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Influence of glycerol concentration and carbopol molecular weight on swelling and drug release characteristics of metoclopramide hydrogels

N. García González [a,*], I.W. Kellaway [b], H. Blanco Fuente [a], S. Anguiano Igea [a], B. Delgado Charro [a], F.J. Otero Espinar [a], J. Blanco Méndez [a]

[a] *Laboratorio de Farmacia Galénica, Facultad de Farmacia, Universidad de Santiago de Compostela, Avda de las Ciencias s / n, 15706 Santiago de Compostela, Spain* [b] *Welsh School of Pharmacy, UWCC, Cardiff CF1 3XF, UK*

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Abstract

The formulation of glycerol-crosslinked Carbopol 907 and Carbopol 941 metoclopramide hydrogels for buccal administration were investigated. Infrared spectroscopy showed that crosslinking was the result of ester formation between Carbopol carboxyl groups and glycerol hydroxyl groups. The effects of Carbopol molecular weight and glycerol concentration on swelling and drug release characteristics were evaluated. In all glycerol-containing formulations drug dissolution efficiencies were low, and both dissolution efficiency and swelling rate decreased with increasing glycerol concentration, confirming the very high crosslinking capacity of glycerol.

Key words: Hydrogel; Metoclopramide; Swelling; Dissolution; Glycerol; Carbopol; Crosslinking; Bioadhesion

1. Introduction

Drug dosage forms based on mucoadhesive polymers have been the subject of considerable interest in recent years for the following reasons (Park and Robinson, 1984; Veillard et al., 1987; Spence Leung and Robinson, 1988; Ranga Rao et al., 1989). Firstly, they can be targeted to specific regions, thus optimising the availability of the active principle. Secondly, they ensure a large area of contact with the absorption surface and facilitate the modification of membrane permeability which is necessary for the absorption of macromolecules such as peptides. Thirdly, they prolong drug residence time, reducing the dosage frequency required and thus making the treatment more acceptable to the patient. Of the potentially useful polymers (Gayot, 1985), the Carbopols or poly(acrylic acid)s (PAAs) are of particular value because of their very high bioadhesiveness (Smart et al., 1984; Lejoyeux et al., 1989) and their biocompatibility. The buccal mucosa is one of the preferred sites for drug administration, since it is easily accessible (Ranga Rao et al., 1989) and has an abundant blood supply. It is also highly permeable: an area of 2 cm^2 can

* Corresponding author.

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absorb 10–20 mg of drug in 24 h (Robinson et al., 1987).

In this study we have evaluated the influence of crosslinking agent (glycerol) concentration and polymer molecular weight on swelling characteristics and drug (metoclopramide) release kinetics of Carbopol hydrogels. We also used infrared spectroscopy to investigate bond formation between glycerol and Carbopols.

2. Materials and methods

2.1. Materials

Carbopol 907 (nominal molecular weight 450 000) was supplied by B.F. Goodrich (batch F445028) and Carbopol 941 (nominal molecular weight 1 250 000) by J. Escuder (batch 0014). Metoclopramide base was obtained by neutralisation of metoclopramide dihydrochloride ($C_{14}H_{22}ClN_3O_2 \cdot 2HCl \cdot H_2O$) supplied by J. Escuder (batch 012). Glycerol was supplied by Sigma (batch 50H0703). Solvents were of analytical grade.

2.2. Preparation of hydrogels

Solutions containing 5 g of polymer (Carbopol 907 or Carbopol 941), 1 g of metoclopramide, 200 ml of solvent (1 : 1 water : acetone) and 0, 0.0625, 0.25, 0.5, 0.75 or 1 g of glycerol were made up in glass vessels, which were then placed in a drying oven at 40°C until the solvent had evaporated, leaving the hydrogel as a thin film. Curing was completed by further heating at 110°C for 4 h. The films were then left in a moist chamber (98% relative humidity) for 24 h to make them flexible, and the 1 cm discs used in the subsequent studies were punched out.

2.3. Infrared spectroscopy

Hydrogels were characterized in KBr pellets by Fourier transform infrared (FT-IR) spectroscopy in a Cygnus 100 apparatus (Mattson Instruments, U.S.A.).

2.4. Swelling studies

1-cm diameter hydrogel discs were placed in Petri dishes containing 75 ml of distilled water at room temperature, and disc diameter was recorded at regular intervals. Discs were also weighed before wetting and after 24 h. This experiment was run four times for each formulation.

2.5. Drug release studies

Metoclopramide release kinetics were investigated by enclosing 1 cm diameter hydrogel discs (containing approx. 12 mg of metoclopramide) in 1 mm mesh stainless-steel baskets which were placed in the bottom of a dissolution flask containing 500 ml of distilled water at 37°C with mechanical stirring at 100 rpm. 5-ml samples were removed at regular intervals; following filtration, metoclopramide concentration in these aliquots was determined by spectrophotometry at 273 nm. Drug release profiles were characterized by cal-

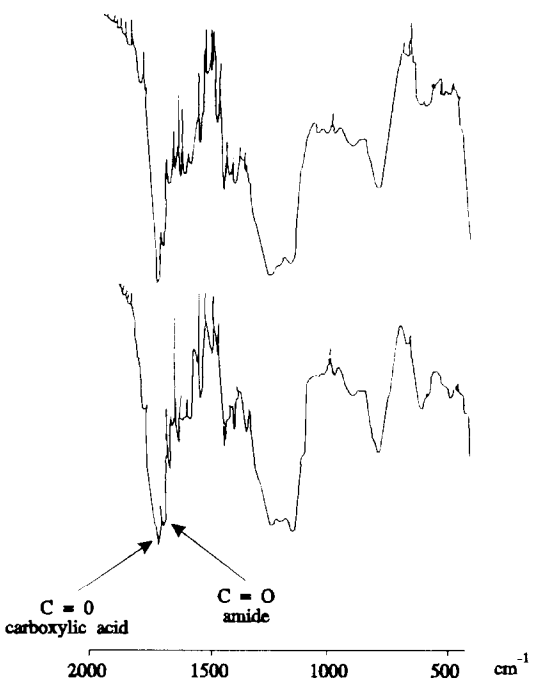

Fig. 1. FT-IR spectra of metoclopramide hydrogels [(a) Carbopol 907; (b) Carbopol 941] formulated without glycerol.

culation of the dissolution efficiency (DE) (Khan and Rhodes, 1975).

3. Results and discussion

3.1. Infrared spectroscopy

Fig. 1 shows the characteristic FT-IR spectroscopic absorption bands of Carbopol discs formulated without glycerol. The band at 1651 cm^{-1} corresponds to the metoclopramide amide groups (C=O stretching of amide) and that at 1712 cm^{-1} corresponds to polymer acidic groups (C=O stretching of acid). When glycerol is included in the hydrogels (Fig. 2) a new band appears at 1737 cm^{-1} (C=O stretching of ester), corresponding to the ester formed between the polymer carboxyl groups and the glycerol primary hydroxyl groups during the crosslinking process.

3.2. Swelling studies

The degree of swelling is related to both drug release kinetics and bioadhesiveness. Slightly swollen hydrogels are mucoadhesive but the bonds

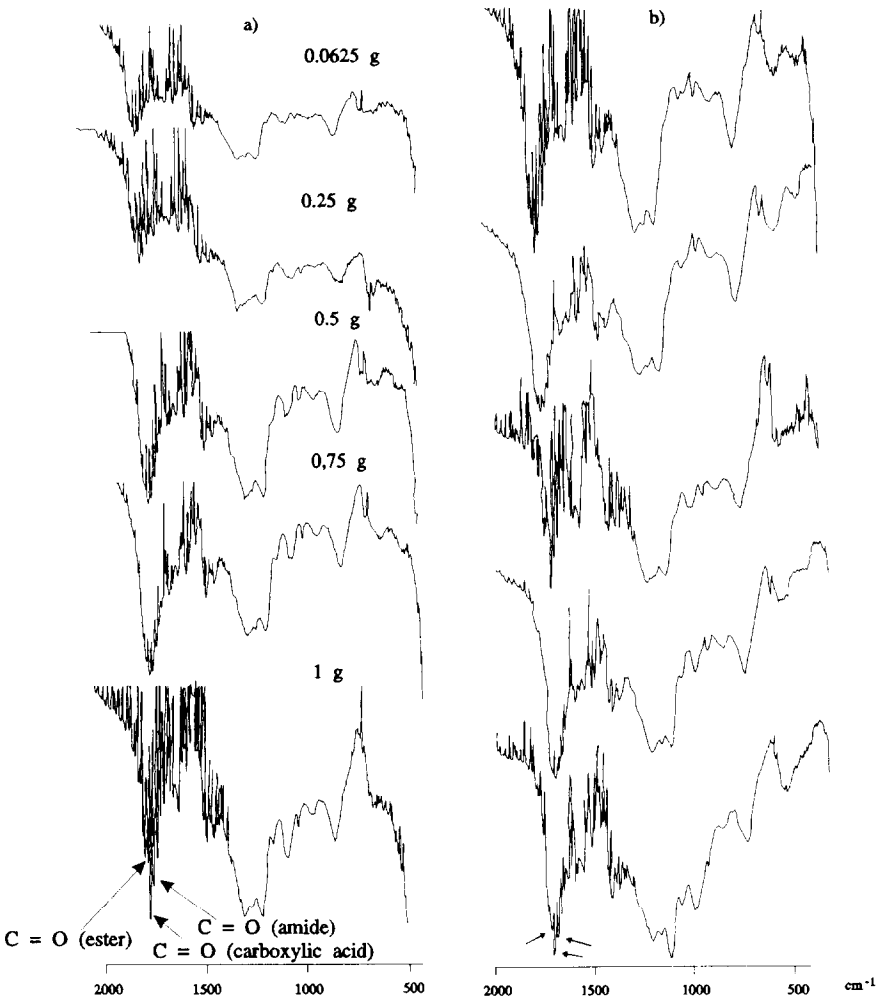

Fig. 2. FT-IR spectra of metoclopramide hydrogels [(a) Carbopol 907; (b) Carbopol 941] formulated with 0.0625, 0.25, 0.50, 1 g of glycerol per 5 g of polymer.

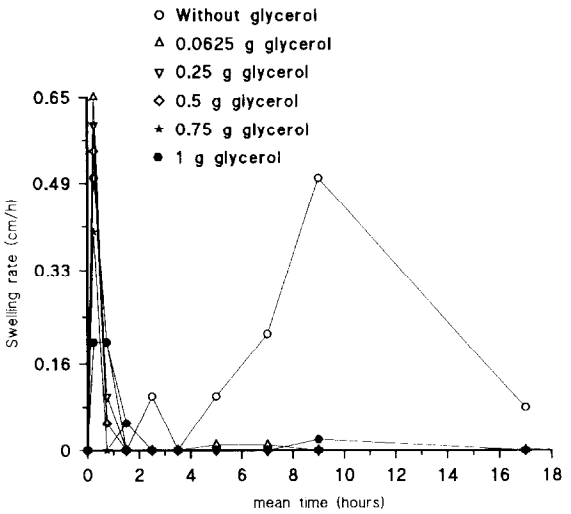

Fig. 3. Swelling rate plotted vs time for Carbopol 941 metoclopramide hydrogels.

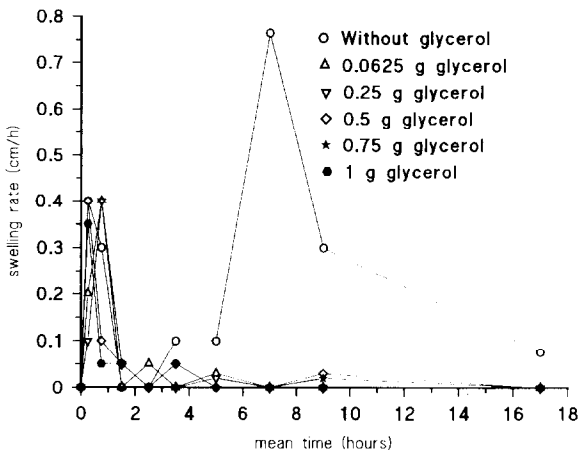

Fig. 4. Swelling rate plotted vs time for Carbopol 907 metoclopramide hydrogels.

formed are not very strong (Gurny et al., 1984); excessive swelling again leads to reduced mucoadhesiveness, because water molecules bind to the polymer carboxyl groups required for adhesion (Deasy and O'Neill, 1989). In order for both drug release and adhesiveness to be acceptable, it is necessary to control the swelling characteristics of the hydrogel, and this can be achieved with the aid of crosslinking agents.

Swelling rate peaked rapidly for all formulations, though maximum rates were higher in Carbopol 941 hydrogels (Fig. 3) than Carbopol 907 hydrogels (Fig. 4). Water uptake by crosslinked hydrogels (when crosslinking takes place during drying) may occur initially through metastable pores (hysteresis of the swelling) and as swelling proceeds, the mechanism is replaced by diffusion (Stoy, 1990). In the case of glycerol-crosslinked Carbopol hydrogels only the first of these mechanisms was observed for each formulation. This suggests that incorporation of a strong crosslinking agent like glycerol leads to a rigid structure.

The effects of glycerol concentration (GLY) and Carbopol molecular weight (MW) on disc diameter after 6 and 24 h wetting were investigated using two-way analysis of variance (ANOVA). In both cases the effects of the two factors, and of the interaction between them, were significant at the 1% level (6 h: GLY $F_{4,30} = 243.00$, MW $F_{1,30} = 75.00$, GLY × MW $F_{4,30} = 15.00$; 24 h: GLY $F_{4,30} = 1000.00$, MW $F_{1,30} = 1000.00$, GLY × MW $F_{4,30} = 1000.00$). The ratio of disc weight after 24 h to disc weight before wetting (W_{24}/W_0) decreased with increasing glycerol concentration (Fig. 5).

The results of our swelling studies confirm the very high crosslinking capacity of glycerol.

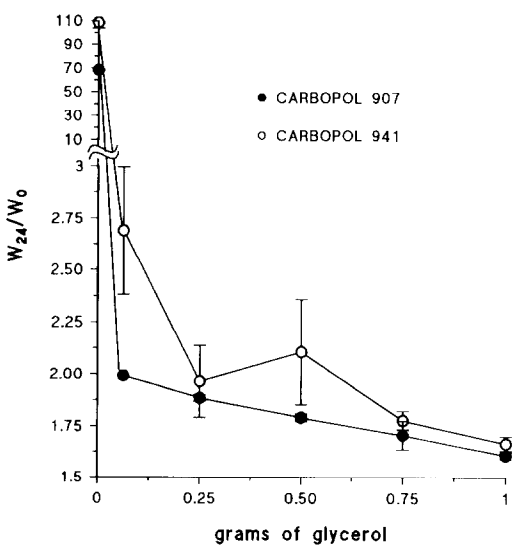

Fig. 5. Influence of glycerol concentration on the W_{24}/W_0 swelling index for Carbopol 907 and 941 metoclopramide hydrogels.

3.3. Drug release studies

Drug release profiles from the different hydrogels are shown in Fig. 6 and 7. When glycerol is absent the profiles are characteristic of systems in which release is due not only to diffusion but also to erosion of the vehicle. Drug release profiles from the glycerol-crosslinked Carbopol hydrogels show a burst effect phenomenon in the first 30 min. This phenomenon may be due to the instantaneous release of drug molecules accummulated on the device surface during storage in a moist chamber and by the diffusivity of the drug through metastable pores. The second part of release curves exibit a quasi-zero-order release of metoclopramide. When the rate of active agent transport through the gel region is higher than that of movement of the gel-glassy polymer interface, the release rate is then independent of time (pseudo-case II transport mechanism).

The amount of drug released was appreciably higher in hydrogels containing only 0.0625 or 0.25 g of glycerol per 5 g of Carbopol. The effects of glycerol concentration (GLY) and Carbopol molecular weight (MW) on dissolution efficiency (DE) after 1, 6 and 8 h were investigated using two-way analysis of variance (ANOVA). At all three times the effects of the two factors, and of

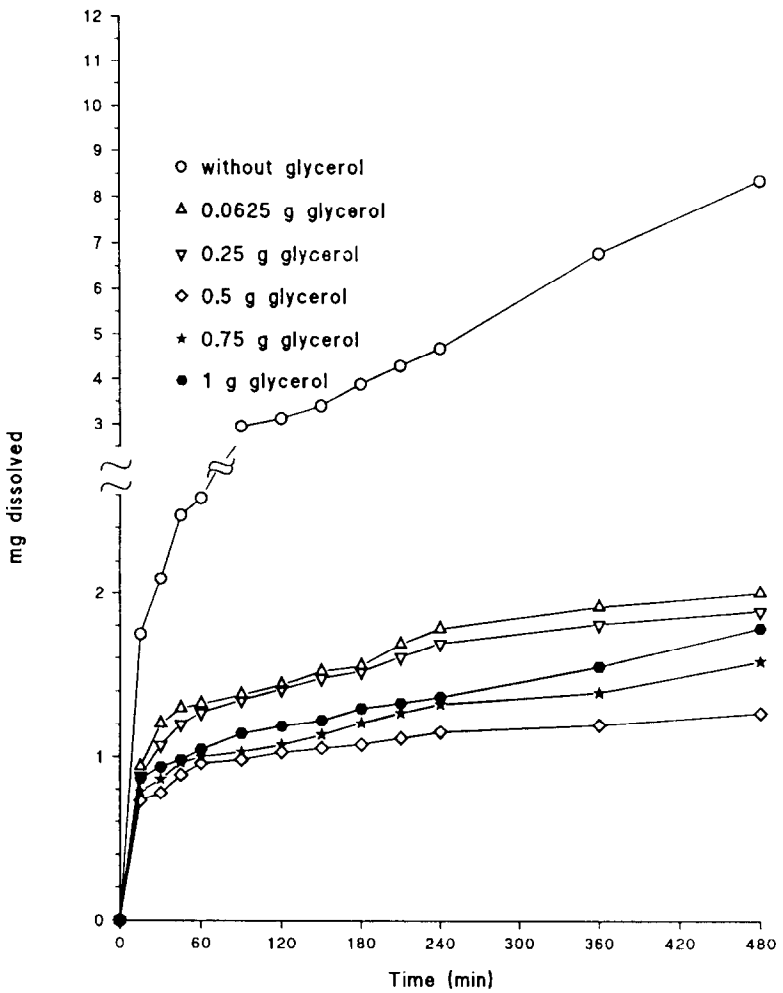

Fig. 6. Dissolution profiles for Carbopol 941 metoclopramide hydrogels formulated with different glycerol concentrations.

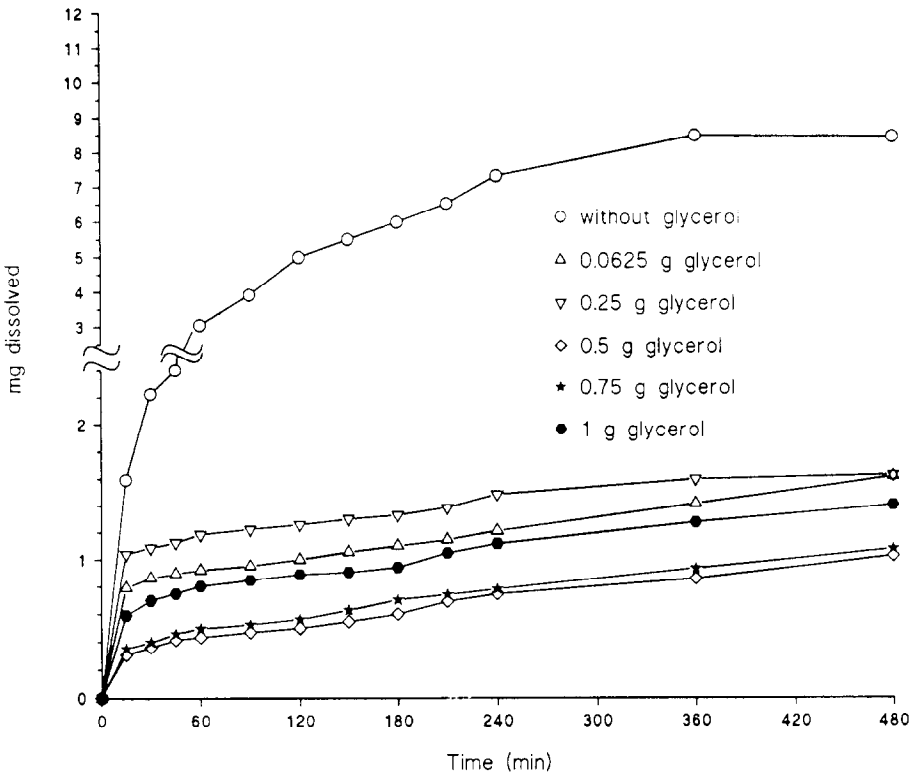

Fig. 7. Dissolution profiles for Carbopol 907 metoclopramide hydrogels formulated with different glycerol concentrations.

the interaction between them, were significant at the 1% level (except in the case of the GLY × MW interaction after 8 h) (1 h: GLY $F_{4,30} = 36.84$, MW $F_{1,30} = 83.69$, GLY × MW $F_{4,30} = 7.58$; 6 h: GLY $F_{4,30} = 54.03$, MW $F_{1,30} = 140.85$, GLY × MW $F_{4,30} = 4.46$; 8 h: GLY $F_{4,30} = 56.50$, MW $F_{1,30} = 136.89$, GLY × MW $F_{4,30} = 3.51$, n.s.). In all cases, the amount of drug liberated was small (less than 20% of the dose released in 8 h). Glycerol-crosslinked Carbopol hydrogels may only therefore be suitable for drugs which act at very low dosages.

4. Acknowledgement

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