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Drug release from complexes with a series of poly(carboxyalkyl methacrylates), a new class of weak polyelectrolytes

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Abstract

Carboxyalkyl methacrylates, a new class of non-cross-linked, hydrophobic weak polyelectrolytes, were synthesized, and then bound to cationic drugs (propranolol·HCl, diltiazem·HCl and verapamil·HCl) to form water-insoluble complexes that release the bound drug only in ionic media (pH 7.4). Compressed tablets were prepared from these cation exchange polyelectrolytes. Release profiles followed zero order kinetics ($n > 0.90$; n is the release exponent). As the hydrophobicity of the polyelectrolytes increased, the rate of release decreased and deviated from linearity ($n = 0.7$). Both the ionic strength of the medium as well as the solubility of the drug affected the rate of release. In acidic media (pH 1.2) a burst of drug was released but the release was halted by a layer of non-ionized polymer precipitated on the surface of the tablets. The results indicate that it is possible to "tailor-make" the release kinetics by using a polyelectrolyte from the series with the suitable hydrophobicity.

Keywords: Polyelectrolyte; Hydrophobic; Sustained drug release; Methacrylates; Ion exchange

1. Introduction

Ion exchange has been extensively studied as a method for controlled release of ionic drugs from their complexes with oppositely charged polyelectrolytes. Most investigations involve cross-linked ion exchange resins, from which the rate of release is affected by the swelling of the network, with the result that release kinetics are Fickian (square root time dependency) and suffer severe tailing toward the end of the drug release process (Kanhere et al., 1969; Moldenhauer and Nairn, 1990; Irwin et al., 1990; Raghunathan et al., 1982; Hariharan and Peppas, 1992; Burke et al., 1986).

To overcome this disadvantage, drug complexes with linear polyelectrolytes have been studied (Nujoma and Kim, 1996; Konar and Kim, 1997, 1998, 1999,

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2001; Khalil and Sallam, 1999; Lee et al., 1991). In this approach the drug is released by an ionic exchange process with the electrolytes of the dissolution medium. Upon drug release, the ionized polymer dissolves without forming a gel, eroding the delivery system. If the polymer does not dissolve prior to dissociation of the drug by incoming counterions, a synchronism between drug ion exchange and erosion is obtained, producing pseudo-zero order release. Most materials studied consisted of copolymers of an ionogenic monomer with a non-ionizable, hydrophobic one (e.g. methyl methacrylate) (Nujoma and Kim, 1996; Konar and Kim, 1997, 1999; Khalil and Sallam, 1999; Lee et al., 1991). While the charged monomer imparts the ionic binding capability, the hydrophobic monomer imposes the slow chain hydration and dissolution required for extended release.

The copolymerization reaction brings some disadvantages. First of all, composition characterization of the copolymers is required for each study. Due to differences in the reactivity ratios of the monomers, differences between the composition feed and the composition of the copolymers are commonly found, making it difficult to obtain the desired composition (Konar and Kim, 1999). A further disadvantage is the inclusion of non-ionizable monomer in the polymer chain, possibly decreasing the loading capacity of the polyelectrolyte.

In our efforts to design efficient carriers for the extended release of drugs, we recently developed a synthesis of a series of poly(carboxyalkyl methacrylates) (Licea-Claverie et al., 2004). These weak polyelectrolytes are shown in Fig. 1. In these materials hydrophobicity increases as the number of methylene groups (n) in the side chain increases, maintaining the ionizable group in each monomeric unit. These materials, allow us to control hydrophobicity without decreasing the proportion of ionizable groups, which can interact with cationic drugs.

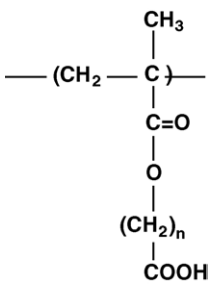

Fig. 1. Structure of series of carboxyalkyl methacrylates studied (n = 4, 5, 7 and 10).

In this article, we present the drug release characteristics of complexes formed by basic drugs (propranolol, diltiazem and verapamil) and this series of polyelectrolytes. The effect of pH, ionic strength and drug solubility were studied.

2. Materials and methods

2.1. Materials

All chemicals and solvents used were obtained either from Aldrich Chemicals or from Productos Químicos Monterrey. 2,2′-Azobisisobutyronitrile (AIBN) was recrystallized from hexane. Tetrahydrofuran (THF) was dried over elemental sodium. Methanol, petroleum ether, ethyl ether, KOH, KH_2PO_4, propranolol·HCl, diltiazem·HCl and verapamil·HCl were used as received.

2.2. Polymer preparation

Monomers (n = 4, 5, 7 and 10) were prepared according to a previously reported method (Licea-Claverie et al., 2004). Monomers were polymerized by free radical polymerization in tetrahydrofuran (1 M monomer concentration), using AIBN as initiator (1% molar with respect to the monomer) at 60 °C for 24 h. Polymers were purified by precipitation in petroleum ether and redissolution in THF, repeating the process five times. Afterward the polymers were dried under vacuum. Molecular weights of the polymers were determined by static light scattering, using a Zetasizer Nano-ZS, Malvern Instruments (Southborough MA). Glass transition temperature (T_g) was determined by differential scanning calorimetry (DSC), using a TA-Instruments calorimeter model MDSC 2920 (New Castle, Delaware).

Polymers (Pn4, Pn5, Pn7, Pn10, where the number represents the number of methylene groups in the side chains) were converted to their corresponding potassium salts by neutralizing a methanolic solution of each polymer with an equimolar amount of KOH in methanol. The polymeric salts were precipitated and

washed with ethyl ether, then dried under vacuum at 40 °C for several days.

2.3. Drug–polyelectrolyte complex preparation and characterization

An excess amount of drug solution (1.5 the mole ratio of drug to polyelectrolyte) was added to an aqueous solution of the corresponding polyelectrolyte (potassium salt) to obtain a precipitated drug–polyelectrolyte complex. It was then thoroughly washed with distilled water and dried under vacuum. The dried drug–polymer complexes were pulverized in a mortar with pestle, followed by screening through a 100 mesh sieve.

The FTIR spectrum (Perkin-Elmer 1600) of the complexes was obtained using the KBr tablet method.

DSC analysis was performed for all complexes prepared at a heating rate of 5 K/min, using a modulated heating program.

The content of drug in each complex was then determined. Dissolution of each complex in 1 M phosphate, pH 7.4, was followed by filtration through a 0.22 μm syringe filter, then measuring the concentration by UV spectrophotometry, using a reconstructed Perkin-Elmer Lambda 3A (Boston, MA) at 288, 274 and 278 nm for propranolol·HCl, diltiazem·HCl and verapamil·HCl, respectively. For the Pn10–propranolol complex a pH 8.0 solution was used.

Tablets containing 200 mg of the complex were compressed using a 13 mm diameter die in a Carver press (Wabash, IN) with a compression force of 2500 kg. Tablets of about 1.5 mm thickness were obtained.

2.4. Drug release kinetics

The release kinetics from tablets of the drug–polymer complexes were carried out at 37 °C in 900 mL of (a) pH 7.4 phosphate buffer (0.05 M), at different NaCl concentrations, or (b) HCl solution pH 1.2 ([NaCl] = 0.056 M), using the USP paddle method at 100 rpm in a Sotax AT7 Smart dissolutor (Basel, Switzerland). Samples (5 mL) were withdrawn every 15 min for the first hour and then every hour for a total sampling time of 12 h. Each sample was replaced with fresh medium. Drug concentration in the samples (filtered through 0.22 μm syringe filter) was determined by UV spectrophotometry. Each experiment was performed in triplicate.

The linearity of drug release was assessed by fitting the release data, up to 80% release, to the phenomenological equation (Ritge and Peppas, 1987):

$$\frac{M_t}{M_\infty} = kt^n \quad \text{or} \quad \ln\left(\frac{M_t}{M_\infty}\right) = n\,\ln(t) + \ln(k) \quad (1)$$

The terms in this equation are as follows: M_t is the amount of drug released at time t; M_∞ the total drug released over a long time period; k the kinetics constant and n is the mechanism of drug release. The value of n ranges from 0.5 ($t^{1/2}$ dependence, generally referred to as Fickian release) to 1 (representing the case-II transport which is purely relaxation controlled). The values in between indicate an anomalous behavior corresponding to coupled diffusion/relaxation.

The dissociation/erosion mechanism of the drug release kinetics was evaluated using the following equation (Nujoma and Kim, 1996):

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_e t}{C_o r_o}\right)^2 \left(1 - \frac{2k_e t}{C_o l}\right) \quad (2)$$

where k_e, C_o, r_o and l are the dissociation/erosion rate constant, the initial drug concentration in a tablet, the tablet radius and the tablet thickness, respectively.

3. Results and discussion

3.1. Drug–polymer complexes characterization

When the polymer solution was poured into an excess of drug solution, a water-insoluble complex formed in all cases studied. Evidence of complex formation between the drug and the polymer was furnished by FTIR studies. Shown in Fig. 2 is the FTIR spectrum of the Pn10–propranolol complex. The absorption band around 1556 cm^{-1} in the spectrum of the complex is assigned to the vibration of the carboxylate group of the polymer ion involved in the complexation with the amine group of the drug. An absorption band around 1397 cm^{-1} is assigned to the stretching of the C–N bond in propranolol. The absorption band around 1724 cm^{-1} corresponds to the carbonyl in the ester group of the polyelectrolyte. All propranolol–polyelectrolyte complexes showed

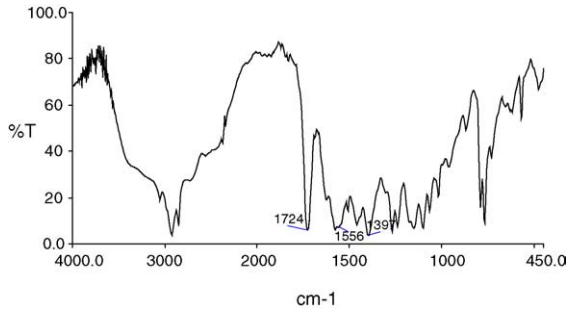

Fig. 2. FTIR spectrum of the Pn10–propranolol complex.

basically the same absorption bands. The FTIR spectrum of the Pn5–diltiazem complex (Fig. 3) shows an absorption band at 1724 cm^{-1} corresponding to the carbonyl group of the polyelectrolyte. This absorption band is broadened through the overlapping of the absorption band at 1742 cm^{-1} due to the stretching of the carbonyl in the amide group of diltiazem.

Fig. 4 presents the FTIR spectrum of the Pn5–verapamil complex. An absorption band around 1724 cm^{-1} corresponds to the carbonyl in the ester

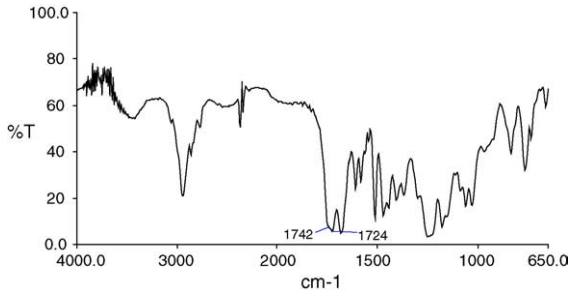

Fig. 3. FTIR spectrum of the Pn5–diltiazem complex.

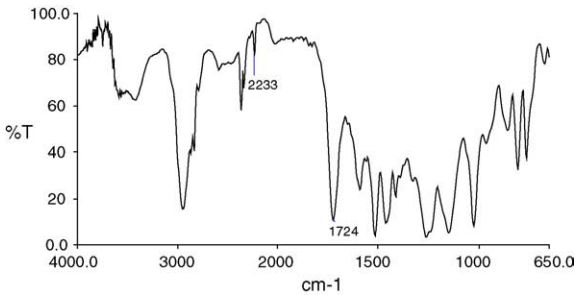

Fig. 4. FTIR spectrum of the Pn5–verapamil complex.

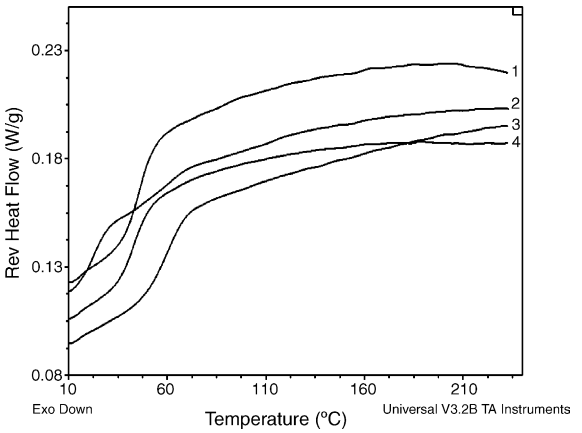

Fig. 5. DSC analysis of the polyelectrolyte–propranolol complexes: (1) Pn5, (2) Pn10, (3) Pn4 and (4) Pn7.

group of the polyelectrolyte. A sharp absorption band at 2233 cm^{-1} is assigned to the stretching of the nitrile group in verapamil.

The DSC curves of the polyelectrolyte–propranolol complexes prepared are shown in Fig. 5. The characteristic fusion peak for propranolol·HCl (166 °C) is not observed. The T_g of the complexes are presented in Table 1. These are higher than the T_g of the pure polyelectrolytes (also presented in Table 1), which indicates that the mobility of the side chains decreases with the formation of the complex. However, in both cases T_g is smaller as the alkyl side chain length increases indicating a higher flexibility of the material. Fig. 6 presents

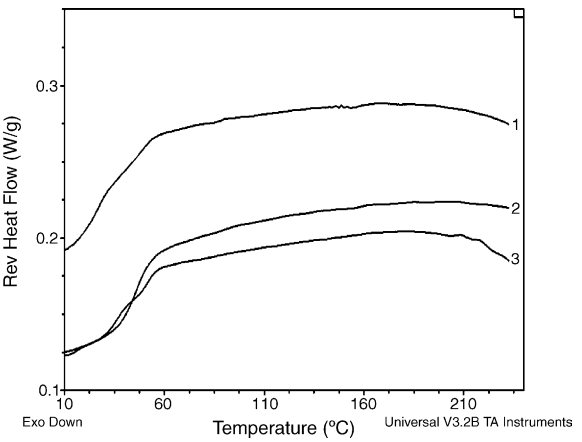

Fig. 6. DSC analysis for the Pn5–drug complexes: (1) verapamil, (2) propranolol and (3) diltiazem.

Table 1
Characteristics of polyelectrolytes and complexes studied

	M_w (g/mol)	T_g polymer (°C)	T_g complex (°C)	Theoretical loading (wt%)	Experimental loading (wt%)	pH of solution
Pn4	74000	30				
Propranolol			59.92	58.43	64.34	5.62
Pn5	106000	15				
Propranolol			45.97	56.64	76.99	6.01
Diltiazem			44.00	66.83	76.00	6.31
Verapamil			30.49	69.57	74.01	6.45
Pn7	102000	−3				
Propranolol			43.00	53.39	51.34	5.93
Pn10	90000	−6				
Propranolol			26.00	49.15	61.45	6.22

the DSC curves for the complexes of Pn5 with each drug studied. Again the fusion points of the drugs are not observed (212 and 144 °C for diltiazem·HCl and verapamil·HCl, respectively). The results indicate that complexes have physicochemical properties different from those of drugs and polymers alone.

Table 1 also shows the molecular weight of the polyelectrolytes studied and drug loading in the complexes prepared. The expected loading, considering that each carboxyl group is attached to one drug molecule by an ionic bond, is also presented. Loadings are higher than expected, probably due to additional hydrophobic interactions between drug and polymer, as has been reported for polyelectrolytes containing hydrophobic domains (Inoue et al., 1997; Chen et al., 2003; Tarvainen et al., 1999).

Table 1 also presents the pH of each supernatant solution formed from the complexes. This is useful to predict the ionization state of the drug in each complex. The pH of each solution is far below the pK_a of the respective drug (9.45, 8.73 and 7.7 for propranolol, verapamil and diltiazem, respectively), so that the presence of drug in the non-ionized form is unlikely. Furthermore, the DSC analysis of the complexes did not show the fusion peaks of the non-ionized drugs either.

3.2. Drug release studies

The effect of the polyelectrolyte on the rate of release of propranolol in phosphate solution, pH 7.4, is presented in Fig. 7. Propranolol was released over a period of 4 h from the complex with Pn4. For the complex with Pn5 release is slowed down to 7 h. The propranolol–Pn7 complex only releases about 20% of the drug in a 12 h period. At the end of the release period, erosion of the tablet was observed since Pn7 is soluble at pH 7.4.

The disproportional reduction in the release rate can be attributed not only to the decrease on the solubility of the polyelectrolyte, due to the higher number of methylene groups in the side chains, but also to the increase on the apparent pK_a of the ionizable groups, since the

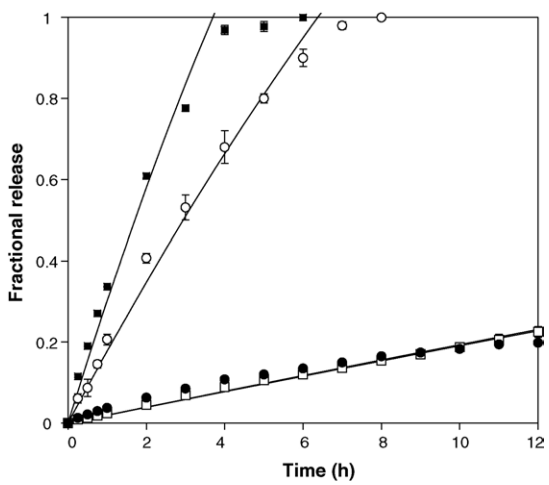

Fig. 7. Drug release kinetics from propranolol–polyelectrolyte complexes, pH 7.4: (■) Pn4, (◯) Pn5, (□) Pn7 and (●) Pn10. Data fittings according to Eq. (2) are presented as solid lines.

hydrophobic microenvironment decreases the dielectric constant, making ionization more difficult (Shatkay and Michaeli, 1966; Cornejo-Bravo and Siegel, 1996). Furthermore, the higher the hydrophobicity of the polyelectrolyte, the higher the proportion of ionized groups in the chains required to obtain dissolution (Licea-Claverie et al., 2003, 2004; Rogel-Hernandez et al., 2001). These factors also decrease the rate tablet erosion, since the chains must have a high proportion of ion-exchanged carboxyl groups before they can dissolve.

A similar fraction of drug release is observed with the Pn10–propranolol complex compared to the Pn7–complex. However, in this case at the end of the dissolution period, the tablets were not eroded, since at this pH the polyelectrolyte is insoluble. The degree of swelling ($W_{\text{wet tablet}}/W_{\text{dry tablet}}$) after the release study was 2.38, indicating that the tablets prepared with this complex behave as swellable matrixes. Swelling occurs because at this pH chains are partially ionized as it has been previously studied (Rogel-Hernandez et al., 2001).

The effect of the ionic strength on the rate of release is presented in Fig. 8 for the Pn7–propranolol complex. An increase in NaCl concentration increases the rate of release, indicative of an ionic exchange process. Drug release profiles are independent of ionic strength higher than 0.1 M NaCl. These results agree with the results obtained with highly ionic polymers (Konar and Kim, 2001).

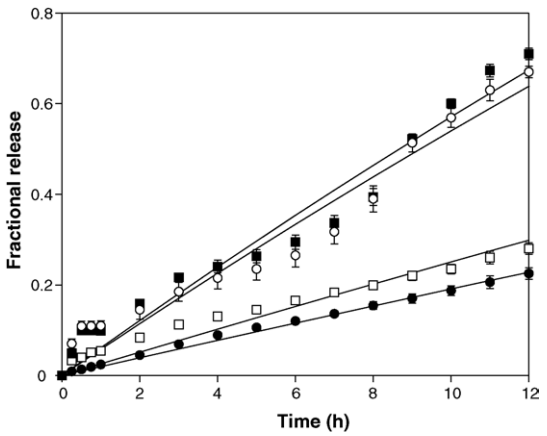

Fig. 8. Effect of NaCl concentration on drug release form Pn7–propranolol complexes, pH 7.4: (●) 0 M, (□) 0.05M, (◯) 0.1 M and (■) 0.2 M. Solid lines are from data fittings according to Eq. (2).

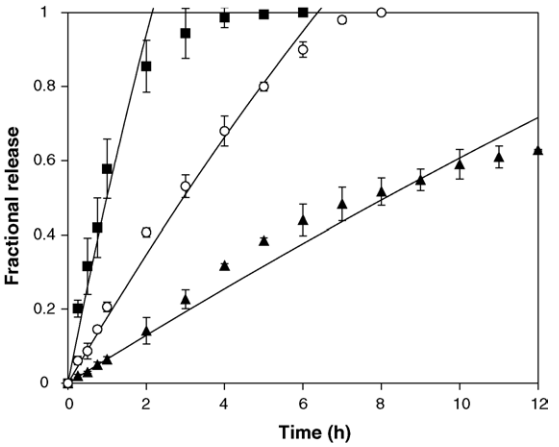

Fig. 9. Kinetics of drug release form Pn5–drug complexes, pH 7.4: (■) diltiazem, (◯) propranolol and (▲) verapamil. Data fittings according to Eq. (2) are presented as solid lines.

Fig. 9 shows the release from the complexes of Pn5 with the three drugs studied. For the Pn5–diltiazem complex, the entire drug is released in about 4 h, while for the Pn5–propranolol complex about 7 h are required for complete release, as previously seen. On the other hand, only about 63% of verapamil is released from its complex in the sampling period. Since most of the drug is expected to be ionically bound to the polymer, producing a neutral molecule, the hydrochlorides' solubilities do not predict the results found since verapamil·HCl and propranolol·HCl have similar solubilities of 90 and 70 g/L, respectively, and diltiazem·HCl has a much higher solubility of 660 g/L (Konar and Kim, 1999). The rate of release can be explained in terms of the solubility of the free bases (465, 61.7 and 4.47 mg/L for diltiazem, propranolol and verapamil, respectively). The less water-soluble drug may make the drug–polymer complex more hydrophobic. The results in this work are different from those reported using strong polyelectrolytes where release rates of propranolol and verapamil were very similar (Konar and Kim, 2001).

One of the major disadvantages of using ionic-exchange resins containing carboxylic acid as the ionizable groups is the fast release of the drug in the stomach (dumping), due to the fast conversion of the carboxylates to the non-ionized form at low pH (Borodkin and Sundberg, 1971; Bruck, 1983). Most studies use copolymers of methacrylic (or acrylic) acid and methyl

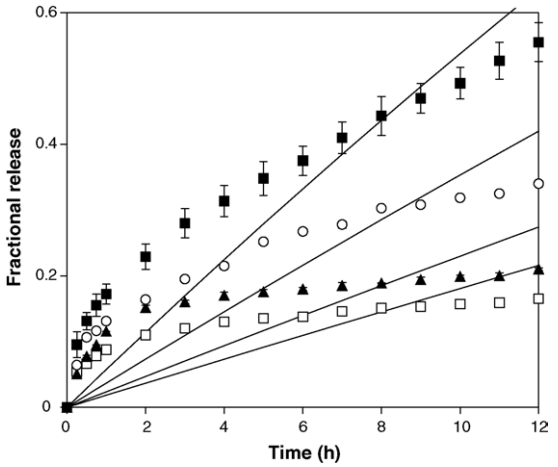

Fig. 10. Drug release at pH 1.2 of the polyelectrolyte–propranolol complexes: (□) Pn4, (▲) Pn5, (◯) Pn7 and (■) Pn10. Solid lines are from data fittings according to Eq. (2).

methacrylate. These kinds of copolymers are below its T_g at body temperature, they have low cohesivity and disaggregate in the solution medium. The polyelectrolytes used in our studies are above their T_g at the release temperature. For instance, they are adhesive when non-ionized.

Fig. 10 shows propranolol release from the complexes prepared at pH 1.2 ([NaCl] = 0.056 M). A burst of drug is observed for all complexes, however, the release rate is drastically reduced after the first hour. This appears to be due to the precipitation of the non-ionized polymer on the surface of the tablet, slowing down the release process. The rate of release at this pH follows an order proportional to the hydrophobicity of the polymers, which is inverse to the behavior at pH 7.4. Physical observation of the tablets after the dissolution test in acidic medium (24 h) indicates that the ones containing Pn4 remained practically intact. However, the tablets of the other complexes are gummy and suffered deformation. For the non-ionized form of the polyelectrolytes, an increase in the side chain increases chain flexibility, as observed from the decrease in T_g (Table 1). As chain flexibility increases, a more pronounced tablet deformation in acidic media occurs, allowing the inner layer to get in contact with the medium, thereby increasing drug release and giving an explanation to the results observed.

The results of the correlation using Eq. (1) are presented in Table 2. The results show that the complex Pn4–propranolol is controlled by relaxation of the chains. As the hydrophobicity of the chains increases, the diffusion/dissolution process has a higher influence in drug release. This is expected for the complex Pn10–propranolol. Since erosion does not occur, however, matrix swelling causes anomalous behavior to be observed.

Drug release from the complex of Pn5–verapamil is also controlled by chain relaxation. For the case of the Pn5–diltiazem, the process is anomalous, allowing control from drug dissolution/diffusion. This may be due to the higher solubility of diltiazem. Drug non-ionically bound to the polymer may dissolve upon contact with the medium, before the chain erosion occurs.

Considering the effect of ionic strength on the release process, regression analysis shows that the

Table 2
Dissociation/erosion rate constants and regression parameters of the release studies performed

Complex	k_e	n	Intercept	k	R^2
Pn4–propranolol pH 7.4	13.07	0.9931	−0.9414	0.390	0.9990
Pn5–propranolol pH 7.4	9.06	0.9183	−1.6298	0.196	0.9892
Pn7–propranolol pH 7.4	0.65	0.8628	−3.6576	0.026	0.9973
Pn10–propranolol pH 7.4	0.79	0.7154	−3.3091	0.037	0.9969
Pn7–propranolol pH 7.4, 0.05 M NaCl	0.86	0.5723	−2.7964	0.061	0.9880
Pn7–propranolol pH 7.4, 0.1 M NaCl	2.05	0.6118	−2.1132	0.121	0.9416
Pn7–propranolol pH 7.4, 0.2 M NaCl	1.93	0.5587	−2.0842	0.124	0.9065
Pn5–diltiazem pH 7.4	26.56	0.7118	−0.6178	0.539	0.9938
Pn5–verapamil pH 7.4	3.16	0.9894	−2.6580	0.070	0.9924
Pn4–propranolol pH 1.2	0.77	0.2883	−2.4801	0.084	0.9906
Pn5–propranolol pH 1.2	1.18	0.3404	−2.3112	0.099	0.9402
Pn7–propranolol pH 1.2	1.23	0.4053	−2.0460	0.129	0.9906
Pn10–propranolol pH 1.2	2.30	0.4477	−1.7490	0.174	0.9977

addition of NaCl to the solution makes the process controlled by diffusion. This indicates that the rate of ionic exchange increases with ionic strength. The linearity of the process was lost at concentrations up to 0.1 M NaCl, indicating that synchronism between the ionic exchange and the erosion of the chains is lost. Regression analysis of the release kinetics at pH 1.2 showed that the model used does not fit the data. This corroborates the formation of an insoluble layer of the non-ionized polymer on the tablets surface, which blocks (Pn4 and Pn5), or at least slows down (Pn7 and Pn10), the diffusion process.

The dissociation/erosion constant (k_e) of the drug complexes was determined using a non-linear regression analysis (PRISM, GraphPad Sofware Inc., San Diego CA) of Eq. (2). The results are also presented in Table 2. Data fitting to this equation (up to 90% release) is presented in Figs. 7–10. Drug release kinetics was accurately predicted by Eq. (2) for the complexes of propranolol with Pn4, Pn5 and Pn7. This corroborates the mechanism of erosion obtained from the exponent in Eq. (1). However, data fitting was poor for the Pn10–propranolol complex since no erosion is observed. A high value k_e (26.56 mg/(cm^2 h)) is obtained for the Pn5–diltiazem complex, indicative of a fast influx of water (carrying counterions) into the tablet, producing diffusion control of the release process (Konar and Kim, 1999). Fitting of Eq. (2) is poor for the Pn5–verapamil complex, which corroborates the exponent obtained from Eq. (1) where anomalous behavior is determined. Predictions of release by Eq. (2) are highly underestimated at the beginning of the process for salt concentrations of 0.05 M and higher (Fig. 8), indicating that ionic exchange is faster than chain erosion at high ionic strength. The release of propranolol at pH 1.2 is not predicted by Eq. (2) for any of the polyelectrolytes studied, demonstrating that at this pH, release is not controlled by erosion of the tablets.

4. Conclusions

The series of poly(carboxylalkyl methacrylates) studied here present advantages over other polyelectrolytes of being homopolymers, therefore composition characterization is not required and high drug loadings are obtained. The rate of drug release from these systems is affected by the chain hydrophobicity as well as drug solubility. It is then possible to select the member of the series to obtain a drug–polyelectrolyte complex that renders the required release kinetics.

The mechanism of release depends on the hydrophobicity of the polyelectrolyte and the water solubility of the drug. For fast releasing systems, the mechanism is anomalous with a combination of diffusion and chain erosion. For certain overall hydrophobicity, release is controlled by erosion and pseudo-zero order kinetics is obtained. However, as hydrophobicity of the complex increases, either by the number of methylenes in the polymer and/or the solubility of the drug, control of diffusion increases, producing an anomalous release behavior.

As expected for ion exchange delivery systems, the ionic strength of the media affects the rate and mechanism of release from the studied complexes.

Even when drug release occurs at pH 1.2 from the propronalol complexes, they fulfill the requirements for a sustained delivery system since no more than 20% of the drug is dumped in 2 h (Bruck, 1983).

Acknowledgement

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