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Cross-linked high amylose starch derivatives for drug release II. Swelling properties and mechanistic study

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Abstract

Acetate (Ac-), aminoethyl (AE-), and carboxymethyl (CM-) high amylose starch cross-linked 6 (HASCL-6) derivatives were previously shown to control the release of drugs over 20 h from monolithic tablets highly loaded (up to 60% drug). This report describes the swelling characteristics, which allow a better understanding of the mechanisms involved in the control of the drug release from the said polymeric matrices. The tablet swelling of HASCL-6, Ac-HASCL-6, and AE-HASCL-6 was found to not be affected by the ionic strength and by the pH between 1.2 (gastric) and 7 (intestinal), whereas the swelling of CM-HASCL-6 was shown to depend on both ionic strength and pH of the release medium. For all the studied polymers the drug loading did not change the equilibrium swelling ratio but affected the initial swelling velocity, seemingly due to the competition between drug and polymer for water uptake, a phenomenon probably influenced by the loading and the drug solubility. It was also shown that the increase of ionic strength would slightly increase the drug release time probably by decreasing the amount of free water still available to solubilize the drug present into the matrix.

Keywords: High amylose starch derivatives; Polymeric networks; Controlled release mechanisms; Swelling properties

1. Introduction

Cross-linked high amylose starch (HASCL) was introduced in the middle 90s under the trade mark of Contramid™ as excipient for drug controlled release (Lenaerts et al., 1991; Mateescu et al., 1994). Tablets made by dry compression of HASCL-6 with 20% drug loading were previously shown to control the release over 18–24 h (Dumoulin et al., 1998). Partial substitution of the hydroxylic groups of HASCL-6 with ionic (carboxymethyl and aminoalkyl) groups as well as with less polar (acetate) groups was recently shown to allow an increase of drug loading capacity of the matrix up to 60% (Mulhbacher et al., 2001). It was also shown that the carboxylic (CM-HASCL-6) or amino (AE-HASCL-6) derivatives are able to modulate the release of drug by ionic interactions whereas acetate groups can modulate the release by enhancing hydrophobic character of the matrix (Mulhbacher et al., 2001). Release kinetics from various formulations based on different polymers showed that the dissolution depends on several parameters such as the

Abbreviations: CM-HASCL-6, carboxymethyl high amylose starch cross-linked 6[1] AE-HASCL-6, aminoethyl high amylose starch cross-linked 6[1]; Ac-HASCL-6, acetate high amylose starch cross-linked 6[1]

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[1] Cross-linking degree (expressed in grams of bifunctional agent used to cross-link 100 g of polymer).

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drug solubility, drug loading (Kim, 1998; Gorner et al., 1999; Govender et al., 1999; Neau et al., 1999), polymer characteristics (Kim, 1998; Ramkisoon-Ganorkar et al., 1999) and/or presence of additional excipients (Durig and Fassihi, 1997; Sintov et al., 2000). The effect of excipient composition in terms of polymer molecular weight (Bronsted and Kopecek, 1992) or hydrophilicity (Ranade, 1990) and the role of neutral, anionic or cationic matrices in the drug release kinetics, was deeply analyzed (Khare and Peppas, 1995). Previous studies with HASCL have showed the important role of hydroxyl groups and of hydrogen bonding (Dumoulin et al., 1998) in the organization of the high amylose starch matrices contributing thus to the control of the drug release (Ispas-Szabo et al., 2000). It was now of interest to see the impact of various polar and less polar functional groups introduced by polymer derivatization on the network organization and on the release mechanisms.

The drug release from hydrophilic matrices is controlled by three main mechanisms: (i) the polymer swelling and drug solubility, (ii) the drug diffusion, and (iii) the matrix erosion. These mechanisms can be influenced by the ionic strength and/or the pH of dissolution media. For polyhydroxylic polymers, particularly for those involved in hydrogen bonding and carrying polar/non-polar groups, the swelling analysis can give useful information for their behavior in aqueous fluids. Furthermore, the matrix swelling in gastric and intestinal fluids is of determinant relevance for the drug liberation. The swelling behavior of ionic polymers depends on the pH and the ionic strength of medium. This aspect can be important since such excipients can be used in formulation for drug release at a specific site (Colombo et al., 2000). With increasing pH, the swelling volume of anionic polymers is expected to increase and that of cationic polymer to decrease. In the case of increasing ionic strength the swelling volume of either anionic or cationic polymer networks will decrease (Khare and Peppas, 1995). The swelling can also depend on the drug solubility and tablet loading (Siepmann and Peppas, 2000; Durig and Fassihi, 2002). The swelling analysis can represent a first step in the elaboration of a mathematical model predicting the release kinetics.

The aim of this study was to evaluate the impact of the HASCL-6 derivatization with aminoethyl, carboxymethyl, and acetate groups on the swelling kinetics in various pH and ionic strength conditions and at different drug loading. These aspects were evaluated with two model drugs (acetaminophen and uric acid) differing in their solubility. The initial swelling velocity, the swelling ratio and the swelling *n* exponent were calculated from swelling measurements.

2. Materials and methods

High amylose starch (Hylon VII) was from National Starch (USA). Monochloroacetic acid, chloroethylamine hydrochloride, acetic anhydride and the other chemicals were reagent grade and used without further purification.

2.1. Synthesis of HAS derivatives

The syntheses were realized in conditions previously described by Mulhbacher et al. (2001).

2.1.1. Synthesis of CM-HASCL-6

An amount of 70 g of HAS was first suspended in 170 mL of water, completed with 235 mL of NaOH 1.5 M and then cross-linked by 3.5 mL of epichlorohydrin for 40 min at 50 °C. The reaction media was then treated with 5 g of monochloroacetic acid at the same temperature for 1 h (Schell et al., 1978). When the reaction time was ended, the CM-HASCL-6 suspension slurry was neutralized with acetic acid at room temperature, then washed by treatment with an equal volume of acetone/water 85/15 (v/v), kept 20 min and filtered. The washing procedure was repeated by resuspending and filtration two more times with 1/2 equivalent volume of acetone/water 70/30 (v/v) and then with 85/15 (v/v). The remaining wet gel was dried with pure acetone (1/2 equivalent of final reaction volume three times).

2.1.2. Synthesis of AE-HASCL-6

A similar procedure as for CM-HASCL-6 was utilized. The same amount of HAS was first cross-linked and then treated with 86 g chloroethylamine chlorohydrate (rapidly solubilized in a minimal volume of water) (Mateescu et al., 1988) for 2 h at 70 °C with the mention that the pH was maintained between 9 and 10 during the synthesis (with small amounts of 5 M NaOH).

2.1.3. Synthesis of Ac-HASCL-6

A procedure similar to that used for CM-HASCL-6 derivatives was used for synthesis of acetate derivatives. An amount 70 g of HAS was treated with epichlorohydrin and then with 70 mL of acetic anhydride (Jarowenko, 1986) at room temperature for 1 h. An erosion phenomenon occurring during the swelling of this highly substituted Ac-HASCL-6 made impossible the evaluation of the swelling parameters. For this reason, another Ac-HASCL-6 derivative, less substituted, was obtained in similar conditions by treatment with 15 mL of acetic anhydride.

2.2. Evaluation of substitution degree of derivatives

The substitution degree was expressed in mmol of substituent/g of powder (mmol/g). Practically, the carboxylic groups of CM-HASCL-6 were potentiometrically titrated with 0.1 M NaOH (Corning pH-meter). The amine groups of AE-HASCL-6 were colorimetrically determined with trinitrobenzene sulfonic acid (TNBS) (Habeeb, 1966). The acetate groups of Ac-HASCL-6 were assayed by ^{1}H NMR, as previously described (Mulhbacher et al., 2001). The obtained substitution degrees were 0.092 mmol/g for CM-HASCL-6, 0.049 mmol/g for AE-HASCL-6, and 0.029 mmol/g for Ac-HASCL-6 (for the less substituted derivative). The substitution degrees were of comparable magnitude and thus the observed characteristics of the polymeric derivatives were ascribed to the nature of the functional groups, rather than to substitution degrees.

2.3. Swelling tests

Tablets (200 mg) were obtained by dry compression at 29.4 kN in a Carver hydraulic press using a punch of 13 mm diameter. Irrespective to the polymeric composition or drug loading, dry tablets dimensions were of 12.72 ± 0.22 mm diameter and 1.23 ± 0.08 mm thickness. The ratio of 1/10 thickness/diameter of tablet was essential to be in conditions of a monodimensional penetration of water (Khare and Peppas, 1995). In this case, the tablet hydration appends via its two faces (first dimension) and the contribution of the two other dimensions (the cylindrical surface) to the hydration can be neglected. Swelling kinetics of the tablets were evaluated by measuring the weight gain of swollen tablets at different times of incubation (Moussa et al., 1998). They were analyzed as a function of pH, ionic strength, and drug (acetaminophen) loading.

2.3.1. The pH effects

For the pH swelling studies, tablets (composed from the polymer only) were incubated (37 °C, 50 rpm) in 50 mL media of pH 1.2 (KCl/HCl solution), pH 3, pH 5 and pH 7 (citric acid/dibasic phosphate buffer), and pH 10 (borate buffer), all at 0.2 M ionic strength.

2.3.2. The ionic strength effects

For the ionic strength studies, citric acid/dibasic phosphate buffers having constant pH (pH 7), and different ionic strength (0.02, 0.1, 0.2, and 0.4 M) were used. The ionic strength was adjusted with NaCl or by dilution in the case of citric acid/dibasic phosphate buffer pH 7.

2.3.3. The loading effects

For the acetaminophen loading studies, two series of tablets were formulated with 10 and 20% acetaminophen, and incubated (37 °C, 50 rpm) in 50 mL citric acid/dibasic phosphate buffer pH 7, ionic strength 0.2 M. The less polar uric acid (10% loading) as tracer was studied similarly. No stearate lubricants were used for these tablet formulations.

2.4. Dissolution tests in vitro

Tablets (200 mg) of HASCL-6 derivatives with acetaminophen (10 and 20%) or uric acid (10%) were obtained by direct compression of mixed dry powders (polymeric excipient and drug, thoroughly homogenized) at 2.3 T/cm^2 in the Carver hydraulic press. The release kinetics were followed in a Distek® dissolution 2100A, paddle system (USP conditions at 37 °C, 50 rpm, in 1 L of citric acid/dibasic phosphate buffer pH 7, ionic strength 0.2 M), with UV detection at 280 nm for acetaminophen and 292 nm for uric acid. Tracer dissolution tests were carried out with $n = 3$ tablets for each HASCL-6 derivative.

2.5. Data analysis and quantification

The kinetics parameters were calculated from the diffusion equation $M_t/M_{\inf} = k \times t^n$, where M_t is the

Table 1
The *n* exponent obtained from the swelling kinetics and from the release kinetics of tablet containing 10% and 20% acetaminophen

Matrices	*n* exponent			
	Swelling (6 h)		Release (6 h)	
	10% acetaminophen	20% acetaminophen	10% acetaminophen	20% acetaminophen
HASCL-6	0.643 ± 0.008	0.678 ± 0.005	0.945 ± 0.029	0.921 ± 0.017
Ac-HASCL-6	0.621 ± 0.018	0.621 ± 0.009	0.885 ±0.030	0.9844 ± 0.054
AE-HASCL-6	0.647 ± 0.007	0.664 ± 0.034	0.971 ± 0.071	1.018 ± 0.019
CM-HASCL-6	0.728 ± 0.022	0.725 ± 0.005	0.925 ± 0.038	0.965 ± 0.085

Table 2
The *n* exponent and 75% time release obtained from tablets containing 10% acetaminophen release in dissolution media of 0.02 and 0.1 M ionic strength

Matrices	Release: 10% acetaminophen			
	n exponent		75% release time (h)	
	Ionic strength (0.02 M)	Ionic strength (0.1 M)	Ionic strength (0.02 M)	Ionic strength (0.1 M)
HASCL-6	0.939 ± 0.043	0.945 ± 0.029	2.92 ± 0.14	3.00 ± 0.01
Ac-HASCL-6	0.944 ± 0.036	0.885 ± 0.030	3.41 ± 0.14	3.00 ± 0.25
AE-HASCL-6	1.086 ± 0.077	0.971 ± 0.071	2.83 ± 0.14	3.25 ± 0.25
CM-HASCL-6	1.026 ± 0.065	0.925 ± 0.038	2.67 ± 0.14	3.08 ± 0.14

Table 3
The *n* exponent obtained from tablets swelling containing 10% acetaminophen or 10% uric acid and 75% time release of respective drugs

Matrices	*n* exponent swelling		75% release time (h)	
	Swelling (6h), 10% acetaminophen	Swelling (12h), 10% uric acid	10% acetaminophen	10% uric acid
HASCL-6	0.643 ± 0.008	0.585 ± 0.007	3.00 ± 0.00	8.66 ± 0.58
Ac-HASCL-6	0.621 ± 0.018	0.578 ± 0.031	3.00 ± 0.25	8.5 ± 0.87
AE-HASCL-6	0.647 ± 0.007	0.602 ± 0.015	3.25 ± 0.25	7.83 ± 0.76
CM-HASCL-6	0.728 ± 0.022	0.708 ± 0.014	3.08 ± 0.14	7.5 ± 0.01

mass of water absorbed at time t, M_{inf} is the mass of water absorbed at equilibrium, t is the time, k is a constant giving the velocity, and the exponent n is a constant giving the kinetic order of swelling (Khare and Peppas, 1995). The comparison between the n exponent obtained from the drug release kinetics and that obtained from the swelling study may provide information for the understanding of the mechanism governing the complex process of release control. For the swelling kinetics, the mass of water absorbed at equilibrium (M_{inf}) was considered at the time corresponding to complete drug release (Tables 1–3). The initial swelling velocity calculation was based on the first 3 h of the swelling kinetics; in fact it corresponds to the mean of the weight gain by hour during the first 3 h. The equilibrium swelling ratio was calculated as the weight of swelling tablet at equilibrium divided by the weight of the dry tablet. For the release, the same diffusion equation was considered with the mention that M_t is the amount of tracer released at time t, M_{inf} is the amount of drug released at equilibrium (Peppas, 1985).

3. Results and discussion

The swelling properties of HASCL-6, CM-HASCL-6, AE-HASCL-6, and Ac-HASCL-6 matrices as a function of the pH and ionic strength of the dissolution media and drug loading of the tablets, where described by the swelling ratio, initial swelling velocity, and value of the n exponent (the kinetic order of the swelling).

The equilibrium swelling ratio values of HASCL-6 and Ac-HASCL-6 were the lowest, followed in increasing order by AE-HASCL-6 and CM-HASCL-6 (Fig. 1). The swelling ratio of the CM- derivative was at least 1.5 times bigger than that of AE- and approximately twice the value of Ac- and HASCL-6. The differences in swelling ratio obtained for HASCL-6 and its derivatives can be explained by the new chemical properties acquired following the substitution. The Ac- derivative and HASCL-6 presented almost the same swelling ratio despite the fact that the acetyl groups can hinder the hydrogen association of the amylose, creating thus some amorphous region in the matrix which could be filled and swollen by water. Higher equilibrium swelling ratio values were found for AE- and CM- derivatives which have more hydrophilic functional groups. The swelling ratio of the HASCL-6 and its Ac- and AE- derivatives did not change with the pH increase from 1.2 to 7 whereas for CM-HASCL-6 the swelling was pH dependent, increasing with the pH increase (Fig. 1a). The swelling ratio of each polymeric material markedly increased at pH 10 (Fig. 1a), probably due to the fact that hydroxyl groups of high amylose starch and derivatives, still involved in hydrogen bonds (chain–chain) at pH 1–7, begin to be deprotonated at values between pH 7–10. Surprisingly, in the case of AE-HASCL-6 tablet, there was no decrease in swelling ratio with the increase of pH as expected for basic polymers in gel slurry. This seems to be an argument in favor of hypothesis of hydrogen bonding mostly occurring in tablet forms (Dumoulin et al., 1998; Ispas-Szabo et al., 2000).

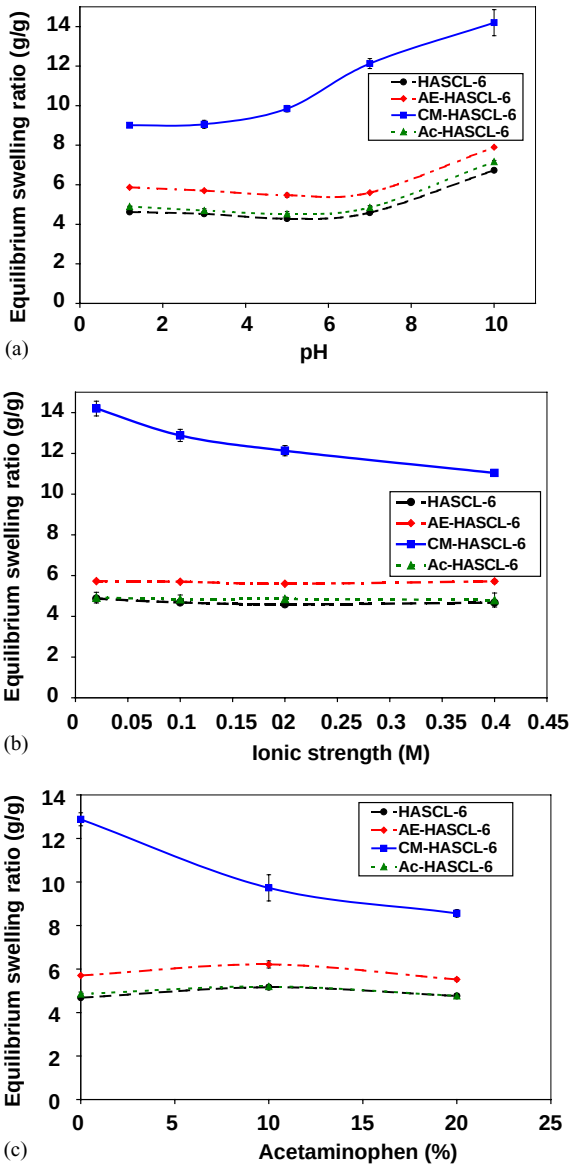

Fig. 1. Equilibrium swelling ratio as a function of pH (a), ionic strength (b), and acetaminophen tablet loading (c). The tablets (200 mg) were obtained by dry compression, and their swelling kinetics were followed in appropriated media (indicated in Section 2) at 37 °C, 50 rpm.

At pH 7, the ionic strength seems to have no effect on the swelling ratio of HASCL-6 and its Ac- and AE-derivatives, whereas for CM-HASCL-6 the increase of ionic strength lead to a marked decrease of the swelling ratio (Fig. 1b). This can be due to the higher initial hydration volume of carboxyl groups, which will be in competition with the salt present in high ionic strength media for the water uptake decreasing thus the swelling of CM-HASCL-6.

No effect was observed on the swelling ratio of HASCL-6 and its Ac- and AE- derivatives at increasing drug loading whereas for CM-HASCL-6 swelling ratio was diminished (Fig. 1c) due to the decrease of the available free water. The acetaminophen dissolution and release will require part of the water available for the high hydration of CM-HASCL-6 tablets.

The pH and ionic strength exerted similar effects on the initial swelling velocity (Fig. 2a and b) as on the equilibrium swelling ratio (Fig. 1a and b). In fact, the

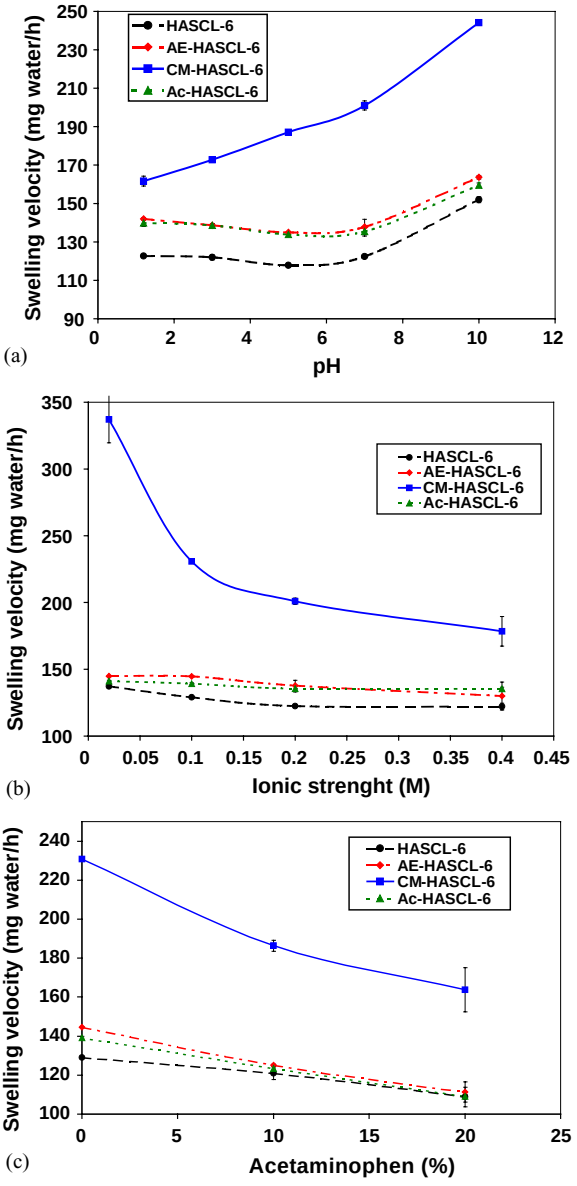

Fig. 2. Swelling velocity as a function of pH (a), ionic strength (b), and acetaminophen tablet loading (c). The tests were run in the same conditions as mentioned in Fig. 1.

initial swelling velocity of HASCL-6 and its Ac- and AE- derivatives was not affected by the ionic strength and the pH, except high pH 10. The CM-HASCL-6 initial swelling velocity was found to decrease with the increase of ionic strength and acetaminophen loading and to increase with the increase of pH, as in the case of the equilibrium swelling ratio. The swelling velocity for HASCL-6, AE-HASCL-6, and Ac-HASCL-6 were slightly decreased (Fig. 2c) at increasing acetaminophen loading (differing thus to the case of swelling ratio almost unchanged (Fig. 1c) at increasing drug loading). Again, the explanation could reside in the competition between the polymer and drug for hydration. This competition would keep low the swelling velocity of the polymer, but would not affect the swelling ratio at equilibrium.

The lowest initial swelling velocity was found for HASCL-6, followed in order by Ac-HASCL-6 and AE-HASCL-6, and CM-HASCL-6 (Fig. 2). The Ac-HASCL-6 equilibrium swelling ratio was lower than that of AE-HASCL-6 whereas its initial swelling velocity was similar to that of AE-HASCL6. Acetyl groups of Ac-HASCL-6, which are not involved in hydrogen bonding, may create some space within the matrix, allowing thus water to enter quickly in the tablet without having to dispatch hydrogen bonding. Differently, amino functions of AE-HASCL-6, also generating some space between the chains within the matrix, contribute at the same time to network stabilization by hydrogen association, which must be displaced by water.

The values of exponent n, calculated from the swelling kinetics presented the same type of dependency upon the pH and ionic strength as the swelling ratio at equilibrium (Fig. 1a and b). Differently to decreasing swelling ratio (Fig. 1c) and initial swelling velocity (Fig. 2c), the n exponent was found to slightly increase at higher acetaminophen loading. The n exponent values for the Ac-HASCL-6 ($n \approx 0.55$) and for HASCL-6 ($n \approx 0.57$) suggested almost a Fickian profile of swelling kinetics whereas for AE-HASCL-6 ($n \approx 0.62$) corresponded rather to an anomalous swelling kinetics. The n exponent of CM-HASCL-6 was of 0.7 (anomalous profile) in conditions allowing a low swelling and grew to 0.8 (closer to linear profile) in a medium ensuring a higher swelling.

The n exponent values obtained from swelling were markedly different to those obtained from the release kinetics at drug loading of 10 or 20% acetaminophen (Table 1), suggesting that the release was controlled not only by the swelling but also by another mechanism (i.e. drug diffusion).

The increase of the ionic strength of dissolution medium from 0.02 to 0.1 M induced only a slight

decrease of the *n* exponent value (obtained from the analysis of release kinetics) and a minor increase of the time for 75% release ($t_{75\%}$) of the drug (Table 2). This behavior suggests that the increase of the ionic strength had no effect on the swelling of HASCL-6 and its Ac- and AE- derivatives (Figs. 1b and 2b). The minor increase of the release time seems probably related to the effect on the solubility of acetaminophen (lower solubility at higher ionic strength). The *n* exponent values 0.8 and 0.9 can be explained by the fact that the tablets (as shown in the Section 2) are very thin. Such tablet will release the drug very quickly because the majority of the drug is on the surface or very close to the surface. The release kinetics was in this case close to order one.

For uric acid, which is less soluble than the acetaminophen, the *n* exponent obtained from the swelling kinetics showed no statistical difference but the release time for 75% dissolution ($t_{75\%}$) is significantly higher compared with those of acetaminophen (Table 3). This show that the solubility of the molecule (drug) used in formulation would moderately influence the polymer swelling, via competition for the water uptake.

In conclusion, the swelling of HASCL-6, Ac-HASCL-6 and AE-HASCL-6 was not affected by the variation of ionic strength and pH in the physiological range (1.2–7). The ionic strength seems however to influence the solubility of the drug (higher ionic strength moderately decreasing the drug solubility). Differently, the swelling of CM-HASCL-6 was found to increase with increasing pH and decrease at higher ionic strength. For all these new polymeric excipients the drug loading from 10 to 20% did not change the equilibrium swelling ratio but affected the initial swelling velocity due to the competition between the drug and the polymers for the water uptake, which has an impact on the drug dissolution.

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