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Development and evaluation of extended release bioadhesive sodium fluoride tablets

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Abstract

Localized fluoride delivery to the oral cavity is important in caries prevention. However, no current marketed dosage forms deliver fluoride for an extended period. This work describes the effect of poly (methyl vinyl ether-co-maleic anhydride) mixed calcium/sodium salt (Gantrez MS), sodium carboxymethylcellulose (NaCMC), polyethylene glycol 8000 (PEG8000) and Carbopol 934 (C934) on the in vitro dissolution and ex vivo bioadhesion of sodium fluoride matrix tablets. Dissolution was studied using USP Apparatus 2 and a low volume (3.1 ml), low flow (0.5 ml/min) dissolution apparatus. In both apparatus, the percent drug dissolved at 2, 4 and 8 h was found to be statistically dependent on the fractions of Gantrez MS and NaCMC. The interaction term was significant at 2 and 4 h (probability > {t} of less than 0.05). Ex vivo bioadhesion was studied using excised bovine gingiva and a TA.XT2i Texture Analyzer. Peak bioadhesive force and work of bioadhesion were found to be statistically dependent on the fractions of Gantrez MS and NaCMC with no interaction (probability > {t} of less than 0.01). Results indicate that bioadhesive matrix fluoride tablets of these mixtures can be designed to exhibit both bioadhesive and extended release properties.

Keywords: Fluoride; Extended release; Bioadhesion; Local drug delivery; Buccal; Gantrez

1. Introduction

1.1. Caries

Dental caries continues to be an important public health issue. The disease is a result of multiple factors. Important factors include the overall condition of the teeth and state of oral hygiene. The primary causative factor is plaque bacteria that generate organic acids from dietary carbohydrates (Pader, 1988). The chem-

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ical interactions in plaque, plaque acids, and enamel during the formation of a caries lesion have been described as follows: (1) the acidic ion, H^+, formed by the plaque acids, will be initially buffered by OH^- and PO_4^{3-} in the saliva and plaque. Eventually, these buffers will be depleted and the pH will drop below pH 5.5; (2) at this point, the saliva is unsaturated with respect to hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$. Hydroxyapatite in the tooth dissolves, beginning formation of a caries lesion (Fejerskov and Clarkson, 1996).

1.2. Fluoride

Preventative measures are focused on removal of plaque or prevention of plaque bacteria. These measures include improved oral hygiene (tooth cleanliness and fluoridated toothpastes), regular dental care (including fluoride treatments), water fluoridation, fluoride supplements, and a diet lower in carbohydrates and acidogenic foods (Vivien Castioni et al., 1998). Fluoride has evolved in the last 50 years into a key role in the prevention of caries. The preventative action has been shown to be mainly topical. A continuous supply of fluoride ions to the plaque/enamel interface aids in prevention of demineralization and contributes to remineralization of the tooth surface. Fluoride produces a cariostatic effect in three ways: (1) it reduces tooth enamel solubility when fluoride is incorporated into the hydroxyapatite of the tooth structure; (2) it aids remineralization of early tooth damage by depositing fluoridated phases within dental plaque, which provides a source of calcium, phosphate, and fluoride under acidic conditions; (3) it causes the precipitation of fluoridated hydroxyapatite, $Ca_{10}(PO_4)_6OHF$, within the tooth enamel, which is resistant to acid attack (Vivien Castioni et al., 1998). Low levels of fluoride have been shown to reduce demineralization in vitro. A solution level of 1 ppm fluoride was sufficient to completely prevent demineralization of extracted human teeth exposed to 0.1 M lactate demineralizing solution at pH 4.3 in vitro. The inhibition of enamel demineralization was accompanied by a significant uptake of fluoride by the enamel. Lower levels (as little as 0.03–0.06 ppm) provided less protection beneath the tooth surface, but still reduced demineralization significantly (Margolis et al., 1986). A fluoride level of 0.1 ppm in a buffered mineralizing solution of calcium and phosphate gave almost complete protection from demineralization in an in-vitro pH cycling model (Featherstone and Zero, 1992).

A link has been established between clinical anticaries efficacy of dentifrices and saliva concentrations of fluoride. Saliva fluoride concentrations were taken after the use of dentifrices containing 0 to 2500 μg F/g. Saliva fluoride levels increased with increasing fluoride content of the dentifrice. The mean saliva and plaque fluoride concentrations (1000–2500 μg F/g) were inversely associated with mean 3 year caries increments for three fluoride dentifrices in a clinical trial. This work established a link between oral fluoride measurements and anticaries efficacy and demonstrated that salivary fluoride levels of 0.1–1 ppm exhibit anti-caries efficacy (Duckworth et al., 1992). A buccal extended release dosage form could be designed to maintain a low concentration of fluoride in the oral cavity over time.

To effectively design a buccal fluoride dosage form, one must take into account a number of factors that will affect the target concentration of fluoride in the oral cavity. The clearance of fluoride in the oral cavity is primarily through the saliva but can be affected by many factors. Without fluoride supplement, salivary fluoride concentrations are quite low, ranging from 0.01 to 0.04 ppm (Vivien Castioni et al., 1998). Saliva has a typical pH value of 5.2–6.8. Salivary flow rates of 0.2–2.0 l per day are typical (Ritschel, 1970). The volume of saliva in the oral cavity is typically 0.5–2.1 ml (Lagerlof and Dawes, 1984). In considering the design of a buccal fluoride tablet, it is important to note that the clearance of fluoride from the oral cavity is not constant throughout the mouth. In general, clearance is much more rapid lingually than buccally. This is attributed to the greater lingual exposure to salivary secretions from the major salivary glands. A buccally placed tablet is exposed to secretions from minor mucous glands. These secretions are very viscous and flow at a slow rate (Dawes and Weatherall, 1990). Thus, a tablet placed buccally may sustain release for an extended period of time.

Because any fluoride in saliva will eventually be swallowed, one must also consider systemic uptake of fluoride and fluoride pharmacokinetics. Systemic fluoride has been studied for the prevention and treatment of osteoporosis. Pharmacokinetic data was measured from peroral intake of sustained-release sodium fluoride tablets (11.3 mg F), immediate-release sodium flu-

oride tablets (11.3 mg F), and sodium monofluorophosphate tablets (10 mg F). Each preparation was given with 400 mg calcium. Serum fluoride was measured for 24 h. The sustained-release peroral dosage form showed fluoride absorption of less than 33% of that of the immediate-release dosage forms. The maximum serum concentration, C_{max}, was less for the sustained-release form. The $t_{1/2}$ and t_{max} of the sustained-release form are increased compared to the immediate-release form (Gitomer et al., 2000). Thus, a sustained-release form buccal fluoride tablet, after swallowing of saliva, may result in systemic fluoride levels that are below levels seen with an equivalent peroral dose. This is highly desirable as it allows systemic fluoride exposure to be kept at minimal level.

1.3. Extended release matrix tablets

A matrix tablet represents a straightforward approach to controlling the release rate of fluoride for the extended release buccal fluoride tablet. Release rates typically vary with the square root of time. The drug release rate diminishes with time as the remaining drug encounters diffusional resistance and a decrease in the area of the diffusion front (Qui and Zhang, 2000). However, a sufficiently slow rate of release may mimic zero-order release (Jantzen and Robinson, 1996).

1.4. Buccal bioadhesive tablets

Bioadhesive preparations are preferred for treatment of diseases of the oral cavity because they can adhere to the mucosa, protect the diseased part, and retain the drug for the desired period. Examples of oral cavity diseases for which buccal dosage forms have been designed include: aphthous stomatitis, oral candidiasis, and periodontal disease (Mathiowitz et al., 1999). In the buccal region, a tablet may be adhered either to the buccal tissue (cheek) or the gingiva. For local drug delivery, the highly keratinized epidermis of the gingiva will present a barrier to systemic absorption (Smart, 1993). The buccal tablet must be sufficiently thin (1–2 mm) and of small diameter (6–8 mm), so as to be comfortable and not obtrusive when placed into the oral cavity. Commercially available buccal tablets include transmucosal dose forms for testosterone (United States Pharmacopeial Convention, 2004 USP D.I., 2004). Bioadhesive fluoride tablets have been reported with Carbopol, starch, hydroxypropylmethylcellulose, polyacrylic acid, polyethylene glycols, carboxymethylcellulose, cellulose acetate phthalate, ethylcellulose, and gelatin (Bottenberg et al., 1989, 1991, 1992; Aithal and Udupa, 1992; Vivien Castioni et al., 2000).

1.5. Evaluation of dissolution

USP Apparatus 2 is specified for dissolution testing of immediate release NaF tablets by the monograph. The ideal dissolution method should be designed so that the conditions closely mimic the biological conditions and chemical environment seen by the dosage form (Jindal et al., 1994). For a buccal tablet, the relatively large volume and rapid agitation of USP Apparatus 2 does not reflect the low volume of saliva and low agitation seen by a bioadhesive tablet in the oral cavity. We developed a low volume (3.1 ml) dissolution apparatus based on a modified diffusion cell (0.5 ml/min media flow through) reported by Khanna et al., (1996) to characterize tablet dissolution under adverse conditions (low volume and minimal agitation). Drug dissolution from this low volume method was compared to that observed in USP Apparatus 2.

1.6. In Vitro (ex vivo) evaluation of bioadhesion

Tablet bioadhesion is assessed by detachment tests measured between the tablet and a substrate to which it has been previously applied. Many of these types of tests have been described with different substrates and means of measuring the detachment forces. Though artificial substrates have been studied, typically the substrate is a mucosa. A mucosa should be chosen which is similar to that at the intended site of adherence of the tablet. The tablet and mucosa are wetted then put into contact for a given time to allow interpenetration of the polymer chains and adhesion to develop. Detachment is typically in the vertical direction and the force is measured via a balance or tensile apparatus (Duchene et al., 1988).

The aim of the present research is to investigate the effect of poly(methyl vinyl ether-co-maleic anhydride) mixed calcium/sodium salt (PVM/MA MS or Gantrez MS), sodium carboxymethylcellulose (NaCMC), polyethylene glycol 8000 (PEG8000) and Carbopol 934 (C934) and their mixtures on the in vitro

release and ex vivo bioadhesive properties of sodium fluoride tablets. Because the tablet is intended to adhere to the gingival tissue and release fluoride at low levels for an extended period of time, a minimal number of excipients were chosen which may exhibit both extended release and bioadhesive properties when formulated into matrix tablets. Gantrez MS was chosen for its bioadhesive properties, being a key ingredient in denture adhesive preparations. Though the extended release properties of several forms of Gantrez have been described (Smart et al., 1984; Nunez Recuero et al., 1991; El Khodiary et al., 1992), no citations were found for the use of the mixed salt, Gantrez MS in bioadhesive extended release tablets. Gantrez MS should exhibit both bioadhesive and extended release properties. NaCMC was chosen for its well known bioadhesive and controlled release properties (Smart, 1993). PEG8000 and C934P were used based on their extended release and bioadhesive properties at relatively low levels (Bottenberg et al., 1991; Vivien Castioni et al., 2000).

2. Materials and methods

2.1. Materials

The following materials were used: Poly (methylvinylether-co-maleic anhydride) mixed calcium/sodium salt (PVM/MA MS or Gantrez MS) from International Specialty Products, Sodium carboxymethylcellulose High Viscosity USP/NF (NaCMC) from Hercules Ltd., Polyethylene glycol 8000 USP/NF (PEG8000) from Spectrum Chemical Mfg., Carbopol 934P NF (C934P) from B.F. Goodrich Specialty Chemicals and Sodium fluoride USP from Fission Chemicals. All other chemicals used were of reagent grade. Commercial sodium fluoride chewable tablets (Amide Pharmaceuticals, 1.0 mg F as 2.2 mg NaF) were used for comparison.

2.2. Formulation of buccal tablets

The levels of Gantrez MS, NaCMC, C934P, and PEG8000 were selected according to preplanned centroid mixture statistical designs shown in Table 1 (centroid experiment 1) and Table 2 (centroid experiment 2). Additional points were added to gain further information in regions of interest. All tablets were formulated with 0.5 mg fluoride per tablet. The components in each formula were mixed via geometric dilution in a mortar and pestle followed by a Turbula T2C mixer for 20 min. The matrix tablets were manufactured by direct compression using a Manesty D3B rotary tablet press (8 mm round, flat faced punch) with a target weight of 120 mg, a target Hardness of 5–10 kP and a target thickness of 1.7–1.8 mm.

Table 1
The fractions of excipients in centroid experimental design 1

Run	Fraction PEG8000	Fraction NaCMC	Fraction Gantrez MS
F1	0.055	0.05	0.895
F2	0.055	0.895	0.05
F3	0.10	0.45	0.45
F4	0.01	0.94	0.05
F5	0.01	0.05	0.94
F6	0.10	0.05	0.85
F7	0.01	0.495	0.495
F8	0.10	0.85	0.05
F9	0.055	0.472	0.472

2.3. In Vitro NaF release using USP Apparatus 2

USP Apparatus 2 (paddle, 70 rpm, 200 ml 50% total ionic strength adjustment buffer (TISAB, glacial acetic acid, sodium chloride and CDTA) in deionized water (pH 6.0), 37 °C, plastic vessels, was used to determine drug release. The USP drug release method for immediate release NaF tablets requires a paddle speed of 70 rpm, which was the speed chosen for the USP Apparatus 2 testing. The fluoride content of the dissolution

Table 2
The fractions of excipients in centroid experiment 2

Run	Fraction Carbopol 934P	Fraction NaCMC	Fraction Gantrez MS
G2	0	1	0
G3	0	0.66	0.33
G5	0	0	1
G7	0	0.33	0.66
G11	0	0.5	0.5
G12	0	0.1	0.90
G13	0	0.95	0.05
G14	0.05	0.95	0
G15	0.05	0.95	0
G16	0.025	0	0.975
G17	0.025	0.975	0
G18	0.05	0.475	0.475

medium was measured directly at each time point using a fluoride selective electrode (Orion©). The standard solutions were maintained and tested at the same temperature as the dissolution medium. Drug release was calculated using a standard curve ranging from 10^{-1} to 10^{-6} M NaF in 50% TISAB in deionized water.

2.4. In vitro NaF release using a low volume dissolution apparatus

As the relatively large volume and high agitation of USP Apparatus 2 may not accurately mimic drug dissolution in buccal conditions, dissolution was also studied using a low volume (3.1 ml), low flow (0.5 ml/min) dissolution apparatus based on that reported by Khanna to evaluate bioerodible buccal tablets (Khanna et al., 1996). The design of this apparatus is based on modification of a flow-through diffusion cell and is shown in Fig. 1. The lower chamber of the apparatus had a small volume compartment (3.1 ml) and the media in it was stirred using a Teflon©-coated magnetic micro stir bar (length, 4 mm, rotation speed 300 rpm). The two chambers were tightly closed using a Viton© O-ring and a clamp. Six low volume dissolution cells were fabricated. Each tablet was secured to the upper surface of the dissolution chamber by affixing with a small amount of instant glue. The aqueous solubility of NaF in water is 4×10^{-2} g/ml. The maximum concentration of fluoride for a 0.5 mg F tablet in the 3.1 ml small volume cell would be 1.6×10^{-4} g/ml. Thus, sink conditions (>10 times drug solubility) exist even in the 3.1 ml chamber. Media (50% TISAB in deionized water (pH 6.0) at 37 °C) was pumped through the cells using a multi-channel peristaltic pump (Masterflex L/S Digital Drive with 6-channel pump head) at 0.5 ml/min. The jacketed cells were maintained at 37 °C using a recirculation bath. Aliquots were collected at regular intervals over an 8 h period and the fluoride content tested directly with a fluoride selective electrode.

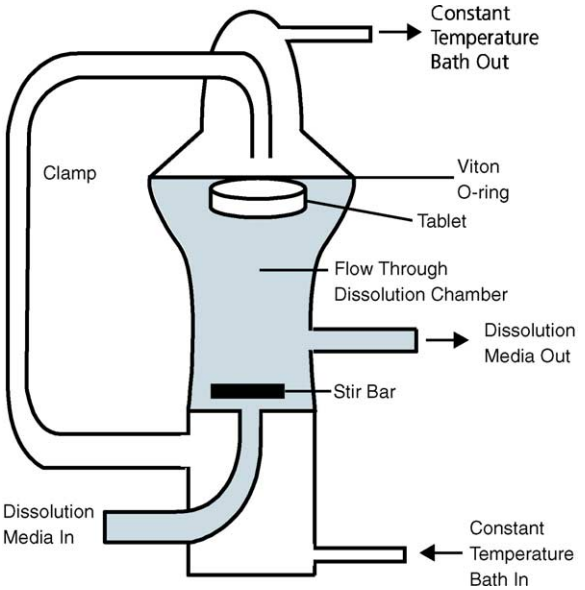

Fig. 1. Design of the small volume dissolution apparatus.

2.5. Ex vivo bioadhesion testing

Peak bioadhesive force and work of bioadhesion were determined using a TA.XT2i Texture Analyzer (Stable Micro Systems, Haslemere, Surrey, UK). The TA.XT2 Texture Analyzer has been used to evaluate bioadhesive gels and bioadhesive tablets (Maggi et al., 1994; Wong et al., 2004). The bioadhesion testing apparatus is shown in Fig. 2.

Bovine gingiva was obtained from a slaughterhouse, excised from freshly slaughtered cows. The area of tissue harvested included the tissue from the palate, just above the maxillary lingual area adjacent to the teeth. The tissue and underlying support tissue were excised and kept in plastic bags and plastic containers and stored at –5 °C until use. The tissue samples were held in place using a Plexiglas fixture (Stable Micro Systems, Surrey, UK), then covered with a 2 ml aliquot of pH 7.0 phosphate buffered saline. The tablet to be tested was fixed to the moveable stainless sample probe using a small amount of instant glue. The entire apparatus was held in a temperature/humidity chamber at 37 °C and 50% R.H. The test conditions were as follows: pre-test probe lowering speed, 1 mm/s, contact force, 10–60 g, Contact time, 30 s to 4 h, probe withdrawal speed, 0.1 mm/s. Conditions chosen for evaluation of centroid experiment 2 were a contact force of 20 g and a contact time of 300 s. Peak bioadhesive force (g) and work of bioadhesion (gs) were recorded for six tablets tested at each condition. All statistical analysis was performed using JMP software (SAS Institute, 1995).

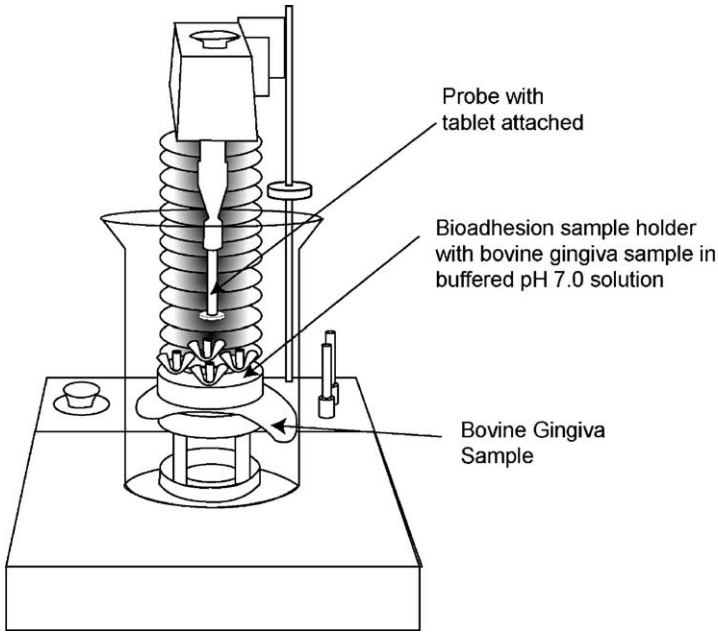

Fig. 2. Design of the bioadhesion testing apparatus.

3. Results

3.1. Dissolution testing

3.1.1. Effect of mixtures on in vitro NaF release using USP Apparatus 2

The dissolution curves for NaF tablets using Centroid Design 1 in USP Apparatus 2 are shown in Fig. 3. Standard deviations (Percent drug release, $n = 6$) for this series ranged from 0.12 to 5.4% in the USP apparatus. The commercial NaF tablet was completely dissolved (100% drug release) within 15 min. Percentage in vitro drug release values for Centroid Design 1 at 2, 4 and 8 h were used as response variables for statistical analysis. Statistical models were fit to the data obtained by multiple linear regression. Parametric estimates for the reduced statistical model are shown in Table 3. The percent drug release at 2, 4 and 8 h was found to be dependent on the fractions of NaCMC and Gantrez MS (probability $> \{t\}$ of less than 0.01). The interaction of CMC and Gantrez MS was significant at 2 and 4 h (probability $> \{t\}$ of less than 0.01). The effect of PEG8000 was not significant at the levels tested. All mixtures exhibited drug release between 31.1 and 63.4% at 4 h and between 55.9 and 100% at 8 h. The near equal mixtures of NaCMC and Gantrez MS (F7, F9) had the lowest drug release at 4 h of 31.1 and 31.4%, respectively. The high percent Gantrez MS tablets (F1, F5) visually exhibited erosion and were completely dissolved by 24 h. These mixtures of greater than 89% Gantrez MS (F1, F5) exhibited the highest drug release at 4 h. The high percent NaCMC tablets (F2, F4) produced a gelatinous mass after approximately 1 h that was completely dissolved by 24 h. These high percent NaCMC formulas (F2, F4) exhibited a square root of time relationship ($R^2 = 0.93$ and 0.99, respectively) when the cumulative percent drug release was plotted versus the square root of time.

3.2. Effect of mixtures on in vitro NaF release using a low volume dissolution method

The dissolution curves for Centroid Mixture 1 in the low volume method are shown in Fig. 4. Standard deviations (Percent drug release, $n = 6$) for this series in the low volume method ranged from 0.10 to 2.1%. The commercial fluoride tablet was completely dissolved (100% drug release) at 2 h. In the Low Volume Method, the percent drug release at 2, 4 and 8 h was found to be dependent on the fractions of NaCMC, Gantrez MS

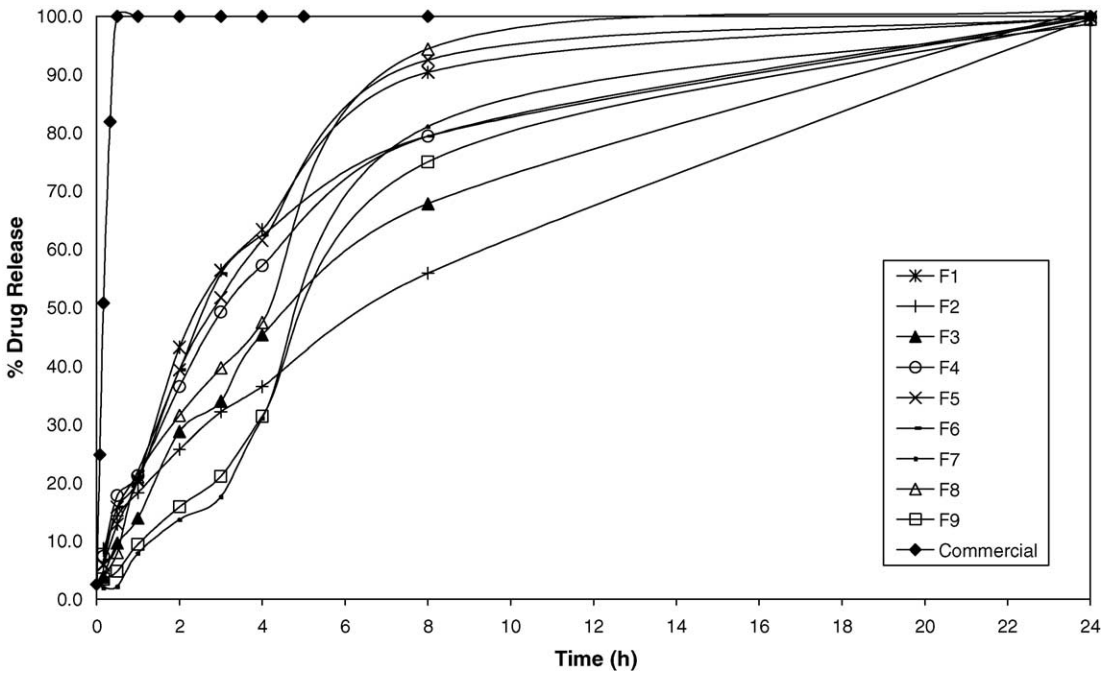

Fig. 3. Mean dissolution of commercial immediate release sodium fluoride tablets and sodium fluoride tablets from centroid experimental design 1 in USP Apparatus 2, ($n = 6$).

and the interaction of NaCMC and Gantrez MS (probability > {t} of less than 0.01). The effect of PEG8000 at the levels tested was not significant. Parametric estimates for the reduced statistical model are shown in Table 3. The cumulative amount of drug dissolved at 2, 4 and 8 h was 27–78% slower in the Low Volume Method than in USP Apparatus 2. As in USP Apparatus 2, the near equal mixtures of NaCMC and Gantrez MS (F7, F9) provided the lowest drug release, with release at 8 h of only 20.7 and 22.3% respectively. Mixtures greater than 89% Gantrez MS (F1, F5) exhibited erosion visually and had the highest drug release at 8 h. These high Gantrez MS tablets (F1, F5) exhibited a square root of time relationship ($R^2 = 0.99$ and 0.99,

Table 3
Reduced model parameters affecting the release of NaF from matrix tablets

Parameter	Release (2 h)		Release (4 h)		Release (8 h)	
	Estimate	*P* value	Estimate	*P* value	Estimate	*P* value
Centroid 1 USP 2						
(CMC–0.05)/0.9	33.47	0.0001	50.33	0.0001	81.54	0.0001
(GN-0.05)/0.9	43.37	0.0001	66.50	0.0001	93.63	0.0001
CMC*GN	−77.66	0.006	−88.19	0.01		
Centroid 1 small cell						
(CMC-0.05)/0.9	19.93	0.0001	26.86	0.0001	35.99	0.0007
(GN-0.05)/0.9	22.70	0.0001	35.42	0.0001	57.14	0.0001
CMC*GN	−52.51	0.005	−70.78	0.0001	−103.75	0.01
Centroid 2 small cell						
CMC	12.84	0.03	27.01	0.004	52.00	0.0008
GN–MS	22.21	0.0007	32.89	0.0004	44.97	0.0007
CMC*GN	−59.05	0.04	−100.12	0.01	−159.15	0.01

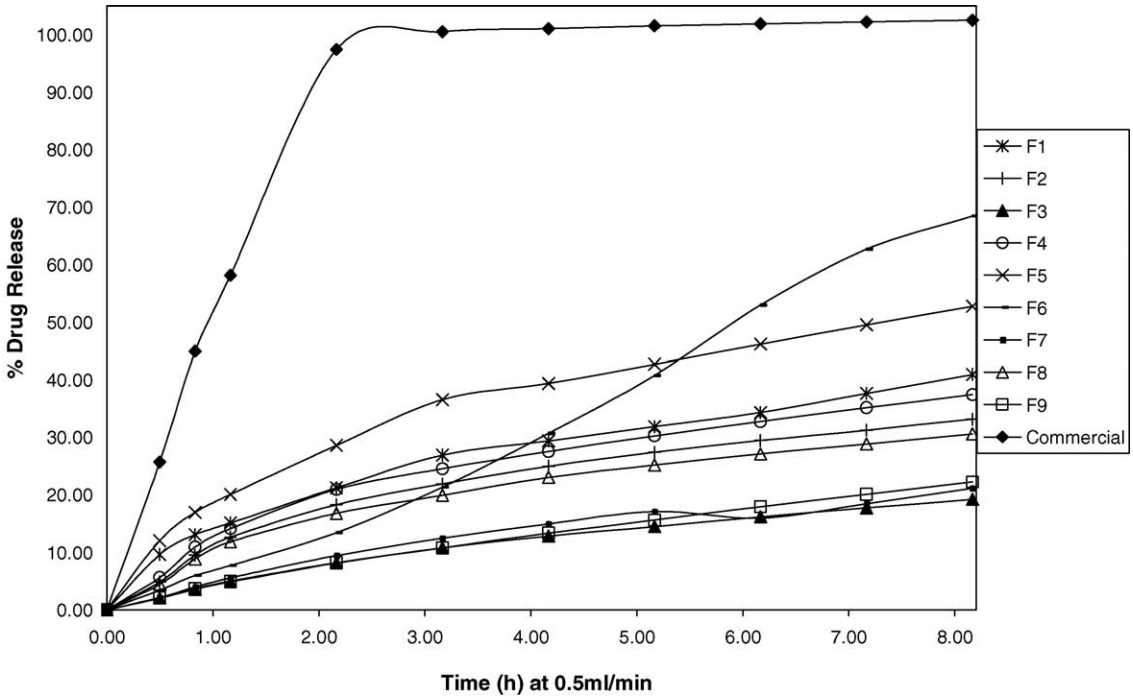

Fig. 4. Mean dissolution of commercial immediate release sodium fluoride tablets and sodium fluoride tablets from centroid experimental design 1 in the low volume method, ($n = 6$).

respectively) when the cumulative drug release was plotted versus the square root of time. The high percent NaCMC tablets (F2, F4) also exhibited a square root of time relationship ($R^2 = 0.99$ and 0.99, respectively) when the cumulative drug release was plotted versus the square root of time. Dissolution results from centroid experiment 1 in USP Apparatus 2 and the low volume method are compared in Table 4.

The dissolution curves for centroid experiment 2 in the Low Volume Apparatus are shown in Fig. 5. The standard deviations for this series (percent drug released, $n = 6$) in the low volume method ranged from 0.11 to 2.1%. As with centroid experiment 1, the percent drug release for Centroid 2 at 2, 4 and 8 h was found to be dependent on the fractions of NaCMC, Gantrez MS and the interaction of NaCMC and Gantrez MS (probability > {t} of less than 0.05). The effect of C934P at the levels tested was not significant. Parametric estimates for the reduced statistical model are shown in Table 3. As was found with centroid experiment 1 in both apparatus, near equal mixtures of NaCMC and Gantrez MS (G11, G18) provided the lowest drug release at 8 h of only 10.2 and 8.2% respectively. Mixtures greater than 97% Gantrez MS (G5, G16) exhibited primarily erosion, being reduced to approximately 25% of their original size after 8 h, and had a linear square root of time relationship (0.98 and 0.97, respectively). Visually, the high percent NaCMC tablets exhibited significant swelling with little erosion. Mixtures of at least 95% NaCMC (G2, G13, G14, G15, G17) exhibited zero order drug release ($R^2 = 0.94$ to 1.0) and had the highest drug release at 8 h of up to 73.7%, shown in Fig. 6. The fluoride concentration in the effluent of these high NaCMC formulas ranged from 0.2 to 1.8 ppm. Mathematical analysis of dissolution curves from centroid experiment 1 and centroid experiment 2 is shown in Table 5.

3.3. Effect of contact force, contact time and mixtures on ex vivo bioadhesion

The effect of contact time on the work of bioadhesion was studied for formula G13 (Table 2). The tablet was placed in contact with the gingival tissue with a

Table 4
Comparison of drug release from centroid experiment 1 in USP Apparatus 2 and low volume apparatus

Row	Fraction of PEG8000	Fraction of CMC	Fraction of Gantrez MS	USP 2 %drug release at 2 h	Small cell %drug release at 2 h	USP 2 %drug release at 4 h	Small cell %drug release at 4 h	USP 2 %drug release at 8 h	Small cell %drug release at 8 h
F1	0.055	0.05	0.895	43.2	21.2	63.4	29.4	90.4	40.9
F2	0.055	0.895	0.05	25.7	18.3	36.5	25.0	55.9	33.2
F3	0.1	0.45	0.45	28.8	8.17	45.3	12.9	67.8	19.2
F4	0.01	0.94	0.05	36.5	20.9	57.2	27.6	79.4	37.4
F5	0.01	0.05	0.94	39.4	28.6	61.5	39.4	92.5	52.7
F6	0.1	0.05	0.85	39.4	13.4	62.4	30.7	79.4	68.4
F7	0.01	0.495	0.495	13.7	8.8	31.1	14.4	81.1	20.7
F8	0.1	0.85	0.05	31.6	16.8	47.4	23.0	94.4	30.6
F9	0.055	0.47	0.47	15.9	8.23	31.4	13.4	100	22.3

contact force of 20 g for times ranging from 30 s up to 4 h ($n = 6$). Results are shown in Fig. 7. The work of bioadhesion increased with increasing contact time up to 1 h, with a maximum work of bioadhesion of 2622 gs. The effect of contact time on work of bioadhesion was linear up to 1 h ($R^2 = 0.97$). At 4 h, the gelled tablet pulled away from the probe and remained attached to the gingiva.

The effect of contact force on work of bioadhesion was studied for formula G13. The tablet was placed in contact with the gingival tissue with contact forces ranging from 10 to 60 g for 300 s ($n = 6$). Results are shown in Fig. 8. The maximum work of bioadhesion of 568 gs was found at a contact force of 20 g and remained level through a contact force of 60 g. Based on these results, the conditions chosen for evaluation of centroid experiment 2 were a contact time of 300 s and a contact force of 20 g.

The bioadhesion results for centroid experiment 2 are shown in Table 6. Both peak bioadhesion and work of bioadhesion were found to be dependent on the fractions of NaCMC and Gantrez MS (probability > {t} of less than 0.01). The interaction term was not significant. The bioadhesive effect of C934P was not significant at the low levels (5.0% or less) used. For this study, bioadhesive values of greater than 20 g (the initial contact force) were considered bioadhesive, with greater values indicating greater bioadhesion. Peak bioadhesive force ranged from 17.8 g (G2) to 73.9 g (G12). Work of bioadhesion ranged from 39.0 gs (G16) to 183.4 gs (G18). Generally, mixtures of greater than 47% Gantrez MS showed the highest bioadhesion, though variation was high. Relative standard deviations ranged from 12.0 to 39.7% consistent with the high variability seen in natural materials (Smart et al., 1984).

4. Discussion

Matrix tablets of mixtures of NaCMC and Gantrez MS can be designed to provide both extended release and bioadhesive properties in vitro. USP Apparatus 2, with a high media volume and rapid agitation, does not adequately model the conditions seen by buccal tablets. The low volume (3.1 ml) and low flow (0.5 ml/min) of the low volume method provides a better model of the small volume of saliva and low agitation in the oral cavity. These findings are consistent with those reported by

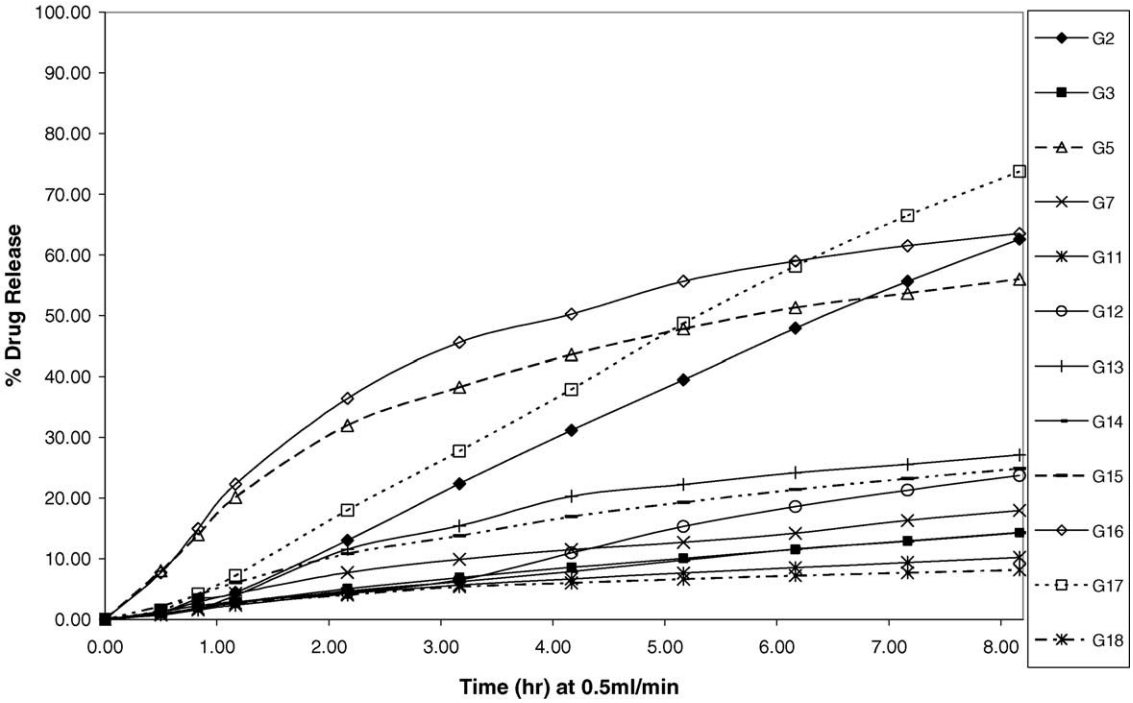

Fig. 5. Mean dissolution of sodium fluoride tablets from centroid experimental design 2 in the low volume method, ($n = 6$).

Khanna et al. (1996). Though the nature of drug release was similar in both apparatus, the rates of drug release were significantly lower at 2, 4 and 8 h in the low volume method. This rate difference can be attributed to differences in hydrodynamics between the low volume apparatus and the USP vessel. The fact that near equal mixtures of NaCMC and Gantrez MS had the lowest rates of drug release in both apparatus suggests that the mixed matrix of the gelled tablets for those formulations provides a more tortuous path for diffusion of the drug.

Tablets high in percent Gantrez MS (F1, F5, G5, and G16) visually exhibited erosion in both apparatus. These high Gantrez MS formulas exhibited a linear relationship when the percent drug released was plotted versus the square root of time indicating diffusion controlled drug release.

Observation of the tablets during dissolution suggests that tablets high in percent NaCMC (F2, F4, G2, G13, G14, G15, G17) showed a combination of swelling and erosion in USP Apparatus 2 while in the low volume, low agitation method the NaCMC matrix swelled significantly without showing erosion. The linear relationship between percent drug release and square root of time for these high NaCMC formulas (F2, F4) in USP Apparatus 2 indicates that drug release in the high agitation USP method is primarily diffusion controlled. Formulas F2 and F4 also showed a linear relationship between drug release and square root of time in the small volume method, which likely was due to increased erosion from those formulas. The zero order release seen in the small volume method for high percent NaCMC formulas (G2, G13, G14, G15, G17) indicates that drug release in that constrained system is primarily swelling controlled (Siepmann and Peppas, 2001). The low agitation of the low volume method allows the NaCMC gelled mass to remain intact through the 8 h experiment, slowing the rate of drug release. The zero order release of fluoride from tablets with at least 95% NaCMC in the low volume method suggests that the swelling controlled release of these formulations may provide ideal, near constant concentrations of fluoride in the oral cavity for up to 8 h. The effluent fluoride concentrations of between 0.2 and 1.8 ppm are consistent with the 0.1–1 ppm levels shown to be effective in vitro and in vivo in caries prevention (Margolis and Moreno,

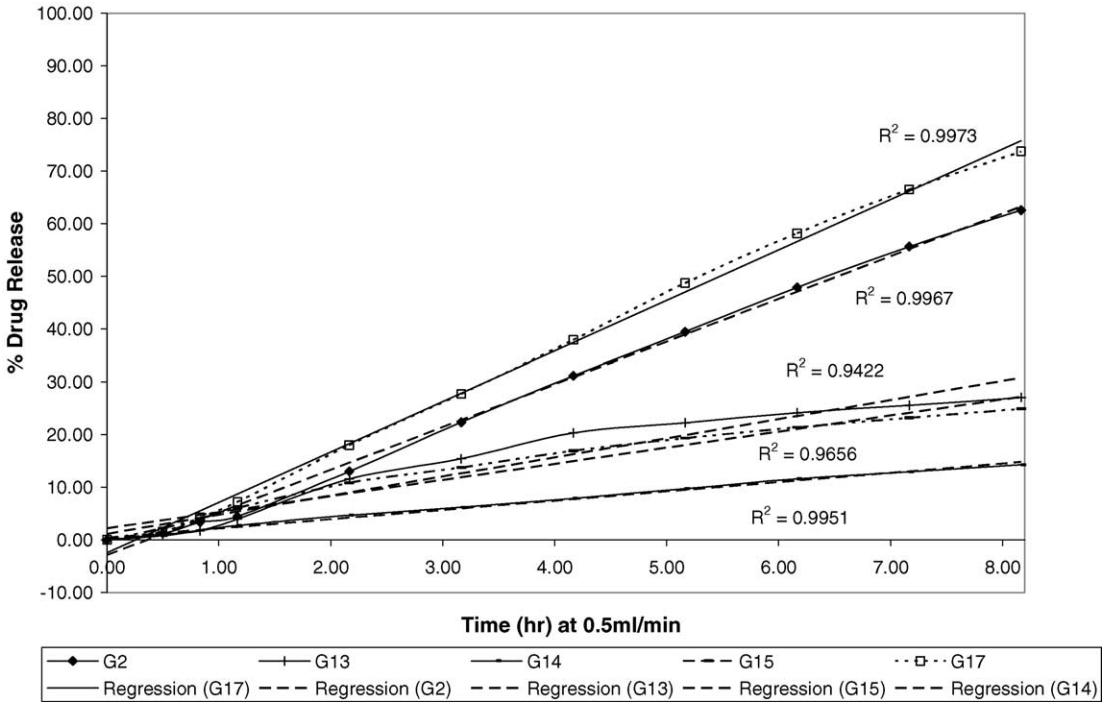

Fig. 6. Mean dissolution in the low volume method of selected sodium fluoride tablets from centroid experimental design 2, showing zero-order drug release from those formulas with high fractions of NaCMC, ($n = 6$). Also shown are regression lines with R^2 values for each dissolution curve.

1990; Margolis et al., 1990; Duckworth et al., 1992; Featherstone and Zero, 1992). Based on the measured ex vivo bioadhesive strength of G13 (95% NaCMC, 5% Gantrez MS), this formula would also appear to have sufficient strength to withstand mechanical erosion in vivo. Thus this formulation of 95% NaCMC/5% Gantrez MS provided near ideal NaF release in vitro as well as significant bioadhesion.

Table 5
Analysis of the dissolution curves (up to 8 h)

Formula no.	Formula	R^2 %drug release vs. sq. rt. time USP Apparatus 2	R^2 %drug release vs. sq. rt. time small volume method	R^2 %drug release vs. time small volume method
High CMC				
F2	89% CMC	0.99	0.99	0.91
F4	94% CMC	0.99	0.99	0.91
G2	100% CMC	–	0.91	1.0
G13	95% CMC	–	0.95	0.94
G14	95% CMC	–	0.95	0.99
G15	95% CMC	–	0.98	0.97
G17	97% CMC	–	0.92	1.0
High Gantrez MS				
F1	89% GN MS	0.99	1.0	0.92
F5	94% GN MS	0.99	0.99	0.90
G5	100% GN MS	–	0.98	0.90
G16	98% GN MS	–	0.97	0.89

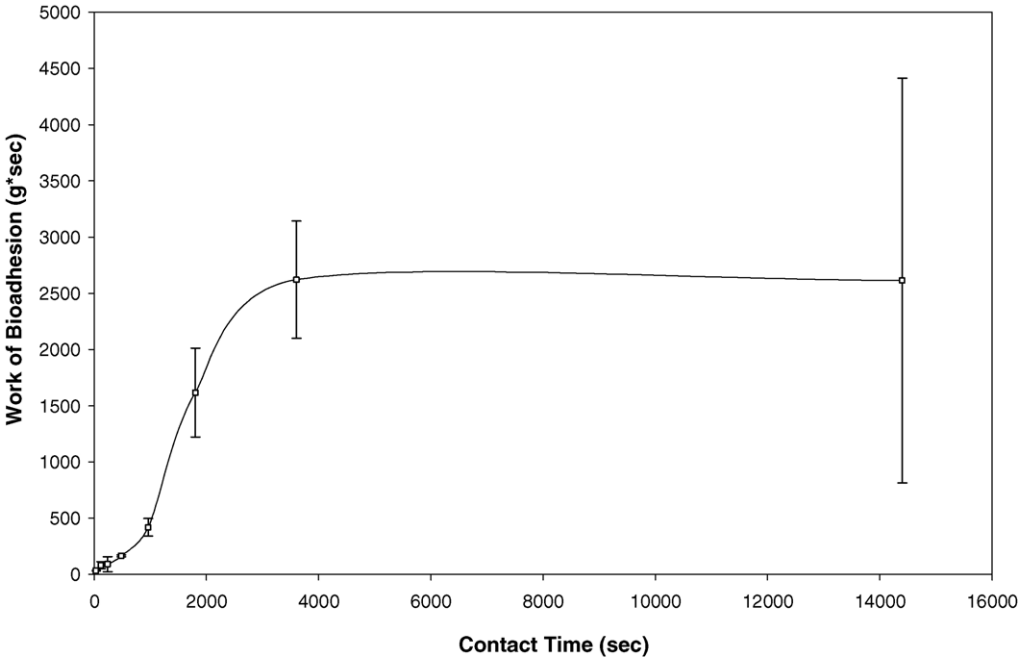

Fig. 7. The effect of contact time on work of bioadhesion (formula G13, mean +/− S.D., $n = 6$).

The ex vivo bioadhesion results illustrate the positive effect of contact time and contact force on work of adhesion. This is predicted by the diffusion theory of Mucoadhesion, which requires interpenetration and entanglement of the polymer chains with mucus chains. The bond strength increases as the degree of interpenetration increases with contact time and contact force (Chickering and Mathiowitz, 1999). This is consistent with the findings reported for contact time and contact force for C943P (Blanco-Fuente et al., 1996). Both NaCMC and Gantrez MS showed bioadhesive and extended release properties and may be used to design extended release buccal fluoride tablets. The research is novel in the use of the combined bioadhesive and extended release properties of Gantrez MS.

Table 6
Bioadhesion results for centroid experiment 2 (Relative Standard Deviation (R.S.D.), $n = 6$)

Run	Peak adhesion force (average g)	Peak adhesion force R.S.D.	Work of adhesion (average gs)	Work of adhesion R.S.D.
G2	17.8	22.6	54.7	19.8
G3	39.6	16.1	82.1	15.5
G5	37.2	20.2	112.9	21.8
G7	20.3	13.3	69.6	31.8
G11	39.1	15.9	177.3	21.3
G12	73.9	39.7	181.2	25.7
G13	58.6	19.8	158.9	21.0
G14	27.6	38.8	43.6	23.3
G15	23.1	34.1	177.5	17.7
G16	33.2	30.6	39.0	27.6
G17	53.1	24.5	126.9	31.0
G18	62.7	12.0	183.4	36.4

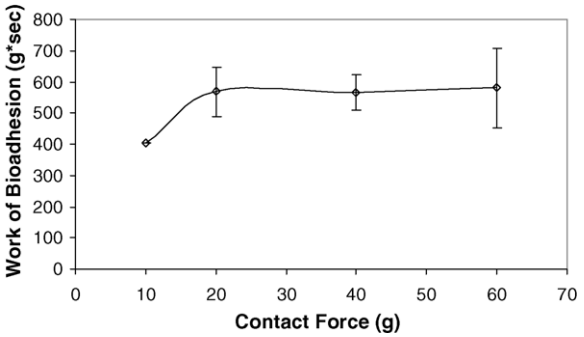

Fig. 8. The effect of contact force on work of bioadhesion (formula G13, mean +/− S.D., $n = 6$).

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