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Investigation on a new scleroglucan/borax hydrogel: Structure and drug release

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Abstract

The aim of this work is to elucidate the structure of the new hydrogel prepared with scleroglucan (Sclg) and borax, suitable for drug delivery, applying theoretical approaches, and to explain its very peculiar swelling. The possible linkages with borate ions have been investigated and original parameters for the 4,6-gluco-borate moiety have been introduced. The structures relative to the Sclg chains in the presence of borax and the possible mutual arrangements among the triple helices are given. According to molecular dynamics simulations, the most probable assembly of the chains in the network is proposed, without and in the presence of three tested model drugs with different molecular dimensions: theophylline (TPH), Vitamin B12 (Vit. B12) and myoglobin (MGB). The hydrogel supramolecular structure, formed via chemical and physical linkages among the polysaccharidic chains, is built up taking into account the steric hindrance of the entrapped molecules. It is shown that molecular dynamics analysis can be a useful tool capable to shed some light on the anomalous swelling of the hydrogel, suitable for drug release, giving a new insight on the network structure and the release rate of the guest molecules.

Keywords: Scleroglucan; Hydrogel; Gluco-borate parameters; Molecular dynamics; Swelling; Drug release

1. Introduction

Numerous chemical and/or physical cross-linking methods have been proposed for the preparation of hydrogels and the obtained networks have often been used as medical devices and in the field of pharmaceutics (Peppas et al., 2000; Hoffman, 2002; Kikuchi and Okano, 2002), in particular for the preparation of modified-release dosage forms. After several studies on the possible use, for these purposes, of chemically cross-linked oxidized derivatives of scleroglucan (Sclg) (Coviello et al., 1999, 2001; Maeda et al., 2001), more recently our attention has been focused on the utilization of borax as a cross-linking agent directly on the natural homopolysaccharide (Sandford, 1979; Coviello et al., 2003a,b, 2005). Borax is actually a cross-linker that can be used for polymers containing hydroxyl groups (Deuel et al., 1948; Shibayama et al., 1988) and that was previously proposed for the preparation of complexes with guar gum suitable for colonic delivery purposes (Rubinstein and Gliko-Kabir, 1995). As already reported, Sclg can form gel in presence of borax (Sandford, 1979) and it is well known that borax cross-links polymers with hydroxyl groups and much work has been carried out on the gelation of poly(vinyl-alcohol) with borax (Cheng and Rodriguez, 1981; Ochiai et al., 1981). In this case the model, proposed by most of the authors, concerns a chemical linkage between the borax and two polymeric chains (Davis and Mott, 1980; Cheng and Rodriguez, 1981; Dawber et al., 1988; Pezron et al., 1989). On the contrary, we have recently shown that adding borax to a Sclg solution a mixed chemical/physical linkage takes place and the intermolecular cross-links are of physical type, therefore, the new system can be better identified as a physical gel (Coviello et al., 2003b).

As reported in our previous investigations the hydrogel obtained from the polysaccharide Sclg and borax (Sclg/borax) appeared to be suitable for sustained drug release formulations. The delivery of model molecules with different steric hindrance (theophylline (TPH), Vitamin B12 (Vit. B12) and myoglobin (MGB)) through and from the Sclg/borax network has been studied. At the same time, a surprisingly notice-

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able anisotropic swelling behavior of tablets obtained from the freeze-dried hydrogel has been described. Release curves that strongly depend on the dimensions of the tested model drug have been analyzed by means of a new mathematical approach that allows a better understanding of the mechanism involved in the delivery (Coviello et al., 2005).

Nevertheless our studies, up to now, are lacking of structural details able to explain, at molecular level, the experimental evidence. In this respect, in the present work, we have first of all analyzed the different possible linkages of borax with Sclg, by using a quantum mechanical approach; then the influence of borax groups on the interactions between two triple helices of Sclg have been studied by means of molecular dynamics simulations, in water solution. These simulations have been performed using a new set of parameters recently proposed by us (Palleschi et al., 2005) and original parameters involving the borax moiety. By combining theoretical results and experimental evidences we propose a model of the new hydrogel that allows a better understanding of the release data as well as the anomalous swelling.

2. Materials and methods

2.1. Materials

The polysaccharidic hydrogel was prepared as previously reported (Coviello et al., 2005), with appropriately purified Sclg (Actigum CS 11, Mero-Rousselot-Satia, France). Borax and TPH were provided by Carlo Erba (Italy), while Vit. B12 and MGB were Fluka (Germany) products. Distilled water was always used.

2.2. Hydrogel and tablet preparation

For the preparation of the tablets about 160 mg of Sclg and 20 mg of the model molecule were magnetically stirred in water for 24 h. Then, the calculated amount (i.e., moles of borax = moles of repeating units of Sclg) of 0.1 M borax solution was added and the system left under magnetic stirring for 5 min. It must be pointed out that pH value remained constant at 9.0 during salt addition because of the self-buffer effect of borax. The obtained sample ($c_p = 0.7\%$ (w/v)) was kept overnight at 7 °C for gel setting and then freeze-dried. Tablets were prepared from the freeze-dried sample with an IR die (Perkin-Elmer hydraulic press) using a force of 5.0 kN for 30 s. The weight of tablets was 230 ± 10 mg, the diameter was 13.00 ± 0.05 mm and the thickness was 1.4 ± 0.2 mm.

For an appropriate comparison, tablets without addition of borax were also prepared following the same procedure.

2.3. Dimensional increase evaluation during swelling

Tablet swelling was carried out soaking the tablets in distilled water at 37 °C. At fixed time intervals, the tablets were withdrawn, the excess of water was removed with soft filter paper for 20 s, and then the corresponding dimensional variations along the longitudinal axis were determined, by means of a caliper with a sensitivity of 0.2 mm. No remarkable variations of tablet diameters were detected during the swelling process.

2.4. Release experiments

Release experiments from the model dosage forms were carried out, in distilled water (pH 5.4), according to U.S.P. XXV, using the rotating basket apparatus at 37.0 ± 0.1 °C and 100 rpm.

Aliquots of dissolution medium were taken at fixed time intervals, the same amount of fresh solvent was added, and the amount of released TPH, Vit. B12 or MGB was spectrophotometrically determined, at the appropriate wavelength, using quartz cells with pathlengths of 1.0 or 0.1 cm.

All experiments were carried out in triplicate.

2.5. Structural analysis

All *ab initio* and semi-empirical calculations were carried out using the MacSpartan software package (MacSpartan Pro, Wavefunction Inc., Irvine, California, 2000).

The molecular dynamics (MD) simulations were performed with the GROMACS software package (Berendsen et al., 1995; Lindhal et al., 2001). The united atoms force field parameters (FFGMX) of GROMACS were used with some modifications that were introduced for a better description of the saccharidic structural features, as previously described (Palleschi et al., 2005).

Original parameters involving the boron atom were introduced, being absent in such force field, while the MD simulation settings used have been already described in a previous paper (Palleschi et al., 2005). For the simulations in water solution two triplexes of four Sclg repeating units for each strand (totally 96 glucose rings), with and without borax, and about 6600 water molecules (SPC/E model) (Berendsen et al., 1987) were used.

The starting structure for the core of the triplex was taken from the X-ray structure for curdlan, a polysaccharide that has the same backbone of Sclg. Glucose residues were added, to every third glucose of such backbone, with β-(1 → 6) linkages having the conformation found in crystalline gentiobiose (Palleschi et al., 2005).

The borax groups were randomly added to let them free to link 4,6 to the glucose units of both backbone and side-chain (see below) and the Na^+ counterions were positioned at about 0.25 nm from each boron atom.

The results of the first 500 ps of the overall MD simulation (5.5 ns) were not taken into account in order to allow the possible relaxation of inter-triplex strains. The *in vacuo* MD simulation (1 ns) was performed with a dielectric constant of 1 and without periodic boundary conditions.

3. Results and discussion

3.1. Drug release and anisotropic swelling of tablets

In order to find out if borax is a cross-linker of Sclg capable to affect the release of the tested model molecules from the

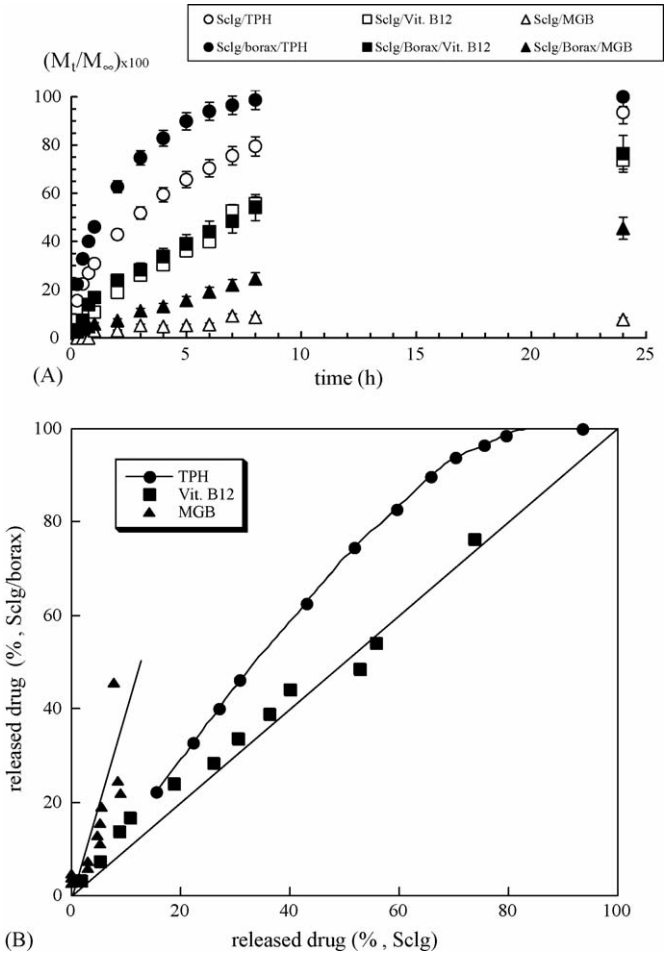

Fig. 1. (A) Comparison of release Profiles of TPH, Vit. B12 and MGB from Sclg and Sclg/borax tablets, in water at 37 °C; (B) the same data shown in (A) reported as the percentage of drug related from the Sclg/borax tablets as a function of the corresponding delivery from the tables prepared with only Sclg.

tablets, the delivery was evaluated from the dosage forms prepared with and without borax. Fig. 1A shows the experimental release profiles from the tablets containing TPH, Vit. B12 and MGB in distilled water at 37 °C. As it is possible to observe, a quite unexpected result has been obtained: in the case of TPH and MGB the delivery from the cross-linked structures is faster than that obtained from the tablets prepared without borax while in the case of Vit. B12 no appreciable difference was detected between the two systems (i.e., with and without borax). This can be further evidenced in Fig. 1B where the different release percentages from the cross-linked samples are reported, at the same times, as a function of the delivery from the matrices without borax. It is clear how, for Vit. B12, the behavior is almost the same in both systems while for THP, and even more for MGB, the release in presence of the cross-linked network is noticeably increased. This result suggests that it is the peculiar mesh size of the hydrogel the main factor affecting the diffusion of the guest molecules, while other parameters, such as solubility, cannot be taken into account for the explanation of the release profile differences; in fact the solubility of TPH is much higher than that of MGB (TPH = 16.5 mg/ml; MGB = 0.93 mg/ml).

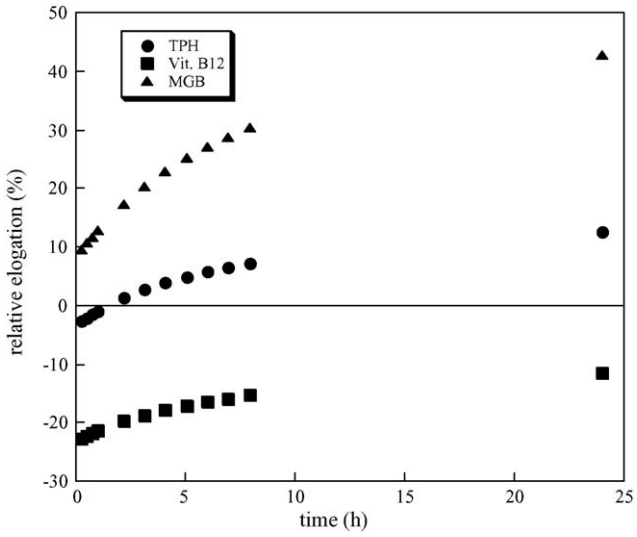

Fig. 2. Elongation, as a function of time, of Sclg/borax tablets, containing the three model molecules, normalized for the elongation relative to the same tablets prepared without borax.

Thus the experimental data indicate that the microscopic structure of the gel, and consequently the release rate, can be affected by the presence of the cross-linker as well as by the dimensions of the guest molecule.

Furthermore, while usually a gel system swells isotropically in all directions (Li and Tanaka, 1991), as already reported (Coviello et al., 2005), an unexpected remarkable anisotropic swelling occurs in the case of the Sclg/borax tablets: the compressed matrix elongates essentially in its axial direction, while radial swelling is almost negligible. Interestingly, the extent of height increase of the tablets is affected by the model drug that is loaded. As it is possible to see in Fig. 2, the elongations of the tablets in the presence of TPH, and even more with MGB, are higher than those obtained with tablets prepared with only Sclg/borax; on the other side, in the case of Vit. B12, the elongation is definitely lower than that observed with the Sclg/borax tablets. This is an indirect evidence that, in presence of the various molecules, the microscopic structure can be slightly different, as it will be better discussed later. Although anisotropic swellings have been already reported in the literature for other tablet systems (Colombo et al., 1990; Papadimitriou et al., 1993; Talukdar and Kinget, 1995) the extent of the elongation, in our samples, is higher, at least of a factor of 10, than in the previous cases. For an appropriate comparison, in Table 1 the relative increases of height ($(h - h_0)/h_0$) for the different tested Sclg/borax tablets are reported and the corresponding values, calculated from the literature data, are also given.

Our hypothesis is that the borax groups, linking together the triple helices of Sclg, stabilize inter-triplex interactions, favouring the formation of ordered domains, similar to the well-known junction zones found in other polysaccharidic physical gels (e.g., agarose, alginate, carrageenan) (Clark and Ross-Murphy, 1987), connected to other domains less structured. The high pressure, applied during the tablet formation, increases the extent of such regular arrangements that are essentially retained during the subsequent swelling, when the cross-linker is present. In addition,

Table 1
Relative increase of height (($h - h_0$)/h_0) of tablets of Sclg/borax, with and without loaded model drugs, after 8 and 24 h in water at 37 °C compared with the data calculated from the literature for tablets prepared with other polymeric matrices

Loaded drug	Tablet matrix	($h - h_0$)/h_0 (8 h)	($h - h_0$)/h_0 (24 h)
–	Sclg/borax	13.5	22.4
TPH	Sclg/borax	15.6	24.6
Vit. B12	Sclg/borax	12.7	19.3
MGB	Sclg/borax	19.7	30.7
Diltiazem HCl	HPMC/mannitol/ethocel	1.4[a]	
–	HPMC (methocel K100 M)	1.3[b]	–
–	Xanthan (rheogel)	0.9 (1 h, plateau value)[c]	–

[a] Calculated from Colombo et al. (1990). Measurements after 5 h and 40 min.
[b] Calculated from Papadimitriou et al. (1993).
[c] Calculated from Talukdar and Kinget (1995).

the presence of drug molecules may affect the stability of these ordered domains, that can be differently retained during the imbibition process and, as a consequence, swelling and release properties can be influenced.

In order to support this hypothesis a theoretical study of our system was carried out, in order to obtain insights from the molecular details.

3.2. Computational results and molecular modelling

The strategy adopted in the computational approach followed three steps:

(I) The most stable configurations of glucose covalently linked with borax, were investigated by means of *ab initio* and semi-empirical methods.
(II) After the definition of the theoretical parameters involving the boron atom, MD simulations on a model consisting of two Sclg triplexes, with and without borax, were performed to evaluate the effect of borax on the packing of the triplexes.
(III) Finally, possible models of locally ordered aggregates of triple helices, as a function of the different van der Waals radii of the loaded drug molecules (TPH, 3.7 Å, MW = 180; Vit. B12, 8.5 Å, MW = 1355; MGB, 21.0 Å, MW = 17,800), are discussed.

3.2.1. Configurations of glucose–borax ester

It is well known that some steric-conformational requirements have to be fulfilled in order to form the linkage between the borate ion and different sugars, including glucose (Dawber et al., 1988; Van der Berg et al., 1994). For this purpose, the potential energies of the three possible configurations (see Fig. 3), that result from the esterification of the glucose unit with the borate ion, were calculated using three theoretical approaches: the PM3, the HF/6-31G* and the SVWN/DN* methods. As it can be easily recognized from the obtained relative energies, reported in Table 2, all the procedures indicate that the 4,6-diol borate ester (Fig. 3c) represents the only statistically meaningful configuration, in full agreement with the ^{11}B and ^{13}C NMR results previously found by Van der Berg et al. (1994). In the

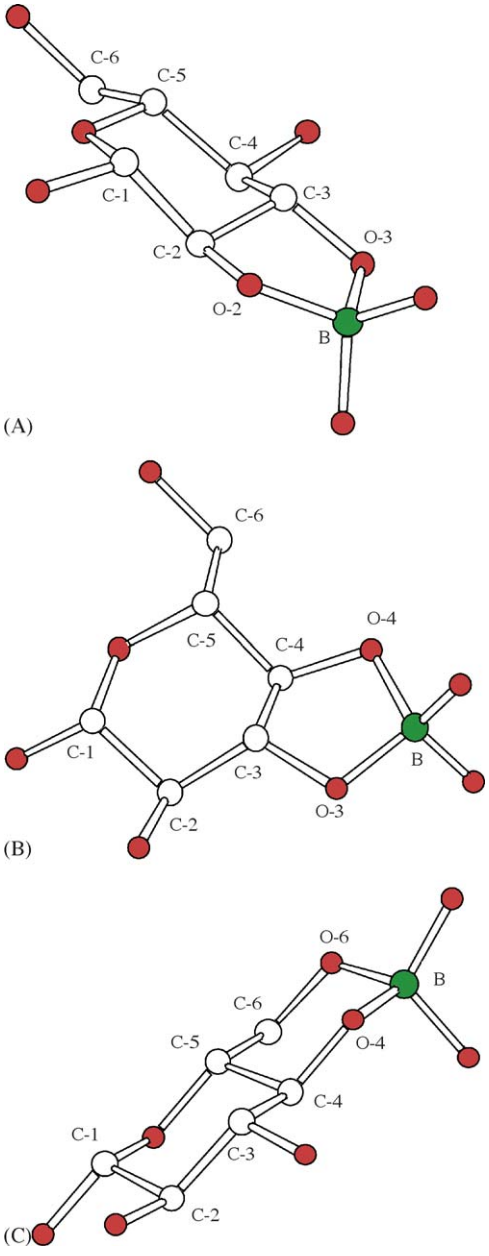

Fig. 3. Different configurations of glucose-borax monodiol. (A) linkage 2-3; (B) linkage 3-4; (C) linkage 4-6.

Table 2
Relative energies (kcal/mol) for different glucose–borax ester configurations

Configuration	PM3[a]	HF/6-31G*[b]	SVWN/DN*[c]
2–3	3.8	5.9	4.2
3–4	4.1	7.0	6.3
4–6	0	0	0

[a] Semi-empirical.
[b] *Ab initio*.
[c] Density functional.

present case, a condensed 1,3,2-dioxaborinane ring in the chair conformation represents the obtained deepest energy minimum structure.

Owing to this result we performed molecular dynamic simulations of the Sclg/borax system considering only the 4,6-diol borate ester, both in the backbone and in the side-chain glucoses.

3.2.2. MD simulations of Sclg and Sclg/borax

In MD simulations of the Sclg/borax models, the parameters used for the linked borax moiety, are reported in Table 3.

The equilibrium parameters for stretching and bending were obtained, after minimization, from the 4,6-diol gluco-borate, by means of *ab initio* calculation at 6-31G* level. Such parameters were tested on the molecule 4,4-bis(hydroxymethyl)-1,1-dimethoxy-2,6-dioxaboracyclohexane (Ref. code DODDOP in Cambridge Structure Database; Allen, 2002), that shows a similar configuration of the borax moiety. The very good agreement obtained (see Table 4), suggests the general usefulness of these parameters to describe the borax diol, being such parameters only poorly dependent on different chemical surroundings (*vacuum* or solid state). The atomic charges, evaluated at the same HF/6-31G* level, were rescaled by a factor of 0.87 to retain the total net charge of −1 for each added borax group. All the other parameters were obtained by fitting them with the corresponding ones present in MM+ force field included in the HyperChem package (HyperChem 7.0, Hypercube, Inc., Gainesville, Fl, USA, 2001) and by a subsequent rescaling in order to harmonize them with the other FFGMX parameters. The overall efficiency of the added parameters was tested performing an *in vacuo* MD simulation of the 4,6-diol borate glucose ester. As it can be seen in Fig. 4, the *ab initio* structure is substantially retained during the simulation confirming the soundness of our parameters.

As above reported, the linkage between borax and glucose occurs mainly in 4,6 position, forming a 4,6-diol borate glucose ester. Since no evidences of preferred positions came out during our experiments, we have randomly linked the borax groups on all the possible glucose moieties of the Sclg unit: two in the backbone and one in the side-chain.

At this stage, with the aim to obtain structural insights on the interactions between the polysaccharidic chains, MD simulations on a model consisting of two triplexes, without and with random borax groups, were performed. In Fig. 5 the root mean square distance (RMSD) of a triplex with respect to the other one after the removal of the roto-translational movements

Table 3
Parameters of the 4,6-gluco-borate group

Stretching[a]

Bond	K_{str} (kJ nm^{-2} mol^{-1})[b]	r_0 (nm)[c]
B4–OS	305752	0.1498
B4–OA	305752	0.1443

Bending[d]

Angle	K_{ben} (kJ rad^{-2} mol^{-1})[b]	θ_0 (°)[c]
CS1/CS2–OS–B4	333.570	117.30
OS/OA–B4–OA/OS	446.540	109.53
B4–OA–HO	333.570	107.00

Dihedral[e,f]

Angle	K_{dh} (kJ mol^{-1})[b]	n	χ (°)
HO–OA–B4–OA/OS OA/OS–B4–OS–CS1/CS2	5.858	3	0

Electrostatic charges[g]

Atom	Point charge (e)
B4	1.06
OS	−0.73
OA	−0.80
HO	0.35

Non-bonded interactions[b,h]

Atom	C_6 (kJ nm^6 mol^{-1})	C_{12} (kJ nm^{12} mol^{-1})
B4	18.08	26072

1–4 Interactions[i]

Bond	C_6 (kJ nm^6 mol^{-1})	C_{12} (kJ nm^{12} mol^{-1})
CS1–B4	29.12	37364

Equivalent atom types are separated by slash. B4 refers to tetrahedral boron in the borate ester group, CS1 and CS2 to saccharidic united atom CH1 and CH2, respectively, OA refers to oxygen atom linked to boron and hydrogen (HO), and OS refers to the oxygen that bridges the boron and a carbon atom (CH1 or CH2).
[a] $E_{str} = (1/2)K_{str}(r - r_0)^2$.
[b] From MM + parameters (HyperChem 7.0, Hypercube Inc., Gainesville, FL, USA, 2001) after a suitable rescaling.
[c] *Ab initio* at HF/6-31G* level.
[d] $E_{ben} = (1/2)K_{ben}(\theta - \theta_0)^2$.
[e] Proper dihedral angles: $E_{dh} = K_{dh}(1 + \cos(n\psi - \chi))$.
[f] The parameters of improper dihedral angles, involving the boron atom, were set according to the GROMACS default values for a tetrahedral angle.
[g] *Ab initio*, at HF/6-31G* level, rescaled by a factor 0.87.
[h] $E_{nb,ij} = (C_{12}/r_{ij}^{12} - C_6/r_{ij}^6)$, where r_{ij} is the distance between the atoms i and j.
[i] As the standard *–CS–CS–* parameters used for the saccharidic ring.

Table 4
Average bond lengths (Å) and bond angles (°) obtained by theoretical calculations and crystal structure

	DODDOP		4,6-Gluco-borate
	(X-ray)[a]	(theor)[b]	(theor)[b]
B–O	1.469 ± 0.024	1.466 ± 0.023	1.470 ± 0.032
O–B–O	109.46 ± 1.59	109.48 ± 1.16	109.47 ± 2.13
B–O–C	114.31 ± 0.80	115.33 ± 1.88	115.51 ± 2.56

[a] From Cambridge Structural Database (2004).
[b] *Ab initio* HF/6-31G* level.

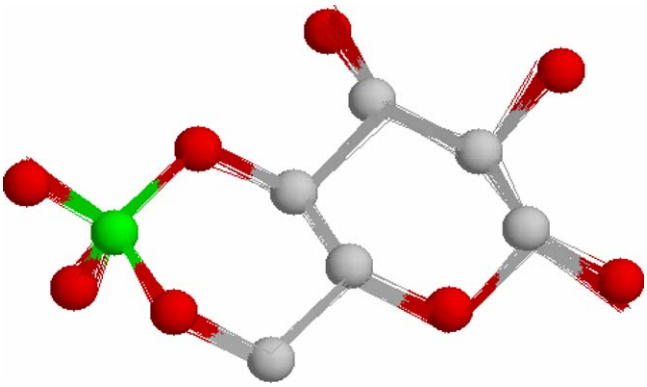

Fig. 4. Overlapping frames, taken each 10 ps, during the MD simulation (1 ns) of the 4,6-gluco-borate, after removal of the overall roto-traslational movements. For an appropriate comparison, the theoretical atomic positions (*ab initio* calculation, at HF/6-31G* level) are also indicated by means of spheres. For clarity the hydrogen atoms are not reported. Green: boron; red: oxygen; grey: carbon.

is reported. The data refer to the first frame of our 5 ns simulation. As it can be seen, in the presence of borax, a reduced relative mobility between triplexes was detected. In other words, in the case of Sclg/borax the starting configuration, with the two triplexes parallel aligned at about 2.5 nm of distance, was substantially retained, while, without borax, the two triplexes tend to assume more changeable configurations during the simulation. To clarify this point, in Fig. 6 we report the structure, at the end of our simulations, for both systems. These results strongly support our hypothesis that the presence of borax affects the inter-triplex

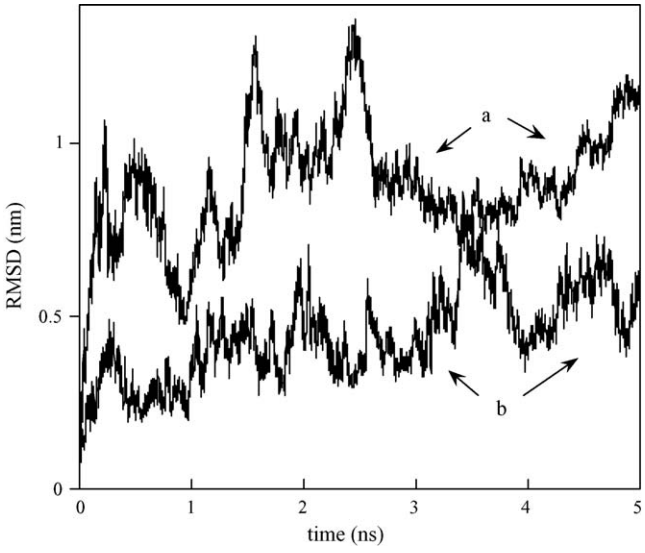

Fig. 5. Root mean square positional distance (*RMSD*) of the atoms of one triplex from their starting positions. *RMSD* is defined according to the following equation: $RMSD(t) = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\left[\vec{r}_i(t) - \vec{r}_i(0)\right]^2}$ where the summation runs over the N atoms of this triplex, $\vec{r}_i(t)$ and $\vec{r}_i(0)$ are the positional vectors of atom i at time t and in the starting structure, respectively. Translational and rotational motions were omitted, during the trajectory, by fitting the positions of all the atoms of the other triplex to their coordinates in the initial structure. (a) Sclg. (b) Sclg/borax.

interactions by favouring the maintenance of a *quasi*-parallel arrangement between the helices.

As shown in Fig. 7, in the case of Sclg/borax, the inter-triplex distance is substantially retained after 1.8 ns (2.1–2.2 nm). Such distance corresponds to the more stable configuration in such conditions (two triplexes in water solution, low ionic strength, absence of drug molecules, etc.). Obviously, we cannot exclude that different surrounding conditions could affect this results leading to different inter-triplexes distances; however, in our system, such distance should anyhow range between 1.5 and 3.0 nm (see below).

3.2.3. *Modelling of Sclg/borax network*

Starting from the results obtained by the MD simulations, we propose a model able to interpret the large amount of experimental evidences that we have acquired, so far, on the Sclg/borax hydrogel. A parallel arrangement of triplex axes, stabilized by borax groups (see Fig. 6), optimizes the interactions among the chains and, as a consequence, it will lead to a more stable and statistically more ordered structure. The compression during tablet preparation can increase the amount of such ordered structures. At present we cannot exclude that these ordered structures are present also when tablet are formed starting from Sclg without borax, but this order, if present, is lost during the imbibition process, as evidenced by the macroscopic non-directional swelling of tablets prepared with only Sclg or with a simple physical mixture of Sclg and borax (Coviello et al., 2005).

On the contrary, the presence of borax, stabilizing the ordered assemblies, somehow favours the peculiar anisotropic swelling in the case of tablets of Scgl/borax.

It is worth to note that in the present physical gel a fine balance occurs between different effects: a large swelling, not allowed in chemical gels, and, at the same time, the maintenance of the order present in the tablet, leading finally to the observed unusual anisotropic swelling (see Table 1).

Obviously, the presence of drug molecules during tablet preparation affects always the packing of triplexes and the subsequent swelling, and produces macroscopic effects in terms of enhanced (TPH and MGB) or reduced (Vit. B12) elongations, as described in Section 3.1.

As we have shown in the previous Section 3.2.2, two Sclg/borax triplexes assume a relative equilibrium distance of roughly 2.2 nm with nearly parallel helical axes. Obviously, when drug molecules are present, the equilibrium distance can vary as a function of the molecular hindrance. However, it is important to underline that two contiguous triplexes become not interacting for inter-axes distances greater than 3.0 nm, corresponding to a fully extended conformation of the side-chains.

The simulation data strongly support our previous idea, based on symmetry and steric considerations, concerning the arrangement of more than two helices of Sclg/borax (Coviello et al., 2003b). In fact, owing to the *quasi*-ternary symmetry of Sclg, three parallel triplexes can realize a “channel” in which, molecules with a diameter smaller than 0.8–0.9 nm (as TPH), can be easily allocated without perturbation of the overall structure (see Fig. 8a).

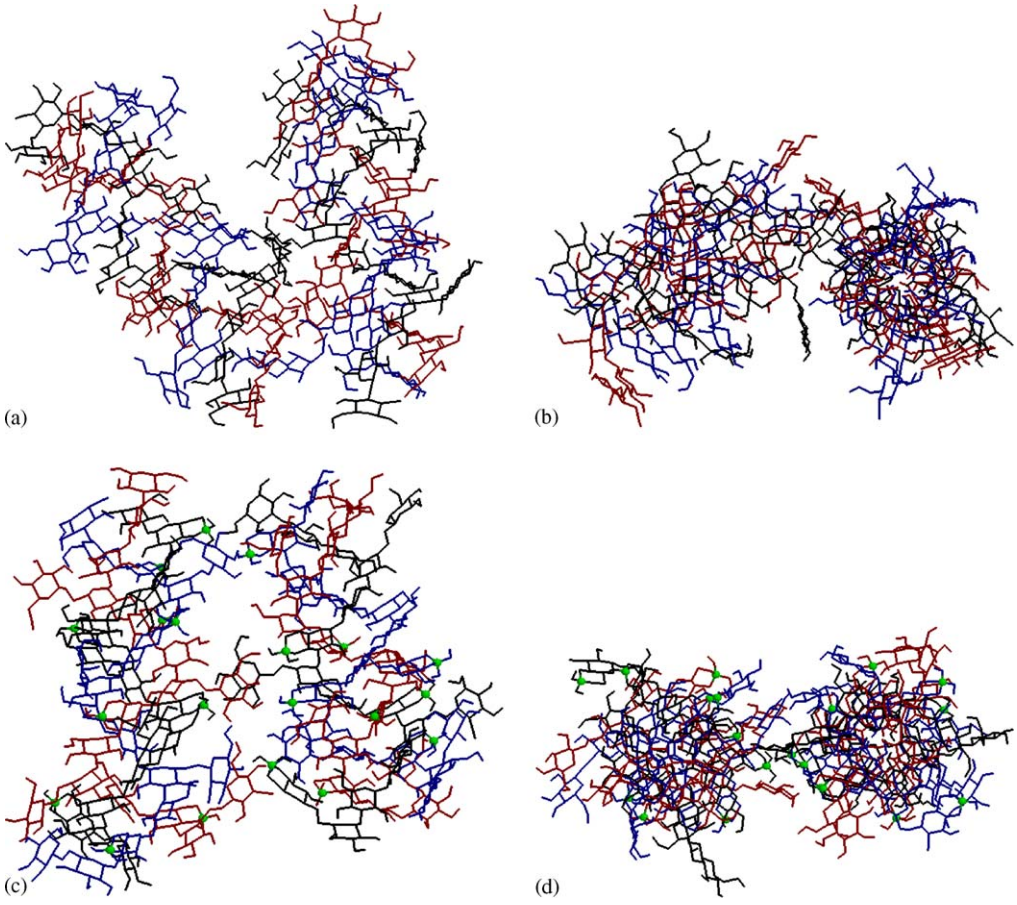

Fig. 6. Molecular structures, at the end of the MD simulations, relative to Sclg (a) and Sclg/borax (b). Left: side view; right: top view. Green spheres indicate the boron atoms.

The diameter of Vit. B12 (1.7 nm), being near to the limiting value of the channel size (see Fig. 8b), does not allow an optimal interaction between the aligned triplexes, that result slightly less stable than in the other cases.

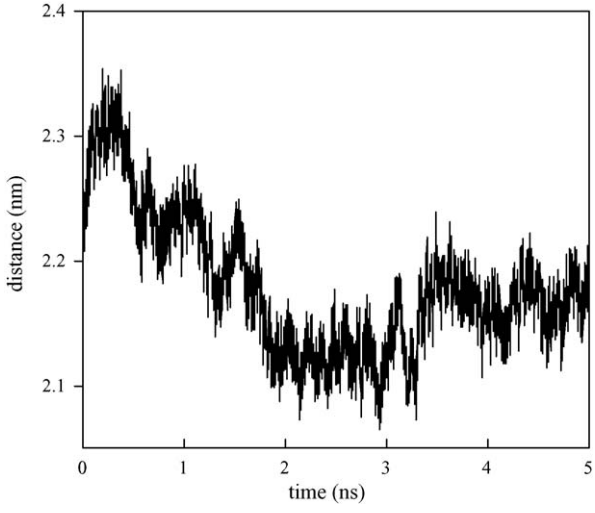

Fig. 7. Trajectory of the intermolecular distances in the case of Sclg/borax. Note the convergence to the range 2.1-2.2 nm after about 1.8 ns of simulation.

For a molecule as MGB (diameter of about 4.2 nm), although present in a lower stoichiometric ratio with respect to the other model drugs, a larger channel is required. A possible arrangement that preserves a parallel alignment of the helices and takes into account both the intrinsic symmetry of the triplexes and the steric requirements can be obtained by means of six interacting triplexes (see Fig. 8c). Such more regular arrangement allows an easier diffusion of a cumbersome molecule as MGB.

In conclusion, the presence of borax favours a parallel arrangement of triplexes that, for their intrinsic symmetry, can form localized and ordered domains with channels representing a preferential way for the diffusion/release of guest molecules. The proposed structures allow a rational explanation, at a molecular level, of the release data reported in Fig. 1, especially in the case of the unexpected and relevant higher mobility of MGB observed for the Sclg/borax hydrogel.

Finally, the elongation, depending also on the molecular hindrances of added drugs, can be likewise explained in terms of the relative stability of the ordered domains. In particular, the ordered domains obtained in the presence of Vit. B12, being less stable with respect to those obtained without the drug, can be less retained during the imbibition process and, as a consequence, a minor anisotropic swelling is observed.

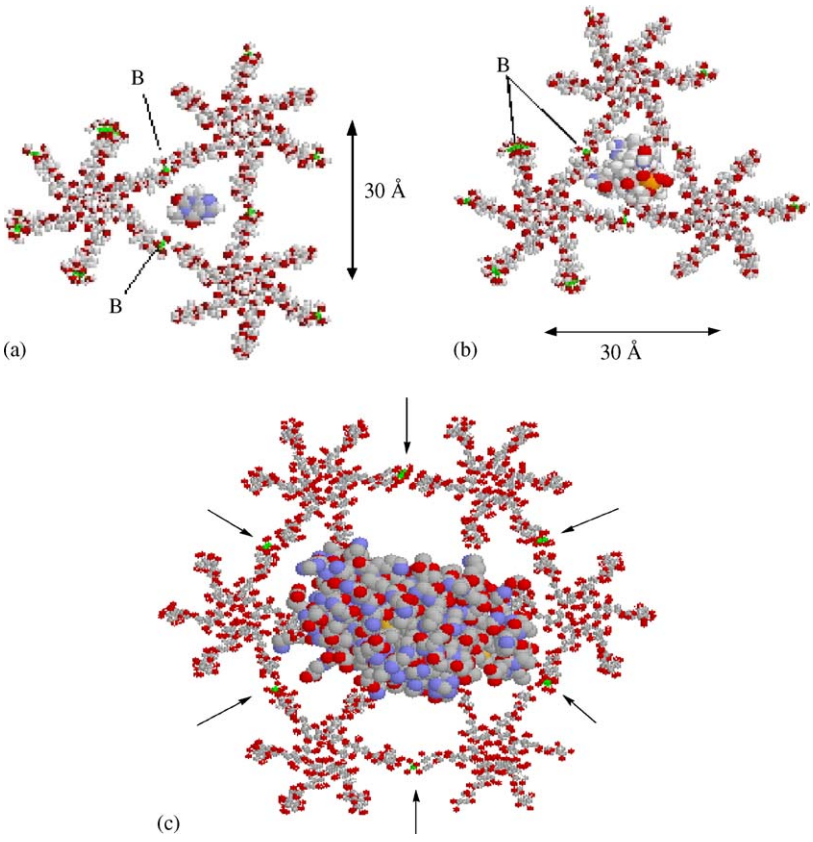

Fig. 8. Models of the proposed channels of Sclg/Borax in the presence of TPH (a), Vit. B12 (b) and MGB (c). The arrows indicate some borate groups located on the side-chains.

4. Conclusions

The gel, formed starting from Sclg/borax, exhibits a very peculiar behavior when a tablet is prepared and then swollen in water. In particular, it shows an anomalous anisotropic swelling, depending on the drug molecules present during gel preparation, and an increase of the release of such drugs if their dimensions are lower or greater than a value of about 0.8 nm.

We have previously shown that in this hydrogel a chemical linkage is present between the borate ions and the Sclg chains, although, the gel is actually a physical one (Coviello et al., 2005). In this work, using theoretical calculations, we have shown that the chemical linkage occurs in the positions 4,6 of the glucose ring. In addition, starting from *ab initio* calculations, we have obtained an original set of parameters involving the borax. Combining such parameters with those successfully used in the first MD simulation of the Sclg triplex, we have simulated a complex system with two tracts of triplex in presence and absence of borax. These simulations demonstrated the ability of borax to keep an ordered configuration of parallel-aligned triplexes that is rapidly lost in the absence of borax.

We believe that the ability to preserve ordered configurations in aqueous media, is responsible for the peculiar behavior of Scgl/borax gel during swelling and drug release from the tablets. Two possible models of triplex configurations in the presence of different guest molecules have been proposed. Channels of triplexes with ternary geometry are possible when small molecules are loaded during gel formations (TPH), while channels with six triplexes are formed around bigger molecules as MGB. The steric compatibility of the molecules with these channels appears to be determinant in the release profiles experimentally observed. Furthermore, in the presence of loaded molecules with a size similar to that of the ternary channels (e.g., Vit. B12), less stable assemblies of triplexes are formed that lead to a minor anisotropic swelling.

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