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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. Extended release local delivery of fluoride may allow the development of more effective caries preventatives. 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 drug dissolution and ex vivo bioadhesion of sodium fluoride matrix tablets. The tablet is intended to adhere to the gingival tissue and release fluoride at a low level for an extended period of time. Excipients were chosen which may exhibit both extended release and bioadhesive properties when formulated into matrix tablets. Dissolution was studied using both USP Apparatus 2 and a low volume (3.1 ml), low flow (0.5 ml/min) dissolution apparatus designed to more closely mimic oral cavity conditions.

In this preliminary investigation, it was found that in both apparatus, the percent drug dissolved at 2, 4 and 8 hours was statistically dependent on the fractions of Gantrez MS and NaCMC (probability $> \{t\}$ of less than 0.05). The interaction term was significant at 2 and 4 hours in the USP apparatus and at 2, 4 and 8 hours in the low volume, low flow apparatus

(probability > {t} of less than 0.05). Mixtures of at least 95 % NaCMC exhibited zero order drug dissolution ($R^2 = 0.94$ to 1.0) in the low volume, low flow apparatus due to swelling controlled release in the constrained low flow apparatus. The fluoride concentration in the effluent of these high NaCMC formulas ranged from 0.2 ppm to 1.8 ppm. These levels have been shown previously by other researchers to provide significant in vitro and in vivo protection from caries.

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.

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1. Introduction

1.1 Caries

Dental caries continues to be an important public health issue. The World Health Organization reports that caries affects 60-90 % of schoolchildren worldwide. Five billion people worldwide have experienced dental caries. Treatment of caries is estimated to make up 5-10 % of health costs in industrialized countries (WHO, 2004). 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). Saliva plays a key role in the process. The chemical 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 plaque acids, will be initially buffered by OH^- and $(PO_4)_3^-$ in the saliva and plaque. (2) Eventually, these buffers will be depleted and the pH will drop below pH 5.5. (3) 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. The initial white-spot lesion can progress into the dentin, then into the pulp, resulting in pulpal necrosis and abscess formation. Eventually, the tooth will no longer be vital (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, $\text{Ca}_{10}(\text{PO}_4)_6\text{OHF}$, within the tooth enamel surface, which is resistant to further acid attack (Vivien Castioni et al., 1998).

Low levels of fluoride have been shown to reduce enamel 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).

In another study, fluoride in sufficiently high concentration (~12,000 ppm) was shown to inhibit bacterial growth and reduce the rate of acid production by cariogenic bacteria in vitro (Margolis et al., 1990).

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 ug F⁻/g. Saliva fluoride levels increased with increasing fluoride content of the dentifrice. The mean saliva and plaque fluoride concentrations (1000-2500 ugF⁻/g) were inversely associated with mean three-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 to 1 ppm exhibit anti-caries efficacy (Duckworth et al., 1992). Salivary fluoride levels and clinical efficacy are shown in Table 1.

Table 1. Salivary Fluoride Levels versus Caries Incidence (Duckworth et al., 1992).

Fluoride level of the dentifrice	Mean zero-time intercept of second-phase of salivary fluoride clearance (p<0.001)	DMFS scores (Decayed, Missing and Filled tooth Surfaces, a measure of caries presence)
0 ug F ⁻ /g	0.46 umol F ⁻ /l	-
1000 ug F ⁻ /g	1.48 umol F ⁻ /l	6.80
1500 ug F ⁻ /g	1.88 umol F ⁻ /l	6.33
2500 ug F ⁻ /g	3.03 umol F ⁻ /l	5.71

To effectively design a fluoride dosage form for local delivery of the drug, 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 to 6.8. Salivary flow rates of 0.5 to 2 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). Multiple factors affecting the clearance of fluoride from the oral cavity are illustrated in Table 2.

Table 2. Parameters Influencing the Clearance of a Product Introduced into the Oral Cavity (Vivien Castioni et al., 1998).

Physiological and/or anatomical parameters

Salivary flow rate

Swallowing frequency

Residual volume of saliva

Anatomical position of the salivary gland

Anatomical factors (space between teeth, tongue position, etc.)

Oral muscular movements

Factors related to the product and its administration

Dose and concentration of the product

Duration and frequency of the administration

Association between products and/or buccal substrates

Dilution (drinking habits, rinsing, etc.)

Time of administration (day or night, proximity of a meal, etc)

In considering the placement of a bioadhesive tablet intended for local drug delivery, 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 into the saliva 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 fluoride 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 hours. 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. The pharmacokinetic parameters are shown in Table 3 (Gitomer et al., 2000).

Table 3. Pharmacokinetic Parameters of Peroral Fluoride Dosage Forms (Gitomer et al., 2000).

	Sustained Release Sodium Fluoride	Immediate Release Sodium Monofluorophosphate	Immediate Release Sodium Fluoride
Change in serum fluoride (Delta AUC), ng x h/ml	466 +/- 150	1452 +/- 269	1562 +/- 377
C _{max} , ng/ml	103 +/-18	427 +/-92	400 +/-78
t _{1/2} , h	4.9 +/-1.2	2.7 +/-0.8	3.2 +/-0.8
t _{max} , h	1.6 +/-0.7	1.0 +/-0.4	1.1 +/-0.3

1.3 Currently Marketed Fluoride Therapies

Numerous dosage forms of sodium fluoride are marketed today for use as dental caries preventatives in the U.S. (Drug Facts and Comparisons, 2002). Some representative examples are shown in Table 4.

Table 4. Marketed Fluoride Dosage Forms (Drug Facts and Comparisons, 2002).

Dosage form	Dose Strength or Concentration (as F-)	Rx or OTC
Tablets, chewable	0.5 mg, 1 mg	Rx
Tablets	1 mg	Rx
Drops	0.125 mg/drop	Rx
	0.25 mg/drop	
	0.5 mg/drop	
Lozenges	1 mg	Rx
Solution	0.2 mg/ml	Rx
Rinse	0.02 %	OTC
	0.04 %	
Gel	1 %	Rx
	0.5 %	
	1.2 %	
Dentifrice	1150 ppm	OTC

The currently marketed dosage forms act both topically and systemically. However, as understanding of caries prevention has improved, the preventative effect is known to be mainly topical (Vivien Castioni et al., 1998).

1.4 Extended Release Matrix Systems

The FDA defines an extended release dosage form as one that allows a reduction in dosing frequency as compared to that presented by a conventional dosage form (for example a solution or an immediate release dosage form). An extended release dosage form makes the drug available over an extended period of time following administration. Other expressions have been used such as controlled release, prolonged action, and sustained release. The United States Pharmacopeia 25 uses the term extended release to describe these dosage forms, but the term controlled release is widely used in the literature. Controlled release systems are designed to provide constant or nearly constant drug levels at the site of drug action with reduced drug level fluctuations over an extended period of time (Qui and Zhang, 2000).

A matrix system is a relatively straightforward approach to achieving extended drug release. In a matrix tablet, the drug is dispersed homogeneously throughout a polymer or polymer mixture. A matrix system can offer the advantages of being relatively easy to produce, lower in cost due to fewer manufacturing steps, adaptable to numerous excipients through blending and avoidance of accidental full-release of the drug (dose-dumping) (Jantzen and Robinson, 1996).

Several disadvantages of matrix systems are that the remainder of the “ghost” tablet must be removed and the drug release may not be the ideal zero-order (i.e. constant rate) release. 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 a zero-order release (Jantzen and Robinson, 1996).

1.5 Mechanisms of Drug Release from Matrix Systems

Drug release from controlled release dosage forms occurs via dissolution or diffusion or a combination of these two mechanisms.

1.6 Dissolution Controlled Systems

The simplest form of a sustained release system relies on the drug dissolution as the rate determining step. A drug with a slow dissolution will exhibit sustained release.

For drugs with high water-solubility, the dissolution rate can be decreased by the formation of salts or less soluble derivatives. Alternately, the drug particles can be coated with a slowly dissolving material (encapsulation) or

by dispersing the drug in a slowly dissolving polymer matrix (matrix dissolution) (Hui et al., 1987).

The principles of dissolution controlled release are based on the rate of diffusion of the drug from a solid surface into the bulk solution through an unstirred liquid film. The Noyes-Whitney equation describes this process at steady-state:

$$dm/dt = (DA/h) \cdot (C_b - C_s) = kA (C_s - C_b)$$

where:

dm/dt = the flow rate of material through a unit area

D = the diffusion coefficient of the drug from the solid surface to the bulk solution

A = a unit area

h = thickness of the diffusion layer

C_s = concentration of drug at the solid surface

C_b = concentration of the drug in the bulk solution

k = the intrinsic dissolution rate constant.

The rate-limiting step for dissolution of a drug is then the diffusion across an aqueous boundary layer. The solubility of the drug provides the driving force for drug release. The rate of dissolution will be dependent on: the

aqueous solubility of the drug, the surface area of the dissolving particle or tablet, and the thickness of the boundary layer (Venkataram et al., 2000).

Thus the Noyes-Whitney equation predicts a constant dissolution rate providing the surface area, diffusion coefficient, diffusion layer thickness and concentration difference all remain constant. However, for inherently slow dissolving drugs, drug encapsulated in a slow dissolving material or a drug dispersed in a slowly dissolving matrix, the surface area will change with time, leading to drug release rates that change with time (Hui et al., 1987).

In a matrix dissolution controlled system, the rate of drug availability is controlled by the rate of penetration of the dissolution fluid into the matrix. This rate can be controlled by the porosity of the tablet matrix, the presence of hydrophobic additives, and the wettability of the tablet and particle surface. A major disadvantage of matrix tablets is that the drug release rate varies continuously with time. This is due to the increased diffusional distance and decreased surface area as the solvent front penetrates the tablet (Hui et al., 1987).

1.7 Diffusion Controlled Systems

Diffusion of the drug molecule through a polymeric membrane describes the basis of diffusion controlled matrix systems. The membrane can be either formed from encapsulating the drug particle in a polymer membrane (reservoir systems) or incorporating the drug into a polymer matrix (matrix devices). The drug is available only after partitioning through the polymer layer (Hui et al., 1987).

In a matrix diffusion controlled system, the drug is dispersed in a hydrophilic or hydrophobic polymer. The release rate is then dependent on the rate of diffusion of the drug through the matrix, not on the rate of solid dissolution. Higuchi described these systems as dependent on: the diffusion coefficient of the drug in the release medium, the porosity of the matrix, the tortuosity of the matrix, the solubility of the drug in the release medium and the concentration of the drug in the tablet (Venkataram et al., 2000).

The Higuchi equation describing the drug release from a matrix diffusion system is:

$$Q = [De/T(2A - eC_s)C_s t]^{1/2}$$

where:

Q = weight of drug released per unit surface area

D = diffusion coefficient of the drug in the release medium

e = the porosity of the matrix

T = the tortuosity of the matrix

C_s = the solubility of the drug in the release medium

A = concentration of drug in the tablet.

The Higuchi equation is based on the following assumptions:

1. A pseudo-steady state is maintained
2. A is much greater than C_s (i.e. excess solute is present)
3. $C = 0$ in the solution at all times (sink conditions)
4. Drug particles are much smaller than those of the matrix
5. The diffusion coefficient remains constant
6. No interaction between the drug and the matrix occurs.

A plot of the amount of drug released versus the square root of time should be linear if drug release from the matrix is diffusion controlled.

One may control the release of drug from a homogeneous matrix system by varying the following parameters:

- initial concentration of the drug in the matrix
- porosity
- tortuosity

- polymer system forming the matrix
- solubility of the drug (Hui et al., 1987).

Drug release from a porous matrix system involves penetration of the dissolution medium into the matrix, dissolution of the drug and leaching of the dissolved drug through tortuous interstitial channels and pores in the matrix. These assumptions are not valid for many controlled release matrix systems as they swell with absorption of the medium (Siepmann and Peppas, 2001).

A more comprehensive semi-empirical equation to describe drug release from hydrophilic polymeric matrix systems is the Power Law:

$$M_t/M_\infty = kt^n$$

where:

M_t = cumulative amount of drug released at time t

M_∞ = cumulative amount of drug released at infinite time

k = a constant incorporating structural and geometric characteristics of the device

n = an exponent indicative of the mechanism of drug release (Siepmann and Peppas, 2001).

Thus the Higuchi equation is a special case of the Power Law where $n = 0.5$.

When the exponent $n = 1.0$, the drug release is independent of time. This corresponds to zero-order release kinetics. The mechanism for zero order release from slabs is known as Case-II Transport. Water imbibes into the matrix, relaxing the polymers. The relaxed polymers swell significantly and their volume expands. The penetration of water into the polymer (swelling) is the rate-determining step.

Thus, when $n = 0.5$ (square-root of time kinetics), release is diffusion controlled (Fickian diffusion) and when $n = 1.0$ (zero-order kinetics), release is swelling controlled (Case-II Transport). Though these values are derived from an assumed slab geometry, other geometries provide values near these. Values of n between 0.5 and 1.0 represent a superposition of the two mechanisms and are called anomalous transport (Siepmann and Peppas, 2001).

1.8 Combination Systems

In practice, matrix systems will exhibit varying degrees of diffusion or dissolution controlled release. The predominant mechanism will allow

description by one of the above mathematical representations. Matrix systems can also exhibit a combination of diffusion and dissolution of both the drug and the matrix itself. Drugs can diffuse out of the matrix at the same time that the matrix undergoes dissolution into the medium. As the polymer dissolves and erodes, the diffusional path length for the drug will change. This results in a moving boundary. Zero order release can only occur if surface erosion occurs and the surface area does not change with time. An advantage of such a bioerodible system is that there is no “ghost” matrix to remove (Jantzen and Robinson, 1996).

1.9 Extended release Fluoride Dosage Forms

Numerous approaches have been taken to attempt to deliver low and constant levels of fluoride to the oral cavity. These include gels, controlled-release films, microcapsules, and buccal tablets.

Englander et al. (1967) used custom-fitted polyvinyl mouthpieces to deliver sodium fluoride 1.1 percent gels (acidulated and neutral, about 1 to 2 mg fluoride) daily to the teeth of 500 children, 11 to 14 years of age, for 21 months. They were tested versus an untreated control. After 21 months, the average child in the NaF gel groups had administered 245

daily topical treatments. Caries increments in children using both of the gels were statistically significantly less than in the control group ($p < 0.01$).

Englander et al. (1969) examined the residual anticaries effect of the above treatment 23 months after the original study. Thus, after the original treatment, no treatment was used for 23 months. There was a significant anticaries effect ($p < 0.01$) 23 months after the regimen of repeated topically applied NaF gels had been discontinued.

Friedman (1980) achieved a sustained fluoride-release system by embedding NaF in ethyl cellulose (EC) and silicone polymer. Chewing gum and orthodontic plates were used as delivery systems. The NaF/EC film demonstrated delayed release for up to 20 hours in vitro. The release of fluoride from these systems was found to be controlled by a diffusion mechanism and dependent on solubility, concentration of F, and effective surface area.

Friedman (1981) prepared an extended release preparation of fluoride by dispersing NaF or CaF_2 in ethyl cellulose (EC) with or without a stearic acid matrix (in order to decrease porosity of the tablets). Orthodontic plates were used as delivery systems. The compressed EC pellets were attached to an acrylic orthodontic plate with silicone adhesive. Fluoride

release was tested in vitro and release seen for up to 420 minutes. Addition of stearic acid to the pellet caused a decrease in the fluoride release rate.

Williams et al. (1982) developed microcapsules containing NaF via a coacervation process using ethyl cellulose. Release up to 24 hours was demonstrated in vitro.

Bhargava et al. (1983) developed a sucrose-free hard lozenge containing fluoride. Sorbitol-based lozenges containing 1.0 mg fluoride were prepared because of its pleasant taste, low toxicity and non-cariogenic properties. In vitro release was tested using USP Apparatus II using 900 ml artificial saliva agitated at either 50, 100 or 150 rpm. Release occurred at up to 20 minutes. In vivo release was tested in six healthy human volunteers. Fluoride levels in saliva were tested with a fluoride selective electrode. In vivo release was demonstrated for up to 30 minutes.

Spooner et al. (1983) investigated a calcium fluoride delivery system. A calcium fluoride (0.5 or 5 mg) slurry was embedded between two ion-permeable membranes and then adhered to a tooth with adhesive. Fluoride uptake into the tooth was measured.

Bottenberg et al. (1989) determined the bioadhesive properties of carbopol/hydroxypropylmethylcellulose tablets containing fluoride in vitro. Sodium fluoride did not influence bioadhesion. Magnesium stearate (1 %) had a negative effect on bioadhesion. This may be explained by the formation of a hydrophobic film around the polymer particles, preventing the interaction between the polymer and the tissue. Bioadhesion was tested via the method of Ponchel using porcine attached gingiva on an Instron tensile strength testing system.

Bottenberg et al. (1991) investigated bioadhesive characteristics of fluoride tablets for oral use made from starch, polyacrylic acid (PAA), polyethylene glycols (PEG), and carboxymethylcellulose (CMC). Adhesion force and energy were determined in vitro using the method of Ponchel, and retention time was evaluated in vivo in human subjects. In vitro, PAA showed the best bioadhesive properties, followed by modified starch and PEG (300,000-400,000 mw). The presence of 0.1 mg fluoride as NaF did not reduce the adhesion force and energy. PAA, despite its excellent in vitro adhesion, proved to be irritating to the mucosa. Modified starch tablets containing 5 % (w/w) PAA and PEG with a mw of 300,000 daltons proved to be the most suitable formulations for a fluoride slow-release tablet with bioadhesive properties. Fluoride was tested via a fluoride specific electrode. In vitro, the tablets released all of the fluoride

within an 8-hour period. In vivo, fluoride levels in saliva were maintained for 8 hours in the oral cavity. The in vivo release was compared to toothpaste. The toothpaste had a 4-fold level of fluoride, but released all fluoride within 30 minutes.

Subsequently, Bottenberg et al. (1992) studied an additional formulation with 95 % PEG 750 (mw 300,000) and 5 % PEG Coagulant (mw 5,000,000) with 0.1 mg F as NaF per tablet. This formulation was compared to a conventional tablet prepared using Avicel PH102. In vitro release experiments showed that the bioadhesive tablets needed 8 hours to release all their fluoride compared to <1 hour for the conventional fluoride tablets. In vivo, the bioadhesive tablets had a retention period of 6 hours and could sustain a salivary fluoride level of more than 10 μ M above the baseline for 7 hours. The fluoride levels of the conventional tablet were sustained for only 1 hour.

Aithal and Udupa (1992) formulated sodium fluoride tablets using cellulose acetate phthalate (CAP) as a matrix material. In vitro dissolution in distilled water showed 80 % dissolution at 90 minutes for formulations containing greater than 30 % CAP.

Aithal et al. (1992) tested five different cellulose derivatives as matrix materials for sustained release NaF tablets (2 mg NaF). Ethylcellulose (EC), cellulose acetate phthalate (CAP) and hydroxypropylmethylcellulose (HPMC) were found to be effective, with in vitro release of up to 180 minutes in USP Apparatus 2 in distilled water at 100 rpm. CAP showed the longest release profiles.

Vivien Castioni et al. (2000) developed an intra-oral bioadhesive tablet to deliver fluoride in the mouth over a prolonged period of time. Several formulas were tested in vivo for their tolerance and adhesiveness. Two formulations were selected for studies on salivary fluoride clearance. They were compared to mouthrinses of differing fluoride concentration. Bioadhesive tablets of carbopol, hydroxypropylmethylcellulose, gelatin, and lubricant demonstrated sustained salivary F concentrations for about 10 hours in vivo without major side effects.

1.10 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. 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 (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 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 (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).

Mucoadhesive materials are typically hydrophilic macromolecules that contain numerous hydrogen-bond-forming groups. They require moisture to become adhesive, which can be supplied by the saliva, which can also

act as a dissolution medium for the drug. The buccal route has been used for both systemic and local delivery of actives (Smart, 1993).

Buccal bioadhesive tablets can have the following advantages: allowing good accessibility, reasonable patient acceptance and compliance, avoiding of first-pass metabolism (for systemic drugs), and involving adherence to a fairly robust mucosa (Smart, 1993).

1.11 Mechanisms of Mucoadhesion

The same theories of adhesion that apply to glues can be used to describe bioadhesion. Five theories are recognized as useful to the study of bioadhesion: the electronic, absorption, wetting, diffusion, and fracture theories.

- a. The Electronic Theory – This theory relies on the assumption that the two materials to be bonded have different electronic structures. When the two materials come together, electron transfer occurs in an attempt to balance Fermi charge levels. This electron transfer causes the formation of an electronic double layer of charges at the interface of the two materials.
- b. The Adsorption Theory – In this model, the adhesive bond between the two materials is due to van der Waals

interactions, hydrogen bonds and related forces. These forces are weak, but the large number of interactions produces the adhesive bond.

- c. The Wetting Theory – The ability of at least one of the two materials being bonded to spread and develop intimate contact with its substrate is an important factor in bond formation. The interfacial tensions are used to predict spreading of the materials and in turn the adhesion. The surface energy of both the polymer and the substrate are studied using surface tension measurements (Chickering and Mathiowitz, 1999).

Lehr et al. (1992) described the possible role of surface energy thermodynamics in mucoadhesion. The surface energy parameters of Polycarbophil and pig intestinal mucosa were determined by contact angle measurements of captive air/octane bubbles. The hydrated Polycarbophil films were relatively hydrophilic (low contact angles). However, the mucosal tissue was found to be highly hydrophobic (high contact angles). Thus the mismatch of surface polarities between the two substrates, Polycarbophil and mucosa, contributes to the mucoadhesiveness.

- d. The Diffusion Theory – Interpenetration and entanglement of the polymer chains with the mucous chains is predicted by the diffusion theory. The bond strength should increase as the degree of interpenetration increases. To aid diffusion, the two materials should be soluble in the other. Therefore, bioadhesive polymers should have similar properties as the mucus glycoproteins.
- e. The Fracture Theory – Fracture theory examines the forces needed to separate two surfaces after adhesion. The tensile stress produced during detachment is related to the maximum force of detachment divided by the total surface area. This model does not, however take into account entanglement and interpenetration of the polymer chains. Bioadhesion is often described by the fracture theory (Chickering and Mathiowitz, 1999).

In practical terms, bioadhesion is due to a combination of all these factors. The complex nature of biological surfaces and the changing nature of a bioadhesive tablet over the attachment time make any analysis complex. Typically, the bioadhesive properties are examined with ex vivo methods or in vivo.

The stages of bioadhesion are: intimate contact which is the result of good wetting of the bioadhesive surface and the swelling of the polymer, then penetration of the polymer strands into the crevices of the tissue surface, or interpenetration of the bioadhesive chains with those of the mucus, sometimes with weak chemical bonding (Duchene et al.,1988).

1.12 Gantrez MS

Gantrez polymers are a family of synthetic copolymers of methylvinyl ether and maleic anhydride (PMVE/MA). PMVE/MA polymer is typically supplied as the anhydride powder (the AN form, Gantrez AN) or in other chemical forms such as the mixed sodium/calcium salt (Gantrez MS). PMVE/MA polymers are used in the pharmaceutical industry as thickening and suspending agents, as a denture adhesive base, as ostomy adhesives, and in transdermal patches. (International Specialty Products Technical Profile).

The mixed-salt of calcium and sodium, Gantrez MS, is used in the preparation of denture adhesive creams. Gantrez MS is a white powder. The copolymer is slowly soluble in water and gives amber colored solutions with high viscosity (International Specialty Products Technical Profile). Gantrez MS is manufactured under cGMP conditions and has a Drug Master File filed with the U.S. FDA. Gantrez MS is not a

pharmacopoeial or NF listed excipient. The structures of Gantrez polymers are shown in Figure 1.

Table 5. Gantrez MS-955 Typical Properties (International Specialty Products Technical Bulletin).

Appearance at 25 deg C	White/off-white powder
% Water Content	6.0-15
pH (1 g/100 ml DI water at 25 degC)	5.5-7.0
% through 400 mesh	75.0 max
Particle Size Range (um)	10-200
Average Particle Size (um)	30-45
Bulk Density Range (g/ml)	0.60-0.75
Tap Density Range (g/ml – 3000 taps)	0.90-1.10
Approx. Mw (SEC/LALLS)	1,060,000
Brookfield Viscosity mPa.s at 25 degC (11.1 % solids aq.) Brookfield RVT, spindle 3, 20 rpm	700-3000
Solubility: Water Ethanol Isopropanol	Slowly soluble Soluble Soluble
Hydration Time (to make a 2 % solution)	Approx. 1 h at r.t.
Toxicology Acute Oral LD ₅₀ (administered as a 20 % aq. solution) Powder Irritation (rabbit eye) Powder Irritation (rabbit skin)	> 5.0 g/kg Mild irritation No irritation

Figure 1. Structure of Poly (methylvinylether-co-maleic anhydride) - Gantrez AN Polymers and Gantrez MS (ISP Technical Bulletin).

Gantrez AN, (the anhydride form), was reported by Smart et al. (1984) to have mucoadhesive properties using an in vitro test of adhesiveness. Glass plates were coated with a series of materials. The force to remove the coated plate from a homogenized mucus sample was recorded. All forces were reported as a percentage of a reference standard (the force required to pull the clean plate from the same mucus sample). The rank order of mucoadhesive force is shown in Table 6.

Table 6. Rank Order of Mucoadhesive Force (Smart et al., 1984).

Coating Material	Mean % Adhesive Force Relative to Clean Glass Plate	Standard Deviation
Sodium CMC 75P	192.5	12.0
Carbopol 934	185.0	10.3
Tragacanth	154.4	7.5
Gantrez AN	147.7	9.7
Sodium Alginate HV	126.2	12.0
Hypromellose MV	125.2	4.8
Gelatin	115.8	5.6
Pectin	100.0	2.4
PVP	97.6	3.9
Acacia	97.6	5.9
PEG 6000	96.0	7.6

Thus the mucoadhesive properties of Gantrez AN are comparable to other widely used mucoadhesive excipients. However, Gantrez has not found widespread use as a bioadhesive excipient for tablets. This is likely due to its lack of compendial status.

Gantrez AN was reported as a dry binder for tablet manufacture by El-Khawas et al. (1974), who reported that disintegration times were increased.

Nunez Recuero et al. (1991) reported controlled release tablet formulations with Gantrez AN, the anhydride form. Tablets were prepared with Gantrez AN, various plasticizers (glycerine, dibutylphthalate, triacetin, butylphthalate) and diluents such as Encompress, ethylcellulose, and polyvinyl chloride. Swelling was increased with increasing portion of polymer. They concluded that tablets prepared with Gantrez AN provided sustained release and increased adhesion and would be useful for controlled drug release.

Moneghini et al. (1991) produced tablets with a co-precipitate of PVME/MA and phenylbutazone that demonstrated extended release rates.

El Khodairy et al. (1992) reported the use of Gantrez AN (butyl half ester) for an extended release nitrofurantoin tablet. The release rate decreased with increasing Gantrez AN content.

El-Faham and Massoud (1994) reported the use of Gantrez AN (anhydride) and cellulose acetate to produce thin films that extended the release of bromohexine hydrochloride in the human eye.

Jones et al. (2003) reported the rheological and mucoadhesive properties of aqueous combinations of PMVE/MA and poly(vinylpyrrolidone) (PVP) polymeric systems using poly(methylvinylether-co-maleic anhydride) as candidates for improved drug delivery to the oral cavity. They concluded that gels composed of PMVE/MA and PVP offered promise as platforms for controlled drug delivery to the oral cavity due to their mucoadhesive properties.

Though these researchers report use of Gantrez AN (the anhydride) as a bioadhesive or extended release excipient, no published reports have been found for the use of Gantrez MS (the mixed salt) for bioadhesive extended release tablets.

Gantrez MS may provide several advantages over commonly used bioadhesive excipients. It has a long safely record in human use. It has been used in denture adhesives for 15 years or more. The mixed-salt form of Gantrez should be less reactive than the anhydride-form. Gantrez MS has the properties required for extended release as well, being a water-soluble hydrophilic polymer. By optimizing the ratio of Gantrez MS in the formulation, both extended release and bioadhesive properties could possibly be achieved in a direct compression tablet.

Gantrez MS is used in this study as both a bioadhesive and an extended release matrix.

1.13 Sodium Carboxymethylcellulose

Carboxymethylcellulose Sodium (NaCMC) is an anionic water-soluble polymer that is produced by reaction of cellulose with sodium monochloroacetate. The resulting products have varying degrees of substitution of the three hydroxyl groups with carboxymethyl groups. The average number of hydroxyl groups substituted per anhydroglucose unit is known as the “degree of substitution” or DS (Hercules Aqualon Technical Bulletin). The structure of NaCMC is shown in Figure 2.

Cellulose ethers, such as NaCMC are long-chain polymers. Their solution characteristics depend on the average chain length or degree of polymerization (DP) as well as the degree of substitution. The average chain length and degree of substitution determine the molecular weight of the polymer. As molecular weight increases, the viscosity of NaCMC solutions increases rapidly. Cellulose ethers are typically specified as High, Medium or Low Viscosity (Hercules Aqualon Technical Bulletin).

NaCMC is used in pharmaceuticals as a coating agent, a tablet and capsule disintegrant, a tablet binder, and a viscosity-increasing agent.

NaCMC is one of the primary excipients in self-adhesive ostomy and wound care patches (Handbook of Pharmaceutical Excipients, 1994).

Table 7. Typical Properties of NaCMC High Viscosity (Handbook of Pharmaceutical Excipients, 1994).

Viscosity, cps (1 % solution)	1500-3000
Degree of Substitution (DS)	0.7
% Water	8 % max.
Appearance	White to off-white powder
pH in 1 % water solution	6.0-8.5
pKa	4.30
Solubility	Soluble in water
Bulk Density	400-800 kg/m ³
Toxicology General	Harmless, non-toxic, non-irritant, non-mutagenic, non carcinogenic, non sensitizing
LD ₅₀ (oral, rat)	27,000 mg/kg
Regulatory Status	Approved as a Food Additive in most countries GRAS listed USP NF XXII

Figure 2. Structure of NaCMC (<http://www.lsbu.ac.uk/water/hymcm.html>)

NaCMC was chosen for its well known bioadhesive and controlled release properties (Smart, 1993). NaCMC is used in this research as both a tablet binder and a bioadhesive excipient.

1.14 Carbopol 934P

Carbopol polymers are very high molecular weight polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl alcohol. They are also called carbomers. Carbopol polymers are produced as flocculated powders with average particle size of 2 to 7 microns. The particles are a network of polymer chains with molecular weights in the billions. The polymers swell up to 1000 times their original volume in water to form a gel when exposed to pH above 4-6. Above their pK_a of 6 +/-0.5, the carboxylate groups on the polymer backbone ionize, resulting in repulsion between the anions and further swelling. The crosslinked polymers do not

dissolve in water but form colloidal dispersions (Noveon Technical Bulletin 16). The structure of C934P is shown in Figure 3.

Carbopol polymers contain between 56-68 % carboxylic acid groups. The approximate molecular weight of Carbopol 934P is 3×10^6 . Carbopol grades with low residual benzene content, such as 934P and 974P, are used in oral preparations (suspensions), as a tablet binder and in sustained release tablets (Handbook of Pharmaceutical Excipients, 1994).

Figure 3. Idealized Structure of Carbopol 934P (Noveon Technical Bulletin 16).

Table 8. Typical Properties of Carbopol 934P (Handbook of Pharmaceutical Excipients, 1994).

Aqueous viscosity (mPa s)	29,400-39,400
Loss on drying	< 2.0 %
Benzene	<0.01 %
PH of 0.5% w/v aqueous dispersion	2.7-3.5 %
Bulk density	1.76 g/ml
Tapped density	1.4 g/ml
Moisture content	Normally <2 %, but hygroscopic
Particle size distribution	2-7 um
Solubility	Soluble in water
Toxicology	LD ₅₀ (rat, oral) 4.1 g/kg
Regulatory status	US FDA Inactive Ingredients Guide USPNF XVII

Bottenberg et al. (1989) reported use of carbopol in combination with hydroxymethylcellulose to produce extended release fluoride tablets.

Combinations of Carbopol 934, hydroxypropylcellulose and hydroxypropylmethylcellulose were used to produce buccoadhesive tablets for insulin delivery (Hosny et al., 2002).

Carbopol 934P will be used in this research at levels of 1-5 % as a bioadhesive matrix excipient.

1.15 Polyethylene Glycol 8000

Polyethylene Glycols are used widely in the pharmaceutical industry in topical, ophthalmic, oral and rectal preparations. Polyethylene glycols are stable, hydrophilic and nonirritating to the skin. Higher molecular weight polyethylene glycols are used to improve tablet binders and to impart plasticity to granules, typically at levels of less than 5 %. Solid grades of polyethylene glycol are also used for the film coating of tablets. Polyethylene glycols of molecular weights of 6000 and above can be used as tableting lubricants. The lubricant action is not as good as magnesium stearate, and stickiness may develop during compression (Handbook of Pharmaceutical Excipients, 1994).

The empirical formula for polyethylene glycol is $\text{HOCH}_2(\text{CH}_2 \text{OCH}_2)_m\text{CH}_2\text{OH}$, where m is the average number of oxyethylene groups. For Polyethylene Glycol 8000, $m=181.4$ and the average molecular weight is 7000-9000 (Handbook of Pharmaceutical Excipients, 1994).

High molecular weight polyethylene glycols were studied by Bottenberg et al. (1991) for extended release of sodium fluoride.

Muco-adhesive erodible tablets of clotrimazole for local delivery to the oral cavity were produced using combinations of Carbopol 974P, hydroxypropylmethylcellulose, PEG 6000 and Mannitol (Khanna et al., 1997).

In this research Polyethylene Glycol 8000 (PEG 8000) will be used at levels of 1 % - 10 % as a tablet lubricant and binder.

Table 9. Typical Properties of PEG 8000 (Handbook of Pharmaceutical Excipients, 1994).

Density	1.15-1.21 g/ml at 25degC
Melting Point	60-63 degC
Solubility	Soluble in water, may form gels
Toxicity	Nontoxic Nonirritant WHO Acceptable Daily Intake 10 mg/kg
Regulatory Status	US FDA Inactive Ingredients Guide USPNF XVII

1.16 Sodium Fluoride

Sodium fluoride, NaF, is used pharmaceutically as a dental caries prophylactic and in the treatment of osteoporosis. The properties are outlined in Table 10.

Table 10. Properties of Sodium Fluoride USP (US Pharmacopeia, 2002, Merck Index, 1996).

Assay %	98.0-102.0
Loss on drying	<1 %
Heavy metals	<0.003 %
Organic volatile impurities	Meets requirements
Solubility in water	4.3 g/ml (25 degC)
pH of freshly prepared saturated solution	7.4
Toxicology	Oral rat LD50 – 52 mg/kg

1.17 Basis for Dose Strength Chosen

A dose strength of 0.5 mg/tablet was chosen for the following reasons:

- 1) Saliva fluoride concentrations of 0.1 ppm to 1 ppm have been shown to significantly inhibit demineralization of teeth in vitro, as

described above (Featherstone and Zero, 1992; Margolis et al., 1986).

- 2) Saliva concentrations of 1.48 to 3.03 $\mu\text{mol F/l}$ (0.03 to 0.06 ppm) were shown by Duckworth et al. (1992) to inhibit caries in humans in clinical trial.

Assuming a dose of 0.5 mg, an exposure period of 12 hours and a salivary flow rate of 250 – 1000 ml in a 12-hour period, an average concentration of 0.5 ppm to 2 ppm could be obtained. Thus a dose strength of 0.5 mg fluoride was chosen for this research.

2. Objective, Hypothesis and Specific Aims

2.1 Significance of the Research

Caries continues to be an important public health issue. This is especially true in areas without naturally fluoridated water. The incorporation of fluoride into the tooth structure is most effective when the saliva constantly contains a low (~ 1 ppm) level of fluoride ion. The presence of fluoride ion in the saliva drives the equilibrium towards the incorporation of fluoride into the tooth, which results in a stronger tooth structure that is resistant to caries attack.

Current fluoride therapies all provide additional fluoride to the saliva for only a limited time, typically less than 30 minutes. There are no extended release fluoride buccal dosage forms in the U.S. market at present. An extended release formulation will provide release of fluoride at a low level over a period of time that is much longer than current therapies. The extended release dosage form presents the opportunity for improved topical fluoride effect. An extended release tablet which delivers fluoride for up to 8 hours could allow simple once per day dosing for exposure during waking hours.

This fluoride dosage form is intended for use where water supplies are low in fluoride (<0.7 ppm) for the prevention of dental caries. In communities without fluoridated water supplies, the American Dental Association's Council on Dental Therapeutics recommends the use of fluoride supplements until the age of 13 (Drug Facts and Comparisons, 2002).

2.2 Rationale for Developing a Bioadhesive Extended release Fluoride Tablet

A bioadhesive tablet adhered to the buccal gingiva would allow delivery of the fluoride locally to the oral cavity, which is the intended site of action, for an extended period of time.

2.3 Objective

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 forms of Gantrez have been described (Smart et al., 1984; Nunez Recuero et al. 1991; El Khodiary et al., 1992; Jones et al.,

2003), 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).

This preliminary study aims to investigate the effects of these polymers and their mixtures on in vitro drug dissolution and ex vivo bioadhesion from matrix tablets. One aim was to demonstrate drug dissolution that is slower than an immediate release tablet and that release is on the order of eight hours. If release of the fluoride is sustained for periods of up to eight hours, then a simple once per day dosing (for waking hours) may be possible as people go through normal daily activities. Additionally, the bioadhesive properties of these mixtures were explored. A positive bioadhesive result was considered to be any bioadhesive force greater than that used to initially place the tablet in contact with the tissue during the adhesion period. For the purposes of this research, higher bioadhesion values were considered better, though in practical terms, some upper limit would be necessary in vivo.

2.4 Hypothesis

The research hypothesis is that the polymer excipients Gantrez MS, NaCMC, PEG 8000 and Carbopol 934 will enable formulation of bioadhesive buccal fluoride tablets that also exhibit extended release properties. Combinations of these excipients will provide in vitro drug release for at least 8 hours, an improvement over currently marketed chewable fluoride tablets,

This hypothesis is based on the following assumptions:

- Eight hours of fluoride exposure is a significantly improvement over current dose forms. The tablet could be in place during the waking hours.
- A positive bioadhesive force is indicative of effectiveness in maintaining the tablet on the gingival tissue for an extended period. Increasingly positive bioadhesive forces are indicative of longer in vivo residence times.
- There is no fluoride absorption through the keratinized gingival tissue. The fluoride would be dissolved into the saliva to act locally.

2.5 Specific Aims

- Determine the effect of Gantrez MS, NaCMC and PEG8000 and their combinations on the in vitro dissolution of fluoride from extended release matrix tablets in USP Apparatus 2 and compare to the release from a marketed immediate release fluoride tablet.
- Determine the effect of medium flow rate on the dissolution of fluoride from extended release matrix tablets in the Low Flow, Low Volume Apparatus.
- Determine the effect of Gantrez MS, NaCMC and PEG8000 and their combinations on the in vitro dissolution of fluoride from extended release matrix tablets in the Low Flow, Low Volume Apparatus and compare the release to a marketed immediate release fluoride tablet.
- Determine the effect of Gantrez MS, NaCMC and Carbopol 934P and their combinations on the in vitro dissolution of fluoride from extended release matrix tablets in the Low Flow, Low Volume Apparatus.

- Determine the effect of contact time on ex vivo bioadhesion for an extended release matrix fluoride tablet.
- Determine the effect of contact force on ex vivo bioadhesion for an extended release matrix fluoride tablet.
- Determine the effect of Gantrez MS, NaCMC and C943P and their mixtures on ex vivo bioadhesion of matrix fluoride tablets.

3. Experimental

3.1 Materials

Acetic acid, glacial (Mallinkrodt Baker, Inc., Phillipsburg, NJ, USA)

Carbopol ® 934P NF (C934P) (B.F. Goodrich Specialty Chemicals, Cleveland, OH, USA)

Commercial sodium fluoride chewable tablets 1.0 mg F as 2.2 mg NaF (Amide Pharmaceuticals, Little Falls, NJ, USA)

Permabond 200 Fast Curing Adhesive (Permabond, 10 Finderne Ave., Bridgewater, NJ, USA)

Polyethylene glycol 8000 USP/NF (PEG8000) (Spectrum Chemical Mfg., Gardena, CA, USA)

Poly (methylvinylether-co-maleic anhydride) mixed calcium/sodium salt (PVM/MA MS or Gantrez MS ®) (International Specialty Products, Wayne, NJ, USA)

Sodium carboxymethylcellulose High Viscosity USP/NF (NaCMC) (Hercules Ltd., Wilmington, DE, USA)

Sodium chloride ACS (Mallinkrodt Baker, Inc., Phillipsburg, NJ, USA)

Sodium fluoride USP (Mallinkrodt Baker, Inc., Phillipsburg, NJ, USA)

Sodium Hydroxide ACS (Mallinkrodt Baker, Inc., Phillipsburg, NJ, USA)

Trans-1,2-Diaminocyclohexane – N,N,N',N' – tetraacetic acid monohydrate (Sigma Aldrich Co., St. Louis, MO, USA)

3.2 Equipment

Accumet ®1002 pH meter (Fisher Scientific, Fair Lawn, NJ, USA)

Balances - B1502, AB104 (Mettler Toledo, Columbus, OH, USA)

Balance 3811024 (Sartorius, Bohemia, NY, USA)

Bioadhesion tissue holder (Texture Technologies Corp., Scarsdale, NY/Stable Micro Systems, Godalming, Surrey, UK)

Carver Press Model C (Fred S. Carver, Inc., Menomonee Falls, WI, USA)

Corning pH/Ion Analyzer 350 (Corning Inc., Corning, NY, USA)

Dial Micrometer 1015MA (L.S. Starrett, Athol, MA, USA)

Dissolution Tester (Vanderkamp 600, Van-Kel Industries, Edison, NJ, USA)

Dissolution Tester (Erweka DT7R, Erweka Instruments, Inc., Milford, CT, USA)

Dissolution Tester (Erweka DT6, Erweka Instruments, Inc., Milford, CT, USA)

Falcon 50 ml polypropylene conical tubes (Becton Dickinson Labware, Franklin Lakes, NJ, USA)

Hardness Tester (Key International HT-300, Englishtown, NJ, USA)

Julabo ® MD F25 Constant Temperature Circulator (Allentown, PA, USA)

Micro-V Stirrers, Model No. 4805-00 (Cole-Parmer, Chicago, IL, USA)

Orion ® Fluoride Electrode (Orion Electrode Products, Boston, MA, USA)

Peristaltic Pump Masterflex Digital Drive L/S with 6-channel head (Masterflex Vernon Hills, NJ, USA)

Peristaltic pump tubing, Norprene, Masterflex 06404 (Masterflex, Vernon Hills, NJ, USA)

Rotary Tablet Press (Manesty D3B Manesty Machines Ltd., Liverpool, UK)

Sieve #25 710 μm , 0.0278" (Gilson Co., Worthington, OH, USA)

Small volume, low flow dissolution cells ($n=6$), custom fabricated (see Figure 4)

Tablet Punch/Die 8 mm, round, flat (Natoli Engineering Co., St. Charles, MO, USA)

TA.XT2i Texture Analyzer ® (Texture Technologies Corp., Scarsdale, NY/Stable Micro Systems, Godalming, Surrey, UK)

Turbula ® Mixer T2G (Willy A. Bachofen, Basel, Switzerland)

3.3 Software

The JMP software program, Version 5.1 (SAS Institute, 1995) was used to generate and analyze the experimental designs. Percent drug dissolved at times 2, 4 and 8 hours; peak bioadhesive force and work of bioadhesion were the dependent variables.

3.4 Fluoride Analysis

The fluoride content of the dissolution 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. 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 dissolution. Percent drug dissolved was calculated using a standard curve ranging from 10^{-1} M to 10^{-6} M NaF in 50 % TISAB in deionized water.

3.5 In Vitro Drug Dissolution

The dissolution test is intended to measure drug release into solution. Though dissolution time and rate provides an indication of dosage form

effectiveness, any in vitro dissolution test must be correlated with in vivo bioavailability (Lachman et al., 1986).

The dissolution test is designed to determine two important factors (1) that the release of the drug from the tablet is as close to 100 % as possible and (2) that the rate of release is uniform from batch to batch and is the same as the release rate from those batches shown to be bioavailable and clinically effective. Drug products must comply with the dissolution time limits stated in the individual drug monograph (Lachman et al., 1986). Dissolution testing can also give an indication of possible in vivo performance during the dosage form development process.

The USP/NF Dissolution Test <711> is performed to demonstrate compliance with the dissolution limits given in the monograph for a tablet or capsule drug product.

For this research, drug dissolution was measured using USP Apparatus 2 and a novel Low Volume, Low Flow Apparatus.

3.5.1 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 Dissolution Test 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 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 dissolution was calculated using a standard curve ranging from 10^{-1} M to 10^{-6} M NaF in 50 % TISAB in deionized water. The dissolution profiles were fitted to either the Higuchi model or the zero-order curve and the R^2 was determined.

3.5.2 Low Volume, Low Flow Apparatus

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). In vitro dissolution tests for buccal delivery systems should be performed in small volumes of dissolution medium (Hao and Heng, 2003).

No standard in vitro method has been accepted for dissolution studies of buccal formulations. Methods that have been reported include: the Japan Pharmacopeia XII disintegration tester (without the attached disk), a rotating basket dissolution tester, modified USP Apparatus 1 and 2, the Japan Pharmacopeia XII dissolution apparatus and small compartment flow through devices (Khanna et al., 1997).

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). This non-compendial method was used to evaluate drug release from the fluoride tablets.

The design of this apparatus is based on modification of a flow-through diffusion cell and is shown in Figures 4, 5, 6 and 7. The lower chamber of the apparatus had a small volume compartment (3.1 ml) and the medium 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 instant adhesive in each case hardened within approximately 30 seconds to hold the tablet in place. Infiltration of the adhesive into the tablet was observed to be minimal.

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. Medium (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-hour period and the fluoride content tested directly with a fluoride selective electrode. The dissolution profiles were fitted to either the Higuchi model or the zero-order curve and the R^2 was determined.

Figure 4. Design of the small volume dissolution apparatus.

Figure 5. Small volume dissolution apparatus showing attachment of tablet.

Figure 6. Small volume apparatus showing swollen tablet during dissolution.

Figure 7. Design of the small volume dissolution system.

3.5.3 Higuchi Kinetics Evaluation

Drug release kinetics from tablet matrices commonly follow a square-root-of-time dependence first described by Higuchi. A plot of cumulative amount of drug dissolved versus the square root of time should be linear if the drug release is diffusion controlled. The release rate is dependent on the rate of diffusion of the drug through the matrix (Higuchi, 1963).

For each formulation, the cumulative amount of NaF dissolved was plotted versus the square root of time. R^2 values were determined and the applicability of the diffusional release mechanism was assessed.

3.6 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., 1999). The bioadhesion testing apparatus is shown in Figure 8.

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 (Figure 9). The tissue and underlying support tissue were excised and kept in plastic bags and plastic containers and stored at -5°C until use.

The bovine tissue was cut into approximately $1\frac{1}{2}$ inch strips, then allowed to warm to room temperature and rinsed with cool tap water. The thumbscrews on the tissue holder were opened and the upper portion removed. The tissue strip was placed into the tissue holder and the upper tissue holder replaced. The thumbscrews were turned to firmly hold the tissue in place. The tissue samples were held in place using a Plexiglas fixture (Stable Micro Systems, Surrey, U.K.), then covered with a 2 ml aliquot of pH 7.0 phosphate buffered saline in the well of the upper tissue

holder. The tablet to be tested was fixed to the moveable stainless sample probe using a small amount of instant glue. The instant adhesive in each case hardened within approximately 30 seconds to hold the tablet in place. Infiltration of the adhesive into the tablet was observed to be minimal.

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 (g*s) were recorded for six tablets tested at each condition. All statistical analysis was performed using JMP software (SAS Institute, 1995).

Figure 8. Bioadhesion testing apparatus.

Figure 9. Bovine jaw and tissue harvested.

3.7 Tablet Manufacture

All tablets were formulated with 0.5 mg fluoride per tablet. The process flow is shown in Figure 10. The components in each formula were mixed via geometric dilution in a mortar and pestle followed by a Turbula T2C mixer for 20 minutes. 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. The tablets were stored in tightly closed high density polyethylene bottles until testing.

Direct Compression Process Flow:

- The corresponding amounts of drug and excipients were weighed.
- The excipients were mixed with the sodium fluoride via geometric dilution (1:1, 1:2, 1:3) in a mortar and pestle.
- The powder was transferred into the Turbula Mixer jar (plastic) and mixed for 20 minutes.
- The powder was compressed into tablets using a Rotary Tablet Press with 8 mm round flat dies. Tablets were collected during compression for in-process testing (weight target 120 mg, hardness target 5 to 10 kP, thickness target 1.7 to 1.8 mm).

Figure 10. Process flow chart for tablets manufactured by direct compression.

3.8 Tablet Evaluation

Tablet Weight Variation – Twenty tablets from each batch were weighed individually and the average weight (mg) and relative standard deviation were recorded.

Thickness – Thickness was determined for 10 pre-weighed tablets from each batch using a micrometer and the average thickness (mm) and relative standard deviation were recorded.

Hardness – Hardness was determined for 10 tablets (of known weight and thickness) for each batch. The average hardness (kP) and relative standard deviation were recorded.

Uniformity of Dosage Units – Uniformity was assessed for each batch according to the USP requirements <905> for content uniformity using the fluoride selective electrode. The batch meets the USP requirements if the amount of the active ingredient (NaF) in each of the 10 tested tablets lies within the range of 85 % to 115 % of the label claim (target drug content) and the relative standard deviation is less than or equal to 6. According to the USP criteria, if one of these conditions is not met, an additional 20 tablets must be tested. Not more than 1 unit of the total 30 tested should be outside the range of 85 % to 115 % of the label claim (target drug content) and no unit outside the range of 75 % to 125 % of label claim. Additionally, the relative standard deviation should not exceed 7.8

3.9 Experimental Design and Methodology

The levels of Gantrez MS, NaCMC, C934P, and PEG8000 were selected according to preplanned centroid mixture statistical designs (Figure 11) shown in Table 11 (Centroid Experiment 1) and Table 12 (Centroid

Experiment 2). The JMP statistical software program was used to generate the mixtures for each point in the centroid designs. Additional points were added to gain further information in regions of interest. The designs used the proportions of Gantrez MS, NaCMC, Carbopol 934P and PEG 8000 as the independent variables. Percent drug dissolved at times 2, 4 and 8 hours; peak bioadhesive force and work of bioadhesion were the dependent variables. For each sample evaluated, a sample size of six was used.

Mixture designs are statistically derived designs that are used for response surface experiments in which the factors are the fractional components of a mixture and thus must always sum to 1. Responses are a function of the proportion of each component. The mixture experiments were 3-component mixture combinations of Gantrez MS, NaCMC, and Carbopol 934P or PEG 8000. The properties of the product (percent drug dissolved, bioadhesion) are then a function of the proportions of the different excipients and their interactions (Meyer and Montgomery, 2002).

In the centroid mixture studies, the proportion of PEG8000 was constrained to 1-10 % as tablet sticking occurred in the tablet press at higher levels. The proportion of Carbopol was constrained to 1-5 % due to tablet sticking at higher levels.

Mixture designs have been used for evaluation of pharmaceutical formulation variables. A seven-point simplex-centroid experimental design was used to investigate the influence of formulation variables on the in vitro release of diclofenac sodium (Gobel et al., 1998).

Percentage drug dissolved values (n=6) at 2, 4, and 8 hours were used as the response variables for the dissolution studies using JMP software (SAS Institute). These points were selected to evaluate responses throughout the dissolution profile. The peak bioadhesion and work of bioadhesion (n=6) were used as response variables for the bioadhesion studies. After obtaining the responses for all experimental runs, the results were entered into the JMP statistical software. The software completed multiple regression analysis, resulting in mathematical modeling of the effects of the casual factors on the dependent variables (drug dissolution or bioadhesion). ANOVA tables were created by the software including model parameter estimates and parameter significance.

Figure 11. Experimental Centroid Design (Centroid 1) (run fractions selected by JMP software).

Table 11. The Fractions of Excipients in Centroid Experimental Design 1 (run fractions selected by JMP software).

<i>Run</i>	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

Table 12. The Fractions of Excipients in Centroid Experiment 2 (run fractions selected by JMP software).

<i>Run</i>	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	
G18	0.05	0.475	0.475

3.10 Study of the Effect of Gantrez MS, NaCMC, PEG8000 and their Mixtures on the Dissolution of Fluoride from Extended Release Matrix Tablets in USP Apparatus 2

Drug dissolution from Centroid 1 formulas and a commercial immediate release fluoride tablet was evaluated in USP Apparatus 2 (n=6). The fluoride content of the dissolution medium was measured directly at each time point using a fluoride selective electrode (Orion ©) after generation of a standard curve. The standard solutions were maintained and tested at the same temperature as the dissolution medium. Drug dissolution was calculated using a standard curve ranging from 10^{-1} M to 10^{-6} M NaF in 50 % TISAB in deionized water.

3.11 Study of the Effect of Mixing and Medium Flow Rate on Fluoride Dissolution in the Low Volume, Low Flow Apparatus

The conditions for the Low Flow, Low Volume Method included the use of a magnetic stirrer (300 rpm) and a micro-sized magnetic stir bar (length 4 mm) in the 3.1 ml cells. A qualitative test for uniform mixing was first performed in the Low Flow, Low Volume Apparatus. Medium was first

pumped through the small cells at 0.5 and 1.0 ml/min. with agitation. These flow rates were selected based on the resting saliva flow rates of 0.5 to 2 l per day (Ritschel, 1970). After equilibration at each rate, a small amount of blue food dye was added to the container of medium and the cells observed with a stopwatch for signs of blue dye mixing.

Drug dissolution for formula G7 (n=6) was evaluated at two different flow rates in the Low Volume, Low Flow Apparatus. Medium was pumped through the cells at 0.5 ml/min and drug dissolution evaluated. In a separate experiment, medium was pumped through the cells at 1.0 ml/min and the drug dissolution evaluated and compared to that at 0.5 ml/min.

3.12 Study of the Effect of Gantrez MS, NaCMC, PEG8000 and their Mixtures on the Dissolution of Fluoride from Extended Release Matrix Tablets in the Low Volume, Low Flow Apparatus

Drug dissolution from Centroid Experiment 1 formulas and a commercial immediate release fluoride tablet was also evaluated in the Low Volume, Low Flow Apparatus (n=6). Medium (50 % TISAB in deionized water (pH 6.0) at 37°C) was pumped through the cells using a multi-channel

peristaltic pump. The jacketed cells were maintained at 37°C using a recirculation bath. Aliquots were collected at regular intervals over an 8-hour period and the fluoride content tested directly with a fluoride selective electrode.

3.13 Study of the effect of Gantrez MS, NaCMC, CP934P and their Mixtures on the Dissolution of Fluoride from Extended Release Matrix Tablets in the Low Volume, Low Flow Apparatus

Drug Dissolution for Centroid Experiment 2 was evaluated in the Low Volume, Low Flow Apparatus (n=6). Medium (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-hour period and the fluoride content tested directly with a fluoride selective electrode.

3.14 Direct Comparison of Drug Dissolution from Several Extended Release Formulations in the Low Volume, Low Flow Apparatus

Several of the formulas were tested head-to-head in the six cells of the Low Flow, Low Volume Method (n=3 for each formula). This direct comparison provided a confirmation of findings from the other experiments and allowed a direct visual comparison of the behavior of the formulas during the 8 hour experiments. Formulas G16 (97.5 % Gantrez MS, 2.5 % C934P) and G17 (97.5 % NaCMC, 2.5 % C934P) were compared using three tablets each in the six cell apparatus. Medium (50 % TISAB in deionized water (pH 6.0) at 37°C) was pumped through the cells using a multi-channel peristaltic pump 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-hour period and the fluoride content tested directly with a fluoride selective electrode.

Formulas G2 (100 % NaCMC) and G5 (100 % Gantrez MS) were compared using three tablets each in the six cell apparatus. Medium (50 % TISAB in deionized water (pH 6.0) at 37°C) was pumped through the cells using a multi-channel peristaltic pump 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-hour period and the fluoride content tested directly with a fluoride selective electrode.

3.15 Study of the Effect of Contact Time on Ex vivo

Bioadhesion

Peak bioadhesive force and work of bioadhesion were determined using a TA.XT2i Texture Analyzer. The effect of contact time on the work of bioadhesion was studied for formula G13 (Table 2). Formula G13 was selected because it represented one of the high percent NaCMC formulas. The tablet was placed in contact with the gingival tissue with a contact force of 20 g for times ranging from 30 seconds up to 4 hours (n=6). Six tablets were tested at each condition. Peak bioadhesive force (g) and work of bioadhesion (g*s) were determined.

3.16 Study of the Effect of Contact Force on Ex vivo

Bioadhesion

The effect of contact force on work of bioadhesion was studied for formula G13 (Table 2). The tablet was placed in contact with the gingival tissue with contact forces ranging from 10 g to 60 g for 300 s (n=6). Six tablets

were tested at each condition. Peak bioadhesive force (g) and work of bioadhesion (g*s) were determined.

3.17 Study of the Effect of Gantrez MS, NaCMC, C934P and their Mixtures on Ex vivo Bioadhesion

Twelve formulas from Centroid Experiment 2 were tested for ex vivo bioadhesive properties. The test conditions were as follows: Pre-test probe lowering speed 1 mm/s, contact force 20 g, contact time 300 s, probe withdrawal speed, 0.1 mm/s. Conditions were chosen based on the results of the contact time and contact force experiments. Peak bioadhesive force (g) and work of bioadhesion (g*s) were recorded for six tablets tested at each condition.

4. Results and Discussion

4.1 Tablet Evaluation

Sodium fluoride 0.5 mg matrix tablets were manufactured with the nine formulas specified in Centroid Experiment 1 and the 12 formulas specified in Centroid 2. Batch size for each formula was 200 g. Tablets were uniform in weight and thickness and hardness. Content uniformity was

shown to meet USP <905> requirements for each batch. Results are shown in Table 13 and Table 14.

**Table 13. Physical Properties of Sodium Fluoride 0.5 mg Tablets
from Centroid Experiment 1.**

Formula	Assay (n=10)		Weight (mg) (n=20)		Gauge (Thickness, mm) (n=10)		Hardness (kP) (n=10)	
	Content %	RSD	Average	RSD	Average	RSD	Average	RSD
F1	98.5	2.4	118.9	3.0	1.70	2.2	3.2	9.0
F2	100.8	3.5	118.0	3.4	1.78	2.9	3.2	7.1
F3	97.3	4.7	119.7	1.3	1.76	1.1	3.9	8.9
F4	100.4	2.3	119.5	3.8	1.72	2.0	7.1	5.0
F5	98.6	3.5	117.9	3.0	1.67	1.7	3.1	7.3
F6	95.8	5.7	118.5	3.0	1.65	2.2	5.4	5.3
F7	101.4	2.5	119.1	1.1	1.72	0.96	8.1	4.1
F8	99.9	3.6	121.3	0.99	1.86	1.1	3.6	8.7
F9	100.9	3.8	120.9	0.95	1.76	0.86	5.1	6.1

Table 14. Physical Properties of Sodium Fluoride 0.5mg Tablets from Centroid Experiment 2.

Formula	Assay (n=10)		Weight (mg) (n=20)		Gauge (Thickness, mm) (n=10)		Hardness (kP) (n=10)	
	Content %	RSD	Average	RSD	Average	RSD	Average	RSD
G2	98.9	4.5	119.5	3.1	1.70	2.2	4.5	5.3
G3	101.3	2.3	118.1	3.4	1.77	2.9	7.3	4.8
G5	99.8	3.5	119.4	3.0	1.67	1.8	3.2	7.1
G7	100.3	2.1	118.9	3.8	1.71	2.0	7.1	5.0
G11	100.7	2.7	121.4	2.3	1.74	1.1	4.7	3.6
G12	96.6	4.6	119.1	3.8	1.70	2.0	6.8	5.4
G13	101.3	2.9	121.3	0.99	1.76	1.2	4.6	8.7
G14	100.2	3.2	120.9	0.95	1.69	0.86	5.1	6.2
G15	101.4	2.3	118.8	2.7	1.73	2.3	6.4	8.7
G16	96.4	3.7	119.7	3.3	1.71	3.1	5.7	4.8
G17	98.9	2.5	119.7	3.7	1.70	3.8	6.1	4.4
G18	99.3	3.6	121.2	4.5	1.68	3.9	5.3	4.8

4.2 The Effect of Gantrez MS, NaCMC, PEG8000 and their Mixtures on the Dissolution of Fluoride from Extended Release Matrix Tablets in USP Apparatus 2

The dissolution curves for NaF tablets using Centroid Design 1 in USP Apparatus 2 are shown in Figure 12. Standard deviations (Percent drug dissolved, n=6) for this series ranged from 0.12-5.4 % in the USP apparatus. The commercial NaF tablet was completely dissolved (100 % drug dissolved) within 15 minutes. Percentage drug dissolved 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 15.

The percent drug dissolved at 2, 4 and 8 hours 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 hours (probability >{t} of less than 0.01). The effect of PEG8000 was not significant at the levels tested.

All mixtures exhibited drug dissolution between 31.1 % and 63.4 % at 4 hours and between 55.9 % and 100 % at 8 hours. The near equal

mixtures of NaCMC and Gantrez MS (F7, F9) had the lowest drug dissolution at 4 hours of 31.1 % and 31.4 % respectively.

The high percent Gantrez MS tablets (F1, F5) visually exhibited erosion and were completely dissolved by 24 hours. These mixtures of greater than 89 % Gantrez MS (F1, F5) exhibited the highest drug dissolution at 4 hours.

The high percent NaCMC tablets (F2, F4) produced a gelatinous mass after approximately 1 hour that was completely dissolved by 24 hours. 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 dissolved was plotted versus the square root of time.

Figure 12. Mean dissolution of commercial immediate release sodium fluoride tablets and sodium fluoride tablets from Centroid Experimental Design 1 in USP Apparatus 2, (n=6).

4.3 The Effect of Mixing and Medium Flow Rate on Fluoride Dissolution in the Low Volume, Low Flow Apparatus

After the blue medium entered the small cell, the color immediately (within 2-3 seconds) dispersed to the entire interior of the small cell chamber. This was true at both of the medium flow rates, 0.5 ml/min and 1.0 ml/min. Thus mixing variation within the small cells could be ruled out as a factor in the dissolution results. This is important as any evaluation of drug release mechanism depends on an assumption of uniform mixing.

The dissolution curves for G7 at two different flow rates (0.5 ml/min and 1.0 ml/min) are shown in Figure 13. Because the 0.5 ml/min flow rate represents the lower flow rate for evaluation of low flow conditions, a flow rate of 0.5 ml/min was chosen for evaluation of Centroid Experiment 1 and Centroid Experiment 2.

Figure 13. Effect of flow rate on drug dissolution from formula G7 in the low flow, low volume apparatus, +/- Std. Dev.

4.4 The Effect of Gantrez MS, NaCMC, PEG8000 and their Mixtures on the Dissolution of Fluoride from Extended Release Matrix Tablets in the Low Volume, Low Flow Apparatus

The dissolution curves for Centroid Mixture 1 and the commercial NaF tablets in the Low Volume Method are shown in Figure 14. Standard deviations (Percent drug dissolved, n=6) for this series in the Low Volume Method ranged from 0.10-2.1 %. The commercial fluoride tablet was completely dissolved (100 % drug dissolved) at 2 hours.

In the Low Volume Method, the percent drug dissolved at 2,4 and 8 hours 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 0.01). The effect of PEG8000 at the levels tested was not significant. Parametric estimates for the reduced statistical model are shown in Table 15.

The cumulative amount of drug dissolved at 2, 4 and 8 hours 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 dissolution, with percent drug dissolved at 8 hours of only 20.7 % and 22.3 % respectively.

Mixtures greater than 89 % Gantrez MS (F1, F5) exhibited erosion visually and had the highest drug dissolution at 8 hours. These high Gantrez MS tablets (F1, F5) exhibited a square root of time relationship ($R^2=0.99$ and 0.99 respectively) when the cumulative drug dissolved 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 dissolved 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 16. The dissolution curves of the immediate release NaF tablet, formula F2 (89.5 % NaCMC, 5.0 % GN MS, 5.5 % PEG8000) and formula F5 (94 % GN MS, 5 % NaCMC, 1 % PEG8000) from USP Apparatus 2 and the Low Volume, Low Flow Apparatus are compared in Figure 15. The reduced dissolution rates in the small volume cell are evident.

Figure 14. 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).

Figure 15. Comparison of dissolution of selected formulas between USP Apparatus 2 and the Low volume, Low Flow Apparatus (n=6).

4.5 The Effect of Gantrez MS, NaCMC, CP934P and their Mixtures on the Dissolution of Fluoride from Extended Release Matrix Tablets in the Low Volume, Low Flow Apparatus

The dissolution curves for Centroid Experiment 2 in the Low Volume Apparatus are shown in Figure 16. The standard deviations for this series (Percent drug dissolved, n=6) in the Low Volume Method ranged from 0.11-2.1 %. As with Centroid Experiment 1, the percent drug dissolved for Centroid 2 at 2,4 and 8 hours 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 15.

As was found with Centroid Experiment 1 in both the USP apparatus and the Low Volume, Low Flow apparatus, near equal mixtures of NaCMC and Gantrez MS (G11, G18) provided the lowest drug dissolution at 8 hours 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

hours, 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 dissolution ($R^2 = 0.94$ to 1.0) and had the highest drug dissolution at 8 hours of up to 73.7 %, shown in Figure 17. The fluoride concentration in the effluent of these high NaCMC formulas ranged from 0.2 ppm to 1.8 ppm. Mathematical analysis of dissolution curves from Centroid Experiment 1 and Centroid Experiment 2 is shown in Table 17.

**Figure 16. Mean dissolution of sodium fluoride tablets from Centroid
Experimental Design 2 in the Low volume Method, (n=6).**

Figure 17. Mean dissolution in the Low Volume Method of selected sodium fluoride tablets from Centroid Experimental Design 2, showing zero-order drug dissolution from those formulas with high fractions of NaCMC, (n=6). Also shown are regression lines with R^2 .

4.6 Direct Comparison of Drug Dissolution from Several Extended Release Formulations in the Low Volume, Low Flow Apparatus

The dissolution curves for the direct comparison of G16 and G17 are shown in Figure 18 (n=3 each). Direct comparison of the curve shapes and percent drug dissolved at 2, 4 and 8 h shows that the two curves display square root of time dissolution (G16, $R^2 = 0.98$) and zero order dissolution (G17, $R^2 = 0.99$) as was found previously. These curves verify the reproducibility of the dissolutions and allow direct observation of visual changes. As before, the high NaCMC (G17) formula exhibited swelling with little erosion while the high Gantrez MS formula (G16) exhibited erosion over the 8 hour period.

The dissolution curves for the direct comparison of G2 and G5 are shown in Figure 19 (n=3 each). Direct comparison of the curve shapes and percent drug dissolved at 2, 4 and 8 h shows that the two curves display square root of time dissolution (G5, $R^2 = 0.98$) and zero order dissolution (G2, $R^2 = 0.99$) as was found previously. These curves also verify the reproducibility of the dissolutions. The high NaCMC (G2) formula exhibited swelling with little erosion while the high Gantrez MS formula (G5) exhibited erosion over the 8 hour period.

Figure 18. Direct comparison of G16 and G17 (n=3 each, +/- Std. Dev.).

Figure 19. Direct comparison of G2 and G5 (n=3 each, +/- Std. Dev.).

4.7 The Effect of Contact Time 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 contact force of 20 g for times ranging from 30 s up to 4 h (n=6). Results are shown in Figure 20. The work of bioadhesion increased with increasing contact time up to 1 hour, with a maximum work of bioadhesion of 2622 g*s. 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 (Figure 21).

Figure 20. The effect of contact time on work of bioadhesion
(Formula G13, mean $\pm$ Std. Dev., n=6).

Figure 21. Tablet from formula G13 attached to tissue after 4 hours of contact time.

4.8 The Effect of Contact Force on Ex vivo Bioadhesion

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 g to 60 g for 300 s (n=6). Results are shown in Figure 22. The maximum work of bioadhesion of 568 g*s 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.

Figure 22. The effect of contact force on work of bioadhesion
(Formula G13, mean $\pm$ Std. Dev., n=6).

4.9 The Effect of Gantrez MS, NaCMC and C934P on Ex

Vivo Bioadhesion

A typical bioadhesion curve is shown in Figure 23. The curve shows the initial contact force (20g), the contact time (300 s), the peak bioadhesive force as the probe withdraws from the gingiva and reports the work of bioadhesion.

The bioadhesion results for Centroid Experiment 2 are shown in Table 17.

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 g*s (G16) to 183.4 g*s (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).

Figure 23. Typical bioadhesion curve.

Table 15. Bioadhesion results for Centroid Experiment 2

(RSD – Relative Standard Deviation, n=6).

Run	Peak Adhesion Force Avg. g	Peak Adhesion Force RSD	Work of Adhesion Avg. g*sec	Work of Adhesion RSD
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

Table 16. Reduced model parameters affecting the bioadhesion for Centroid Experiment 2.

Parameter	Peak Bioadhesion (g)		Work of Bioadhesion (g*s)	
	Estimate	P Value	Estimate	P Value
Centroid 2				
CMC	36.3	0.011	134.98	0.0031
GN-MS	40.4	0.0023	85.5	0.014
CMC*GN*	28.5	0.61	138.72	0.41

*** Interaction is not significant.**

5. Conclusions

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 medium 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 Khanna et al. (1996).

Though the nature of drug dissolution was similar in both apparatus, the rates of drug dissolution were significantly lower at 2, 4 and 8 hours 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 dissolution 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 dissolved was plotted versus the square root of time indicating diffusion controlled drug dissolution (Figure 24).

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 dissolved and square root of time for these high NaCMC formulas (F2, F4) in USP Apparatus 2 indicates that drug dissolution in the high agitation USP method is primarily diffusion controlled. Formulas F2 and F4 also showed a linear relationship between drug dissolution and square root of time in the small volume method, which likely was due to increased erosion from those formulas.

The zero order dissolution seen in the small volume method for high percent NaCMC formulas (G2, G13, G14, G15, G17) indicates that drug dissolution 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 hour experiment, slowing the rate of drug dissolution (Figure 25). The zero order dissolution of fluoride from tablets with at least 95 % NaCMC in the low volume method suggests that the swelling controlled dissolution of these formulations may provide ideal, near constant concentrations of fluoride in the oral cavity for up to 8 hours.

The effluent fluoride concentrations of between 0.2 ppm and 1.8 ppm from the high NaCMC formulations are consistent with the 0.1 to 1 ppm levels shown to be effective in vitro and in vivo in caries prevention (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 % GN-MS), this formula would also appear to have sufficient strength to withstand mechanical erosion in vivo. Thus these formulations of at least 95 % NaCMC provided near ideal NaF dissolution in vitro as well as significant bioadhesion.

Figure 24. Erosion (diffusion) controlled release from high percent Gantrez MS tablets.

Figure 25. Swelling controlled zero order release from high percent NaCMC tablets.

Table 17. Comparison of drug dissolution 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 Dissolved at 2 h	Small Cell % Drug Dissolved at 2 h	USP 2 % Drug Dissolved at 4 h	Small Cell % Drug Dissolved at 4 h	USP 2 % Drug Dissolved at 8 h	Small Cell % Drug Dissolved 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

Table 18. Analysis of the dissolution curves (Up to 8 h).

Formula No.	Formula	R ² Percent drug dissolved versus sq. rt. time USP App. 2	R ² Percent drug dissolved versus sq. rt. time Small Volume Method	R ² Percent drug dissolved versus time Small Volume Method
High % CMC				
F2	89.5 % CMC 5.0 % GN-MS 5.5 % PEG8000	0.99	0.99	0.91
F4	94 % CMC 5.0 % GN-MS 1.0 % PEG8000	0.99	0.99	0.91
G2	100 % CMC	-	0.91	1.0
G13	95 % CMC 5.0 % GN-MS	-	0.95	0.94
G14	95 % CMC 5.0 % C934P	-	0.95	0.99
G15	95 % CMC 5.0 % C934P	-	0.98	0.97
G17	97 % CMC 2.5 % C934P	-	0.92	1.0
High % Gantrez MS				
F1	89 % GN-MS 5.0 % CMC 5.5 % PEG8000	0.99	1.0	0.92
F5	94 % GN-MS 5.0 % CMC 1.0 % PEG8000	0.99	0.99	0.90
G5	100 % GN-MS	-	0.98	0.90
G16	98 % GN-MS 2.5 % C934P	-	0.97	0.89

Table 19. Reduced Model Parameters Affecting the Dissolution of NaF from Matrix Tablets.

Parameter	2 h Dissolution		4 h Dissolution		8 h Dissolution	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
Centroid 1						
USP 2						
(CMC-.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	32.88	0.0004	44.97	0.0007
CMC*GN*	-59.05	0.04	-100.12	0.01	-159.15	0.01

* Interaction is significant

In the highly constrained small volume cell, the NaCMC tablet swells significantly, filling a portion of the chamber and eventually leaving only one surface (the lower surface of the swollen tablet) in contact with the agitating dissolution medium. Colombo et al., (1992) described four different types of swellable matrix tablets of hydroxypropyl methylcellulose partially coated on various sides. The following cases were studied: Case 0 - no coating; Case1 - impervious coating only on one face; Case 2 – impervious coating on both faces; Case 3 – impervious coating only on the lateral surfaces; Case 4 – impervious coating on top face and the lateral surfaces. Thus Case 4 represents the ability to swell in only one direction, through the open face (Figure 26). The dependence of the release kinetics on the matrix surface area was assessed. Interestingly, Case 4 tablets which were coated with an impervious coating on one face, plus the lateral surfaces (leaving only one side open to the dissolution medium) exhibited drug release that was essentially zero-order. This was attributed to two processes: 1) matrix swelling due to the medium; and 2) drug diffusion into the swollen polymer. Drug release exhibited a substantial dependence on polymer relaxation. A heuristic model proposed by Peppas and Sahlin (1989) for quantifying the two phenomena controlling drug release from swellable matrices is:

$$M_t/M_\infty = k_1 t^{1/2} + k_2 t$$

where the first term describes the Fickian contribution (diffusion control) and the second term describes the Case II relaxational contribution (swelling control due to penetration of medium into the polymer). Case 4, with only one open tablet face, showed a substantial dependence of the drug released on polymer relaxation.

This ability of the partially coated tablet to swell in only one dimension is essentially similar to that experienced by the high percent NaCMC tablets in the Low volume, Low Flow apparatus, as shown in Figure 26. Once swelling begins, the swelling is limited to the constrained volume of the small dissolution cell. Swelling can only occur in the open direction and dissolution can only occur from the open face of the swollen polymer. One can imagine that a buccal tablet, because it is attached to the gingiva on one face and swollen on the lateral surfaces and front face, could exhibit similar release characteristics.

Figure 26. Comparison of constrained swollen tablet in Low Volume Cell to specially coated tablet of Colombo et al. (1992).

Thus the drug release would be from only one surface and be substantially dependent on polymer swelling. The zero order dissolution 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 hours. The effluent fluoride concentrations of between 0.2 ppm and 1.8 ppm are consistent with the 0.1 to 1 ppm levels shown to be effective in vitro and in vivo in caries prevention (Margolis et al., 1990; Duckworth et al., 1992; Featherstone and Zero, 1992). It is significant that these formulations of at least 95 % NaCMC provided near ideal NaF dissolution in vitro.

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).

The hypothesis is proven. Both NaCMC and Gantrez MS showed bioadhesive and extended release properties and may be used to design extended release buccal fluoride tablets. Combinations of the excipients provided in vitro dissolution of fluoride for periods up to eight hours, which is an improvement over commercial dose forms. It is concluded from this preliminary investigation that matrix tablets of NaCMC and Gantrez MS may be designed to provide both bioadhesive and extended release properties. This research is novel in the use of Gantrez MS as a matrix tablet excipient that exhibits both bioadhesive and extended release properties.

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