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Influence of β-cyclodextrin concentration and polyacrylic acid molecular weight on swelling and release characteristics of metoclopramide-containing hydrogels

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Summary

We evaluated the effects of polyacrylic acid (PAA) molecular weight and crosslinking agent (β-cyclodextrin) concentration on swelling and drug (metoclopramide) release characteristics of PAA hydrogels. Both factors, and the interactions between them, were found to have significant effects on both hydrogel swelling and drug release. In particular, increased β-cyclodextrin concentrations led to reduced swelling and reduced drug release efficiency.

Introduction

The use of bioadhesive polymers in pharmaceutical formulations serves to target the dosage form to a specific area and to prolong release of the active principle over an extended period (Takayama et al., 1990; Smart, 1991). When a polymer enters into contact with a compatible solvent, the solvent penetrates the polymer: if the polymer is not crosslinked, it will dissolve; if it is crosslinked, the resulting gel will simply expand until it reaches an equilibrium state (Silberberg, 1975; Korsmeyer and Peppas, 1984; Roorda et al., 1986). The Carbopols (polyacrylic acids, PAAs) are high molecular weight polymers derived from acrylic acid and containing a high proportion of carboxyl groups (Pillai et al., 1988). It is these carboxyl groups which undergo esterification in the presence of primary alcohols, leading to crosslinking by condensation.

Here, we have used β-cyclodextrin (β-CD) as a crosslinking agent, since its primary hydroxyl groups allow binding with the carboxyl groups of the PAAs (Harada et al., 1976a,b, 1977). We have evaluated the influence of β-cyclodextrin concentration and PAA molecular weight on hydrogel

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swelling and metoclopramide release characteristics.

Materials and Methods

Materials

The bioadhesive polymers used were Carbopol 907 (B.F. Goodrich, batch F445028), with a nominal molecular weight of 450 000, and Carbopol 941 (J. Escuder, batch 0014), with a nominal molecular weight of 1 250 000. The active principle was the metoclopramide base obtained by neutralization of the metoclopramide salt ($C_{14}H_{22}ClN_3O_2 \cdot 2HCl \cdot H_2O$) (J. Escuder, batch 012). The crosslinking agent was β-cyclodextrin (Sigma, batch 76F-3462). All reagents were analytical grade.

Preparation of hydrogels

Solutions of PAA (Carbopol 907 or 941), β-cyclodextrin and metoclopramide were made up as shown in Table 1. A 1:1 water/acetone mixture was used as solvent, the β-cyclodextrin being dissolved in the aqueous phase and the active principle in the organic phase. The PAA was then added, with mechanical stirring for 24 h to ensure complete dissolution and dispersion.

40-g aliquots of this homogeneous mixture were poured into the casting devices shown in Fig. 1, and then degassed in a vacuum chamber at 200 mmHg and ambient temperature until all bubbles had been removed. Solvent evaporation was then carried out in an oven at 40°C, and the fine film obtained was stored at 90°C for 4 h to allow esterification to take place (as shown diagramatically in Fig. 2). The crosslinked hydrogel was left for 24 h in a desiccator at 98% humidity to obtain a flexible film which was then cut in 1-cm diameter discs.

TABLE 1

Hydrogel formulations evaluated in the present study

PAA[a] (g)	β-Cyclodextrin (g)	Metoclopramide (g)	Solvent (ml)
5	0	1	200
5	0.0625	1	200
5	0.25	1	200
5	0.5	1	200
5	0.75	1	200
5	1	1	200

[a] PAA, polyacrylic acid (Carbopol 907 or Carbopol 941).

Studies of swelling

When a hydrophilic gel is placed in contact with an aqueous medium, it spontaneously hydrates until an equilibrium state is reached. The point at which equilibrium occurs depends upon the density of the cross-linking agent used, and upon the number of hydrophilic groups of the polymer (Holly and Refojo, 1975; Kou et al., 1990).

1 cm diameter discs of hydrogels produced by each of the formulations studied were placed at

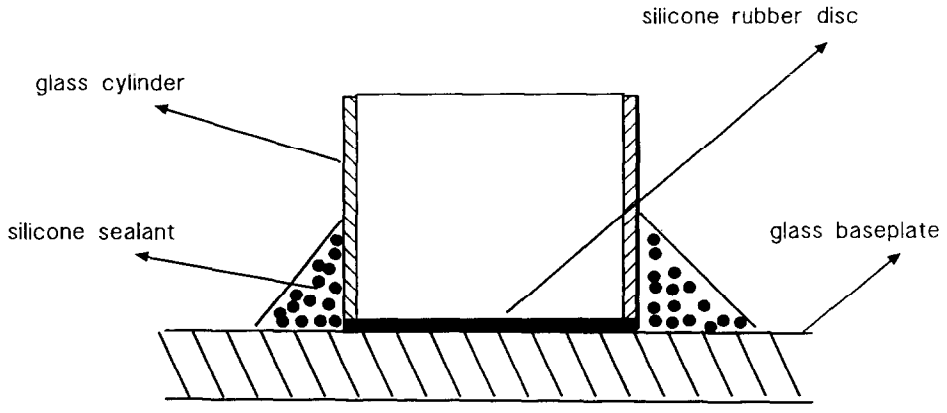

Fig. 1. Devices used for the casting of hydrogels.

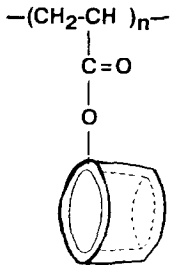

Fig. 2. Structure of the product formed by reaction between the carboxyl groups of a polyacrylic acid and the primary hydroxyl groups of β-cyclodextrin.

the bottom of 9 cm diameter glass dishes to which 75 ml of distilled water at ambient temperature was added. Disc diameter was measured at 0 and 30 min and at 1, 2, 3, 4, 6, 8, 10 and 24 h. Discs were also weighed at 0 and 24 h. Four replicates of each test were carried out.

Dissolution studies

Dissolution studies were carried out with the aid of a dissolution apparatus (Prolabo, France). The 1 cm diameter discs of the hydrogels were placed in 1 mm mesh stainless-steel gauze baskets at the bottom of a dissolution flask containing 500 ml of distilled water at 37°C, with mechanical stirring at 100 rpm. 5-ml aliquots of the dissolution medium were collected at regular intervals; following filtration, metoclopramide concentration in these aliquots was determined by spectrophotometry at 273 nm. Release was characterized by calculation of dissolution efficiency (DE) (Khan and Rhodes, 1972, 1975) at 1, 6 and 8 h:

$$D.E. = \int_0^t M \, dt / M_t t$$

where M_t is the maximum percentage of drug which can dissolve and M denotes the percentage dissolved at time t.

Results and Discussion

Studies of swelling

Both the water content of hydrogels and the way in which they take it up affect drug transport; control of swelling is thus a very important factor in the design of controlled release systems (Katono et al., 1991).

The swelling profiles of the systems (Fig. 3) show that lower β-cyclodextrin concentrations corresponded to greater swelling, as expected given that less crosslinking will allow greater water uptake by polymer chains (Wood et al., 1981; Roorda et al., 1986). This behaviour, typical of network systems swelling in a solvent, is due to the increased crosslink density at higher crosslinker concentrations which decreases the length of the polymer segment between crosslinks. This,

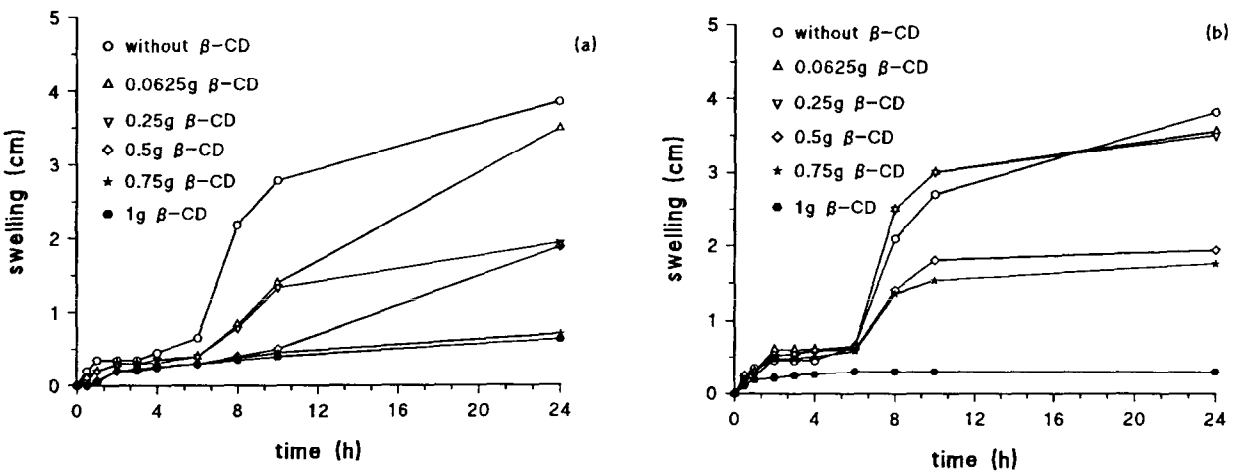

Fig. 3. Swelling profiles of the hydrogels obtained with (a) Carbopol 907 and (b) Carbopol 941, for the various amounts of cross-linking agent (β-cyclodextrin, β-CD) used in the formulation.

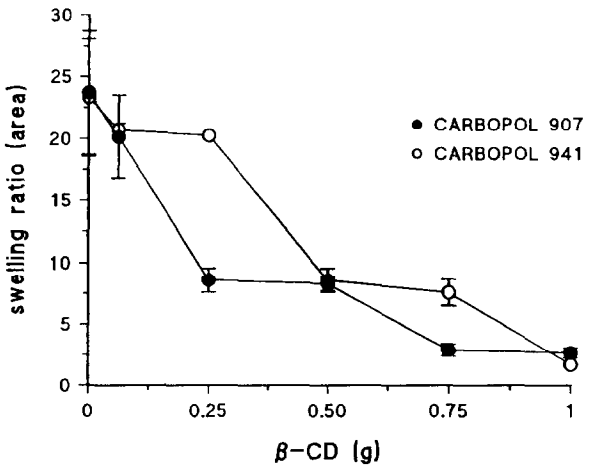

Fig. 4. Swelling ratios (area) (A_{24}/A_0, where A_{24} = disc area at 24 h and A_0 = disc area at 0 h) of Carbopol 907 and Carbopol 941 hydrogels plotted against amount of crosslinking agent (β-cyclodextrin, β-CD) used in the formulation.

in turn, reduces the degree of extensibility of the polymer molecules and so, when swollen, the polymer exerts an elastic retractive force equal to the osmotic potential of the solvent in the polymer at a lower degree of swelling than for lower crosslink densities which therefore exhibit higher degrees of network extensibility (Hunt, 1988). In distilled water at pH 6 (as in the case of the wetting agent used in our studies), the carboxyl groups of the Carbopol (with a pK_a of about 4.75) are ionized: this implies an electrostatic repulsion between adjacent groups, leading to an extension of the polymer chains and, consequently, still greater swelling. Thus, the degree of swelling is the result of a balance between the elastic retractive force and the sum of the osmotic potential of the solvent and the electrostatic repulsion exerted by adjacent carboxyl groups.

The two-way ANOVA applied to the results of our swelling studies showed there were significant differences in swelling after 6 h with respect to both β-cyclodextrin concentration and the PAA molecular weight ($F_{5,36} = 344.000$ and $F_{1,36} = 1000.000$, respectively, for $\alpha < 0.01$). Statistically significant differences were also found for the two factors at 24 h ($F_{5,36} = 217.735$ and $F_{1,36} = 29.813$, respectively, for $\alpha < 0.01$).

Our swelling studies results can also be expressed as A_{24}/A_0, where A_0 is hydrogel disc area at the start of the experiment and A_{24} denotes disc area after 24 h (Fig. 4), and as W_{24}/W_0, where W_0 is disc weight at the start of the experiment and W_{24} represents disc weight after 24 h (Fig. 5). Again it can be seen that swelling increases with reduced crosslinking agent concentration.

When swelling rate (in cm/h) is plotted against time (Fig. 6), it can be seen that there are two peaks, one shortly after the start of the experiment and the other after various hours. The very rapid swelling which occurs initially is due to the entry of water via metastable pores. This mechanism is known as hysteresis of the swelling (Stoy, 1990): such a process occurs when crosslinking takes place during drying, as in the present case. As swelling proceeds, the mechanism is replaced by diffusion, as is characteristic of hydrogels: the second peak in the swelling rate curve indicates the relaxation of polymer chains which occurs on hydration of the interior of the hydrogel (Korsmeyer, 1983). The second peak is more marked in the Carbopol 941 hydrogels than in the Carbopol 907 hydrogels; in the case of the latter, the peak is only evident when crosslinking agent is absent

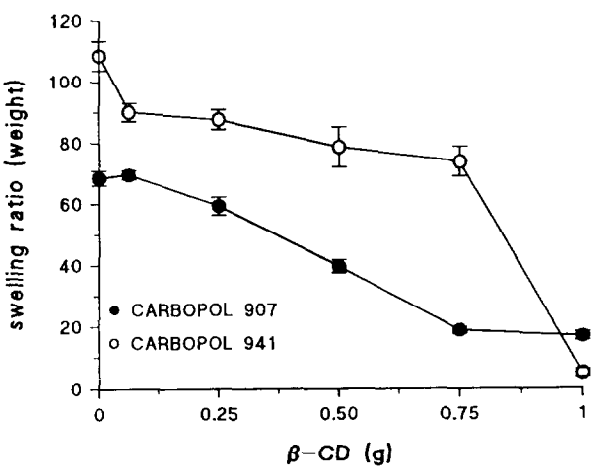

Fig. 5. Swelling ratios (weight) (W_{24}/W_0, where W_{24} = disc weight at 24 h and W_0 = disc weight at 0 h) of Carbopol 907 and Carbopol 941 hydrogels plotted against amount of crosslinking agent (β-cyclodextrin, β-CD) used in the formulation.

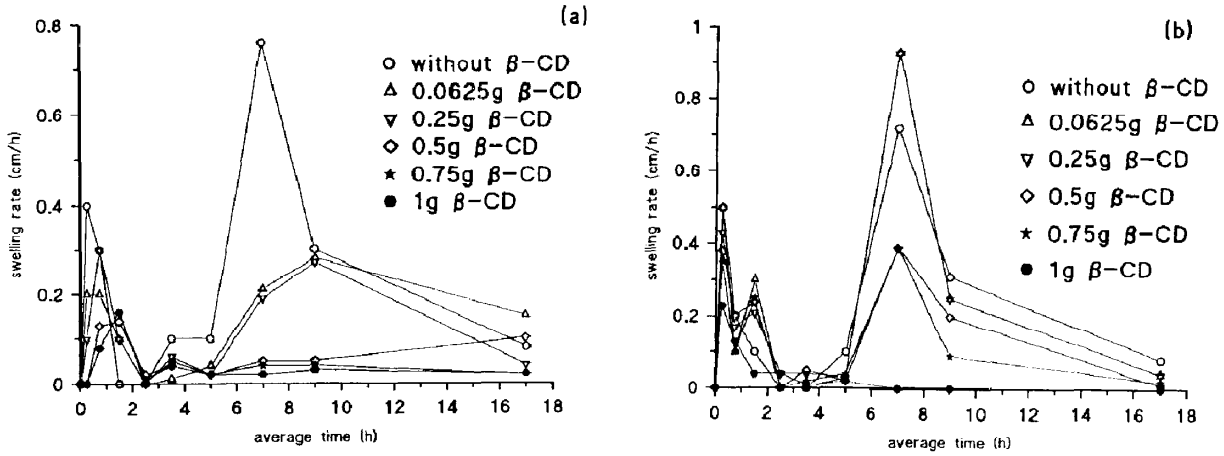

Fig. 6. Mean swelling rates of the hydrogels with (a) Carbopol 907 and (b) Carbopol 941, for the various amounts of crosslinking agent (β-cyclodextrin, β-CD) used in the formulation.

or present at very low concentration. This suggests that incorporation of the crosslinking agent leads to a more rigid structure when the hydrogel is formulated with Carbopol 907: this might be due to structural differences between the two PAAs (García-González et al., 1992).

Release studies

Drug release from hydrogels is generally the result of diffusion processes which are dependent on the degree of swelling and which involve simultaneous absorption of water (Lee, 1985). In the present study, formulation-dependent differences in release profile were apparent from the early stages of the test onwards (Fig. 7).

These curves show that, in addition to greater swelling, lower crosslinking agent concentration leads to more drug release. This is to be expected given that an increase in crosslinking agent concentration leads to a reduction in the average

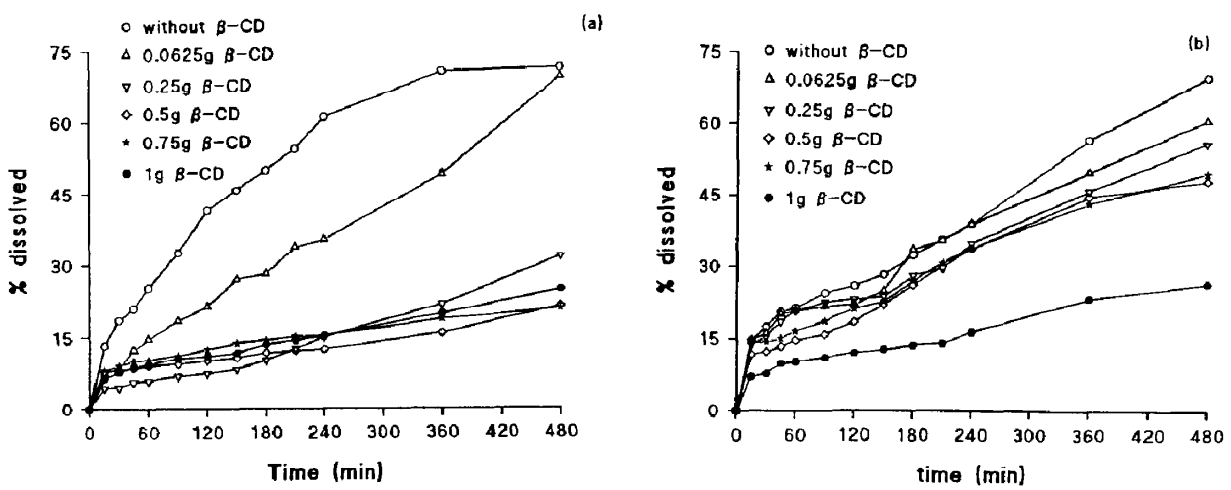

Fig. 7. Drug release profiles from Carbopol 907 (a) and Carbopol 941 (b) hydrogels for the various amounts of crosslinking agent (β-cyclodextrin, β-CD) used in the formulation.

distance between crosslinks, making it more difficult both for the water to enter the gel and for the drug to escape (Hunt, 1988). In crosslinked hydrogels, pores form around the macromolecular chains, so that outward diffusion of the drug is limited by a mesh effect (Peppas and Lustig, 1987); when low concentrations of crosslinking agent are used, these pores are larger and drug release is therefore facilitated.

Drug release from Carbopol 907 hydrogels is less efficient than from Carbopol 941 hydrogels; this may be a consequence of the greater rigidity of the crosslinked Carbopol 907 formulations, as mentioned above in reference to swelling studies.

The effect of β-cyclodextrin and the PAA molecular weight on the dissolution efficiency of the formulatios was assessed using two-way ANOVA. Both factors were statistically significant in the dissolution efficiency after 1 h ($F_{5,36} = 77.465$ and $F_{1,36} = 218.910$, respectively, for $\alpha < 0.01$). Significant differences were also revealed for the dissolution efficiency after 6 h ($F_{5,36} = 167.487$ and $F_{1,36} = 100.583$, respectively, for $\alpha < 0.01$) and 8 h ($F_{5,36} = 181.467$ and $F_{1,36} = 117.072$, respectively, for $\alpha < 0.01$).

Metoclopramide release from PAA hydrogels is thus strongly influenced by the swelling and water uptake characteristics of the polymer. This conclusion is supported by the strong correlations obtained between dissolution efficiency and swelling at 6 h (for Carbopol 907 hydrogels: $r = 0.9283$, $\alpha = 0.007$; for Carbopol 941 hydrogels: $r = 0.9678$, $\alpha = 0.001$) and at 8 h (for Carbopol 907 hydrogels: $r = 0.9177$, $\alpha = 0.010$; for Carbopol 941 hydrogels: $r = 0.8739$, $\alpha = 0.023$). Our results show that both swelling and drug release characteristics of PAA hydrogels are strongly influenced by both crosslinking agent concentration and PAA molecular weight.

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