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ORIGINAL ARTICLE

Mechanism of sorption and release of a weak acid from β-cyclodextrin polymers

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Abstract The mechanisms of sorption and release of solutes from polymeric materials synthesised by cross-linking β-cyclodextrin (β-CD) with epichlorohydrin have been investigated. Gemfibrozil (pKa 4.7) was chosen as model solute. The polymers were obtained by suspension (P1) and block polymerisation (P2). Both P1 and P2 had similar β-CD contents (65 and 64%) and their swelling capacities were 5.0 and 5.8 cm^3/g, respectively. The sorption of gemfibrozil kinetic data in water and in aqueous solutions at pH 2.8 and 7.0 were fitted to a hyperbolic equation and they were studied by applying the Weber and Morris and the Elovich equations. P2 presented faster rates and higher sorption capacities in water and at pH 2.8. The mechanisms of sorption were pH-dependent. In water, the sorption rate was determined by the diffusion of gemfibrozil in the polymer network and fitted the Weber and Morris equation. At pH 2.8 a better adjustment to the Elovich equation suggested a significant influence of the inclusion in the β-CD cavities. The release kinetics at pH 7.0 was controlled by drug solubilisation and presented maximum release values of 90 (P1) and 95% (P2), with a suitable regeneration of the loaded polymer. In water, the release was slower, fitted a hyperbole and the mechanism was controlled by drug solubility and also by the polymeric geometry. Finally, release assays were carried out from discs of loaded polymer in a medium that simulated the gastrointestinal tract. The release in basic medium was governed by diffusion, but at pH 1.2 the mechanism was more complex.

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Introduction

Water insoluble polymers, capable of forming hydrophilic gels by absorbing high amounts of water, can be synthesised by cross-linking β-cyclodextrin (β-CD) with epichlorohydrin or other bi- or poly-functional reagents. These amphiphilic polymers exhibit interesting sorption properties for a variety of solutes such as drugs [1], organic pollutants of soils and industrial wastewater contaminants [2–4].

The sorption mechanism of these polymers involves the inclusion complexation of the solute within the β-CD cavities and also the interactions of the sorbate with the polymer network, either with the tails of the cross-linking agent or with the flexible secondary cavities formed by the polymeric structure. Therefore, the cross-linking process provides other possible binding sites to the sorbate different from the CD cavities. Depending on the polymerisation conditions it is possible to modify the network geometry of the gel in order to obtain a wide variety of materials with manifold applications [2–5].

Several studies have been carried out to elucidate the mechanisms involved in the processes of both sorption and release of solutes from these polymeric hydrogels. The sorption kinetics is often complex, because the sorption rate depends on the geometry of the gel network. In general, intraparticle diffusion is the rate-limiting step of the sorption process, but the inclusion inside the β-CD cavity and the diffusion through the boundary layer of the gel particles can have some influence as well. In this sense, some models have been applied to determine the role of

different processes in the sorption of a solute by a cyclodextrin polymer [6, 7].

The release studies of a solute from a hydrogel are often focussed on pharmaceutical applications. The release of a drug from a hydrogel is a complex process, determined by different factors such as polymer swelling and relaxation, solubility, dissolution rate and diffusion of the solute [8, 9]. When the polymer presents a high swelling rate, the release of the drug is determined by the interaction with the polymer network and by drug solubility. A great number of models have been applied to describe the release from hydrogel tablets or discs, showing that soluble solutes often fit to first order kinetics while those insoluble ones tend to present zero order kinetics [9–11].

Gemfibrozil (GEM) is a benzene derivative of valeric acid [5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid] used as hypolipidemic agent. This drug was chosen as model compound because it is able to form a GEM-β-CD inclusion complex with a high binding constant that is pH-dependent. Complexation results in an enhancement of drug solubility and native fluorescence [12, 13]. There are additional reasons for this choice, based on the possible application of the cyclodextrin polymers employed. Firstly, acidic drugs have been detected in sewage treatment plants [14], specifically, gemfibrozil has been found in concentrations around 3–6 nM in aquatic toxicological studies of municipal effluents, due to its widespread use as a lipid-regulating agent [15]. Therefore, the retention of the drug in the CD polymer could be applied in the treatment of wastewater. In addition, this drug could be a good model for sustained release studies of drugs.

The aim of this work was to analyse the mechanisms involved in the processes of both sorption and release of GEM from two polymeric materials synthesised by crosslinking β-CD with epichlorohydrin. The strong pH-dependence of complexation provides the possibility to gain insight in the mechanism of sorption and release of the drug by analysing the contribution of the inclusion in the β-CD cavity on the sorption and desorption kinetics.

Materials and methods

Materials

Gemfibrozil was purchased from Sigma. All the other reagents were from Panreac. The aqueous solutions were prepared with HCl (pH 2.8), NaOH (pH 10) and phosphate buffer solution (pH 7.0).

β-CD polymers (P1 and P2) were obtained by crosslinking with epichlorohydrin. P1 was purchased from Cyclolab as spherical beads prepared by suspension and P2 was synthesised in our laboratory by block polymerisation [4, 5]. Both P1 and P2 had similar β-CD contents (65 and 64%) and their swelling capacities were 5.0 and 5.8 cm^3/g. The polymers were sieved to obtain particle sizes ranging from 160 to 250 μm.

Methods

Sorption rate studies

The GEM:β-CD molar ratio employed was approximately 1:30, and the polymer was swollen before the assay. 200 mL of a 2×10^{-5} M aqueous solution of GEM were stirred in the presence of the polymer. 5.0 mL samples were taken at different times and centrifuged at 3500 rpm during 30 min. Later, the concentration of GEM was analysed by fluorescence spectroscopy ($\lambda_{exc} = 272$ nm, $\lambda_{em} = 303$ nm), considering the GEM solution without polymer as reference. The amount sorbed (q) was expressed as a percentage uptake in relation to the initial amount of drug.

Release studies

As a previous step before the assays of release kinetics, loaded gels were prepared by stirring particles of polymer in a 2×10^{-5} M solution of GEM in water during 12 h. The amount of drug loaded was 3 mg/g. The desorption kinetics were carried out by stirring the loaded polymer in 200 mL of an aqueous solution at 37 °C. Samples (4 mL) were withdrawn at different times, replaced by the same volume of fresh solution and subsequently analysed by fluorescence spectroscopy.

In addition, freeze-dried discs of polymer P2 (diameter 13.5 mm and thickness 3.3 mm) were loaded from a 4.7×10^{-3} M solution of GEM in a 40:60 ethanol–water mixture. The amount of drug loaded was 19 mg/g. Release assays from discs were carried out in a medium that simulates the gastrointestinal tract; the assay started at pH 1.2 during 2 h and was followed by a rapid change up to pH 10.

Results and discussion

Sorption rate studies

The sorption kinetic experimental data obtained in water and in aqueous solution of pH 2.8 and 7.0 were fitted to a hyperbolic equation:

$$q = \frac{q_{max} t}{t_{1/2} + t} \quad (1)$$

where q is the amount sorbed, q_{max} is the sorption capacity (maximum amount sorbed) and $t_{1/2}$ represents the time at

which half q_{max} is sorbed. This equation provides useful parameters to quantify the sorption rate processes.

Figure 1 shows a tight fitting of the sorption data to the hyperbolic equation, which allows the determination of the q_{max} and $t_{1/2}$ parameters. Because P1 and P2 polymers display high swelling capacities, the expansion of the gel structure enables a fast diffusion of GEM through the network of the polymers, leading to short values of $t_{1/2}$ which ranged from 5 (P1 in water) to 0.7 min (P2 at pH 2.8).

The sorption capacities of both polymers were higher at pH 2.8 than in water. This fact can be related with a higher extent of complexation and also with the lower solubility of GEM, a weak acid, at pH 2.8 [12, 13].

The comparison of the behaviours of P1 and P2 can be related with the contribution of the polymeric network, because, as it was said before, the β-CD content was similar in both of them. Polymer P2 presented faster rates and higher sorption capacities than P1 and the differences were greater in water ($q_{max} = 38 \pm 2$ and $64 \pm 1\%$ for P1 and P2, respectively) than at pH 2.8 ($q_{max} = 77 \pm 1$ and $82 \pm 1\%$ for P1 and P2, respectively).

The comparison of the results obtained at pH 2.8, a medium where the role of inclusion complexation is predominant, with those obtained in water provides information about the polymeric network. It seems that the most suitable secondary cavities to host the drug are those of P2, the polymer synthesised by a block polymerisation method. Depending on the polymerisation conditions, the size of the secondary cavities and the tails of the gel network can be modified to obtain different polymeric materials with similar β-CD contents [4, 5].

The mechanisms of sorption were analysed by fitting the experimental data to the equation of Weber and Morris for intraparticle diffusion [6] and to the Elovich equation, which has been widely applied in adsorption on heterogeneous surfaces and can be derived from either the diffusion controlled process or the reaction controlled process [7].

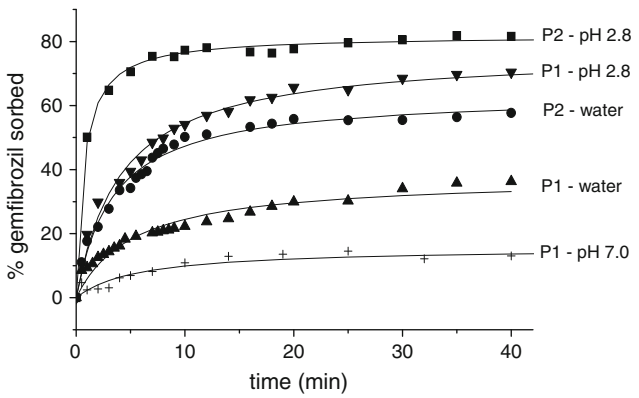

Fig. 1 Fitting of the sorption kinetic data to the hyperbolic equation at 25 °C

The Weber and Morris equation (Eq. 2) predicts a linear relationship between the amount sorbed (q) and the square root of time (t)

$$q = kt^{1/2} + C \tag{2}$$

where k is the intraparticle diffusion rate constant and C is the intercept.

In the Elovich model (Eq. 3) a straight line is obtained by plotting q against ln t. The simplified equation of Elovich becomes:

$$q = \frac{1}{\alpha}\ln(\alpha\beta) + \frac{1}{\alpha}\ln t \tag{3}$$

where α and β are the Elovich coefficients.

The application of both models to GEM sorption kinetics is depicted in Fig. 2. The fitting of the experimental data suggested that the sorption mechanism was pH-dependent. In water, the sorption rate was determined by the diffusion of GEM in the polymer network and fits the Weber and Morris equation. The influence of the diffusion through the boundary layer of the gel particles was lower because the plots passed nearly through the origin [6]. However, at pH 2.8 a better adjustment to the Elovich equation together with a deviation from the Weber and Morris model suggested a significant influence of inclusion in the β-CD cavities, in accordance with the higher binding constants of the GEM- β-CD complexes at pH 2.8 [7].

Release studies

The release kinetic data were also fitted to the hyperbolic equation (Eq. 1). The values of the amounts of GEM desorbed (q) at different times are depicted in Fig. 3.

Regarding the studies at pH 7.0, a rapid initial release was observed ($t_{1/2}$ values of 10 ± 1 and 5 ± 1 min for P1 and P2, respectively), followed by a period of supersaturation before equilibrium was reached. The values of maximum release (q_{max}) obtained (90 for P2 and 95% for P1) evidenced an almost complete regeneration of the polymers at this pH. Because the driving force of GEM release at pH 7.0 is the solubility of the drug in the buffer solution, the release kinetic curves of both polymers were almost superimposable.

With respect to the release of GEM in water, significant differences in the behaviour of both polymers were observed. The release was slower compared with pH 7.0 ($t_{1/2}$ values of 23 ± 1 and 17 ± 1 min for P1 and P2, respectively). The values of maximum release (q_{max}) were 57 ± 1 and $65 \pm 1\%$ for P1 and P2, respectively. The faster release from polymer P2 suggested the simultaneous influence of both drug solubility and molecular interactions of the drug with the polymer in the desorption of GEM.

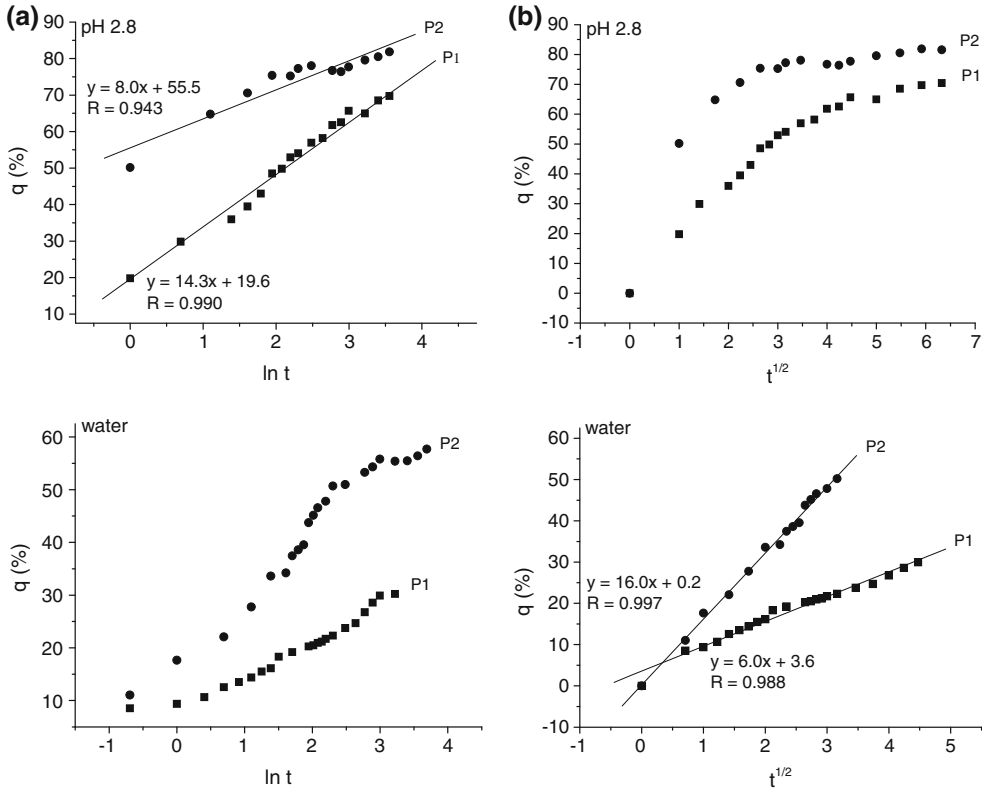

Fig. 2 Fitting of the sorption kinetic data to the Elovich (**a**) and Weber and Morris (**b**) equations at 25 °C

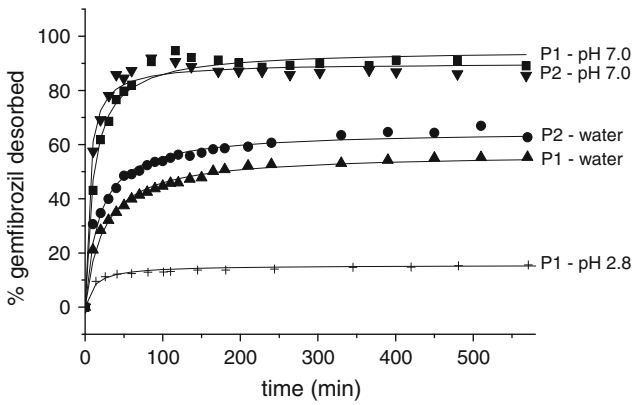

Fig. 3 Fitting of the release kinetic data to the hyperbolic equation at 37 °C

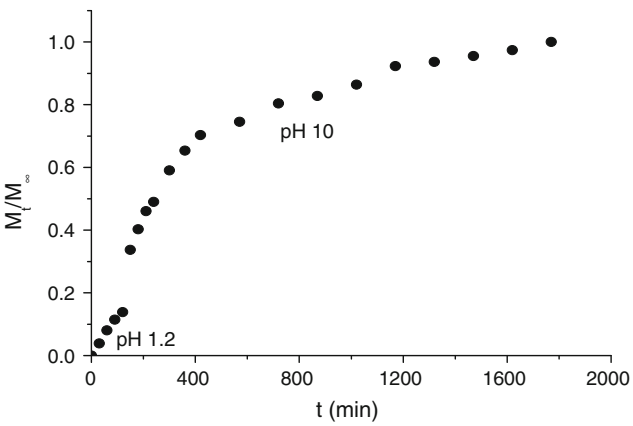

Fig. 4 Release curves from loaded discs at pH 1.2 followed by a rapid change up to pH 10, at 37 °C

Finally, release kinetic studies were carried out from discs in a medium that simulated the change of pH that takes place in the gastrointestinal tract (Fig. 4). The experiments began at pH 1.2 during 2 h, followed by a rapid change of pH to 10. The release data were fitted to the power law:

$$\frac{M_t}{M_\infty} = Kt^n \tag{4}$$

where M_t and M_∞ are the absolute cumulative amount of drug released at time t and infinite time, respectively. K is a constant which depends on structural and geometric characteristics of the polymer and n is the release exponent, which can be related with the mechanism of drug release [11].

At pH 1.2 the release exponent obtained $n = 1.0 \pm 0.1$ corresponds to a zero order process, in which drug release is independent of time. This fact can be related with the low solubility of GEM in this medium [9]. Dissolved and not dissolved GEM is present in the polymer but not dissolved GEM is not available for diffusion.

On the other hand, at pH 10 the adjustment of the release data to the equation gives rise to a release exponent $n = 0.5$, so it seems that in basic medium release is governed by diffusion. The drug is more soluble at this pH value, so upon contact with water the drug dissolves and diffuses out of the polymer.

In conclusion, gemfibrozil has been employed as a successful model to infer the possible sorption mechanisms of an acid solute in cyclodextrin polymers crosslinked with epichlorohydrin. The sorption processes were directly related with the pH-dependence of the GEM-β-CD binding constant. This drug resulted useful to discriminate between two polymers with similar characteristics.

In relation with the possible application of these polymers in the treatment of wastewater containing GEM, the results show high sorption capacities and the important possibility of regenerating the polymer almost completely. Finally, the possibility of modulating drug release by different mechanisms supports the potential of these polymers as drug carrier systems.

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