Carbohydrate Research 344 (2009) 1325–1331

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Preparation and characterization of a novel starch-based interpolyelectrolyte complex as matrix for controlled drug release

Héctor J. Prado [a,c], María C. Matulewicz [a,*], Pablo R. Bonelli [b], Ana L. Cukierman [b,c]

[a] Departamento de Química Orgánica (CIHIDECAR-CONICET), Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Ciudad Universitaria, (C1428EGA), Buenos Aires, Argentina
[b] PINMATE-Departamento de Industrias, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Ciudad Universitaria, (C1428EGA), Buenos Aires, Argentina
[c] Cátedra de Farmacotecnia II, Departamento de Tecnología Farmacéutica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 956, (C1113AAD), Buenos Aires, Argentina

ARTICLE INFO

Article history:
Received 21 March 2009
Received in revised form 17 April 2009
Accepted 27 April 2009
Available online 3 May 2009

Keywords:
Cationized starch
Kappa-carrageenan
Interpolyelectrolyte complex
Ibuprofen
Matrix system
Controlled release

ABSTRACT

A novel cationized starch-based interpolyelectrolyte complex (IPEC) was formed using kappa-carrageenan as the counter polyion. Characterization of the product by turbidity measurements and elemental analyses indicated a 1:1 interaction of the repeating units. FT-IR spectra for the IPEC showed some differences in comparison with either IPEC constituents or physical mixture. The swelling of tablets obtained by direct compression was independent of pH, and a maximum value of 742% was attained after 24 h. The performance of the IPEC as matrix for controlled release of ibuprofen indicates that drug delivery takes place in a zero-order manner. Experimental dissolution data in the buffer stage were properly represented by a model accounting for contributions of Fickian diffusion and relaxation phenomena; this model suggests that the former predominates over the latter, for the modeled range.

1. Introduction

Starch is known to produce low toxicity products that are biodegradable and quite stable in biological environments. Due to the cost-effective attraction of starch-based products, they can be important materials for use in drug delivery applications. However, in oral administration, native starch is almost completely broken down after its ingestion.[1] In addition, the use of native starch as an excipient is limited due to its low compactibility leading to the formation of weak tablets subject to capping.[2]

To improve the properties of starch as a controlled release matrix, chemical modifications of its functional groups have been proposed. A common modification is chemical cross-linking with epichlorohydrin (a bifunctional agent).[1,3,4] Other researchers introduced, after the crosslinking step, cationic (aminoethyl), anionic (carboxymethyl), or acetate groups to further modify the matrix behavior.[5]

In recent years, there has been an increasing interest in physically cross-linked hydrogels. The main reason is to avoid the use of toxic chemical cross-linking agents to prepare such hydrogels. These agents have to be subsequently removed from the gels before application.[6,7] Thus, the preparation and evaluation of starch-based interpolymer complexes by hydrogen bonding with polyacids have also been reported.[8]

Starches conveniently modified by the introduction of cationic groups could be easily crosslinked to form hydrogels by the interaction with an anionic polymer; this kind of complex is known as an interpolyelectrolyte complex (or IPEC). IPECs form readily between most polyanions and polycations and are constituted by ionic association of repeating units on the polymer chains.[9]

On the other hand, different types of carrageenans have been employed for controlled release applications. Gupta et al.[10] used lambda- and iota-carrageenan in its pure form as matrix, while other researchers used carrageenans as part of IPECs. In this sense, Tapia et al.[11] employed predominantly kappa with a lower amount of lambda carrageenan and chitosan, whereas we previously explored the use of kappa-carrageenan and Eudragit E PO for IPEC formation.[12]

IPEC systems involving a variety of anionic and cationic macromolecules have been formed and characterized. Nevertheless, studies devoted to IPECs for controlled release applications are still rather scarce.[11–16] Furthermore, to the best of our knowledge, cationized starch for IPECs formation has not been previously investigated.

Herein, we report a novel IPEC between a commercial cationic corn starch (MS), cationized by the introduction of a 2-hydroxy-3-(*N*,*N*,*N*-trimethylammonium)propyl group, with a degree of

* Corresponding author. Tel./fax: +54 11 45763346.
E-mail address: cristina@qo.fcen.uba.ar (M.C. Matulewicz).

0008-6215/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2009.04.026

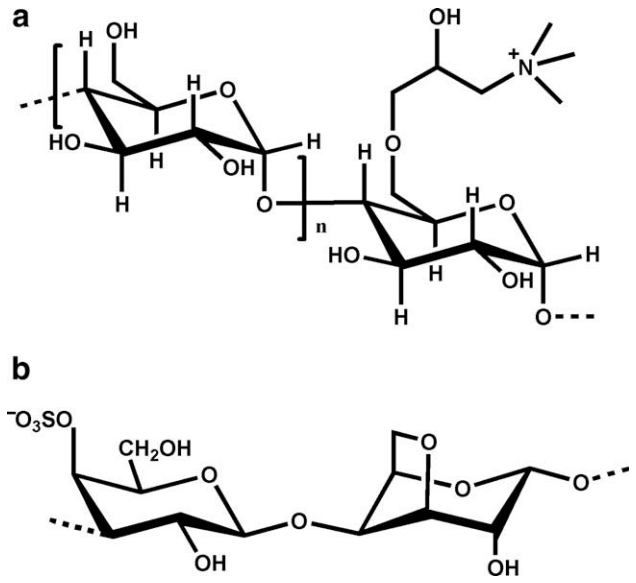

Figure 1. One possible repeating unit of modified (cationized) starch (MS) (a) and repeating unit of kappa-carrageenan (KC) (b).

substitution of 0.04 (amylose–amylopectin ratio = 27:73) (Fig. 1a), and kappa-carrageenan (KC) (Fig. 1b) as the counter-polyion. We also characterized the complex formed, and tested its performance as a matrix for controlled release of drugs, using ibuprofen (IBF) as a model.

2. Results and discussion

Turbidity measurements were initially employed to study the formation of the IPEC. Figure 2 shows the turbidimetric titration curve of a solution of MS with a solution of KC, and of a solution of KC with a solution of MS, where the relative turbidity is plotted as a function of the MS:KC molar ratio for a fixed final volume. The maximum turbidity was found for MS:KC molar ratio of 1:1, indicating that in this point equivalent quantities of both polymers reacted. The similarity of both curves and the same point of maximum turbidity are in agreement with the fact that IPEC composition is independent of the order of mixing.

The interaction or binding ratio of each component in the solid IPEC was confirmed by elemental analysis. The experimental values and those theoretically calculated by considering a 1:1 interaction of the repeating units (Fig. 1) are reported in Table 1. As seen, experimental and calculated results were alike.

The FT-IR spectra of MS–KC physical mixture and of IPEC were very similar to those corresponding to MS (not shown). This result is consistent with the composition of the physical mixture and IPEC that are constituted by 91% w/w of MS. The IPEC spectrum, however, presented small differences when compared with the spectrum of the physical mixture (Fig. 3): the band at 850 cm^{-1} assigned to the sulfate group of KC[17] shifted to 835 cm^{-1}, while the band at 1491 cm^{-1} assigned to the C–N bond of MS[18] shifted to 1480 cm^{-1}. These displacements could be due to ionic interactions between the sulfate groups and the quaternary ammonium groups in the IPEC.

The thermograms of MS and KC exhibited glass transition temperatures (T_g) of 90.2 °C and 82.4 °C, respectively. These values are in agreement with published data.[19,20] The IPEC presented a T_g of, 119.1 °C. A higher glass transition temperature is expected for a system with decreased mobility, due to interpolymer interaction.[14]

Typical SEM micrographs of MS, KC and of the IPEC are shown in Figure 4; the irregular shape of the IPEC particles, preliminary seen by optical microscopy, was also observed.

The Brunauer, Emmet, and Teller (BET) area determined for the IPEC was 0.58 $m^2\ g^{-1}$. This value agrees with a non-porous structure presenting a mean volume surface diameter (d_{vs}) of 91 μm, as calculated by optical microscopy[21] and observed by SEM. The static angle of repose measured was 38°, indicating a fair flowing

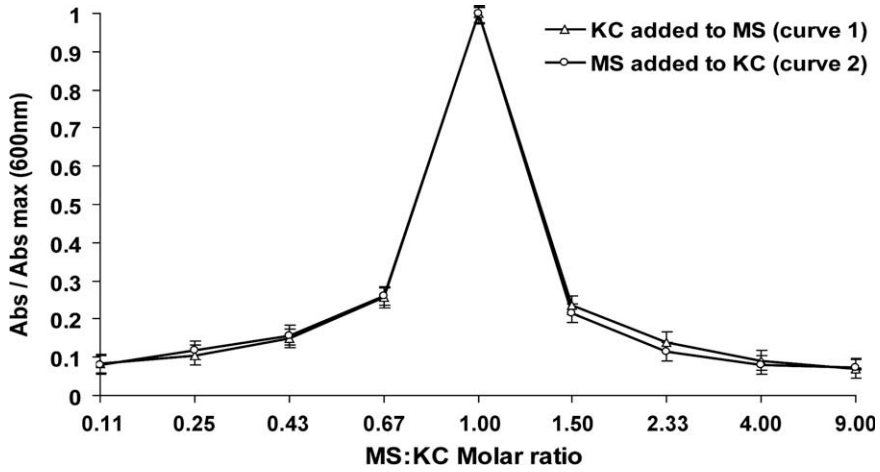

Figure 2. Turbidity of the MS–KC system as a function of the composition of the mixture and the mixing order.

Table 1
Elemental analyses of the IPEC

n	Experimental value, %				Calculated value, %				Molar ratio MS:KC
	C	H	N	S	C	H	N	S	
1	42.61	6.30	0.31	0.69					
2	44.87	6.17	0.33	0.74					
Mean	43.74	6.24	0.32	0.72	44.30	6.17	0.31	0.70	1:1

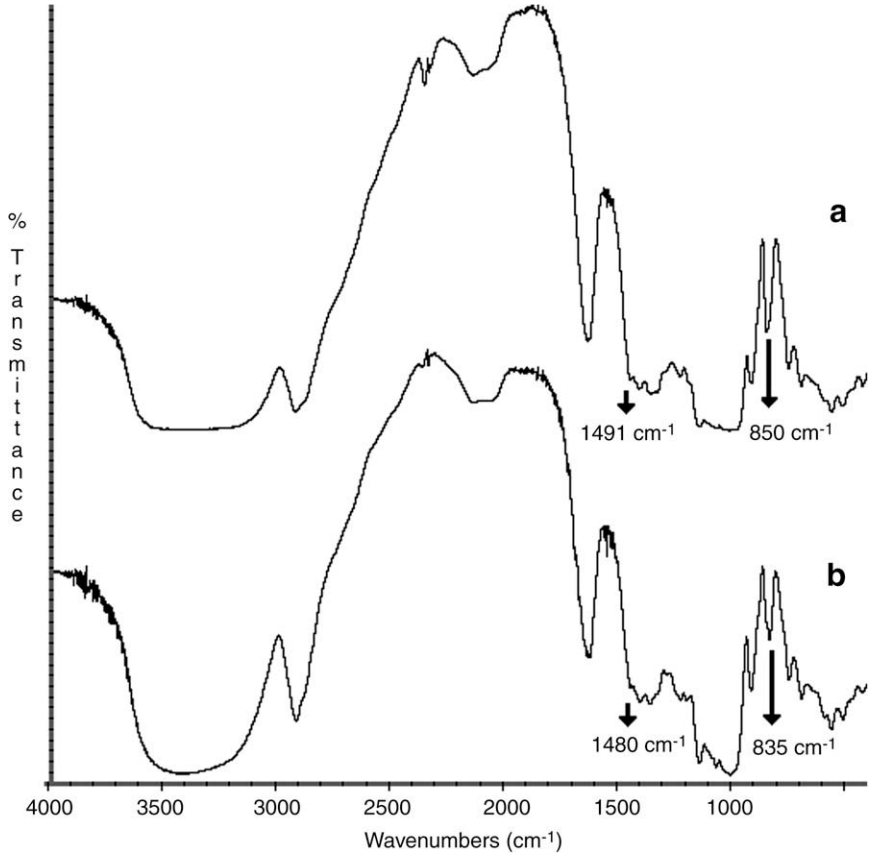

Figure 3. FT-IR spectra of (a) MS–KC physical mixture, and (b) IPEC.

material (aid not needed).[22] The compactibility profile (Fig. 5) showed that the material presented good compactibility and that adequate values of hardness could be attained by applying low compressional pressures.

During the swelling test (Fig. 6), the IPEC tablet maintained its integrity in agreement with the formation of a hydrogel-type structure. In the first stage of the experiment (acidic medium), a rapid swelling was observed during the first hour. Then, the swelling increased more slowly and a value of 380% was reached at the end of this stage. At time = 2 h, the buffer stage began and the degree of swelling continuously increased, at a rate similar to that corresponding to the two last determinations of the acid stage. An equilibrium value of swelling of 742% was observed at time = 24 h. The erosion of the IPEC tablets after 24 h was 4.2%; this indicates that erosion is less important than swelling for the IPEC, at least, for the experimental conditions employed.

The degree of substitution (DS) of the two polymers used to prepare the IPEC is very different: MS presents a DS of 0.04 (confirmed by elemental analysis), which means that 1 of 25 units of glucose is modified with a cationic group. KC, however, has a DS of 0.5 (1 of 2 units of galactose is substituted with a sulfate group). This could allow MS to eventually form long hydrophilic loops of glucose protected from disentanglement by means of the physical crosslinking with KC. The described structure is consistent with the high swelling observed. In addition, the similar rate of swelling between the acidic and buffer stages could be attributed to the fact that the two polymers involved present ionic groups (quaternary ammonium and sulfate) whose ionization is independent of the pH.

The swelling/erosion behavior of the MS–KC physical mixture tablets was completely different. Swelling reached a maximum of 317% at time = 0.5 h. Extensive turbidity of the medium observed from the initial minutes of the experiments provided evidence of erosion. At time = 2 h, the tablet was completely disintegrated. Starch constitutes an important class of tablet disintegrant.[18] Moreover, in 0.1 M hydrochloric acid solution, both polysaccharides acting independently are also known to suffer dissolution, and also a certain degree of hydrolysis in the case of KC.[23] Native starches poor in amylose reportedly reach a higher degree of swelling.[24]

The drug release profiles from tablets containing 50 mg IPEC plus 50 mg IBF, 100 mg IPEC plus 50 mg IBF, and 100 mg of the MS–KC physical mixture plus 50 mg IBF, are presented in Figure 7. The release from the tablets of the MS–KC physical mixture plus IBF is much faster than that observed in the tablets with IPEC plus IBF: ~100 % during the first 2 h. This result may be attributed to the disintegration with disruption of the bonds that hold tablet particles together[25] thereby exposing ibuprofen for rapid dissolution.

The analysis of the drug release profiles of the tablets with IPEC plus IBF, could be divided into two regions: acid stage and buffer stage. During the acid stage, the release was below 12%; being the release in the first 30 min of the experiment similar to that observed in the equivalent successive intervals for the acid medium, burst effect in this system is not significant.[26] However, a small degree of burst effect was observed for IBF formulated in a basic butylated methacrylate copolymer/kappa-carrageenan IPEC matrix using the same dissolution medium.[12]

As sink conditions were not reached in the acid stage because of the low solubility of IBF in this medium, only the experimental data of dissolution in the buffer stage were fitted to a model (Model I) based on previous proposals.[12,27,28] The term (α) was added to account for the drug dissolved in the acid stage (0–2 h).[26] The model equation is given by

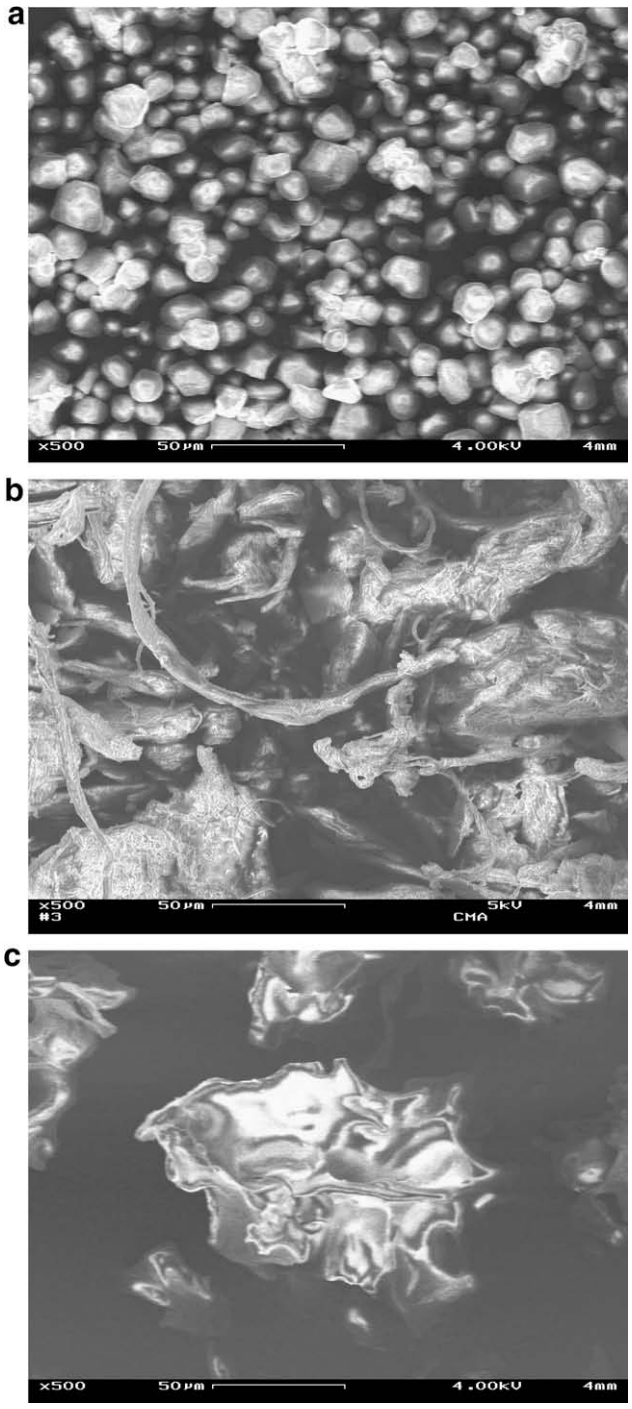

Figure 4. SEM micrographs of (a) MS, (b) KC, and (c) IPEC.

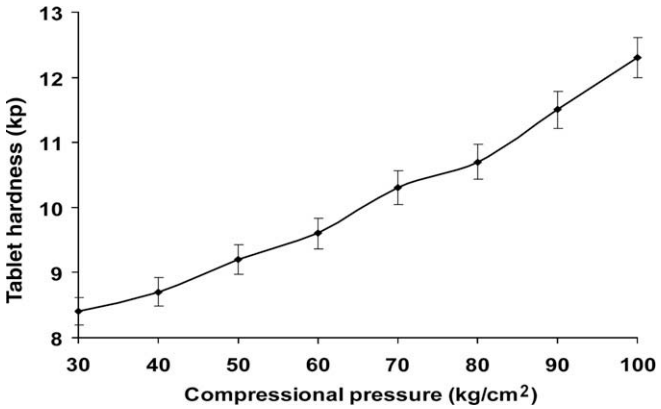

Figure 5. Compactibility profile of the IPEC.

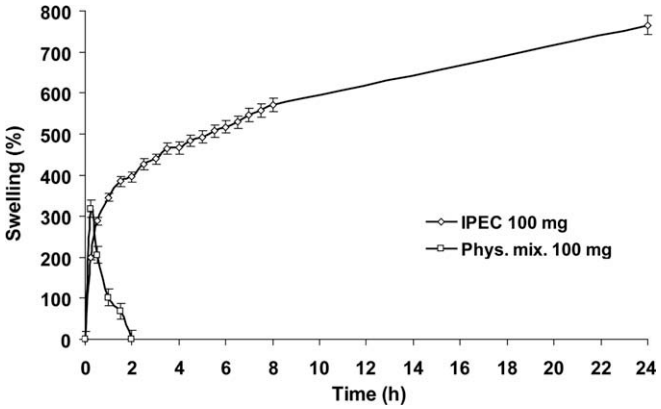

Figure 6. Temporal evolution of swelling for the IPEC and the MS–KC physical mixture.

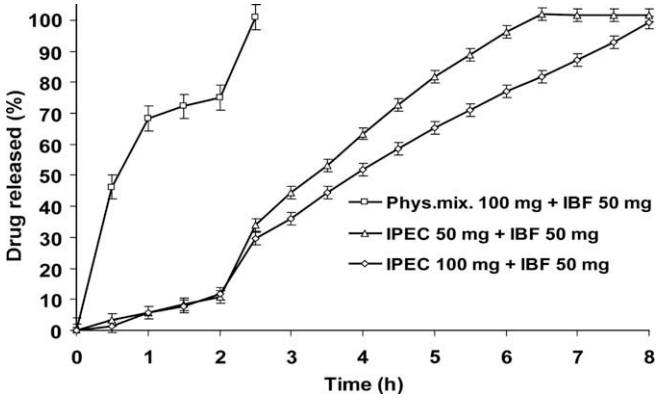

Figure 7. Release of IBF from matrix tablets.

$$M_t/M_\infty = k(t - t')^n + \alpha \quad (1)$$

where M_t/M_∞ is the fraction of the total drug released, k, the apparent release rate constant that incorporates the structural and geometric characteristics of the drug delivery device, t, the time elapsed from the start of the dissolution test, t', the duration of the acid stage ($t' = 2$ h), and n, the diffusional release exponent. The characteristic parameters of this model (k, n, and α), as evaluated by non-linear regression analysis for the results corresponding to the buffer stage, are presented in Table 2. Comparison between the experimental data and model predictions is shown in Figure 8.

For cylindrical geometry, a value of the diffusional release exponent of 0.45 ($n = 0.45$) points to Fickian transport, while values $0.45 < n < 0.89$ suggest non-Fickian transport; n values close to 0.89 indicate that the system is releasing drug in a zero-order manner (case-II transport) regardless of the actual mechanism of release.[27,28] As seen in Table 2, n values are close to 0.89 for both IPEC formulations.

As inferred from r^2 values, the model properly describes the experimental data. In addition, the k parameter for the formulation containing equal proportions of IPEC and IBF is higher than the one

Table 2
Characteristic parameters of Model I (Eq. 3) and Model II (Eq. 4)

Model	Parameter	IPEC 50 mg + IBF 50 mg	IPEC 100 mg + IBF 50 mg
I	k	19.98	16.01
	n	0.97	0.93
	α	24.01	20.93
	r^2	0.996	0.999
II	k_1	25.40	17.35
	k_2	8.33	7.94
	m	0.48	0.49
	r^2	0.996	0.996

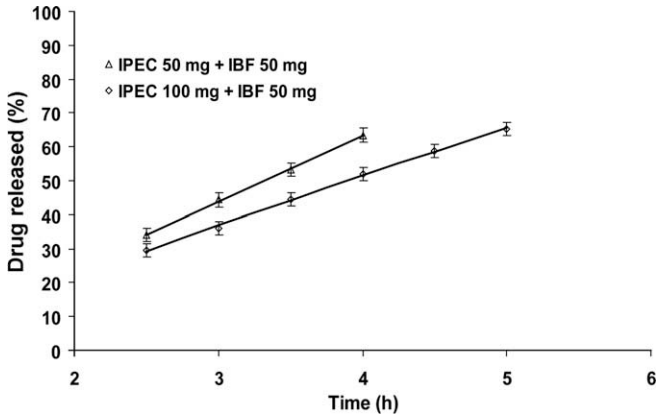

Figure 8. Comparison between the experimental data (points) and Model I predicted release profiles (solid lines) of IBF for the buffer stage and $M_t/M_\infty < 0.65$.

for the other IPEC-based formulation, for which the amount of IPEC was twice. In agreement with our own previous results,[12] this indicates that the k value could be modified changing the proportion of the IPEC in the tablet.

To obtain insight in the mechanisms involved in the release, the results of the dissolution studies in the buffer stage were also fitted to a second model (Model II) based on a previously reported one.[28,29] The equation representing the modified model applied is

$$M_t/M_\infty = k_1(t-t')^m + k_2(t-t')^{2m} + \alpha' \quad (2)$$

The meaning of the terms M_t/M_∞, t', is the same as that for Eq. 1. The estimated model characteristic parameters k_1, k_2, and m, as evaluated by non-linear regression, are presented in Table 2. It should be mentioned that, in this case, the α' term added is the experimental dissolution value corresponding to time = 2 h (end of the acid stage) in order to reduce the number of model parameters to be fitted. Comparison between the experimental data and model predictions is shown in Figure 9.

The first term on the right hand side of Eq. 2 represents the Fickian diffusional contribution, F, whereas the second term represents the case-II relaxational contribution, R. The ratio of both contributions can be calculated as follows:

$$R/F = k_2(t-t')^m/k_1 \quad (3)$$

The model characteristic parameters estimated in Table 2 and experimental data for the IPECs systems were used to build Figure 10, namely to represent R/F ratio against fraction released. For this purpose, the fraction released at different times was taken into account.

The results in Figure 10 indicate that, in general, Fickian diffusional contribution predominates for both formulations. In turn, for a particular fraction released, the relaxational contribution is relatively more important for the formulation containing the larger amount of IPEC. Besides, for each formulation, matrix relaxation also becomes relatively more important as the fraction released increases.

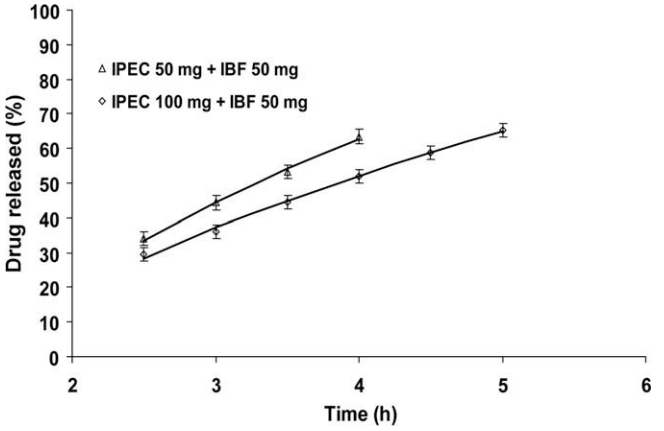

Figure 9. Comparison between the experimental data (points) and Model II predicted release profiles (solid lines) of IBF for the buffer stage and $M_t/M_\infty < 0.65$.

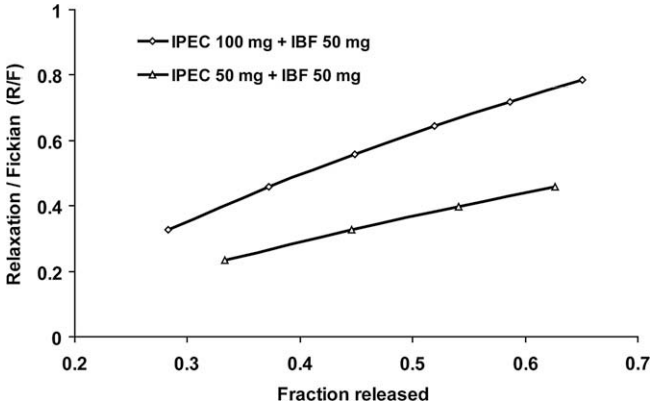

Figure 10. Relaxation to Fickian diffusional contribution (R/F) of the two IPEC formulations.

3. Conclusion

The feasibility of a novel interpolyelectrolyte complex based on two natural polysaccharides (cationized starch and kappa-carrageenan, as counterion) has been investigated for potential use as controlled release matrix. Direct compression was applied for tablets preparation, an advantageous method from both operational and economic viewpoints. Another advantage implies the use of water as the only solvent. The matrix system released IBF, used as model drug, in a zero-order manner during the buffer stage. Higher proportion of IPEC leads to reduced drug release rates. As judged from a model, which enables to properly describe experimental dissolution data in the buffer stage, Fickian diffusion seems to predominate over relaxation, for the modeled range.

4. Experimental

4.1. Materials

Modified (cationized) starch from maize (*Zea mays* L.), commercialized with the trademark Farmal MS 5960(r) (MS), and the kappa-carrageenan Gelcarin GP911(r) (KC) were kindly provided by Productos de Maíz S.A./Corn Products Int., Buenos Aires, Argentina and Productos Destilados/FMC Biopolymer Corp., Buenos Aires,

Argentina, respectively. All the reagents employed were of analytical grade. Ibuprofen (IBF) was purchased from Droguería Todofarma S.A. (Buenos Aires, Argentina), also complied with USP requirements.

4.2. Turbidity measurements

The repeating unit of each polyelectrolyte (Fig. 1) was used to calculate the concentration of the polymer solutions. Repeating unit of MS: 4166 Da; repeating unit of KC: 408 Da.

MS (104.2 mg) and KC (10.2 mg) were separately dissolved in 100 mL of distilled water by heating at 80 °C for 20 min. Nine different mixtures were prepared adding different volumes of KC solution (0.25 mM) to volumes of MS solution (0.25 mM) to obtain different MS:KC molar ratios, ranging from 1:9 (0.11) to 9:1 (9.00); the final volume was kept constant. This procedure was repeated but inverting the order of addition of the polysaccharides. The samples were allowed to rest for 1 h and then after stirring, turbidity was immediately measured at 600 nm, where no absorption of the polysaccharides was observed.

4.3. Synthesis of solid IPEC

KC (1.02 g) was readily dissolved in distilled water (1 L) at room temperature, while dissolution of MS (10.42 g in 1 L) required heating for 20 min at 80 °C. The preparation of the IPEC was carried out at 80 °C in order to ensure solubilization of both polysaccharides: the two heated solutions (2.5 mM) were simultaneously poured into a vessel provided with magnetic stirring. Agitation was maintained for 1 h and the system was left at rest for another hour. After isolation by centrifugation at 9000 rpm for 10 min at 4 °C, the precipitate was washed with distilled water. Centrifugation and washing were repeated twice. The suspension of the IPEC was freeze-dried for 3 days. The dried product was manually milled in a mortar and the fraction of particle size smaller than 150 μm (100 mesh US sieve) was employed.

4.4. Elemental analysis

The composition of the starting materials and the IPEC were investigated by elemental analysis using a Carlo Erba EA 1108 CHNS analyzer.

4.5. Infrared spectroscopy

FT-IR spectra of the starting materials, the physical mixture prepared in the same proportion to that of the IPEC, and the IPEC was determined with a 510P Nicolet FTIR spectrophotometer using the KBr disk method, at 4000–250 cm^{-1}; 32–64 scans were taken with a resolution of 2–4 cm^{-1}.

4.6. Thermal analysis

MS, KC, and the IPEC were dried overnight, under vacuum, in a desiccator with $CaCl_2$ and then subjected to thermal analysis using a TA Instruments DSC Q20, equipped with a DSC refrigerated cooling system RCS 90, with nitrogen as purge gas at a flow rate of 50 mL min^{-1}, indium was used to calibrate the enthalpy and temperature values. The experiments were conducted in non-hermetic crimped aluminium pans. The sample size used was 7–8 mg and the heating rate was 10 °C min^{-1} from −50 to 250 °C.

4.7. Optical and electronic microscopy

Size determination was performed manually using a Carl Zeiss Primo Star microscope, equipped with a graduated ocular previously calibrated with a Zeiss graded object micrometer. The accuracy of this system is ±1 μm. For each sample, 625 particles were chosen at random and its Feret diameter was measured.[21,30] Preliminary observations of the shape of the particles were also performed.

Images of MS, KC and of the IPEC were obtained using a Zeiss DSM 982 Gemini scanning electronic microscope equipped with a field emission gun (FEG) and an in-lens secondary electron (SE) detector. The acceleration voltage was 4–5 kV. Magnifications used ranged from ×500 to ×20,000.

4.8. Determination of specific surface areas

The conventional BET procedure was applied to evaluate the specific surface areas of the starting materials and the IPEC, employing a Micromeritics Gemini 2360 sorption instrument. The samples were outgassed overnight at 310 K at a final pressure of 1.33×10^{-4} Pa (10^{-6} mmHg). Nitrogen (77 K) adsorption isotherms were determined by the volumetric technique.

4.9. Flow properties

Flowability of the IPEC was evaluated semi-quantitatively by measuring the static angle of repose.[21,22] A funnel filled with IPEC was maintained 2 cm above a graduated surface, the funnel was drained and the angle of repose was calculated measuring the diameter of the cone formed.

4.10. Preparation of tablets

For swellability and erosion tests of the IPEC and of the MS–KC physical mixture in the same proportion as in the IPEC, flat-faced tablets (100 ± 1 mg total weight, 7.0 ± 0.1 mm of diameter) were prepared by compressing a given amount of the solid IPEC or MS–KC physical mixture using a W.A. Whitney hydraulic press. A pressure of 50 kg cm^{-2} was applied. For the compactibility profile, flat-faced tablets of the IPEC (100 ± 1 mg total weight, 7.0 ± 0.1 mm of diameter) were compressed applying pressures in the range of 30–100 kg cm^{-2}. For dissolution testing, IPEC plus IBF was manually mixed and flat-faced tablets of 100 ± 1 mg or 150 ± 1 mg total weight (7.0 ± 0.1 mm of diameter) were prepared by compressing a mixture of 50 mg IPEC plus 50 mg IBF or 100 mg IPEC plus 50 mg IBF, respectively. Control tablets containing the MS–KC physical mixture in the same relation than in the IPEC (100 mg) plus IBF (50 mg) were also prepared. The pressure applied was 50 kg cm^{-2}.

4.11. Compactibility profile

The compactibility profile was determined by measuring the hardness of tablets, prepared with different compressional pressures (30–100 kg cm^{-2}), using the automatic durometer Vanderkamp VK200 tablet hardness tester. The mean of three tablets for each compressional pressure is reported.

4.12. Degree of swelling

The degree of swelling of the IPEC and of MS–KC physical mixture tablets was investigated simulating the physiological conditions of the gastrointestinal tract. For this purpose, the tablets were placed in a pre-weighed basket of the dissolution equipment and immersed for 2 h in 30 mL of 0.1 M HCl, then 10 mL of 0.20 M Na_3PO_4 was added to pH 6.8 ± 0.05 and the experiment was allowed to continue for another 22 h. The temperature of the medium was 37.0 ± 0.5 °C. The measurements consisted in removing the basket from the medium, drying by filter paper, and weighting in an analytical balance. Weight differences were determined at

15 min and from 0.5 h to 8 h every 30 min; an equilibrium swelling was attained after 24 h as evaluated from measurements for longer times.

The degree of swelling (S %) at each time was calculated using the formula:

$$S\ \% = ((m_2 - m_1)/m_1) \times 100 \quad (4)$$

where m_1 is the weight of the initial (dry) tablet, and m_2 is the weight of the swollen tablet at different times. The results reported are the mean of three determinations.

4.13. Degree of erosion

The degree of erosion (E %) of the IPEC and the MS–KC physical mixture was determined by freeze-drying the tablets after attaining the equilibrium swelling, and was calculated using the formula:

$$E\ \% = ((m_1 - m_3)/m_1) \times 100 \quad (5)$$

where m_1 is the weight of the initial (dry) tablet, and m_3 is the weight of the freeze-dried tablet previously subjected to erosion. The results reported are the mean of three determinations.

4.14. Release testing of IBF

The IBF release profile was determined using a USP compliant Apparatus I (basket) dissolution tester (Alycar Instrumentos, Argentina). The rotating speed was 100 rpm and a temperature of 37.0 ± 0.5 °C was used. The dissolution media used were: 750 mL of 0.1 M hydrochloric acid for the first 2 h, then 250 mL of 0.20 M solution of tribasic sodium phosphate were added to the solution of pH 6.8 ± 0.05 for other 6 h (total release time of 8 h).[22] Tablets containing 50 mg IPEC plus 50 mg IBF, 100 mg IPEC plus 50 mg IBF, and 100 mg of MS–KC physical mixture plus 50 mg IBF were evaluated.

Aliquots of 3 mL of solution were taken every 30 min; the reduction of the total volume was taken into account to calculate the concentrations. The amount of IBF released was determined spectrophotometrically at 221 nm. The results informed for each kind of tablet are the mean of three determinations. Previous studies indicated that these polysaccharides did not interfere with the determination of the model drug.

Acknowledgments

This work was supported by grants of the National Research Council of Argentina (CONICET, PIP 5467), Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT, PICT 06-14237) and the University of Buenos Aires (X137 and B041). M.C.M., A.L.C., and P.R.B. are Research Members of CONICET. H.J.P. receives a Doctoral Fellowship from CONICET.

References

1. Mundargi, R. C.; Shelke, N. B.; Rokhade, A. P.; Patil, S. A.; Aminabhavi, T. M. *Carbohydr. Polym.* **2008**, *71*, 42–53.
2. Rowe, R. C.; Sheskey, P. J.; Owen, S. C. *Handbook of Pharmaceutical Excipients*, 5th ed.; Pharmaceutical Press: London, UK, 2005.
3. Dumoulin, Y.; Alex, S.; Szabo, P.; Cartilier, L.; Mateescu, M. A. *Carbohydr. Polym.* **1998**, *37*, 361–370.
4. Ispas-Szabo, P.; Ravenelle, F.; Hassan, I.; Preda, M.; Mateescu, M. A. *Carbohydr. Res.* **2000**, *323*, 163–175.
5. Mulhbacher, J.; Ispas-Szabo, P.; Lenaerts, V.; Mateescu, M. A. *J. Controlled Release* **2001**, *76*, 51–58.
6. Hennink, W. E.; van Nostrum, C. F. *Adv. Drug Delivery Rev.* **2002**, *54*, 13–36.
7. Satish, C. S.; Satish, K. P.; Shivakumar, H. G. *Indian J. Pharm. Sci.* **2006**, *68*, 133–140.
8. Clausen, A. E.; Bernkop-Schnürch, A. *J. Controlled Release* **2001**, *75*, 93–105.
9. Lowman, M. A. Complexing Polymers in Drug Delivery. In *Handbook of Pharmaceutical Controlled Release Technology*; Wise, D. L., Ed.; Marcel Dekker: New York, USA, 2000; pp 89–98.
10. Gupta, V. K.; Hariharan, M.; Weathley, T. A.; Price, J. C. *Eur. J. Pharm. Biopharm.* **2001**, *51*, 241–248.
11. Tapia, C.; Escobar, Z.; Costa, E.; Sapag-Hagar, J.; Valenzuela, F.; Basualto, C.; Gai, M. N.; Yazdani-Pedram, M. *Eur. J. Pharm. Biopharm.* **2004**, *57*, 65–75.
12. Prado, H. J.; Matulewicz, M. C.; Bonelli, P.; Cukierman, A. L. *Eur. J. Pharm. Biopharm.* **2008**, *70*, 171–178.
13. Moustafine, R. I.; Kabanova, T. V.; Kemenova, V. A.; Van den Mooter, G. *J. Controlled Release* **2005**, *103*, 191–198.
14. Moustafine, R. I.; Zaharov, I. M.; Kemenova, V. A. *Eur. J. Pharm. Biopharm.* **2006**, *63*, 26–36.
15. Moustafine, R. I.; Kemenova, V. A.; Van den Mooter, G. *Int. J. Pharm.* **2005**, *294*, 113–120.
16. Meshali, M. M.; Gabr, K. E. *Int. J. Pharm.* **1993**, *89*, 177–181.
17. Matsuhiro, B.; Rivas, P. *J. Appl. Phycol.* **1993**, *5*, 45–51.
18. Zhang, M.; Ju, B. Z.; Zhang, S. F.; Ma, W.; Yang, J. Z. *Carbohydr. Polym.* **2007**, *69*, 123–129.
19. Mizuno, A.; Mitsuiki, M.; Masao, M. *J. Agric. Food Chem.* **1998**, *46*, 98–103.
20. Mitsuiki, M.; Yamamoto, Y.; Mizuno, A.; Motoki, M. *J. Agric. Food Chem.* **1998**, *46*, 3528–3534.
21. Lieberman, H. A.; Lachman, L. *Pharmaceutical Dosage Forms: Tablets*, 1st ed.; Marcel Dekker: New York, USA, 1980.
22. The United States Pharmacopeia 30/National Formulary 25 (USP 30/NF 25), United States Pharmacopeial Convention, USA, 2007.
23. Capron, I.; Yvon, M.; Muller, G. *Food Hydrocolloids* **1996**, *10*, 239–244.
24. Li, J. Y.; Yeh, A. I. *J. Food Eng.* **2001**, *50*, 141–148.
25. Adebayo, S. A.; Brown-Myrie, E.; Itiola, O. A. *Powder Technol.* **2008**, *181*, 98–103.
26. Huang, X.; Brazel, C. S. *J. Controlled Release* **2001**, *73*, 121–136.
27. Peppas, N. A. *Pharm. Acta Helv.* **1985**, *60*, 110–115.
28. Siepmann, J.; Peppas, N. A. *Adv. Drug Delivery Rev.* **2001**, *48*, 139–157.
29. Peppas, N. A.; Sahlin, J. J. *Int. J. Pharm.* **1989**, *57*, 169–172.
30. Allen, T. Particle Size Analysis by Image Analysis. In *Powder Sampling and Particle Size Determination*, 1st ed.; Elsevier B.V.: Amsterdam, The Netherlands, 2003; pp 142–207. Chapter 3.