Computer Simulation of Crystal-liquid Interface: Application to Wettability of Solids

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Purpose. This study describes the development and application of a molecular simulation technique for investigating the solid-liquid interface. It attempts to relate the molecular and crystal structure to the observed wettability of solids.

Method. Molecular simulations have been carried out for the crystal-water interface of a series of N-n-alkyl-D-gluconamide crystals using the Monte Carlo technique. The molecular system simulated consisted of a layer of water bounded by two crystal slabs. The interfacial potential energies were calculated for the crystal-water interactions and compared with experimental enthalpy values obtained from contact angle measurements.

Results. The simulations clearly reveal the distinct hydrophilic and hydrophobic nature of the respective (010) and (0$\bar{1}$0) faces of these compounds. The distribution of water at the interface observed in the simulations is in accord with the nature of the crystal faces. The calculated interfacial potential energies are in the right ball park, but consistently higher than the experimental values. The disparity, however, is justifiable, resulting from the highly simplified model simulated.

Conclusions. Using the developed molecular simulation technique one can calculate the wettability of a solid given the crystal structure. This approach represents an important step towards the goal of engineering crystals with desired wettability characteristics.

KEY WORDS: molecular simulation; interfacial energy; wettability; crystal structure; Monte Carlo method; potential energy calculations; contact angle.

INTRODUCTION

Wettability, the tendency of a solid to wet, is an important parameter for characterising solids (1). It can, for example, be correlated with the dissolution rate and stability of pharmaceuticals. It is useful for selecting an appropriate binder or granulating fluid for granulation, and for deriving optimum formulations for suspensions and film coating. The solid-liquid interaction also has an important role in determining the morphology of crystals (2,3) as well as the polymorphic form (4).

The interactions at the solid-liquid interface can be readily investigated using various experimental techniques that include contact angle measurements, vacuum microbalance and microcalorimetry. Our understanding of the molecular interactions involved, however, still remains relatively rudimentary. The ability to relate the molecular and crystal structure to the observed wettability would, if it were possible, represent a fundamental advance. This would enable the development of formulations on a rational basis. It would also open up the possibility of engineering crystals (of both drugs and excipients) with desired wettability characteristics.

This paper presents a computer simulation technique based on the atom-atom potential method (5) for calculating the interfacial energy of any given crystal surface against a given solvent. The methodology has been validated by simulating the interface between water and selected faces of a series of N-n-alkyl-D-gluconamides. These gluconamides yield polar crystals that exhibit a hydrophilic and a hydrophobic face in the same crystal (6), and thus serve as an excellent model for the calculations.

THEORY AND COMPUTATIONAL METHOD

Recent advances in our knowledge of the forces between atoms and the exponential rise in computing power now make it possible to calculate both the potential energy and the forces of an interacting system of atoms or molecules (7). Indeed via such calculations it is possible to simulate the dynamics of the molecular system (7). The basis for such simulations is the atom-atom potential method (5). The potential energy function depends on the positions of the atoms and typically takes the form:

$$U(r) = \sum U_{LJ}(r) + \sum U_{qq}(r) + \sum U_{bond}(r) + \sum U_{angle}(r) + \sum U_{torsion}(r)$$

where the summations for U_{LJ} and U_{qq} terms are over all atom pairs, and those for U_{bond}, U_{angle} and $U_{torsion}$ are over all respective bonds, angles and torsions present in the molecular system. $U(r)$ represents the total energy of the system. The terms U_{LJ} and U_{qq} are the Lennard-Jones and the coulombic interactions respectively for describing the pairwise interaction between two non-bonded atoms and are given by:

$$U_{LJ} = 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right]$$

$$U_{qq} = \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}$$

where ϵ_{ij} is the value of the minimum in the energy-distance curve of the two interacting atoms i and j, σ_{ij} is the shortest possible distance between the two atoms without experiencing any repulsion, r_{ij} is the separation distance between the two atoms, q_i and q_j are the partial charges, and ϵ_o is the permitivity of vacuum. It is clear from the expressions that at all separations other than closest approach, the total non-bonded interaction (U_{LJ} and U_{qq}) decreases in significance with increase in the separation distance between the two atoms. For the Lennard-Jones term the interaction energy becomes insignificant above a separation distance of about 3.5σ, whereas for the coulombic term the decay is less pronounced. The implication is that as a good approximation the non-bonded interactions can be ignored at long distances. It is usual to limit the interactions to a cut off that is typically between 8 and 12 Angstroms. The U_{bond}, U_{angle}, and $U_{torsion}$ represent the bond stretching, bond

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angle and the torsional energy contributions of the molecular system.

A common approach to calculating the potential energy of a molecular system is to minimise the energy by allowing the system to relax and then take the final minimum energy value. This single-point energy calculation, however, is not valid for a liquid. It is necessary to consider all possible orientations and positions of the liquid and then average the interaction energy in an appropriate manner. Such a calculation can be done using either the Monte Carlo (MC) technique or the method of molecular dynamics (MD) (7). MC is a little easier to implement and was the method of choice for the present study. It involves sampling all the possible configurations of the system and averaging the potential energy in an appropriate manner.

The Metropolis Monte Carlo technique (8) that is commonly employed in molecular simulations involves the generation of new configurations or states of the system by small random displacements of the molecules. The displacements are followed by calculation of the potential energy of the system, which is then compared with that of the previous state (before the displacement). The new state is then either accepted or rejected using a criteria based on the Boltzmann factor. If the energy of the new state is lower, the new state is accepted unconditionally and becomes the current state. If the energy is higher and the factor $e^{-\Delta U/kt}$ (where U is the energy and k is Boltzmann's constant) is higher than a generated random number the move is accepted. Otherwise it is rejected. This algorithm ensures that the molecular configurations are generated with an appropriate probability that is consistent with the statistical mechanics of molecular systems. The system evolves towards lower free energy. Once the system has equilibrated, the average of the potential energy of the subsequently generated states gives the ensemble average for the system (7).

The molecular system simulated consisted of a thin layer of water bounded by two crystal slabs. The simulation box is shown in Figure 1. Both crystal slabs expose the same crystal face to the liquid. The simulations were carried out using an in-house computer program, called INTERFACE (9). INTERFACE consists of two modules: BOX and ENERGY. The BOX module generates the simulation box containing the crystal-liquid interface for the desired crystal face, whilst the ENERGY module performs the Monte Carlo calculations. The required input includes the structural data for both the crystal and liquid, the Miller indices of the crystal face, and the forcefield parameters characterising the atoms of the crystal and the liquid. The interaction energy was calculated between the solvent and the crystal slabs subject to a cut off radius of 8.5Å. The overall dimensions of the simulation box were typically 20 × 30 × 60Å. The number of crystal molecules in the simulation box varied between 44–64 depending on the crystal and the selected face whilst the number of water molecules varied between 630–880. The simulations were carried out using the microca-

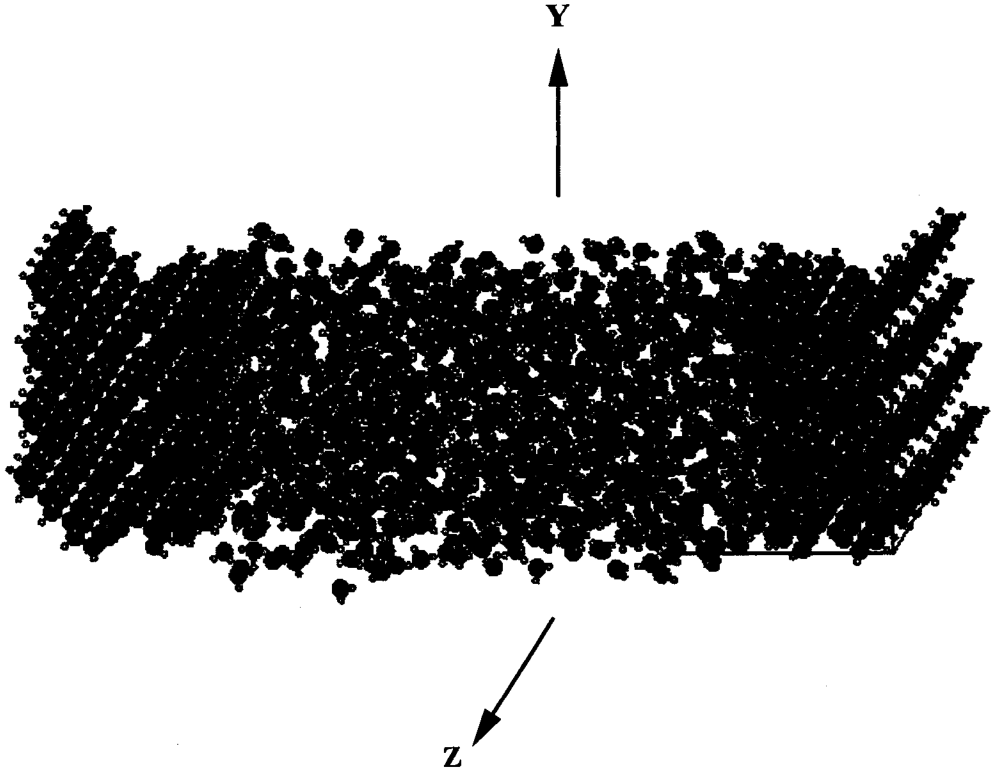

Fig. 1. A snapshot of the simulation box showing the distribution of the water molecules between the crystal surfaces after equilibration. Molecules of the solvent (water) are bounded by the two crystal slabs each exposing the same face to the solvent. Periodic boundaries exist along the Y and Z directions as indicated by the arrows but not along the X-axis. The thickness of the water layer was at least 4 times the cut off which ensured that molecules in the vicinity of one of the faces were not seen by the other face. The interaction energy was calculated between each of the crystal faces and the solvent molecules subject to the cut off. (Figure generated using the MOVIE graphics package (14)).

nonical (NVT) ensemble at a temperature of 298 K. The number of water molecules were set to give a density of 1.0 gml^{-1}. The structures of the crystals were minimised prior to the Monte Carlo simulation but then kept static throughout the simulation.

The force field consisted of a Lennard-Jones and a coulombic term. The non-bonded parameters used were from the Amber forcefield (10). The atomic partial charges were calculated using MOPAC with the AM1 approximation (11). The model used for water was TIP4P (12). The simulations were carried out for ten thousand cycles to achieve equilibration and then continued for a further 5000 to get the final averages.

Simulations were carried out for the (010) and $(0\bar{1}0)$ crystal faces of the heptyl, octyl and the decyl derivative of N-n-alkyl-D-gluconamides in contact with water.

RESULTS AND DISCUSSION

The N-n-alkyl-D-gluconamide molecules all contain an oxygen-rich and an oxygen-poor moiety. In the crystal structures the oxygen rich part is exposed at the (010) face while the oxygen-poor part is exposed at the $(0\bar{1}0)$ face (Figure 2). The compounds crystallise as flat plates with the (010) and $(0\bar{1}0)$ being the dominant faces. The (010) faces are relatively hydrophilic while the $(0\bar{1}0)$ faces are hydrophobic. The contact angle of water on the (010) and $(0\bar{1}0)$ faces is known for each of the 3 gluconamides studied (6). The contact angles for the heptyl, octyl and decyl derivatives are 46°, 47°, and 48° for the (010) faces and 78°, 80°, 83° for the $(0\bar{1}0)$ faces respectively.

The calculated potential energies of interaction of the faces $(0\bar{1}0)$ and (010) of the three alkyl gluconamides with water at 25°C are given in Table I. These potential energies correspond directly to the interfacial enthalpy, ΔH, assuming that the PΔV contribution is negligible. The latter assumption is reasonable since we are dealing with condensed phases i.e. a solid and a liquid. The lower total energy of interaction between water and the face (010) for all three compounds is an indication of the higher affinity of water for this surface. On the other hand the relatively higher energy of interaction for the faces $(0\bar{1}0)$ implies some degree of hydrophobicity. For (010) faces the coulombic contribution is the main part of the total energy whilst for the $(0\bar{1}0)$ faces the Lennard-Jones interactions dominate. This is as expected since the polar oxygen atoms are exposed at the (010) faces whilst the hydrocarbon moiety of the molecules is exposed at the $(0\bar{1}0)$ faces.

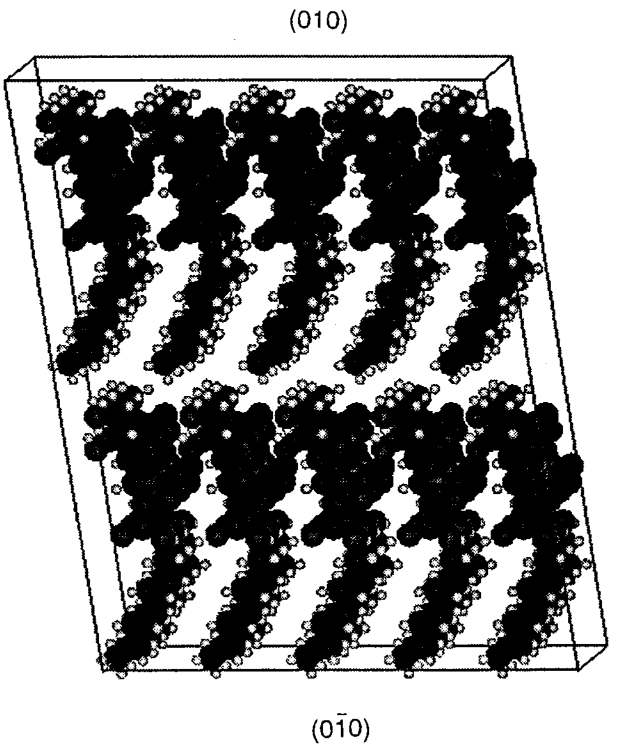

Fig. 2. Crystal packing of N-n-alkyl-D-gluconamides. The oxygen atoms are exposed mostly at the hydrophilic (010) face whilst the hydrophobic $(0\bar{1}0)$ face is dominated by the hydrocarbon chains (Figure generated using the MOVIE graphics package (14)).

Plots of the number-density of water as a function of distance from the crystal surface after equilibration for all three gluconamides are shown in Figure 3. These illustrate the average distribution of the water molecules in the simulation box. In general for the $(0\bar{1}0)$ interfaces the distribution is dome-shaped, indicating that the water molecules are less concentrated close to the hydrophobic crystal surface. In contrast, the distribution of water at the (010) interfaces is relatively even with a higher density close to the surface. These distributions clearly reveal the difference in the degrees of hydrophilicity of the two faces.

A more rigorous test of the validity of the molecular simulation would be a comparison between the calculated interfacial energy and an experimentally determined value. An approximate value of the experimental interfacial enthalpy can in fact be determined from the contact angle measurement. The contact angle θ is related to interfacial free energies by Young's equation:

$$\cos\theta = \frac{\gamma_{SV} - \gamma_{SL}}{\gamma_{LV}}$$

where γ_{SV}, γ_{SL}, γ_{LV} are the solid-vapour, solid-liquid and liquid-vapour interfacial free energies respectively. Using this equation one can express the interfacial enthalpy, ΔH, for the solid-liquid interface (usually termed the work of adhesion) in terms of the contact angle viz (13).

$$\Delta H = \gamma_{SL} - (\gamma_{SV} + \gamma_{LV})$$

$$\Delta H = -\gamma_{LV}(\cos\theta + 1)$$

Thus from the knowledge of the surface energy of the liquid and the contact angle, the interfacial enthalpy of a given crystal in contact with that liquid can be determined. The interfacial enthalpies of the faces of interest of the three gluconamide

Table I. Calculated Energies of Interaction ($\mathrm{mcal/m^2}$) of the Two Faces of Alkyl Gluconamides with Water Along with the Experimental Interfacial Enthalpies (ΔH_{Exp}) Calculated from Contact Angle Values. ΔU_T Is the Calculated Total Energy, ΔU_{LJ} and ΔU_{qq} Are the Lennard-Jones and Electrostatic Components of ΔU_T Respectively

	(010)				$(0\bar{1}0)$			
	ΔH_{exp}	ΔU_T	ΔU_{LJ}	ΔU_{qq}	ΔH_{Exp}	ΔU_T	ΔU_{LJ}	ΔU_q
Heptyl	−29.59	−15.0	−4.0	−11.0	−21.08	−4.0	−3.1	−0.9
Octyl	−29.35	−15.1	−6.7	−8.4	−20.48	−4.6	−3.9	−0.7
Decyl	−29.12	−20.0	−5.6	−15.0	−19.57	−2.2	−1.6	−0.6

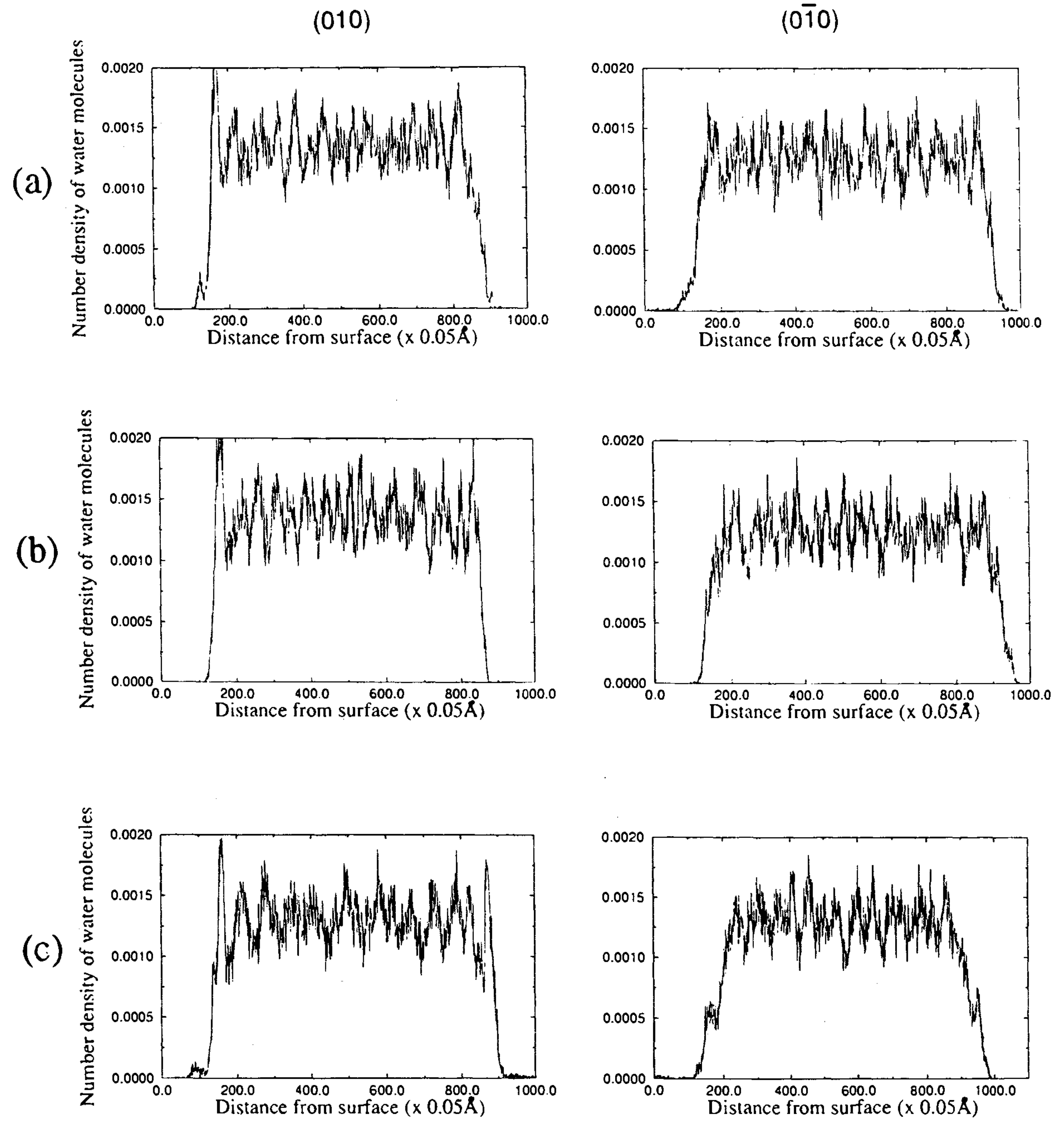

Fig. 3. Number-density distributions of water as a function of distance from the crystal faces (010) and (0$\bar{1}$0) of N-n-alkyl-D-gluconamides after equilibration: (a) = heptyl gluconamide, (b) = octyl gluconamide, and (c) = decyl gluconamide. The distribution is the average over 10 million configurations. The respective high and low densities of water near the surface clearly reflect the hydrophilic and hydrophobic character of the faces (010) and (0$\bar{1}$0).

crystals with water calculated from the contact angle measurements are tabulated in Table I. Interfacial enthalpies calculated in this manner are considered to be only an approximation. This is because there is some doubt regarding Young's equation.

Comparing the calculated interfacial energies with their experimental counterparts, the calculated values are clearly in the right ball park. Given that the contact angle can only be within the range 0 and 180 degrees, the available range for the experimental enthalpy is 0 to 34.9 mcal/m^2. The calculated potential energies lie within this range but are generally higher than the experimental values, with the difference being the greatest for the hydrophobic faces of the crystals. Physically, this means that the real crystal surfaces are apparently more hydrophillic than the ideal crystal surfaces simulated. This disparity is expected, being primarily attributed to the highly simplified model used to represent the interface in the simulation. Unlike the ideal crystal surface simulated, real crystal surfaces will have molecular defects coupled with adsorbed impurity atoms and molecules. The nature of the defects and their density, the kind of impurities involved, as well as their significance is not known. The presence of crystal defects is expected to enhance the liquid-crystal interaction resulting in a lower interaction energy. As for the effect of impurities, the water vapour in the ambient environment is likely to encourage adsorption of atoms and molecules that reduce the interfacial energy. In view of these considerations, since neither defects nor adsorbed impurities are considered in the current simulation, the calculated energies are expected to be higher than the experimental values. An additional factor that can also lead to calculated energies being higher is a limitation of the current method, the lack of relaxation of the crystal molecules during the simulation. Relaxation of the crystal surface will optimise the interactions of the surface molecules with the liquid. The effect of this would be to decrease the interaction energy.

Thus both the energies and the distribution of water at the interface are entirely consistent with the experimental observations that the faces $(0\bar{1}0)$ are hydrophobic whilst the faces (010) are hydrophilic. Although the calculated energies are consistently higher than their experimental counterparts, the disparity is, as explained above, justifiable. These results clearly validate the methodology. With the knowledge of the crystal structure we can assess the wettability and relate the molecular and the crystal structure to the observed macro phenomena.

The present study has focused on specific crystalline faces. The extension of the methodology to powders is straightforward. In a powder the sample presents numerous crystal faces to the liquid, with each face in general exposing different atomic or molecular groups (as molecular crystals are generally anisotropic). To relate the interfacial potential energy obtained from molecular simulations to, for example, contact angle measurements or interfacial enthalpy, the potential energy would need to be calculated for each face and multiplied by a factor that reflects the morphological importance of that face. This procedure would yield the required average.

In conclusion a molecular simulation technique has been developed that enables the crystal-liquid interface to be investigated. It has been shown that given a crystal structure of the solid and the molecular structure of the liquid the interfacial enthalpy can be calculated, and be used to ascertain the wettability characteristics of the solid. This ability to relate the molecular and crystal structure to macroscopic wetting phenomena should enhance our understanding of interfacial processes and enable the development of formulations on a rational basis. This approach represents an important step towards the goal of engineering crystals with desired wettability characteristics.

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