMC molecules did not directly interact with the crystal surfaces (Fig 5). The closest distance between $\{1\ 1\ 0\}$ crystal surface and HPMC molecules (Fig. 5) was always higher than $6.42\ \text{\AA}$ which indicated the absence of any direct interaction between them.³¹ Similar patterns were also observed with all other facets. The interactions accountable here can only be physical, as chemical interaction were ruled out by molecular dynamics. Physical interaction like van der Waals interactions and electrostatic interactions are reversible in nature, which might have contributed to the process.^{9, 14-16}

The most important crystal facets were $\{1\ 1\ 1\}$, $\{1\ 1\ 0\}$ and $\{1\ 0\ -2\}$ with a surface area of $\sim 50\%$, $\sim 21\%$ and $\sim 17\%$ respectively which shows the nearly equal presence of non-polar and polar facets. These proportional surface areas of Nif-0 facets can be correlated to polarity index of crystallizing solvent DCM, which lies at bottom of polar aprotic solvents with weak hydrogen bond formation capacity. DCM is aprotic solvent with weak H-bonding capacity; hence will not direct crystal growth according to any specific surface functionality unlike polar or non-polar solvents. Thus, this kind of nature will give nearly

iso-diametric crystals. In the present molecular dynamics study, HPMC molecules found surrounded by DCM molecules which might have further inhibited HPMC interaction with Nif molecules. This resulted in significant changes in modified attachment energies due to which different morphology obtained. This change in modified attachment energies became more significant with higher concentration of HPMC. It was hence concluded that the probable mechanism responsible for this surface anisotropy could be a HPMC induced disorder in the molecular environment of the crystallizing medium, thereby inducing a change in solvent property like dielectric constant or polarity.³² For instance, varying the amount of additive changed the pattern of crystal growth from columnar (Fig. 2a) to plate crystals (Fig. 2e) as HPMC induced a remarkable reduction of growth on various facets except $\{1\ 1\ 0\}$ and $\{0\ 0\ 2\}$. This effect was more pronounced at higher concentrations of HPMC. Growth of particular facets $\{1\ 1\ 0\}$, $\{0\ 0\ 2\}$ and retarded growth of other facets changed the habit from columnar to plate. Under provided conditions of crystallization, the growth of one kind of crystal facets were retarded, and the other facets were induced to grow faster.³³ It is suggested that polar solvents are preferentially adsorbed by polar faces and non-polar solvents by non-polar faces.³³ As a result, the polar surfaces are thought to be dominant when highly polar solvents are used while non-polar surfaces are thought to be dominant when non-polar solvents are used.³⁴ In this study, proportion of non-polar facets $\{1\ 1\ 0\}$ increased with HPMC concentration. Thus, the reason could be the reduced polarity of medium with HPMC which helps in growth of non-polar facets (non-polar functional groups in majority). The interaction was different on different facets according to their surface chemistry, thus controlling the crystal shape.

This study was further complemented with the description of the contact angle values and surface free energies of the Nif crystals in following section. It can be inferred that addition of HPMC to the crystallization medium altered the mean growth rate of individual crystal facets, resulting in crystal habit modification. In the present example of Nif, the habit alteration originated by surface - solvent - additive interactions had a differential effect on the growth rate of the polar and non-polar facets. There subsists a significant resemblance ($p > 0.05$), amid experimental and simulated habits of all three selected combinations (table 1). From the outcome of experimental crystal habits, it was demonstrated that iso-diametric

shape of crystals was altered when Nif was re-crystallized with DCM (Nif-0) in presence of varying concentrations of HPMC (Nif-2, Nif-4 and Nif-6).

3.2 Solid state characterization of modified crystals

It is a well-known fact that the alterations in crystal habit maybe indicative of phase transition. Thus, to examine the effect of HPMC in the crystallization medium on the solid-state and crystallinity of Nif, the samples were characterized by means of P-XRD, DSC and TGA. The DSC heating curve of each sample was identical with that of untreated Nif (Fig 6). The DSC curve in all samples demonstrated a sharp single endothermic peak close to 173°C corresponding to the melting point of Nif. All Nif crystals obtained with different HPMC concentrations also showed a solitary melting point endotherm in the range of 173.16 °C – 175.41 °C. Three mono-tropically related polymorphs of Nif have been reported.^{35, 36} α form (commercially available with melting point~173 °C) is thermodynamically stable at ambient temperature while β form (melting point~163 °C) and γ form (metastable modification with melting point~135 °C), can be obtained only from the Nif quench cooled melt.^{37, 38} Therefore a single melting point endotherm (173.16 °C – 175.41 °C) ruled out any polymorphic transformation. Absence of any solvate was established as no other endothermic peak was observed in the DSC analysis. This absence of any polymorphic transformation and solvate was further supported by TGA thermographs (supplementary figure 2), where no weight loss was detected till 200 °C.

P-XRD pattern of Nif is shown in Fig 7. All characteristic peaks of Nif monoclinic form were present in selected Nif crystals. The decrease in intensity of Nif-2 and Nif-4 could be because of the different preferred orientations in crystal habit samples.³⁹ P-XRD pattern of these crystals demonstrated similarity of 2θ values to calculated diffraction pattern of α polymorph (supplementary figure 3). This proved that solid form did not undergo any change. It was thus concluded from P-XRD, TGA and DSC analysis that no other polymorphs and solvates were generated and merely habit modifications took place during re-crystallization of Nif with varying concentrations of HPMC.

3.3 Comparative dissolution rate

Modified Nif crystal habits in HPMC; Nif-2, Nif-4 and Nif-6 showed significant decrease in dissolution rate in dissolution medium 0.05% v/v Tween 20 when compared to Nif-0. The order of dissolution rate was Nif-0 > Nif-2 > Nif-4 > Nif-6 (Fig 8). The crystals of similar size range were used to avoid the impact of particle size on dissolution rate. D_{10} , D_{50} and D_{90} values of all re-crystallized samples were found nearly similar (supplementary table 2). The reduction in dissolution rate can be partially attributed to their higher aspect ratio and lower crystal surface area/volume ratio. The simulated surface area/volume ratio of these simulated habits were found in the order Nif-6 (1.24) > Nif-4 (1.20) > Nif-2 (1.19) > Nif-0 (1.114) which correlates well with the order of dissolution rate.

Crystal habits and their closely related properties such as aspect ratio, surface anisotropy and effective surface area exposed to dissolution medium are known to control the dissolution rate of crystals. Difference in dissolution profile can be ascribed to changes in relative abundance of different crystal facets in various habits. The surface area of facet $\{1\ 1\ 0\}$ increased continuously with increase in concentration of HPMC. The facet area of $\{1\ 1\ 0\}$ is ~ 22 % in Nif-0, ~ 44% in Nif-2, ~ 50% in Nif-4 and ~ 67% in Nif-6. Thus, nearly 67% of total facet area of platy crystals (Nif-6) was contributed by $\{1\ 1\ 0\}$ which is of non-polar nature (surface chemistry study in Fig. 3). This enhancement in non-polar surface area coupled with reduced surface/volume ratio due to altered aspect ratio (table 1) probably resulted in decrease in dissolution rate. The facet area of $\{0\ 0\ 2\}$ was also increased along with HPMC concentration. However, it could not have significant impact on the dissolution rate, as the increased facet area was not significantly increased.

Quantification of HPMC is a difficult task due to the absence of UV-active chromophores and generally requires development of alternative detection method like ELSD, which was out of the scope of the current study. However, authors analyzed the crystals for HPMC by LC-MS (liquid chromatography-mass spectroscopy) (supplementary figure 4) which showed the absence of HPMC on crystal surface/interiors.⁴⁰ Hence, difference in dissolution rate can be ascribed to changes in crystal habit.

3.4 Contact Angle, wettability and surface free energy

The wetting property is usually quantified by contact angle values. The contact angle limits are 0° for complete wetting and 180° for absence of wetting. Wetting behavior of Nif crystals was evaluated by contact angle values. The contact angles (table 2), with double-distilled water, were $61.50^\circ \pm 3.78^\circ$, $65.88^\circ \pm 0.86^\circ$, $68.60^\circ \pm 1.43^\circ$ and $70.17^\circ \pm 1.69^\circ$ for Nif-0, Nif-2, Nif-4 and Nif-6 crystals, respectively. Thus, contact angle values, with double-distilled water (polar in nature) increased with an increase in the HPMC concentration. This enhancement in contact angles was found statistically significant ($p < 0.05$). Similarly, the contact angle values with EG (semi polar medium) also displayed a non-significant increasing trend with increase in HPMC concentration (table 2). Hence, from the contact angle values with water and EG, it can be concluded that Nif without HPMC had a higher wetting tendency in both semi-polar and polar media and the wettability of the crystals in polar aqueous media decreased when the concentration of HPMC in their crystal growing medium was increased. In contrast, crystals of Nif-0, Nif-2, Nif-4 and Nif-6 showed a continuous decrease in contact angle values when DIM (less polar with only dispersive component)¹⁵ was used as the probe liquid leading to conclusion that Nif-6 had a higher wetting tendency in less polar medium (table 2). These observations were also in agreement with the dissolution rate profiles discussed in above section 3.3. Thus from the contact angle pattern in solvents of different polarity it can be concluded that untreated Nif had higher wetting tendency in polar medium and lower wetting tendency in DIM less polar medium.

Surface free energies were also calculated to study the impact of HPMC on surface free energies of crystal grown with different concentrations of HPMC (Fig. 9). No significant difference in dispersive component of surface free energy was observed in all the Nif samples. On the other hand, values of polar surface energies showed a continuous decreasing trend along with concentration of HPMC when compared Nif-0. It can be clearly observed from fig. 9 that Nif-0 had relatively higher total surface free energy, higher polar component and higher acidic component, which contribute to its higher polar nature when compared to Nif crystals obtained with HPMC (Nif-2, Nif-4 and Nif-6). This decrease in polar surface free energy of Nif-6 provides an explanation for reduction in its

dissolution rate and is in line with the trend observed in surface chemistry study where proportion of non-polar facet exhibited a HPMC concentration dependent increase.

The variation in the contact angle values can be explained by the variations in the surface area of different facets and their related surface polarity (differences in type of functional groups on different crystal facets). As mentioned earlier in dissolution section, that the area of facet $\{1\ 1\ 0\}$ showed a concentration dependent increase for HPMC, which modified the habit from slightly cubical to plate. Surface chemistry study established facet $\{1\ 1\ 0\}$ was non-polar in nature. This resulted in decrease in dissolution rate and polarity wherever $\{1\ 1\ 0\}$ was the major facet. Thus, decline in polar energy of these crystal habits is well correlated with decrease in dissolution rate and increase in surface area of non-polar facet.

4. Conclusion

The impact of different concentration of HPMC (polymer) on Nif crystal growth was supported by means of molecular dynamics (MD) simulation, to give an insight into the interplay of solvent DCM and HPMC molecules at the interface of chemically diverse Nif crystal facets. Crystal habit of Nif was modified by the presence of low amounts of HPMC. Existence of any solvates/polymorphs was ruled out by means of DSC, TGA and P-XRD. Simulation studies were helpful in understanding the mechanism of interaction between Nif molecules and HPMC molecules. Based on the crystal surface chemistry, the mechanism accountable for the alteration in morphology was suggested. Finally, the effect of crystal habit modification on dissolution behavior of Nif was demonstrated. Nif without HPMC gave nearly iso-diametric crystals with majority of facets occupied by polar dominant surfaces, ultimately resulting in higher dissolution rate. This conclusion was supported by wetting property and surface free energy determination from contact angle measurements. The method used here could be an influential tool for studying the mechanism responsible in additive assisted crystal habit modifications.

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Notes

The authors declares no competing financial interest

Abbreviations

DCM, dichloromethane; MD, molecular dynamics; Nif, nifedipine; BFDH, Bravais Friedel Donnay Harkel; DSC, differential scanning calorimetry; TGA, thermogravimetric analysis; P-XRD, powder X-ray diffraction

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Supporting information available

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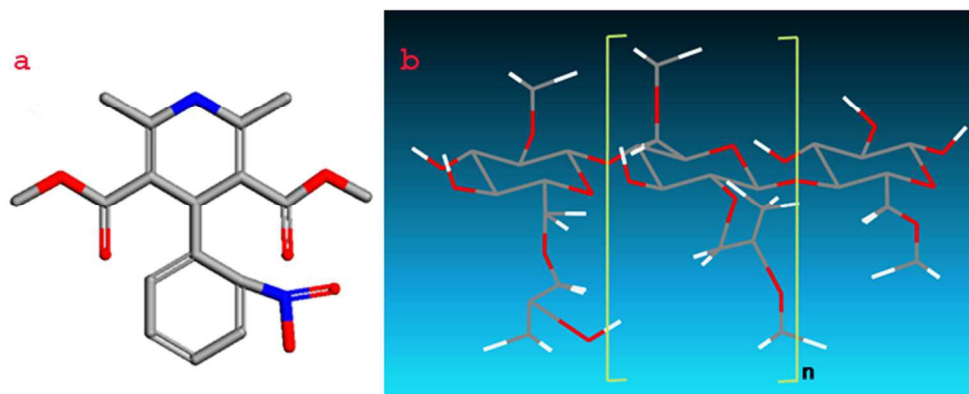
Table 1. Aspect ratio of Nif crystals with different concentrations of HPMC

Additive	% Concentration (w/v)	Experimental aspect ratio	Predicted aspect ratio
HPMC	0	1.34 ± 0.22	1.84
	0.2	1.62 ± 0.32	1.88
	0.4	1.91 ± 0.27	1.89
	0.6	2.12 ± 0.31	2.19

All values are expressed as mean ± SD (n = 200)

Table 2. Contact angles of modified re-crystallized Nif

Formulation	Contact angle with water (mean ± SD)	Contact angle with EG (mean ± SD)	Contact angle with DIM (mean ± SD)
Nif -0	61.50 ± 3.78	43.87 ± 2.89	16.45 ± 1.94
Nif -2	65.88 ± 0.86	44.52 ± 5.14	16.31 ± 1.31
Nif -4	68.60 ± 4.43	44.72 ± 3.41	16.26 ± 1.21
Nif -6	70.17 ± 3.69	44.26 ± 3.55	15.84 ± 0.82

**Figure 1.** Chemical structure of a. Nifedipine and b. HPMC

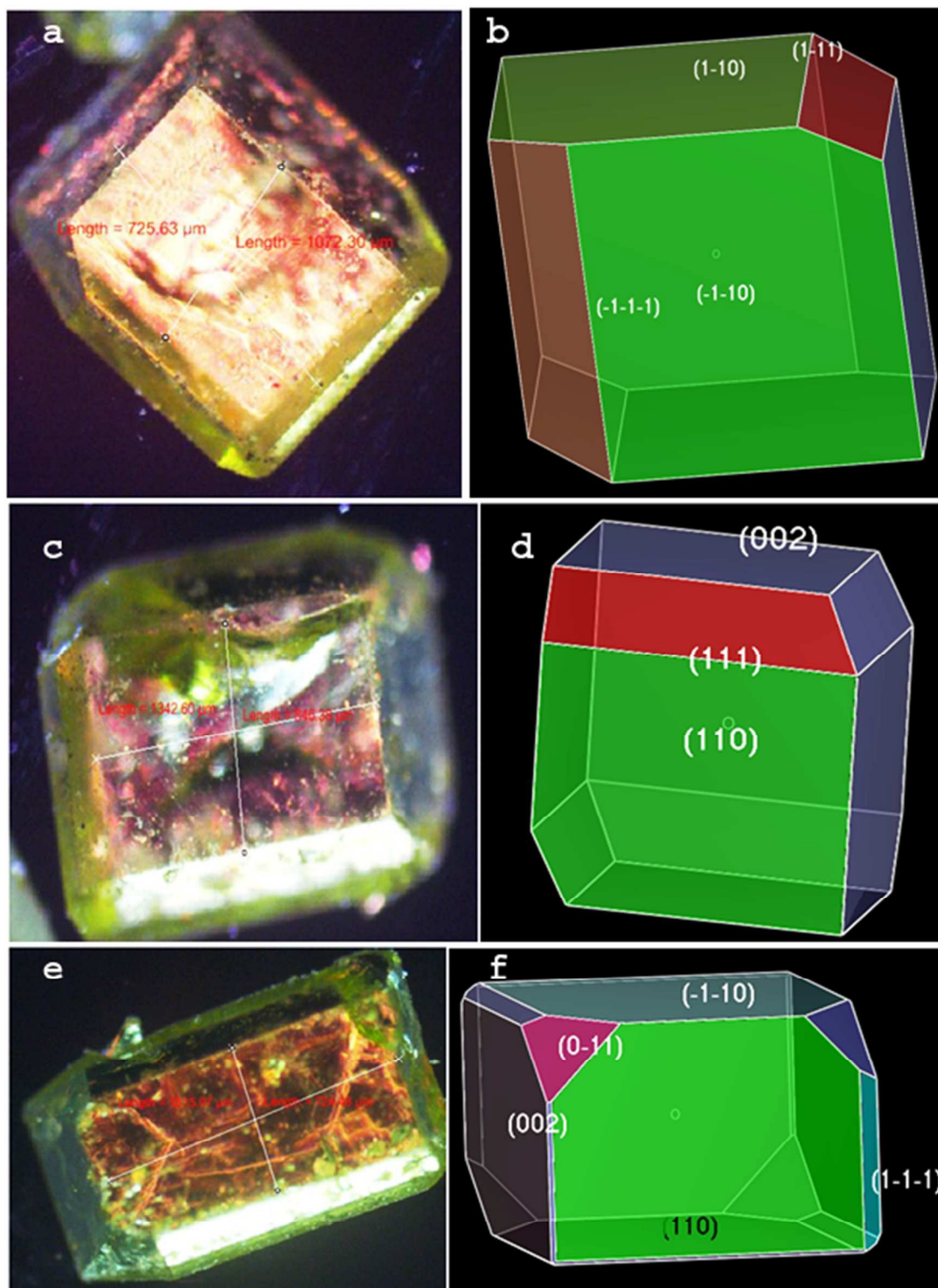


Figure 2. Modified crystal habits of Nif with DCM as solvent and HPMC as additive (a) Experimental Nif-2 habit (b) Predicted Nif-2 habit (c) Experimental Nif-4 habit (d) Predicted Nif-4 habit (e) Experimental Nif-6 habit (f) Predicted Nif-6 habit

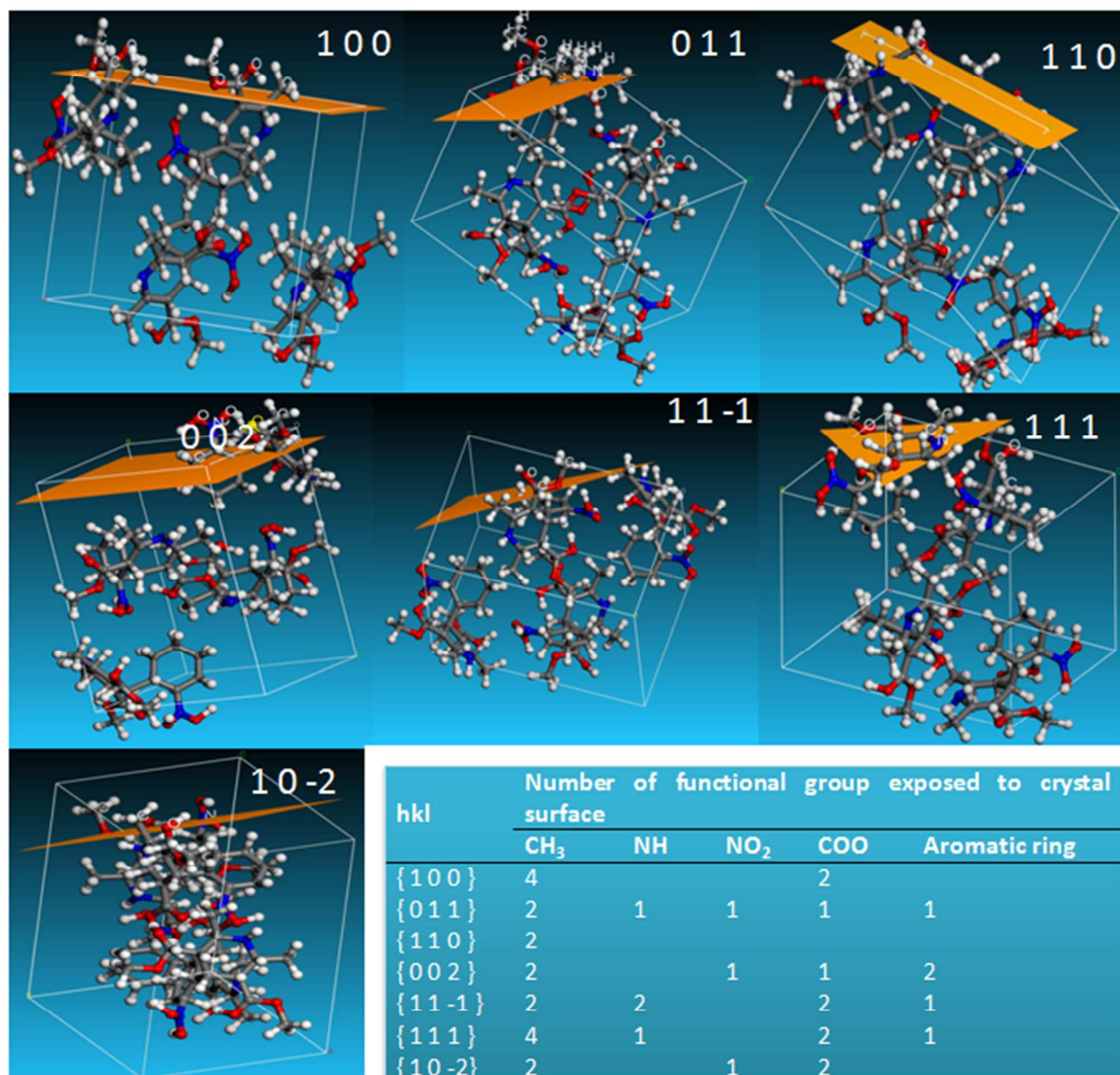


Figure 3. Surface Chemistry of the Dominant Crystal Faces (hkl) of Nifedipine

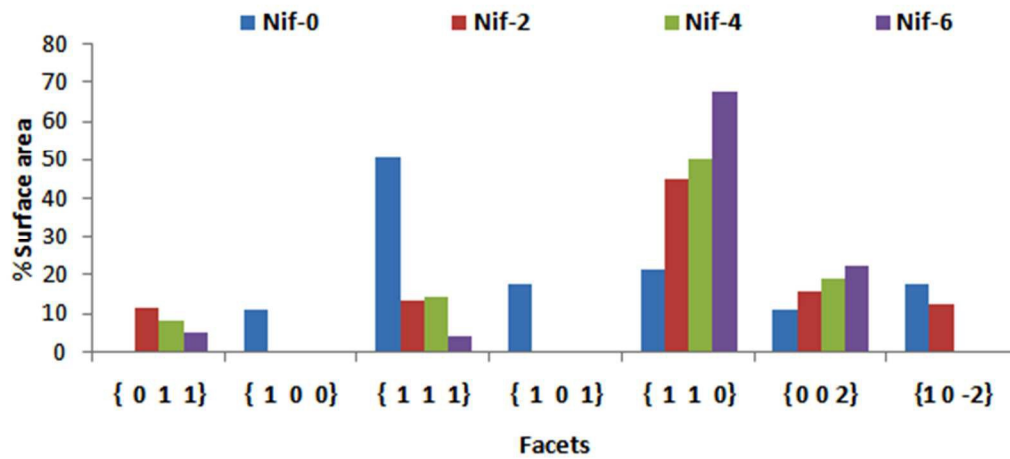


Figure 4. Comparative % surface areas of different important facets in modified crystal habits

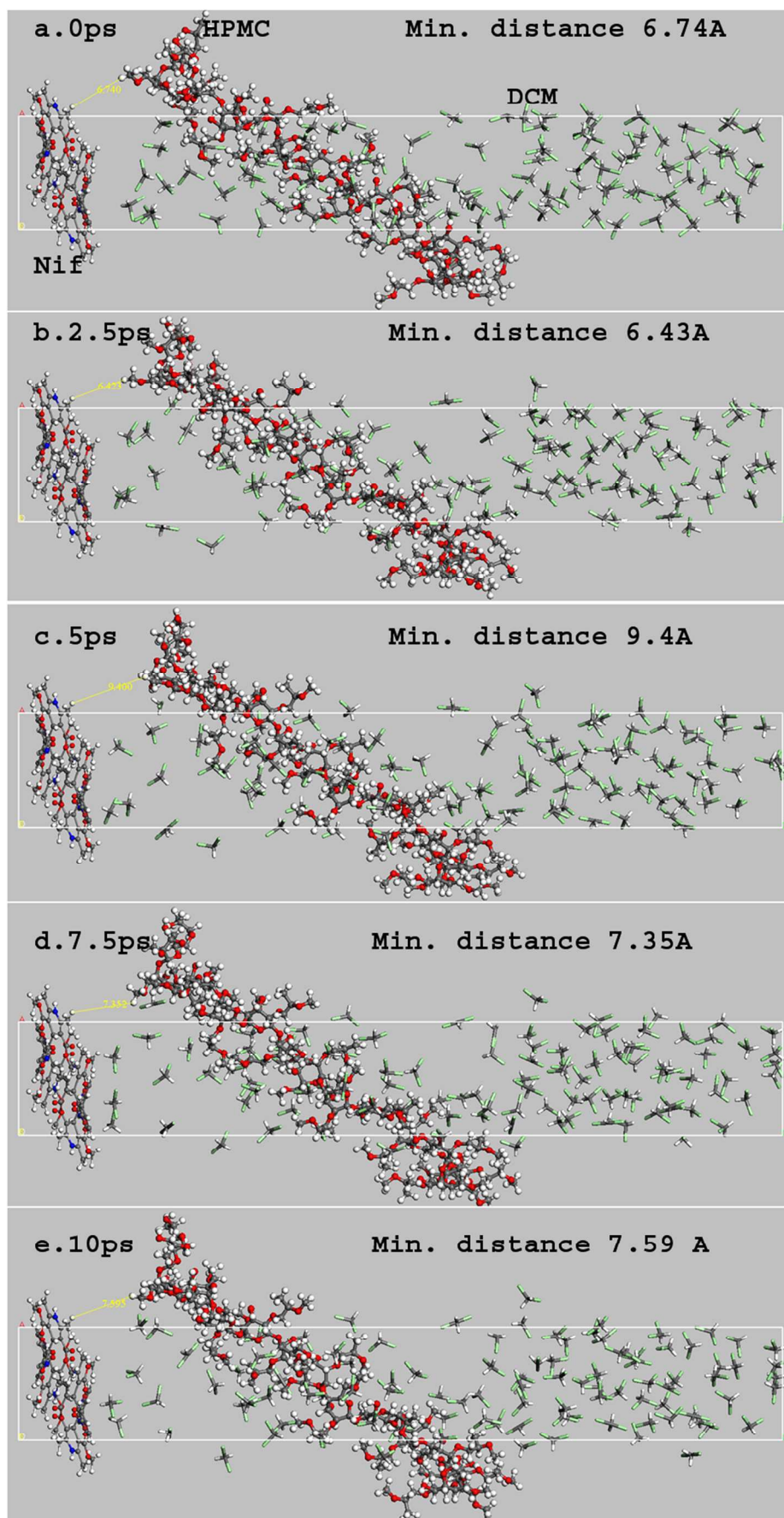


Fig. 5 Sequential snapshots of molecular dynamics at facet {1 1 0} at different time points (0 ps, 2.5ps, 5ps, 7.5 ps, 10ps) showing the level of interaction between Nif crystal surface, DCM and HPMC

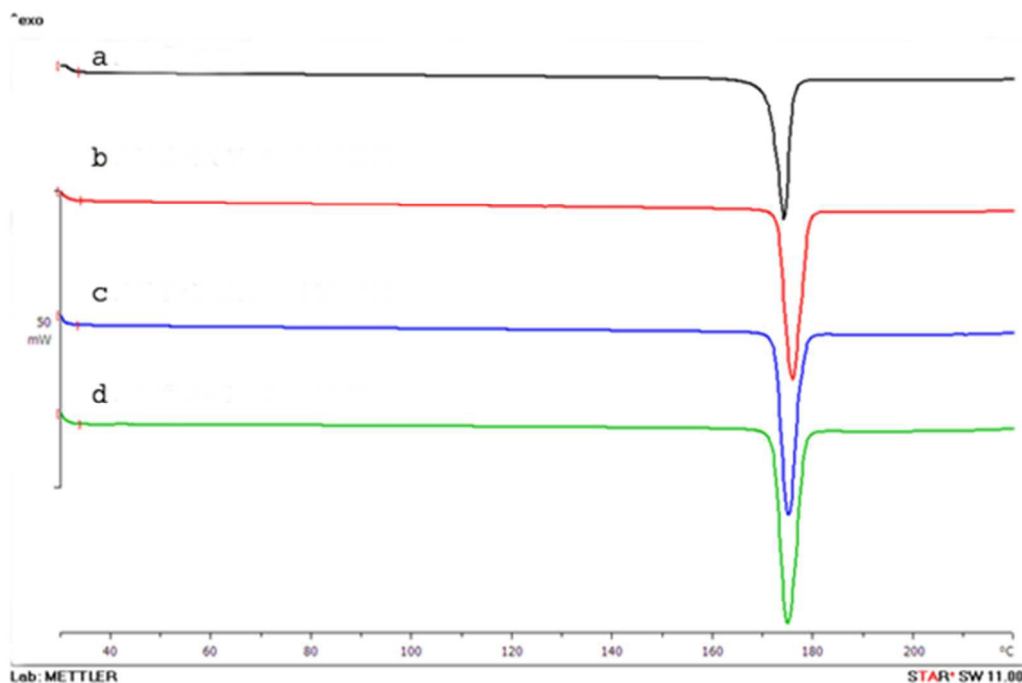


Figure 6. DSC heating curves of Nif re-crystallized in different concentrations of HPMC (a) Nif-0, melting point (M.P.) = 173.01 °C, $\Delta H_f = -109.58$ J/g, (b) Nif-2, M.P. = 174.51 °C, $\Delta H_f = -109.41$ J/g, (c) Nif-4, M.P. = 173.42 °C, $\Delta H_f = -112.84$ J/g, (d) Nif-6, M.P. = 173.16 °C, $\Delta H_f = -110.90$ J/g

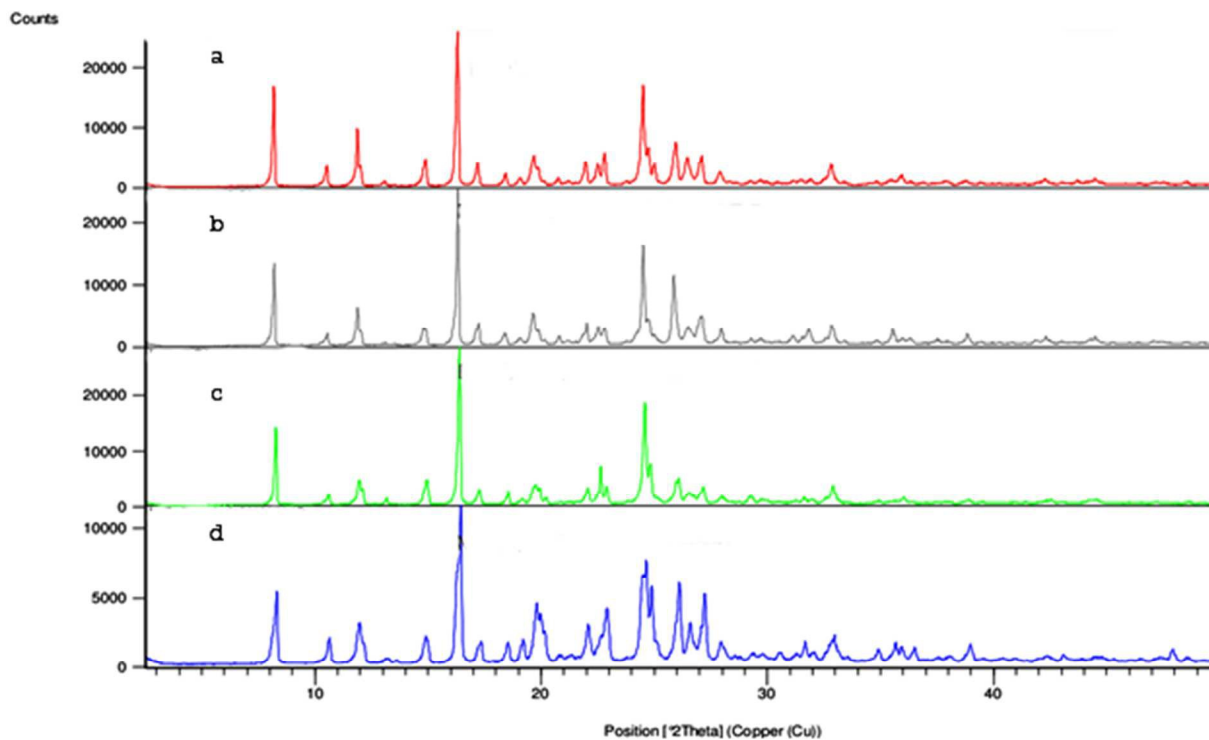


Figure 7. P-XRD results of Nif crystals from different concentrations of HPMC (a) Nif-0 (b) Nif-2 (c) Nif-4 (d) Nif-6

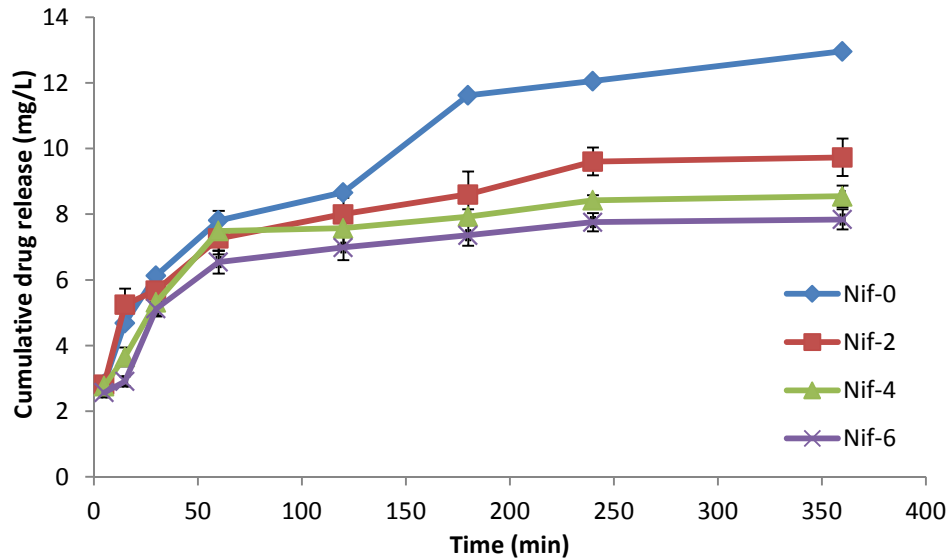


Figure 8. Comparative dissolution profiles of Nif re-crystallized in different concentrations of HPMC with 0.05% v/v Tween 20 as dissolution medium

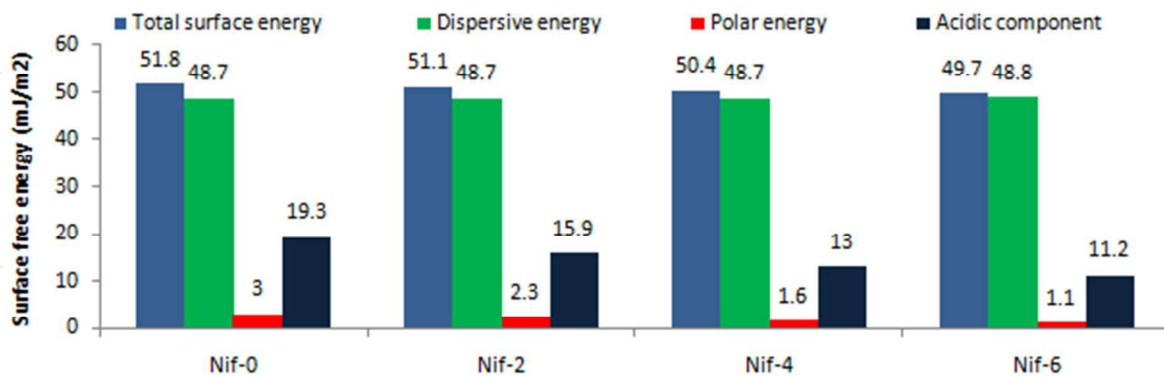
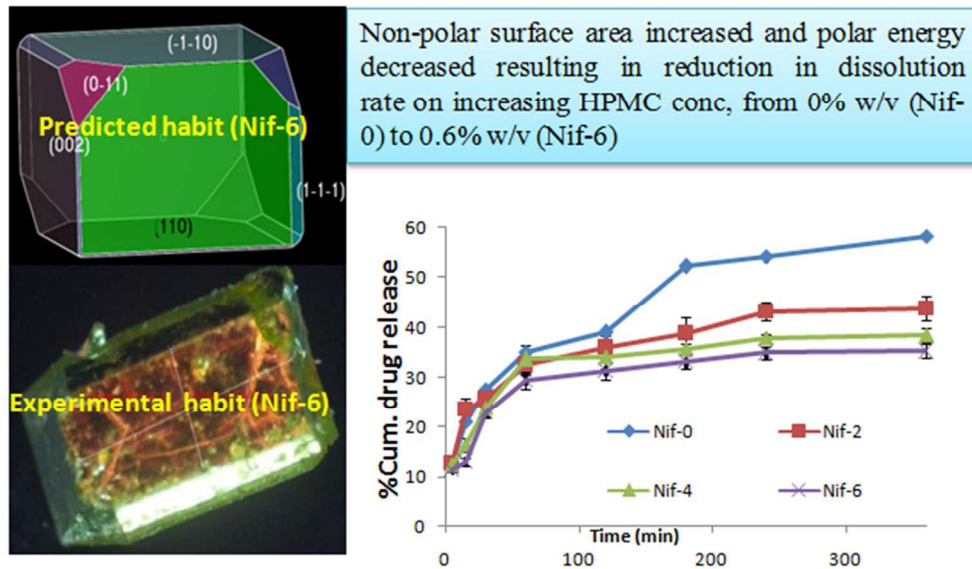


Figure 9. The Total (γ^S), Dispersive (γ^{LW}), Polar (γ^{AB}), Basic (γ^B), and Acidic (γ^A) Surface Energies of Nif Crystal Habits



55x33mm (300 x 300 DPI)