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A new hydrogel for the extended and complete prednisolone release in the GI tract

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Abstract

The issue of incomplete release of poorly soluble drugs from sustained-release oral formulations is addressed using prednisolone (PDS) as the model drug and a novel highly swelling hydrogel as the rate-controlling material. The hydrogel was formed by heating *N*-carboxymethylchitosan (CMC) to 80 °C for 24 h. Swelling, alkalimetry, FTIR, DSC, and solid-state NMR studies showed that the treatment produced physical crosslinking, i.e., polymer chain entanglement. A controlled-release system was prepared by coating an inert compacted support of ethylcellulose (50 mg; diameter, 6 mm) with a CMC layer containing dispersed PDS powder (10–50 μm). The system was heated to crosslink the CMC coating, then drug release to simulated GI fluids was studied in vitro. The drug release pattern and term were modulated via the layer mass (LM) (10 or 14 mg cm^{-2}) and/or the drug–polymer wt ratio (*D*/*P*) (1:5 or 2:5). The rate parameter, *K*, and the time exponent, *n*, of the Peppas equation were: $K = 26.6 \pm 0.3\ h^{-n}$, $n = 0.78 \pm 0.02$ (LM, 10 mg cm^{-2}; *D*/*P*, 1:5); $K = 24.7 \pm 0.7\ h^{-n}$, $n = 0.56 \pm 0.02$ (LM, 14 mg cm^{-2}; *D*/*P*, 1:5); $K = 20.7 \pm 0.3\ h^{-n}$, $n = 0.76 \pm 0.01$ (LM, 10 mg cm^{-2}; *D*/*P*, 2:5). Hydrogel swelling was faster than drug release. This was controlled, in a first stage, by drug dissolution–diffusion in the swollen gel, and subsequently, by diffusion. The drug release rate was unaffected by the GI pH variations, and slightly affected by the environmental hydrodynamics. The system promises an extended and complete release of poorly soluble drugs in the GI tract.

Keywords: Prednisolone; Controlled-release system; Hydrogel; *N*-Carboxymethylchitosan; Solid-state NMR; Release mechanism

1. Introduction

Realizing extended and, at the same time, complete release of hydrophobic drugs in the GI tract could be problematic. Generally, prolonging release of these barely soluble drugs is not difficult, but realizing the completion of release within the transit time of the release system across the GI tract could be a problem. Various researchers have addressed the issue of an incomplete drug release from sustained-release formulations due to the low solubility of the drug. In the particular case of weakly basic drugs, which deprotonate in the intestinal fluids resulting in the sparingly soluble unionized form, low molecular weight weak acids such as citric, succinic, and adipic have been incorporated with the purpose of keeping the matrix microenvironmental pH below the deprotonation value (Thoma and Zimmer, 1990; Gabr, 1992; Streubel et al., 2000). However, the pH-modulating action of these acids has a short duration because they exit the matrix in comparatively short times due to their comparatively high diffusion coefficients. In order to overcome this limitation, other authors incorporated the water-insoluble acidic polymer, Eudragit® L100-55 (Akiyama et al., 1994; Tatavarti et al., 2004). This polymer is capable of preventing the matrix microenvironmental pH from increasing in intestinal fluids, and moreover, it has a longer residence time within the matrix, whereby its pH modulation effect lasts longer compared to low molecular weight acids. However, such an effect comes to an end if and when the polymer carboxyl groups are completely neutralized by the buffering action of the intestinal fluids. Another approach to enhancing release of poorly soluble drugs by increasing drug solubility has been drug complexation (Adeyeye and Price, 1994; Okimoto et al., 1998; Rao et al., 2001; Smith et al., 2005), especially by sulfobutylether-beta-cyclodextrins (Okimoto et al., 1998; Rao et al., 2001; Smith et al., 2005). Increasing the drug solubility has not been the only way to address the issue of incomplete release of poorly soluble drugs. Indeed, Zambito et al. (2005) resorted to erodi-

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ble matrix tablets, based on poly(ethylene oxide), to achieve an extended and complete release of the virtually insoluble oxybutynin in the intestinal tract. The release was exclusively controlled by matrix surface erosion, which could be modulated via the polymer molecular weight to obtain an adequate release term.

The present study is concerned with an alternative approach to the above-illustrated problem. In principle, the release of a little soluble drug dispersed in a highly swollen hydrogel can both be prolonged, in virtue of the poor drug solubility, and completed in time, thanks to the high dissolution surface and to the comparatively high drug diffusivity in the free water of the hydrogel. The hydrogel approach implies addressing the following issues:

(i) Controlled drug doses must be loaded into the hydrogel. A method apt to the purpose consists in dispersing controlled drug fractions into an aqueous solution of the prepolymer, then crosslinking the prepolymer. Chemical crosslinking, with formation of covalent links, brings about the risk of involving functional groups of the drug, with consequent irreversible binding of the latter to the polymer network. On the other hand, physical crosslinking through formation of crystalline regions in polymer or of polymer chain entanglements is believed to avoid such a risk, and moreover, no initiators nor catalysts are required.
(ii) The release system must be given suitable mass and shape.
(iii) Modulation of release-controlling factors must be possible, in order that modulation of release rate and term is feasible.

In the present work the above issues have been addressed to prepare and evaluate a controlled-release system based on a novel hydrogel, intended for the extended and complete release of the barely soluble prednisolone (PDS) (solubility, 0.32 mg ml^{-1}, according to Di Colo et al., 1986) in the GI tract. A rapidly and highly swelling hydrogel was formed by thermal treatment of *N*-carboxymethylchitosan, a biocompatible noncytotoxic chitosan derivative, not absorbable across the intestinal mucosae (van der Lubben et al., 2001; Thanou et al., 2001). The nature of the hydrogel crosslinks was investigated by swelling studies, alkalimetry, IR spectroscopy, DSC, and ^{1}H and ^{13}C low- and high-resolution solid-state NMR techniques.

2. Materials and methods

2.1. Materials

The following materials were used: prednisolone (PDS), chitosan (CH) (minimum 85% deacetylated), sodium borohydride, glyoxylic acid, and ethylcellulose (all from Sigma). Buffer substances and all other chemicals or solvents were of reagent grade. The average viscometric molecular weight, the deacetylation degree and the water content of commercial CH, determined as described in a previous paper (Di Colo et al., 2004), were 700 kDa, 90%, and 12.3%, respectively.

2.2. Preparation of the N-carboxymethylchitosan (CMC) hydrogel

The method of synthesis of *N*-carboxymethylchitosan (CMC) was taken from the literature (Muzzarelli et al., 1982; Thanou et al., 2001) and modified (Di Colo et al., 2004). CMC was characterized by IR spectroscopy and alkalimetry (Di Colo et al., 2004), which showed the presence of 0.84 *N*-carboxymethyl groups per repeating unit. CMC is soluble at pH values below or above its isoelectric point (pH 5–6). CMC was transformed into a hydrogel by the following procedure: a film of CMC sodium salt was obtained by the casting of an aqueous CMC solution at pH 10; the film was immersed into a pH 5.2 phosphate buffer for 10 min to make the polymer to its isoelectric point; the film was desiccated, then kept at 80 °C for 24 h. After this treatment the CMC film (14 mg cm^{-2}) was no longer soluble, but rather, it would swell in either acidic or neutral buffered solution. The treated film was stored over calcium chloride and used for the swelling, alkalimetry, and DSC studies. For the IR spectra (Mattson 3000 FTIR spectrophotometer), thinner treated and untreated films (about 3.5 mg cm^{-2}) were prepared.

2.3. Determination of the hydrogel swelling kinetics

The swelling kinetics of the CMC hydrogel film in simulated gastric fluid (SGF), simulated jejunal fluid (SJF), or simulated large intestine environment (SLIE) were measured. At time 0, a weighed (sensitivity, 10^{-5} g) film piece was immersed in the appropriate medium at 37 °C. At intervals, the film was withdrawn, rapidly blotted dry and weighed, then it was added again to the medium. The swelling ratio (ratio of swollen to initial dry film weight) was plotted against time. SGF consisted of hydrochloric acid 0.04 M, pH 1.2, made isotonic with sodium chloride; SJF was phosphate buffer pH 6.8, 0.13 M, made isotonic with sodium chloride; SLIE was phosphate buffer pH 7.4, 0.13 M, isotonic.

2.4. Alkalimetry

Alkalimetric curves for CMC before and after the thermal treatment were constructed by the procedure described in the previous paper (Di Colo et al., 2004). Before analysis, both samples were equilibrated in a dry atmosphere (calcium chloride). The samples were added to pre-boiled water, the pH was brought to about 2 with hydrochloric acid, and sodium hydroxide was gradually added under nitrogen. With the hydrogel film, a comparatively long time was required between successive sodium hydroxide additions to attain stable pH values.

2.5. Differential scanning calorimetry (DSC) measurements

A Pyris DSC6 differential scanning calorimeter (Perkin-Elmer), connected to an MC480 cooler circulator (FTS, Stone Ridge, NY, USA), was used. Treated and untreated film samples of 8–10 mg were scanned in sealed aluminium pans in the −35 to 100 °C temperature interval, at a heating rate of 10 K min^{-1}, with nitrogen purge.

2.6. Solid-state NMR studies

^{1}H low-resolution solid-state NMR experiments were performed on CMC before and after the thermal treatment, at the Larmor frequency of 25 MHz, using a single-channel Varian XL-100 spectrometer interfaced with a DS-NMR Stelar acquisition system and equipped with a 5 mm probehead. In all experiments the Free Induction Decays (FID) were acquired under on-resonance conditions using a solid echo pulse sequence, in order to avoid the dead time effect. The 90° pulse length and the echo delay were 2.8 and 12 μs, respectively.

The ^{13}C high-resolution solid-state NMR experiments were performed using a Varian Infinity Plus 400 double channel spectrometer, operating at the ^{1}H frequency of 399.89 MHz and at the ^{13}C frequency of 100.56 MHz. The spectrometer was equipped with a CP-MAS probe for rotors with outer diameters of 7.5 mm. Both the ^{13}C and the ^{1}H 90° pulses were 4.1 μs. The carbon spectra were acquired under Magic Angle Spinning and high-power decoupling conditions, using the cross polarization (CP) pulse sequence and a spinning rate of 4 kHz: for both samples, the optimized contact time and relaxation delay were 0.5 ms and 5 s, respectively. The CMC samples used for the studies were obtained by the following procedure. The polymer was made to its isoelectric pH (5.2) by acidification of its aqueous solution (pH 9). The resulting milky suspension was centrifuged at 5000 rpm to obtain a compact sediment which was dried by an air stream at room temperature and next cut into small granules (untreated sample). A portion of granules was kept at 80 °C for 24 h to convert the polymer into the hydrogel (treated sample).

2.7. Preparation of release systems

Each release system was prepared by coating an inert support of ethylcellulose with a layer of a PDS dispersion in CMC. The support was a tablet of 50 mg (diameter, 6 mm; thickness, 1.6 mm), obtained by compression (force, 9800 N) of commercial ethylcellulose with a Perkin-Elmer hydraulic press. The support was dipped into a 1% (w/v) solution of CMC at pH 10, containing commercial PDS in suspension (particle size, 10–50 μm, determined by an optical microscope; drug–polymer wt ratio, 1:5 or 2:5), then the coating was dried by an air stream at room temperature. This procedure was repeated until the coating attained the pre-established mass. The system was immersed in pH 5.2, 0.13 M phosphate buffer for 10 min to make CMC to its isoelectric point, then CMC was crosslinked by the thermal treatment described in Section 2.2.

2.8. Release experiments

An already described method was used to measure the drug release kinetics (Carelli et al., 2000; Di Colo et al., 2002; Zambito and Di Colo, 2003). The method was a modification of the USP rotating basket method, designed to realize strictly controlled hydrodynamics of the matrix environment. The dissolution medium volume was 100 ml, the temperature was maintained at 37 ± 0.1 °C, the stirring speed was 60 rpm or, in one case, 150 rpm, and the sample volume was 10 ml. Sink conditions were maintained throughout the release experiment. The matrices were eluted with simulated GI fluids, i.e., SGF, SJF, and SLIE used in sequence. SGF and SJF were used for 2 h each, followed by SLIE till the end of the experiment. The withdrawn samples of receiving phase were analysed spectrophotometrically for the drug at 247 nm. Blank runs demonstrated the absence of interference with the measurements.

2.9. Statistical analysis

Differences between values of the cumulative dose fraction released at time t were considered significant, on the basis of the Student's t-test, at $p < 0.05$. The experimentally determined release kinetics were analysed by nonlinear regression, using the GraphPad Prism computer program. The relevant parameters were compared on the basis of the respective 95% confidence intervals.

3. Results and discussion

3.1. Preparation of the release system

Commercial ethylcellulose is granular and easily compactable. The PDS dispersion in the 1% CMC solution was stable and did not need any stirring to prevent settling, thanks to the sufficiently high viscosity of the solution. The coating technique was suitable for small batches; however, an automated industrial pan-coating process is believed to be applicable.

3.2. Hydrogel characterization

3.2.1. Swelling, IR, alkalimetry, and DSC studies

Fig. 1 shows the plots of the swelling degree of the CMC hydrogel film at pH 1.2, 6.8, and 7.4 against time. At pH 1.2, at

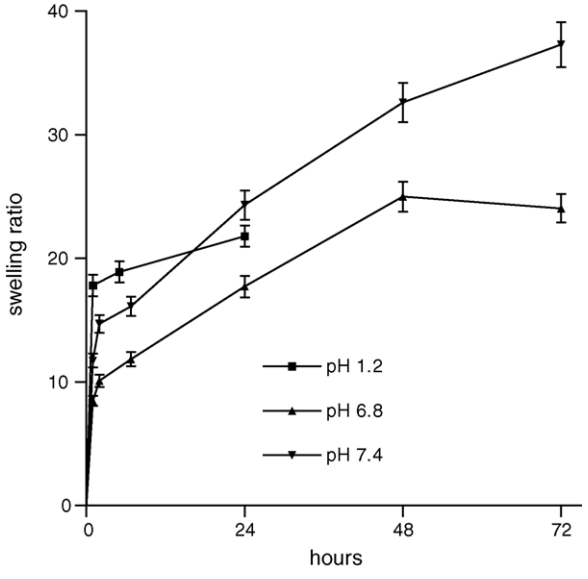

Fig. 1. Plots of the swelling ratio (ratio of swollen to initial dry weights) of the CMC hydrogel film (14 mg cm^{-2}) in simulated gastric fluid (SGF, pH 1.2), simulated jejunal fluid (SJF, pH 6.8), and simulated large intestine environment (SLIE, pH 7.4) against time. Each data point is the mean ± S.D. of three values.

which the amino groups of CMC are ionized, the swelling was fast, but after 24 h the polymer became tacky and the swollen weight could no longer be measured. At pH 6.8, at which the carboxyls are partially ionized, the swelling ratio went through a maximum, then it tended to decrease before the polymer became tacky and the measurements were interrupted. At pH 7.4, at which the ionization degree of carboxyls was higher than at pH 6.8, the swelling was faster, but no maximum was reached before interruption of measurements caused by the polymer tackiness. The behaviour of the polymer sample immersed in the pH 7.4 buffer was observed even after interruption of the swelling measurements: after about two weeks the polymer dissolved, indicating that the crosslinks between polymer chains had been disrupted. This suggests that such crosslinks were of the physical, reversible type. Nevertheless, the hydrogel shows promise of existing in vivo for the entire duration of the transit across the GI tract. The fast and high swelling appearing in Fig. 1 is in keeping with the hydrogel requirements as a release system for PDS.

The IR spectrum of a CMC film at the isoelectric pH (5.2) (not shown) remained unchanged following the thermal treatment. This suggests that no chemical reaction between CMC functional groups was caused by the treatment.

Not even the alkalimetric curve relative to CMC (not shown), obtained as described in the methods section, was altered by such a treatment, indicating that the number of carboxyls per unit polymer mass was unchanged (0.84 groups per repeating unit, as shown in the previous work; Di Colo et al., 2004).

No transition in the −35 to 100 °C temperature range was shown by the DSC thermogram of either the untreated or the treated CMC, suggesting that no formation of any crystalline zones in polymer was induced by the thermal treatment.

3.2.2. Solid-state NMR studies

The ^{13}C CP-MAS spectra of treated and untreated CMC are shown in Fig. 2. The poor spectral resolution observable in the figure could not be improved by varying both spinning rate and decoupling field strength. This indicates that the poor resolution is due to an intrinsic behaviour of samples, i.e., both the treated and the untreated CMC are amorphous, and the extremely broad peaks are due to the large distribution of isotropic chemical shifts occurring in disordered systems. In particular, carbon C(1) gives rise to a very large and asymmetric signal, ascribable to the presence of different conformational situations (γ-gauche effect) (Gast et al., 1980), a pattern similar to that previously observed for chitosans with low chemical crosslinking degrees (Capitani et al., 2001). On the other hand, chitosans in their various crystalline forms are characterized by peculiar spectra, showing both different chemical shift values and much narrower linewidths (Saito et al., 1987). Thus, the thermal treatment of CMC did not produce any appreciable polymer crystallinity. No spectral differences can be observed in Fig. 2 between the two samples, which confirms the absence of any significant chemical modifications caused by the treatment.

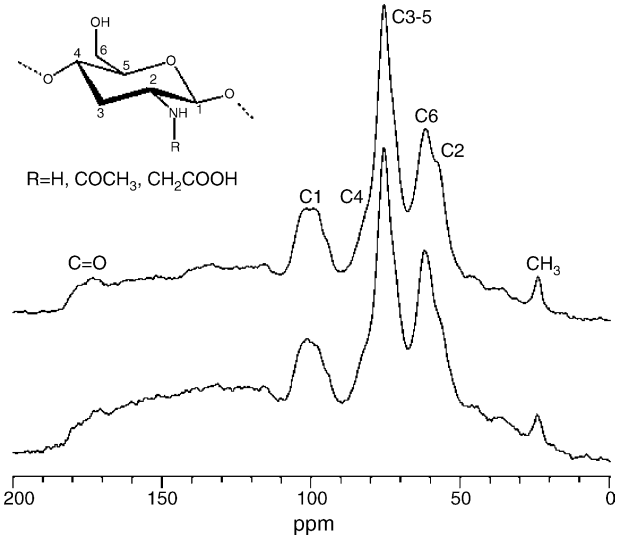

Fig. 2. ^{13}C CP-MAS spectra of untreated (top) and thermally treated (bottom) CMC.

The ^{13}C CP dynamics experiments (CP spectra recorded at different contact times) monitor the magnetization transfer rate among ^{1}H and ^{13}C dipolarly coupled nuclei. Such a rate is sensitive to the strength of the dipolar coupling, which in turn strongly depends on the molecular dynamics of the system. The values of the contact times corresponding to the maximum intensity in the ^{13}C spectrum, resulting from these experiments, were 0.5 ms, for the untreated CMC sample, and 0.4 ms, for the treated one. Both values are typical of very rigid phases, but the lower value for the treated sample suggests a slight increase of the phase rigidity following the thermal treatment.

In order to obtain more detailed and quantitative information on the molecular dynamics of these systems, strictly related to their crosslinking degrees, an analysis of the ^{1}H free induction decay (FID) of the treated sample and of the untreated one was performed at room temperature. Generally, the experimental intensity versus time signal produced in a solid sample by the on resonance excitation of ^{1}H nuclei can be reproduced through a linear combination of different analytical functions by means of a suitable nonlinear least-squares fitting procedure (Hansen et al., 1998). Each function corresponds to a different dynamic domain of the sample. The best-fitting parameters of the function (for instance, the spin–spin relaxation times, T_2) are related to the dynamic behaviour of the domain, while the percent weight of the function is proportional to the number of protons present in the domain. In both cases of the treated CMC sample and the untreated one, the FID was well reproduced by a linear combination of the following two functions, a Gaussian and an exponential, usually associated to protons in very rigid and relatively mobile environments, respectively (Calucci et al., 2004):

$$\mathrm{FID}(t) = w_\mathrm{e}\, \mathrm{e}^{-t/T_2^\mathrm{e}} + w_\mathrm{g}\, \mathrm{e}^{-(t/T_2^\mathrm{g})^2} \quad (1)$$

In Eq. (1), w_e and w_g are the percent weights of the exponential and of the Gaussian, respectively, while T_2^e and T_2^g are the respective spin–spin relaxation times.

The values of T_2 are simply related to the dynamic behaviour, since they increase monotonically with the activation of

Table 1
Best fitting parameters obtained from the ^{1}H FID analysis of the untreated and the thermally treated CMC using Eq. (1)

Sample	Exponential		Gaussian	
	w_e (%)	T_2^e (μs)	w_g (%)	T_2^g (μs)
Untreated CMC	36.6	197	63.4	13.2
Treated CMC	23.7	116	76.3	12.1

molecular motions or with the increase of their characteristic frequencies. The results of the FID analysis of the treated and the untreated CMC are compared in Table 1. As can be seen, the treated sample is characterized by a higher weight percentage of the Gaussian function and by lower T_2 values for both functions. This means that the thermal treatment resulted in a larger amount of the more rigid fraction of the sample, as well as in a higher rigidity of both the polymer domain described by the Gaussian function and that described by the exponential function. On the whole, the FID analysis indicates that the thermal treatment caused a remarkable polymer stiffening. These results, in agreement with the high-resolution solid-state NMR ones, concur with the above discussed swelling, IR, alkalimetry, and DSC results in substantiating the hypothesis that the crosslinking of CMC was physical in nature and consisted in the development of polymer chain entanglements. These were probably promoted by the increased chain mobility at 80 °C and by electrostatic interactions between amino and carboxyl groups of CMC at its isoelectric point. The importance of such interactions is supported by the observation that no crosslinking occurred following thermal treatment of CMC films cast from solutions having pH lower or higher than the isoelectric point.

3.3. Release studies

Fig. 3 shows the effect of the mass of the hydrogel layer covering the inert support on PDS release, at a drug–polymer wt ratio of 1:5. For the computation of the dose fraction released, the drug mass lost when the systems were immersed in the pH 5.2 buffer to make CMC to its isoelectric point was taken into account. In all cases it was less than 10% of the nominal dose. Apparently, the release from the lightest hydrogel coating (7 mg cm^{-2}) was not reproducible. In fact, detachment of the swollen hydrogel coating from the ethylcellulose support was observed in the course of some runs with this system type. Conversely, no detachment was observed with the heavier coatings, which indeed yielded reproducible data. As results from a comparison of data in Figs. 1 and 3, the swelling of the crosslinked CMC in SGF was rapid as compared to PDS release. Hence, release control by polymer swelling is ruled out. Most probably, release was controlled by PDS dissolution and/or diffusion in the swollen hydrogel. The release data were analysed, up to about 50% release, by the following phenomenological equation, now known as Peppas equation (Ritger and Peppas, 1987):

$$F = Kt^n \quad (2)$$

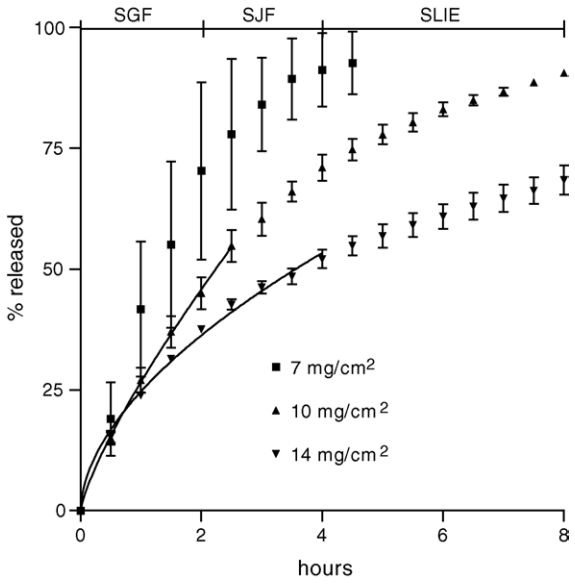

Fig. 3. Effect of the mass of the hydrogel layer (drug–polymer wt ratio, 1:5) on PDS release. Systems eluted with simulated gastric fluid (SGF), simulated jejunal fluid (SJF), and simulated large intestine environment (SLIE). Mean ± S.D. of six runs. Regression lines are reported.

where F is the dose fraction released in time t, K a rate parameter, and the time exponent, n, measures the curvature of the release profile and, hence, is related to the release mechanism. Eq. (2) is applicable up to a released fraction of 60%. For a planar geometry, as in the case of the present hydrogel layer, an n value of 0.5 corresponds to purely diffusion-controlled release (Ritger and Peppas, 1987). In order to estimate the n value for a release solely controlled by drug dissolution, in the hypothetical case that the hydrogel behaved as a sink, reference was made to the following "cube-root law" assuming that the dissolution rate is proportional to the surface area of spherical particles (Wang and Flanagan, 1999; Hixson and Crowell, 1931):

$$W_0^{1/3} - W^{1/3} = W_0^{1/3} K_{diss} t \quad (3)$$

where W_0 is the initial drug mass, W the drug mass still undissolved at time t, and K_{diss} is the dissolution rate constant.

Eq. (3) was readily transformed into the following expression of the dissolved fraction, F, as a function of time:

$$F = 1 - (1 - K_{diss} t)^3 \quad (4)$$

Eq. (4) was used to generate hypothetical particle dissolution data points up to 50% dissolution. Eq. (2) was fitted to these data to yield the relevant n value. Since the dissolution mechanism, and hence, the n value, is independent of the particular K_{diss}, this was given the arbitrary value of 0.0515 reciprocal time units. Hence, the time for 50% dissolution, calculated from Eq. (4), is 4 time units. From this value, 8 F versus t hypothetical data points, spaced by an interval of 0.5 time units, were computed from Eq. (4). The fitting of Eq. (2) to these data yielded 0.88 (r^2 = 0.9995) as the n value for the hypothetical, purely dissolution-controlled release from the hydrogel.

Table 2
Parameters from the fitting of Eq. (2) to data on PDS release from CMC hydrogel layers of different mass (LM) and drug–polymer wt ratio (*D*/*P*), under different stirring speeds (SS)

LM (mg cm^{-2})	*D*/*P*	SS (rpm)	$K \pm$ S.E. (h^{-n}) (CI[a])	$n \pm$ S.E. (CI[a])	r^2
10	1:5	60	26.63 ± 0.32 (25.74–27.52)	0.782 ± 0.017 (0.736–0.828)	0.9994
14	1:5	60	24.67 ± 0.66 (23.11–26.23)	0.556 ± 0.024 (0.498–0.615)	0.9955
10	2:5	60	20.73 ± 0.28 (20.05–21.41)	0.765 ± 0.013 (0.732–0.797)	0.9994
10	1:5	150	45.35 ± 0.02 (45.24–45.45)	0.589 ± 0.001 (0.583–0.594)	1

[a] 95% Confidence interval.

The parameters obtained from the fitting of Eq. (2) to real release data are listed in Table 2. Apparently, the lowest *n* value in the table is higher than 0.5, whereas the highest *n* value is lower than 0.88. This demonstrates that in all cases the release was controlled by both drug dissolution and diffusion in the swollen hydrogel.

From the 95% confidence intervals of the parameters it appears that the values of the rate parameter, *K*, for the 10 mg cm^{-2} coating and for the 14 mg cm^{-2} one, at 1:5 drug–polymer wt ratio, are not significantly different. Instead, the parameter *n* is significantly higher with the thinner hydrogel layer. In order to account for this difference it should be considered that the release process is composed of two steps in series: the first one is the drug diffusion in the hydrogel toward the receptor medium, the second one is the dissolution of drug particles to compensate for the drug diffused away. At the earlier times the diffusion path is short, the diffusion is comparatively rapid, and the dissolution rate of the particles adjacent to the releasing surface is insufficient to compensate for the drug released. So, also the inner particles start dissolving (stage I). In this stage the process is controlled by both dissolution and diffusion. Subsequently, a retreating solid front is formed, the diffusion path becomes much longer than the interparticle distance, the diffusion slows down and the dissolution rate of the particles at the solid front is sufficient to compensate for the drug mass diffused away. In this stage the dissolution occurs only at the solid front and the process is controlled by diffusion, which is the slower step (stage II) (Higuchi, 1961). These concepts are schematically represented in Fig. 4. This hypothesis is in keeping with the higher *n* value for the 10 mg cm^{-2} hydrogel layer compared to the 14 mg cm^{-2} one, seen in Table 2. Indeed, since the data were analysed up to a released fraction of about 50%, the mass released from the 10 mg cm^{-2} hydrogel layer up to this fraction was comparatively small, and hence, it could be insufficient for release to attain stage II. Instead, the mass released from the 14 mg cm^{-2} hydrogel up to 50% release could be sufficient to reach stage II. That the release mechanism during the initial phase was the same, irrespective of the coating thickness, was confirmed by plotting the data of Fig. 3 as drug mass released versus time, up to the time of 50% release from the 10 mg cm^{-2} hydrogel layer. As can be seen in Fig. 5, the data for the different hydrogel layers are indeed almost superimposable. According to this mechanism, a thinner coating should be a better guarantee of a complete release. However, the coating

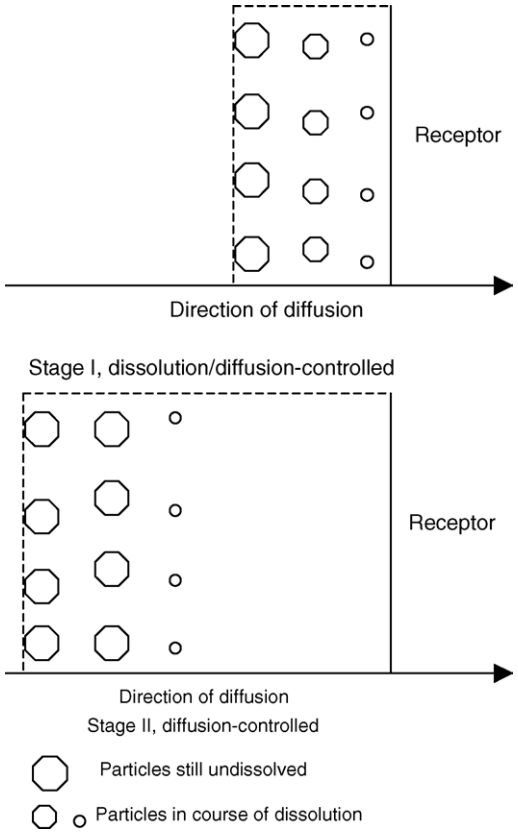

Fig. 4. Schematic representation of the release model.

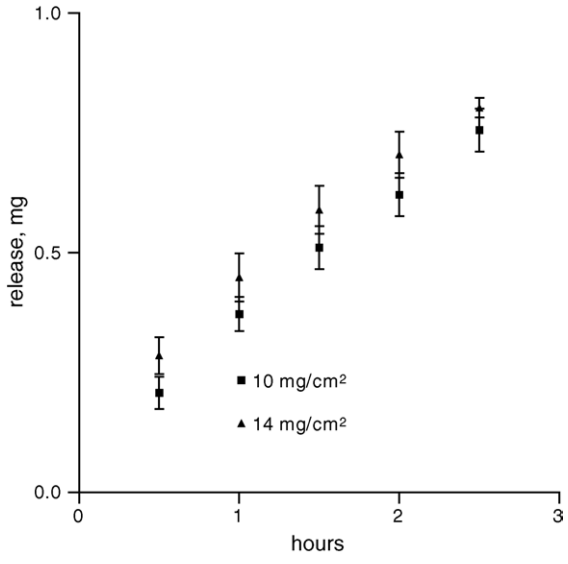

Fig. 5. Data of Fig. 3 relative to hydrogel layers of 10 and 14 mg cm^{-2} reported as drug mass released vs. time.

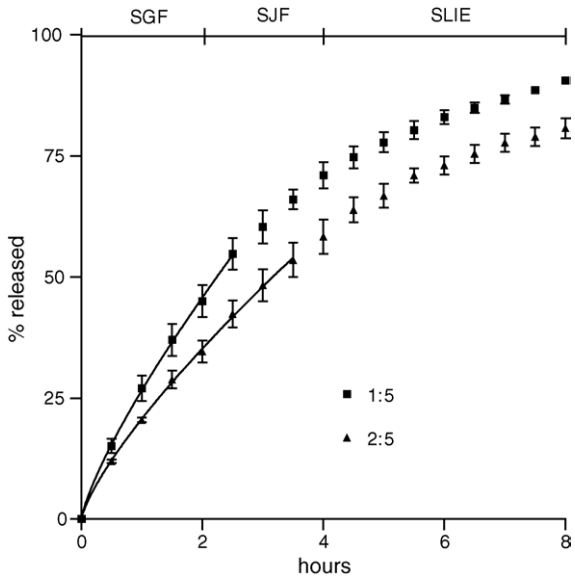

Fig. 6. Effect of drug–polymer wt ratio on PDS release from 10 mg cm^{-2} CMC hydrogel layers. Systems eluted with simulated gastric fluid (SGF), simulated jejunal fluid (SJF), and simulated large intestine environment (SLIE). Mean ± S.D. of six runs. Regression lines are reported. The data for the 1:5 ratio were reproduced from Fig. 4 for a direct comparison.

must contain and release a therapeutic dose. The dose could be increased without increasing the thickness of the coating by increasing the drug–polymer ratio. The effect of increasing such a ratio while keeping the coating mass at 10 mg cm^{-2} is shown in Fig. 6 and in Table 2. The parameter n was virtually unaffected (about 0.8) because both the release mechanism and the thickness of the hydrogel layer were unvaried. On the other hand, the rate parameter, K, was lower with the higher drug concentration. Anyway, the dose fraction released over 8 h remained satisfactory (about 80%). It should be noticed that the dose could be increased without changing the release parameters, K and n, nor the overall release term, simply by coating a support of larger surface with a hydrogel layer of same mass per unit surface.

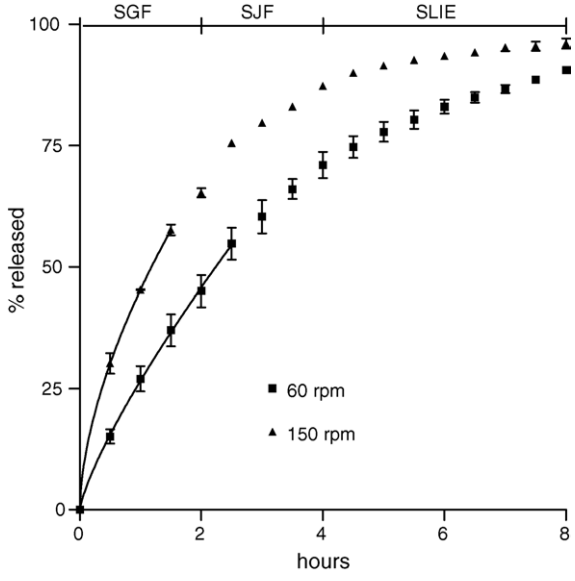

Fig. 7. Effect of the stirring speed on PDS release from 10 mg cm^{-2} CMC hydrogel layer (drug–polymer wt ratio, 1:5). Systems eluted with simulated gastric fluid (SGF), simulated jejunal fluid (SJF), and simulated large intestine environment (SLIE). Mean ± S.D. of six runs. Regression lines are reported. The data for 60 rpm were reproduced from Fig. 3 for a direct comparison.

When it comes to the in vivo behaviour of the present system, the hydrodynamics of its surroundings is an important consideration, because they affect the thickness of the stationary fluid layer adjacent to the hydrogel surface, which could influence the release (Flynn et al., 1974). Since the in vivo hydrodynamics were not closely matched by our in vitro apparatus, we studied the strength of the effect by markedly increasing the stirring speed from 60 to 150 rpm. It appears from Fig. 7 that an acceleration effect was essentially exerted during the first hour of release, therefore, it resulted in an increase of the curvature of the release profile (n decreased from 0.78 to 0.59). The effect is explained by considering that the thickness of the boundary fluid layer was of the same order as the length of the diffusion path within the hydrogel, only at the early times of the release process, therefore its effect on release was essentially exerted at the early times.

4. Conclusions

A novel hydrogel capable of rapidly attaining high swelling degrees has been prepared by subjecting CMC, in its dry solid state, to a thermal treatment. Swelling, IR, alkalimetry, DSC, and solid-state NMR studies have shown that the formation of the hydrogel results from the development of polymer chain entanglements which constitute physical crosslinks. A controlled-release system with the potential of ensuring extended and complete release of the poorly soluble PDS during transit across the GI tract has been prepared by coating an inert support with a hydrogel layer containing PDS in dispersion. PDS release to simulated GI fluids can be modulated by the layer thickness and/or by the drug–polymer wt ratio, in order to obtain the desired release pattern. The release is controlled, in a first stage, by drug dissolution and diffusion in the swollen hydrogel and, subsequently, only by diffusion. The former mechanism is operative with comparatively thin hydrogel layers, while the latter is predominant with thicker ones. The release rate is unaffected by the pH variations of the GI regions, and little affected by the environmental hydrodynamics. With PDS particles of 10–50 μm the release shows promise of being both extended and complete. The drug dose can be modulated without changing the release pattern simply by varying the surface of the inert support while keeping the hydrogel layer thickness constant. Alternatively, a pharmacologically effective dose can be made up by introducing an adequate number of the present small matrices into a size No. 00 gelatin capsule.

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