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Evaluation of polymeric films for buccal drug delivery

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Received June 27, 2008; accepted September 4, 2008

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Pharmazie 64: 197–201 (2009) *doi: 10.1691/ph.2009.8188*

The objective of this study was to evaluate the suitability of the bioadhesive polymers Carbopol 981 NF, Carbopol 1382 and sodium alginate as possible carriers for films for buccal drug delivery. Films were prepared by casting and solvent evaporation method, using propylene glycol as plasticizer and hydoxypropylmethyl cellulose to modify the properties of the films. The bioadhesive and mechanical properties of the films were evaluated with a TA-XT2i Texture Analyser. The alginate films exhibited greater bioadhesion and showed higher tensile strength and elasticity than the Carbopol films. There was a marked difference in the way the polymeric films hydrated in simulated saliva solution. Upon swelling the diameter of the alginate films did not increase but their thickness increases slightly, however the surface area of the Carbopol films increased significantly which points to them being unsuitable for drug delivery to the buccal mucosa. Excessive hydration of a polymeric film for buccal delivery could lead to decreasing adhesive strength and possibly loss of adhesion and hence shorter duration of retention. HPMC appeared to improve the properties of the films, affecting the bioadhesiveness and increasing tensile strength. For the alginate films an increase in HPMC leads to an increase in elasticity but for the Carbopol polymers this was not the case. The release profile of a model drug, sumatriptan succinate, showed that drug release was by diffusion rather than due to disintegration of the films. The results indicate that sodium alginate may be a suitable carrier for polymeric films for use in the buccal cavity.

1. Introduction

There are several advantages to using the oral cavity for transmucosal drug delivery. The buccal mucosa is readily accessible, it is relatively permeable with a rich blood supply and by delivering drugs via the buccal mucosa the first-pass effect is avoided (Hao and Heng 2003; Shojaei 1998; Smart 2004). The main limiting factor for using the buccal route for drug delivery is the limited retention at the site of absorption as the dosage form can be washed away by the salivary flow. With the use of mucoadhesive polymers in the dosage form the drug is localized in a particular region and the retention time is prolonged thereby increasing bioavailability (Bruschiand and de Freitas 2005).

A number of dosage forms containing mucoadhesive polymers have been developed for buccal drug delivery, including tablets, beads, ointments, hydrogels, patches and films (Genta et al. 2005; Nagai and Machida 1993; Park and Munday 2002; Remunan-López et al. 1998; Sveinsson and Holbrook 1993). There has been a growing interest in using bioadhesive films in the buccal cavity for enhanced systemic delivery or for prolonged localized delivery (Peh and Wong 1999). Buccal drug delivery films could be a better option than other dosage forms especially with regard to ease of use and the flexibility of the delivery system and additionally films can give a protective layer across ulcers thereby reducing pain or discomfort. Films are matrix systems, where a drug is dispersed in a polymer and the release of drug is due to diffusion of the drug out of the system or because of the disintegration of the system. It is relatively simple to control the size and shape of films according to the area intended for treatment and application to the oral mucosa is easy and usually straightforward for the patient (Vyas 2000).

Many polymers have good bioadhesive properties and could therefore be potential excipients for use in buccal films (Salmat-Miller 2005). The ideal polymer should have good bioadhesive properties, form a flexible continuous film of sufficient tensile strength but upon hydration the degree of swelling should be limited as else it could become uncomfortable for the patient. Excessive hydration could lead to decreasing adhesive strength and possibly loss of adhesion.

The objective of this study was to evaluate the suitability of different polymers which have previously been shown to have bioadhesive properties, as possible carriers in films for buccal delivery. The polymers chosen were the biopolymer sodium alginate and the synthetic polymers Carbopol 981 NF, Carbopol 1382. The Carbopol polymers differ in that Carbopol 981 (CP981) is a homopolymer of acrylic acid with a lower viscosity than Carbopol 1382 (CP1382) which is a copolymer. Films (Table 1) were prepared using hydoxypropylmethyl cellulose (HPMC) to

Table 1: Compositions of mucoadhesive films

Formulations	2% Alginate	2% CP981	2% CP1382	2% HPMC	PG
Alg	1			0	1
Alg/HPMC 70/30	0.7			0.3	1
Alg/HPMC 50/30	0.5			0.5	1
Alg/HPMC 30/70	0.3			0.7	1
CP981		1		0	1
CP981/HPMC 70/30		0.7		0.3	1
CP981/HPMC 50/30		0.5		0.5	1
CP981/HPMC 30/70		0.3		0.7	1
CP1382			1	0	1
CP1382/HPMC 70/30			0.7	0.3	1
CP1382/HPMC 50/50			0.5	0.5	1
CP1382/HPMC 30/70			0.3	0.7	1

modify the properties of the films and propylene glycol as a plasticizer. The polymeric films were evaluated in terms of bioadhesion and tensile strength as well as swelling properties and to assess drug release rate from the films sumatriptan succinate was chosen as a model drug.

2. Investigations and results

The prepared films were clear and transparent, with a thickness of 0.04–0.05 mm. Without added HPMC the CP981 films were highly elastic and sticky, CP1382 films were uneven with holes and alginate films were fragile and difficult to handle. Plasticizer content did not affect appearance of films but increased amount of plasticizer lead to increase in flexibility as expected.

2.1. Bioadhesion

The presence of HPMC in the films had a marked effect upon the bioadhesiveness. For films without HPMC the CP981 films showed the highest work of adhesion (Fig. 1). For alginate films with 30% and 50% HPMC the work of adhesion was significantly higher than for films without HPMC. However when the amount of HPMC in alginate films was increased to 70%, the bioadhesion decreased. The inclusion of HPMC in the films did not have a significant effect on the bioadhesion of CP1382 films but in CP981 films the presence of HPMC caused a significant lowering of adhesive strength. In general the alginate films with HPMC showed higher bioadhesive strength than the Carbopol films with HPMC. The increased amount of propylene glycol had a lowering effect on the bioadhesion of alginate films and also the Carbopol films although not statistically significant (Table 2 and Fig. 2).

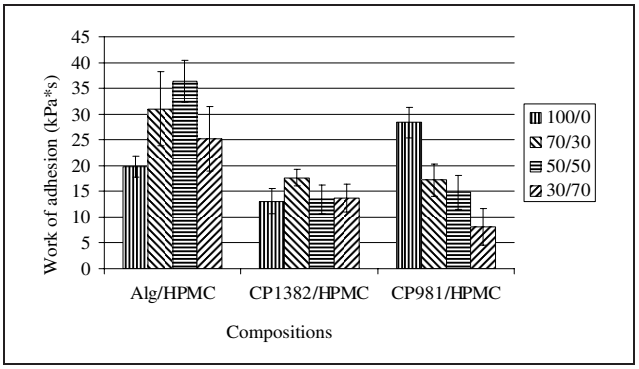

Fig. 1: Mucoadhesion of polymer films as function of alginate : HPMC and Carbopol : HPMC ratio. Ratio of plasticizer to polymer 1 : 1

Table 2: Compositions of films with changing propylene glycol concentration

Alg/HPMC/PG	CP1382/HPMC/PG
0.5/0.5/0.5	0.5/0.5/0.5
0.5/0.5/1.0	0.5/0.5/1.0
0.5/0.5/1.2	0.5/0.5/1.2
0.5/0.5/1.5	0.5/0.5/1.5

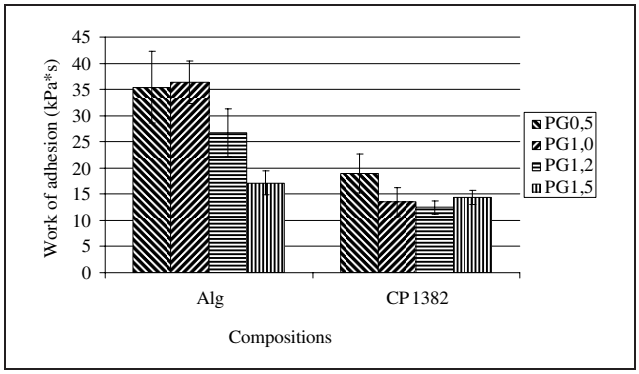

Fig. 2: Effect of PG concentration on mucoadhesion of alginate : HPMC (50/50) and CP1382 : HPMC (50/50) films

2.2. Swelling/disintegration

The effect of different compositions on the swelling index of the films is shown in Figs. 3 and 5. At the outset the alginate films take up water and hydrate faster than the Carbopol films but then reach equilibrium before starting to disintegrate. It should be noted that the swelling index shows the increase in weight but does not indicate change in the surface area. There was a clear difference in the way the different polymer films hydrated. Fig. 4 shows photographs of the swelling of alginate and CP1382 films in simulated saliva solution. Upon hydrating the surface area of the CP films increased significantly (Fig. 4c). The diameter of alginate films (Fig. 4b) did not increase but their thickness increased slightly. The degree of surface increase of the CP films could be different *in vivo* when the films have already adhered to mucus membranes which would restrict the surface increase.

The swelling of CP981 films did not appear to be affected by the presence of HPMC, however for CP1382 as well as alginate films there was less swelling of films not containing HPMC. The alginate films disintegrated over a period of time and the higher the concentration of sodium alginate the faster they disintegrated. It appears that HPMC plays an important role in the swelling of the films; there is little swelling in the alginate film which is free of HPMC, but the

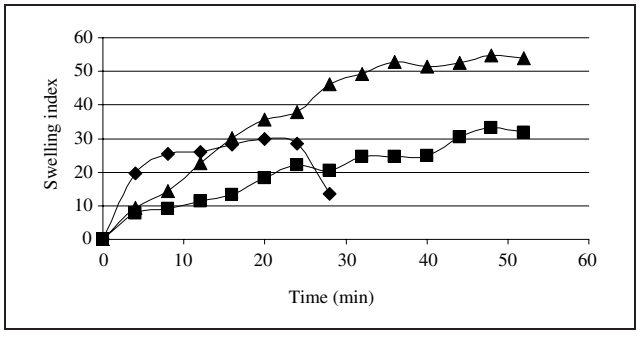

Fig. 3: Comparison of the swelling index for films made from alginate, Carbopol 981 and Carbopol 1382 in simulated saliva solution

Fig. 4:
Swelling of alginate and Carbopol 1832 films in simulated saliva solution: a) initial size; b) alginate film disintegrating after 30 min; c) Carbopol 1382 film expanding after 30 min. The films contain a dye to make them visible in the solution

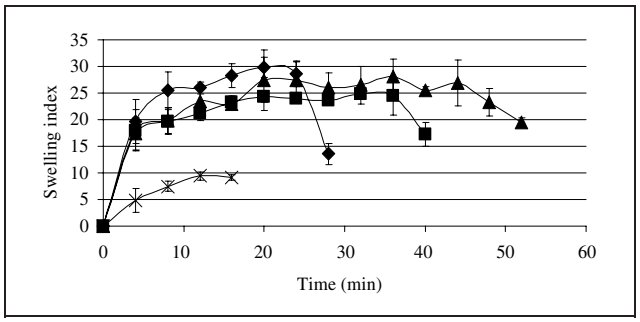

Fig. 5: Effect of alginate : HPMC ratio on the swelling and disintegration of alginate films

swelling increases with higher concentrations of HPMC and shows the water retaining capacity of HPMC. As is seen in Fig. 5 alginate films without HPMC started to disintegrate after 16 min, those containing 30% HPMC in 28 min and films containing 70% HPMC in 48 min. The bioadhesive properties of the polymeric films can be related to their hydration state and in comparing the results for films containing 30% HPMC, as seen in Figs. 1 and 2, it is apparent that the alginate films hydrate faster than the Carbopol films and show higher adhesion.

2.3. Tensile strength and elasticity

The mechanical tests carried out involved measurements of the tensile strength and the elongation at break of the films. The alginate films showed the highest tensile strength (Fig. 6) but had nevertheless the lowest elongation at break (Fig. 7). Increased amount of HPMC in the films always lead to increased tensile strength. For the alginate films an increase in HPMC lead to an increase in elasticity but this was not the case for the Carbopol polymers. CP981 films had higher tensile strength and elasticity than CP1382 films.

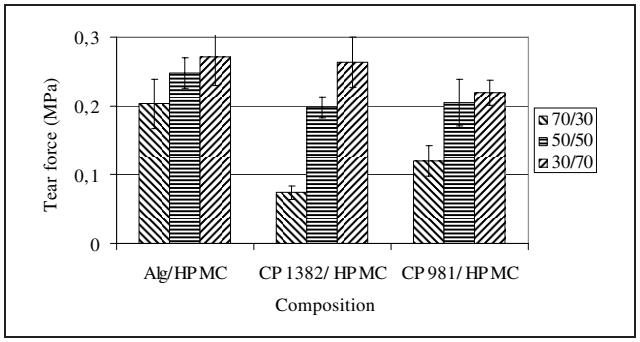

Fig. 6: Tensile strength of films; alginate : HPMC and Carbopol : HPMC ratio

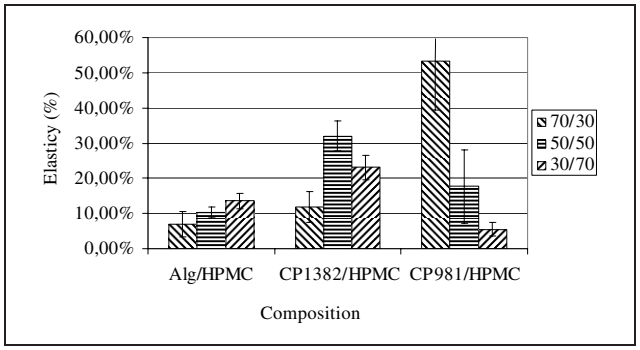

Fig. 7: Elasticity of films; alginate : HPMC and Carbopol : HPMC ratio

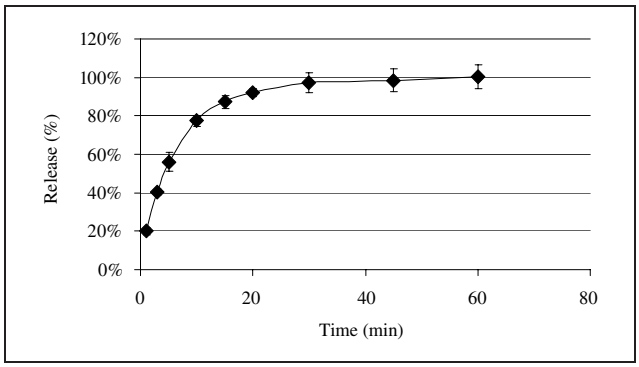

Fig. 8: Release of sumatriptan succinate from sodium alginate film

2.4. Release of sumatriptan from alginate film

The release of a model drug sumatriptan succinate from alginate films was evaluated and shows that 80% of the drug was released from the film within 10 min (Fig. 8). The film disintegrated over a period of 60 min; this indicates that the release of drug from the film is by diffusion rather than due to disintegration.

3. Discussion

The alginate films exhibited greater bioadhesion and showed higher tensile strength but lower elasticity than the Carbopol films. Upon swelling the surface area of the Carbopol films increased significantly which might point to them being unsuitable for mucosal drug delivery whereas the alginate films did not enlarge. It is however uncertain that the increase in surface area would be so extensive *in vivo* with the Carbopol films but might increase the thickness instead. Excessive hydration of a polymeric film for buccal delivery could lead to decreasing adhesive strength and possibly loss of adhesion and hence shorter duration of retention. It has been reported that the bioadhesion of sodium carboxymethylcellulose films decreased with increasing contact time and increased hydration and swelling (Eouani et al. 2001). Also an evaluation of the mucoadhesion of films made from copolymers of acrylic acid showed that there was a linear increase in mucoadhesive forces for up to 60 s but a longer contact time led to a plateu or leveling off in tensile strength mucoadhesion (Shojaei et al. 2000).
HPMC appeared to improve the properties of the films, affecting the bioadhesivness and increasing tensile strength. For the alginate films an increase in HPMC lead to an increase in elasticity but for the Carbopol polymers this was not the case. From the results it can be concluded that Carbopol 981 is more suitable than Carbopol 1382 for films.

The results indicate that sodium alginate may be a suitable carrier for polymeric films for use in the buccal cavity. Alginate has previously been used for preparing beads for sustained drug release and then frequently cross linked with calcium chloride or other cross linking material, this decreases the adhesive properties of the alginate but prolongs the disintegrating time (Hagesaether et al. 2008; Wittaya-areekul et al. 2006). The beads are typically described for drug delivery in the gastrointestinal tract rather than buccal mucosal drug delivery and then with cross linking to different extent to adjust the controlled release of an active compound. By altering the concentration of alginate vs. HPMC there is a possibility of controlling the disintegration time of the films and thus the time the film is present at the mucosa for drug delivery.

4. Experimental

4.1. Materials

Carbopol 981 NF (CP981) and Carbopol 1382 (CP1382) were gifts from BF Goodrich Co. Cleveland, OH, USA. Sodium alginate medium viscosity (SM) and Crude Porcine mucin (Gastric), Type II were purchased from Sigma Chemical Company, St. Louis, MO, USA. Hydoxypropylmethyl cellulose 4000 (HPMC) and propylene glycol (PG) were purchased from Norsk Medisinaldepot AS (NMD), Norway. Duoderm®, hydrocolloid membrane (H-7961) from ConvaTec. Sumatriptan Succinat was obtained form Dr. Reddy's, India. All other reagents were of analytical grade.

4.2. Preparation of polymeric films

Films were prepared containing different ratios of Carbopol or alginate to HPMC. Ratio of plasticizer to polymer was also varied (see Table 1) where 50% weight of PG of total polymer weight was found to give best results. A 2% w/v polymeric solution was prepared with water and combined with plasticizer, the solution was centrifuged for 20 min and then cast onto a Petri dish and dried in an oven at 60 °C until dry. The film was then removed from the Petri dish and cut to the required size. The films were stored in a glass container maintained at 25 °C until used. Films with air bubbles or other imperfections were discarded. In manufacturing films containing sumatriptan succinate the drug was added to the polymeric solution before casting onto a Petri dish.

4.3. In vitro evaluation of mucoadhesive properties

The bioadhesive and mechanical properties of the films were evaluated using Texture Analyzer model TA-XT2i (Stable Microsystems, UK). A modification of a previously described method was used for mucoadhesive evaluation (Thirawong et al. 2007). A piece of film was attached to the end of a probe (1.33 cm^2) with a double sided adhesive tape and the probe fastened onto the Texture Analyzer arm. The artificial membrane used was Duoderm®, and 30 mg of artificial mucus solution (17% porcine mucin Type II SigmaAldrich, pH 6.00 and viscosity 39 ± 2 cPs) was spread over the membrane prior to testing. Each film type was measured at least six times. The speed was 0.1 mm/s at all times. The probe was then lowered onto the artificial membrane and maintained in contact with the membrane with 0.30 N force for 60 s for hydration between film and mucus to occur. This time chosen to simulate real life situation of applying the film, since it would not be realistic to hold film in place for a longer time. The probe was then pulled upwards at a constant speed of 0.1 mm/s and the force required detaching the film from the membrane determined from resultant force-time plot. Results were collected in $N \times s$ as an Area under Curve (AUC), this value is then converted to $KPa \times s$ by dividing $N \times s$ with the area of film sample (1.33 cm^2) which gives work of adhesion.

4.4. Tensile strength and elasticity

1.2 cm × 4 cm film strips were fastened by their edges to the TA-XT2i tensile strength apparatus and measurements repeated at least six times taking care that the breaking point was not caused by the grips of the tensile apparatus. The speed of separation was constant at 0.1 mm/s until breaking point and gathered results were the force (N) needed to tear the film and elasticity was measured in mm and presented in percentages.

4.5. Swelling/disintegration

Simulated saliva solution previously described by Peh and Wong (1999) (consisting of 2.38 g of Na_sHPO_4, 0.19 g of $K_sH_sPO_4$ and 8.00 g of NaCl dissolved in 1 L of purified water, pH adjusted to 6.75 using phosphoric acid) was used to evaluate the swelling and disintegration properties of the films. Samples of each film (2.89 cm^2) were cut and weighed. The film square was then placed onto a stainless steel wire mesh (diameter 9 cm, mesh size 0.2 cm) and the film and the wire mesh weighed before they were placed into a Petri dish. Sufficient simulated saliva solution was poured onto the Petri dish to cover the wire mesh. After 4 min the wire mesh with the film were removed, dried of excess solution and weighed, this was repeated every 4 min until constant weight was observed or disintegration began. Each measurement was repeated three times. The degree of swelling was calculated from Eq. (1) where W_t is the weight of the films at time t and W_0 is the weight at time 0.

$$SI = \frac{W_t - W_0}{W_0} \times 100 \quad (1)$$

4.6. Release studies

Release studies of sumatriptan succinate from the films were carried out according to the USP29 (2006) – Transdermal delivery systems – General Drug Release standards, Apparatus 5 – (Paddle over disk) (13), at 37 °C in place of 32 °C as the dosage system is intended for buccal delivery but not on skin. Dissolution fluid was 0.05 M KH_2PO_4 with pH 6.75 maintained at 37 °C. A film was placed in 70 mL of 0.05 M KH_2PO_4 and the medium was stirred at 50 rpm. Samples were taken at predetermined time points and analysed by HPLC.

4.7. Analytical method

Sumatriptan succinate was quantified using a modification of a method by Nozal et al. (2002). The HPLC component system consisted of a Thermo Separations Products Spectra Series P200 HPLC solvent delivery system, a Cosmosil C_{18} (4.6 × 150 mm) column, a Phenomenex C_{18}, (10 × 4.6 mm) (L × ID) Security Guard pre-column, a Hitachi type L-7200 Autosampler, a Thermo Separations Products SP4400 Integrator, and a Thermo Separations Products Spectra Series UV150 detector. The wavelength was 228 nm, and the mobile phase consisted of acetonitrile, and 0.05 M KH_2PO_4 (16 : 84) with the retention time being 4.00 min at 1.0 mL/min flow rate.

Acknowledgements: This project was supported in part by grant G5RD-CT-2001-00542 from the European Union.

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