Silica-based materials as drug adsorbents: First principle investigation on the role of water microsolvation on ibuprofen adsorption

UNIVERSITÀ DEGLI STUDI DI TORINO

Massimo Delle Piane, Stefano Vaccari, Marta Corno and Piero Ugliengo, Silica-Based Materials as Drug Adsorbents: First Principle Investigation on the Role of Water Microsolvation on Ibuprofen adsorption, J. Phys. Chem. A, 2014, 118, 5801−5807

Silica-Based Materials as Drug Adsorbents: First Principle Investigation on the Role of Water Microsolvation on Ibuprofen adsorption

Massimo Delle Piane, Stefano Vaccari, Marta Corno, Piero Ugliengo*

Università di Torino, Dipartimento di Chimica and NIS (Nanostructured Interfaces and Surfaces) Centre, via P. Giuria 7, 10125 Torino – Italy

**Corresponding author: Phone: +39-011-6704596, Email: piero.ugliengo@unito.it*

Abstract

Silica based materials find applications as excipients and, particularly for those of mesoporous nature, as drug delivery agents for pharmaceutical formulations. Their performance can be crucially affected by water moisture, as it can modify the behavior of these formulations, by limiting their shelf life. Here we describe the role of water microsolvation on the features of ibuprofen adsorbed on a model of amorphous silica surface by means of Density Functional Theory (DFT) simulations. Starting from the results of the simulation of ibuprofen in interaction with a dry hydrophobic amorphous silica surface, a limited number of water molecules have been added to study the configurational landscape of the microsolvated system. Structural and energetics properties, as well as the role of dispersive forces, have been investigated. Our simulations have revealed that the silica surface exhibits a higher affinity for water than for ibuprofen, even if several structures coexist at room temperature, with an active competition of ibuprofen and water for the exposed surface silanols. Dispersive interactions play a key role in this system, as pure DFT fails to correctly describe its potential energy surface. Indeed, van der Waals forces are the leading contribution to adsorption, independently of whether the drug is hydrogen-bonded directly to the surface or via water molecules.

Keywords: Ibuprofen, amorphous silica, PBE-D, dispersion, adsorption, microsolvation, water.

Introduction

Silicon dioxide, commonly known as silica (SiO_2), is one of the most abundant oxidic materials in the Earth's crust and exists in many crystalline forms as well as an amorphous mineral.[1] Silica-based materials find applications in various areas[1-3] and in particular in pharmaceutical industry, where they are commonly used as solid additives in dosage forms, primarily as tableting excipients, to facilitate the manufacturing and durability of tableted products.[4] Among them, mesoporous silica materials, such as MCM-41,[5-6] are characterized by an ordered arrangement of homogeneous pores resulting in very high pore volume and surface area.[7] For these features, they are considered excellent candidates for drug delivery systems (DDSs),[9,10] *i.e.* pharmaceutical formulations that can control the dissolution rate of the active principle in the body and/or target specific organs.[8]

When a material is employed in a pharmaceutical formulation, the interactions that occur between its surface and drug molecules are of great importance. They can deeply influence stability, absorption and manufacturability of the formulation[9-10] and, for DDSs, are essential for determining the final performance of the product. Consequently, a comprehensive understanding of the drug-material interactions is required to the development of improved and safer pharmaceutical preparations. Despite the scientific and technological relevance of this topic, the atomistic details of the implied interactions are rarely investigated. In that respect, molecular modeling can be an important tool in addressing the problem. This is especially true for amorphous materials, like silica, for which experimental results are either missing or difficult to interpret. Considering silica-based materials, much work has been done in studying their interactions with several biomolecules.[11] Notwithstanding, to the best of our knowledge, only two theoretical works exist dealing with drug-silica interactions, one by Abbasi *et al.* and the other by our group.[12-13] Abbasi *et al*. simulated the adsorption of aspirin on the fully hydroxylated (001) α-quartz surface, while our own work dealt with aspirin and ibuprofen interacting with two dry amorphous silica surfaces. In all cases, the role of water on the drug/surface features has never been addressed, not even in amount only slightly higher than that of the adsorbed drug (microsolvation). This is, indeed, an important point as, due to the natural humidity of air, every pharmaceutical formulation is in contact with moisture ahead of consumption and dissolution in the body fluids. The behavior of the product in presence of water moisture is crucial in limiting its shelf life and the effect of excipients on the moisture content of the pharmaceutical preparation is

therefore very relevant.[14] As a general rule, the high moisture content of excipients decreases the stability of several drugs.[14] This phenomenon is related to the excipient ability to adsorb water at variable humidity.[15] Many authors have studied the adsorption of water on silica surfaces, both experimentally and computationally, and found that this process is strictly dependent on water coverage and degree of hydrophilicity/hydrophobicity of the silica surface.[11] Less work has been accomplished dealing with the concurrent adsorption of water and biomolecules on silica, despite the ubiquitous nature of the first.[16] Simulations have been done on the microsolvation of the catechol-silica[17] and glycine-silica[18-19] systems, but no similar work exists for the drug-silica case.

Some of us have very recently modeled, through accurate Density Functional Theory (DFT) calculations, the interaction of aspirin and ibuprofen, on two realistic models of amorphous silica surfaces,[20] with different concentration of surface silanols (Si-OH groups, the key feature in silica surface chemistry), *i.e.* diverse hydrophilic/hydrophobic behavior.[13] Ibuprofen, in particular, is the common test drug for the development of new DDSs based on mesoporous silica.[7] In the present work, we have extended our simulations of the ibuprofen-silica system by gradually increasing the degree of solvation, through a methodology already proved successful for the microsolvated glycine-hydroxyapatite system.[21] The main objective of the present study is to understand whether water alters the adsorption of ibuprofen on silica surfaces by making a bridge between them or if the direct contact of the microsolvated drug is the preferred one. The energetics of these processes can provide hints on the behavior of a mesoporous silica-based DDS in the time gap between its synthesis and consumption, which represents a crucial topic for the stability and the practical industrial applicability of such a formulation. As in our previous work,[13] we are also interested in revealing the role of dispersive interactions in the mechanisms of adsorption on amorphous silica surfaces. It is worth noting that, despite the fact that the large size of these drugs implies a considerable dispersion interaction with the surface, many studies focus only on the hydrogen-bonding interactions between carboxylic functionality and the Si-OH surface groups.

Computational Details

A development version of the CRYSTAL09 code,[22-24] in its massively parallel version,[25-26] was adopted for most of the calculations All the calculations were run

within the Density Functional Theory (DFT) adopting the Perdew, Burke and Enzerhof GGA (Generalized Gradient Approximation) exchange-correlation functional (PBE).[27] Electron density and its gradient were integrated over a pruned grid consisting of 75 radial points and 974 angular points, generated through the Gauss–Legendre quadrature and Lebedev schemes.[28] Values of the tolerances that control the Coulomb and exchange series in periodical systems[22] were set to ITOL1 = ITOL2 = ITOL3 = ITOL4 = ITOL5 = 7 and ITOL6 = 16. A true slab model, periodic only in 2 dimensions, was simulated. Due to the large surface unit cell, the Hamiltonian matrix was diagonalized only at the central point of the first Brillouin zone (Γ point).[29] The eigenvalue level-shifting technique was used to lock the system in a non-conducting state,[22] with level shifter set to 0.6 Ha. To help SCF convergence, the Fock/KS matrix at a cycle was mixed with 30% of the one of the previous cycle.[22] The same split valence double- and triple-ζ Gaussian type basis sets plus polarization functions of Ref.[13] has been applied to describe the system. For silica surfaces, Si and O atoms were represented by a 88-31G* and a 8-411G* basis set by Nada[30], respectively. H atoms and all ibuprofen and water atoms were described by the VTZP basis set by Ahlrichs,[31] adopting a 511111-411G* basis set for C and O and a 3-11G* set for H. Internal coordinates were optimised using the analytical gradient method. The Hessian is upgraded with the Broyden-Fletcher-Goldfarb-Shanno (BFGS) algorithm.[32-34] Tolerances for the maximum allowed gradient and the maximum atomic displacement for convergence were kept at the default values (0.00045 $Ha \cdot Bohr^{-1}$ and 0.00030 Bohr, respectively). For the drug(water)/slab structures, we only optimized the two most exposed layers of each slab, to compensate for the reduced thickness of the surface models.

To study the role of dispersive interactions in these systems, we applied the empirical dispersion correction originally proposed by Grimme[35] and referred as D2 correction. All the standard parameters for the dispersion correction from the original Grimme's paper[35] were used. In the following, calculations inclusive of the Grimme's correction will be labeled as PBE-D.

Adsorption energies were corrected through the counterpoise method, to compensate for the basis set superposition error (BSSE).[36] However, application of this procedure to microsolvated systems is not straightforward, due to the multicomponent interactions. For this reason, the correction was evaluated for just one model and the calculated BSSE (~50%, in line to those previously computed on similar systems[13]) adopted also for all other structures, being the number of atoms, the atomic elements

and the total number of Gaussian basis functions constant across all considered cases. For the PBE-D calculations, the correction was applied only on the purely electronic contribution to the energy, since the dispersion part does not depend on the basis set and, thus, is not affected by the BSSE.

To verify the role of the BSSE in defining the final optimized geometries, a number of PBE and PBE-D calculations were performed also by using the plane-waves based VASP code,[37-38] as BSSE is only present in calculations adopting localized basis functions. The electron–ion interaction was described by the projector augmented-wave method (PAW),[39-40] while the plane-wave expansion was truncated at a cut-off energy of 450 eV. Convergence criteria on total energy and gradient were set close to CRYSTAL09 defaults, *i.e.* $2.5\ 10^{-6}$ eV and $5\ 10^{-3}$ eV/Å, respectively.

Results and discussion

The microsolvated silica surface described in this paper was simulated starting from an amorphous silica model already designed and validated by Ugliengo *et al.* in 2008.[20] More recently, the same amorphous surface, together with a more hydrophilic one, was used to probe the adsorption of aspirin and ibuprofen in anhydrous conditions.[13] In this work, only the more hydrophobic model was considered ($H_{14}O_{73}Si_{33}$, a=11.6 Å, b=13.6 Å, α=88.6°) that is with a surface silanol concentration of 1.5 OH/nm^2, and its top face is reported in Figure 1 (I).

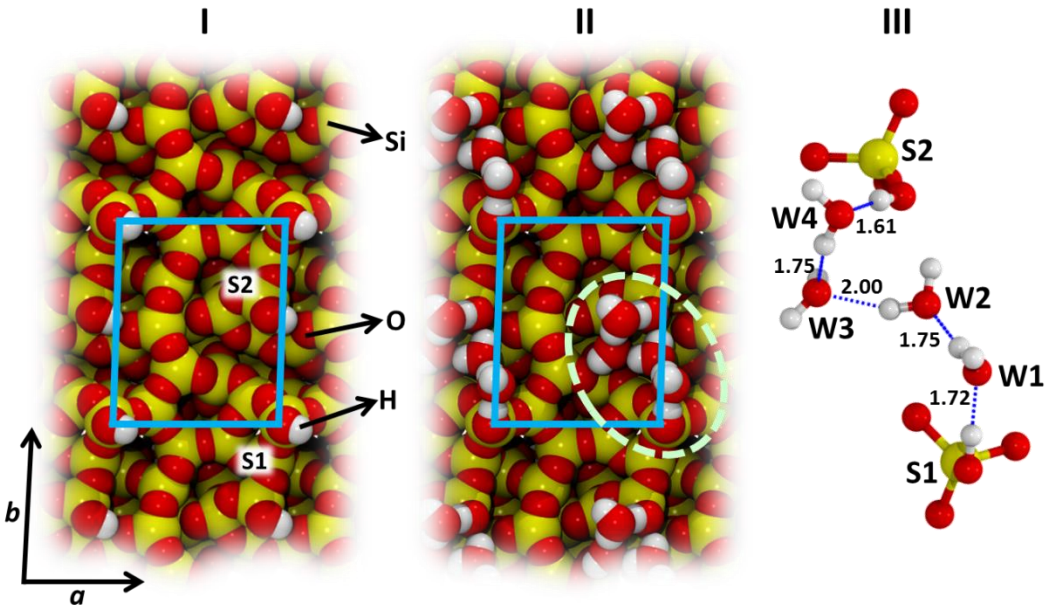

Figure 1. Top: Space-filling representation of the PBE-D optimized amorphous 1.5 OH/nm^2 silica slab models ($H_{14}O_{73}Si_{33}$, a=11.6 Å, b=13.6 Å, α=88.6°) as viewed along the z axis (top), both as anhydrous (I) and as microsolvated by 4 water molecules (II). S1 and S2 refers to the two silanols per unit cell. Bottom (III): ball-and-stick local view of the microsolvation pattern, involving the two interacting silanols (S1 and S2).Unit cell borders in light blue, H-bonds as blue dashed lines. Bond lengths in unit of Å.

The average silanol concentration on fully hydroxylated silica surfaces is known to be around 4.5 OH/nm^2 and similar values have been measured for the pore walls of synthesized mesoporous silica materials.[41-42] Therefore, the adopted model is representative of a real silica sample outgassed at high temperature (T> 600°C) in which the OH population is reduced by condensation of SiOH pairs to give siloxane bridge and water. Our choice to focus on a much less hydroxylated surface was

motivated mainly by its modeling simplicity. Particularly, the presence of only two silanols per unit cell (labeled S1 and S2 in Figure 1 and hereafter) allowed us to dock only 4 water molecules as a "minimal microsolvation" of the system. As a matter of fact, we were specifically interested in the local role of water on the ibuprofen-silica interaction and a limited number of water molecules allows for a more systematic exploration of the possible configurations. Furthermore, this hydrophobic surface represents a valuable testing ground to study the role of the missing dispersive term in standard DFT calculations, as the H-bond interaction is somehow limited by the small OH surface density.

Figure 1 (II) shows the PBE-D optimized structure of the abovementioned silica surface microsolvated by 4 water molecules, labeled from W1 to W4. As evident from the local view of Figure 1 (III), water molecules bridge the two formerly isolated silanols S1 and S2. Noteworthy, when starting from an initial geometry in which each silanol was independently solvated by two water molecules, the optimization process still resulted in the structure of Figure 1 (III). This is expected as longer water chains are stabilized by H-bond cooperativity and in agreement with previous findings that, on hydrophobic silica, the lateral H_2O-H_2O interaction is favored over H_2O/silica interaction.[43]

In the present work, to investigate microsolvation, we adopted the same approach used by some of us for studying the competition between water and glycine when adsorbed on hydroxyapatite surfaces.[21] This approach consists in gradually shifting from the drug-surface direct interaction to the model where water is interposed between the surface and the drug. In our case, the starting points were the optimized PBE and PBE-D structures obtained by our simulations of the ibuprofen-silica interaction described in Ref.[13] The PBE-D model is reported in Figure 2: ibuprofen interacts through its carboxylic functionality with the most exposed silanol group of the surface, S1, through two weak hydrogen bonds (Figure 2, right).

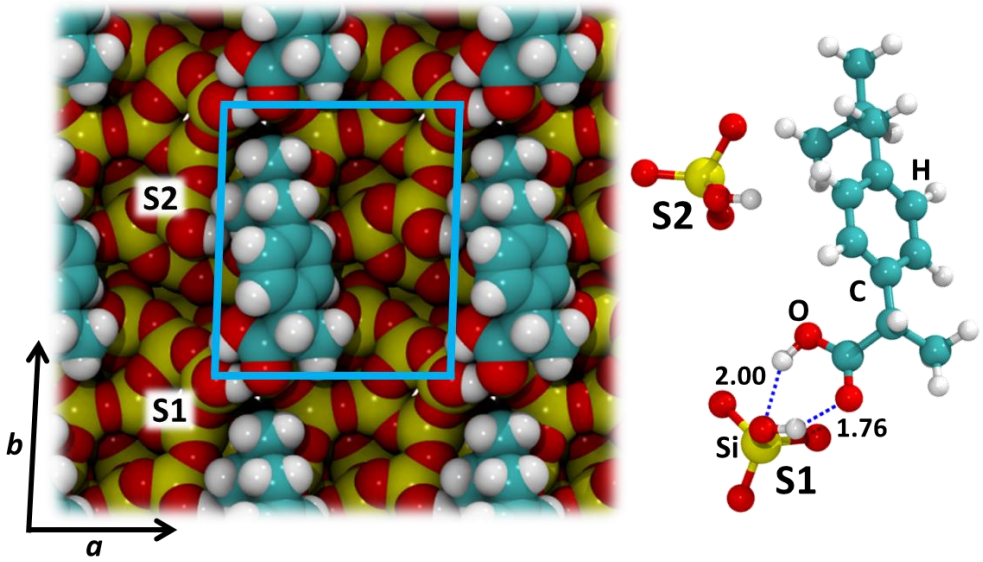

Figure 2. PBE-D optimized structure for the anhydrous ibuprofen-silica interaction (Ref.[13]). Left: space filling model of the PBE-D optimized geometry. Right: local view of the interaction (only the two exposed silanols, S1 and S2, are shown). Cell borders in light blue lines, H-bonds as blue dashed lines, bond lengths in units of Å.

To model the microsolvation process with the abovementioned step by step procedure, we have considered four structures, displayed, respectively, in Figures 3 and 4, labeled from A to D. The first A and the last D structures represent the cases of full direct and indirect contact of ibuprofen with the silica surface. The two remaining cases, B and C, represent two intermediate structures, in which ibuprofen interacts both with the S1 silanol and with water molecules. In the following subsections, for each of the four microsolvated models, structural and energetics properties, as well as the role of dispersive forces, will be described in detail.

Geometrical effects of microsolvation

As already described, in structure A (Figures 3 and 4) ibuprofen is directly interacting with the S1 silanol, with the 4 water molecules solvating the remaining sites. The three water molecules labeled W2, W3 and W4 form a hydrogen-bond bridge between S2 and the carboxylic OH group of ibuprofen, which, in turn, interacts both with S1 and W1 (via its CO group). A comparison between Figure 2 (left) and Figure 3A reveals a different packing of the drug molecules on the surface.

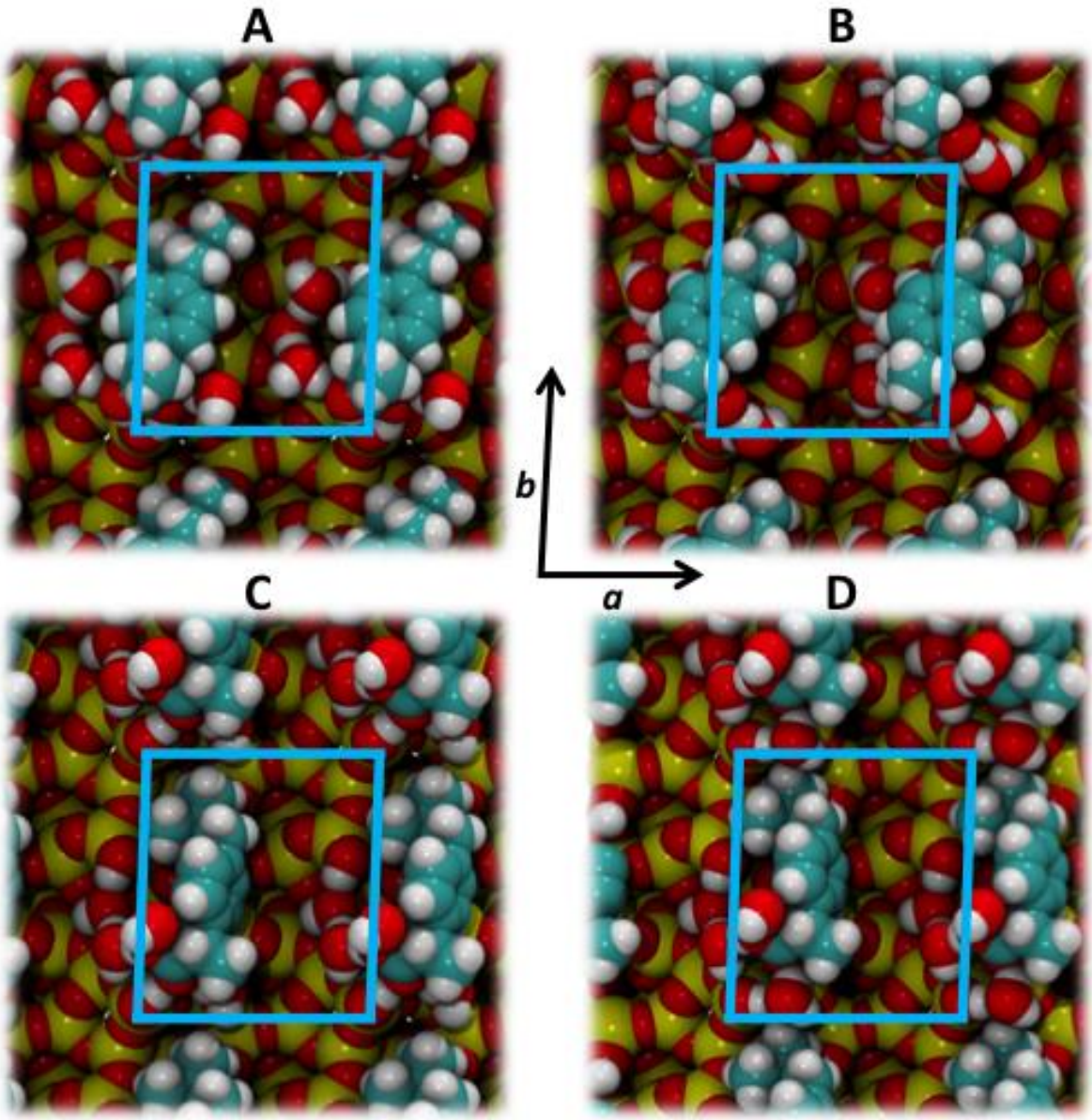

Figure 3. Space-filling top views of the four PBE-D optimized microsolvated ibuprofen-silica models: A) ibuprofen in direct interaction with S1 silanol; B) ibuprofen interacting only through its carboxylic OH group; C) ibuprofen interacting only through its carboxylic CO group and D) ibuprofen interacting indirectly with the silanol. Unit cell borders as light blue lines.

Indeed, in the former, weak van der Waals interactions between the methyl-propyl substituent of one molecule and the propionic acid of its replica induce a linear arrangement. In the second case, water W1 shields these interactions and ibuprofen follows an "oblique" packing. Focusing on the local structure, the hydrogen bond between ibuprofen OH and S1 (Figure 4A) is significantly shorter than that of Figure 2 (1.68 *vs* 2.00 Å, respectively), as a consequence of being part of an H-bond chain. The

CO-S1 interaction is, on the contrary, weaker since the group is also interacting with W1 (1.92 *vs* 1.76 Å, respectively).

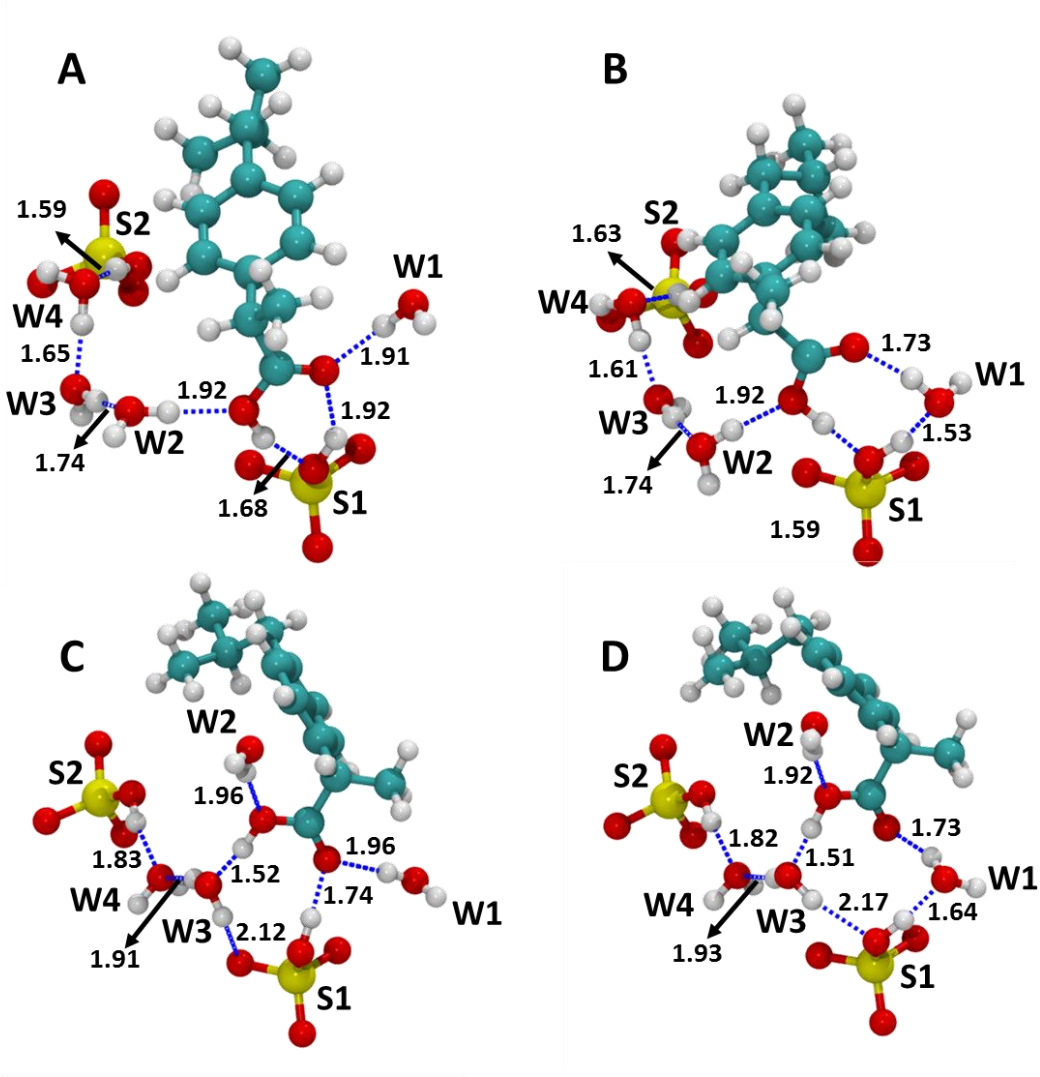

Figure 4. PBE-D optimized ball-and-stick local views of the four microsolvated ibuprofen-silica models. See caption of Figure 3 for description. Only silanols (S1, S2) and water molecules (W1-W4) are shown. H-bonds as blue dashed lines. Bond lengths in units of Å.

The geometrical effect is more limited for structure B, in which W1 bridges to ibuprofen CO group and S1 (Figures 3B and 4B). Drug packing is maintained and the molecule is pushed only slightly away from the surface, to accommodate the water molecule in between. Effect on hydrogen-bond distances is modest, apart from a significant shortening of the drug OH-S1 interaction (1.59 *vs* 2.00 Å, respectively), with water W1 releasing some steric strain. The strengthening of this interaction has important stabilizing consequences, as later described.

Structure C is shown in Figures 3C and 4C and represents an alternative configuration to the B model, in which another water molecule (W3 in this case) was inserted between ibuprofen OH and silanol S1. In this structure, the drug is directly interacting with the surface through its CO group. Insertion of W3 caused the drug to bend, in such way that the aromatic plane is almost perpendicular to the surface. The shielding effect of water W1 is lost: ibuprofen packing (Figure 3C) comes back to the linear arrangement of Figure 2. Analysis of the hydrogen-bond network (Figure 4C) reveals that water W3 bridges ibuprofen and water W4, with formation of a very weak hydrogen-bond with a siloxane oxygen (> 2 Å). Its interaction with ibuprofen OH is particularly strong and is favored over the interaction with the surface.

The last structure, labeled D in Figures 3 and 4, is obtained by combining two geometrical aspects of structures B and C. The end-point resulted with ibuprofen losing any direct contact with silanol S1. Both W3 and W1 water molecules are interposed between the drug and the surface, bridging silanol S1 and ibuprofen OH and CO, respectively. The spatial arrangement of the drug molecules (Figure 3D) is very similar to the previous case, due to water W3 which forces ibuprofen to bend toward the surface. Interposition of water W1 further increases this effect. Considering hydrogen-bond distances, interaction between water W3 and silanol S1 is partly recovered (2.17 Å), but the interaction with ibuprofen OH is still favored (1.51 Å). Interestingly, in this configuration, the ibuprofen O-H length is significantly elongated from equilibrium, suggesting an incipient proton transfer, a fact which can be relevant for the stability of ibuprofen itself.

Dispersion interactions

Dispersion interactions (London interactions) play a key role in many chemical systems and, in particular, is relevant in determining the orientation of molecules on surfaces.[13] Since pure DFT generally misses the dispersive contribution, it is possible to study the role of these interactions by switching on and off an *a posteriori* empirical dispersion correction to the computed energy and gradient. In Ref.[13], this procedure revealed a striking effect of dispersion in determining the final drug-silica adsorption geometries. This contribution forced the molecule to bend in order to fully contact the hydrophobic patch of the silica surface (Figure 2, left). Therefore, we have compared PBE and PBE-D optimized geometries for the case of microsolvation, as described in the following.

Comparison between structures A and B of Figure 3 and their PBE counterparts (not shown here for brevity) reveals only some subtle changes, mainly in the position of the alkyl tail. Indeed, water microsolvation strengthens the drug-silanol H-bond interaction, reducing the role of dispersion. For structures A and B, most of the hydrogen-bond distances are shortened by some 2% in the PBE-D case compared to PBE structures.

For structures C and D, insertion of water between the drug OH and silanol S1 brings ibuprofen closer to the surface, as described above. The geometrical contribution of dispersion becomes important and helps maximizing the contact between the drug and the surface. In particular, this effect is remarkable when ibuprofen loses direct contact with the surface (structure D). A local view of both PBE and PBE-D optimized D structures is reported in Figure 5. For the PBE optimized structure, ibuprofen is lifted from the surface due to the interposition of water. This arrangement is stabilized by a very weak interaction between one methyl group and the replica of water W1 in the adjacent cell. For PBE-D structure, the dispersion interaction has a dramatic effect as ibuprofen is pushed toward the hydrophobic patch of the silica surface. Furthermore, Figure 5 (bottom) reveals that the non-specific dispersion interaction between the apolar tail of ibuprofen becomes dominant compared with the hydrogen-bond interactions of the carboxyl functionality.

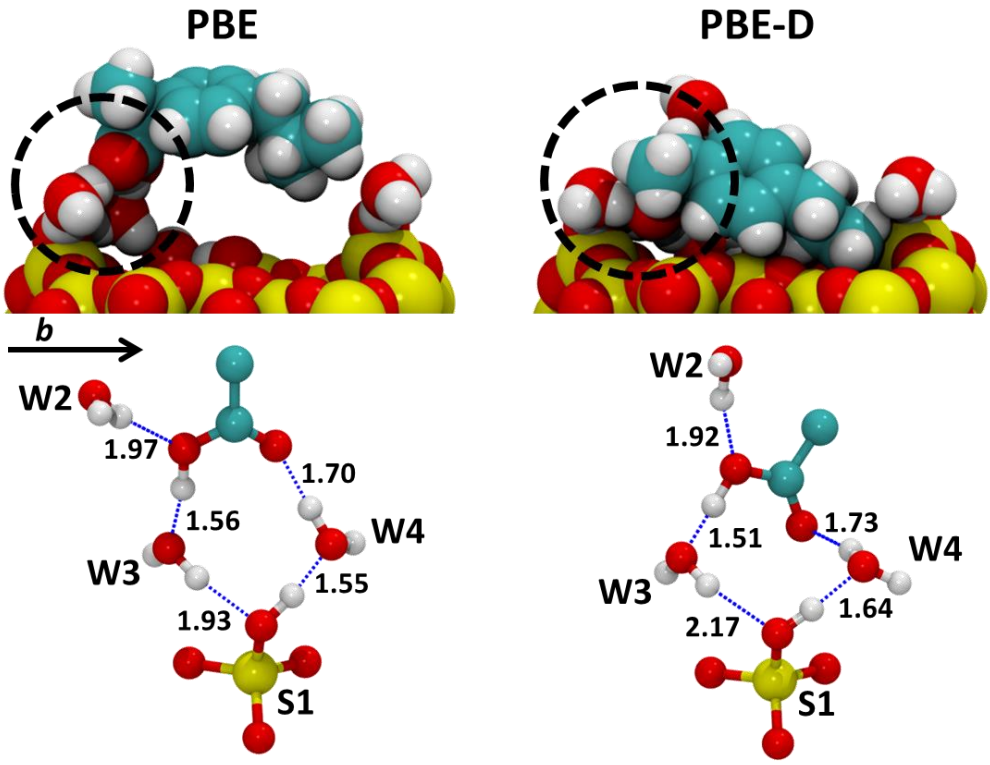

Figure 5. Effect of the dispersive interactions on the structure of model D of Figures 3 and 4. Top: space-filling side views; bottom: ball-and-stick local views (only the C_2OOH functionality of ibuprofen is shown). H-bonds as blue dashed lines, bond lengths in units of Å.

Indeed, all the hydrogen-bonds (apart from the one between water W3 and the drug OH), are significantly elongated and deformed in the PBE-D structure with respect to the PBE one. This subtle competition between non-specific dispersion and H-bond interactions has already been invoked in Ref.[13] and surely plays a significant role also in drug design and drug-receptor interactions.

The effect of including dispersion interactions on geometry is so dramatic that one can argue whether BSSE may drive these changes due to a non-physical attractive effect during geometry optimization. We have repeated the geometry optimization for structure D only, with the BSSE free plane-wave based VASP code. Exactly the same geometrical features computed with Gaussian basis set have been found for the PBE and PBE-D structures of Figure 5 with the plane-waves based calculations, giving credits to the genuine physical effect as the true reason for the dramatic changes in geometries upon inclusion of dispersion interactions.

Energetics of the microsolvation processes

As all the considered A-D structures have the same number of atoms, direct comparison between absolute energies is feasible and allows establishing a rank of relative stability. The most stable configuration is structure C, *i.e.* the one with water breaking the interaction between the CO and the surface (Figures 3 and 4). Its stability is due to the particularly strong H-bond between ibuprofen OH and silanol S1 (1.52 Å). As for the other three structures, the decreasing order of stability is: D < B < A, respectively. The correspondent ΔE ($kJ \cdot mol^{-1}$) values for PBE (and PBE-D) structures are: C 0.0 (0.0), D 29.5 (3.4), B 33.9 (8.8) and A 41.4 (51.0). Considering PBE-D energies, the three structures with water interposed between the drug and the surface are rather close in energy (C, D and B), suggesting a competition between these configurations at room temperature. This is at variance with PBE energies, showing that neglecting the dispersive interaction dramatically alters the potential energy surface for the system, since all the interactions between the apolar portion of the molecule and the silica surface are underestimated. Notwithstanding, in both PBE and PBE-D cases, the configuration with ibuprofen directly interacting with silanol S1 is the least stable, hinting that microsolvation is able to displace ibuprofen from the silica surface.

The energies of three different adsorption processes involving silica, ibuprofen and water are reported in Table 1. Firstly, the simultaneous adsorption of drug and water from gas-phase (SiO_2 + IBU + $4H_2O$) is considered (Table 1.I). This is an unphysical process but informative anyway. The PBE-D order of stability changes from the abovementioned relative ΔE values, due to the BSSE correction. This error affects only the pure DFT contribution to the energy and, when dispersion is prevalent, the total energy is less affected. Nevertheless, the least favorable process is still the one leading to structure A, *i.e.* the one envisaging direct ibuprofen-silica interaction as a final product. In Ref.[13] the PBE-D energy for the dry gas-phase ibuprofen adsorption was calculated as -83.8 $kJ \cdot mol^{-1}$. The increased energies of Table 1.I (A) reflect the newly formed H-bonds by water molecules. For the same reason, the dispersion contribution which was largely predominant in Ref.[13], is no longer dominant here.

Table 1. Reaction energies (kJ·mol^{-1} per unit cell) for three possible adsorption processes: I) water and ibuprofen simultaneously approaching the silica surface, II) microsolvation of the anhydrous silica-drug complex, III) ibuprofen interacting on a microsolvated surface, computed with respect to the four microsolvated structures of Figure 3 and 4. PBE and PBE-D data are BSSE corrected (see Computational Details) and the dispersion contribution is evaluated as the difference between the PBE-D and PBE reaction energies.

I. $SiO_2 + IBU + 4H_2O \rightarrow$	A	B	C	D
PBE	-121.0	-124.8	-141.7	-127.0
PBE-D	-199.4	-229.6	-234.8	-249.6
Dispersion (%)	39	46	40	49
II. IBU-$SiO_2 + 4H_2O \rightarrow$	**A**	**B**	**C**	**D**
PBE	-90.5	-94.3	-111.3	-69.5
PBE-D	-104.8	-134.9	-140.2	-154.9
Dispersion (%)	14	30	21	38
III. $(H_2O)_4$-$SiO_2 + IBU \rightarrow$	**A**	**B**	**C**	**D**
PBE	-26.6	-30.4	-47.3	-32.6
PBE-D	-39.0	-69.1	-74.3	-89.1
Dispersion (%)	32	56	36	63

Data in Table 1.II refer to the process of microsolvating the dry ibuprofen-silica system (IBU-SiO_2 + $4H_2O$) and mimic the adsorption of moisture on a dry drug/excipient system. The expected order of stability is retained and the average adsorption energy per water molecule is about -33 kJ·mol^{-1}. For comparison, the values recorded in literature for low water coverage on hydroxylated crystalline silica surfaces are between -48 and -58 kJ·mol^{-1}.[11] On completely hydrophobic crystalline silica, this energy was computed between 0 and -48 kJ·mol^{-1}.[43] Experimentally, TPD measurements for water adsorption on silica thin films grown on Mo(112) has reported an energy of -45 kJ·mol^{-1}.[44] Surprisingly, the most favorite reaction for the PBE-D case is still the one in which water breaks the direct interaction of ibuprofen with the silanol, leading to structure D of Figures 3 and 4. A comparison with the PBE values, however, suggests that the energetic cost of breaking the H-bond interactions is overcome by an increased role of dispersion interactions responsible of the contact with the surface. In

general, dispersion is less critical in process II, since water interacts mainly through the formation of H-bonds.

Finally, Table 1.III reports the process of ibuprofen adsorption on the microsolvated silica surface ($(H_2O)_4$-SiO_2 + IBU) and represents the interaction of ibuprofen on an already wet silica surface. Reaction energies are in all cases much smaller than in the I and II cases, since restructuring the arrangement of water molecules on the surface is a costly process. Dispersion becomes the dominant contribution when the presence of water allows for a better contact between the ibuprofen apolar portion and the silica surface.

As a further step, we have simulated a gradual water desorption process starting from the microsolvation model with ibuprofen directly interacting with the surface (structure A), to see whether the structure of Ref.[13] will be recovered (Figure 2). Structures and reaction energies are reported in Figure 6.

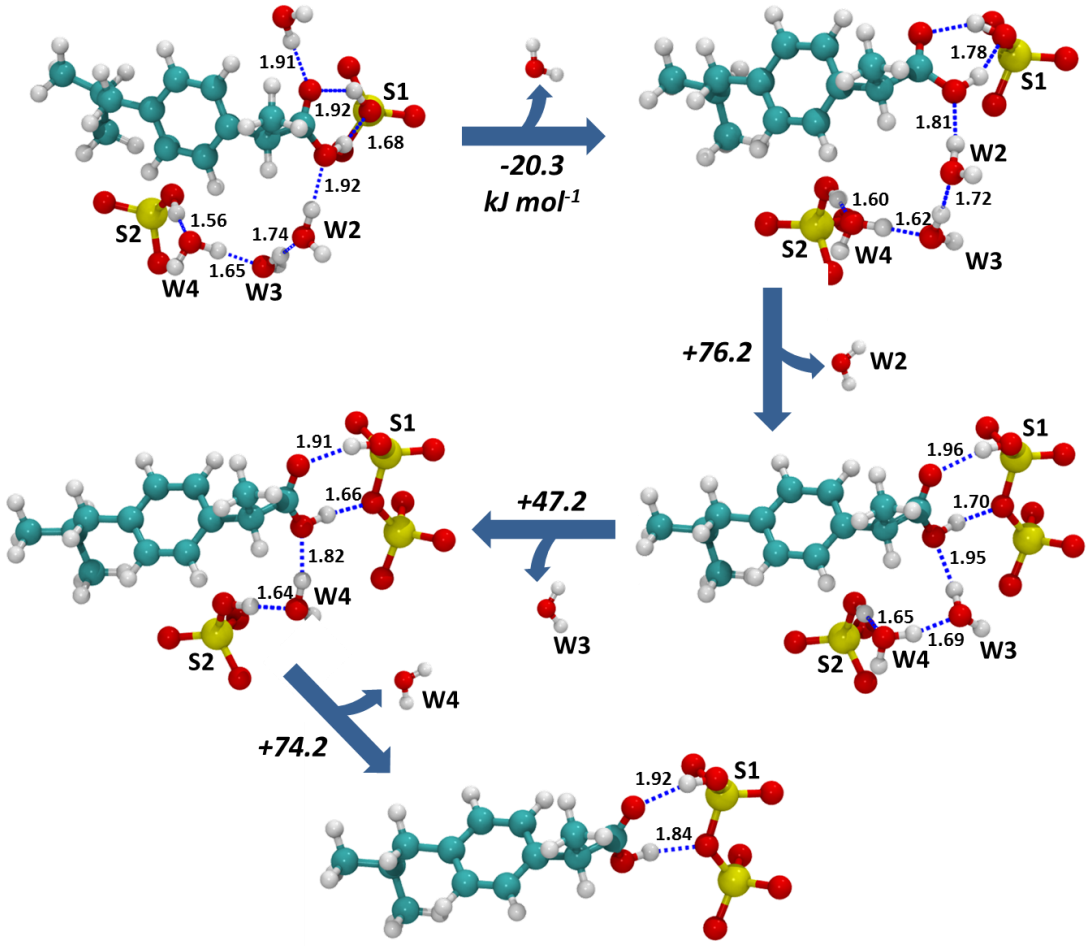

Figure 6. Ball-and-stick local views of the step by step water desorption process, starting from structure A (ibuprofen in direct interaction, see Figure 3 and 4); H-bonds as blue dashed lines, bond lengths in units of Å.

Based on the strength of their H-bonds, as measured by the H···O bond lengths, water molecules were subsequently removed one by one and each resulting structures re-optimized at the PBE-D level of theory. Quite unexpectedly, the removal of water W1 is an exothermic process, due to the removal of some geometrical strain in the remaining H-bonds. All the other steps are strongly endothermic, since they shorten the H-bond chain connecting the two silanols. Indeed, removal of water W2 changes the ibuprofen position with respect to silanol S1 to maintain the water chain, monitored by a strong stabilization of the system. One consequence of this displacement is that, after desorption of all water, the original anhydrous structure of Ref.[13] is not recovered and the new structure, with ibuprofen OH group hydrogen-bonded to one siloxane oxygen, is 26 $kJ \cdot mol^{-1}$ higher in energy.

Conclusions

In the present work, we have studied the effect of water microsolvation on the ibuprofen-amorphous silica surface interacting system by means of quantum mechanical calculations based on density functional theory inclusive of the dispersion contribution to the energy. The main motivation was to investigate, at the molecular level, the fate of a silica-containing pharmaceutical formulation during its shelf life, when it is exposed to ambient moisture. In our simulations, we have described the structural and energetic features of different configurations of a microsolvated ibuprofen-silica system.

The computed energetics reveals that the silica surface exhibits a higher affinity for water than for ibuprofen. However, a complex configurational landscape is hinted, in which structures almost coexist at room temperature, with ibuprofen and water actively competing for the exposed silanols. This is in accordance with similar studies on the co-adsorption of glycine and water on silica surfaces.[18-19] Small geometrical changes can greatly influence the energetics of the system and, in particular, the release of the steric strain of H-bond chains on the surface is the dominant contribution to the relative stabilities. The formation of H-bond chains in which cooperativity is at work is more important than the intrinsic acidity of the participating functionalities (COOH and OHs).

In all configurations, interaction of ibuprofen with the surface is significantly exothermic. Indeed, also when the drug interacts with water adsorbed on silica, the dispersive attraction between the apolar portion of ibuprofen and the surface remains

important. This may still guarantee a reasonable shelf life for silica-based drug formulations, which may maintain their initial characteristics until consumption, *i.e.* when the drug is finally released in the body fluids. However, these simulations do not take into account the possible drug modifications that may happen due to interaction with water moisture.

In conclusion, our results have demonstrated once more that pure GGA calculations give large errors when dealing with adsorption of moderately large molecules on oxidic surfaces, due to the missing dispersive contribution.[13, 45]

Further study is needed to understand the dynamics (and reactivity) of the microsolvated drug-silica system, particularly when the configurational analysis is not feasible with the simple static procedure that has been applied in this work, as in the case of a fully hydroxylated silica surface in which the structural variability of the surface H-bond pattern is too complex.

Acknowledgments

The vast majority of the calculations have been carried out due to the generous allowance of computing time by CINECA supercomputing center through the IBUEXCIP-HP10BC33PV and IBUMCM-HP10A7WAF8 projects. Models have been visualized and manipulated by MOLDRAW[46] and VMD.[47] Progetti di Ricerca di Ateneo-Compagnia di San Paolo-2011-Linea 1A, progetto OR-TO11RRT5 is acknowledged for funding.

References

1. Iler, R. K. *The Chemistry of Silica: Solubility, Polymerization, Colloid and Surface Properties and Biochemistry*. Wiley-Interscience: New York, 1979.

2. Giraldo, L. F.; López, B. L.; Pérez, L.; Urrego, S.; Sierra, L.; Mesa, M. Mesoporous Silica Applications. *Macromolecular Symposia* **2007,** *258*, 129-141.

3. Pagliaro, M. *Silica-Based Materials for Advanced Chemical Applications*. RSC Publishing: Cambridge, 2009.

4. Qian, K. K.; Bogner, R. H. Application of Mesoporous Silicon Dioxide and Silicate in Oral Amorphous Drug Delivery Systems. *J. Pharm. Sci.* **2012,** *101*, 444-463.

5. Vartuli, J. C.; Schmitt, K. D.; Kresge, C. T.; Roth, W.; Leonowicz, M. E.; McCullen, S. B.; Hellring, S. D.; Beck, J. S.; Schlenker, J. L.; Olson, D. H.; et al. Development of a Formation Mechanism for M41s Materials. *Stud. Surf. Sci. Catal.* **1994,** *84*, 53-60.

6. Kresge, C. T.; Leonowicz, M. E.; Roth, W. J.; Vartuli, J. C.; Beck, J. S. Ordered Mesoporous Molecular Sieves Synthesized by a Liquid-Crystal Template Mechanism. *Nature* **1992,** *359*, 710-712.

7. Vallet-Regi, M.; Balas, F.; Arcos, D. Mesoporous Materials for Drug Delivery. *Angew. Chem. Int. Ed.* **2007,** *46*, 7548-7558.

8. Sriwastawa, B.; Tiwari, G.; Bhati, L.; Pandey, P.; Tiwari, R.; Pandey, S.; Bannerjee, S. Drug Delivery Systems: An Updated Review. *Int. J. Pharm. Inv.* **2012,** *2*, 2-11.

9. Pifferi, G.; Restani, P. The Safety of Pharmaceutical Excipients. *Il Farmaco* **2003,** *58*, 541-550.

10. Pifferi, G.; Santoro, P.; Pedrani, M. Quality and Functionality of Excipients. *Il Farmaco* **1999,** *54*, 1-14.

11. Rimola, A.; Costa, D.; Sodupe, M.; Lambert, J.-F.; Ugliengo, P. Silica Surface Features and Their Role in the Adsorption of Biomolecules: Computational Modeling and Experiments. *Chem. Rev.* **2013,** *113*, 4216-4313.

12. Abbasi, A.; Nadimi, E.; Plänitz, P.; Radehaus, C. Density Functional Study of the Adsorption of Aspirin on the Hydroxylated (001) alpha-Quartz Surface. *Surf. Sci.* **2009,** *603*, 2502-2506.

13. Delle Piane, M.; Corno, M.; Ugliengo, P. Does Dispersion Dominate over H-bonds in Drug-Surface Interactions? The Case of Silica-Based Materials as Excipients and Drug-Delivery Agents. *J. Chem. Theory Comput.* **2013,** *9*, 2404-2415.

14. Yosioka, S.; Stella, V. *Stability of Drugs and Dosage Forms*. Kluwer Academic Publishers: 2002.

15. Qiu, Y.; Chen, Y.; Liu, L.; Zhang, G. *Developing Solid Oral Dosage Forms. Pharmaceutical Theory and Practice*. Elsevier: 2009.

16. Morra, M. *Water in Biomaterials Surface Science*. John Wiley & Sons Ltd: Baffin Lane, Chichester, 2001.

17. Mian, S.; Gao, X.; Nagase, S.; Jang, J. Adsorption of Catechol on a Wet Silica Surface: Density Functional Theory Study. *Theor. Chem. Acc.* **2011,** *130*, 333-339.

18. Costa, D.; Tougerti, A.; Tielens, F.; Gervais, C.; Stievano, L.; Lambert, J. F. DFT Study of the Adsorption of Microsolvated Glycine on a Hydrophilic Amorphous Silica Surface. *Phys. Chem. Chem. Phys.* **2008,** *10*, 6360-6368.

19. Rimola, A.; Civalleri, B.; Ugliengo, P. Neutral vs Zwitterionic Glycine Forms at the Water/Silica Interface: Structure, Energies, and Vibrational Features from B3LYP Periodic Simulations. *Langmuir* **2008,** *24*, 14027-14034.

20. Ugliengo, P.; Sodupe, M.; Musso, F.; Bush, I. J.; Orlando, R.; Dovesi, R. Realistic Models of Hydroxylated Amorphous Silica Surfaces and MCM-41 Mesoporous Material Simulated by Large-scale Periodic B3LYP Calculations. *Adv. Mater.* **2008,** *20*, 4579-4583.

21. Rimola, A.; Corno, M.; Zicovich-Wilson, C. M.; Ugliengo, P. Ab initio Modeling of Protein/Biomaterial Interactions: Competitive Adsorption between Glycine and Water onto Hydroxyapatite Surfaces. *Phys. Chem. Chem. Phys.* **2009,** *11*, 9005-9007.

22. Dovesi, R.; Saunders, V. R.; Roetti, C.; Orlando, R.; Zicovich-Wilson, C. M.; Pascale, F.; Civalleri, B.; Doll, K.; Harrison, N. M.; Bush, I. J.; et al. *CRYSTAL09, User's Manual*. 2009.

23. Dovesi, R.; Civalleri, B.; Orlando, R.; Roetti, C.; Saunders, V. R. Ab initio Quantum Simulation in Solid State Chemistry. *Rev. Comp. Chem.* **2005,** *21*, 1-125.

24. Dovesi, R.; Orlando, R.; Civalleri, B.; Roetti, C.; Saunders, V. R.; Zicovich-Wilson, C. M. CRYSTAL: a Computational Tool for the ab initio Study of the Electronic Properties of Crystals. *Z. Kristallogr.* **2005,** *220*, 571-573.

25. Bush, I. J.; Tomic, S.; Searle, B. G.; Mallia, G.; Bailey, C. L.; Montanari, B.; Bernasconi, L.; Carr, J. M.; Harrison, N. M. Parallel Implementation of the ab initio CRYSTAL Program: Electronic Structure Calculations for Periodic Systems. *Proc. R. Soc. A-Math. Phys. Eng. Sci.* **2011,** *467*, 2112-2126.

26. Orlando, R.; Delle Piane, M.; Bush, I. J.; Ugliengo, P.; Ferrabone, M.; Dovesi, R. A New Massively Parallel Version of CRYSTAL for Large Systems on High Performance Computing Architectures. *J. Comput. Chem.* **2012,** *33*, 2276-2284.

27. Perdew, J. P.; Burke, K.; Ernzerhof, M. Generalized Gradient Approximation Made Simple. *Phys. Rev. Lett.* **1996,** *77*, 3865-3868.

28. Prencipe, M.; Pascale, F.; Zicovich-Wilson, C. M.; Saunders, V. R.; Orlando, R.; Dovesi, R. The Vibrational Spectra of Calcite ($CaCO_3$): an ab inito Quantum-Mechanical Calculation. *Phys. Chem. Miner.* **2004,** *31*, 1-6.

29. Monkhorst, H. J.; Pack, J. D. Special Points for Brillouin-Zone Integration. *Phys. Rev. B.* **1976,** *8*, 5188-5192.

30. Nada, R.; Nicholas, J. B.; McCarthy, M. I.; Hess, A. C. Basis Sets for ab initio Periodic Hartree-Fock Studies of Zeolite/Adsorbate Interactions: He, Ne, and Ar in Silica Sodalite. *Int. J. Quantum Chem.* **1996,** *60*, 809-820.

31. Schäfer, A.; Horn, H.; Ahlrichs, R. Fully Optimized Contracted Gaussian Basis Sets for Atoms: Li to Kr. *J. Chem. Phys.* **1992,** *97*, 2571.

32. Broyden, C. G. The Convergence of a Class of Double-rank Minimization Algorithms 1. General Considerations. *IMA J. Appl. Math.* **1970,** *6*, 76-90.

33. Fletcher, R. A New Approach to Variable Metric Algorithms. *Computer J.* **1970,** *13*, 317-322.

34. Shanno, D. F.; Kettler, P. C. Optimal Conditioning of Quasi-Newton Methods. *Math. Comput.* **1970,** *24*, 657-664.

35. Grimme, S. Semiempirical GGA-Type Density Functional Constructed with a Long-Range Dispersion Correction. *J. Comput. Chem.* **2006,** *27*, 1787-1799.

36. Boys, S. F.; Bernardi, F. The Calculations of Small Molecular Interaction by the Difference of Separate Total Energies. Some Procedures with Reduced Error. *Mol. Phys.* **1970,** *19*, 553-566.

37. Kresse, G.; Furthmüller, J. Efficiency of ab-initio Total Energy Calculations for Metals and Semiconductors Using a Plane-Wave Basis Set. *Comput. Mat. Sci.* **1996,** *6*, 15-50.

38. Kresse, G.; Furthmüller, J. Efficient Iterative Schemes for ab initio Total-Energy Calculations Using a Plane-Wave Basis Set. *Phys. Rev. B* **1996,** *54*, 11169-11186.

39. Blöchl, P. E. Projector Augmented-Wave Method. *Phys. Rev. B* **1994,** *50*, 17953-17979.

40. Kresse, G.; Joubert, D. From Ultrasoft Pseudopotentials to the Projector Augmented-Wave Method. *Phys. Rev. B* **1999,** *59*, 1758-1775.

41. Zhuravlev, L. T. The Surface Chemistry of Amorphous Silica. Zhuravlev Model. *Colloids Surf., A* **2000,** *173*, 1-38.

42. Zhuravlev, L. T. Concentration of Hydroxyl-groups on the Surface of Amorphous Silica. *Langmuir* **1987,** *3*, 316-318.

43. Tosoni, S.; Civalleri, B.; Ugliengo, P. Hydrophobic Behavior of Dehydroxylated Silica Surfaces: A B3LYP Periodic Study. *J. Phys. Chem. C* **2010,** *114*, 19984-19992.

44. Kaya, S.; Weissenrieder, J.; Stacchiola, D.; Shaikhutdinov, S.; Freund, H. J. Formation of an Ordered Ice Layer on a Thin Silica Film. *J. Phys. Chem. C* **2006,** *111*, 759-764.

45. Rimola, A.; Civalleri, B.; Ugliengo, P. Physisorption of Aromatic Organic Contaminants at the Surface of Hydrophobic/Hydrophilic Silica Geosorbents: a B3LYP-D Modeling Study. *Phys. Chem. Chem. Phys.* **2010,** *12*, 6357-6366.

46. Ugliengo, P.; Viterbo, D.; Chiari, G. MOLDRAW: Molecular Graphics on a Personal Computer. *Z. Kristallogr.* **1993,** *208*, 383-383.

47. Humphrey, W.; Dalke, A.; Schulten, K. VMD: Visual Molecular Dynamics. *J. Mol. Graph.* **1996,** *14*, 33-8, 27-8.

Table of Contents Graphics