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In-vitro Bioadhesion of a Buccal, Miconazole Slow-release Tablet

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Abstract—The bioadhesive characteristics of thermally modified starch/polyacrylic acid (PAA) tablets, containing miconazole nitrate, were determined. The detachment force and work of adhesion were significantly affected by the ratio of drum-dried waxy maize starch and PAA. Pure PAA showed the highest detachment force and work of adhesion while the lowest force and work of adhesion were observed for pure starch. There was a pronounced effect of molecular weight of PAA on the bioadhesive characteristics. Miconazole nitrate did not influence bioadhesion up to a concentration of 30%. The influence of additives was negligible and fluctuations of pH did not influence the bioadhesive strength of the tablet.

Miconazole nitrate is an established drug for the treatment of topical and systemic fungal infections (Holt 1980). For the treatment of topical fungal infections, e.g. oral candidiasis, buccal gels containing miconazole nitrate are currently used. As the drug does not persist in the oral cavity (Odds 1981), these gels have to be applied several times a day. Maximal salivary concentrations of miconazole nitrate are seen immediately after application, but the drug is rapidly cleared from the oral cavity (Odds 1981; Turner & Warnock 1982). To increase the buccal residence time of miconazole, a buccal miconazole-releasing device was developed in the form of a bioadhesive tablet which can reversibly adhere to the oral mucosa and release miconazole nitrate during the adhesion time.

Several polymers, including polyethylene glycol (Chen & Cyr 1970), cellulose derivatives (Gurny et al 1984) and polyacrylic acid (Ponchel et al 1987) have been described for the formulation of bioadhesive systems. Some of these polymers adhere well for a few hours, although some are mildly irritating to the oral mucosa (Deasy & O'Neill 1989; Bottenberg et al 1991). Bottenberg et al (1991) concluded that thermally modified starches are promising as non-irritant bioadhesive excipients for buccal fluoride application.

In this study, the influence of tablet composition, based on a mixture of thermally modified starch and polyacrylic acid, on bioadhesion was investigated. The effects of different concentrations of miconazole nitrate, a glidant and a lubricant, on bioadhesion were also evaluated.

Materials and Methods

The bioadhesive tablet

The tablets were prepared with drum-dried waxy maize starch (DDWM, mol. wt 4000 kDa), drum-dried corn starch (DDCS, mol. wt 4000 kDa), extruded from corn starch (ECS, mol. wt 4000 kDa) and polyacrylic acid (PAA, Carbopol 907, 910, 934 and 934P, B. F. Goodrich Co., Cleveland, USA). The modified starches were kindly supplied by Cerestar (Vilvoorde, Belgium). The composition of the tablets is given in Table 1.

The effect of the addition of increasing concentrations of miconazole nitrate (Sigma Chemical Co., St Louis, MO, USA), of sodium benzoate 2% (w/w) ($\leqslant 90$ μm, UCB, Brussels, Belgium) as the lubricant and silicon dioxide 0·2% ($\leqslant 90$ μm, Aerosil 200, Pharmachemic, Antwerp, Belgium) as the glidant, was investigated. The powders were blended for 10 min in a Turbula mixer (Type T2A, W. A. Bachofen, Basel, Switzerland). Tablets of 100 mg were directly compressed at a pressure of 150 MPa on an eccentric compression machine (Korsch, type EKO, Frankfurt, Germany), equipped with 7 mm flat punches.

In-vitro determination of bioadhesion

The bioadhesion of the tablets was evaluated in-vitro as previously described by Ponchel et al (1987). With this experimental arrangement, it is possible to determine the detachment force and the work of adhesion, when tablet and tissue are pulled apart. The work of adhesion is defined as the area under the curve of the detachment force vs extension.

Porcine gingiva obtained at slaughter were rapidly frozen to −20°C. Before use, the tissue fragments were thawed and stored in isotonic phosphate-buffered saline pH 7·4 (2·38 g $Na_2HPO_4 \cdot 2H_2O$, 0·19 g KH_2PO_4 and 8·0 g NaCl made up to 1000 mL with demineralized water, all reagents p.a. grade). The test media used for the bioadhesive experiments were isotonic phosphate-buffered solutions of pH 5 and 7·4. The isotonicity was obtained by the addition of NaCl.

The apparatus used for the determination of the bioadhesive characteristics consisted of a tensile testing machine (type L1000R, Lloyd Instruments, Segentworth, Fareham, UK), equipped with a 20 N load cell.

The tablet under test was attached to an upper aluminium support, connected to the superior cross-sectional bar, with cyanoacrylate glue (Loctite Super Glue gel, Loctite Belgium, Kontich, Belgium). The porcine gingival tissue (100 mm^2) was glued (mucosal side out) with the same adhesive to a teflon support, which was connected to a PVC cylinder situated at the bottom of a 150 mL thermostatic beaker (37 ± 1°C). The beaker was fixed on the base of the tensile tester. Next, 15 μL isotonic phosphate buffer (pH 5 or 7·4)

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was spread evenly over the mucosa and the crosspiece (bearing the tablet) was then lowered at a crosshead speed of 1 mm min^{-1}. After initial contact, the thermostatic beaker was filled with the buffer solution up to a total volume of 125 mL to act as a counterweight. The mucosa and the tablet were then pressed together with a force of 0·5 N for 5 min after which the tablet and mucosa were pulled apart with a constant extension rate of 5 mm min^{-1} until a complete rupture of the tablet–mucosa bond was obtained. A force vs extension diagram was recorded.

The maximal detachment force and the work of adhesion necessary to break the bond between tablet and mucosa were calculated.

Statistical analysis

Statistical analysis was performed using one-way analysis of variance (Sokal & Rohlf 1981).

Results and Discussion

In recent years, significant interest has been shown in the development of novel bioadhesive polymers to be used as controlled-release devices (Park & Robinson 1984; Peppas & Buri 1985; Junginger 1990). To determine the bioadhesive potential of these polymers, several techniques were reported and reviewed (Park et al 1987; Duchêne et al 1988; Peppas & Mikos 1989). Polyacrylic acid has been shown to induce severe irritation of the mucosa in volunteers (Bottenberg et al 1991). In this study the bioadhesive characteristics of a combination of thermally modified starches with polyacrylic acid were investigated.

The detachment force and work of adhesion data for the different formulations, tested with buffer solution at pH 7·4, are shown in Table 1. Fig. 1 shows a typical force vs extension graph for one of the formulations studied. Among the thermally modified starches, drum-dried waxy maize starch (DDWM) containing almost 100% amylopectin, showed the highest detachment force and work of adhesion. Both parameters were significantly ($P<0·001$) higher than for the extruded corn starch (ECS) and the drum-dried corn starch (DDCS). The data for ECS and DDCS were not significantly ($P>0·1$) different, suggesting that the method of thermal modification had no influence on the bioadhesive characteristics of tablets made of corn starches.

The highest detachment force and work of adhesion were recorded for the formulations consisting of pure polyacrylic acid. These findings are in agreement with the literature data (Smart et al 1984). No significant ($P>0·25$) difference in detachment force amongst the different Carbopol types was seen, but the work of adhesion of pure Carbopol 934 was significantly ($P<0·025$) lower in comparison with the two other types of polyacrylic acid.

Among the formulations with 5% polyacrylic acid, the highest detachment force ($P<0·001$) was obtained after incorporation of 5% Carbopol 910. This confirms the trend (although not significantly different) observed in our data and those of Lejoyeux et al (1989) on pure polyacrylic acids, where a maximum in detachment force and work of adhesion was reached with the formulation containing Carbopol 910. The work of adhesion of DDWM/PAA910 (95/5) was not significantly ($P>0·75$) different compared with DDWM/PAA907 (95/5), whereas it was significantly ($P<0·001$) higher compared with DDWM/PAA934 (95/5). The detachment forces for the formulations containing Carbopol 907 and 934 in DDWM were not significantly ($P>0·05$) different from each other, although the work of adhesion for DDWM/PAA907 (95/5) was twice the value obtained for DDWM/PAA907 (95/5) (Table 1). Duchêne & Ponchel (1989) have

Table 1. Composition and characteristics of different formulations at pH 7·4.

Composition	Abbreviation	n	Detachment force (N)	Work of adhesion (mJ)
Extruded corn starch	ECS	11	0·504 ± 0·107	0·065 ± 0·026
Drum-dried corn starch	DDCS	10	0·547 ± 0·154	0·080 ± 0·015
Drum-dried waxy maize starch	DDWM	15	2·399 ± 0·532	0·495 ± 0·130
Carbopol 907	PAA907	13	4·701 ± 0·456	2·293 ± 0·343
Carbopol 910	PAA910	16	4·996 ± 0·642	2·469 ± 0·411
Carbopol 934	PAA934	14	4·830 ± 0·644	1·987 ± 0·407
DDWM 95% + PAA907 5%	DDWM/PAA907 (95/5)	11	2·708 ± 0·573	1·154 ± 0·212
DDWM 95% + PAA910 5%	DDWM/PAA910 (95/5)	12	3·286 ± 0·702	1·185 ± 0·296
DDWM 95% + PAA934 5%	DDWM/PAA934 (95/5)	12	2·621 ± 0·562	0·549 ± 0·132
DDWM 95% + PAA934P 5%	DDWM/PAA934P (95/5)	10	2·578 ± 0·492	0·498 ± 0·160
DDWM 90% + PAA907 10%	DDWM/PAA907 (90/10)	14	3·489 ± 0·568	1·552 ± 0·482
DDWM 80% + PAA907 20%	DDWM/PAA907 (80/20)	12	3·631 ± 0·524	1·547 ± 0·218
DDWM 85% + PAA907 5% + miconazole 10 mg	DDWM/PAA907/mic (85/5/10)	12	2·908 ± 0·374	1·009 ± 0·140
DDWM 75% + PAA907 5% + miconazole 20 mg	DDWM/PAA907/mic (75/5/20)	11	2·646 ± 0·482	0·809 ± 0·126
DDWM 65% + PAA907 5% + miconazole 30 mg	DDWM/PAA907/mic (65/5/30)	13	2·323 ± 0·584	0·690 ± 0·168
DDWM 45% + PAA907 5% + miconazole 50 mg	DDWM/PAA907/mic (45/5/50)	10	1·342 ± 0·562	0·243 ± 0·097
DDWM 94·8% + PAA907 5% + aerosil 0·2%	DDWM/PAA907/aer (94·8/5/0·2)	20	2·610 ± 0·551	1·100 ± 0·261
DDWM 93% + PAA907 5% + sobenzoate 2%	DDWM/PAA907/sobenz (93/5/2)	12	2·701 ± 0·601	0·990 ± 0·137
DDWM 82·8% + PAA907 5% + aerosil 0·2% + sobenzoate 2% + miconazole 10 mg	DDWM/PAA907/aer/sobenz/mic (82·8/5/0·2/2/10)	10	2·783 ± 0·337	1·011 ± 0·218
DDWM 82·8% + PAA910 5% + aerosil 0·2% + sobenzoate 2% + miconazole 10 mg	DDWM/PAA910/aer/sobenz/mic (82·8/5/0·2/2/10)	10	3·341 ± 0·569	1·015 ± 0·218
DDWM 82·8% + PAA934 5% + aerosil 0·2% + sobenzoate 2% + miconazole 10 mg	DDWM/PAA934/aer/sobenz/mic (82·8/5/0·2/2/10)	10	2·518 ± 0·582	0·590 ± 0·210

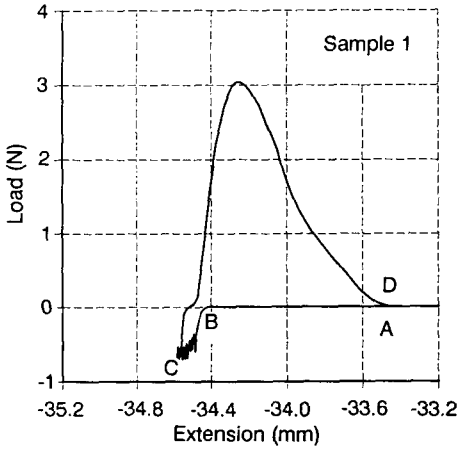

FIG. 1. A force vs extension diagram for a formulation consisting of DDWM/PAA910 (95/5). Line A–B shows the descent of the upper support with the bioadhesive tablet. Line B–C shows the phase after initial contact where mucosa and tablet were pressed together with a force of 0·5 N for 5 min. Line C–D depicts the phase where tablet and mucosa were pulled apart with a crosshead speed of 5 mm min^{-1}.

already suggested that the work of adhesion could be a more relevant parameter to consider when evaluating a bioadhesive polymer. In-vitro/in-vivo correlation studies are proceeding to elucidate which parameter (detachment force or work of adhesion) must be considered for an accurate assessment of the bioadhesive performance of polymers.

The difference in bioadhesive characteristics of the tablets containing different types of Carbopol might be due to their differences in mol. wt, configuration and structure. Carbopol 907 is a linear macromolecule with a mol. wt of 450 kDa in comparison with Carbopol 910 and 934, which are cross-linked polymers with mol. wts of 750 and 3000 kDa, respectively. Carbopol 910 and 934 are both ramified polymers with cross-linked segments of comparable length. Lejoyeux et al (1989) suggested that differences in molecular characteristics might lead to different levels of bioadhesion in terms of work of adhesion. It is unclear how the molecular differences of polyacrylic acid might explain the differences observed in our results, although an explanation could be given for the difference seen in bioadhesive characteristics between DDWM/PAA910 (95/5) and DDWM/PAA934 (95/5). Carbopol 910 and 934, used in these formulations, are both cross-linked molecules and only differ in their mol. wt. Lower bioadhesive characteristics were seen with the formulation with the highest mol. wt. It is likely that the diffusibility of the polymer chains into the mucin network decreases with increasing mol. wt. The comparison of DDWM/PAA907 (95/5) with DDWM/PAA934 (95/5) or DDWM/PAA910 (95/5) is more difficult to perform, as there is not only a difference in mol. wt between the different Carbopols used, but also a difference in cross-linking density. Although the interpretation of cross-linked polymers with large chains is more difficult, the conformation, mobility and flexibility of the macromolecule have to be considered. A higher chain mobility allows a greater interdiffusion and interpretation of the bioadhesive polymer with the mucous network (Mikos & Peppas 1986).

No significant difference ($P > 0{\cdot}5$) was seen between the incorporation of 5% Carbopol 934 and 5% 934P, indicating that the difference in purity between the products did not influence the bioadhesive properties.

An increase in the concentration of Carbopol 907 up to 20% in the DDWM formulation resulted in a significant ($P < 0{\cdot}001$) increase of both bioadhesive parameters. However, no significant differences were seen in adhesion parameters between DDWM/PAA907 (90/10) and DDWM/PAA907 (80/20). After addition of 10 mg miconazole nitrate to the tablet containing 5% PAA907 a slight, but not significant, increase in the detachment force and work of adhesion was observed. Detachment force and work of adhesion gradually decreased with higher concentrations of miconazole nitrate in the tablet. A significant ($P < 0{\cdot}001$) decrease in bioadhesion was seen at a concentration of 50% miconazole nitrate. A concentration of 30% miconazole nitrate could be used without influencing the bioadhesive characteristics of the physical combination of thermally modified starch and Carbopol 907.

Table 2. Mean detachment force (N) and work of adhesion (mJ) (±s.d.) of the different formulations at pH 5.

Formulation	n	Detachment force (N)	Work of adhesion (mJ)
DDWM	10	1·156±0·280	0·257±0·061
PAA907	14	4·782±0·877	2·055±0·460
PAA910	12	4·801±0·721	1·953±0·399
PAA934	10	4·349±0·570	1·828±0·240
DDWM/PAA907 (95/5)	10	2·866±0·496	1·285±0·253
DDWM/PAA910 (95/5)	12	3·207±0·586	1·202±0·301
DDWM/PAA934 (95/5)	12	2·455±0·322	0·538±0·119
DDWM/PAA907 (90/10)	12	3·225±0·457	1·462±0·272
DDWM/PAA907 (80/20)	12	3·651±0·689	1·479±0·321
DDWM/PAA907/mic (85/5/10)	12	2·775±0·515	1·028±0·245
DDWM/PAA907/mic (75/5/20))	12	2·579±0·538	0·801±0·220
DDWM/PAA907/aer (94·8/5/0·2)	12	2·497±0·312	1·095±0·171
DDWM/PAA907/sobenz (93/5/2)	10	2·626±0·458	1·056±0·189
DDWM/PAA907/aer/sobenz/mic (82·8/5/0·2/2/10)	12	2·725±0·436	0·989±0·177
DDWM/PAA910/aer/sobenz/mic (82·8/5/0·2/2/10)	12	3·267±0·621	1·132±0·238
DDWM/PAA934/aer/sobenz/mic (82·8/5/0·2/2/10)	10	2·634±0·436	0·573±0·197

The addition of 0·2% silicon dioxide or 2% sodium benzoate did not significantly influence the detachment force and work of adhesion. Sodium benzoate was chosen as a lubricant since it has been reported that magnesium stearate increased the drug release rate when used in combination with thermally modified starches (Herman & Remon 1989). Bottenberg et al (1989) reported that magnesium stearate had a negative effect on the bioadhesion of tablets consisting of polyacrylic acid and hydroxypropylmethylcellulose.

The combination of the polymers (DDWM/PAA(907, 910, 934) (95/5)), the drug and the two additives showed no significant ($P > 0.5$) difference in bioadhesive characteristics in comparison with DDWM/PAA(907, 910, 934) (95/5), respectively.

Patients with oral candidiasis have a pH of the oral cavity fluctuating between 5 and 7·4 (Arendorf & Walker 1980); thus, the influence of the environmental pH on in-vitro bioadhesion of the different formulations was tested in an isotonic phosphate-buffered solution of pH 5. Although the increase in pH from 5 to 7·4 induces an increase in numbers of ionized carboxylic acid groups in the polyacrylic acid molecules (pK_a 6) from 9 to 96%, the differences seen between the measurements at pH 7·4 and 5 were not significant (Table 2). Surprisingly, the formulation consisting of pure DDWM showed a different behaviour at both pH values. For DDWM the detachment force and the work of adhesion at pH 5 were half the values at pH 7·4. This could be explained by a change of the configuration of the starch molecule at a higher pH from a compact coil to an expanded random coil, resulting in a lower swelling capacity of DDWM at pH 5 (Young 1984). The swelling characteristics for adhesion are important, considering that the main physical mechanism of bioadhesion is the interpenetration of the chains of polymer and mucus to a sufficient depth to create a semi-permanent adhesive bond (Peppas & Buri 1985).

Different formulations consisting of DDWM and polyacrylic acid (PAA907, 910, 934), silicon dioxide, sodium benzoate and miconazole nitrate have been used for experiments in volunteers (Bouckaert et al 1992), which demonstrated an excellent bioadhesive with slow-release properties, as was previously suggested by Bottenberg et al (1991).

In conclusion, we can say that the physical combination of thermally modified starch with 5% polyacrylic acid has excellent properties as a buccal bioadhesive device. The influence of drug and additives was not significant at certain concentrations and fluctuations of pH between 5 and 7·4 did not influence the bioadhesive characteristics of the bioadhesive tablet.

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