DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 30, No. 9, pp. 985–993, 2004

Mucoadhesive Delivery Systems. I. Evaluation of Mucoadhesive Polymers for Buccal Tablet Formulation

Noha Adel Nafee, Fatma Ahmed Ismail, Nabila Ahmed Boraie,* and Lobna Mohamed Mortada

Department of Pharmaceutics, Faculty of Pharmacy, University of Alexandria, Alexandria, Egypt

ABSTRACT

Different types of mucoadhesive polymers, intended for buccal tablet formulation, were investigated for their comparative mucoadhesive force, swelling behavior, residence time and surface pH. The selected polymers were carbopols (CP934, and CP940), polycarbophil (PC), sodium carboxymethyl cellulose (SCMC) and pectin representing the anionic type, while chitosan (Ch) as cationic polymer and hydroxypropylmethyl cellulose (HPMC) as a non-ionic polymer. Results revealed that polyacrylic acid derivatives (PAA) showed the highest bioadhesion force, prolonged residence time and high surface acidity. SCMC and chitosan ensured promising bioadhesive characteristics, whilst HPMC and pectin exhibited weaker bioadhesion. Different polymer combinations as well as formulations were evaluated to improve the mucoadhesive performance of the tablets. Bioadhesive tablet formulations containing either 5% CP934, 65% HPMC and 30% spray-dried lactose or 2% PC, 68% HPMC and 30% mannitol showed optimum mucoadhesion and suitable residence time. SCMC, when formulated individually, exhibited promising bioadhesion, acceptable swelling, convenient residence time and surface pH. In-vivo trials of these formulations proved non-irritative and prolonged residence of the mucoadhesive tablets on human buccal mucosa for 8 to 13 h.

Key Words: Bioadhesion; Buccal; Tablet; Mucoadhesive; Polymer; Swelling; Residence time.

*Correspondence: Nabila Ahmed Boraie, Department of Pharmaceutics, Faculty of Pharmacy, University of Alexandria, Alexandria, Egypt; E-mail: m_a_omar2@link.net.

DOI: 10.1081/DDC-200037245
0363-9045 (Print); 1520-5762 (Online)

INTRODUCTION

The buccal region, within the oral cavity, offers an attractive route of administration for systemic drug delivery. The mucosa has a high vascular nature enabling easy access to the systemic circulation via the internal jugular vein, thus bypassing the first-pass effect. However, one of the major disadvantages associated with conventional buccal drug delivery is the low flux, which results in low drug bioavailability in addition to the lack of dosage form retention at the site of absorption.[1] Consequently, buccal drug delivery necessitates the use of mucoadhesive polymers as these dosage forms should ideally adhere to the mucosa and withstand salivation, tongue movement and swallowing for a significant period of time. Bioadhesive systems also provide the possibility of holding large quantities of active ingredients and the release of which in a controlled manner over relatively prolonged periods.[2]

Mucoadhesive polymers can be naturally occurring such as chitosan and pectin or synthetic such as polyacrylic acid derivatives and cellulose derivatives. They are generally identified as macromolecular organic hydrocolloids that contain numerous hydrogen bond-forming groups, notably carboxyl, hydroxyl, amide and amine groups. High molecular weight, sufficient degree of polarity and flexibility of the polymer chains are considered vital in order to provide sufficient driving force for polymer-mucus adsorption and interpenetration.[3]

Bioadhesive polymers are classified as anionic, cationic or non-ionic. Among anionic polymers, carbopols (CP) are synthetic, high molecular weight cross-linked polymers of acrylic acid. The carboxyl groups provided by the acrylic acid backbone are responsible for strong bioadhesion.[4] Polycarbophil (PC) is a lightly cross-linked polyacrylic acid derivative; it exhibits highly stable long-term adhesive bond.[5] Sodium carboxymethylcellulose (SCMC) is anionic polymer having an exceedingly good mucoadhesive force, biocompatibility and stability.[6] Pectins are non-toxic, low cost hydrophilic polysaccharides derived from plant cell walls; the residual carboxyl groups of uronic acid ensure good bioadhesion.[7] Chitosan is a cationic, high molecular weight, non-toxic, biocompatible and biodegradable polysaccharide obtained from crab shells. It is a linear copolymer of N-glycosamine and N-acetyl glycosamine.[8] The non-ionic neutral polymer, hydroxypropylmethyl cellulose (HPMC) is characterized by moderate mucoadhesive properties.[9]

This study focused on the development and evaluation of buccal mucoadhesive tablets. The characteristics of individual polymers were estimated. To improve the mucoadhesive performance, different polymer combinations as well as formulae containing water-soluble diluents are designed and evaluated.

EXPERIMENTAL

Materials

Carbopol 934 (CP934), carbopol 940 (CP940) of nominal molecular weight 3×10^6 and 4×10^6, respectively (Goodrich Chemical Co, USA), hydroxypropylmethylcellulose 4000 cp (HPMC), high methoxyl pectin citrus (not less than 6.7% of methoxy groups and not less than 74% of galactouronic acid calculated on the dried basis), gum tragacanth (GT) and microcrystalline cellulosePH102 (Avicel®) (A) were all kindly supplied from Alexandria Pharmaceutical Co, Egypt. Polycarbophil (PC) supplied from Pharco Pharmaceuticals, Egypt. Sodium carboxymethyl cellulose (SCMC) supplied from ADWIC, El-Nasr Pharmaceutical Chemicals Co, Egypt. Chitosan (Ch), maximum granule size 0.2 mm, degree of acetylation >80%, was purchased from CarboMer, Inc., USA. Spray-dried lactose (L) (Zeparox®), Borculo Whey Products, was supplied from Amriya Pharmaceutical Industries, Egypt. D(−)-mannitol (M), Riedel-De Haen AG Sleeze-Hannover. Gantrez AN-169 (G), polyvinyl methyl ether-maleic anhydride, GAF Corp., New York, USA.

METHODS

Preparation of Bioadhesive Tablets

Weighed amounts of individual polymers or mixture of polymers, screened through a 125 μm sieve, were thoroughly blended. The formulations were then directly compressed into flat-faced tablets, 9 mm in diameter, using a single punch tablet machine (Erweka, GmbH, Frankfurt, Germany). For each formula, tablets (n=20) were separately weighed. The thicknesses as well as the crushing strength (kg) were determined. The mean and the standard deviation (SD) were calculated.

Determination of the Surface pH

The surface pH of the tablets was determined in order to predict the possible irritative effects of each formulation on the buccal mucosa. The tablets were allowed to swell at 37°C, for 2 h in 40 ml isotonic

phosphate buffer (IPB) pH 6.75. The surface pH of the swollen tablets was measured by means of a pH paper. The experiment was carried out in duplicate and the mean surface pH was determined.

Bioadhesion Force Test

The tensile strength required to detach the bioadhesive tablet from the mucosal surface was applied as a measure for the bioadhesive performance. The apparatus was locally assembled and was composed mainly of a modified two-arm balance. The device was previously described by Nafee et al.[10] The bioadhesion force was calculated per unit area of the tablet as follows:

$$F = (W \cdot g)/A$$

where, F is the bioadhesion force (dyne.cm^{-2}), W is the minimum weight required to break the bioadhesive bond (g), g is the acceleration due to gravity (cm.s^{-2}), A is the surface area of the tablet (cm^2). The adhesion force data reported represented the mean of five determinations.

Swelling Test

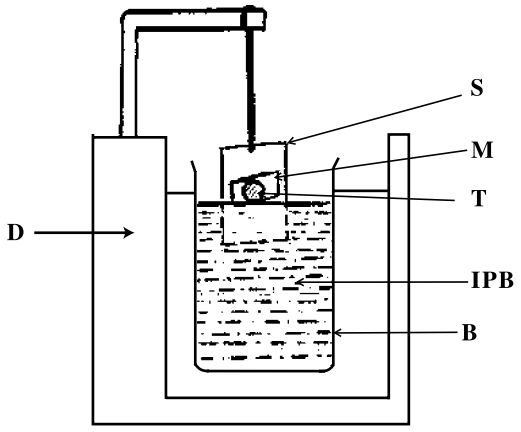
A number of tablets of each formulation were separately placed in a series of baskets made of stainless steel mesh. Each set (the tablet and the basket) was accurately weighed before being vertically placed in a beaker containing 40 ml IPB pH 6.75 at 37°C. At fixed intervals (0.5, 1, 2, 3, 4, 5, and 6 h), excess fluids were removed; the set containing the swollen tablet was weighed. The weight of the swollen tablet was calculated. The swelling index *(S.I.)* was determined from the following relation:

$$S.I. = (W_t - W_o)/W_o$$

where, W_t is the weight of the swollen tablet at each interval t, W_o is the initial weight of the tablet. Each set was applied to record one reading. The experiment was carried out in triplicate.

Determination of the Residence Time

a) The in-vitro residence time was determined using a locally modified USP disintegration apparatus (Disintegration tester, type ZT4, Erweka, Germany), Fig. 1. The disintegration medium was composed of 800 ml isotonic phosphate buffer pH 6.75 (IPB) maintained at 37°C. A segment of rabbit intestinal mucosa, 3 cm long, was glued to the surface of a glass slab, vertically attached to the apparatus. The mucoadhesive tablet was hydrated from one surface using 15 µl IPB and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the tablet was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the tablet from the mucosal surface was recorded (mean of triplicate determinations).



(S) glass slab, (D) disintegration apparatus, (B) glass beaker, (M) mucosal membrane,
(T) mucoadhesive tablet, (IPB) isotonic phosphate buffer.

Figure 1. Schematic diagram of the apparatus used for the in-vitro determination of residence time.

b) In-vivo residence time test: Four human healthy volunteers (25–50 years old) participated in this study (informed consent from the volunteers was obtained). Plain bioadhesive tablets with optimized properties were selected for the in-vivo evaluation. The bioadhesive tablet was placed on the buccal mucosa between the cheek and gingiva in the region of the upper canine and gently pressed onto the mucosa for about 30 s. The tablet and the inner upper lip were carefully moistened with saliva to prevent the sticking of the tablet to the lip. The volunteers were asked to monitor the ease with which the system was retained on the mucosa and note any tendency for detachment. The time necessary for complete erosion of the tablet was simultaneously monitored by carefully observing for residual polymer on the mucosa. In addition, any complaints such as discomfort, bad taste, dry mouth or increase of salivary flux, difficulty in speaking, irritation or mucosal lesions were carefully recorded. Repeated application of the bioadhesive tablets was allowed after a two days period for the same volunteer.

RESULTS AND DISCUSSION

Anionic polymers CP934, CP940, PC, SCMC, and pectin as well as a cationic polymer chitosan, and a non-ionic polymer HPMC, were compressed individually in the form of bioadhesive tablets (Table 1). The surface pH of the tablets differed according to the polymer nature; SCMC, HPMC and chitosan showed surface pH 6.5 to 7. No irritation is expected from these polymers when applied to the buccal mucosa. On the other hand, the polyacrylic acid (PAA) derivatives; CP934, CP940, and PC, being acidic, measured a surface pH of 3 to 3.5. Similarly, pectin, being a partially methoxylated polygalactouronic acid, showed also a slightly acidic surface pH of 4. This surface acidity may induce high mucosal irritation.

The values of the bioadhesion force (Table 1) demonstrate the superiority of the anionic polymers, except pectin, over the cationic and the non-ionic ones; the bioadhesive force ranged from 46.48×10^3 dyne.cm^{-2} for SCMC to 230×10^3 dyne.cm^{-2} for CP934. The bioadhesion of CP934 was >PC> CP940>SCMC> pectin (Table 1). This ranking is almost comparable to that obtained by Wong et al.[11] The physicochemical interactions at the adhesive-substrate interface was studied by Jacques and Buri,[4] they suggested that mucoadhesiveness of cellulose derivatives resulted mainly from the pressure developed by their swollen gels against the mucin gels whereas that of PAA polymers was driven by attractive interactions at the polymer-mucin interface. Even acting by the same bioadhesive mechanism, the tested PAA derivatives showed different bioadhesive capacity. Although, both CP934 and CP940 are branched molecules with more or less cross-linked segments of comparable length they exhibit different bioadhesive

Table 1. Characteristics of plain mucoadhesive tablets containing individual polymers.

	Anionic polymers					Cationic polymer	Non-ionic polymer
Characteristics	SCMC	CP934	CP940	PC	Pectin	Chitosan	HPMC
Tablet weight (mg)	180 (0.03)*	150 (0.094)	150 (0.018)	150 (0.104)	150 (0.063)	120 (0.021)	180 (0.099)
Tablet thickness (mm)	1.68 (0.011)	2.2 (0.058)	2.27 (0.042)	2.04 (0.069)	1.87 (0.022)	1.67 (0.088)	2.52 (0.101)
Hardness (kg)	14	8.5	7	7.5	10	9	12
Surface pH	6.5	3	3.5	3.5	4	7	7
Bioadhesion force ($\times 10^3$ dyne.cm^{-2})	46.48 (3.196)	230 (13.6)	118.71 (9.979)	150.91 (3.58)	26.53 (2.786)	34.14 (1.293)	22.44 (2.5)
Swelling index, S.I. (after 6 h)	12.83 (0.53)	9.9 (0.872)	9.9 (0.661)	9.35 (0.375)	1.62 (0.421)	0.948 (0.021)	5.67 (0.225)
In-vitro residence time (h)	8 (0.695)	>24	>24	>24	5 (0.406)	>24	8 (0.744)

*Values between brackets represent the standard deviation (n=3 except in case of bioadhesion force n=5).

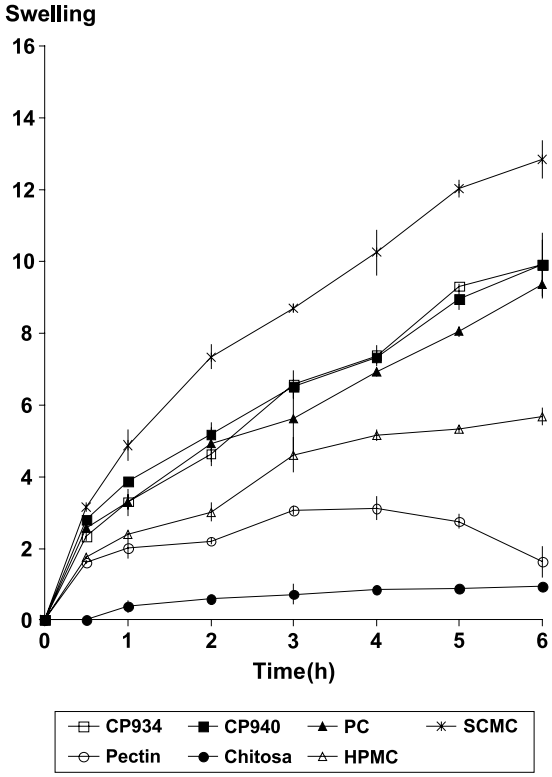


Figure 2. Swelling profiles of plain mucoadhesive tablets containing individual polymers.

capacity (Table 1). This may be attributed to their different molecular weights (3×10^6 and 4×10^6 respectively). The diffusibility of the PAA molecules into mucin network decreases when the molecular weight increase. Concequently, bioadhesion may be decreased when using a high molecular weight PAA.[12] The adhesion force of PC was less than that of CP934. The difference observed in adhesion force of these high molecular weight polymers may reflect their structural difference as CP934 is a polyacrylic acid cross-linked with allyl sucrose while PC is a polyacrylic acid cross-linked with divinyl-glycol.

The bioadhesion force of the cationic polymer chitosan was less than that of the anionic polymers PAA and SCMC (Table 1). These results are comparable to those obtained by Mortazavi and Smart.[13]

The comprtatively weak bioadhesion force of the non ionic polymer HPMC (22.4×10^3 dyne cm^{-2}) may be attributed to the absence of a proton-donating carboxyl group which reduce its ability for the formation of hydrogen bonds.[13]

Figure 2 demonstrates the swelling profiles of plain mucoadhesive tablets containing individual polymers. SCMC showed a maximum swelling behavior at all intervals. PAA derivatives exhibited relatively moderate swelling profiles. No remarkable difference was observed between the water uptake of CP934, CP940, and PC. Pectin did not swell much (S.I.=1.6 at $^1/_2$ h). Maximum swelling for pectin was attained within 4 h (S.I.=3.1), after which the polymer started to erode slowly in the medium and returned to the initial value (S.I.=1.6 after 6 h, Table 1, Fig. 2).

Negligible swelling was observed for chitosan (Fig. 2), this could be explained by its poor water solubility at pH 6.8. Hydrophobicity and weak gel-forming capacity at neutral and alkaline pH were reported to be responsible for the weak swelling characteristics of chitosan.[8,14]

The non-ionic polymer, HPMC showed comparatively limited water uptake; S.I. varied from 1.7 after $^1/_2$ h to 5.7 after 6 h. Mortazavi and Smart[15] suggested that the limited hydration of HPMC was responsible for its prolonged duration of adhesion despite its relatively weak mucoadhesive strength.

The swelling behavior of the mucoadhesive polymer was extensively related to its bioadhesive performance. According to Jacques and Buri,[4] materials having highest initial rate of hydration reach the highest mucoadhesive strength. Fabregas and Garcia[16] found a relationship between the swelling rate and the in-vitro bioadhesion force. Paradoxically, no correlation was observed, in this study, between swelling at different intervals and bioadhesion; the considerable swelling characterizing SCMC may be one of the factors responsible for its reduced adhesion, as swelling induces over-extension of hydrogen bonds and other forces. Besides, water molecules may bind to polymer groups required for bioadhesion.[17] Bottenberg et al.[18] observed that SCMC formulations had the highest swelling rates and low adhesion force compared to other polymers.

Values of the in-vitro residence time are shown in Table 1. None of the polymers tested was detached from the membrane along the time of the experiment (24 h). Pectin, which is freely soluble in water, exhibited rapid erosion and disintegrated completely within 5 h. A moderate residence time ($\sim$8 h) was obtained for SCMC and HPMC. PAA derivatives resided on the mucosal surface for very prolonged periods (>24 h). Chitosan indicated negligible erosion, which might result from minimum solubility and swelling in alkaline medium.

From individual polymer evaluation, we concluded that PAA derivatives are characterized by very strong mucoadhesion force, prolonged residence time as well as acidic nature. SCMC exhibits satisfactory mucoadhesion, moderate residence time and excessive swelling

Table 2. Composition and characteristics of plain mucoadhesive tablets containing polymer combinations.

Formula code	Composition (%w/w) CP	PC	HPMC	SCMC	Diluent	Surface pH (n=2)	Bioadhesion force ($\times 10^3$ dyne.cm^{-2}) (n=5)	Swelling index (after 6 h) (n=3)	In-vitro residence time (h) (n=3)
CP_1	2	–	98	–	–	6.3	23.92±5.11	6.25±0.38	8.0±0.47
CP_2	5	–	95	–	–	6.0	37.5±5.98	6.17±0.77	>12
CP_3	10	–	90	–	–	5.7	38.23±3.4	6.24±0.56	>12
CP_4	20	–	80	–	–	5.4	174.6±6.1	5.52±0.81	>12
CP_{2L}	5	–	65	–	30L	6.0	37.62±0.38	9.28±0.39	11.5±0.52
CP_{2M}	5	–	65	–	30M	6.0	31.18±0.28	9.88±0.48	11.5±0.87
CP_{2G}	5	–	65	–	30G	6.0	23.19±2.56	8.47±0.22	8.0±0.23
CP_{2A}	5	–	65	–	30A	6.0	21.84±1.74	9.14±0.45	13±0.64
PC_1	–	2	98	–	–	6.0	48.66±3.92	6.12±0.55	>12
PC_2	–	5	95	–	–	5.5	47.61±6.76	5.46±0.15	>12
PC_3	–	10	90	–	–	4.5	105.6±2.54	6.43±0.31	>12
PC_4	–	20	80	–	–	4.2	135.7±5.81	6.17±0.38	>12
PC_{1L}	–	2	68	–	30L	6.0	26.32±0.02	10.56±0.62	9.0±0.93
PC_{1M}	–	2	68	–	30M	6.0	37.99±3.44	9.52±0.36	11.25±0.84
C_1	–	–	20	80	–	6.5	33.36±4.91	11.57±0.71	6.5±0.24
C_2	–	–	40	60	–	6.5	25.66±3.92	13.42±0.65	5.5±0.1
C_3	–	–	50	50	–	6.5	18.67±5.74	10.41±0.34	4.8±0.35
C_4	–	–	60	40	–	6.5	16.17±2.81	9.3±0.88	6.25±0.27
C_5	–	–	80	20	–	6.8	14.43±3.53	8.9±0.52	8.0±0.44
C_6	–	–	–	75	25GT	6.5	46.08±1.22	6.93±0.64	7.45±0.25
C_7	–	–	–	60	40GT	6.5	47.26±3.97	5.1±0.11	7.5±0.12

behavior. These characteristics may induce some problems upon application onto the buccal mucosa.

Mixtures of CP934 or PC and HPMC were compressed into tablets 150 mg weight. Table 2 demonstrates the composition and properties of these combinations. Values of the surface pH, as listed in Table 2, increased with reduced percentage of PAA in the formulation. Combinations containing 2% to 5% CP or 2% PC showed considerable reduction in the surface acidity (surface pH=6 and 6.3). No mucosal irritation would be expected with these ratios of PAA derivatives.

Table 2 illustrates the bioadhesion force of CP, HPMC and their mixtures. The force of adhesion gradually decreased with the increase in HPMC percentage in the formulation. These values indicated that the addition of 2% CP did not affect the adhesion force of HPMC, whereas, 5 and 10% CP caused an increase in adhesion by 67.25, and 70.37%, respectively (Table 2). When 2% PC was added, the adhesion force increased from 22.44×10^3 dyne/cm^2 for HPMC to 48.66×10^3 dyne.cm^{-2}. There was no significant difference between the addition of 2% and 5% PC on the adhesion of HPMC. On the other hand, formulation containing 10, and 20% PC indicated very high values of 105.63 and 135.71×10^3 dyne.cm^{-2}, respectively, which were close to the adhesion force of PC alone (150.91×10^3 dyne.cm^{-2}). It was noticed that although the adhesion force of CP was higher than that of PC, the use of only 2% PC with HPMC increased the adhesion force of HPMC more than 5% CP934 when added to the same polymer (Table 2).

The in-vitro residence time of CP/HPMC combination was recorded in Table 2. The data revealed that mixtures containing 5 to 20% CP were characterized by prolonged residence time (>12 h), compared to HPMC (8 h). The addition of 1 and 2% CP did not alter the residence time of HPMC. Generally, the addition of PC (at all ratios) to HPMC delayed the time necessary for the disintegration of the tablet from 8 h to >12 h (Tables 1 and 2).

The addition of 5% CP934 to HPMC did not cause any change in swelling capacity of HPMC (Tables 1 and 2). At 6 h, HPMC had a S.I. of 5.67 while CP_2 showed a S.I. of 6.17. The increase in CP content from 5 to 10% also exhibited a negligible effect on the swelling properties of HPMC. The addition of PC to HPMC had no obvious effect on the swelling of HPMC. For all the combinations, the values of S.I. changed by ±1 compared to HPMC at all time intervals (Tables 1 and 2).

In general, it was concluded that the swelling capacity and bioadhesion performance of CP & PC

were regulated by the addition of HPMC. The hydrosolubility of HPMC, despite to its moderate swelling properties, promoted the liquid entry and entrapment in the polymer network.[16] Many authors, hence, favored the application of CP/HPMC mixture as a bioadhesive drug delivery device.[16,19]

To improve PAA/HPMC systems, which suffered from prolonged residence time (>12 h), various diluents were tried in order to facilitate erosion and promote tablet disintegration. Thirty percent HPMC was replaced by one of the following diluents, spray dried lactose (L), mannitol (M), Gantrez (G), and Avicel (A). Tablets containing 5% CP or 2% PC/65% HPMC/30% diluent were compressed. The physical parameters were shown in Table 2. The addition of diluent did not affect the tablet hardness and surface pH. However, the adhesive performance was generally reduced. For CP/HPMC system, lactose-containing formula (CP_{2L}) had the highest bioadhesion followed by mannitol-containing formula (CP_{2M}) then mixtures containing Gantrez (CP_{2G}) and finally Avicel-containing formula (CP_{2A}) In case of PC/HPMC formulations, spray dried lactose (PC_{1L}) caused relatively marked reduction in bioadhesion indicated by a value of 26.32×10^3 dyne.cm^{-2} compared to 37.99×10^3 dyne.cm^{-2} for mannitol-containing formula (PC_{1M}), Table 2. The influence of tablet diluents on the mucoadhesive performance of CP934 was formerly studied by, Tobyn et al.[20] Spray-dried lactose and Avicel showed significantly lower adhesion than pure CP934P. Polymer blends containing Avicel indicated poorer mucoadhesion. It is suggested that Avicel adsorbs water, swells and hence reduces the water content of the mucin/mucoadhesive bond. However, lactose is less likely to remove water from the system and appears to be a more successful diluent for CP934P with regard to influencing mucoadhesion.[21]

Data of the residence time, shown in Table 2, revealed that enhanced tablet erosion was achieved by the addition of these diluents. Both spray dried lactose and mannitol reduced the residence time on the mucus membrane from >12 h to 11.5 h. Gantrez ensured faster erosion; the tablet resided 8 h onto the substrate. On the contrary, Avicel-containing formulation remained in place for more prolonged periods (13 h). In case of PC/HPMC system, formula PC_{1L}, containing spray dried lactose, eroded within 9 h compared to 11.25 h for mannitol-containing formulation, PC_{1M}.

In general, all formulations exhibit considerably moderate swelling, which is expected to permit promising bioadhesion, comfort, as well as prolonged residence time (Table 2). Formulae CP_{2L} and PC_{1M} are, thus, chosen as good candidates for the formulation of buccal mucoadhesive drug delivery systems.

Table 2 summarizes the characteristics of the SCMC/HPMC tablets; the surface pH of all formulae was 6.5 indicating minimum probability of ulceration when applied to the buccal mucosa. Being anionic polymer, SCMC had superior mucoadhesion, (46.48×10^3 dyne.cm^{-2}) relative to the non-ionic polymer HPMC (22.44×10^3 dyne.cm^{-2}). The gradual decrease in SCMC content in the tablet resulted in a subsequent decrease in adhesive performance. It is noticed that formulae C_3, C_4, and C_5, containing $\leq 50\%$ SCMC, had bioadhesion force of 18.67, 16.17, and 14.43×10^3 dyne.cm^{-2}, respectively, which is weaker than the bioadhesion strength of either polymer alone.

The formula based on SCMC/HPMC, C_5 disappeared completely from the mucosal surface within 8 h, while the other mixtures eroded faster; formulae C_1, C_2, and C_4 had a residence time value of 6 ± 0.5 h, whilst formula C_3 resided for only 4.8 h. (Table 2).

Figure 3 demonstrates the swelling pattern of SCMC/HPMC mixtures. SCMC alone had a higher swelling capacity than HPMC at all intervals. Tablets containing 80 and 60% SCMC showed comparable swelling behavior to SCMC alone. Thus, the addition of HPMC, in a concentration up to 40% w/w, to tablets

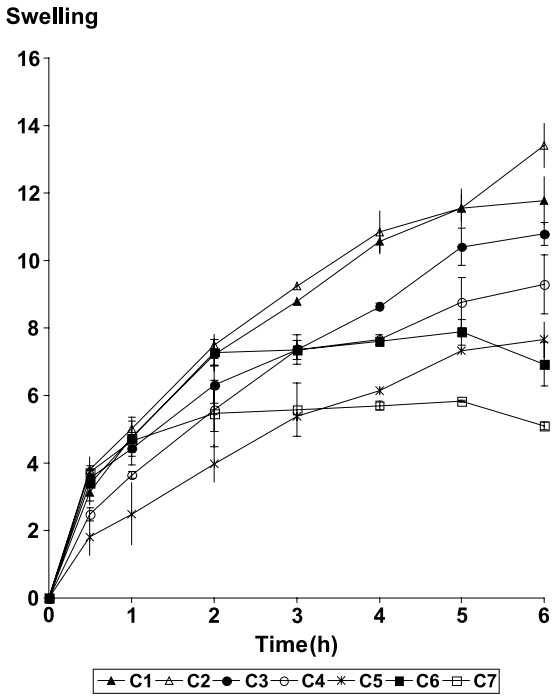


Figure 3. The swelling profiles of different mucoadhesive tablets containing SCMC.

Table 3. In-vitro and in-vivo residence time of tablet formulations possessing satisfactory mucoadhesive features.

Formula code	Formula composition	Tablet weight (mg)	Bioadhesion force ($\times 10^3$ dyne.cm^{-2}) (n = 5[a])	In-vitro residence time (h) (n = 3)	In-vivo residence time (h) (n = 4)	Observations	
						Detachment	Irritation
C	SCMC	180 mg	46.48 (3.196)[b]	8 (0.695)	8 (1.09)	–	+
	SCMC	120 mg	46.48 (3.196)	8 (0.695)	8 (0.998)	–	–
C_6	SCMC 75%/Gum 25%	150 mg	46.08 (1.22)	7.45 (0.254)	7.45 (1.006)	–	+
CP_{2L}	CP5%/HPMC65%/ lactose30%	150 mg	37.62 (0.38)	11.5 (0.523)	13 (0.895)	–	–
PC_{1M}	PC2%/HPMC68%/ mannitol 30%	150 mg	37.99 (3.44)	11.25 (0.843)	12 (1.117)	–	–

[a]n is the number of repetition.
[b]Values between brackets indicate the standard deviation.

containing SCMC did not reduce the swelling properties of SCMC. Further increase in HPMC content in the tablet tended to limit the swelling behavior; formulae C_3, and C_4 showed a S.I. of 10.41, and 9.29, respectively, after 6 h (Table 2).

From the previous results, it can be concluded that the combination of SCMC with HPMC slightly reduced the excessive swelling behavior of SCMC, however, a subsequent fall in bioadhesion force as well as very short residence time were noticed. Such mixtures are hence considered poor candidates as bioadhesive delivery systems.

Combinations of SCMC with gum tragacanth were prepared in two ratios. Characteristics of the two formulations C_6 and C_7 were given in Table 2. It was observed that the addition of 25–40% gum tragacanth to the tablets containing SCMC resulted in a significant reduction in swelling from 12.83 for SCMC to 6.93 and 5.1 for C_6 and C_7, respectively, after 6 h (Fig. 3). However, no marked reduction in the in-vitro residence time was noticed. The adhesion force of SCMC was not affected by the addition of gum tragacanth (Tables 1 and 2). Based on these trials, it is concluded that combination of SCMC with gum tragacanth provides promising bioadhesive capacity with considerable swelling and suitable retention time on the mucosal substrate. Formula C_6 is, thus, one of the selected formulae applied for further studies.

Formulations with optimized adhesive parameters; SCMC alone (C), SCMC/Gum tragacanth (C_6), CP 5%/HPMC 65%/lactose 30% (CP_{2L}), and PC 2%/HPMC 68%/mannitol 30% (PC_{1M}) were evaluated in-vivo in four healthy human volunteers for their residence time on the buccal mucosa, besides, any signs of discomfort, irritation, or ulceration were noted. Observations were reported in Table 3. None of the tablets was dislodged or detached from the buccal mucosa. This indicates that the bioadhesion force ranging from 37 to 46×10^3 dyne.cm^{-2}, obtained from in-vitro experiments, was sufficient to keep the tablet in the oral cavity. In addition, no sign of irritation, ulceration was reported by any volunteer. Tablets composed of 180 mg SCMC remained 8 h on the mucus surface, but all volunteers complained from excessive swelling and difficulty in speaking. This drawback disappeared completely upon reduction of the tablet weight to 120 mg. Formula (C_6) was retained in place for 7.5 h. The major disadvantage was a bad feeling of stickiness and unpleasant taste due to gum tragacanth. Formula CP_{2L} recorded an in-vivo residence time of 13 h, whereas formula PC_{1M} resided in the mouth for 12 h without any complaints. As shown in Table 3, values of the in-vivo residence time are close to those previously obtained from the in-vitro residence time test. Statistically (Student's t-test) non significant difference between in-vitro and in-invivo residence time for all studied formulations was found ($t = 0.104$; tabular $t = 4.6$ at $p < 0.01$). This reveals that the in-vitro test can provide good information about the length of stay of the tablet in the oral cavity.

CONCLUSIONS

Plain bioadhesive tablet formulations containing 2–5% PAA derivatives, 65–68% HPMC, and 30% water-soluble diluent (spray-dried lactose or mannitol) showed optimum mucoadhesion, suitable residence time, and no irritant effect either in-vitro or in-vivo. Similarly, SCMC—formulated individually or with

gum tragacanth—exhibited promising bioadhesion, acceptable swelling, as well as convenient in-vitro and in-vivo residence time. These optimized plain formulae are selected to design medicated mucoadhesive buccal tablets (part II) and are expected to be the basis for the formulation of prolonged release bioadhesive buccal tablets.

REFERENCES

1. Shojaei, A.H. Buccal mucosa as a route for systemic drug delivery: a review. J. Pharm. Pharm. Sci. **1998**, *1* (1), 15–30.
2. Khanna, R.; Agarwal, S.P.; Ahuja, A. Mucoadhesive buccal drug delivery: a potential alternative to conventional therapy. Indian J. Pharm. Sci. **1998**, *60* (1), 1–11.
3. Junginger, H.E. Mucoadhesive hydrogels. Pharm. Ind. **1991**, *53* (11), 1056–1065.
4. Jacques, Y.; Buri, P. An investigation of the physical behavior of moisture-activated mucoadhesive hydrogels upon contact with biological and non-biological substrates. Pharm. Acta. Helv. **1997**, *72*, 225–232.
5. Smart, J.D. An in-vitro assessment of some mucosa-adhesive dosage forms. Int. J. Pharm. **1991**, *73*, 69–74.
6. Mortazavi, S.A.; Smart, J.D. An investigation of some factors influencing the in-vitro assessment of mucoadhesion. Int. J. Pharm. **1995**, *116*, 223–230.
7. Sungthongjeen, S.; Pitaksuteepong, T.; Somsiri, A.; Sriamornsak, P. Studies on pectins as potential hydrogel matrices for controlled release drug delivery. Drug Dev. Ind. Pharm. **1999**, *25* (12), 1271–1276.
8. Illeum, L. Chitosan and its use as a pharmaceutical excipient. Pharm. Res. **1998**, *15* (9), 1326–1331.
9. Rao, K.V.R.; Buri, P. A novel in-situ method to test polymers and coated microparticles for bioadhesion. Int. J. Pharm. **1989**, *52*, 265–270.
10. Nafee, N.A.; Ismail, F.A.; Boraie, N.A.; Mortada, L.M. Design and characterization of mucoadhesive buccal patches containing cetylpyridinium chloride. Acta Pharm. **2003**, *53*, 199–212.
11. Wong, C.F.; Yuen, K.H.; Peh, K.K. An in-vitro method for buccal adhesion studies: importance of instrument variables. Int. J. Pharm. **1999**, *180* (1), 47–57.
12. Anlar, S.; Capan, Y.; Hincal, A. Physico–chemical and bioadhesive properties of polyacrylic acid polymers. Pharmazie **1993**, *48*, 285–287.
13. Mortazavi, S.A.; Smart, J.D. Factors influencing gel strengthening at the mucoadhesive-mucus interface. J. Pharm. Pharmacol. **1994**, *46*, 86–90.
14. Kristmundsdottir, T.; Ingvarsdottir, K.; Saemundsdottir, G. Chitosan matrix tablets: the influence of excipients on drug release. Drug Dev. Ind. Pharm. **1995**, *21* (13), 1591–1598.
15. Mortazavi, S.A.; Smart, J.D. An in-vitro method for assessing the duration of mucoadhesion. J. Control. Release **1994**, *31*, 207–212.
16. Fabregas, J.L.; Garcia, N. In-vitro studies on buccoadhesive tablet formulations of hydrocortisone hemisuccinate. Drug Dev. Ind. Pharm. **1995**, *21* (14), 1689–1696.
17. Parodi, B.; Russo, E.; Caviglioli, G.; Cafaggi, S.; Bignardi, G. Development and characterization of a buccoadhesive dosage form of oxycodone hydrochloride. Drug Dev. Ind. Pharm. **1996**, *22* (5), 445–450.
18. Bottenberg, P.; Cleymaet, R.; De Muynck, C.; Remon, J.P.; Coomans, D.; Michotte, Y. Development and testing of bioadhesive fluoride containing slow release tablets for oral use. J. Pharm. Pharmacol. **1991**, *43*, 457–464.
19. Agarwal, V.; Mishra, B. Design, development, and biopharmaceutical properties of buccoadhesive compacts of pentazocine. Drug Dev. Ind. Pharm. **1999**, *25* (6), 701–709.
20. Tobyn, M.J.; Johnson, J.R.; Dttmar, P.W. Factors affecting in-vitro gastric mucoadhesion. IV. Influence of tablet excipients, surfactants, and salts on the observed mucoadhesion of polymers. Eur. J. Pharm. Biopharm. **1997**, *43*, 65–71.
21. Garcia-Gonzalez, N.; Blanco-Fuente, H.; Igea, S.; Delgado-Charro, B.; Otero-Espinar, F.J.; Blanco-Mendez, J. In-vitro characterization of bioadhesive metoclopramide tablets for buccal application prepared with poly (acrylic acid) and hydroxypropylmethyl cellulose. STP Pharma Sci. **1992**, *2* (6), 494–499.