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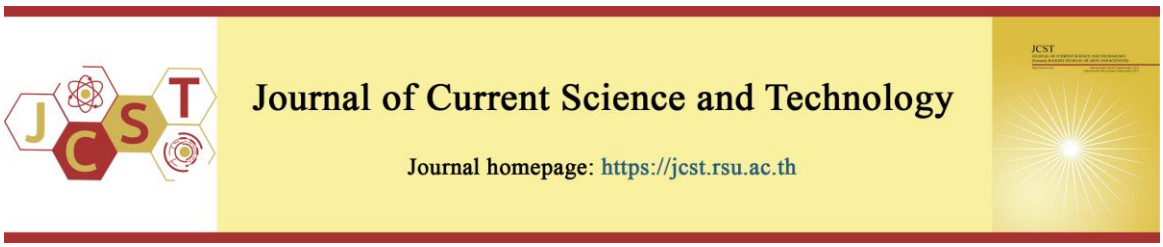

Development of 2% w/w sodium fluoride oral gels for prevention of dental caries in patients with xerostomia

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Abstract

For prevention of dental caries in xerostomic patients, 2% w/w sodium fluoride oral gel is frequently prescribed; however, the product has not been officially approved for clinical use in Thailand. Therefore, this study aimed to develop 2% w/w sodium fluoride oral gels dispensed specifically to patients in Rajavithi Hospital. Both single and combined gel bases were prepared from different gelling agents, including gelatin, xanthan gum, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, and Carbopol 940P. They were subsequently characterized according to their physicochemical properties, i.e., clarity, spreadability, pH values, and apparent viscosity. All the gel bases were clear viscous liquids of good spreadability, except the xanthan gum gel bases, which were slightly cloudy. The pH values indicate that the gelatin, xanthan gum, and Carbopol 940P gel bases were acidic, while the cellulose gel bases were neutral. The apparent viscosity ranged from 3 to 11.5 x 10^5 cPs, depending mainly on type and concentration of the gelling agents. After preparation, the gel bases were then incorporated with 1 M pH 7.4 phosphate buffer solution to the final concentration of 5% w/w. Macroscopic characteristics of the buffered gel bases were generally unchanged, except for the apparent viscosity, which decreased slightly. Sodium fluoride was subsequently added to the selected buffered gel bases. The resulting sodium fluoride gels were neutral and transparent viscous liquids of good spreadability and exhibited good stability against the heating-cooling cycle and accelerated testing. Thus, it is conceivable that 2% w/w sodium fluoride oral gels with acceptable physicochemical characteristics and excellent stability were successfully developed.

Keywords**:** *Carbopol 940P; dental caries; oral gel; sodium carboxymethylcellulose; sodium fluoride; stability; xerostomic patients*

1. Introduction

Xerostomia is a subjective feeling of oral dryness that results from salivary gland dysfunction or hypofunction (Jose et al., 2018; Kapourani et al., 2022; Kubbi, Reddy, Duggi, & Aitha, 2015). It is caused by several conditions. The most common causes are radiation therapy for treatment of head and neck tumors (as the salivary tissue is very sensitive to radiation), chemotherapy, and diseases of the salivary glands such as Sjögren's syndrome (Jose et al., 2018; Kapourani et al., 2022; Kelly, Deasy, Busquet, & Torrance, 2004; Kubbi et al., 2015). Others which have been reported include HIV or HCV infection, uncontrolled diabetes mellitus, and a number of commonly used medications (Kapourani et al., 2022; Kelly et al., 2004; Porter, Scully, & Hegarty, 2004; Schiødt et al., 1992). Interestingly, a number of patients with confirmed COVID-19 infections also complained about suffering from xerostomia (Fantozzi et al.,

2020; Kapourani et al., 2022). Due to the lack of saliva, the xerostomic patients characteristically possess dry and sticky mucosa (Cassolato, & Turnbull, 2003), the conditions then cause dry cracked lips, a dry irritated tongue, numerous mouth sores, and burning sensation. Sufferers usually encounter increased problems with chewing and swallowing (dysphagia), altered taste perception (dysgeusia), unpleasant breath (halitosis), and/or difficult or slowed speech (dysarthria) (Cassolato, & Turnbull, 2003; Jose et al., 2018; Kapourani et al., 2022; Kubbi et al., 2015). Although xerostomia is not considered a serious illness, it can reduce patients' quality of life considerably (Kapourani et al., 2022; Porter et al., 2004).

Saliva contains various kinds of lipids, glycoproteins, and proteins. The substances are usually deposited onto the tooth enamel to develop the dental pellicle (Devarajan, & Somasundaram, 2019; Su, Marek, Ching, & Grushka, 2011). This pellicle is selectively permeable to calcium and phosphate ions required for remineralization of the tooth surface. In contrast, it is almost impermeable to acids, which are able to dissolve calcium and phosphate ions from the enamel. This aids in prevention of a process called demineralization (Devarajan, & Somasundaram, 2019; Hara et al., 2006; Su et al., 2011). Saliva also possesses buffering activity, which maintains neutral oral pH through bicarbonate and phosphate buffer systems (Cassolato, & Turnbull, 2003; Devarajan, & Somasundaram, 2019; Su et al., 2011). In prolonged xerostomia, the reduction in or loss of salivary flow often causes a change in the composition of saliva, leading to the loss of salivary buffering capacity, and, subsequently, acidic oral pH (Su et al., 2011). Concurrently, the proliferation of the oral cariogenic bacteria, including *Streptococcus mutans, Streptococcus sobrinus,* and *Lactobacillus* species, and the subsequent production of acids as byproducts of their carbohydrate metabolism also lower the oral pH (Cassolato, & Turnbull, 2003; Devarajan, & Somasundaram, 2019; Featherstone, 2000; Seethalakshmi, Jagat Reddy, Asifa, & Prabhu, 2016). As the pH falls below 5.5, demineralization takes place, leading to increased risks of dental caries and other complications such as oral and oesophageal infection, mucositis, gingivitis, and periodontitis (Cassolato, & Turnbull, 2003; Devarajan, & Somasundaram, 2019; Kelly et al., 2004; Pankhurst, Dunne, & Rogers, 1996; Seethalakshmi et al., 2016; Su et al., 2011).

For prevention of xerostomia-induced dental caries, the combination of a comprehensive oral hygiene regimen and application of topical fluorides is remarkably effective (Agarwal, Purohit, Ravi, Priya, & Kumar, 2022; Dreizen, Brown, Daly, & Drane, 1977; Jose et al., 2018; Kapourani et al., 2022; Nayak, 2020). Supplemental fluoride promotes the prevention of dental caries in several ways. It inhibits bacterial carbohydrate metabolism by interfering with the activity of enzyme enolase, and strongly adsorbs onto the surface of enamel mineral (Agarwal et al., 2022; Featherstone, 2000; Nayak, 2020; Su et al., 2011). The resulting mineral fluorapatite provides strong protection against the acid dissolution of the tooth mineral, markedly inhibiting the demineralization process. Meanwhile, the fluorapatite also attracts calcium and phosphate ions to the tooth surface, leading to the new mineral formation, i.e., enhancing the remineralization process. Topical fluorides are available in many forms, including varnish, rinses, dentifrices, toothpastes, and gels (Nayak, 2020; Su et al., 2011). Among these, fluoride gels have been reported to be more effective than fluoride dentifrices despite lower fluoride concentration, possibly because gels can reach deeper layers of the tooth surface than dentifrices (Agarwal et al., 2022). Fluoride gels have shown to be capable of preventing tooth decay regardless of frequency and schedule of application (Englander, & Keyes, 1966). It has also been found that the presence of plaque-forming streptococcal strains recovered from fluoride-protected molar surfaces were not associated with enamel demineralization or cavitation due to alteration of the bacterial metabolic activity (Englander, & Keyes, 1966). For high-risk patients, products containing high fluoride concentrations of 1% to 5% are preferred (Agarwal et al., 2022; Cassolato, & Turnbull, 2003; Su et al., 2011). However, no such products have been officially approved for clinical use in Thailand. As a consequence, there is a need to develop high-concentration sodium fluoride products that can be dispensed to xerostomic patients, especially those at Rajavithi Hospital.

2. Objectives

The main objective of this study was to develop 2% w/w sodium fluoride oral gels. The effect of type and concentration of gelling agents on

gel characteristics was investigated. Gel bases, both single and in combination, of different gelling agents were prepared and subsequently characterized by their physicochemical properties. The prospective gel bases were then selected for preparation of sodium fluoride gels, after which the physicochemical characteristics and the stability of these fluoride gels were examined.

3. Materials and methods

3.1 Materials

Sodium fluoride (NaF) was obtained from Ajax Finechem (New Zealand). Gelatin (GLT) and xanthan gum (XTG), used as natural gelling agents, were supplied by Fisher Chemical (UK) and S Tong Chemicals (Thailand), respectively. Two derivatives of cellulose were used as representatives of semi-synthetic gelling agents. Hydroxypropyl methylcellulose, Methocel E 15 LV (HPMC-E) and Methocel F4M (HPMC-F), were purchased from Rama Production (Thailand). Sodium carboxy-methylcellulose (Na CMC), was supplied by Vidhyasom (Thailand). Carbopol 940P (CBP), a synthetic gelling agent, was obtained from Triumph Supply (Thailand). Colors, flavours, sweeteners, and preservatives were purchased from reliable local suppliers. All other chemicals were of analytical grade and used as received.

3.2 Methods

3.2.1 Preparation of gel bases and buffered gel bases

Different gel bases at different concentrations were separately prepared as described below. GLT was first dispersed into hot water and stirred gently until it dissolved completely. Hot water was then added in the required amount in order to obtain GLT gel base of desired concentrations. XTG and Na CMC gel bases were prepared the same way, except that room temperature water was used instead of hot water. HPMC-E and HPMC-F were separately dispersed into pre-boiled water comprising about one-third of the required amount. The remaining two-thirds of the required amount comprised cold water that was subsequently added, and then the mixture was stirred thoroughly. CBP was dispersed into water at room temperature. The mixture was adjusted by the addition of water to reach the required weight, and then set aside overnight to achieve complete swelling. Sodium hydroxide solution (10% w/w) was added dropwise until the gel was clear. In addition, gel bases were combined in order to optimize the gel characteristics.

For the preparation of buffered gel bases, the pH values were adjusted to 6-8 by adding 10% w/w sodium hydroxide solution and controlled by adding 1 M pH 7.4 phosphate buffer solution. The gel bases were finally adjusted with water to a pre-determined weight in order to obtain desired concentrations of the gelling agent(s) and total concentration at 5% w/w of the buffer solution.

3.2.2 Preparation of NaF gels

NaF was dissolved in a small amount of distilled water and subsequently incorporated into selected gel bases. The formulation pH was adjusted to 6-8 by adding 10% w/w sodium hydroxide solution and controlled by adding 1 M pH 7.4 phosphate buffer solution. Certain amounts of coloring (1% w/w erythrosine + 1% w/w brilliant blue, ratio 5:1), grape flavor, xylitol as a sweetener and paraben concentrate (methylparaben 20% and propylparaben 2% in propylene glycol solution) as a preservative were then added to obtain acceptable formulations. The mixtures were eventually adjusted with water to a pre-determined weight to obtain desired concentrations of both NaF and gelling agent(s).

3.2.3 Macroscopic analysis

The appearance and the clarity of gel bases and formulations were visually inspected by three evaluators. The spreadability was assessed by applying a small amount of each sample on a glass plate. They were scaled as described in Table 1.

Table 1 The scales of clarity and spreadability of gel bases and formulations

Scale	Clarity	Spreadability
+	Turbid	Slightly spread when applied
++	Translucent	Moderately spread when applied
+++	Transparent	Readily spread when applied

3.2.4 Determination of pH

The pH values were measured on a pH/Ion meter (Seven Compact S220, Mettler Toledo, Schwerzenbach, Switzerland) equipped with the Inlab® Micro electrode (Mettler Toledo, Schwerzenbach, Switzerland) (n = 1).

3.2.5 Viscosity measurement

The apparent viscosity was determined on the Brookfield Viscometer DV-II+ Pro (Brookfield Engineering Laboratories, Middleboro MA, USA). The spindle S 64 was attached to the lower shaft of the viscometer and subsequently immersed into the sample until the level reached the immersion groove on the spindle shaft. The spindle speed was set at a fixed shear rate of 0.5 rpm. Values were recorded every 10 seconds for 10 runs.

3.2.6 Determination of NaF content (The United States Pharmacopeial Convention, 2018)

Standard solution

The Fluoride ISE Standard solution (1,000 mg/L as F^-, Mettler Toledo, Schwerzenbach, Switzerland) was diluted with deionized water to the concentration of F^- ranging between 1-100 mg/mL. One mL of the total ionic strength adjustment buffer (TISAB III, Mettler Toledo, Greifensee, Switzerland) was added to about 50 mL of the diluted standard solutions and constantly stirred by a magnetic stirrer. The combined fluoride ion selective electrode (perfectION™, Mettler Toledo, Schwerzenbach, Switzerland), attached to a pH/Ion meter (Seven Compact S220, Mettler Toledo, Schwerzenbach, Switzerland), was subsequently immersed in the solutions. The values were read, and the corresponding fluoride concentration was adjusted to that of the standard solution.

Sample solution

About 0.5 g of NaF gel was accurately transferred to a 100-mL volumetric flask. The sample was diluted to volume with water and mixed thoroughly. Five mL of the diluted solution was subsequently transferred to a 50-mL volumetric flask, diluted with water to volume, and then thoroughly mixed. One mL of TISAB III was added to about 50 mL of the diluted sample solutions and constantly stirred by a magnetic stirrer. The fluoride concentration was read on a pH/Ion meter, installed with the perfectION™. The experiment was done in triplicate.

3.2.7 Extrudability

The method was modified from a previous report (Hasan et al., 2022). Briefly, 60-mL polyethylene bottles were fully filled with the gels and weighed. Each bottle was pressed by application of finger pressure to the depth of about 2.0-2.3 mm and held for 5 s. It was then re-weighed, and the percentage of extrudability was calculated using the following equation (n = 3).

$$\% \text{ Extrudability} = \frac{\text{Weight of extruded gel (g) x 100}}{\text{Initial weight of gel (g)}}$$

3.2.8 Stability studies

Heating-cooling cycle

The formulations were kept for 5 cycles at alternate temperatures of 4 ± 2°C in a refrigerator, and 40 ± 2°C in an incubator. In each cycle, the sample remained at a particular temperature for a period of 24 h. Changes in gel appearance and viscosity were determined as described above.

Accelerated testing

Accelerated stability testing at 40 ± 2°C and 75 ± 5% RH was carried out for 6 months, as per ICH guidelines. The formulations were analyzed periodically for changes in color, appearance, viscosity, pH and drug content, as described above.

3.2.9 Statistical analysis

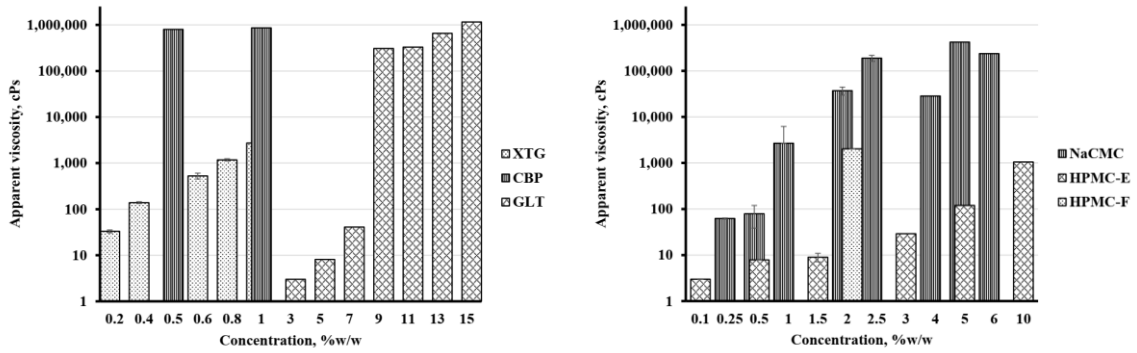
Values are expressed as mean ± S.D. One-way analysis of variance (ANOVA) was performed on all experimental measurements, except the heating-cooling cycle, the results of which were subjected to the paired t-test. Data were then compared by the least significant difference (LSD) test.

4. Results

4.1 Macroscopic analysis of gel bases and buffered gel bases

Gel bases of different gelling agents were prepared, following the suggested concentrations for gel preparation (Rowe, Sheskey, Cook & Fenton, 2012), and subsequently characterized for their macroscopic properties. The results are presented in Table 2. At low concentrations of 3% w/w to 7% w/w, GLT gel bases were clear yellowish solutions with good spreadability. When the concentration of GLT was further increased, the gel bases were found to be thicker and less

dispersible. Additionally, the GLT gel bases presented some characteristic odors. XTG gel bases were turbid and spreadable. Taking the cellulose derivatives into account, HPMC-E, HPMC-F, and NaCMC gel bases were clear solutions. At the concentrations of more than 10% w/w, 5% w/w, and 4% w/w, for HPMC-E, HPMC-F, and NaCMC, respectively, the gel bases became thick and less easy to spread. CBP gel bases were clear and viscous. Increasing the CBP concentration resulted in slightly cloudy gel bases with reduced dispersibility. With respect to pH values, the GLT and XTG gel bases were slightly acidic, while the gel bases of cellulose derivatives were observed to be neutral or slightly basic, ranging from about 5.0 to 9.6. As the concentration was increased, the pH values decreased. In cases of CBP, the gel bases were obviously acidic. The apparent viscosity of gel bases was then determined; the results are summarized in graphic form in Figure 1. At low concentrations of 3% w/w to 7% w/w, the apparent viscosity of GLT gel bases was lower than 100 cPs. When the concentration of GLT was further increased, the apparent viscosity of GLT gel bases abruptly increased to 3.0 x 10^5 cPs, 3.5 x 10^5 cPs, 6.5 x 10^5 cPs, and 11.5 x 10^5 cPs, for the gel concentration of 9% w/w, 11% w/w, 13% w/w and 15% w/w, respectively (Figure 1A). At the suggested concentrations of 0.2% w/w to 1% w/w for XTG gel preparation, the gel bases possessed relatively low viscosity, ranging from 33.0 cPs to 2,720.1 cPs (Figure 1A). For the celluloses, the apparent viscosity of HPMC-E gel bases was similarly low, at 3.0 cPs to 1,050.7 cPs, as the gel concentration was varied from 0.1% w/w to 10% w/w (Figure 1B). The 2% w/w HPMC-F gel base also exhibited low viscosity of 2,029.7 cPs (Figure 1B). At the higher investigated concentrations, the gel viscosity was not measurable, likely due to the limitation of equipment. Taking the NaCMC gel bases into consideration, the gel viscosity was inconsistently increased from 62.1 cPs to 4.2 x 10^5 cPs, as the gel concentration was increased from 0.25% w/w to 6% w/w (Figure 1B). The synthetic CBP gel bases showed high viscosity of 8.0 x 10^5 cPs and 8.6 x 10^5 cPs, for the gel concentrations of 0.5% w/w and 1% w/w, respectively. At the higher concentration, the gel viscosity was undeterminable, again, likely due to equipment limitations. It was noticed that the results of gel viscosity determination corresponded well with those obtained from the study of gel spreadability (Table 2).



(A) (B)

Figure 1 The apparent viscosity of (A) gelatin (GLT), xanthan gum (XTG) and Carbopol 940P (CBP) and (B) hydroxypropyl methycellulose E 15 LV (HPMC-E), hydroxypropyl methycellulose F4M (HPMC-F) and sodium carboxymethylcellulose (NaCMC) gel bases at different concentration.

Table 2 Macroscopic characterization of different gels

Gelling agent	Concentration (% w/w)	Clarity	Spreadability	pH
GLT	3	+++	+++	5.81
	5	+++	+++	5.73
	7	+++	+++	5.53
	9	+++	++	5.78
	11	++	++	5.99
	13	++	++	5.64
	15	++	++	5.58
XTG	0.2	+	+++	6.72
	0.4	+	+++	5.55
	0.6	+	+++	5.32
	0.8	+	+++	5.29
	1	+	++	5.06
HPMC-E	0.1	+++	+++	9.60
	0.5	+++	+++	8.53
	1.5	+++	+++	8.06
	3	+++	+++	7.62
	5	+++	+++	7.25
	10	++	++	6.76
	15	++	+	4.99
HPMC-F	2	+++	+++	8.96
	3	+++	+++	7.61
	5	+++	+	7.62
Na CMC	0.25	+++	+++	9.28
	0.5	+++	+++	8.52
	1	+++	+++	7.42
	1.5	+++	+++	6.64
	2	+++	+++	8.13
	2.5	+++	+++	6.80
	3	+++	+++	6.45
	4	+++	++	7.10
	5	+++	++	5.09
	6	+++	+	5.68
CBP	0.5	+++	+++	4.33
	1	+++	+++	3.51
	1.5	+++	+++	4.11
	2	++	++	4.09
	2.5	++	++	3.90

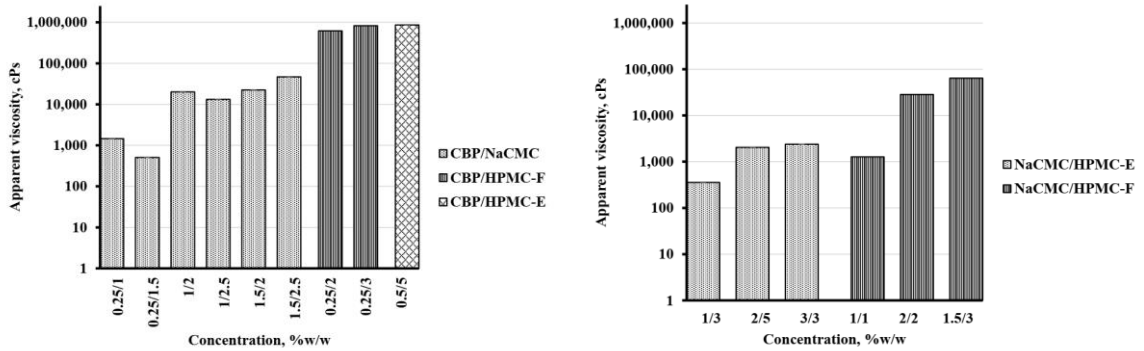
Prospective gel bases were then selected for combination in order to optimize the gel characteristics. GLT and XTG were not investigated, primarily due to the specific odor and the gel turbidity, respectively. The macroscopic properties of combined gel bases are presented in Table 3. CBP at the concentrations of 0.25% to 1.5% w/w were combined with NaCMC, HPMC-F, and HPMC-E at the concentration of 1% to 2.5% w/w, 2% to 3% w/w, and 5% w/w, respectively. All the investigated combinations of CBP and cellulose gel bases were clear viscous liquids of good spreadability, except those of CBP/HPMC-F gel bases, whose spreadability was only moderate. In addition, they were observed to be acidic.

The combinations among cellulose gel bases were also prepared. NaCMC at the concentrations of 1% to 3% w/w was combined with HPMC-E or HPMC-F at the concentrations of 3% to 5% w/w and 1% to 3% w/w, respectively. All the investigated combinations among cellulose gel bases were transparent and well dispersible, except those containing 2% to 3% w/w HPMC-F, which were slightly translucent. It was noticed that all the gel combinations were neutral.

Table 3 Macroscopic characterization of combined gel bases

Gelling agent	Concentration (% w/w)	Gelling agent	Concentration (% w/w)	Clarity	Spreadability	pH
CBP	0.25	NaCMC	1	+++	+++	3.91
	0.25		1.5	+++	+++	4.54
	0.25	HPMC-F	2	+++	++	5.01
	0.25		3	+++	++	6.00
	0.5	HPMC-E	5	+++	+++	5.46
	1		5	+++	+++	4.92
	1	NaCMC	2	+++	+++	3.45
	1		2.5	+++	+++	3.41
	1.5		2	+++	+++	3.28
	1.5		2.5	+++	+++	2.61
NaCMC	1	HPMC-E	3	+++	+++	6.21
	2		5	+++	+++	6.94
	3		3	+++	+++	6.25
	1	HPMC-F	1	+++	+++	6.77
	1.5		3	++	+++	6.79
	2		2	++	+++	6.72

Apparent viscosity of the combined gel bases was then determined, as illustrated in Figure 2. The combination of 0.25% w/w CBP and 1% to 1.5% w/w NaCMC exhibited low viscosity of 1,455.6 cPs and 507.5 cPs (Figure 2A). As the concentration of the components was increased to 1% to 1.5% w/w CBP and 2% to 2.5% w/w NaCMC, the apparent viscosity of the combined gel bases increased to the range of 13,245.2 to 46,766.0 cPs. For the CBP/HPMC-F and the CBP/HPMC-E gel bases, the apparent viscosity was as high as 6.2 x 10^5 to 8.6 x 10^5 cPs (Figure 2A). The combinations of cellulose gel bases consisting of 1% to 3% w/w NaCMC and 3% to 5% w/w HPMC-E or 1% w/w HPMC-F possessed low viscosity, ranging between 354.8 cPs and 2,402.8 cPs (Figure 2B). Increasing the concentration of HPMC-F to 2% and 3% w/w resulted in increased viscosity of 28,505.9 cPs and 64,234.3 cPs, respectively. It was found that the apparent viscosity of combined gel bases was a consequence of balancing the viscosity of corresponding gel components. In addition, the viscosity of combined gel bases (Figure 2) was observed to correlate well with the gel spreadability (Table 3).



(A) (B)

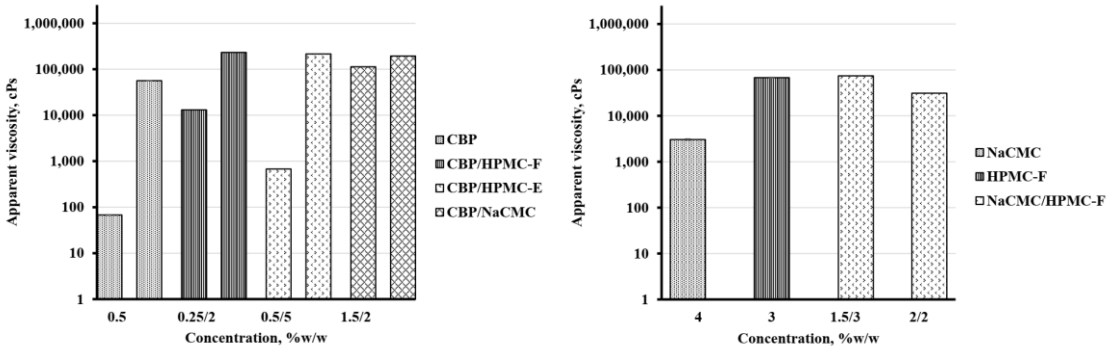
Figure 2 The apparent viscosity of different combinations of (A) CBP and NaCMC, HPMC-F, or HPMC-E gel bases and (B) NaCMC and HPMC-F or HPMC-E gel bases

Table 4 Macroscopic characterization of buffered gel bases

Gelling agent	Concentration (% w/w)	Gelling agent	Concentration (% w/w)	Clarity	Spreadability	pH
CBP	0.5			+++	+++	7.46
	1			+++	+++	7.26
HPMC-F	3			+++	+++	7.22
	5			+++	++	7.10
NaCMC	4			++	+++	7.28
CBP	0.25	HPMC-F	2	+++	+++	7.87
	0.25		3	+++	+++	7.00
	0.5	HPMC-E	5	+++	+++	7.13
	1		5	+++	+++	7.18
	1.5	NaCMC	2	+++	+++	7.47
	1.5		2.5	+++	+++	7.13
NaCMC	1.5	HPMC-F	3	++	+++	7.08
	2		2	++	+++	7.04

Subsequently, the prospective gel bases, either single or in combination, which were transparent, well spreadable, and moderately viscous were incorporated with 1 M pH 7.4 phosphate buffer solution at the final concentration of 5% w/w. The HPMC-E gel bases were not studied because the viscosity that they exhibited was too low, even at high concentrations. Macroscopic characterization of the buffered gel bases was then performed, and is presented in Table 4. The buffered 0.5% to 1% w/w CBP and 3% to 5% w/w HPMC-F gel bases were transparent, while the buffered 4% w/w NaCMC gel base was slightly translucent. They also exhibited good dispersibility, except the buffered 5% w/w HPMC-F gel base, the spreadability of which was only moderate. The buffered gel combinations of 0.25% to 1.5% w/w CBP and 2% to 3% w/w HPMC-F, 5% w/w HPMC-E, or 2% to 2.5% w/w NaCMC were clear liquids of good dispersibility. For the buffered gel combinations of 1.5% to 2% w/w NaCMC and 2% to 3% w/w HPMC-F, the gels were slightly cloudy and well dispersible. It was evident that the phosphate buffer solution was able to effectively maintain gel neutrality.

The buffered gel bases were then subjected to viscosity measurement. The results are graphically illustrated in Figure 3. The buffered 0.5% and 1% w/w CBP gel bases possessed the apparent viscosity of 67.49 cPs and 56,220.01 cPs, respectively (Figure 3A). In combinations, the apparent viscosity of buffered 0.25% to 1.5% w/w CBP and 2% to 3% w/w HPMC-F, 5% w/w HPMC-E or 2% to 2.5% w/w NaCMC gel bases varied between 676.06 cPs and 2.32 x 10^5 cPs, depending on type and concentration of each gel component (Figure 3A). Taking the buffered cellulose gel bases into account, the apparent viscosity of 3% w/w HPMC-F was as high as 67,905.51 cPs (Figure 3B), whereas that of the 5% w/w HPMC-F was not measurable, likely due to the limitations of the equipment. The buffered 4% w/w NaCMC gel base exhibited apparent viscosity of 3,047.35 cPs. In the cases of the buffered 1.5% w/w NaCMC/3% w/w HPMC-F and 2% w/w NaCMC/2% w/w HPMC-F gel combinations, they showed apparent viscosity of 74,264.16 cPs and 31,193.34 cPs, respectively. It was noticed that the viscosity of gel bases was lowered upon incorporation of the phosphate buffer solution (Figure 3 vs. Figures 1 and 2).



(A) (B)

Figure 3 The apparent viscosity of buffered (A) CBP and combinations of CBP and HPMC-F, HPMC-E, or NaCMC and (B) NaCMC, HPMC-F, and combinations of NaCMC and HPMC-F gel bases

4.2 Macroscopic analysis and stability studies of NaF gels

The buffered gel bases that exhibited apparent viscosity greater than 1 x 10^5 cPs were incorporated with NaF and essential excipients in order to obtain the final concentration of 2% w/w NaF and acceptable gel formulations. Unfortunately, some white flaky materials were separated out of the HPMC-containing NaF gels, i.e., those which consisted of 0.25% w/w CBP/3% w/w HPMC-F and 1% w/w CBP/5% w/w HPMC-E. Therefore, only two NaF gels – those that comprised 1.5% w/w CBP and 2% or 2.5% w/w NaCMC, which were designated as F1 and F2, respectively – were further investigated. Their macroscopic properties are presented in Table 5. The NaF gels were clear and well spreadable. The percentage of gel extrudability was observed to be 9.17% and 9.31% for F1 and F2 gels, respectively. In addition, the gel neutrality was well preserved, as evidenced by the pH values. The NaF gels were then tested for their resistance against degradation during the heating-cooling cycle. The appearance of both gels was noticeably unchanged. In addition, the gel viscosities determined before and after performing the experiment were compared. The results are depicted in Figure 4. The apparent viscosity of F1 and F2 gels was 1.40 x 10^5 cPs and 2.23 x 10^5 cPs, respectively. It was observed that the apparent viscosity seemed unaffected as NaF and essential excipients were incorporated into the corresponding buffered gel bases (Figure 4 vs. Figure 3A). After going through the heating-cooling cycles, the apparent viscosity was found to have slightly decreased to 1.37 x 10^5 cPs and 2.16 x 10^5 cPs, for F1 and F2 gels, respectively; however, the differences were not statistically significant ($p > 0.05$).

Table 5 Macroscopic characterization of the NaF gels

	Gelling agent	Conc. (% w/w)	Gelling agent	Conc. (% w/w)	Clarity	Spread-ability	Extrudability (%)	pH
F1	CBP	1.5	NaCMC	2	+++	+++	9.17 ± 1.28*	7.16
F2		1.5		2.5	+++	+++	9.31 ± 1.26	7.17

*Standard deviation

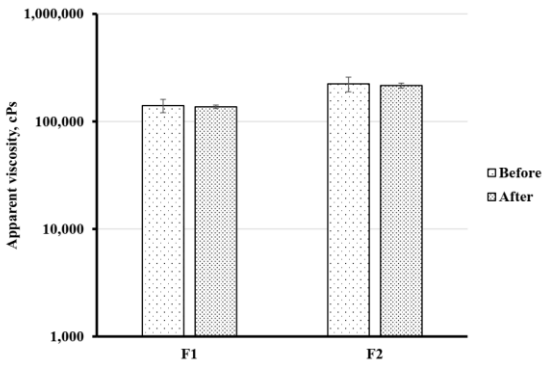


Figure 4 The apparent viscosity of NaF gels, containing 1.5% w/w CBP/2% w/w NaCMC (F1, left panel) and 1.5% w/w CBP/2.5% w/w NaCMC (F2, right panel), determined before and after performing the heating-cooling experiment.

Subsequently, the accelerated stability study of the NaF gels was carried out. The physicochemical properties, including viscosity, NaF content and pH were characterized at various time intervals. The results are illustrated in Figures 5 and 6. At Months 0, 1, and 3, the apparent viscosities of F1 and F2 gels ranged from 1.14 x 10^5 to 1.16 x 10^5 cPs and from 1.50 x 10^5 to 1.64 x 10^5 cPs, respectively (Figure 5). It was obvious that the viscosity was well maintained throughout the first three months of the experiment. At Month 6, the apparent viscosity was found to have significantly increased to 1.27 x 10^5 cPs and 2.10 x 10^5 cPs, for F1 and F2 gels, respectively ($p < 0.05$). The NaF contents of the gels ranged between 1.85% w/w and 1.95% w/w (Figure 6A), corresponding to 92.50% and 97.50% of the labeled claim of 2% w/w, respectively. It was found that the content at different points in time were not significantly different from one another ($p > 0.05$). In terms of the pH values, they obviously dropped from 7.16 and 7.17 to 6.71 and 6.39 within a month, for F1 and F2 gels, respectively (Figure 6B); however, they remained between 6.42 and 6.51 throughout the rest of the experiment.

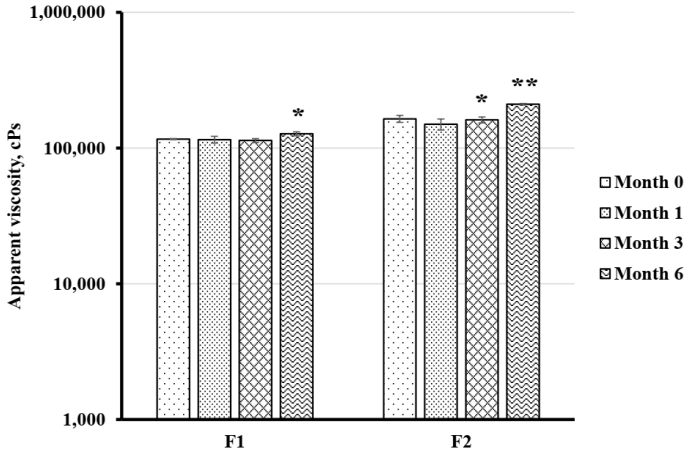
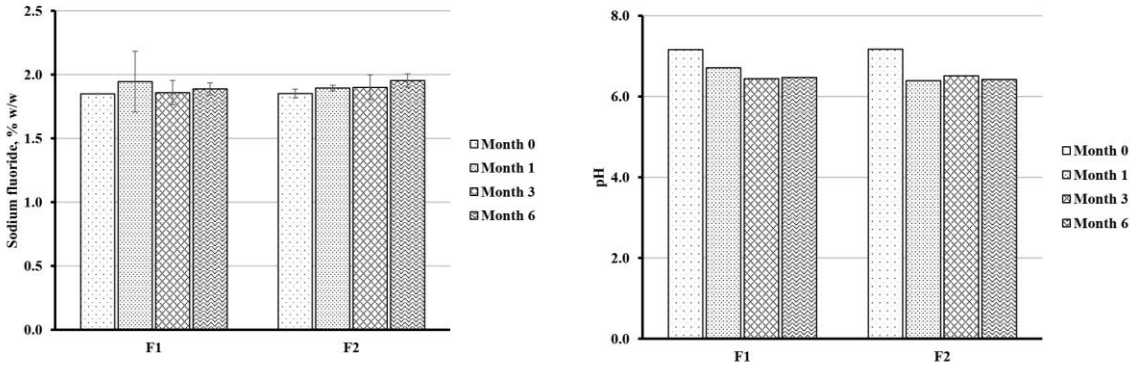


Figure 5 The apparent viscosity of NaF gels, containing 1.5% w/w CBP/2% w/w NaCMC (F1, left panel) and 1.5% w/w CBP/2.5% w/w NaCMC (F2, right panel), measured at month 0, 1, 3, and 6 of the accelerated stability study.



(A) (B)

Figure 6 The (A) NaF content (n = 3) and (B) pH of the NaF gels (n = 1), containing 1.5% w/w CBP/2% w/w NaCMC (F1, left panel) and 1.5% w/w CBP/2.5% w/w NaCMC (F2, right panel), measured at Month 0, 1, 3, and 6 of the accelerated stability study.

5. Discussion

The macroscopic properties of the gel bases, particularly their color and/or water solubility, were found to depend mainly on the physicochemical properties of the gelling agents. As GLT is yellow in nature, yellowish gel bases were thus obtained. Differences in substituted groups and/or degree of substitution on the polymer chain might affect the water solubility of gelling agents and, subsequently, the clarity of resultant gel bases. XTG is a polysaccharide, consisting of β-1,4-D-glucose units, similarly to cellulose (Brunchi, Morariu, & Bercea, 2021; Patel, Maji, Moorthy, & Maiti, 2020; Shah, & Singh, 2012; de Moura, & Moreno, 2019). The pendant tri-saccharide sidechains, comprising inner mannose (β-1,4), glucuronic acid (β-1,2), and terminal mannose residues, attach to alternate anhydroglucose units in the polymer backbone by α-1,3 linkages. The inner mannose sugar is acetylated at C-6, while the terminal mannose moiety is partially substituted with a pyruvate residue, linking as an acetal to the 4- and 6-positions of mannose. Upon dispersion into water, such steric chemical structure possibly led to improper hydration and subsequent incomplete dissolution of XTG (Patel et al., 2020). As a result, turbid gel bases were attained.

The pH values of the gel bases were consistent with those reported previously (Ahuja, Khar, & Ali, 1997; Podczeck, 2012; Shah, & Singh, 2012). They directly corresponded to the functional groups of the monomeric units or the substituted residues on the polymer chains. GLT is a high-molecular-weight polypeptide derived from collagen. It predominantly contains glycine, proline, and hydroxyproline, which, together, represent more than 50% of the total amino acid content (Poppe, 1997). Nevertheless, aspartic acid and glutamic acid, which represent about 17-19% of the total amino acid content, likely contributed to the slight acidity of GLT gel bases. In the cases of XTG gel bases, glucuronic acid on the tri-saccharide sidechains, and pyruvic acid, which was partially substituted on the terminal mannose of the sidechains, possibly accounted for the gel acidity. Cellulose is a polysaccharide consisting of structurally repetitive units of anhydroglucose dimer (Zuppolini, Salama, Cruz-Maya, Guarino, & Borriello, 2022). It is etherified with either methylate/hydroxypropylate or carboxymethylate groups to produce HPMC or NaCMC, respectively (Bialik, Kuras, Sobczak, & Oledzka, 2021). As the cellulose backbone and the etherified functional groups are neutral, the cellulose gel bases thus exhibited neutral pH values of about 6 to 8. CBP is a synthetic high-molecular-weight polymer of acrylic acid that is crosslinked with either allyl sucrose or allyl ether of pentaerythritol (Ahuja et al., 1997; Draganoiu, Rajabi-Siahboomi, & Tiwari, 2012; Jaworski, Spychaj, Story, & Story, 2021). It contains between 52% and 68% carboxylic acid groups, calculated on a dry basis (Bialik et al., 2021; Draganoiu et al., 2012) and expresses the dissociation constant as pK_a of 6.0 ± 0.5 (Jaworski et al., 2021). Therefore, it is considered a weak acidic gelling agent (Daryab, Faizi, Mahboubi, & Aboofazeli, 2022; Jaworski et al., 2021) that conveyed acidity to the CBP gel bases.

Upon dispersion into an aqueous medium, the polymeric chains of the gelling agents likely extended themselves in the solution, and subsequently developed a three-dimensional network (Valenta, & Auner, 2004). The macromolecules either lay separately in the diluted solution or were entangled in a more concentrated one (de Moura, & Moreno, 2019). They likely interacted intramolecularly and/or intermolecularly with themselves and/or solvent molecules. The forces imposed on the macromolecules possibly reduced their mobility in the structured network, leading to the increased stiffness and firmness of samples (Huang, Theng, Yang, & Yang, 2021) and the subsequent resistance toward applied stress and/or the relative motion of adjacent liquid layers, thereby affecting the viscosity of gels (Huang, Mao, Li, & Yang, 2021; Lee, Moturi, & Lee, 2009; de Moura, & Moreno, 2019). Increasing the polymer concentration in the media yielded higher interaction among the relevant molecules, limiting the stretching and the movement of macromolecules in the system. As a result, an incremental increase in gel viscosity was obtained (Hao et al., 2018; de Moura, & Moreno, 2019). This is consistent with results reported previously (Sanjana, Ahmed, & Bh, 2021; Amaral et al., 2019; Jaber, Sulaiman, & Rajab, 2020; Ma et al., 2021; Shao et al., 2019).

In addition to the gel concentration, gel viscosity can be manipulated by combining gelling agents at various compositions. Since there is an inverse relationship between the viscosity and the spreadability and/or extrudability of gels (Sanjana, Ahmed, & Bh, 2021; Budiman, Praditasari, Rahayu, & Aulifa, 2019; Daryab et al., 2022; Lee et al., 2009; Lucero, García, Vigo, & León, 1995; Maraie, & Kadhium, 2019; Pavithra, Jeganath, & Iqbal, 2018), which affects the ease of application (Jaber et al., 2020), gels need to be optimized to possess a proper viscosity – that is, to simultaneously hold the formulations and to stay at site of application with sufficient retention time (Daryab et al., 2022; Jaber et al., 2020; Kotwal, Bhise, & Thube, 2007).

Incorporation of either active ingredients or excipients is reported to cause a significant change in rheological properties of the gel systems (Aslani, Zolfaghari, & Davoodvandi, 2016; Kelly et al., 2004; Lee et al., 2009). In particular, the presence of buffers and/or inorganic salts strongly affects gel formation, and, hence, the gel viscosity (Kristmundsdóttir, Sigurdsson, & Thormar, 2003; Moore, Croy, Mallapragada, & Pandis, 2000). Their ionic nature possibly shielded the charged functional groups on the polymeric chains of ionizable gelling agents and suppressed the electrostatic repulsion among them. Subsequently, the polymeric molecules likely reverted to a more compact conformation, leading to a reduction in the hydrodynamic size of the molecules and the subsequent contracted network structure. As a result, a decrease in the interaction among the polymeric chains and between the polymeric chains and the solvent molecules presumably occurred, causing a significant drop in gel viscosity (Amaral et al., 2019; Das, Konale, & Kothamasu, 2014; Hao et al., 2018; Kelly et al., 2004; Kristmundsdóttir et al., 2003; Ma et al., 2021; Shao et al., 2019). This is in accordance with results previously reported by several studies (Amaral et al., 2019; Bak & Yoo, 2018; Hao et al., 2018; Shao et al., 2019).

The HPMC-containing gels seemed highly sensitive to the presence of NaF. As a strongly polar substance, NaF likely exhibited good competitive hydration that extensively influenced the hydration and/or aggregation behavior of the macro-molecules, leading to the impaired gel forming ability of HPMC (Hao et al., 2018). In addition, the cellulose gels were reported to lose their homogenous structure, and eventually precipitated out upon incorporation of the flower extract (Aslani et al., 2016) and cetylpyridinium chloride (Zagorulko, & Karavaeva, 2021).

The NaF gels exhibited good macroscopic properties. In addition to satisfactory clarity and spreadability, they were easily extruded from the bottle and conveniently applied. It was obvious that the NaF gels were physically stable, contributing to the excellent stability of the CBP/NaCMC-containing gels (Aslani et al., 2016; Ullah, Zafar, Al-Munawwarah, & Arabia, 2015). Furthermore, the NaF content was well preserved throughout the time course of experiment. Although the pH values fell slightly, they remained within the range of 6-8 specified by the US Pharmacopeia under the monograph of Sodium Fluoride Gel (The United States Pharmacopeial Convention, 2018). In addition, they maintained the nearly neutral pH (6.7 – 7.3) of the oral cavity (Seethalakshmi et al., 2016), which is considered acceptable for avoiding the risk of irritation or any possible inflammation upon application (Sanjana et al., 2021; Daryab, et al., 2022; Jaber et al., 2020; Maraie & Kadhium, 2019;

Pavithra et al., 2018). Moreover, the formulation pH was higher than the critical pH of 5.5, facilitating the prevention of demineralization (Sahlan, Prakoso, Darwita, & Hermansyah, 2017). In general, a 2-year shelf life of the NaF gels could be expected given their ability to withstand undesirable conditions during the stability studies (Aslani et al., 2016).

In short, the attempt to develop NaF oral gels composed of appropriate types and concentrations of gelling agents and essential excipients was successfully made. Gels of acceptable physicochemical characteristics and favorable stability for prevention of dental caries in xerostomic patients were certainly obtained, setting the stage for the prospective gel formulations to be subjected to irritation and/or efficacy studies in the near future.

6. Conclusion

In this study, 2% w/w sodium fluoride oral gels were successfully developed. All the investigated gel bases were clear viscous liquids of good dispersibility, except the XTG gel bases which were slightly translucent. Increasing the concentration of gelling agents resulted in the increased viscosity of gel bases. It was observed that the gel spreadability correlated well with the gel viscosity. Incorporation of pH 7.4 phosphate buffer solution brought about a slight decrease in gel viscosity. The developed NaF gels evidently exhibited satisfactory macroscopic and physicochemical properties. The physical stability and NaF content of the formulations were able to be well maintained during the heating-cooling cycle and accelerated stability testing. The outcome of this study should definitely provide great benefits to xerostomic patients, especially those in Rajavithi Hospital.

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