Structure and Energetics of Biocompatible Polymer Nanocomposite Systems: A Molecular Dynamics Study

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Isothermal−isobaric (NPT) molecular dynamics simulations have been performed to investigate the structure, morphology, and energetics of polymer organoclay nanocomposites based on seven nonsteroidal antiinflammatory drugs (NSAIDs), two biocompatible polymers, and hydrotalcite as the clay mineral, both in an anhydrous and in a solvated environment. The results of our theoretical computations show that nanoconfined conformations of smaller NSAIDs are more affected by the presence of water molecules in the clay gallery with respect to their larger counterparts. Moreover, the presence of water in the mineral interlayer space decreases the interaction energy between the NSAID molecules and the clay, and this detrimental effect is further enhanced by the presence of polar moieties onto the NSAIDs. Finally, from the thermodynamics standpoint, the best intercalation results in a solvated environment could be obtained with PVA in the case of less polar drugs, while PHB could be the polymer of choice in the case of highly polar NSAIDs.

Introduction

The structural arrangement and dynamical behavior of H_2O molecules, ions, and other molecular species in the confined spaces of nanoscale pores and mineral interlayers are a key factor in understanding transport and reactivity in many technological and biological systems. In this respect, considerable research efforts have been focused on the design of nanoscale oral sustained- and controlled-release drug delivery systems.[1] Special attention has been spent devising how to regulate the rate of drug release by means of monolithic devices in which the drug is dispersed or included in an inert matrix.[2,3] A way to produce inclusion compounds with drugs consists of their intercalation in a lamellar host lattice. As an example, it has been shown recently that Mg/Al-hydrotalcite (HT), an inorganic and biocompatible anionic layered solid, can intercalate different kinds of nonsteroidal antiinflammatory drugs (NSAIDs) and modify their release.[4,5] Natural or synthetic hydrotalcites are of particular interest because they are the only known family of layered host with positively charged layers balanced by exchangeable anions. They have been further studied as catalysts, support for catalysts, anion exchangers, adsorbents, and additives.[6] Hydrotalcite has the general formula $[M(II)_{1-x}M(III)_x(OH)_2]^{x+}[A^{n-}_{x/n}]^{x-}mS$, where M(II) is a divalent metal cation, usually Mg, M(III) is a trivalent metal cation, usually Al, A^{n-} is an exchangeable inorganic or organic anion that compensates for the positive charge of the layer, and m is the number of moles of solvent S, usually water, co-intercalated per mole of compound.

The nature of the layer cations can vary in a wide range, mainly including main group cations (e.g., Mg, Ca, Al, Ga, or In) or transition metals, such as V, Cr, Mn, Fe, Co, Ni, Cu, Zn, or Y, generally in the divalent or trivalent state, although preparation of hydrotalcites with tetravalent cations has been also claimed;[7−9] also, the interlayer anions can be quite different, including halides, oxoanions, oxometalates, polyoxometalates, coordination compounds, and organic anions.[7−11] Mg/Al-hydrotalcite (HT) is biocompatible[6] and has found pharmaceutical applications as antacid,[12] an ingredient in sustained-release pharmaceuticals containing nifedipine,[13] pharmaceutical compositions stabilizer, and in the preparation of aluminum−magnesium salts of antipyretic, analgesic, and antiinflammatory drugs. As already mentioned above, hydrotalcite is also a potential host structure for intercalation of different kinds of NSAID molecules, thus exerting a controlled-drug release function.[4,5,14,15] To couple these features with enhanced mechanical properties in systems to be exploited, for instance, as degradable polymeric implants that can also be used simultaneously to deliver therapeutic drugs to treat infections, polymer clay nanocomposite loaded with NSAIDs can be envisaged and designed.

One way of improving the mechanical properties of such a nanocomposite material (and also affecting the rate of drug release) is to achieve the exfoliation of the drug-modified layers of hydrotalcite in biocompatible polymers, such as poly(β-hydroxybutyrate) (PHB) or poly(vinyl alcohol) (PVA). On the basis of our experience in the field,[16−18] in this work we present the results obtained from the use of atomistic computer modeling to investigate the structure, morphology, and energetics of different polymer nanocomposite systems based on several NSAIDs, hydrotalcite, and the two above-mentioned biopolymers (PHB and PVA), two different biocompatible polymers, poly(β-hydroxybutyrate) and poly(vinyl alcohol). PHB belongs to the group of polyhydroxyalkanoates (PHA), a class of microbial biopolymers that have recently attracted a lot of attention from tissue engineers as a potential medical material.[19−22]

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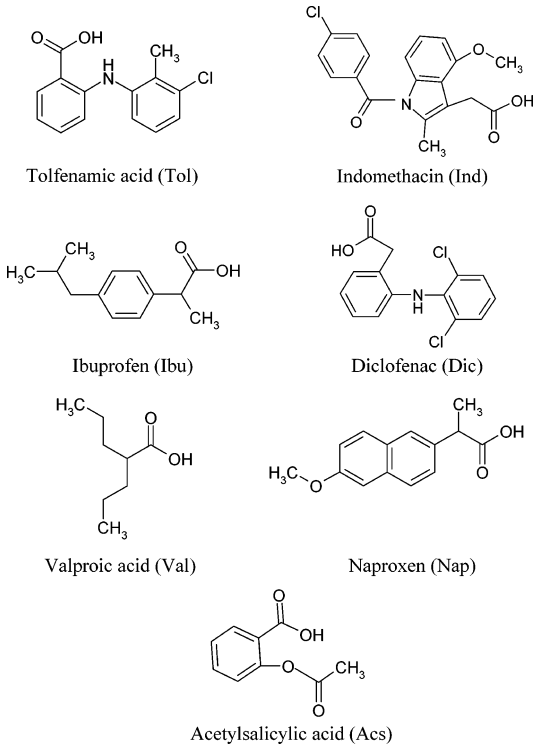

Figure 1. 2D chemical structures of the seven NSAIDs considered.

PHB is produced on a large scale through bacterial fermentation,[23] and it can degrade in the human body environment. It has been used as drug carrier,[24] regulator of fluoride release,[25] and also as matrix for organoclay nanocomposites[26] and biodegradable implants.[20] PVA is a water-soluble, biodegradable, and biocompatible polymer that has been used as matrix in biodegradable polymer/clay nanocomposites[27] and for medical applications.[28,29]

NSAIDs may be structurally classified as carboxylic or enolic acids.[30,31] Thus, in the form of salts, they are able to substitute the anions in the hydrotalcite interlayer. NSAIDs are used in both human and veterinary medicine.[31,32]

In detail, in this paper we have investigated the effects of different parameters, such as NSAID volume, presence of polar moieties in the NSAID scaffold, absence/presence of water in the mineral gallery, and polymer intercalation.

Computational Details

The chemical structure of HT was derived from the crystal structure of Mg/Al hydrotalcite as determined by Bellotto et al.[33] Starting from relevant crystallographic coordinates, we built the unit cell of HT crystal using the Crystal Builder modulus of the *Materials Studio* molecular modeling package (v. 3.2, Accelrys, San Diego, CA). The resulting lattice is hexagonal, with space group *R*3*m*, and characterized by the following lattice parameters: $a = b = 3046$ Å, $c = 22\,772$ Å, $\alpha = \beta = 90°$, $\gamma = 120°$.

The model structures of all NSAIDs (see Figure 1) were generated using the sketcher tool of *Materials Studio*. All molecules were subjected to an initial energy minimization using the Compass force field,[34,35] the convergence criterion being set to 10^{-4} kcal/(mol Å). The choice of the Compass resulted from a compromise between good accuracy and availability of force field parameters for all atom types present in the molecular model. The generation of accurate model amorphous structures for both polymers was conducted as follows. First, the constitutive repeating unit (CRU) was built and its geometry optimized by energy minimization again using Compass. Hence, the CRU was polymerized to a conventional degree of polymerization (DP) equal to 15. Although, this chain may be too short to capture the genuine response of a long polymer molecule; in the case of polystyrene (PS) it has been verified that a polymer with the same DP is longer than the average persistence length of PS in polymer clay nanocomposites.[36] Further, polymers of similar lengths have been already successfully employed by us in similar studies.[16−18] Explicit hydrogens were used in all model systems. The Rotational Isomeric State (RIS) algorithm,[37] as modified by Theodorou and Suter,[38] was used to create the initial polymer conformation at $T = 460$ K. The structure was then relaxed to minimize energy and avoid atom overlaps using the conjugate-gradient method.

Table 1. Binding Energies between NSAID Molecules and Hydrotalcite in the Binary (E_{bind}(HT/NSAID)) and Water-Based Ternary Systems (E_{bind}(HT/H_2O/NSAID))[a]

NSAID	*V* (Å^3)	SA (Å^2)	E_{bind}(HT/NSAID)	E_{bind}(HT/H_2O/NSAID)
Acs	153	194	766	335
Val	155	205	566	486
Nap	211	261	745	378
Tol	223	271	585	406
Ibu	226	289	548	603
Dic	237	289	576	462
Ind	301	359	499	481

[a] All energies are in kcal/mol.

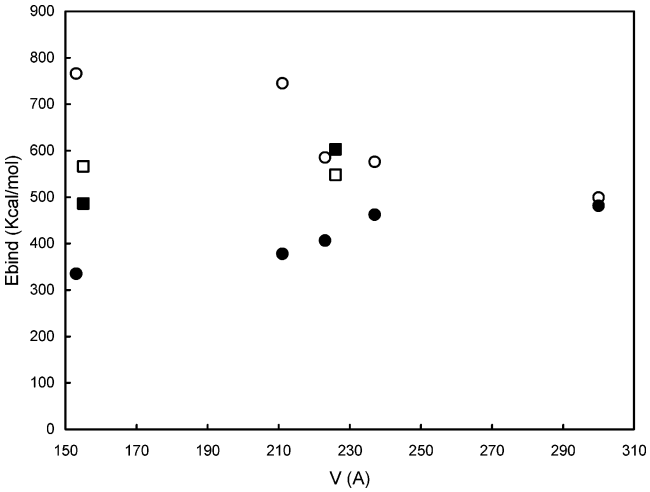

Figure 2. Predicted binding energies of anhydrous (open symbols) and hydrated (filled symbols) binary (HT/NSAID) systems. The outlier data for Valproic acid and Ibuprofen are highlighted by square symbols.

After each component was modeled (HT platelet, NSAIDs, PHB, and PVA), for each possible drug/polymer combination we built one binary system (HT/NSAID), two ternary systems (HT/H_2O/NSAID and HT/NSAID/polymer), and one quaternary system (HT/H_2O/NSAID/polymer). The TIP3P model was chosen to represent water molecules.[39] To generate a mineral surface apt for the simulation, the lattice constant *c* of the HT cell with three NSAID molecules on one side was extended to 150 Å. Coulombic and van der Waals interactions were treated with a direct cut off radius of 8.5 Å. To equilibrate the system, we then performed one cycle of combined molecular mechanics/molecular dynamics simulated annealing (MDSA)[40−42] protocol (from 60 to 460 K) to achieve temperature and velocity of atoms. Next, 250 ps of isothermal−isochoric (NVT) molecular dynamics experiments was run at 460 K on the frame obtained from MDSA simulation at 460 K. During the productive MD simulations, the positions of the HT and Cl^- atoms were fixed, but all remaining system components (polymer, water, and NSAID molecules) were allowed to move accordingly.

The estimation of the molecular surface areas (SA) and volumes (V) was performed via the Connolly dot algorithm,[43−45] corrected to account for quantum effects using the method proposed by Rellick and

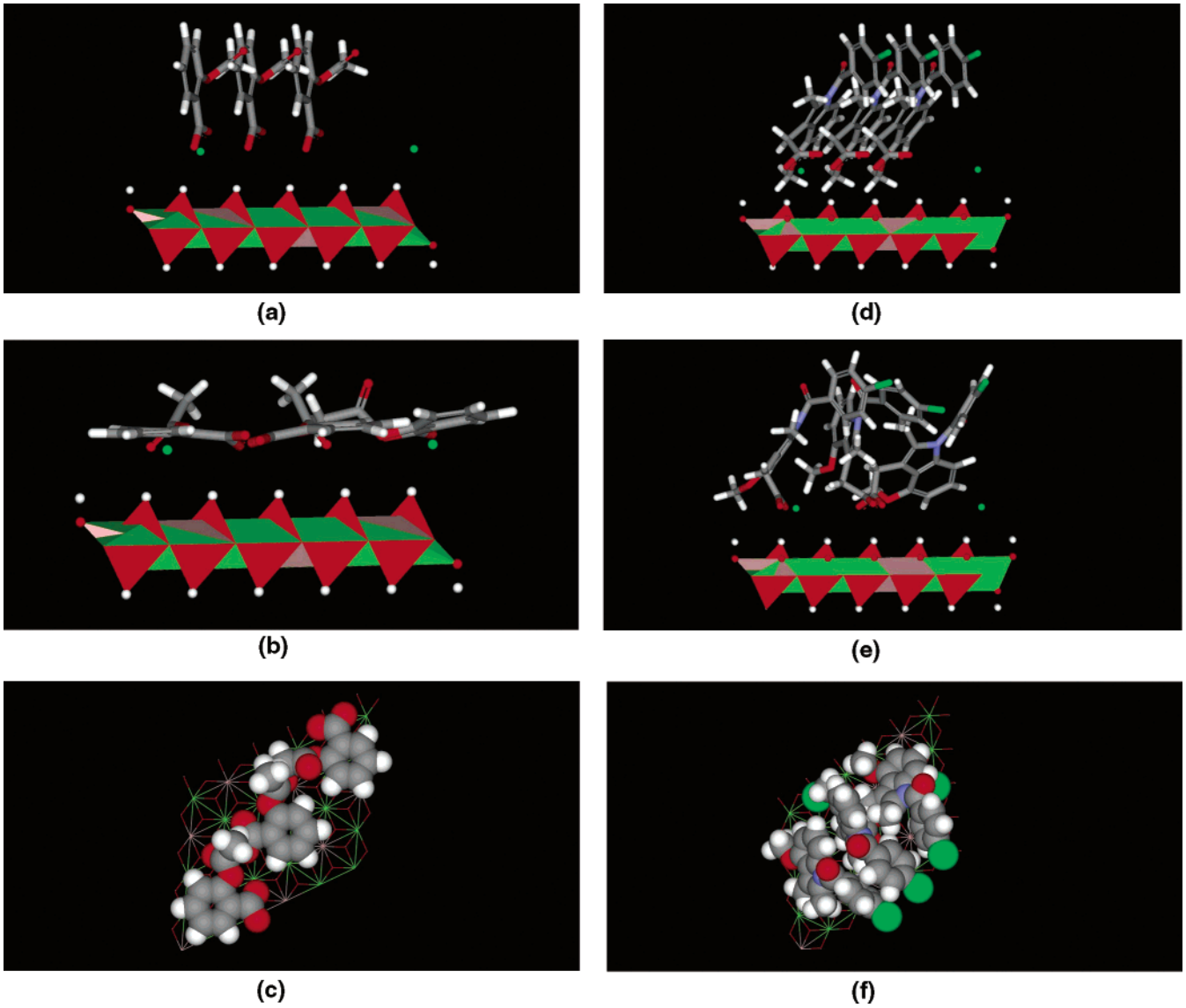

Figure 3. Initial (a) and equilibrated (b) frames extracted from a MD trajectory of the binary system HT/Asc (HT in icosahedral representation, Asc in stick format). (c) Top view of HT with Asc conformation after MD equilibration (HT in line representation, Asc in CPK format). Initial (d) and equilibrated (e) frames extracted from a MD trajectory of the binary system HT/Ind (HT in icosahedral representation, Ind in stick format). (f) Top view of HT with Ind conformation after MD equilibration (HT in line representation, Asc in CPK format).

Becktel.[46] In this way, no assumption was made about the value of the radii of individual atoms.[47]

The total potential energy of a ternary system composed, for example, by PHB, HT, and NSAID molecule, $E_{(PHB/HT/NSAID)}$, may be written as:

$$E_{(PHB/HT/NSAID)} = E_{PHB} + E_{HT} + E_{NSAID} + E_{PHB/HT} + E_{PHB/NSAID} + E_{HT/NSAI} \quad (1)$$

where the first three terms represent the energy of PHB, HT, and NSAID molecule, respectively, and consist of both valence and nonbonded components. The last three terms are the interaction energies between each of two component pairs (made up of nonbonded terms only). By definition, the binding energy is the negative of the interaction energy. To calculate each binding energy term, E_{bind}(PHB/HT) taken as an example, we first created a PHB/HT system by deleting the NSAID molecules from an energy minimized conformation, and then calculated the potential energy of the system $E_{PHB/HT}$ without further minimization. Next, we deleted the HT platelet and Cl anions, leaving a PHB molecule alone, and thus calculated the energy of the PHB molecule, E_{PHB}. Similarly, we deleted the PHB molecule from the PHB/HT system and calculated E_{HT}. According to this procedure, the binding energy E_{bind}(PHB/HT) can then be calculated from the following equation:

$$E_{bind}(PHB/HT) = E_{PHB} + E_{HT} - E_{PHB/HT} \quad (2)$$

Similarly, the binding energies E_{bind}(PHB/NSAID) and E_{bind}(HT/NSAID) can be computed as follows:

$$E_{bind}(PHB/NSAID) = E_{PHB} + E_{NSAID} - E_{PHB/NSAID} \quad (3)$$

$$E_{bind}(HT/NSAID) = E_{HT} + E_{NSAID} - E_{HT/NSAID} \quad (4)$$

Analogous procedures were applied for the other ternary and quaternary systems.

Results and Discussion

Table 1 reports the calculated binding energies between all of the NSAID molecules considered and hydrotalcite for the corresponding binary (HT/NSAID) and water-based ternary systems (HT/H_2O/NSAID), respectively. As we can see from

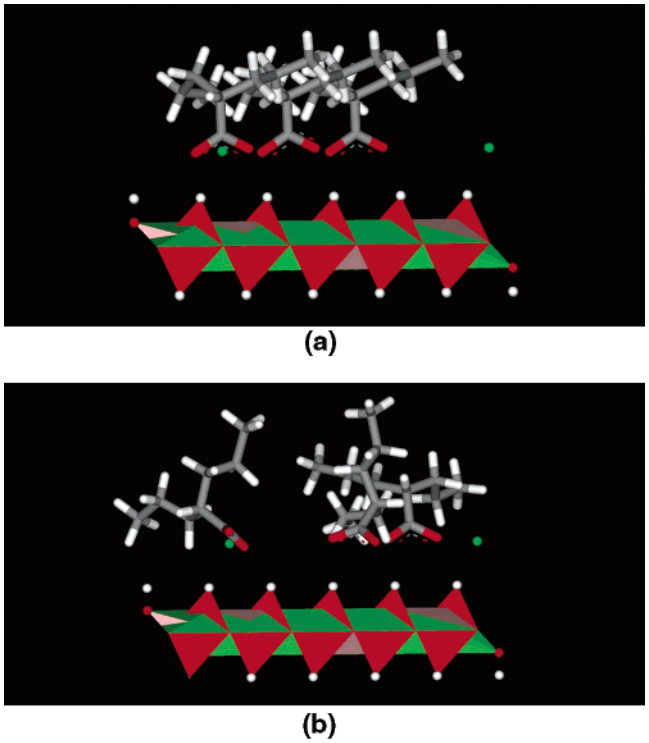

Figure 4. Initial (a) and equilibrated (b) frames extracted from a MD trajectory of the binary system HT/Val (HT in icosahedral representation, Val in stick format).

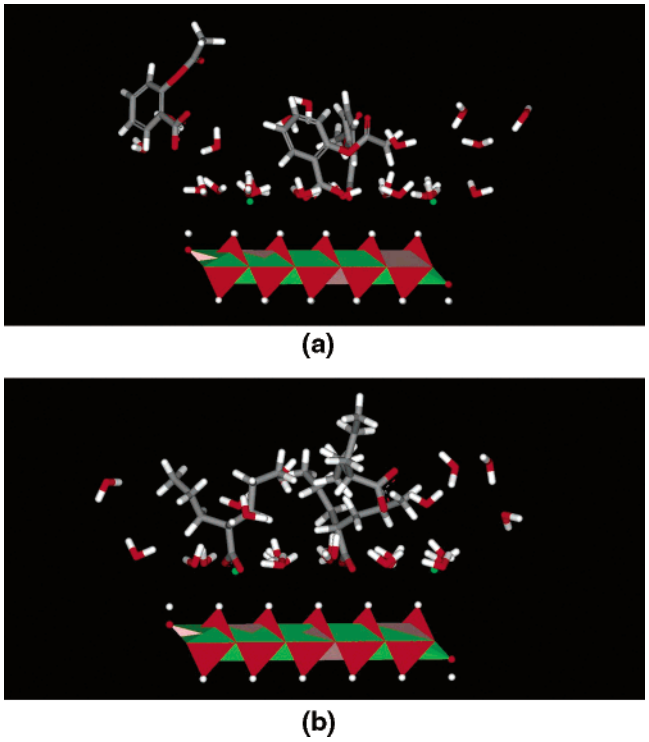

Figure 5. Equilibrated frame extracted from a MD trajectory of the ternary systems HT/H_2O/Asc (a) and HT/H_2O/Val (b).

this Table, in the case of two-component systems the binding energy between clay and drug decreases with increasing drug volume. This is also graphically illustrated in Figure 2, in which the dependence of E_{bind}(HT/NSAID) on the drug volume V is evident. On the contrary, the opposite trend is observed in the water-based ternary system (see Table 1 and Figure 2). To understand and discuss this behavior in the light of the molecular conformations near the clay surface, in Figures 3−5 we report the snapshots taken from a molecular dynamics simulation at T = 460 K of the corresponding binary and water-based ternary systems, respectively. In detail, Figure 3 shows the frames of the (HT/NSAID) systems comprising the largest (Ind) and the smallest (Acs) NSAID molecules, respectively. As the simulation progresses, the molecules of Acs completely flatten onto the clay surface (see Figure 3a−c), thus resulting in the highest binding energy (see Table 1). Conversely, the bigger dimensions and the different conformational arrangement of the Ind molecules hamper the flattening process onto the hydrotalcite surface (see Figure 3d−f). Other remarkable evidence is given by the fact that the calculated binding energy between HT and Valproic acid is quite lower than the corresponding value between HT and Acs, despite the comparable values of their molecular volumes (see Table 1). One of the reasons for this behavior can be found in the fact that Val, contrarily to all other NSAIDs except Ibuprofen, does not feature any further polar moiety in its structure. Figure 4a and b shows that, during the simulation, Val does not flatten onto the mineral surface. This scarce mutual molecular surface interaction unavoidably results in the corresponding low binding energy between clay and Val; also, it reflects the detrimental effect of the absence of the polar functional groups in the clay−drug interactions. In the corresponding water ternary systems, the binding energy values of the systems characterized by the presence of the Valproic acid and Ibuprofen are higher than all other sets (see Table 1 and Figure 2). Figure 5a shows a frame extracted from the equilibrated MD trajectory at T = 460 K of the (HT/H_2O/Acs) system. By comparing these snapshots with the relevant ones obtained in an anhydrous environment (i.e., Figure 3b), a conformational change of the Acs molecules can be observed. Indeed, the water molecules close to the mineral layer assume a bridging role between the clay surface and the drug, contemporarily shielding the drug/surface interactions and hampering the drug flattening process by the formation of stable hydrogen bonds. Accordingly, this globally results in a significant decrease of the corresponding energy term E_{bind}(HT/NSAID). On the other hand, the conformational change induced by water in the case of Val is less effective, as could be expected (compare Figure 5b and Figure 4b). From this evidence, as well as from the dependence of the binding energy on the molecular volume shown in Figure 2, we can sensibly conclude that the influence exerted by the presence of water in the mineral interlayer galleries is greater in the case of smaller and more polar NSAID molecules. This phenomena is attributed to the shielding effect of the water molecules, which increases the binding energy E_{bind}(H_2O/NSAID) between drug and water via hydrogen bonding and hence decreases E_{bind}(HT/NSAID).

Let us now consider the effect of the presence of the polymer chain. Tables 2 and 3 illustrate the binding energies values between clay, NSAID molecules, and polymers in the ternary and quaternary systems, respectively. As one of the major parameters that plays a role in designing these systems is the interaction energy between drug and host molecules,[16−18] we also calculated the sum of the binding energies for the clay/drug and polymer/drug systems (see last columns of Tables 2 and 3). In all cases, we observe a decrease of this quantity when water molecules are present, as the solvent, in its shielding effect, also contributes to decrease substantially the binding energy between the polymer and the drug.

To find out how the exfoliation of drug-modified hydrotalcite layers in the polymer matrix can affect the interactions between the drug and its host structure, we have compared the binding energies in the systems with and without polymers, characterized by E_{bind}(HT/NSAID) + E_{bind}(polymer/NSAID) and E_{bind}(HT/

Table 2. Binding Energies between Clay and NSAID Molecules (E_{bind}(HT/NSAID)), Clay and PHB (E_{bind}(HT/PHB)), and PHB and NSAID Molecules (E_{bind}(PHB/NSAID)) in the Corresponding Ternary and Quaternary Systems[a]

system	E_{bind}(HT/NSAID)	E_{bind}(HT/PHB)	E_{bind}(PHB/NSAID)	E_{bind}(HT/NSAID) + E_{bind}(PHB/NSAID)
HT+Ibu+PHB	568	−23	114	683
HT+H_2O+Ibu+PHB	565	−2	17	582
HT+Dic+PHB	625	−25	76	701
HT+H_2O+Dic+PHB	599	5	24	623
HT+Acs+PHB	832	−86	83	915
HT+H_2O+Acs+PHB	344	4	84	428

[a] Last column reports the sum of the values listed in the second and fourth columns, respectively (see text). All energies are in kcal/mol.

Table 3. Binding Energies between Clay and NSAID Molecules (E_{bind}(HT/NSAID)), Clay and PVA (E_{bind}(HT/PVA)), and PVA and NSAID Molecules (E_{bind}(PVA/NSAID)) in the Corresponding Ternary and Quaternary Systems[a]

system	E_{bind}(HT/NSAID)	E_{bind}(HT/PVA)	E_{bind}(PVA/NSAID)	E_{bind}(HT/NSAID) + E_{bind}(PVA/NSAID)
HT+Ibu+PVA	552	18	209	761
HT+H_2O+Ibu+PVA	568	−47	86	654
HT+Dic+PVA	451	55	138	589
HT+H_2O+Dic+PVA	306	19	120	426
HT+Acs+PVA	666	36	154	820
HT+H_2O+Acs+PVA	220	−24	62	282

[a] Last column reports the sum of the values listed in the second and fourth columns, respectively (see text). All energies are in kcal/mol.

Table 4. Comparison of the Binding Energies in Systems with Water[a]

NSAID	E_{bind}(HT/NSAID)	E_{bind}(HT/NSAID) + E_{bind}(PHB/NSAID)	E_{bind}(HT/NSAID) + E_{bind}(PVA/NSAID)
Acs	335	428	282
Ibu	603	582	654
Dic	462	623	426

[a] All energies are in kcal/mol.

Table 5. Comparison of Binding Energies in Systems without Water[a]

NSAID	E_{bind}(HT/NSAID)	E_{bind}(HT/NSAID) + E_{bind}(PHB/NSAID)	E_{bind}(HT/NSAID) + E_{bind}(PVA/NSAID)
Acs	766	915	820
Ibu	548	683	761
Dic	576	701	589

[a] All energies are in kcal/mol.

NSAID), respectively (see Tables 4 and 5). In the models without water molecules (Table 5), the value E_{bind}(HT/NSAID) + E_{bind}(polymer/NSAID) is always higher than E_{bind}(HT/NSAID) alone in the corresponding two component systems. The situation is undoubtedly more interesting in the models with H_2O molecules included in the clay gallery. Indeed, E_{bind}(HT/NSAID) + E_{bind}(PHB/NSAID) is higher in the case of Acs and Dic, while E_{bind}(HT/NSAID) + E_{bind}(PVA/NSAID) is higher in the case of Ibu. In light of all of the above-reported evidence, we can conclude that, to promote the favorable interactions between drug and clay, drug-modified hydrotalcite layers should be preferentially exfoliated in PVA in the case of Ibuprofen, while PHB is the polymer of choice in the case of Acetylsalycilic acids and Diclofenac.

Conclusions

The global results obtained from the atomistic, molecular dynamics simulations performed on different binary, ternary, and quaternary systems made up of two biodegradable polymers (PHB and PVA), HT, and seven nonsteroidal antiinflammatory drugs (Asc, Ind, Ibu, Nap, Dic, Tol, and Val) allow us to draw some general conclusions. First, smaller and polar NSAID compounds are more easily influenced by the presence of water molecules in the clay gallery, with respect to their less polar counterparts. Indeed, by virtue of the establishment of a hydrogen-bond network between clay, water, and drug molecules, the solvent presence in the interlayer space smoothes off the NSAIDs strong, favorable interaction with the clay surface. Notwithstanding, the binding energy between a drug and its host HT layers can be increased by intercalating polymers in the galleries of the drug-pretreated HT. In particular, in the case of hydrophobic drugs such as Ibuprofen, the simulation results tentatively indicate that, from a thermodynamics point of view, the best results for a solvated environment could be obtained via intercalation with PVA, while for acidic drugs such as Acetylsalicylic acid and Diclofenac, PHB could be the polymer of choice for intercalation.

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References and Notes

(1) Jantzen, G. M.; Robinson, J. R. In *Modern Pharmaceutics*; Banker, G. S., Rhoders, C. T., Eds.; Marcel Dekker: New York, 1996.
(2) Vergnaud, J. M. In *Controlled Drug Release of Oral Dosage Forms*; Vergnaud, J. M., Ed.; Ellis Horwood: London, 1993.
(3) Kim, C. *Controlled Release Dosage from Design*; CRC Press: Boca Raton, FL, 1999.
(4) Ambrogi, V.; Fardella, G.; Grandolini, G.; Perioli, L. *Int. J. Pharm.* **2001**, *220*, 23.
(5) Aamir, I.; Khan, L. L.; Norquist, A. J.; O'Hare, D. *Chem. Commun.* **2001**, *22*, 2342.
(6) Cavani, F.; Trifirò, F.; Vaccai, A. *Catal. Today* **1991**, *11*, 173.
(7) Velu, S.; Suzuki, K.; Okazaki, M.; Tomura, S.; Ohashi, F. *Chem. Mater.* **1999**, *11*, 2163.
(8) Velu, S.; Suzuki, K.; Kapoor, M. P.; Tomura, S.; Ohashi, F.; Osaki, T. *Chem. Mater.* **2000**, *12*, 719.
(9) Velu, S.; Suzuki, K. *Stud. Surf. Sci. Catal.* **2000**, *129*, 451.

(10) Aamir, I.; Khan, L. L.; O'Hare, D. *J. Mater. Chem.* **2002**, *12*, 3191.
(11) Rives, V.; Ulibarri, M. A. *Coord. Chem. Rev.* **1999**, *181*, 61.
(12) Goodman-Gilman, A.; Goodman, L. S.; Gilman, A. *The Pharmacological Basis of Therapeutics VI*; MacMillan Publishing Co. Inc.: New York, 1975.
(13) Doi, N.; Yonetani, A.; Unno, T. *Stable Topical Tolnaftate Preparations*; Japan Kokai Tokkyo Koho JP 01 275 527, 1989.
(14) del Arco, M.; Cebadera, E.; Gutierrez, S.; Martin, C.; Montero, M. J.; Rives, V.; Rocha, J.; Sevilla, M. A. *J. Pharm. Sci*. **2004**, *93*, 1649.
(15) Li, B.; He, J.; Evans, D. G.; Duan, X. *Int. J. Pharm*. **2004**, *287*, 89.
(16) Toth, R.; Coslanich, A.; Ferrone, M.; Fermeglia, M.; Pricl, S.; Miertus, S.; Chiellini, E. *Polymer* **2004**, *45*, 8075.
(17) Fermeglia, M.; Ferrone, M.; Pricl, S. *Mol. Simul*. **2004**, *30*, 289.
(18) Fermeglia, M.; Ferrone, M.; Pricl, S. *Fluid Phase Equilib.* **2003**, *212*, 315.
(19) Hasirci, V.; Lewandrowski, K.; Gresser, J. D.; Wise, D. L.; Trantolo, D. J. *J. Biotechnol.* **2001**, *86*, 135.
(20) Ni, J.; Wang, M. *Mater. Sci. Eng., C* **2002**, *20*, 101.
(21) Luklinska, Z. B.; Bonfield, B. *J. Mater. Sci.: Mater. Med.* **1997**, *8*, 379.
(22) Zhao, K.; Deng, Y.; Chen, J. C.; Chen, G. *Biomaterials* **2003**, *24*, 1041.
(23) Chiellini, E.; Solaro, R. *Adv. Mater.* **1996**, *8*, 305.
(24) Pouton, C. W.; Akthar, S. *Adv. Drug Delivery Rev.* **1996**, *18*, 133.
(25) Yldrmaz, G.; Akgöl, S.; Arca, M. Y.; Sönmez, H.; Denizli, A. *J. Appl. Polym. Sci.* **2003**, *87*, 976.
(26) Choi, W. M.; Kim, T. W.; Park, O. O.; Chang, Y. K.; Lee, J. W. *J. Appl. Polym. Sci.* **2003**, *90*, 525.
(27) Ray, S. S.; Bousmina, M. *Prog. Mater. Sci.* **2005**, *50*, 962.
(28) Ostrovidova, G. U.; Makeev, A. V.; Shamtsian, M. M. *Mater. Sci. Eng., C* **2003**, *23*, 545.
(29) Cerchiara, T.; Luppi, B.; Bigucci, F.; Orienti, I.; Zecchi, V. *Eur. J. Pharm. Biopharm.* **2003**, *56*, 401.
(30) Kourounakis, A. P. Galanakis, D.; Tsiakitzis, K.; Rekka, E. A.; Kourounakis, P. N. *Drug Dev. Res.* **1999**, *47*, 9.
(31) Van Hoof, N.; De Wasch, K.; Poelmans, S.; Noppe, H.; De Brabander, H. *Rapid Commun. Mass Spectrom.* **2004**, *18*, 2823.
(32) Lefebvre, H. P.; Laroute, V.; Alvinerie, M.; Schneider, M.; Vinclair, P.; Braun, J. P.; Toutain, P. L. *Biopharm. Drug Dispos.* **1997**, *18*, 79.
(33) Bellotto, M.; Rebours, B.; Clause, O.; Lynch, J. *J. Phys. Chem*. **1996**, *100*, 8527.
(34) Sun, H. *J. Phys. Chem. B* **1998**, *102*, 7338.
(35) Rigby, D. *Fluid Phase Equilib.* **2004**, *217*, 77.
(36) Manias, E.; Kuppa, V. In *Polymer Nanocomposites*; Vaia, R., Krishnamoorti, R., Eds.; ACS Symposium Series, Vol. 804; Oxford University Press: Oxford, 2002; Chapter 15, pp 193−207.
(37) Flory, P. J. *Principles of Polymer Chemistry*; Cornell University Press: Ithaca, 1974.
(38) Theodorou, D. N.; Suter, U. W. *Macromolecules* **1986**, *19*, 139.
(39) Jorgensen, W.; Chandrasekar, J.; Madura, J.; Impey, R.; Klein, M. *J. Chem. Phys.* **1983**, *79*, 926.
(40) Fermeglia, M.; Pricl, S. *AIChE J*. **1999**, *45*, 2619.
(41) Metullio, L.; Ferrone, M.; Coslanich, A.; Fuchs, S.; Fermeglia, M.; Paneni, M. S.; Pricl, S. *Biomacromolecules* **2004**, *5*, 1371.
(42) Felluga, F.; Pitacco, G.; Valentin, E.; Coslanich, A.; Fermeglia, M.; Ferrone, M.; Pricl, S. *Tetrahedron: Asymmetry* **2003**, *14*, 3385.
(43) Connolly, M. L. *J. Appl. Crystallogr*. **1983**, *16*, 548.
(44) Connolly, M. L. *Science* **1983**, *221*, 709.
(45) Connolly, M. L. *J. Am. Chem. Soc*. **1985**, *107*, 1118.
(46) Rellick, L. M.; Becktel, W. J. *Biopolymers* **1997**, *42*, 191.
(47) Fermeglia, M.; Pricl, S. *Fluid Phase Equilib*. **1999**, *166*, 21.

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