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A new scleroglucan/borax hydrogel: swelling and drug release studies

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Abstract

The aim of the work was the characterization of a new polysaccharidic physical hydrogel, obtained from Scleroglucan (Sclg) and borax, following water uptake and dimension variations during the swelling process. Furthermore, the release of molecules of different size (Theophylline (TPH), Vitamin B12 (Vit. B12) and Myoglobin (MGB)) from the gel and from the dried system used as a matrix for tablets was studied. The increase of weight of the tablets with and without the loaded drugs was followed together with the relative variation of the dimensions. The dry matrix, in the form of tablets was capable, during the swelling process, to incorporate a relevant amount of solvent (ca. 20 g water/g dried matrix), without dissolving in the medium, leading to a surprisingly noticeable anisotropic swelling that can be correlated with a peculiar supramolecular structure of the system induced by compression. Obtained results indicate that the new hydrogel can be suitable for sustained drug release formulations. The delivery from the matrix is deeply dependent on the size of the tested model drugs. The experimental release data obtained from the gel were satisfactorily fitted by an appropriate theoretical approach and the relative drug diffusion coefficients in the hydrogel were estimated. The release profiles of TPH, Vit. B12 and MGB from the tablets have been analyzed in terms of a new mathematical approach that allows calculating of permeability values of the loaded drugs.

Keywords: Hydrogel; Scleroglucan; Anisotropic swelling; Sustained drug release; Modelling

1. Introduction

Numerous hydrophilic polymers, and in particular polysaccharides, as well as their derivatives, have been proposed for the formulation of modified-release

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dosage forms. It must also be pointed out that, in recent years, an ever increasing interest has been focused on the use of hydrogels for these purposes (Peppas et al., 2000; Hoffman, 2002; Kikuchi and Okano, 2002); in fact, hydrogels are versatile materials in relation to their physico-chemical properties, to the properties of the drug molecules that can be loaded in the polymeric network, and to the mechanism and rate of delivery.

We report here the results of an investigation on a new type of hydrogel obtained from the polysaccharide Scleroglucan (Sclg) and borax as a cross-linking agent. Sclg is a natural homopolysaccharide consisting of a main chain of (1→3)-linked β-D-glucopyranosyl units; every third unit it bears a single β-D-glucopyranosyl unit linked (1→6) and it has a triple-helical backbone conformation. Sclg finds a wide variety of applications (secondary oil recovery, ceramic glazes, food additive, paints and cosmetics) and has also been proposed for the preparation of sustained-release swellable matrices and as a vehicle for ocular topical administration (Touitou et al., 1989; Alhaique et al., 1990a; Romanelli et al., 1993; Rizk et al., 1994). Oxidized and cross-linked derivatives of this polysaccharide have been prepared and studied for pH-controlled delivery systems (Alhaique et al., 1985, 1990b). Borax, a cross-linker suitable for polymers containing hydroxyl groups, has been used, in the field of pharmaceutics, with guar gum for a colon delivery formulation based on a swelling-dependent enzymatic degradation (Rubinstein and Gliko-Kabir, 1995). After a preliminary publication (Coviello et al., 2003) on the Sclg/borax hydrogel, in this paper a wide comment on the anomalous swelling behaviour of the new hydrogel system that leads to an anisotropic dimensional increase is reported and the release of model drug molecules of different steric hindrance (namely, Theophylline (TPH), Vitamin B12 (Vit. B12) and Myoglobin (MGB)) (Table 1) from the freshly prepared Sclg/borax hydrogel and from the freeze-dried matrix in the form of tablets is described and discussed. Furthermore, release profiles from the gels and from the tablets are analyzed according to innovative mathematical models that allow a better understanding of the mechanism ruling swelling/drug release and their fitting with the experimental results.

2. Materials and methods

2.1. Hydrogel preparation

The gel was prepared with Sclg (Actigum CS 11); the polysaccharide (molecular weight = 1.4×10^6 from viscometric measurements) was provided by Mero-Rousselot-Satia (France) and was used after purification, as already described in a previous paper (Coviello et al., 2003). The appropriate amount of Sclg was dissolved in distilled water by continuous magnetic stirring for 24 h. The hydrogel was then obtained, in a beaker, by addition of a calculated amount (i.e., moles of borax = moles of repeating unit of Sclg) of 0.1 M borax (Carlo Erba, Italy) to the polymer solution previously prepared; the mixture was magnetically stirred for 5 min and then left overnight for gel setting. The final polymer concentration (c_p) was 0.7% (w/v). Distilled water was always used. When needed the gel was loaded with TPH (Carlo Erba), Vit. B12 or MGB (Fluka, Germany). For this purpose a given amount of drug was dissolved in the polymer solution before the addition of borax.

2.2. Tablet preparation

For the preparation of the tablets about 160 mg of Sclg and 20 mg of the model drug were magnetically stirred in water for 24 h. Then, the calculated amount

Table 1
Drugs loaded in the hydrogel and in the tablets, Van der Waals radii, relative release of drugs at 8 and 24 h and the half-life obtained by means of dissolution experiments from hydrogel and tablets (in water)

Loaded drug (MW)	Van der Waals radius (Å)	Gel (7 °C)			Tablets (37 °C)		
		$M_t/M_\infty \times 100$ (8 h)	$M_t/M_\infty \times 100$ (24 h)	$t_{1/2}$ (min)	$M_t/M_\infty \times 100$ (8 h)	$M_t/M_\infty \times 100$ (24 h)	$t_{1/2}$ (min)
TPH (180)	3.7	87 ± 8	92 ± 9	78 ± 7	100	100	64 ± 6
Vit. B12 (1355)	8.5	69 ± 7	91 ± 8	186 ± 10	52 ± 5	100	449 ± 20
MGB (17800)	21.0	55 ± 5	84 ± 8	417 ± 20	23 ± 2	43 ± 4	more than 25 h

of 0.1 M borax solution was added and the system left under magnetic stirring for 5 min. The obtained gel (c_p = 0.7% (w/v)) was kept overnight at 7 °C, frozen by immersion in liquid nitrogen and then lyophilized. Tablets were finally 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 1.40 ± 0.10 mm. For an appropriate comparison, tablets were also prepared with only Sclg and by compression of a physical mixture of Sclg and borax.

2.3. FT-IR spectroscopy

FT-IR measurements were carried out at room temperature on a Nicolet Nexus 670 FTIR spectrometer (USA) equipped with an attenuated total reflection (ATR) accessory (ZnSe crystal, 45° angle of incidence), a DTGS KBr detector and a KBr beam splitter. All spectra were recorded in the wavelength range of 650–4000 cm^{-1}. The samples (powder for Borax, tablets for Sclg and Sclg/borax) were placed on the ZnSe and a pressure device has been used for assuring a uniform contact with the ATR crystal.

2.4. Water uptake and dimensional increase studies

Water uptake was evaluated by the relative increase of weight of the tablets, in distilled water at 37 °C. During the experiment, the dimensional variations of the tablets along the longitudinal axes were evaluated with a caliper with appreciation to 0.2 mm. No remarkable variations of tablet diameters were detected during the swelling process. In order to better check tablet swelling behaviour, a suitable experimental apparatus was assembled to evaluate tablet diameter increase during swelling, while the axial expansion was completely hindered (Fig. 1). The system was similar to devices already described in the literature (Alhaique et al., 1993; Bettini et al., 1994). In our case, the tablet was placed in the centre of a circular Plexiglas disc (diameter 12.33 cm) supported by a metallic plate: on the top of the circular disc another transparent Plexiglas plate was posed (thickness 0.63 cm) that was kept parallel to the lower plate by means of micrometric screws fixed at the edges. The upper and the lower surfaces of the tablet were adherent to the plates and therefore the tablet could expand only in the radial direction. The whole system was then placed in distilled water at a fixed temperature (37 °C). The relative increase in diameter was then recorded as a function of time by means of a ruler.

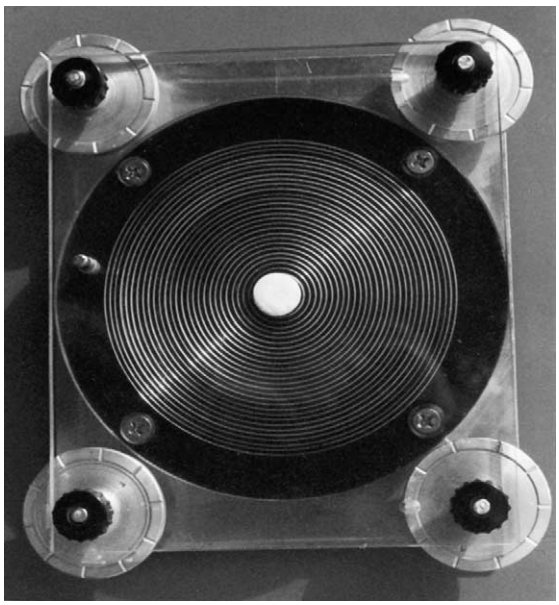

Fig. 1. Picture of the apparatus for the evaluation of the increase of tablet diameter during swelling while hindering axial expansion.

2.5. Release experiments from gel

The hydrogel, freshly prepared in a beaker as previously described (thus in its swollen form), kept the cylindrical shape of the vessel (height = 1.0 cm, diameter = 2.2 cm) and was tested for the release of the three molecules, chosen as model drugs, at 7 and 37 °C. For release experiments the gel was immersed in 200 ml of distilled water (pH 5.4), while it was kept at a certain height from the bottom of the container by a thin web. The medium was gently magnetically stirred and 3 ml samples were withdrawn from the solution at appropriate time intervals and replaced with the same amount of fresh solvent. The amount of released model drug was spectrophotometrically detected (TPH at 272 nm, Vit. B12 at 361 nm and MGB at 409 nm) with a Perkin-Elmer (lambda 3a, UV–vis) spectrometer using quartz cells with pathlengths of 1.0 or 0.1 cm.

All experiments were carried out in triplicate.

2.6. Release experiments from tablets

Release experiments from the model dosage forms were carried out, in distilled water (pH 5.4) and in Simulated Intestinal Fluid (SIF, pH 7.4), according to U.S.P. XXV, using the rotating basket apparatus at $37.0 \pm 0.1\,^{\circ}C$ 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.

3. Data analysis

3.1. Modelling of release from gels

A fundamental prerequisite for an appropriate utilization of a swollen gel as a modified release system is the knowledge of its diffusive characteristics, usually represented by the diffusion coefficient exhibited by a model drug moving through the network meshes. Among the different experimental set-ups that can be designed for the calculation of the diffusion coefficient (Westrin et al., 1994) we considered the one involving the release from a not eroding/swelling cylindrical gel. Accordingly, supposing a constant drug diffusion coefficient D and a negligible gel density variation due to the diffusion process, Fick's second law, in a 2D cylindrical coordinates system, can be written as:

$$\frac{\partial C}{\partial t} = \frac{D}{R}\frac{\partial}{\partial R}\left(R\frac{\partial C}{\partial R}\right) + D\frac{\partial^2 C}{\partial Z^2} \quad (1)$$

where t is the time, C the drug concentration (mass/volume) in the cylinder, R and Z are the radial and longitudinal coordinates, respectively. This equation must satisfy the following initial and boundary conditions.

Initial conditions:

$$C(Z, R) = C_0, \quad -Z_c \le Z \le Z_c, \quad 0 \le R \le R_c \quad (2)$$

$$C_{rel} = 0 \quad (3)$$

boundary conditions:

$$C(Z, R_c, t) = C(\pm Z_c, R, t) = k_p C_{rel}(t) \quad (4)$$

$$V_{rel}C_{rel}(t) = \pi R_c^2 2Z_c C_0 - \int_{-Z_c}^{Z_c}\int_0^{R_c} C(Z, R, t)2\pi R\,dR\,dZ \quad (5)$$

where $2Z_c$ and R_c are, respectively, the cylinder height and the radius, C_0 the initial drug concentration in the cylinder, C_{rel} the drug concentration in the release medium, V_{rel} the volume of the release medium and k_p the drug partition coefficient between the cylindrical gel and the environmental release fluid. Eqs. (2)–(3) state that the release environment is initially drug free, while the cylinder is uniformly loaded by a drug concentration C_0. Eq. (4) expresses the partitioning condition at the cylinder/release fluid interface, while Eq. (5) is a drug mass balance for the cylinder/release fluid system, that allows to state the relation between C_{rel} and $C(Z, R, t)$. The equations set (1)–(5) can be numerically solved by means of the control volume method (Patankar, 1990).

3.2. Modelling of dissolution from tablets

While the theoretical analysis of drug release from a not swelling and/or eroding cylinder does not show particular problems, the study of drug release from a swelling tablet can represent a very hard task. Indeed, for instance, a polymer that undergoes a swelling process, strictly connected with the non-fickian nature of solvent uptake, requires considerable efforts to be modelled (Hayes and Cohen, 1992; Lustig et al., 1992; Siegel, 1992; Grassi et al., 1998; Peppas and Korsmeyer, 1998). Moreover, it must be remembered that, upon swelling, the tablet undergoes the complex transition from a heterogeneous medium to a continuous one and this, of course, highly complicates the physical frame to be described. Consequently, the numerous efforts devoted to tackle this problem led to very complex and powerful models that, unfortunately, are not so easy to handle as they require considerable computational efforts (Zhou and Wu, 1997; Siepmann et al., 1998; Wu and Zhou, 1998; Siepmann et al., 1999; Siepmann and Peppas, 2000, 2001). A possible alternative to overcome this problem is that of avoiding a detailed and complex physical description in favour of a simpler global vision of the release process (Dokoumetzidis and Macheras, 1997). By doing so, of course, we renounce to the determination of some

physical parameters, but we can anyhow get the essence of the phenomenon through a semi-empirical interpretation, as it will be explained below.

We assume that the release process is controlled by two resistances in series, namely drug dissolution and diffusion through the swelling matrix, so that the mean (averaged on tablet volume) resistance Re to drug release is simply the sum of the resistances relative to the above mentioned phenomena. Obviously, due to the simplified approach adopted, it is not possible to discriminate the relative importance of these two resistances and only the sum can be determined by data fitting. According to the hypothesis concerning a mean value for *Re*, and always in the optic of a simplified but powerful approach, we also assume that drug concentration C_m inside the swelling tablet is uniform. Indeed, it would be questionable taking into account the position dependence of C_m while considering a mean value for tablet resistance *Re*, that is, in principle, position dependence. Finally, we assume that swelling takes place only in the axial direction (as evidenced by the experimental observations (Coviello et al., 2003)). Accordingly, C_m can be expressed in terms of C_r (drug concentration in the release environment) resorting to the following mass balance:

$$M_0 = V_r C_r(t) + V_c C_m(t) \tag{6}$$

where M_0 is the drug amount initially present in the tablet, V_r the release environment volume, t the time and V_c the tablet volume. In order to apply a reasonable kinetics equation describing the release process, we refer to the classical equation ruling drug release from a solid drug tablet (Banakar, 1992), properly modified for our purpose:

$$\frac{dm}{dt} = A(t)\frac{(C_m - C_r)}{Re(t)} \tag{7}$$

$$C_r = \frac{m}{V_r} \tag{7'}$$

where $A(t)$ is the cylindrical tablet surface, $Re(t)$ the overall drug release resistance and m the drug amount present in the volume V_r. $Re(t)$ accounts for two different factors, namely the variation, during tablet swelling, of both drug diffusion coefficient and tablet thickness. Obviously, $1/Re$ can be seen as an overall tablet permeability (P) accounting for drug dissolution and tablet properties.

As V_c and V_r modify with time due to tablet swelling, we prefer to focus our attention on m rather than considering C_r, whose variation depends also on V_r value (Grassi et al., 1998).

On the basis of our experimental evidences (tablet swelling occurs practically only in the axial direction), A and V_c dependence on time t can be expressed as follows:

$$A(t) = 2\pi R_0^2 \left(1 + \frac{h(t)}{R_0}\right) \tag{8}$$

$$V_c(t) = \pi R_0^2 h(t) \tag{9}$$

where R_0 is the tablet initial radius and $h(t)$ is its thickness. It will be shown in Section 4 that $h(t)$ can be well described by means of a stretched exponential function:

$$h(t) = h_0 \left(1 + \alpha \left(1 - e^{-kt^n}\right)\right) \tag{10}$$

where h_0 is the tablet initial thickness, k and n are fitting parameters and α represents the limit value of the relative thickness increase.

Inserting Eqs. (6)–(7′) into Eq. (7) and dividing for M_0, we get the model final expression:

$$\frac{dm^+}{dt} = \frac{A(t)}{V_c(t)Re(t)}\left(1 - m^+\left(1 + \frac{V_c(t)}{V_r(t)}\right)\right) \tag{11}$$

where $m^+ = m/M_0$.

From experimental release curves (m^+, dm^+/dt) and from the trend of $h(t)$, by means of Eqs. (8) and (9) it is possible to determine $1/Re(t)$ (i.e., P) as a function of time according to Eq. (11).

4. Results and discussion

4.1. FT-IR measurements

To investigate the interaction between borax and Sclg, we have used the IR spectroscopy. Fig. 2 reports the absorbance of Sclg/borax (a), that of a physical mixture of the two components (b) and a linear combination of the single absorbances of Sclg and borax (c) in the range 750–900 cm^{-1} diagnostic of borax (tetrahedral B-symmetric stretching (Ross, 1974; Davis and Mott, 1980)). As we can see the spectra (b) and (c) are very different from the spectrum (a). This result

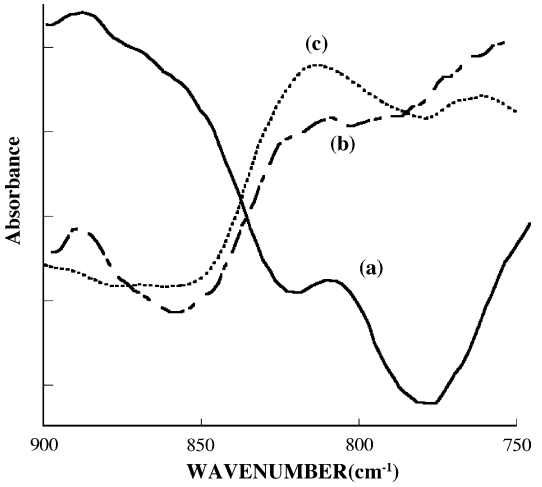

Fig. 2. IR absorbance of: Sclg/borax complex (a), physical mixture of Sclg and borax (b), linear combination of the absorbances of the single components.

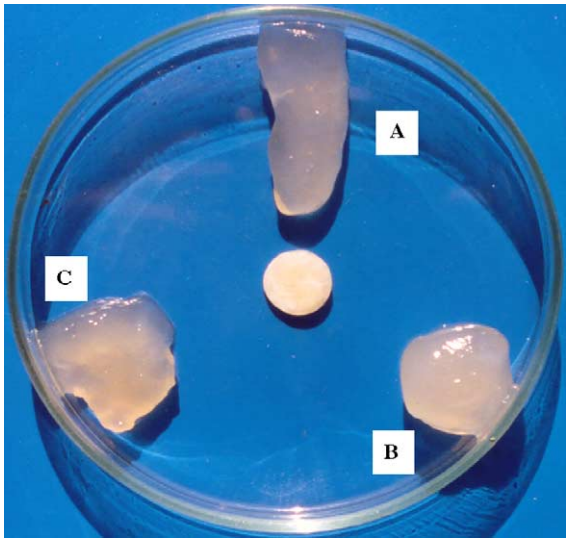

Fig. 3. Picture of a tablet before swelling (centre) and of the swelled tablets, prepared with Sclg/borax (A); Sclg + borax physical mixture (B) and Sclg (C).

indicates the presence of chemical bonds between Sclg and borax.

4.2. Water uptake studies

The weight increase of the tablets, prepared from the freeze-dried gels, was determined at 37 °C as a function of time. When the experimental data are calculated as the ratio between the weight of absorbed water ($W - W_0$) and the weight of the dry tablet (W_0), after 24 h the relative increase of weight ($(W - W_0)/W_0$) for the samples varies from 18.0 ± 1.0, in the case of Sclg/borax, to 12.0 ± 2.0, in the case of the tablets loaded with the model drugs (TPH, Vit. B12 and MGB). These values evidenced the relevant amount of solvent uptaken from the matrices, indicating the new hydrogel as a very hydrophilic system. Furthermore, it can be pointed out that tablet swelling obtained with Sclg/borax alone is more relevant than that observed when a model drug is present in the formulation; in this second case water uptake is also related to the size of the loaded drug.

Anyhow, besides the raw values of weight increase, the peculiarity of tablet swelling is represented by the anomalous shape variation of the Sclg/borax hydrogel during water uptake, as it can be observed in Fig. 3 where a dry tablet is shown in the centre as a reference. In fact, when a tablet prepared with the freeze-dried hydrogel of Sclg/borax is swelled in water, a very peculiar phenomenon takes place: water uptake leads to an anisotropic swelling of the matrix which elongates essentially in its axial direction while it does not practically expand in the radial direction (Fig. 3, A); such unusual effect, although reported in two other cases, but in much less extent (Colombo et al., 1990; Papadimitriou et al., 1993; Talukdar and Kinget, 1995), is not detectable with tablets obtained using a physical mixture of the polysaccharide and borax; in this last case an isotropic swelling is obtained (Fig. 3, B). Furthermore, the tablets prepared with Sclg alone, after swelling, look like a not self-sustaining gel (Fig. 3, C).

According to the Tanaka's theory (Li and Tanaka, 1991), a gel system, regardless of its starting geometry, swells isotropically in all directions, thus the anomalous behaviour observed with the tablets obtained from the freeze-dried Sclg/borax hydrogel could be ascribed to the existence of domains with an intrinsic ordered structure that, in the presence of a spatial mechanical perturbation (e.g., compression), are being enhanced leading to an asymmetrical disposition of the helices along a preferentially oriented pre-established direction.

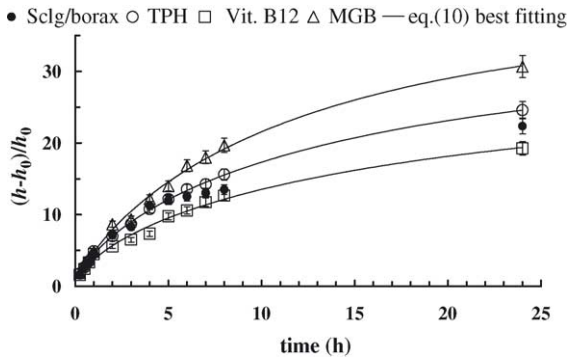

Fig. 4. Relative increase of height for tablets of Sclg/borax, with and without the loaded model drugs, in water at 37 °C, as a function of time. The solid line represents the best fitting according to Eq. (10).

Consequently, for a deeper characterization of this anomalous swelling, together with the water uptake, also the tablet thickness increase was followed as a function of time.

In Fig. 4 the trend of $(h - h_0)/h_0$ versus time is reported; here h_0 is the dry tablet height and h is the actual tablet height during swelling. Although the experimental data, when reported for the first 8 h, as a function of the square root of time (Coviello et al., 2003), tend to dispose approximately on a straight line, thus suggesting that solvent penetration within the matrix occurs, at least macroscopically, according to a fickian process (Peppas, 1984), a stretched exponential trend, as that expressed by Eq. (10) (solid line, Fig. 4), allows a more refined analysis that takes into account a wider time interval and leads to a plateau value, as it actually occurs. In Table 2 Eq. (10) fitting parameters are reported, as obtained using the information acquired from tablet swelling experiments.

The comparison between tablet weight and height increase allows a raw estimation of Sclg/borax density. Indeed, assuming negligible the dry tablet porosity and excluding possible volume variations due to polymer/water mixing, the following relation has to hold:

$$\frac{W - W_0}{W_0} = \frac{h - h_0}{h_0} \times \frac{\rho_{H_2O}}{\rho_{sb}} \quad (12)$$

where ρ_{H_2O} and ρ_{sb} represent the water and the Sclg/borax densities, respectively. Accordingly, for each experimental weight and height measurement it is possible to evaluate ρ_{sb} (assuming $\rho_{H_2O} = 0.992$ g/ml) and then its mean value, $\rho_{sb} = 1.3 \pm 0.2$ g/ml. This value does not differ significantly from the Sclg density that is 1.5 g/ml (Grassi, 1996).

Furthermore, the tablets, made from the freeze-dried Sclg/borax samples with and without the loaded molecules, were placed in the above described apparatus allowing only the tablet radial swelling. At fixed time intervals, the diameter d was measured and the value is reported in Fig. 5 (d_0 is the dry tablet radius). It can be observed that the diameter increase is much smaller than the height increase obtained in the free swelling experiments (Fig. 4). This observation can represent an experimental evidence of the greater matrix mechanical resistance in the radial direction with respect to that in the axial direction, as evidenced by means of texture analysis measurements carried out with a dynamometer (data not shown). Accordingly, this is a clear proof of tablet anisotropy induced by the compression of the Sclg/borax system. It is worth to underline that all the samples with borax, once they have been taken out from the device and transferred into a glass container, within a short period of time, show a spontaneous deformation along the direction perpendicular to the base of the cylinder representing the tablets. Thus, tablets try to elongate along the

Table 2
Fitting parameters relative to general model (Eq. (10)) (tablet height fitting)

	TPH	Vit. B12	MGB
n	0.71 ± 0.02	0.67 ± 0.06	0.80 ± 0.04
α	32.14 ± 1.39	27.80 ± 5.23	37.43 ± 2.63
k (h^{-n})	0.149 ± 0.006	0.144 ± 0.024	0.136 ± 0.008

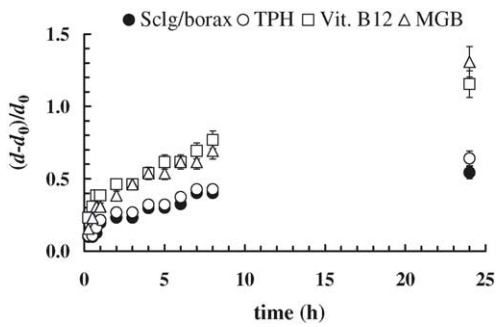

Fig. 5. Relative increase of the diameter of the tablets of Sclg/borax, with and without the loaded model drugs, in water, at 37 °C, as a function of time.

same preferential direction detected when the systems are free to swell in all directions; this represents a clear evidence of an internal microscopic anisotropy, due to the peculiar structure of the network assembled by the polysaccharidic chains in the presence of the borate ions and then compressed. In addition, it is evident from Fig. 4 that the hydrogel samples follow two different trends. The first one is followed by Sclg/borax and Sclg/borax + TPH, and the second one by Sclg/borax + Vit. B12 and Sclg/borax + MGB. The samples of the first group (i.e., with no loaded drug and with the smallest loaded molecule) swell less than the others in the radial direction and this can be related to a more compact and stable internal structure of the hydrogel whose network is, on the other side, affected by the presence of the larger molecules, that lead to an appreciably bigger relative increase in diameter.

4.3. Release of model drugs from the gel

Fig. 6 shows, in terms of $M_t/M_\infty \times 100$ versus t, the release profiles from the freshly prepared gel system (i.e., in its swelled form) of the three examined model molecules in water. The experiments were carried out in distilled water at 7 and 37 °C. Since at 37 °C a slight erosion of the gel was observed towards the end of the experiment, we report here only the data relative to the lower temperature, were no dissolution at all of the physical gel was detected that, if present, would invalidate data analysis of our model (Eqs. (1)–(5)). The shape of release profiles indicates how the gel behaviour is appreciably influenced by the molecular size

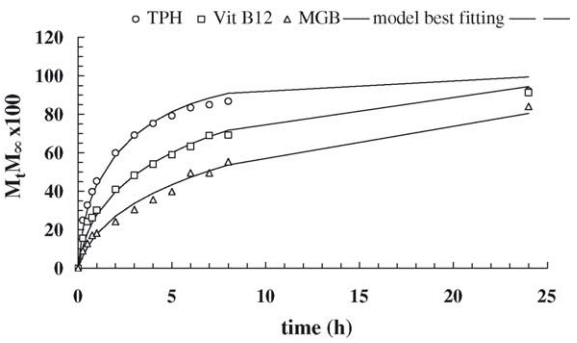

Fig. 6. Release profiles of TPH, Vit. B12 and MGB from the gel, in water, at 7 °C. The lines represent the best fitting to the experimental data according to Eqs. (1)–(5).

Table 3
Diffusion coefficients of the studied drugs in the gel system

Molecule	D_{drug} (cm^2/s)
TPH	5.0×10^{-6}
Vit. B12	2.1×10^{-6}
MGB	1.0×10^{-6}

Experimental conditions: $R_c = 1.1$ cm; $V_{rel} = 200$ ml; $Z_c = 1.0$ cm; $C_0 = 4209$ μg/ml; $T = 7$ °C (distilled water, pH 5.4).

of the model molecules. Accordingly, as it is possible to see from the data in Table 1, the reported release half-lives show how the values for Vit. B12 and MGB are respectively about two and five times bigger than the value obtained for TPH.

Together with the experimental data, also model best fitting (solid line) (Eqs. (1)–(5)) is shown in Fig. 6. It can be noticed that model description of experimental data is satisfactory for all tested drugs even if, in the case of TPH, a certain lack of description is detectable as far as the last point is concerned (24 h). Nevertheless, we can assert that the physical hypotheses on which the model was built (release kinetics ruled by diffusion; no gel erosion or swelling during drug release) are reasonable. Knowing cylinder radius (R_c) and height ($2Z_c$), release environment volume (V_{rel}), initial drug concentration (C_0) and assuming the drug partition coefficient $k_p = 1$, model fitting yields the drug diffusion coefficients D_{drug} listed in Table 3. It should be pointed out that, as expected, drug diffusion coefficient decreases as the Van der Waals radius of loaded molecules increases.

4.4. Release of model drugs from tablets

Fig. 7 shows the experimental release data from tablets containing TPH, Vit. B12 and MGB, in distilled water and in SIF at 37 °C. It can be seen that, as in the case of the release in water from the freshly prepared gel, TPH, the smallest tested model drug, shows the highest release rate followed by Vit. B12 and MGB, according to their molecular weight and/or Van der Waals radius (see Table 1).

As expected, no appreciable differences were detected in the release profiles of the model drugs in water and in SIF; this result is in agreement with the behaviour of Sclg as it is well known that the rheological properties of aqueous solutions of this polymer do not

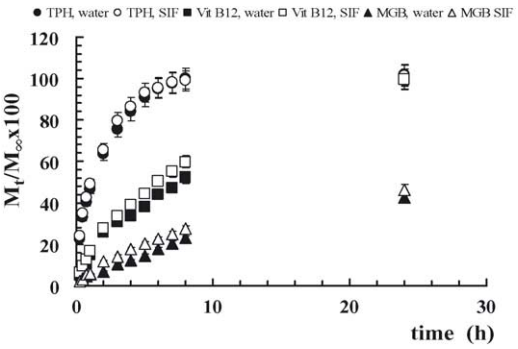

Fig. 7. Release profiles of TPH, Vit. B12 and MGB from tablets, in water and in SIF, at 37 °C.

change up to pH 13. Therefore, due to the similar release profiles reported in Fig. 7, modelling analysis is focused to the data obtained in distilled water.

As above pointed out, permeability (P) was calculated from experimental data, according to Eq. (11), and its trend, as a function of time, is reported in Fig. 8. As it is possible to observe P values follow the expected sequence related to steric hindrance (i.e., $P_{TPH} > P_{Vit.\ B12} > P_{MGB}$). Furthermore, after an initial more rapid increase obtained for the three model drugs (initial matrix swelling), the permeability of THP (i.e., the smallest molecule) continues to increase – although at a lower rate – with increasing swelling and corresponding mesh size widening of the hydrogel network; the larger Vit. B12 shows only a slight further increase as swelling continues, while permeability has an almost constant and low value in the case of MGB that has the highest Van der Waals radius. It is obvious that MGB

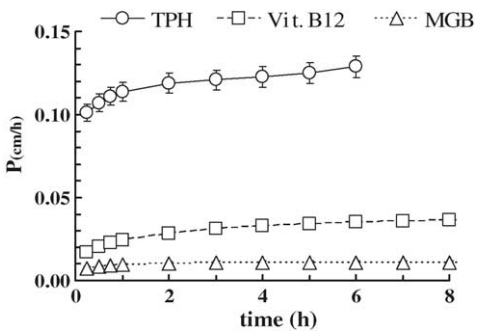

Fig. 8. Permeability values, reported as a function of time for the three model drugs, as obtained from the experimental data (i.e., release from tablets in water at 37 °C) and according to Eq. (11).

is always remarkably slowed down by the surrounding network, also when swelling reached its maximum value; in fact, as previously pointed out, even after 24 h only 40% of MGB is delivered from the matrix. Anyhow, such reduced release, even after 24 h, cannot be attributed to an interaction between the Sclg and MGB as indicated by the remarkably higher percentage of MGB released from the swollen hydrogel (Fig. 6). In Fig. 8, the curve representing permeability as a function of time, in the case of TPH, is reported only up to 6 h because after that time almost all the drug is released and consequently P calculation becomes meaningless.

Finally, it is significant to compare the release obtained from gels and tablets (see Figs. 6 and 7, and Table 1). While in the case of TPH, the smallest tested molecule, there is no much variation between the release from gel and from tablets, for the other two molecules a noticeable delay is observed for the delivery from tablets. This is surely due to the fact that while drug release from gel takes place from a gel freshly prepared, in the case of the tablet drug release and system swelling take place simultaneously. Accordingly, the drug, during its movement through the network, experiences a mesh dimension increase that, starting from the dry state, reaches the equilibrium-swollen state. Furthermore, the lowest polymer concentration in the swollen tablets, i.e., the c_p at 24 h, is remarkably higher (c_p = 3.5%, w/v) than that of the freshly prepared gel (c_p = 0.7%, w/v).

5. Conclusions

The hydrogel, obtained with Sclg and borax, appears to be suitable for a sustained drug delivery as indicated by the results obtained when the hydrogel is loaded with molecules of different size. The release is strongly dependent on the dimensions of the model drugs and therefore the delivery can be tailored in function of the steric hindrance of the entrapped molecule. A comparable relative behaviour was observed, in distilled water and at constant temperature, both when a swollen gel or tablets were used.

A theoretical approach to evaluate the diffusion coefficients, from the freshly prepared hydrogel of TPH, Vit. B12 and MGB, has been applied.

The release profiles of TPH, Vit. B12 and MGB, from tablets undergoing an anisotropic swelling in dis-

tilled water, have been analyzed in terms of a new mathematical approach. The model allows calculating the permeability values of the loaded drugs.

The anomalous hydrogel swelling, that occurs almost exclusively in the axial direction, can be related to the supramolecular structure of the gel network.

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