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Research paper

Basic butylated methacrylate copolymer/kappa-carrageenan interpolyelectrolyte complex: Preparation, characterization and drug release behaviour

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Abstract

The formation of a novel interpolyelectrolyte complex (IPEC) between basic butylated methacrylate copolymer and kappa-carrageenan was investigated and the product formed was characterized. Turbidity measurements and elemental analyses pointed to a 1:1 interaction of the repeating units. These results and FT-IR confirmed IPEC formation. Electronic microscopy images, particle size determination by image analysis and N_2 (77 K) adsorption measurements were consistent with a porous material. This IPEC formed presented very good flowability and compactibility. Two maxima were observed in the swelling behaviour as a function of pH. The performance of the IPEC as a matrix for controlled release of drugs was evaluated, using ibuprofen as a model drug. Release profiles were properly represented by a mathematical model, which indicates that the system releases ibuprofen in a zero-order manner. These profiles could be controlled by conveniently modifying the proportion of the IPEC in the tablets.

Keywords: Kappa-carrageenan; Basic butylated methacrylate copolymer; Interpolyelectrolyte complexes; Ibuprofen; Matrix systems; Controlled release

1. Introduction

Polymer complexes are insoluble, macromolecular structures formed by the non-covalent association of polymers with an affinity for one another. The complexes form due to association of repeating units on different chains (interpolymer complexes) or on separate regions of the same chain (intrapolymer complexes). Polymer complexes are classified by the nature of the association. The major classes of polymer complexes are stereocomplexes, interpolyelectrolyte complexes (or polyelectrolyte complexes, IPECs), and hydrogen-bonded complexes. IPECs form readily between most polyanions and polycations. These complexes are formed by the ionic association of repeating units on the polymer chains [1].

Basic butylated methacrylate copolymer (EE) is a copolymer of 2-dimethylaminoethyl methacrylate, methyl methacrylate and *n*-butyl methacrylate, having a mean relative molecular mass of about 150,000. The ratio of dimethylaminoethyl methacrylate groups to butyl methacrylate and methyl methacrylate groups is about 2:1:1. The content of dimethylaminoethyl groups is between 20.8% and 25.5% (calculated from the dried substance) [2]. The repeating unit is shown in Fig. 1a.

Carrageenan is the hydrocolloid obtained by extraction with water or aqueous alkali, from some members of the class Rhodophyceae (red seaweeds). Carrageenan consists chiefly of potassium, sodium, calcium, magnesium, and

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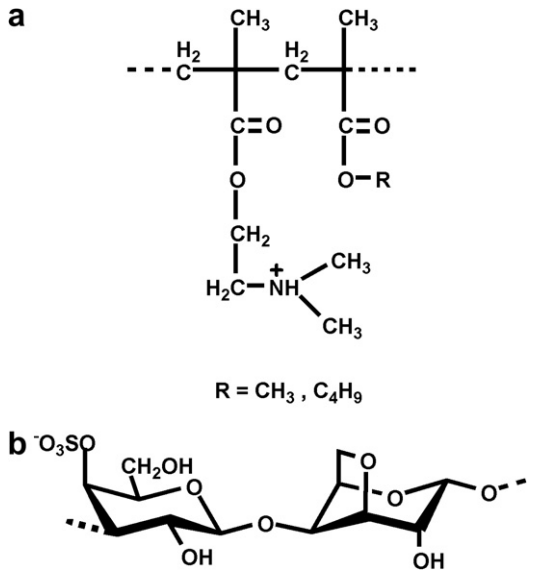

Fig. 1. Repeating unit of (a) Basic butylated methacrylate copolymer interpolyelectrolyte (EE) and (b) Kappa-carrageenan (KC).

ammonium sulfate esters of galactose and 3,6-anhydrogalactose copolymers. These hexoses are alternately linked α-1,3 and β-1,4 in the polymer. The ester sulfate content for carrageenan ranges from 18% to 40%. Kappa-carrageenan (KC) is mostly the alternating polymer of D-galactose 4-sulfate and 3,6-anhydro-D-galactose [3] (Fig. 1b).

Ibuprofen ((±)-α-methyl-4-(2-methylpropyl) benzeneacetic acid, labeled as IBF) is a non-steroidal anti-inflammatory agent belonging to the group of propionic acid derivatives (apparent pK_a of 5.2); it presents a plasmatic half-life of 1.8–2.0 h, as a result it has to be administered three to six times a day, making this drug a suitable candidate for a controlled release formulation [4].

In recent years a growing interest in polyelectrolyte complexes has led to the formation and characterization of systems involving a variety of anionic and cationic polymers: Eudragit E-Eudragit L [5,6], Eudragit E-sodium alginate [7], chitosan–alginate/chitosan–carrageenan (mainly kappa-carrageenan with low amounts of lambda-carrageenan) [8], chitosan–polygalacturonic acid [9], chitosan–carboximethylcellulose [10] and chitosan–alginate [11]. However, a more limited research has been directed towards controlled release applications.

The purpose of this study is to investigate the formation of a novel IPEC between basic butylated methacrylate copolymer and kappa-carrageenan (two excipients codified in pharmacopeias), to characterize the product formed, and to test its performance as a matrix for controlled release of drugs, using ibuprofen as a model.

2. Materials and methods

2.1. Materials

Basic butylated methacrylate copolymer, commercialized with the trademark Eudragit E PO(r) (EE), and the kappa-carrageenan Gelcarin GP911(r) (KC) were kindly provided by Etilfarma S.A./Degussa Argentina S.A. and Productos Destilados/FMC Biopolymer Corp., respectively. All the reagents employed were of analytical grade. Ibuprofen, which was used as a model drug, also complied with USP requirements.

2.2. Turbidity measurements

The concentration of the polymer solutions was calculated according to the repeating unit of each polyelectrolyte (Fig. 1). Thus, values of 278 and 408 Da were used for EE and KC, respectively.

EE (13.9 mg) and KC (20.4 mg) were separately dissolved in 100 mL of acetic acid/sodium acetate buffer 0.05 M (pH 5.0). Nine different mixtures of the solutions were prepared adding different volumes of KC solution (0.5 mM) to volumes of EE solution (0.5 mM) to obtain different EE:KC molar ratios, ranging from 1:9 (0.11) to 9:1 (9.00), with constant final volume. The process was repeated for all the mixtures but inverting the order of addition of the polymers. The samples were allowed to rest for 1 h and then vigorously agitated. Turbidity was immediately measured at 600 nm (Cary 1E, Varian Inc., Palo Alto, CA, USA), which is a wavelength where no absorption due to the polymers occurred.

2.3. Synthesis of solid IPEC

EE (1.39 g) and KC (2.04 g) were separately dissolved in 1 L of acetic acid/sodium acetate buffer 0.05 M (pH 5.0). Both solutions (5 mM) were simultaneously poured at room temperature in a vessel provided with magnetic stirring. Agitation was maintained for 1 h and the system remained quiet for another hour. After isolation by centrifugation at 9000 rpm for 10 min at 4 °C (Sigma 4K15, Sigma Laborzentrifugen GmbH, Osterode am Harz, Germany), the precipitate was washed with distilled water. The process of centrifugation and washing was repeated twice. The suspension of the IPEC was freeze-dried for 3 days (Freezemobile 3, Virtis Co., Gardiner, NY, USA).

2.4. Infrared spectroscopy

FT-IR spectra of EE, KC, EE–KC physical mixture, and of the solid IPEC were determined with a 510 P Nicolet FT-IR spectrophotometer (Thermo Fisher Scientific, Inc., Waltham, MA, USA) using the KBr disk method, at 4000–250 cm^{-1}; 32–64 scans were taken with a resolution of 2–4 cm^{-1}.

2.5. Elemental analysis

The composition of the IPEC formed was investigated by elemental analysis using a Carlo Erba EA 1108 CHNS analyzer (Carlo Erba, Milan, Italy).

2.6. Determination of specific surface areas

The samples were outgassed overnight at 310 K at a final pressure of 1.33×10^{-4} Pa (10^{-6} mm Hg). N_2 (77 K) adsorption isotherms were determined for the IPEC by the volumetric technique. The conventional Brunauer, Emmet and Teller (BET) procedure was applied to evaluate the specific surface areas of the samples. A Gemini 2360 sorption instrument (Micromeritics Instrument Corp., Atlanta, Georgia, USA) was employed.

2.7. Particle size determination by image analysis

Size determination was performed manually using a Primo Star microscope (Carl Zeiss, Oberkochen, Germany), equipped with a graduated ocular previously calibrated with a Zeiss-graded object micrometer. The accuracy of this system is ±1 μm. For each sample 100 particles were chosen at random and its Feret diameter was measured [12,13]. Preliminary observations of the shape of the particles were also performed.

2.8. Scanning electronic microscopy

Images of EE, KC, EE–KC physical mixture and of the IPEC were obtained using a Zeiss DSM 982 Gemini scanning electronic microscope equipped with a Field Emmision Gun (FEG) and an in-lens secondary electron (SE) detector (Carl Zeiss, Oberkochen, Germany). The acceleration voltage was 4–5 kV. Magnifications used ranged from 500× to 50000×.

2.9. Flowability

The flow properties of the IPEC were semi-quantitatively evaluated by measuring the dynamic angle of repose [3,12]. 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.

2.10. Preparation of tablets

For swellability tests and evaluation of the compactibility profile of the IPEC, round, 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 using a hydraulic press (W.A. Whitney, Rockford, IL, USA). A pressure of 50 kg/cm^2 was applied to carry out the swellability tests. For the compactibility profile, pressures within a range of 40 to 100 kg/cm^2 were used.

For dissolution testing, IPEC plus IBF were manually mixed and round, flat-faced tablets of 100 ± 1 mg, 125 ± 1 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, 75 mg IPEC plus 50 mg IBF or 100 mg IPEC plus 50 mg IBF, respectively. Control tablets containing the EE–KC physical mixture in the same relation as in the IPEC (100 mg) plus IBF (50 mg) were also prepared. The pressure applied was 50 kg/cm^2.

2.11. Compactibility profile

The hardness of the tablets prepared by applying different compressional pressures (40–100 kg/cm^2) was measured using an automatic durometer (Vanderkamp VK200 tablet hardness tester, VanKel Technologies, Inc, NJ, USA). The mean of three tablets for each compressional pressure is reported.

2.12. Degree of swelling of tablets

The degree of swelling of tablets of the IPEC and of tablets of the physical mixture was investigated simulating the physiological conditions of the gastrointestinal tract [5,6]. 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 hydrochloric acid, then 10 ml of 0.20 M tribasic sodium phosphate were added to pH of 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 (Mettler AL 204, Mettler-Toledo Int. Inc., Greifensee, Switzerland). Weight differences were determined from 0 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

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

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.

2.13. Release testing of IBF

The release of IBF from matrix tablets was determined using a standard dissolution tester that complies with USP requirements for Apparatus I (basket) (Alycar instrumentos, Buenos Aires, Argentina). Tablets containing 50 mg IPEC plus 50 mg IBF, 75 mg IPEC plus 50 mg IBF, 100 mg IPEC plus 50 mg IBF, and 100 mg of EE–KC physical mixture plus 50 mg IBF were evaluated. A rotating speed of 100 rpm and temperature of 37.0 ± 0.5 °C were used in all the experiments. The dissolution media used for the first two hours was 750 ml of 0.1 M hydrochloric acid, then 250 ml of 0.20 M solution of tribasic sodium phosphate were added to pH of 6.8 ± 0.05 and the experiment was allowed to continue for other 6 h (total release time of 8 h) [3,5,6].

Aliquots of 3 ml of solution were taken every 30 min without any volume replacement. Corrections in the total

volume were taken into account to calculate the concentrations. The amount of IBF released was determined spectrophotometrically at 221 nm (Cary 1E, Varian Inc., Palo Alto, CA, USA). The results informed for each kind of tablet are the mean of three determinations. Previous studies indicate that polymers did not interfere with the determination of the model drug.

3. Results and discussion

According to the manufacturer, EE is soluble in acidic medium up to pH 6.0 due to the hydration of protonated dimethylamine groups; KC presents ionized sulfate groups in the whole range of pH, although it is stable at pH 5.0–7.0. An acetic acid/sodium acetate buffer of pH 5.0 was selected in order to obtain solutions of both reactants.

In recent years, there has been an increasing interest in physically crosslinked hydrogels. The main reason is that the use of chemical crosslinking agents to prepare such hydrogels is avoided. These agents have to be removed from the gels before they can be applied [14,15].

The formation of the IPEC was initially studied by turbidity measurements. Fig. 2 shows the turbidimetric titration curve of a solution of EE with a solution of KC, and of a solution of KC with a solution of EE. The relative turbidity is plotted as a function of the EE:KC molar ratio for a fixed final volume. As seen in that Fig., the maximum turbidity was found when the EE:KC molar ratio was unity. Both curves were very similar showing that the maximum amount of IPEC was formed when equivalent quantities of both polymers reacted. They also indicated that the order of mixing did not influence the point of maximum turbidity.

In order to confirm the interaction or binding ratio of each component in the solid IPEC, elemental analyses were performed. Table 1 shows the experimental values and those calculated by considering a 1:1 interaction of the repeating units presented in Fig. 1. Good agreement between experimental and calculated results was found.

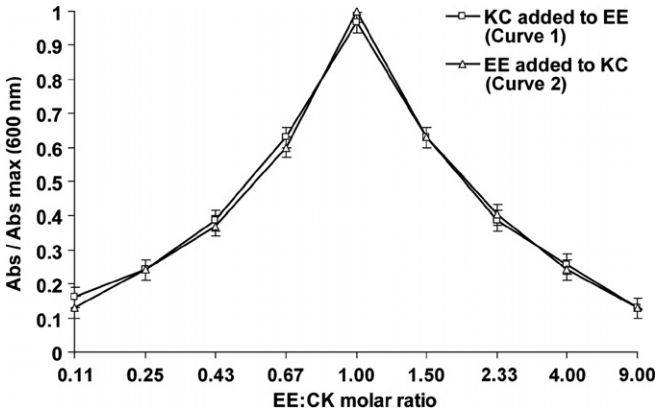

Fig. 2. Turbidity of the EE–KC system as a function of the composition of the mixture and the mixing order; curve 1: addition of KC solution to EE solution, curve 2: addition of EE solution to KC solution.

Table 1
Elemental analyses of the IPEC

n	Experimental value (%)				Calculated value (%)				Molar ratio EE:KC
	C	N	H	S	C	N	H	S	
1	46.09	1.99	6.65	4.70					
2	46.05	1.97	6.66	4.83					
Mean	46.07	1.98	6.66	4.77	47.89	2.11	6.67	4.82	1:1

The FT-IR spectra of EE, KC, EE–KC physical mixture, and the IPEC are presented in Fig. 3. As may be appreciated, the latter is different from the rest of the spectra. The two bands of absorption at 2770 and 2824 cm^{-1}, corresponding to non-ionized dimethylamine groups in EE spectrum [5–7] that are also present with a similar intensity in the spectrum of the physical mixture, were considerably reduced for the IPEC, indicating the formation of an ammonium salt. In addition, differences are observed in the fingerprint region of the IPEC compared to those of the reactants and the physical mixture.

Fig. 4 shows the SEM micrographs of EE, KC, EE–KC physical mixture and of the IPEC. The irregular shape of IPEC particles preliminarily observed by optical microscopy was confirmed. Higher magnifications revealed a three-dimensional reticular structure, with pore diameters in the range of 100–300 nm.

The BET area determined for the IPEC was 3.0 m^2/g. This value is too high for a sample with a mean volume surface diameter (d_{vs}) of 171 μm, as calculated by optical microscopy. It points to a porous structure in agreement with observations by SEM. Theoretically, spheres of a non-porous material of diameter similar to the particles of the IPEC sample would result in a BET area two orders of magnitude lower [1].

Taking into account the height (2.0 cm) and the diameter (7.9 cm) of the cone, the calculated dynamic angle of repose was 27°, indicating a free flowing material [3,12]. Likewise, the compactibility profile (Fig. 5) showed that the material presents good compactibility and that proper hardness values can be achieved by applying low compressional pressures.

Furthermore, it is well known that release properties of polymeric carriers can be somehow predicted by the determination of their swelling characteristics. The swelling behaviour of the IPEC is presented in Fig. 6. In the first stage of the experiment (acidic medium) the swelling reached a value of 103% after 1.5 h. At time = 2 h, the buffer stage began and the degree of swelling increased to a maximum value of 145% half an hour later. This could be due to gradual neutralization of the protonated dimethylamine groups, causing a reduction in the interaction between both polymers and a consequent relaxation of the matrix. Further, these free dimethylamine groups could intervene as acceptors in hydrogen bonding with the hydroxyl groups of the KC chain, and the rearrangement would subsequently lead to the measured equilibrium value of

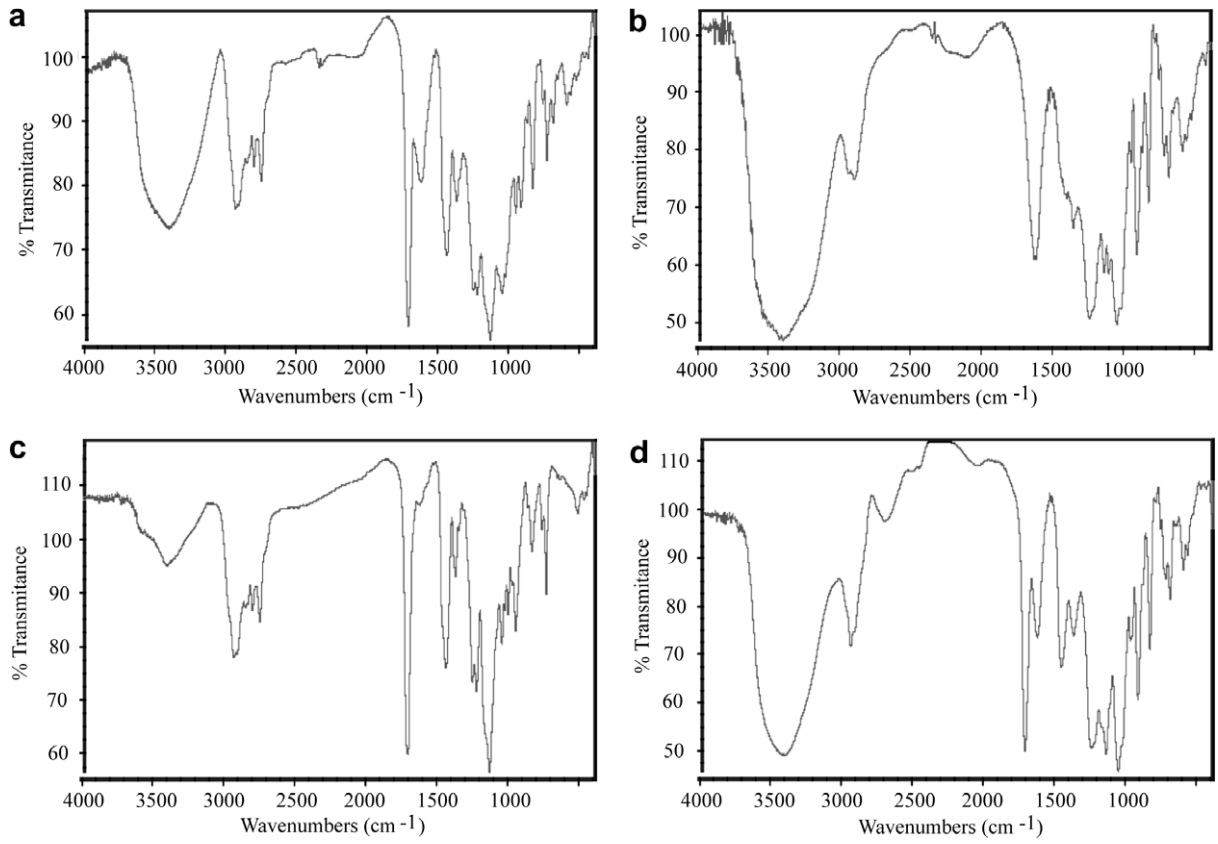

Fig. 3. FT-IR spectra of (a) EE, (b) KC, (c) EE–KC physical mixture, and (d) IPEC.

swelling of 125% at time = 24 h. The physical mixture showed higher values of swelling than the IPEC (Fig. 6). The maximum in acid medium was 450%, and the swelling continued growing during the buffer stage up to a value of 522% at time = 2.5 h; at equilibrium (time = 24 h) the swelling was 429%. This behaviour could be attributed to negligible ionic crosslinking between both polymers acting independently in the physical mixture.

The drug release profiles from tablets containing 50 mg IPEC plus 50 mg IBF, 75 mg IPEC plus 50 mg IBF, 100 mg IPEC plus 50 mg IBF, and 100 mg of EE–KC physical mixture plus 50 mg IBF are presented in Fig. 7. The release from the tablets of physical mixture plus IBF is slower that the observed in the tablets with IPEC plus IBF; Meshali and Gabr [16] working with chlorpromazine HCl and other ionic polymers reported that drug release from physical mixtures affords more sustained effect than the preformed complexes.

From the drug release profiles of the tablets with IPEC plus IBF, two regions can be clearly differentiated: acid stage and buffer stage. In the two hours of the acid stage, the release was below 14%. This could be attributed mainly to the action of the matrix and the low solubility of IBF in the acid medium. The release in the first 30 min of the experiment is higher than in the equivalent successive intervals in the acid medium, suggesting a small degree of burst effect [17].

The results of the dissolution studies in the buffer stage were fitted to a model based on previous proposals [18,19]. An additional term (α) was added to account for the drug dissolved in the initial period, comprising between 0 and 2 h (acid stage) [17]. The model equation is given by

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

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.

Model characteristic parameters (k, n, α), as evaluated by non-linear regression analysis for the results corresponding to the buffer stage, are shown in Table 2. Comparison between the experimental and predicted data is shown in Fig. 8.

For the four cases, the results in Table 2 indicate n values between 0.5 and 1. If the value of n is 0.5, it points to Fickian transport, a value of $n > 0.5$ and $n < 1.0$ suggests non-Fickian transport, and n values close to 1.0 indicate that the system is releasing drug in a zero-order manner regardless of the actual mechanism of release [18,19]. As seen in Table 2, n values are close to unity for the three IPEC formulations. Instead, the n value corresponding to the physical mixture formulation (0.571) indicates a non-

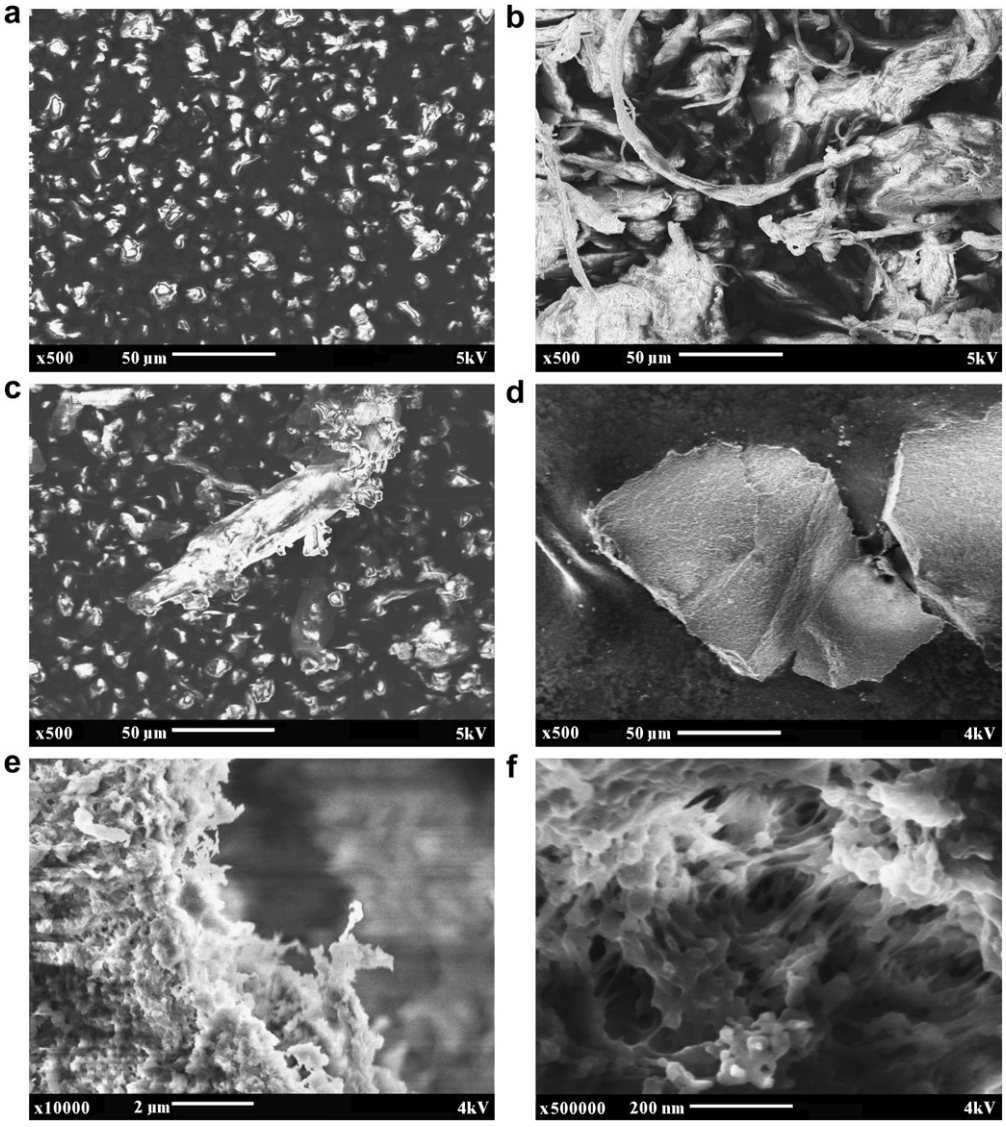

Fig. 4. SEM micrographs of (a) EE, (b) KC, (c) EE–KC physical mixture, and the IPEC at three different magnifications (d–f).

Fickian transport and therefore distant from zero-order release behaviour.

As inferred from R^2 values, experimental data are better described by the model for the formulations containing IPEC than for the physical mixture. In addition, the k parameter for the formulation containing 50 mg IPEC plus 50 mg IBF is approximately twice the formulation, where the double amount of IPEC was used (100 mg IPEC plus 50 mg IBF). An intermediate k parameter was determined for the 75 mg IPEC plus 50 mg IBF formulation. This indicates that the k value could be modified changing the proportion of the IPEC in the tablet.

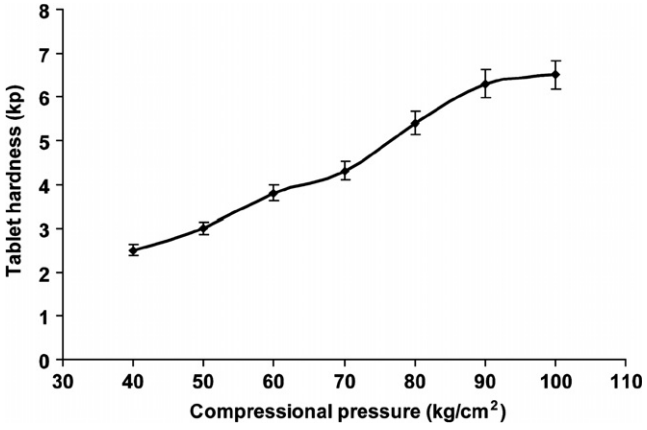

Fig. 5. Compactibility profile of the IPEC.

4. Conclusion

A novel interpolyelectrolyte complex, formed between EE and KC, was obtained and characterized to evaluate its potentiality as a controlled release matrix. The starting materials were excipients codified in pharmacopeias and tablets were prepared by direct compression, which is an

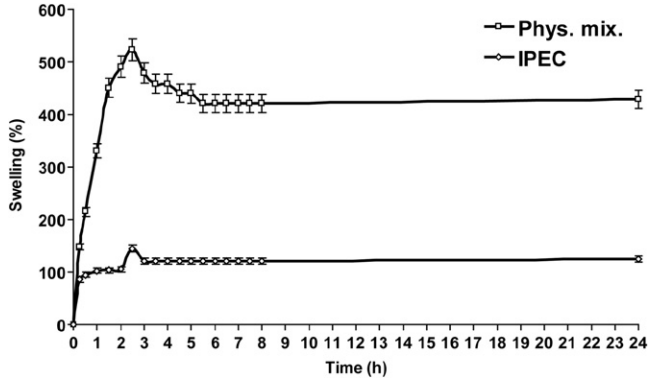

Fig. 6. Temporal evolution of swelling for the IPEC and the EE–KC physical mixture.

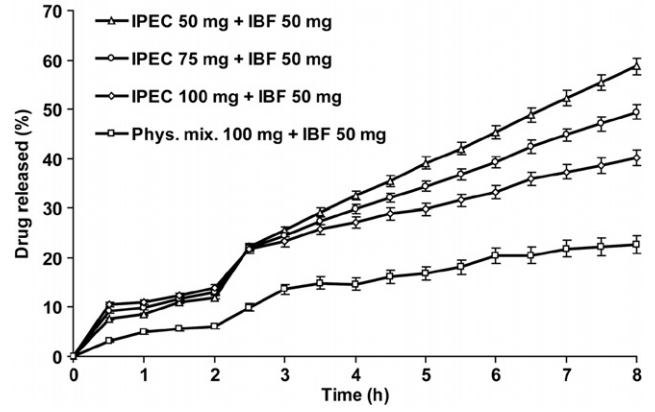

Fig. 7. Release of IBF from matrix tablets containing 50 mg IPEC plus 50 mg IBF, 75 mg IPEC plus 50 mg IBF, 100 mg IPEC plus 50 mg IBF, and 100 mg of EE–KC physical mixture plus 50 mg IBF.

Table 2
Model characteristic parameters

Composition of the tablets (mg)	k	n	α	R^2
IPEC 50 + IBF 50	6.768	0.989	18.853	1.000
IPEC 75 + IBF 50	5.241	0.990	20.800	0.996
IPEC 100 + IBF 50	3.409	0.993	20.137	0.996
Physical mixture 100 + IBF 50	5.843	0.571	6.660	0.971

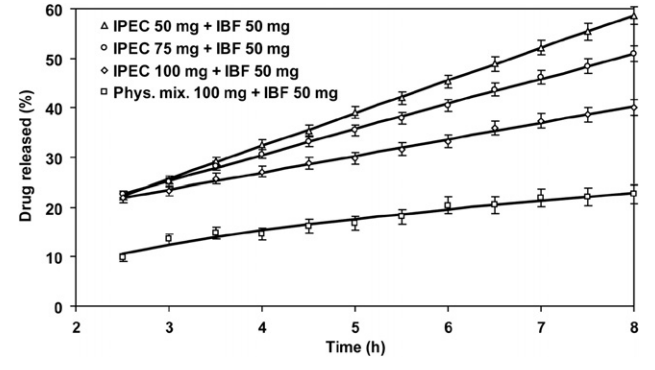

Fig. 8. Comparison between the experimental (points) and predicted (solid lines) release profiles of IBF for the buffer stage.

easy, rapid, and cheap method. No organic solvent was used during the preparation of the formulations. This matrix system released drug in a zero-order manner. Present results also indicate that release profiles could be controlled by modifying the proportion of IPEC in the tablets. They could be particularly useful for companies interested in controlled release technologies but limited to direct compression techniques.

Acknowledgements

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