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Design and evaluation of buccoadhesive metoclopramide hydrogels composed of poly(acrylic acid) crosslinked with sucrose

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Summary

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

Introduction

Dosage forms designed for buccal administration should not cause irritation and should be small and flexible enough to be accepted by the patient. These requirements are met by crosslinked hydrogels, which can be defined as substances that absorb water and swell without dissolving (Graham and McNeill, 1984). The use of hydrogels as adhesive preparations for drug delivery has acquired considerable importance in recent years (Doelker, 1987; Safwat et al., 1988; Bremecker, 1989; De Vries et al., 1989); this is largely because earlier formulations for buccal and sublingual drug delivery interfered with eating, drinking and speaking, and could therefore only be used for limited periods. The hydrogels are highly flexible and thus much more readily tolerated by the patient. Buccal administration of drugs is suitable for a wide range of applications: notable examples include the administration of local analgesics and antibiotics for the treatment of aphthas (Yotsuyanagi et al., 1985), and of local anaesthetics and antiseptics for the treatment of complications following tooth extraction (Turakka et al. 1986). Size of the dosage form should not exceed 12 cm^2 for buccal application or 3 cm^2 for sublingual or gingival application (Anders and Merkle, 1989).

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Here, we have evaluated the influence of crosslinking agent (sucrose) concentration and PAA molecular weight on hydrogel swelling and metoclopramide release characteristics.

Materials and Methods

Materials

The bioadhesive PAAs 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 0012). Crosslinking agent was sucrose (Probus, batch 18862). All reagents were analytical grade.

Preparation of hydrogels

Solutions of PAA (Carbopol 907 or Carbopol 941), metoclopramide and sucrose were made up as shown in Table 1. A 1:1 water/acetone mixture was used as solvent. Aliquots of the solutions were placed in 5-cm diameter glass vessels, and the solvent was evaporated in an oven at 40°C; the fine film obtained was stored at 90°C for 4 h to allow completion of the crosslinking process (which occurs as a result of a condensation reaction). 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

Composition of the formulations studied

PAA [a] (g)	Sucrose (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] Carbopol 907 or Carbopol 941.

Studies of swelling

1-cm diameter discs of hydrogels produced by each of the formulations studied were placed in 9-cm diameter Petri dishes; 75 ml of distilled water was then added, and disc diameter was measured at 0 and 30 min and at 1, 2, 3, 4, 6, 8, 10 and 24 h. Four replications of each test were carried out.

Release studies

Release studies were carried out with the aid of a modified USP No. II dissolution apparatus (Probus, France) set to a stirring velocity of 100 rpm. Samples of each hydrogel formulation in steel baskets were placed in the dissolution flasks in 500 ml of distilled water at 37°C. 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 (D.E.) (Khan and Rhodes, 1972, 1975) at 1, 6 and 8 h.

Results and Discussion

Studies of swelling

The swellability of a hydrogel can be controlled by modifying its chemical structure: for example, crosslink density can be varied and comonomers can be incorporated (Bae et al., 1989). Here, we have carried out a study of the effects of sucrose concentration and polymer molecular weight on hydrogel swelling. Swelling curves for the various formulations studied are shown in Fig. 1.

Two-way ANOVA applied to the results of our swelling trials indicated that the effects on swelling of PAA molecular weight (PMW), sucrose concentration (SC) and the interaction between them (PMW × SC) were all significant, both at 6 h (PMW: $F_{1,36} = 45.176$, $\alpha < 0.01$; SC: $F_{5,36} = 194.576$, $\alpha < 0.01$; PMW × SC: $F_{5,36} = 6.000$, $\alpha < 0.01$) and at 24 h (PMW: $F_{1,36} = 48.442$, $\alpha < 0.01$; SC: $F_{5,36} = 169.826$, $\alpha < 0.01$; PMW × SC: $F_{5,36} = 9.015$, $\alpha < 0.01$).

Higher sucrose concentrations led to reduced swelling. This can be explained as follows. In hydrogels formulated with a higher crosslinking agent concentration, crosslink density will be higher and interlink length will be correspondingly lower. Chain extensibility will thus be lower, and the retractive elastic force exerted by the chain during swelling will accordingly be of comparable magnitude to solvent osmotic potential in the polymer. A lower crosslink density, on the other hand, would lead to increased chain extensibility (Hunt, 1988).

The results of our swelling studies can be expressed as S_t/S_{24}, where S_t is swelling at time

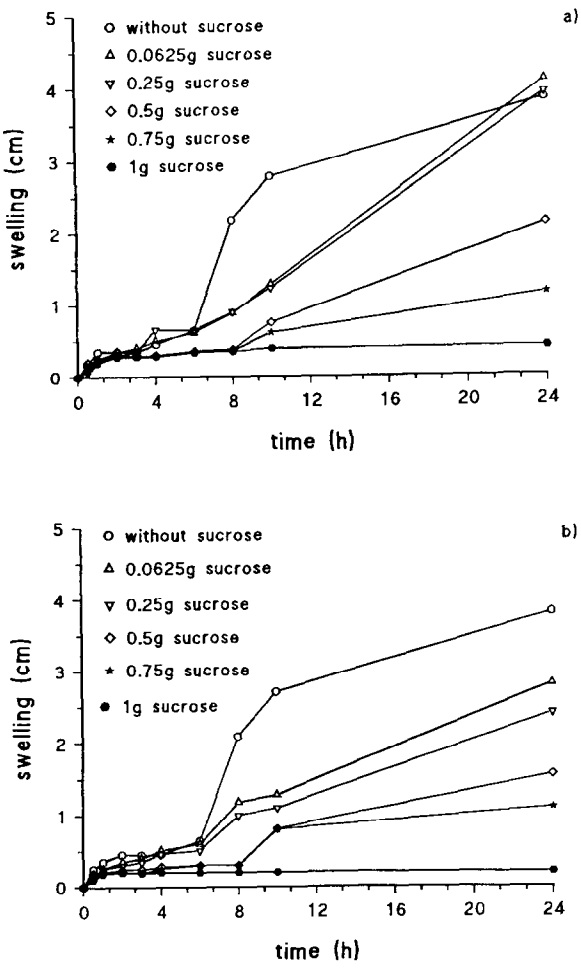

Fig. 1. Swelling profiles (increase in disc diameter against time) for Carbopol 907 hydrogels (a) and Carbopol 941 hydrogels (b).

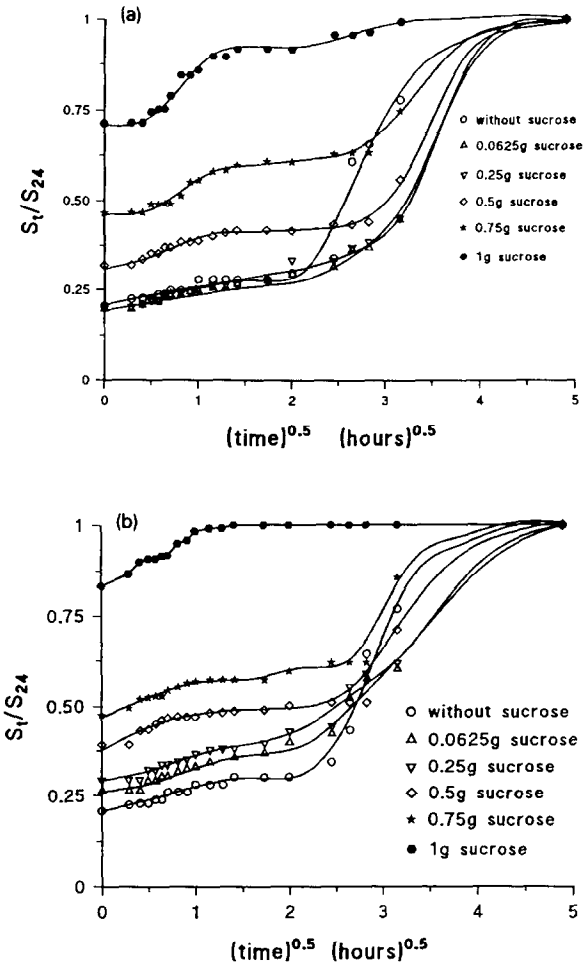

Fig. 2. Plots of S_t/S_{24} against time$^{0.5}$ for Carbopol 907 hydrogels (a) and Carbopol 941 hydrogels (b), where S_t is swelling at time t and S_{24} swelling after 24 h.

t and S_{24} denotes swelling after 24 h. The ratios S_t/S_{24} for each formulation were plotted against the square root of time (h) from the start of the test in Fig. 2. In systems conforming ideally to Fick's law, a plot of this type gives a straight line. Our data, however, resulted in sigmoidal curves, indicating that diffusion of water into these systems does not conform to Fick's law, as is characteristic of PAA hydrogels (Hunt, 1988). During the first 4 h, water uptake is proportional to the square root of time, and the system initially conforms to Fick's law. Similar results were obtained in studies of crosslinked albumin hydrogels (Shalaby and Park, 1990). However it should be

pointed out that in the highly crosslinked systems studied by us the initial phase is not linear but sigmoid. This may be attributable to the hysteresis mechanism of swelling which is typical of systems in which crosslinking takes place during drying (Stoy, 1990), as follows: when crosslinking takes place during drying, metastable pores form in the hydrogel. When the hydrogel comes into contact with the solvent, swelling initially occurs as a result of the entry of water via these pores; this is followed by swelling as a result of diffusion processes. The 'initial sigmoid' observed in some formulations is thus attributable to these metastable pores, and in fact provides an indirect measure of the degree of crosslinking.

The swellabilities of hydrogels are often compared using the weight swelling ratio W_{24}/W_0, where W_{24} is disc weight after 24 h and W_0 represents disc weight at the outset of the study (Park and Robinson, 1987), and the area swelling ratio A_{24}/A_0, where A_{24} is disc area after 24 h and A_0 denotes disc area at the outset of the study (Ricka and Tanaka, 1985). In the present case, the tendency for swellability to decline with increasing crosslinking agent concentration is apparent both when data are expressed as weight swelling ratios (Fig. 3) and as area swelling ratios (Fig. 4).

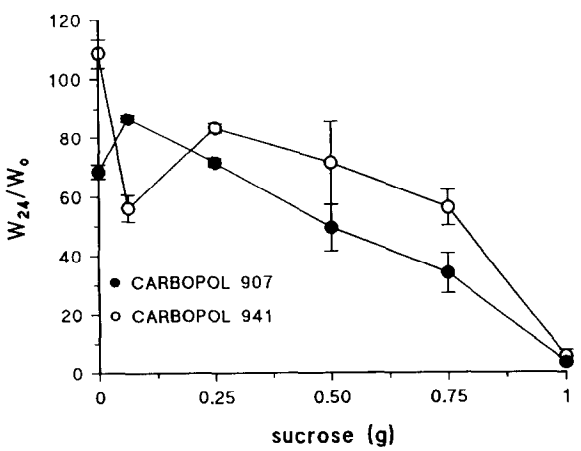

Fig. 3. Weight swelling ratio (W_{24}/W_0, where W_{24} is disc weight after 24 h and W_0 denotes disc weight at outset) plotted against sucrose concentration for Carbopol 907 and Carbopol 941 hydrogels.

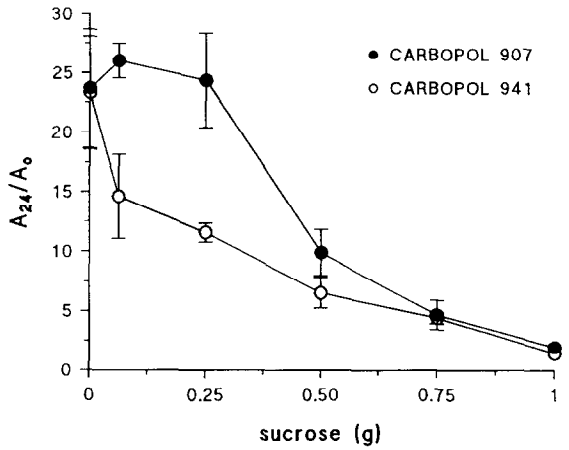

Fig. 4. Area swelling ratio (A_{24}/A_0, where A_{24} is disc area after 24 h and A_0 the disc area at outset) plotted against sucrose concentration for Carbopol 907 and Carbopol 941 hydrogels.

Release studies

Metoclopramide release profiles from the different hydrogel formulations are shown in Fig. 5. When sucrose is absent or present at very low concentrations, the profiles are characteristic of systems in which release is due not only to diffusion but also to erosion of the vehicle (Doelker, 1985). Drug release is more rapid from the hydrogels formulated without sucrose; this is as expected since in these formulations there is a reduced barrier to release.

Two-way ANOVA indicated that the effects on dissolution efficiency of PAA molecular weight (PMW), sucrose concentration (SC) and the interaction between them (PMW × SC) were all significant, at 1 h (PMW: $F_{1,36} = 24.637$, $\alpha < 0.01$; SC: $F_{5,36} = 49.892$, $\alpha < 0.01$; PMW × SC: $F_{5,36} = 13.464$, $\alpha < 0.01$), 6 h (PMW: $F_{1,36} = 9.478$, $\alpha < 0.01$; SC: $F_{5,36} = 149.196$, $\alpha < 0.01$; PMW × SC: $F_{5,36} = 40.089$, $\alpha < 0.01$) and 8 h (PMW: $F_{1,36} = 20.465$, $\alpha < 0.01$; SC: $F_{5,36} = 170.804$, $\alpha < 0.01$; PMW × SC: $F_{5,36} = 30.229$, $\alpha < 0.01$).

Fig. 6 shows the percentage of total metoclopramide released, at 1, 6 and 8 h, plotted against amount of crosslinking agent used in the formulation. Drug release from Carbopol 907 hydrogels reaches a constant level with 0.25 g of sucrose or more (6 and 8 h), the value decreasing to 0.0625 g for the 1 h results. In the case of Carbopol 941

hydrogels, the constant level was reached with 0.0625 g of sucrose.

The most efficient release is displayed by the formulations without sucrose or with only 0.0625 g of sucrose: these formulations are those in which swelling is most pronounced and the quantity of absorbed water is highest, favouring drug release to the medium.

Our results indicate that, on the basis of an understanding of parameters such as water uptake capacity, the release of active principle from hydrogels can be modified and even quantitatively controlled from these mucoadhesive drug delivery systems (Liebowitz et al., 1987; Michaud et al., 1987).

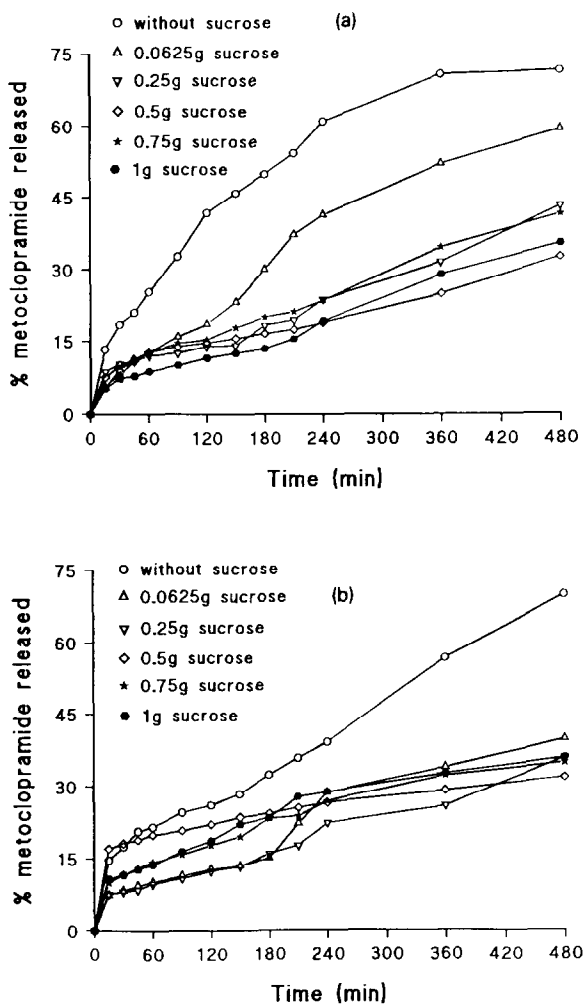

Fig. 5. Drug release profiles (i.e., percentage of total drug content released plotted against time) for Carbopol 907 hydrogels (a) and Carbopol 941 hydrogels (b).

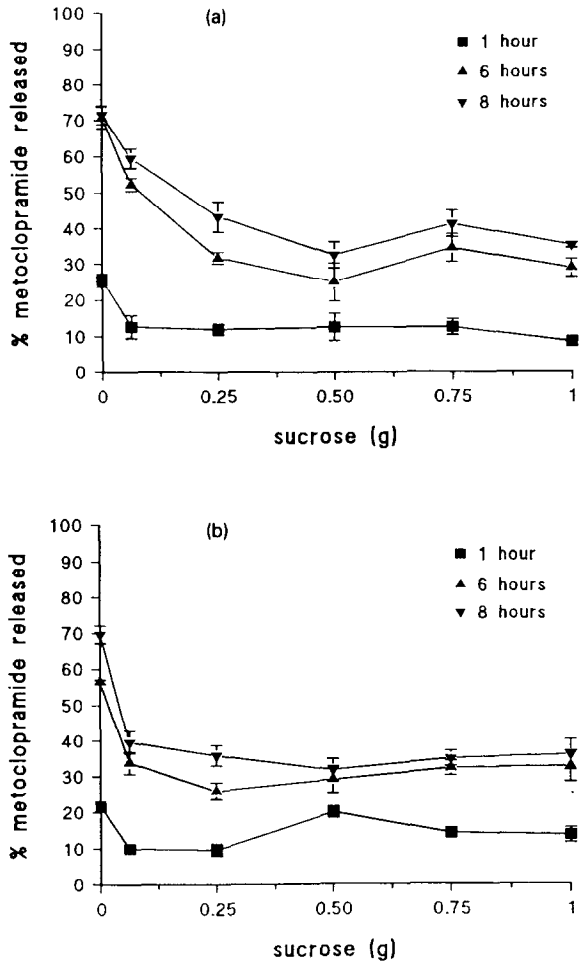

Fig. 6. Percentage of total drug content released, at 1, 6 and 8 h, plotted against sucrose concentration, for Carbopol 907 hydrogels (a) and Carbopol 941 hydrogels (b).

Acknowledgements

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