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NMR imaging of chitosan and carboxymethyl starch tablets: Swelling and hydration of the polyelectrolyte complex

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ABSTRACT

The hydration and swelling properties of the tablets made of chitosan, carboxymethyl starch, and a polyelectrolyte complex of these two polysaccharides have been studied by NMR imaging. We studied the effect of pH and ionic strength on the swelling of the tablets and on the diffusion of fluid into the tablets in water and simulated physiological fluids. The pH value of the fluids exerts a more significant effect than their ionic strengths on the swelling of the tablets. The tablets are compared also with those made of cross-linked high amylose starch. The formation of complex helps to keep the integrity of the tablets in various media and render a slow and restricted swelling similar to that of the tablets of the cross-linked high amylase starch, which is significantly lower than the swelling of chitosan and of carboxymethyl starch. The capacities to modulate the release rate of drugs in different media are discussed by comparing the matrices and evaluating the preparation process of the complex. A sustained release of less soluble drugs such as aspirin in gastrointestinal fluids can be provided by the complex, due to the ionic interaction and hydrogen bonding between the drug and the biopolymer complex.

1. Introduction

Polysaccharides are among the most abundant macromolecules in nature and present several advantageous characteristics for pharmaceutical applications. They are highly stable, non-toxic, hydrophilic, biodegradable and some of them bio-adhesive. The presence of hydroxyl groups and of amine groups in certain polysaccharides allows for chemical derivatization and cross-linking. Improved physicochemical properties can be achieved by chemical modifications. For these reasons, drug delivery with solid oral dosage forms has often used polysaccharides, such as starch, cellulose, chitosan, collagen and pectin. For example, hydroxypropyl methylcellulose (HPMC) is one of the most widely used polymer carriers in the pharmaceutical industry. The ratio of hydroxypropyl groups to methoxyl groups can be modified to produce HPMC products of different hydrophilicities (Jain, 2008).

Cross-linked high amylose starch (CHAS) is an excellent excipient for controlled drug release because the cross-linking and hydrogen bonding keep the polymeric network from erosion and retrogradation and, more importantly, restrains swelling of the matrix. The sustained release was optimized for a CHAS matrix with a cross-linking degree of 6% (often defined as the weight ratio of the cross-linking agent to the starch) (Dumoulin et al., 1998). The pK_a of natural starch is about 12–14 (Lammers et al., 1993; Wong, 1989). Therefore, pH has no effect on the swelling of the CHAS tablets at pH 2–8 in the gastrointestinal tract. Carboxymethyl starch (CMS), on the other hand, is an anionic polymer with a pK_a of about 4.8 (Assaad and Mateescu, 2010) due to the presence of carboxyl groups (Mulhbacher et al., 2004; Sen and Pal, 2009). Its swelling is thus suppressed in gastric fluid. The resultant oral dosage forms could decrease irritation to the stomach caused by soluble drugs and increase their bioavailability. In intestine surroundings, CMS is deprotonated and the polymer chains swell, leading to the release of the drug entrapped in the matrix. CMS was proposed as a pharmaceutical excipient for oral dosage forms of bioactive agents such as peptides (Calinescu et al., 2007), enzymes (Rathbone, 2008) and probiotics (Calinescu and Mateescu, 2008). In contrast to starch, chitosan is a non-ramified cationic polysaccharide due to the presence of amine groups. Its pK_a value is about 6.3 (Kumar et al., 2004). In acidic media, unmodified chitosan dissolves due to protonation of its amine groups. The control of drug release depends on the dissolution rate and this can be modulated by the excipients used in formulations.

The pH-dependent drug release can cause *in vivo* variability, and thus it is difficult to correlate *in vitro* release with *in vivo* drug availability. Complexation of ion pairs represents an effective way to modulate the pH-sensitive swelling of polyelectrolytes. A complex can be formed (Bhattarai et al., 2010) in the presence of chitosan and a polyanionic polymer (such as polysaccharides (Kaur et al., 2010), synthetic polymers (Park et al., 2008), proteins (Zhang

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et al., 2009) and DNA (Mao et al., 2001)). The complexation occurs without cross-linking agents, catalysts or organic solvents, which alleviates the concerns on their safety in the body (Berger et al., 2004; Bhattarai et al., 2010). In this study, the complex of CMS and chitosan obtained from direct precipitation has been investigated.

In general, the water uptake properties of anionic and cationic polymeric excipients are provided by the ionization of the functional groups, which depends on the pH and on the ionic strength of the external medium (Swarbrick, 2006). Although the effect of pH on the swelling of the above-mentioned four excipients is qualitatively predictable, a quantitative study will generate useful information on their capabilities to control the drug release. The hydration data will also serve to the modulation of the excipient preparation for better reproducibility.

Nuclear magnetic resonance imaging (NMRI) is one of the ideal methods to record *in situ* the swelling behavior of solid oral dosage forms, thanks to its noninvasive and nondestructive nature. Magnetic field gradients are used to encode the spatial distribution of the spin density (Richardson et al., 2005). Researchers can use NMRI to evaluate the polymer concentration profile in the tablets (Baumgartner et al., 2005; Djemai and Sinka, 2006), quantify dimensional properties (thickness, area and volume) during the swelling (Baille et al., 2002; Malveau et al., 2002; Thérien-Aubin et al., 2005, 2008; Wang et al., 2010), and define the diffusion front by a sharp gradient in signal intensity (Baille et al., 2002; Malveau et al., 2002). Furthermore, the NMRI studies can provide the diffusion coefficient of a liquid component (Thérien-Aubin et al., 2008; Wang et al., 2010), and the spin-lattice and spin–spin relaxation times which relate to the environment of the penetrant and its physical bonding to the polymer system (Fyfe and Blazek, 1997).

We have used NMRI in the study of the CHAS tablets with and without loaded drugs (Baille et al., 2002; Malveau et al., 2002; Thérien-Aubin et al., 2005, 2008; Thérien-Aubin and Zhu, 2009; Wang et al., 2010), and investigated the effect of temperature, tablet size and the drug loading on the swelling and water uptake of the CHAS tablets. In this study, we would like to compare the characteristics of the tablets of the four matrices in three different media, i.e., simulated gastric fluid (SGF), simulated intestinal fluid (SIF) and water. The tablets were made to be homogenous and do not contain any drugs in an effort to compare their swelling properties, as the dissolution studies of the drug-containing tablets have been done previously (Assaad et al., 2011). This present work should provide a better understanding of the polysaccharides used in drug delivery systems. CHAS, a well-characterized polymer matrix for sustained release of drugs, served as a basis of comparison in the study of the other three matrices.

2. Materials and methods

2.1. Preparation of matrices and tablets

High amylose starch (corn starch Hylon VII) was cross-linked at 6% with epichlorohydrin as reported (Dumoulin et al., 1998). The CMS was prepared by the alkali-catalyzed reaction of the high amylose corn starch with chloroacetic acid as previously described (Assaad et al., 2011; Mulhbacher et al., 2001). The degree of substitution of CMS determined by back-titration method is about 0.14 (Assaad et al., 2011). Chitosan (Marinard Biotech, Rivière-au-Renard, QC, Canada) was purified by solubilization in acetic acid followed by filtration (Assaad et al., 2011). The degree of deacetylation of the chitosan was about 80% according to acid–base titration and its approximate molecular weight determined by Mark–Houwink–Sakurada method was about 700 kDa (Assaad et al., 2011). A stoichiometric CMS–chitosan complex was prepared by coagulation of CMS and chitosan in an aqueous medium. The complex contains 14 wt% of chitosan. The unloaded tablets of 200 mg were obtained by direct compression (2.5 tons) of the excipient powder. Flat-faced punches and a Carver hydraulic press were used to obtain tablets of 9.6 mm × 2.1 mm.

2.2. Preparation of media

Simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) were prepared following the USP methods (2009), without pepsin nor pancreatin being added. SGF (pH 1.2) was prepared by dissolving 2.0 g of NaCl in 1 L of solution containing 7 mL of concentrated HCl (35 wt%). SIF (pH 6.8) was prepared by dissolving 6.8 g of KH_2PO_4 in 250 mL of distilled H_2O, and adding 77 mL of 0.2 M NaOH solution followed by dilution to 1 L with distilled water.

2.3. NMR imaging

All NMR imaging experiments were carried out at 37.0 °C on a Bruker Avance-400 NMR spectrometer operating at a frequency of 400.27 MHz for protons and equipped with a microimaging probe with a 20 mm inner diameter. A standard spin-echo pulse sequence was used to obtain spin density images of each tablet in a 20 mm o.d. NMR tube containing 20 mL of the media (distilled water, SGF, or SIF). A slice of 0.5 mm in thickness was selected either perpendicular or parallel to the main magnetic field using a sinc-shaped pulse. Eight scans were accumulated to obtain 128 × 128 pixel images for a field of view of 2.0 cm, leading to an in-plane resolution of 156 μm. An echo time of 3 ms and a repetition time of 1 s were fixed, leading to an acquisition time of about 17 min for each image.

In addition to observing the tablet swelling in the same medium until equilibrium, some tablets were studied by changing the media: first observing the tablets in SGF for 2 h and then in SIF until swelling equilibrium was reached. This was used to simulate the situation of a tablet's transit through the gastrointestinal tract, which is denoted as SGF–SIF hereafter.

3. Results and discussion

3.1. NMR imaging and proton density profiles

NMR imaging provides a visual representation of the spatial distribution of water by acquiring signals directly from the protons. Fig. 1 presents the NMR images of tablets based on the CMS–chitosan complex in media of different pH values. The images of the tablets made of other excipients are shown in Figs. S1–S3 in the Supporting Information. The image cross-sections clearly demonstrate the time-dependent ingress of water into the polymer matrix. Moreover, the swelling of a tablet in the fluid can be visualized from the NMR images. ^{1}H tuning and matching strongly depend on the ionic strength of the sample. A buffer solution, such as SGF, may cause de-tuning of the probe and some artifacts in the NMR images of the highly ionic samples (Bock et al., 2001, 2002), as observed in some images in Fig. 1. The higher intensity of the water inside the tablets is attributed to the different longitudinal relaxation time (T_1), 5 s for the bulk water vs. 800 ms for the water inside the tablet. The repetition time was fixed at 1 s, so that all the images obtained are T_1-weighted. The magnetization of the bulk water does not have enough time to return to equilibrium, contrary to the magnetization of water inside the tablet, leading to a higher proton signal intensity than that of the bulk water initially at the interface of the tablet and aqueous media.

The proton density profiles shown in Fig. 2 are taken from the NMR images of the samples and offer a clearer picture of magnitude of the water signal as a function of time. The profiles were plotted along the radial direction going through the center of the tablets. As mentioned earlier, all the images are T_1-weighted due to the short repetition time. Water concentration in the gel layer is not strictly

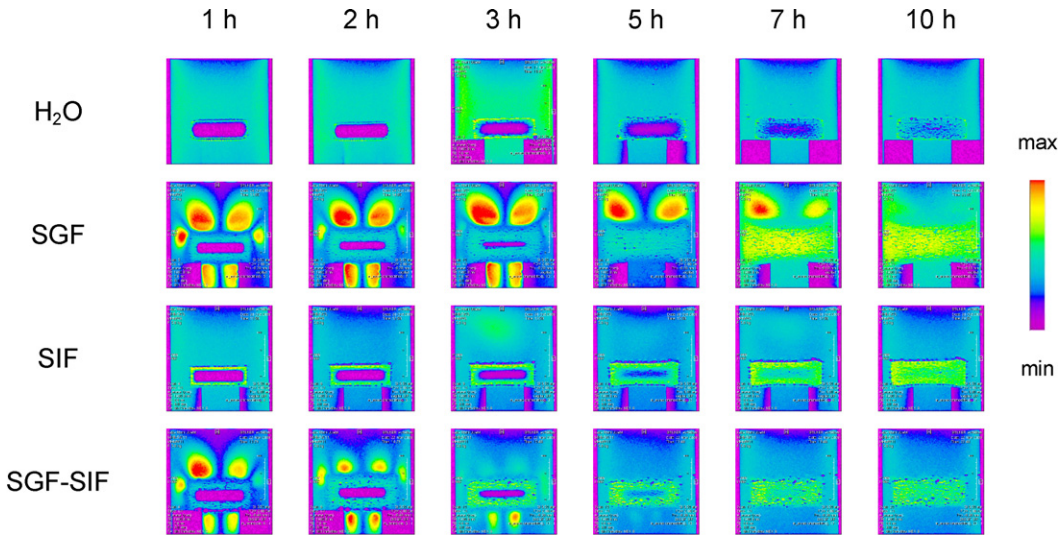


Fig. 1. The NMR images of the CMS–chitosan complex tablets immersed in various media at 37 °C for 1, 2, 3, 5, 7 and 10 h. The bright spots above the tablets resulted from an abrupt change of magnetic susceptibility at the interface between the gel layer and the liquid. SGF–SIF indicates that the tablets were transferred from SGF to SIF after immersion for 2 h in SGF.

proportional to the proton density but the trend is correct inside a tablet.

3.2. Comparison of polymer matrices

The NMR images and the proton density profiles show that the CHAS tablets swell at the slowest rate among the four matrices (Figs. S1 and S4). The dry core of a CHAS tablet disappears after immersion in a medium for more than 7 h. The hydrated tablet continues to swell very slowly until reaching an equilibrium at more than 24 h. As expected, the swelling of the CHAS tablet shows little difference in the different external media used since the matrix is stabilized mainly by hydrogen bonding. Basket-shaped spin-density profiles with flat bottoms present the slow process of water penetration in a CHAS tablet. Low water signals have already been detected in the core after 2 h, long before the polymer concentration becomes homogeneous in 10 h. The signal intensity of the core gradually increases with time.

The NMRI studies provide a direct comparison on the diffusion of water in the tablets made of different polymer matrices. The slow diffusion of water as shown by NMRI explains in part the prolonged drug delivery by the PEC tablets in comparison to the tablets made of CMA previously (Assaad et al., 2011). In contrast, water moves very fast in CMS and the water fronts meet inside a CMS tablet after immersion for only 3 h. It appears (Fig. S2) that the CMS tablets lack a well-defined edge owing to the similar proton density of the loose gel at the periphery. Since SGF has a pH lower than the pK_a (4.8) of CMS, the carboxyl groups are protonated and

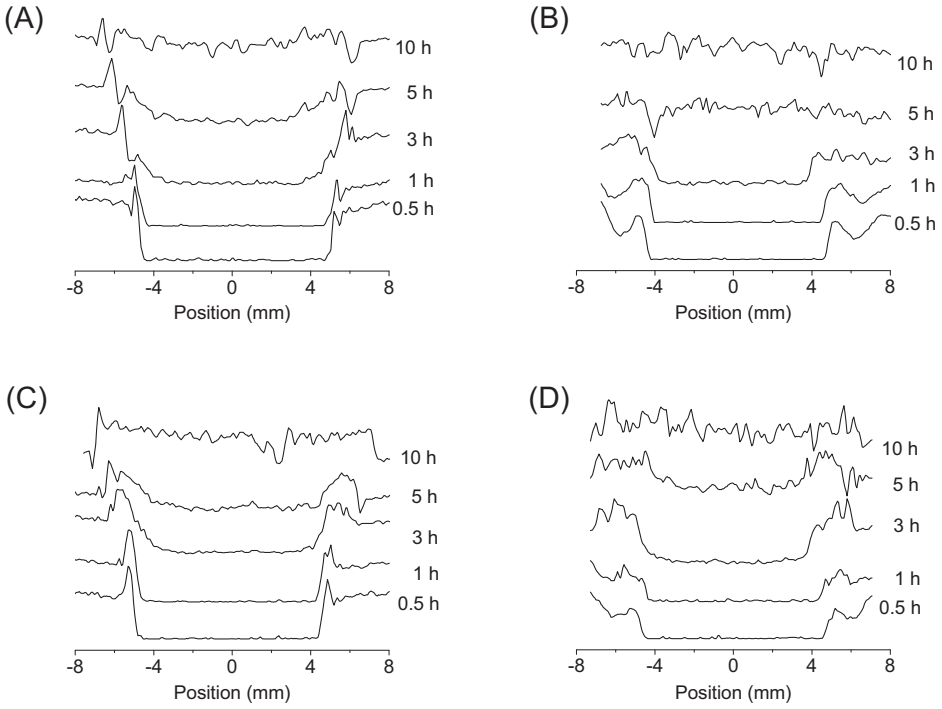


Fig. 2. The change of the proton density profiles of CMS–chitosan complex tablets immersed in (A) H_2O, (B) SGF, (C) SIF, (D) SGF–SIF at 37 °C at different immersion times.

the resultant hydrogen bonding in the polymer network restricts the movement or relaxation of the gel and keeps the integrity of the tablets. The swelling ratio in SGF is the lowest for the CMS tablets. These results fit well with previous observation of the shape and behavior of the CMS tablets (Assaad and Mateescu, 2010; Calinescu et al., 2005; Lemieux et al., 2010). In SIF and water with pH values higher than the pK_a of CMS, the carboxyl groups are ionized. Hydrogen bonds involving carboxylic groups were disrupted and an electrostatic repulsion occurred among polymer chains, allowing water to readily diffuse into the hydrogels. A higher swelling ratio was observed. A bump-shaped change in the proton density was observed in the hydrated outer layer when the gel is very loose, which is common for the CMS tablets in SIF and water (Fig. S5). The water front moves the most slowly in the case of SGF. A sharp "peak" well defines the border of a tablet at 0.5 h. The slow rate to reach equilibrium for a CMS tablet in SIF and water shows that the anionic matrix may offer limited sustained drug release.

Chitosan dissolved in acidic SGF and a thick layer of transparent gel was formed very quickly around the hard core. The size of the core decreases gradually with time while the matrix dissolves in the medium. Within 2 h the hydrogel already filled the NMR tube with a diameter of 18.2 mm. No proton signal was detected in the dry core during the process, as shown by the clear-cut feature of the proton density profile (Figs. S3 and S6). The chitosan tablets rapidly disintegrated in both SIF and H_2O, and no NMR image could be acquired to allow any measurement of the swelling ratio.

A tablet made of CMS–chitosan complex presents swelling characteristics similar to those of CHAS, but with slightly faster swelling. The features are very different from those of the individual components, CMS and chitosan. The interaction between CMS and chitosan retards the diffusion of water. The tablets of the complex swell much more slowly than those of CMS and chitosan. A gel layer was formed more rapidly in SGF than in other media and kept expanding until reaching the tube wall in 7 h (Fig. 1). The gel is mostly formed by chitosan which dissolves in SGF. At the same time, the dry core diminishes faster than in the other media. At the 5th hour, the proton density profile shows that the proton signal inside the tablets became uniform, while the tablets in the other media needed a few more hours to complete the process. When the fluid was changed from SGF to SIF, the volume of the gel layer either leveled off or decreased due to the still protonated chitosan having a strong interaction with ionized CMS.

The preparation procedure may help to explain the compact shape of the complex tablets in neutral media (H_2O and SIF) and their pronounced swelling in SGF. The chitosan solution (pH 3.6) was added to the CMS solution (pH 6.8) to prepare the complex. During the mixing process, the pH value (5.2–6.8) became close to the pK_a of chitosan. The formation of the complex was due to the electrostatic interaction between NH_3^+ and COO^- and the hydrogen bonds between the NH_2, OH and COOH groups. Since at pH 5–7 the majority of the amino groups of the chitosan were non-ionized while the carboxyl acid groups were ionized (deprotonated) when the precipitation took place, the complex formed by these two polymers may contain idle NH_2 groups (not involved in the interaction). In SGF (pH 1.2), most of the carboxylic acid groups and the amino groups were protonated, leading to the dissociation of the NH_3^+ and COO^- groups. The chitosan (non-associated) in the complex exhibited significant swelling. A similar chitosan-based complex

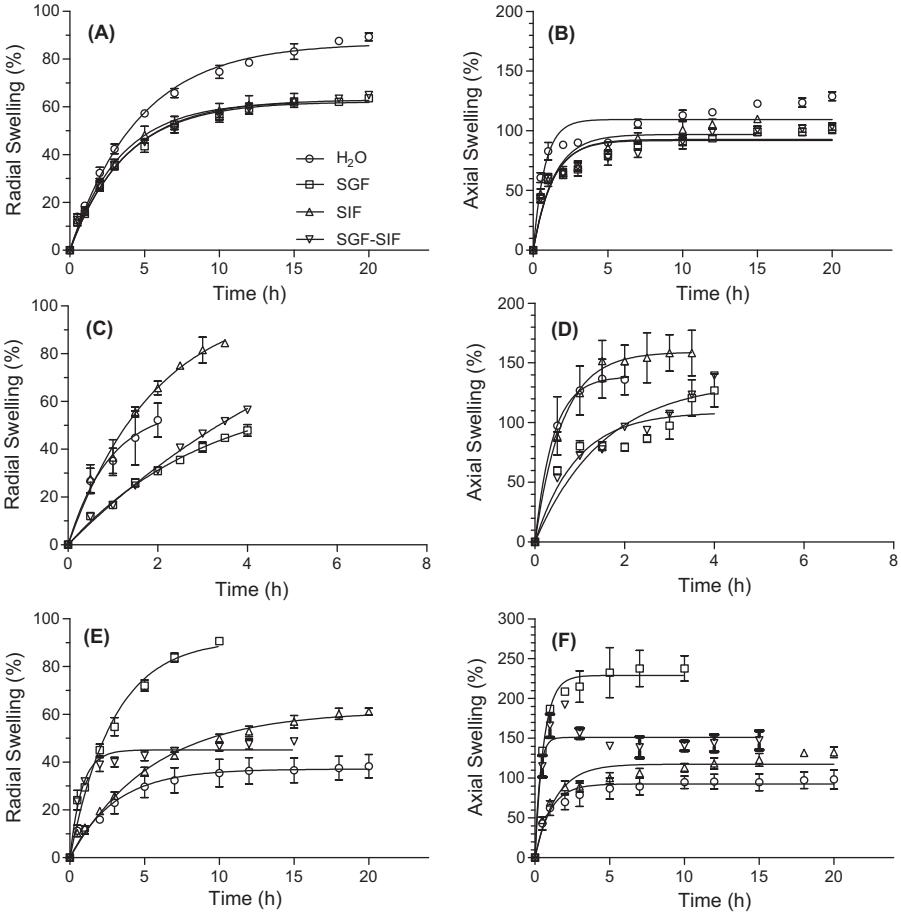


Fig. 3. The radial and axial swelling of the CHAS tablets (A and B), the CMS tablets (C and D), and the CMS–chitosan complex tablets (E and F) in H_2O (circles), SGF (squares), SIF (up triangles), and SGF–SIF (down triangles). Lines are best fits to Eq. (2). For the CMS tablets, the swelling reached equilibrium quickly within ca. 4 h.

Table 1
The swelling behaviors of the tablets made of CHAS, CMS and CMS–chitosan complex. Parameters obtained by fitting to Eq. (2).

Media	Radial dimension			Axial dimension		
	S_{max} (%)	k_s (10^{-5} s^{-1})	R^2	S_{max} (%)	k_s (10^{-4} s^{-1})	R^2
CHAS						
H_2O	86.8 ± 1.1	6.1 ± 0.2	0.992	109 ± 3	3.6 ± 0.5	0.877
SGF	62.2 ± 0.7	7.5 ± 0.3	0.989	91.8 ± 2.1	2.2 ± 0.2	0.894
SIF	62.2 ± 1.2	8.2 ± 0.4	0.985	96.9 ± 3.1	2.0 ± 0.3	0.886
SGF–SIF	63.0 ± 0.7	7.4 ± 0.3	0.990	92.7 ± 2.3	2.1 ± 0.3	0.878
CMS						
H_2O	57.4 ± 7.9	30 ± 9	0.903	139 ± 7	6.8 ± 1.5	0.932
SGF	66.6 ± 3.8	8.8 ± 0.8	0.991	109 ± 6	3.0 ± 0.6	0.841
SIF	103 ± 7	14.2 ± 1.8	0.982	159 ± 4	4.5 ± 0.5	0.963
SGF–SIF	128 ± 24	4.1 ± 1.0	0.996	135 ± 14	1.8 ± 0.5	0.937
CMS-chitosan complex						
H_2O	37.1 ± 1.2	9.2 ± 1.1	0.907	92.6 ± 2.1	2.8 ± 0.4	0.890
SGF	91.4 ± 2.8	9.6 ± 0.8	0.976	229 ± 4	4.6 ± 0.4	0.959
SIF	61.4 ± 1.1	5.0 ± 0.2	0.987	117 ± 3	2.0 ± 0.2	0.911
SGF–SIF	45.1 ± 0.7	34.9 ± 2.6	0.966	151 ± 4	9.4 ± 2.0	0.883

The measurements were carried out on triplicates; the reported values are the averages and the uncertainties correspond to the standard deviations.

with pectin (Bigucci et al., 2008) was prepared at pH 5.0 at mixing molar ratios (pectin:chitosan) of 9:1, 7:3, and 1:1. The swelling of the complex of chitosan (pK_a 6.3) and pectin (pK_a 4.0) showed significant pH dependence when the molar ratio is high. The pH effect was substantially reduced when the molar ratio decreased (Bigucci et al., 2008).

3.3. Swelling characteristics of the tablets

The radial and axial swelling data extracted from the images at different immersion times (Fig. 3) provide quantitative information of the change in shape and dimension of the tablets. In the case of SGF–SIF treatment, when the tablets are switched to SIF at 2 h, a sudden change occurs and the swelling curve is approaching the curve of SIF. This behavior is most obvious in the case of the complex tablets (Figs. 3E–F).

The percentage of the swelling of the tablets is defined by

$$S = \frac{d - d_0}{d_0} \times 100\% \quad (1)$$

where S is the percentage of swelling and d and d_0 are the dimensions (thickness or diameter) of the tablet at immersion time t and at the beginning, respectively. The swelling data can be fitted to

$$S = S_{max}(1 - e^{-k_s t}) \quad (2)$$

where S_{max} is the swelling at equilibrium, and k_s the rate constant of the swelling process.

For all the tablets, the swelling in the axial dimension was higher than that in the radial direction, and the rate constant along axial direction is an order of magnitude higher (Table 1). As expected, the swelling of the CHAS tablets did not show any pH effect, while ionic strength influenced the swelling. The dimensions of the swollen tablets in both SGF and SIF are smaller than those in distilled water (65% vs. 90% radially and 100% vs. 130% axially). An increase in the ionic strength causes a decrease in the osmotic pressures (due to the hydration of ionic species), leading to a reduced swelling. For the other three matrices, i.e., CMS, chitosan and the complex, the effect of pH was more significant than that of ionic strength (Figs. 3C–F). The swelling of the CMS tablets was lower in SGF than in neutral media due to the protonation of the COOH groups. In SGF–SIF, the tablets swelled to a similar extent as in SGF. In contrast, the swelling of the complex tablets in SGF was almost twice of those in other media (Table 1). The tablets in distilled water had the solid-like appearance due to a very slow swelling process. According to the swelling characteristics, drug could be released in a controlled way by the complex after an initial burst dissolution of the drug located near the surface of the tablet.

The swelling process of the tablets in the different media can be directly observed, even though the content of water and water penetration fronts cannot be visualized in this case. Table 2 shows the photographs of the PEC tablets in 4 different media at 2, 5 and 10 h. Several observations can be made. In pure water, the tablet swells to a less extent than in the other media. SIF is also a neutral medium, but the presence of ionic species such as K^+ and Na^+ facilitates the hydration of the tablet. It is in SGF that the tablet swells the most and the fastest. Apparently in an acidic environment such SGF, the protonation of functional groups in the polymer matrix favors the swelling of the tablet, leading to the partial dissolution of the tablets and the formation of a hydrogel. The swelling remained continuous even after a long incubation, while in other media the swelling reaches a stable plateau at shorter time intervals. When the tablet is transferred to SIF (a neutral medium) after 2 h in SGF, the swelling of tablet is slowed down, with similar dimensional change at the end as the tablet in SIF alone. The radial swelling properties of the tablets observed in the four different media are plotted as a function of time in Fig. 4. These results are in good agreement with those obtained by NMRI analyses (Fig. 3E). It is to be noted that NMRI provides additional information on the water diffusion in the tablet.

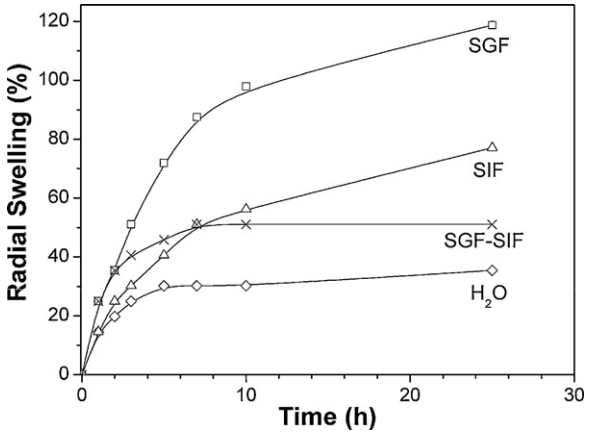
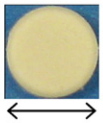


Fig. 4. The apparent radial swelling of the PEC tablets observed visually as a function of time in the four different media tested.

Table 2
Photographs showing the swelling of the PEC tablets in water, SGF, SIF and SGF–SIF (SGF for 2 h followed by replacing SGF by SIF) and at three different time intervals.

Dry Tablet	Time (h)	Medium			
		H_2O	SGF	SIF	SGF-SIF
 0.96 cm	2				
	5				
	10				

3.4. Comparison to the dissolution characteristics of the tablets

The *in vitro* dissolution experiments of monolithic tablets made of the complex loaded with 20 wt% aspirin have been carried out in a previous study (Assaad et al., 2011). It showed a sustained release up to 30 h, longer than expected. In contrast, 90% of the loaded aspirin was released in about 11 h when CMS or chitosan alone was used as the excipient (Assaad et al., 2011). Therefore, the water diffusion rate as visualized by NMRI is related to the drug release rates obtained. Slower water diffusion leads to prolonged drug release. Aspirin is slightly soluble in water and its pK_a is 3.5 (Dewick, 2006; Schrör, 2009). The relatively long sustained drug release of aspirin from the complex tablets can be a result of a binding interaction with either CMS or chitosan in acidic and neutral media, respectively. During the first 2 h in SGF, the carboxyl acid groups of aspirin form hydrogen bonds with CMS, which slowed down the drug release. In SIF, the ionic interaction between aspirin and CMS may become more predominant than the hydrogen bonding in the system, reducing the diffusion rate of aspirin toward the outside of the matrix. In the case of acetaminophen (Assaad et al., 2011), a drug with higher water solubility and with higher pK_a (9.5) (Dewick, 2006), the longer release was afforded by the chitosan excipient alone due to the formation of an outer layer hydrogel in SGF. The CHAS tablets showed a similar release profile of acetaminophen to those of the complex (Assaad et al., 2011; Wang et al., 2010).

4. Conclusion

Tablets made of both CMS and chitosan have demonstrated pH-dependent swelling capabilities. The comparison of the tablets revealed that the tablets made of the CMS–chitosan complex presented a combined benefit of a lower swelling in acidic media than the chitosan tablets and a slower water uptake than the CMS tablets in neutral media. A large decrease in swelling (60% radially and 150% axially) in neutral media is observed by NMRI for the complex tablets in comparison with those of CMS and of chitosan. Similar to CHAS, the complex tablets can keep their integrity even after their swelling reaches an equilibrium. The interaction between the carboxyl groups of CMS and amine groups of chitosan showed a stabilizing effect (in terms of limited swelling) similar to that of hydrogen bonding in the case of covalently cross-linked starch. The *in vitro* dissolution experiments presented a particularly slow release of aspirin from the monolithic tablets with 20 wt% drug loading (Assaad et al., 2011). The results showed that the CMS–chitosan complex is a promising polymer excipient for sustained drug release, by partially retaining the gastro-protective effect of CMS and by modulating its solubility in neutral media through ionic association with chitosan. This behavior makes the novel complex a good excipient to colon delivery. Its swelling properties may be modulated by pH and ionic strength of the processing medium and by the molar ratio of the two components.

Supporting information

Figures providing the NMR images, the proton density profiles, and the comparison of the radial and axial swelling of the CHAS, CMS, and CMS–chitosan complex tablets.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijpharm.2011.08.008.

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