NANO-SCALED INORGANIC/BIOPOLYMER COMPOSITES: MOLECULAR MODELING VISTAS

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INTRODUCTION

Mg/Al hydrotalcite (HT) is biocompatible [1], and has found pharmaceutical applications as antacid [2], ingredient in sustained-release pharmaceuticals containing nifedipine [3], pharmaceutical compositions stabilizer, and in the preparation of aluminum-magnesium salts of antipyretic, analgesic, and anti-inflammatory drugs. Hydrotalcite is a potential host structure for intercalation of different kinds of nonsteroidal anti-inflammatory drug (NSAID) molecules, thus exerting a controlled drug release function. One way of improving the mechanical properties of such a nanocomposite material (and also of affecting the rate of drug release), is to achieve the exfoliation of drug-modified layers of hydrotalcite in biocompatible polymers, such as poly(ß-hydroxybutyrate) (PHB) or poly(vinyl alcohol) (PVA). The aim of this work is to characterize the structure, morphology, and energetics of biocompatible nanocomposites consisting of hydrotalcite, different kinds of NSAIDs and the two above mentioned polymers (PHB and PVA) by using molecular mechanics (MM) and molecular dynamics (MD) simulations. In details, we have investigated the effects of different parameters, such as NSAID volume, presence of polar functional groups in NSAID chains, presence of H_2O molecules in the mineral gallery, and polymer intercalation.

COMPUTATIONAL DETAILS

The chemical structure of HT was derived from the crystal structure of Mg/Al hydrotalcite determined by Bellotto et al. [4]. Starting from relevant crystallographic coordinates, we built the unit cell of HT crystal using the Crystal Builder modulus of the *Cerius*[2] molecular modeling package (v. 4.2, Accelrys, San Diego, CA, USA). The resulting lattice is hexagonal, with space group R3m, and characterized by the following lattice parameters: a = b = 3,046 Å, c = 22,772 Å, α = β = 90°, γ = 120°.

The model structures of all NSAIDs (Tolfenamic acid (Tol), Indomethacin (Ind), Ibuprofen (Ibu), Diclofenac (Dic), Naproxen (Nap), Acetylsalicylic acid (Acs), Valproic acid (Val)) were generated using the 3D sketcher tool of *Cerius*[2]. All molecules were subjected to an initial energy minimization using the Universal force field [5] (UFF), the convergence criterion being set to 10^{-4} kcal/(mol·Å). The choice of the UFF 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 Universal force field. Hence, the

CRU was polymerized to a conventional degree of polymerization (DP) equal to 15. The Rotational Isomeric State (RIS) algorithm [6] at T = 460 K was used to create the initial polymer conformation. The structure was then relaxed to minimize energy and avoid atoms overlaps using the conjugate—gradient method. The TIP3P model was chosen for water molecules.

After each component was modeled (HT platelet, NSAIDs, PHB, and PVA), for each possible drug/polymer combination the following systems were built: HT+NSAID, HT+H_2O+NSAID, HT+NSAID+Polymer, HT+H_2O+NSAID+Polymer. To generate a 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. Isothermal–isochoric (NVT) molecular dynamics experiments were run at 460 K. During the simulations the positions of the HT and Cl^- atoms were fixed, but polymer, water, and NSAID molecules were all allowed to move accordingly. More details on the computational procedures followed can be found in references [7-9].

Results and Discussion

Table 1 reports the binding energies [7-9] between NSAID molecules and hydrotalcite in the corresponding two component system and in the water three component systems, respectively. Figure 1 shows the changes in the binding energy (E_{bind}) with drug volume. As we can see from both Table 1 and Figure 1, in the case of two component systems the binding energy between clay and drug decreases with increasing drug volume. On the contrary, the opposite trend is observed in the water three component systems. Two outliers must be pointed out, and are worth commenting:

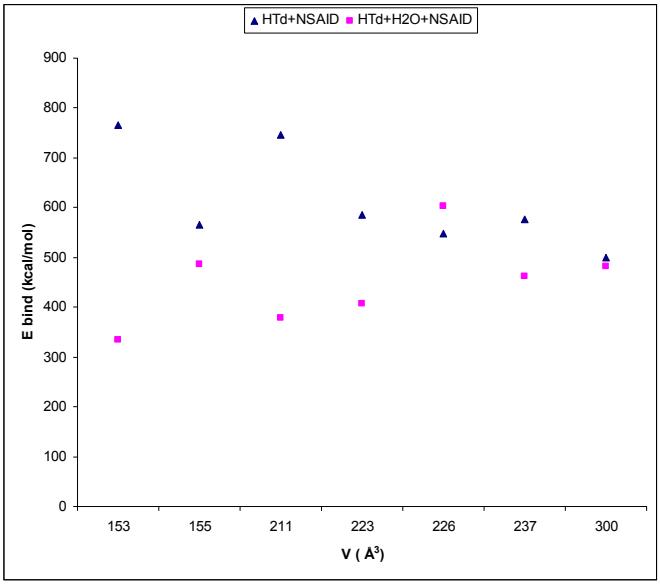
- in the two-component system set, the calculated binding energy between HT and Valproic acid is much lower than the corresponding value between HT and Acetylsalicylic acid, despite the close value of the molecular volumes of these two drugs (see Table 1). However, Val does not feature any further polar functional group, similarly to Ibuprofen. All other NSAID molecules, in fact, have more than one polar functional group in their structures;
- the same situation can be envisaged in the corresponding water three-component systems, where the binding energy values of the system with Valproic acid and Ibuprofen are different (i.e., higher) from all other systems.

Table 1 - Binding energies between NSAID molecules and hydrotalcite in two component system and in water three component system. Table legend: V: volume of NSAID molecules; SA: surface area of NSAID molecules; E_{bind}: binding energies between NSAID and clay in two component systems; E_{bind} (H_2O): binding energies between NSAID and clay in water three component systems.

NSAID	V(Å^3)	SA(Å^2)	E_{bind} (kcal/mol)	E_{bind}(H_2O) (kcal/mol)
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

From all these evidences we can conclude that the influence exerted by water molecules on the binding energy between HT and the NSAIDs is stronger for smaller molecules. Further, the water molecules decrease the binding energy between the clay and the drugs, although, in the case of NSAID without polar functional group, this decrease is less pronounced.

Figure 1 - Binding energy versus NSAID volume in binary and water ternary systems.



Tables 2 and 3 illustrate the binding energies values between clay, NSAID molecules, and polymers in three and four component system, respectively. In the case of three-components systems without water (HT+NSAID+Polymer), the presence of polar groups or bigger functional moieties in the NSAID molecules increases the binding energy between clay and drug. As one of the major parameter that play a role in designing these systems are the interactions between drug and host molecules, we calculated also the sum of the binding energies between clay-drug and polymer-drug (see last column of Tables 2 and 3). In all cases, we observe a decrease of this sum in the presence of water molecules. To find out how the exfoliation of drug modified hydrotalcite layers in the polymer matrix can affect the interactions between drug and 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/NSAID, respectively (see Tables 4 and 5). In the models without water molecules (Table 5), the sum of the energies are always higher than E_{bind} HT/NSAID alone in the two component systems. The situation is 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, whilst E_{bind} HT/NSAID + E_{bind} PVA/NSAID is higher in the case of Ibu. In the light of all the above reported evidences, we can conclude that, in order to promote the favorable interactions between drug and clay, drug modified hydrotalcite layers should be 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 simulations performed on all different two, three, and four component systems lead us to the following, general conclusions:

1. Smaller NSAID compounds are more easily influenced by the presence of water molecules in the gallery;
2. water molecules in the interlayer space are more likely to affect the binding energy values when polar functional groups are present in the drug molecular structure;
3. by virtue of the generation of hydrogen bond networks, water molecules in the gallery decrease the energy of interaction between clay and NSAID molecules;
4. the binding energy between drug and 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 best results are obtained via intercalation with PVA, whilst for acidic drugs such as Acetylsalicylic acid and Diclofenac, PHB is the polymer of choice for intercalation.

Table 2 - Binding energies between clay, NSAID molecules, and poly-(hydroxybutyrate) in three and four component systems. All energies are in kcal/mol.

System	E_{bind} HT/NSAID	E_{bind} HT/Polymer	E_{bind} Polymer/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

Table 3 - Binding energies between clay, NSAID molecules, and poly-(vinyl alcohol) in three and four component systems. All energies are in kcal/mol.

System	E_{bind} HT/NSAID	E_{bind} HT/Polymer	E_{bind} Pol/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+PHB	220	-24	62	282

Table 4 - Comparison of binding energies in systems with water. All energies are in kcal/mol.

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

Table 5 - Comparison of binding energies in systems without water. All energies are in kcal/mol.

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

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