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Effect of Strong Electrolyte Containing Gelling Aids on the Sol-Gel Transition Temperature of Hypromellose 2910

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By

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D.D.S IN DENTISTRY

THESIS

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ABSTRACT

Hypromellose, or hydroxypropyl methylcellulose (HPMC) - has been widely used for biomedical and pharmaceutical applications due to its advantages, including that it is modifiable in terms of viscosity, and it has the ability to form thermally reversible hydrogels. The thermal gelation temperature (T_{Gel}) of a given HPMC solution strongly depends on its characteristic grade and the solution concentration. Applying certain additives can modify the T_{Gel} even further; depending on their nature and concentration. With the addition of said additives, a lower or higher T_{Gel} can be obtained. For example, the addition of sodium chloride (NaCl) reduces the T_{Gel}, whilst sodium iodide (NaI) increases the T_{Gel}, for a given HPMC solution. Therefore, for a certain application, the gelation temperature of a solution could be modified by adding a selected additive at an appropriate concentration. The effects of various additives have been described in the literature. However, there has been no in-depth experimental reporting on the effect of sodium fluoride (NaF) on the T_{Gel}. Here, we investigate the impact of NaF in comparison to NaCl on the thermal gelation temperature of HPMC 2910 using rheological analyses. The sol-gel transition temperature was evaluated by examining the viscosity, the storage modulus, and the loss modulus of HPMC

solutions as a function of concentration. The results indicated that both NaCl and NaF were able to reduce the T_{Gel} of HPMC 2910. However, the effect of NaF was found to be significantly greater in reducing the T_{Gel} compared to NaCl; the change in T_{Gel} as a function of additive composition was approximately 3.6 times higher for NaF compared to that of NaCl. In conclusion, these findings suggest that NaF is a suitable additive to combine with HPMC solutions for *in-situ* gelation at body temperature. Furthermore, the data indicated that only 1.6% NaF was needed to reduce the gelation temperature of HPMC from 60 ˚C to body temperature (approx. 37 ˚C). HPMC solutions containing NaF can form a viscoelastic solid gel at body temperature; this could potentially be used to prolong the release of fluoride for dental remineralization purposes.

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CHAPTER 1.

1.1- INTRODUCTION

Thermoresponsive hydrogels are polymers that show a phase transition(s) (e.g. sol-gel transition) at specific temperatures that are of particular interest for biomedical and pharmaceutical applications, including: gene delivery, drug delivery, and tissue engineering [16]. The appeal of these hydrogel systems is that they can be used in a liquid state (sol) at ambient temperature before transitioning into a viscoelastic solid (gel) at body temperature (approx. 37 °C). Furthermore, where temperature is the only factor that initiates gelation, and no other chemical or environmental stimuli are required, these types of formulations could be a safe approach for *in situ* gelation at body temperature [21]. *In situ* gelation of a pharmaceutical formulation may also enable sustained release of a given drug at the site of administration, and so could be a means to enhance therapeutic effectiveness.

Cellulose derivatives have gained popularity among the available thermoresponsive polymers for their potential usefulness in biomedical and pharmaceutical fields. These polymers are biodegradable, have low toxicity, and are obtained from renewable sources [13].

1.1.1- Cellulose and Derivatives

Cellulose (Figure 1.1) is the most abundant natural polymer, having a repeating structure of anhydroglucose units [42]. Cellulose itself is insoluble in water because of strong intramolecular hydrogen bonding between cellulose polymer chains. It is insoluble in water, this complicates its use in bioprocesses.

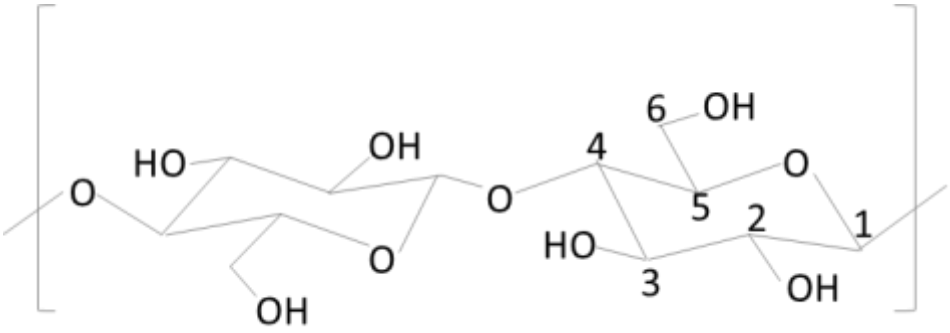

Figure 1. 1 Structure of native cellulose. Adapted from[9].

Etherification of a specific fraction of hydroxyl groups within the cellulose polymer structure yields water-soluble cellulose derivatives (Figure 1.2). Substituents decrease intramolecular hydrogen bonding and force the polymer chains to closely interact [9]. However, etherification of all hydroxyl groups with hydrophobic groups results in the synthesis of insoluble cellulose derivatives [28]. The “extent” or “degree of substitution” refers to the average number of substituted hydroxyl groups per anhydroglucose unit. The

optimum degree of substitution is between 1.4 and 2, rendering the cellulose derivatives obtained water-soluble.

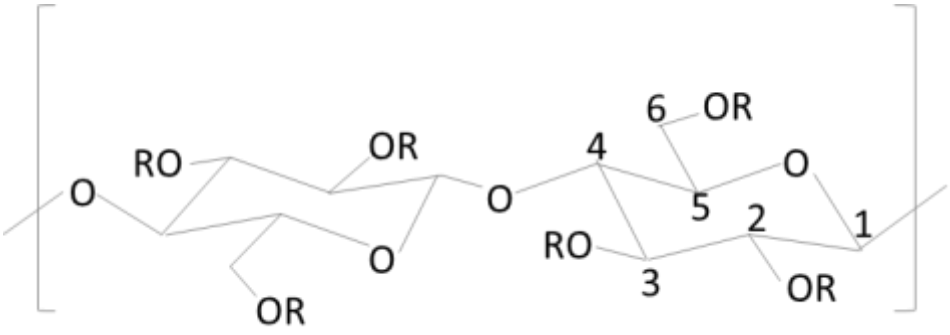

Figure 1. 2 Chemical Structure of water-soluble cellulose derivatives (R=H or R from Table 1.1 or 1.2 or 1.3). Adapted from [9].

Three distinct types of bonding occur once a cellulose derivative is dissolved in cold water: (1) intramolecular hydrogen bonding between unaltered hydroxyl groups of polymer chains, (2) hydrogen bonding between water molecules and hydrogen groups of the hydrophobic polymer substituents, and (3) hydrophobic-hydrophobic interactions between the hydrophobic substituent groups. Hydrogen bonding decreases and the hydrophobic associations become more prominent at higher temperatures, leading to a reduction in the water solvent capacity; this results in thermal gelation [28]. The specific temperature where a viscoelastic solid structure is formed is known as the sol-gel transition temperature (T_{Gel}) [21].

Cellulose esters and cellulose ethers are two groups of cellulose derivatives with different substituents of the available hydroxyl groups present on the native cellulose. Table 1.1, 1.2, and 1.3 represent different water-soluble cellulose esters, ethers, and mixed ethers, respectively. A common use for cellulose ethers is as rate controlling excipients for drug release, and as such they have been widely used as coating and film forming ingredients in pharmaceutical products [25].

Table 1. 1 Substituents of water- soluble cellulose esters. Adapted from [9].

Cellulose ester	−R
Cellulose acetate	$-C(O)CH_3$
Cellulose xanthogenate	$-C(S)SNa$
Cellulose sulfate	$-SO_3Na$
Cellulose phosphate	$-P(O)(OH)_2$
Cellulose phthalate	$-C(O)(C_6H_4)COONa$

Table 1. 2 Substituents of water-soluble cellulose ethers. Adapted from [9].

Cellulose ether	− R
Carboxymethyl cellulose (CMC)	$-CH_2COONa$
Sulfoethyl cellulose (SEC)	$-CH_2CH_2SO_3Na$
Methyl cellulose (MC)	$-CH_3$
Ethyl cellulose (ES)	$-CH_2CH_3$
Hydroxyethyl cellulose (HES)	$-CH_2CH_2OH$
Hydroxypropyl cellulose (HPC)	$-CH_2CH_2CH_2OH$
Cyanoethyl cellulose (CyEc)	$-CH_2CH_2CN$

Table 1. 3 Substituents of water-soluble mixed ethers. Adapted from [9].

Mixed cellulose ether	− R
Methylcarboxymethyl cellulose (MCMC)	$-CH_3$, $-CH_2COONa$
Hydroxyethylcarboxymetyl cellulose (HECMC)	$-CH_2CH_2OH$, $-CH_2COONa$
Hydroxyethylcarboxymetyl methylcellulose (HEMCMC)	$-CH_2CH_2OH$, $-CH_3$, $-CH_2COONa$
Sulfoethylcarboxymethyl cellulose (SECMC)	$-CH_2CH_2SO_3Na$, $-CH_2COONa$
Hydroxyethylhydroxypropyl cellulose (HEHPC)	$-CH_2CH_2OH$, $CH_3CH_2CH_2OH$
Hydroxyethylmethyl cellulose (HEMC)	$-CH_2CH_2OH$, $-CH_3$
Hydroxyethylethylcellulose (HEEC)	$-CH_2CH_2OH - CH_2CH_3$
Hydroxypropylmethyl cellulose (HPMC)	$-CH_2CH_2OH$, $-CH_2CH_2CH_3$
Hydroxyethylsulfoethyl cellulose (HESEC)	$-CH_2CH_2OH$, $-CH_2CH_2SO_3Na$

In general, cellulose derivatives are biocompatible polymers which are of particular interest

in the cosmetic, food, and pharmaceutical industries due to their broad applications that include acting as: binding agents, suspension aids, stabilizers, thickeners, film formers, and surfactants [16, 40, 8].

The studies described in this work focus on thermal gelation properties of hypromellose, a widely used cellulose derivative in the pharmaceutical field.

1.1.2- Hypromellose

Hypromellose (Figure 1.3) is manufactured from cellulose using an etherification process. During etherification, native cellulose fibers are heated with acoustic alkalizing solution before treatment with methyl chloride and propylene oxide [40]. The resultant hypromellose product has a specific ratio of hydroxypropyl and methyl substitution, identified as the minimum and maximum amount of methoxy and hydroxypropoxy substitution in Tables 1.4 and 1.5 [44]. The specific ratio of substitution is dictated by that initial ratio of methyl chloride to propylene oxide that is introduced after the alkalizing step. The difference between these ratios influences viscosities and the T_{Gel} of aqueous solutions. Differing molecular weights of hypromellose (polydispersity) is a result of the initial processing (mechanical or otherwise) of the cellulose fibers prior to etherification. Hypromellose or hydroxypropyl methylcellulose (HPMC), is a high purity excipient

monographed in the USP [26]. As indicated above, hypromellose is an excipient that has been widely used in pharmaceutical preparations.

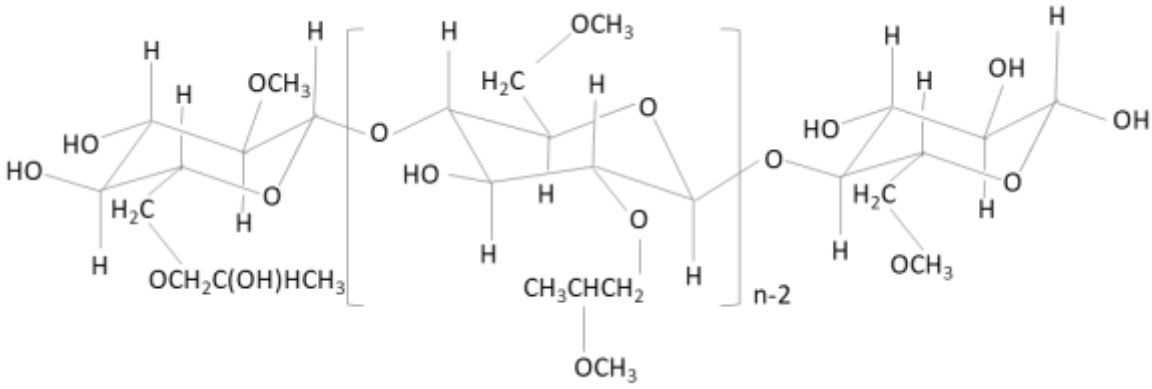

Figure 1. 3 The general chemical structure of hypromellose. Adapted from [38].

The general formula for hypromellose is C8H15O8-(C10H18O6) n-C8H15O8, and Figure 1.2 exhibits the structure of hypromellose where the R group represents hydrogen atom, a -CH3 (Methyl), or a -CH2CH (CH3) OH (Hydroxypropyl) group.

The methyl and hydroxypropyl groups are attached to the cellulose structure via etherification. The resultant fraction of methoxy, hydroxypropoxy groups, as well as the molecular weight are the factors that can affect the physiochemical properties of hypromellose [34], [43], [2]. As mentioned above, the degree of substitution is the average number of methoxy groups per anhydroglucose subunit. The term molar substitution (MS) refers to the average number of hydroxypropoxy groups per anhydroglucose subunit. The methoxy groups in hypromellose are relatively hydrophobic domains, while hydroxypropoxy groups are relatively hydrophilic by contrast [8].

Four different types of hypromellose are listed in The U.S. Pharmacopeia (USP) : hypromellose 2208, hypromellose 1828, hypromellose 2910, and hypromellose 2906 (United States Pharmacopeia Convention, 1980). With this numerical designation, the first two digits represent the nominal percentage of methoxy groups and the last two numbers are designated to the nominal percentage of the hydroxypropoxy groups. Table 1.4 indicates the maximum and minimum amount of methoxy and hydroxypropoxy for the four monographed hypromellose types, with the average values used in the naming system classification. However, it should be noted that if the upper or lower limit of the actual values were present in a particular batch sample then the precise value for T_{Gel} is likely to be altered considerably (i.e. a higher methoxy content would result in the lowering of the T_{Gel}) [46].

Another type of classification identifies HPMC by the letters K, E, and F. Table 1.5 lists the content of methoxy and hydroxypropoxy applied using this system. The letter designation indicates the chemical properties of hypromellose, this is followed by a number designation which indicates the viscosity grade of a 2% w/v aqueous solution of hypromellose in mPa.s at 20 °C. Another letter comes after the numerical designation and identifies a viscosity multiplier, if appropriate. Examples include M (representing the value is multiplied by 1000). In addition, there are some suffixes used for special products such as LV, suggesting low viscosity products, and G indicating granular products, whereas S identifies surface treated products [40]

Table 1. 4 USP specification for different types of HPMC, classified according to their degree of methoxy and hydroxypropyl substitution. Adapted from [41].

Substitution Type	Methoxy (%)		Hydroxypropoxy (%)	
	Min.	Max.	Min.	Max.
1828	16.5	20.0	23.0	32.0
2208	19.0	24.0	4.0	12.0
2906	27.0	30.0	4.0	7.5
2910	28.0	30.0	7.0	12.0

Table 1. 5 Various grades of HPMC. Adapted from [32].

HPMC Type	Methoxy (%)	Hydroxypropoxy (%)	Also known as:
K	19-24	4-12	Hypromellose 2208
E	28-30	7-12	Hypromellose 2910
F	2730	4-7.5	Hypromellose 2906

Hypromellose solutions are stable over a wide range of pH values, provide stable viscosity during long term storage conditions, and are widely used in pharmaceutical formulations [35]. The properties of a given solution of hypromellose are affected by the difference in degree of substitution, molar substitution, the concentration of hypromellose, and the amount and nature of additives, as well as the temperature.

1.1.3- Thermal-Gelation of Hypromellose

Aqueous solutions of hypromellose are able to transform into viscoelastic solid gels upon heating. This phenomenon is reversible and plays a critical role in biomedical applications, such as drug release systems. It has been reported that the methoxy groups of hypromellose are important in the gelation process. [44]

Figure 1.4 shows the sol-gel transition of hypromellose upon heating. At low temperatures (below the thermal gelation temperature), water molecules surround the hydrophobic methoxy groups, acting to form a cage-like structure. These structures are likely to exist due to water-water hydrogen bonding [23]. Therefore, at low temperatures the hypromellose is soluble in the water, however with an increasing temperature, and with an overall reduction in hydrogen bonding, a breakdown of the methoxy group water cages occurs; this in turn causes hydrophobic group exposure. Consequently, a hydrophobic association occurs, and this results in the formation of a 3D network and finally, a hydrogel structure is formed [22].

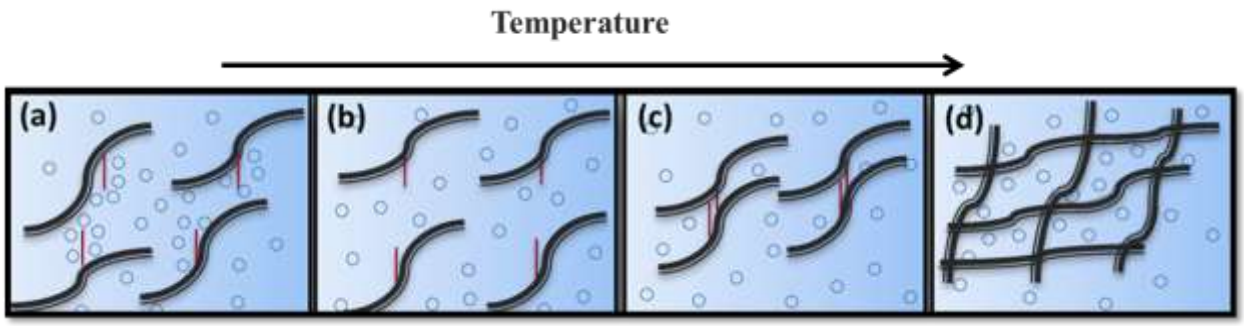

Figure 1.4 Schematic of sol-gel transition of hypromellose upon heating. (a-d) Small circles represent water molecules and the large dark lines are polymers. Red vertical lines are the hydrophobic groups (methoxy)

The specific temperature at which this gelation occurs is dependent on the grade of hypromellose, its concentration, and the properties and concentration of other components. Each grade of hypromellose demonstrates a different thermal gelation temperature due to differences in the substituent groups on the anhydroglucose subunits. For all different grades of hypromellose substitution, gelation temperature decreases with an increase in the concentration of the hypromellose solute [40].

Salts or ions are able to shift the T_{Gel} of hypromellose solutions to lower or higher temperatures, based on their ability to decrease or increase the hydrophobicity of the hypromellose in water relative to a salt-free hypromellose solution [45]. It has been reported that the effect of salts on gelation temperature of hypromellose are consistent with the Hofmeister series [45]. In 1888, Hofmeister reported the effect of salts on the solubility

of the proteins in water. According to Hofmeister, these ions could be ranked in terms of their strength in changing the hydrophobicity of a solute in water. Using this classification, ions are divided into "chaotropes" (structure breakers) and "kosmotropes" (structure makers) due to their ability to destroy or stabilize the structure of water, respectively. The Hofmeister order for anions is: $SO_4^{2-} > F^- > Cl^- > Br^- > NO_3^- > ClO_4^- > I^- > SCN^-$. The first four anions are kosmotropes, having a strong ability of hydration and interaction with water molecules. The later four anions are chaotropes, and demonstrate a little ability for hydration. Therefore, kosmotrope anions results in a "salt-out" effect, and elevate solute hydrophobicity in water, whereas chaotrope anions results in a "salt-in" effect, reducing solute hydrophobicity [19].

As mentioned above, water molecules form hydrogen bonds along the polymer chains and around the methoxy substituted groups. Increasing the temperature results in disruption of the water cages surrounding the methoxy groups, their aggregation, and the subsequent formation of gel. However, adding salts can change T_{Gel}. Kosmotrope ions (salt-out) have a strong ability of hydration, so have more tendency to attract water molecules as compared to the polymer chains themselves. Therefore, once added into the solution, water molecules rapidly surround the salt, this directly causing the water-cages around the methoxy groups to be disrupted at lower temperatures. As a result, more hydrophobic groups are exposed and interact with each other at that lowered temperature, compared to comparable hypromellose solutions that do not contain any salt-out ions. Thus, the gelation effect

occurs at lower temperature in the presence of these types of salts [45].

In contrast to salt-out ions, the mechanism of the salt effects on sol-gel transition for salt-in ions, such as the iodide ion (I^-), is different. The iodide ion is a large negative ion which effectively causes water to intersperse throughout the polymer chains; this has a preventative effect on hydrophobic association and gelation. This preventative effect causes the gel to form at higher temperatures than a comparable salt-free hypromellose solution. Overall, this phenomenon is related to weak interactions between these types of salts and water, and their lack of ability to break water-cage structures that surround the methoxy groups [44].

1.1.4- Advantages of Lowering Sol-Gel Temperature

The research presented in this work focuses on lowering the thermal gelation temperature of hypromellose because of its advantages in terms of drug delivery.

In situ gelation at body temperature is a type of delivery system that requires a "sol" phase at ambient temperature which turn into gel at body temperature, potentially this can be injected into the body (for example into a wound or fissure) and the subsequent gel would be formed at 37 °C, allowing drug to be released gradually when compared to the solution because the drug may be trapped in the hydrogel network. Decreasing the gelation temperature of a hypromellose solution from about 60 to 37 °C could make it suitable for this kind of delivery.

The current study investigated the effect of sodium fluoride, a strong electrolyte which is

expected to reduce gelation temperature significantly, due to its dehydrating ability. Previous studies have reported the effect of several inorganic salts; NaCl, NaBr, and NaI as well as some organic molecules; sucrose, glycerin, and sorbitol [36]. However, the effect of NaF on gelation temperature has not been reported in the literature. Therefore, a part of this research aimed to provide information about the effect of different concentrations of NaF on the thermal gelation temperature of HPMC, and contrast the differences between comparable amounts of sodium chloride (NaCl) in terms of lowering the T_{Gel}.

1.1.5- Mechanism of Drug Release from Hypromellose Formulations

The first step of drug release from a hypromellose containing formulation occurs during contact with an aqueous medium. Highly soluble small molecule drugs are released by a process of diffusion, through the gel layer and into a bulk aqueous media. For a hypromellose containing matrix tablet the mechanism is different for insoluble drugs, in this case the gel itself must dissolve and disperse at the aqueous interface (polymer erosion), and the insoluble drug is released during this process. A combination of these mechanisms can occur for a variety of different small molecule drugs, with varying physicochemical properties in tablet formulations. It remains unclear what the overall processes may be for an already formed hydrogel matrix. Studies have shown that drug release from swellable hydrophilic matrices is dependent on the thickness of the gel layer. Increasing in thickness of the gel results in slowing the rate of drug release [32]. In these studies, the NaF active ingredient (as well as the salting out gelling aid) is water highly soluble, and thus the principle release mechanism was predicted to occur by diffusion.

Chapter 2.
2.1- REVIEW OF RELATED LITRATURE

As previously mentioned, the thermal gelation of cellulose ether aqueous solutions has become important in biomedical and pharmaceutical fields. Methyl cellulose (MC) and

hypromellose or hydroxypropyl methylcellulose (HPMC) are two cellulose ethers that are commonly used with applications in these fields, due to their advantages over other thermo-responsive polymers. As previously described, MC or HPMC gelation occurs as a result of hydrophobic association among the methoxy groups, causing the formation of an ordered 3D gel network upon heating at approximately >60 °C for a 2 % w/v solution of HPMC 2910 [14]. The sol-gel transition temperature is influenced by various factors such as: pH, presence of additional solutes, and solvent type. The inclusion of salts are one of the most important elements which are able to change the temperature at which the gelation is occurs [5].

Previous studies have shown that the effect of the individual sodium halide salts, e.g. NaCl, NaBr, or NaI on the T_{Gel} of hypromellose, are different [45]. During these studies, the cation was used as a control to study the effect of different anions. The research concluded that both NaCl and NaBr shift a given sol-gel transition to a lower temperature. Furthermore, it was shown that NaCl decreased the gelation temperature more than that of NaBr. By contrast, NaI was seen to cause a delay in gel formation, indicating a different mechanism (as described in Section 1.1.3). Xu et al. went on to describe that the effect of cations on the T_{Gel} is less than that of anions which was attributed to the asymmetry of charges in water molecules. Figure 2.1 represents a comparison between interactions of water molecules with cations and anions. Anions have a stronger electrostatic potential than cations (because of the charge distribution on the water molecule), and are able to associate more intimately [10].

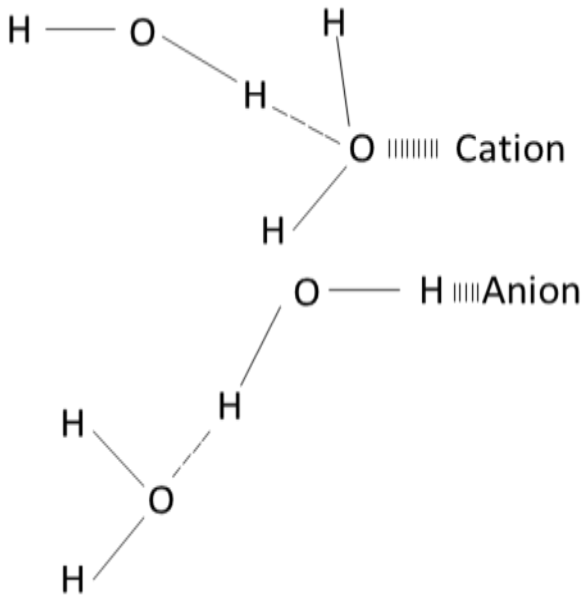

Figure 2. 1 The schematic of interactions of water molecules with cations and anions. Adapted from [45].

Xu et al. found that the effect of NaCl on the T_{Gel} was very close to that of KCl. Furthermore, a comparable effect was also found for NaI and KI as it is obvious in Figure 2.2 Therefore, the affect of anions on water structure is more important than that of cations.

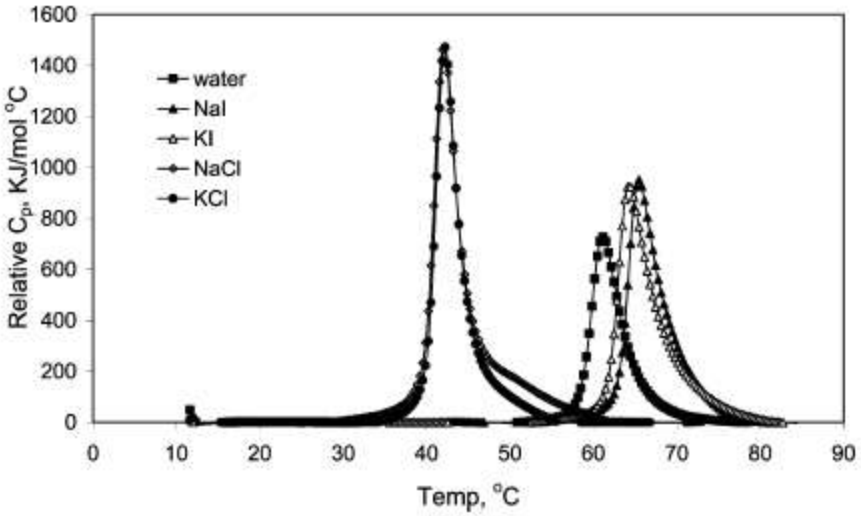

Figure 2. 2 Relative thermal capacity (Cp) as a function of temperature for MC solutions and various salts including NaCl, KCl, NaI, and KI. Reprinted with permission from [48]. Copyright (2018) American Chemical Society.

During the course of the aforementioned studies, a DSC was used to determine the thermal gelation temperature. Since gelation is an endothermic process, endothermic peak in the DSC scan is an indicator of the T_{Gel} during the heating cycle. DSC scans showed that endotherms for KCl and NaCl were almost superimposable, along with peaks for NaI and KI (Figure 2.2). Kundu et al. also added sodium chloride (NaCl), ammonium sulfate $(NH_4)_2SO_4$, and sodium carbonate Na_2CO_3 to MC solutions to investigate the effect of each salt. The results of these studies consistently showed that the thermal gelation temperature of MC solutions decreases with the addition of the salts investigated [24]. The effect of different concentrations for each salt was also investigated by Xu et al. According to their

results, the higher the concentration of the salt the greater change for thermal gelation temperatures. Each salt investigated was found to have its own concentration limit, given a fixed cellulose ether concentration in solution. At this salt limit, gels were either found to form at room temperature, or polymer solutions were found to precipitate. This limitation was shown to be dependent on the degree of anionic charge.

For example, the limitation for the sulfate anion (SO_4^{2-}) which has a valency of -2, was less than that of the nitrate anion (NO_3^-) which has a valency of -1 [45]. An investigation into the effect of salt mixtures (combinations of salt-out and salt-in salts) was also studied. Xu et al went on to study different concentrations of NaCl and NaI in MC aqueous solutions. When the ratio of NaCl to NaI ratio was >1, the salt-out effect occurred and the T_{Gel} was reduced. Conversely, at a ratio of <1, T_{Gel} was increased. Furthermore, the authors concluded that the effect of each salt was not dependent on each other, since a linear rule for mixing was observed [44]. Figure 2.3 shows the results of this study obtained by a micro differential scanning calorimeter. As mentioned above, an endothermic peak indicates the T_{Gel} during heating.

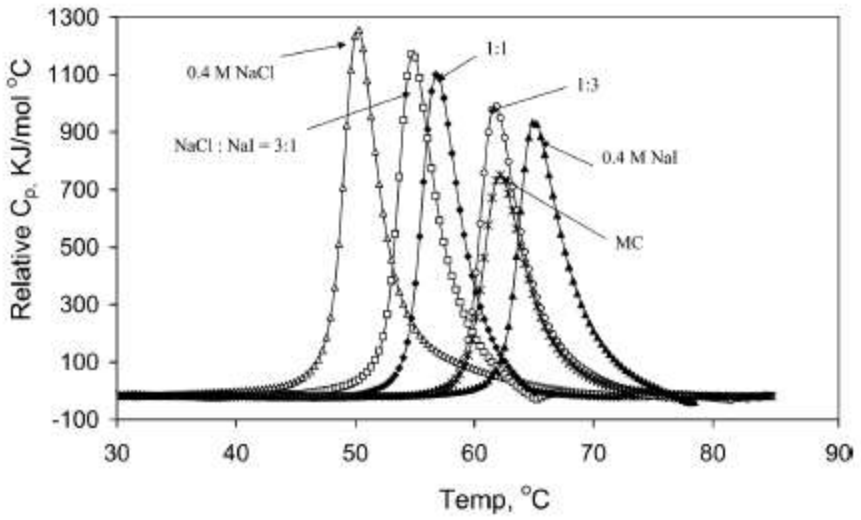

Figure 2. 3 Relative thermal capacity (Cp) as a function of temperature for MC solutions in the presence of salt mixtures with various NaCl versus NaI ratios. The curve with stars (*) represents the salt-free MC solution. Reprinted with permission from [44]. Copyright (2018) American Chemical Society.

Earlier studies investigated the effect of salts on the thermal gelation of MC solutions, however only a few of them examined this effect on HPMC solutions, despite the fact that HPMC has more applications in pharmaceutical field [14]. Mitchell et al. determined that HPMC sol- gel transition temperatures decreased with salt-out salts and followed the Hofmeister series in the same trend as that of the MC solutions [30]. In 2007, Liu et al. examined the effect of different salts with different HPMC concentrations using Differential Scanning Calorimeter (DSC) and rheology. The salts studied included: NaCl, KCl, NaBr, NaI, Na_2HPO_4, K_2HPO_4, Na_2SO_4, Na_3PO_4, and NaSCN. Most of the salts

displayed a salting-out effect (decreasing T_{Gel}), conversely NaI and NaSCN exhibited a salt-in effect (increasing T_{Gel}). As with other studies, the concentration of the salts demonstrated a linear relationship with T_{Gel}. Figure 2.4 shows the effect of salt concentration on the T_{Gel}.

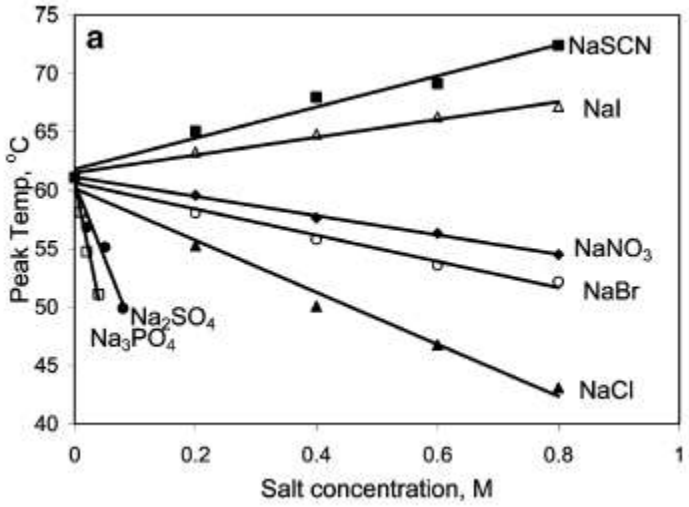

Figure 2. 4 Salt effects on gelation temperature as a function of salt concentration. The MC concentration was 0.03 mM. Reprinted with permission from [45]. Copyright (2018) American Chemical Society.

Among the salts investigated, Na_3PO_4 had the strongest effect of decreasing the T_{Gel}. In addition, Na_2HPO_4, K_2HPO_4, and Na_2SO_4 had a stronger salting-out affect compared to NaCl, KCl, and NaBr. Therefore, the results suggested the greater the negative valency of the anion, the stronger the salting-out effect [29].

While most of previous studies looked at the effects of salts on high molecular weight HPMC solutions, Almeida et al. studied the effect of NaCl and $CaCl_2$ on the viscoelastic properties of low molecular weight HPMC solutions [3], although it has been reported that molecular weight has little effect on gelation. [40]

In 2016, a hydrogel mixture of MC containing NaCl and Gallic acid (GA) was made by Sangafi et al. In this study the thermal gelation temperature was reduced to body temperature (approx. 37 °C) with the addition of NaCl and GA. As observed in previous studies, NaCl was able to lower the T_{Gel} of MC. Gallic acid was also seen to decrease the T_{Gel}, however the mechanism was found to be different. As previously described above, NaCl interacts with water molecules to reduce the T_{Gel}, but the authors indicated that the GA interacts directly with the MC chains via hydrophobic interactions. As a result, they showed that GA/NaCl/MC gelled at body temperature. The authors go on to suggest that a potential application for this mixture of GA/NaCl/MC could be *in situ* gelation to deliver drugs which could benefit from being in a gel at body temperature; such as doxycycline which was selected for the study. Doxycycline (DX) is an antibiotic for treating infections. Hence, doxycycline can be loaded into GA/NaCl/MC mixture and injected into deep wound in the liquid "sol" phase before transforming into a gel at body temperature, to release the DX gradually [36].

Overall, the effect of salts on the T_{Gel} of cellulose derivatives such as MC and HPMC has been appealing, since the modifications are relatively straightforward for changing the T_{Gel}, with the addition of a suitable gelling aid or combination of gelling aids. As a result, many

studies have been performed in this area [45]. However, the effect of several salts that are strong electrolyte additives are notably absent from those previous studies. Sodium fluoride (NaF), is an extremely strong electrolyte, with the fluoride anion being the most electronegative in existence, as indicated by its position on the periodic table, at the top of group seven. Even though it could be predicted that the fluoride anion (F^-) would be able to reduce the gelation temperature (based on Hofmeister series: $F^- > Cl^- > Br^- > I^-$), there is little support for this in the literature. As a result, this gap in knowledge directs these studies to investigate the effect of NaF on thermal gelation of HPMC. As an additional consideration, NaF is an inorganic salt which is commonly used to prevent/reverse tooth decay [39] and may benefit from in *situ* gelation for dental treatments which could be investigated in future studies. A mixture of HPMC and NaF in the form of a low viscosity solution (sol) may have applications for dental remineralization for deep areas of dental caries (prior to the onset of a cavity that may only be treated by filling with a composite or amalgam). It is hypothesized that a subsequent gel, formed at body temperature, would be able to adhere to the cavities and gradually release the fluoride at the site where it is most needed; useful for preventing dental caries and repairing/reversing the initial tooth decay. Fluoride has been used for remineralization of teeth in dentistry. In addition it has been shown to reduce dental demineralization [1]. Demineralization is the process in which the important element calcium in teeth is depleted by the lactic acid, produced by bacteria in the oral cavity. Remineralization is the process in which the part of the tooth which has demineralized can be replenished with calcium. The use of fluoride at the dental enamel

automatically results in remineralization, since the fluoride is able to bind to calcium ions in the hydroxyapatite of enamel, whilst preventing bacteria from producing destructive lactic acid [1].

Currently, fluoride is delivered onto dental surfaces by a variety of different means, for example: mouthwash, foam, or gel. The problem with mouthwash, and foam preparations is that they only have a finite time for effectiveness following their application [7]. On the other hand, using a pre-formed gel for fluoride therapy does not allow for penetration into the deep fissures and pits of dental caries due to the initial high viscosity of that gel [33]. With the fluoride contained within a liquid or "sol" state, the deep area of tooth decay can be reached, subsequently (and above the T_{Gel}) the liquid could gel and provide a longer contact time, while releasing fluoride gradually. It is hoped that further research following the completion of these studies will demonstrate this. Therefore, NaF can play an important role as an additive for HPMC solutions in pharmaceutical applications.

CHAPTER 3.

3.1- MATERIALS AND METHODS

3.1.1- Materials

1. **Hypromellose**

In this work, the cellulose derivative used was hydroxypropyl methylcellulose or

hypromellose (HPMC) with the trade name of Methocel® E4M, obtained from Colorcon, Inc. (Harleysville, Pennsylvania, USA). The percentage of methoxy and hydroxypropoxy substitution were 28-30, 7-12 respectively.

The HPMC was odorless, tasteless, as a white fine powder. This type of HPMC has an average degree of substitution of 1.8 and molecular weight in the range of 300000-500000, as provided by the distributor. The viscosity range for a 2% w/v aqueous solution at 20 °C was 2,663-4,970 mPa.s, as indicated by manufacturer.

2. Gelling Aid Additives

Sodium fluoride and sodium chloride powder were provided by the Sigma-Aldrich Company (St. Louis, MO, USA).

3.1.2- Methods

3.1.2.1- HPMC Solution Preparation

To prepare an HPMC solution a hot/cold technique was used. In this method half of the total required volume of water was heated to at least 90 °C to prevent powder agglomeration, then the pre-weighed Methocel E4M powder was added to the water whilst stirring. Stirring continued once the powder was fully dispersed. After that, the remainder of the water was added to the solution as cold water. The solution was then kept in ice bath until the solution reached the temperature at which the HPMC becomes water-soluble. At this temperature, a transparent solution is observed. It is recommended to keep solution in

the refrigerator overnight for full hydration [4].

HPMC (2% w/v) was prepared according to the technique explained above for this study and it was stored in the refrigerator before use

3.1.2.2- HPMC/NaCl and HPMC/NaF Samples Preparation

To prepare samples containing gelling aids, the appropriate amount of NaCl or NaF were dissolved in cold water. The volume of cold water was half of the total required volume of water for the correct final % w/v for the appropriate gelling aid. Then HPMC powder was dispersed in the remaining water volume (hot water). The required gelling aid cold water solution (either NaCl or NaF) was added to the HPMC dispersion. Further cooling allowed the HPMC to dissolve into solution.

For NaCl four different concentrations were prepared: 1, 2, 3, or 4% w/v. For NaF, three different concentrations were prepared: 1, 2, or 3% w/v. As mentioned earlier, each salt has a concentration limit which above that gel forming happens below or at room temperature [45]. When the NaF was used at 4% w/v the solution precipitated and formed a cloudy gel during preparation.

3.1.2.3- Analytical Methods to Determine Thermal Gelation of HPMC

Rheological analysis was chosen as the method to determine thermal gelation properties of solutions. There are several other common methods employed to determine the gelation

temperature of HPMC, these include: *Test Tube Tilting*: For this method, a solution is heated in a temperature-controlled water bath. The temperature is increased from 20 to 80 °C at increments of 2 °C, every 5 minutes. After each increment, sample is allowed to equilibrate and then inverted to assess whether the sol-gel transition has occurred. The thermal gelation point can be evaluated when the liquid ceases to flow. However, this method is not very sensitive and could be considered to be more qualitative and subjective. *Micro- Differential Scanning Calorimeter (DSC)*: The Differential Scanning Calorimeter (DSC) has been commonly used to determine the thermodynamic properties of aqueous solutions of HPMC. Since the thermal gelation is an endothermic process, an endothermic peak can be observed to indicate sol-gel transition. During this method, a sample is usually injected into the large volume sample cell (0.5 mL) and is then heated from 25 °C (or less) to 80 °C, commonly at a rate of 1 °C/min. A reference cell is filled with pure water. An important limitation of this system is that very high viscosity liquids may not injected into sample cell. Therefore, only some types of HPMC solutions investigated using this method, since a high proportion of HPMC solutions might be too viscous [28]. *Turbidimetry*: Turbidity measurements are commonly performed using UV/visible spectrophotometers equipped with temperature control. Cuvettes are used to contain each sample, and are fitted with a plastic cap to avoid water evaporation during heating. Each HPMC containing sample is generally heated from 10 to 80 °C at a rate of 1 °C/min. The sol-gel transition temperature is recorded once the transmittance becomes 50% of the original low temperature solution transmittance value, designated as an increase in turbidity [36].

3.1.2.3.1 Rheological Analysis

Rheology is the most direct and reliable way to determine the sol-gel transition temperature, as well as characterize the rheological properties of both solution and

subsequent gel [27]. As a result, a rheometer was chosen to determine the sol- gel transition temperature of the HPMC solutions prepared throughout these studies. Rheological properties such as dynamic moduli G', G", and complex viscosity η* change when the temperature is in the vicinity of the sol-gel transition. The rheometer is able to measure these properties during heating.

During the routine measurements in these studies, the following procedure was observed: (i) Each HPMC solution was placed on to the bottom Peltier plate of the Discovery Hybrid HR-2 rheometer (TA Instruments, Newcastle, DE, USA) equipped with a Peltier concentric cylinder temperature system and a 50 mm parallel plate; (ii) Oscillation temperature sweep was performed to determine the effect of temperatures on complex viscosity (η*), storage modulus (G'), and loss modulus (G") at angular frequency of 1 rad/s and stress applied was 0.4 Pa; (iii) In this study samples were heated in the range of 10-80 °C at a rate of 1 °C/min. A thin layer of low-viscosity silicon oil was placed around the sample to prevent dehydration during measurements; (iv) All measurements were repeated in triplicate.

Previously, the intersection point of G' and G" were used to define the thermal gelation temperature. This method was easy and convenient, however it has subsequently been considered inaccurate. This is because the gel point, as determined by this method, is

usually far from the gel point as determined by other methods, such as DSC and visual inspection. Therefore, the abrupt increase in G', which is accompanied by a sharp increase in viscosity has since been considered a more suitable way to define a thermal gelation temperature and was used in these studies [28].

3.1.2.4 Analysis of Fluoride Convention using a Fluoride-Selective Electrode

The fluoride combination electrode (Thermo Fisher Scientific, Waltham, MA, USA) was used for fluoride determination. First the standards, having known fluoride concentration, were measured with the fluoride ion selective electrode and ion meter to ensure calibration. Four standards in 10, 50, 500, and 1000 ppm (µg/mL) were used since the maximum amount of fluoride in our sample was theoretically calculated to be approximately 500 ppm. All standards and samples include total ionic strength adjustment buffers (TISABs) which require to adjust the pH and prevent complex formation between H^+ and F^- in acidic solutions [39].

For the solution measurement, 5 mL of a 2% w/v HPMC with 2% w/v NaF was taken and poured into 50 mL of deionized water and 50 mL TISABs at 22 °C (below the determined gelation temperature, so as to stay in as a solution). Separately, 5 mL of an identical 2% w/v HPMC/NaF was heated to form the gel, and then placed into 50 mL of deionized water with 50 mL of TISABs at 40 °C (above the T_{Gel} so as to maintain the gel). In each case, the fluoride release was determined over a three minute period using the specific ion

electrode. This method is depicted in Figure 3.1.

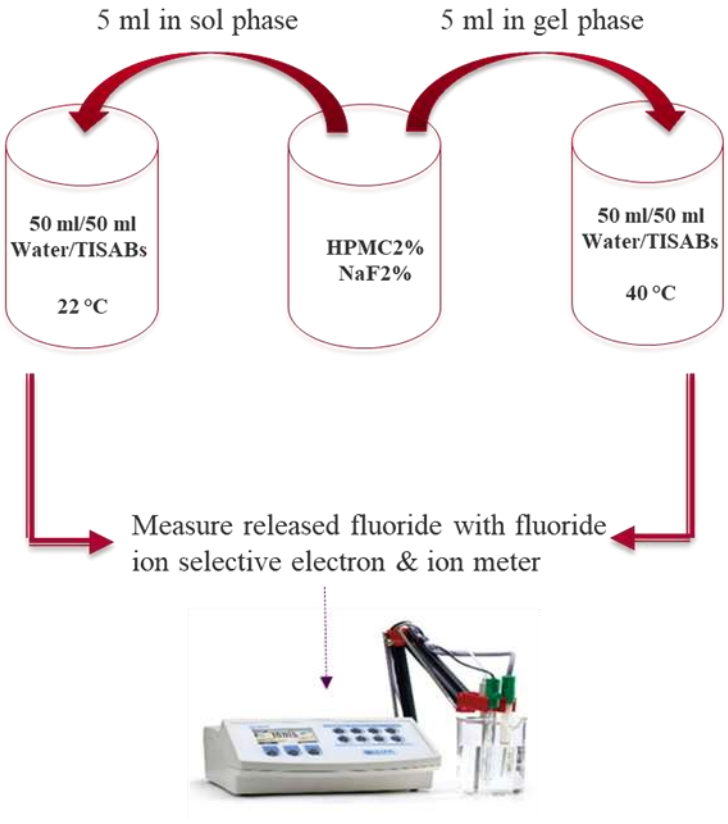

Figure 3. 1 Schematic of experiment to compare the rate of releasing fluoride using fluoride ion selective electrode and ion meter.

3.1.2.4- Statistical Methods

3.1.2.4.1 Rheological Analysis

Statistical differences in the thermal gelation temperature of different hypromellose

formulations containing different halide salt concentrations were determined using a one-way ANOVA test using Microsoft Excel Analysis Toolpak (Microsoft Inc., Redmond, WA). P values of <0.05 were considered statistically significant.

3.1.2.4.2 Fluoride Release rate comparison

A dissolution profile comparison was used to assess the similarity of the fluoride drug release from either a liquid "sol" state or a pre-gelled state. Using this approach, the similarity factor (f_2) was used to compare the two drug release profiles. The *similarity factor* (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves, this is represented by Equation 1, below

$$f_2 = 50 \times \log\left[\left(1 + (1/n)\sum_{t=1}^{n}\left(R_t - T_t\right)^2\right)^{-0.5} \times 100\right] \qquad (1)$$

Where n is the number of time points, R represents the fluoride release of the "sol" sample batch at time t, and T is the fluoride release of the gel sample at time t.

Using this approach f_2 values greater than 50 mean that there is less than 10% difference between the two release profiles, indicating that they are similar.

CHAPTER 4.
4.1- RESULTS AND DISCUSSION

4.1.1- Sol-gel transition of a 2% w/v HPMC E4M solution

The rheological data of 2% w/v E4M solution (HPMC) heated from 10 to 80 °C is shown in Figure 4.1. In the initial stage of heating, since the sample was in a liquid solution form, G" is greater than G' in the range of 10 to 57 °C, indicating the common viscoelastic behavior of a liquid. However, both moduli decreased gradually, with increasing temperature, until the temperature reached 57 °C. A gradual decrease in this range is related to the reduced hydrogen bonding and disrupted structure of polymer chains [4]. Haque and Morris suggested that the gelation process of MC and HPMC includes disruption of the polymer structure in the solution upon heating which is followed by development of a distinct structure at higher temperatures, this is similar to the thermogelation of globular protein which requires unfolding of the original structure for network formation [17]. This gradual decrease can also be explained as a viscosity-temperature correlation for liquids [37].

At approximately 57 °C, a sharp drop was observed in both G' and G" as well as viscosity. This dramatic fall can be ascribed to the precipitation of high molecular weight fractions of polymer chains which causes phase separation to a polymer-rich phase and a polymer-poor phase [20].

A sharp increase that occurred in both G' and G" after reaching a minimum at approximately

60 °C indicated that a continuous network was being formed in the polymer rich phase due to the hydrophobic association. In addition, G' became higher than G" indicating the common viscoelastic behavior of a gel.

Therefore, a sharp increase in G' can be defined as the gelation temperature. After that G' and G" both continue to increase upon heating due to the development of the viscoelastic gel structure.

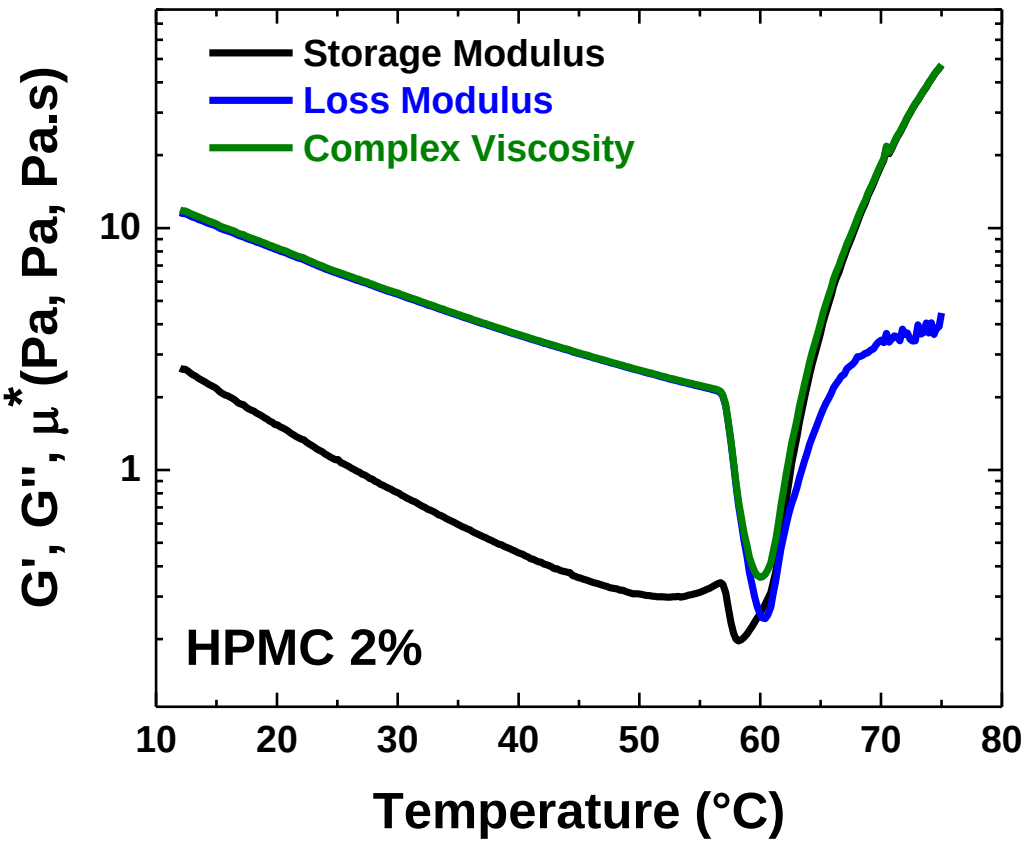

Figure 4. 1 Thermorheogram of 2% (w/v) HPMC E4M solution.

Figure 4.2 shows the visual inspection of 2% w/v E4M solution during heating from 10 to 80 °C. In the Figure 4.2(a), the HPMC sample is a transparent solution at 25 °C. At this temperature polymer chains are hydrated and are soluble in water. However, by increasing the temperature, the polymer chains become less soluble as hydrogen bonding between the polymer chains decreases and the sample shows the onset of clouding at 57 °C (Figure 4.1),

this correlates well to phase separation related to precipitation of the methoxy groups. Further increasing the temperature leads to gel formation in a polymer-rich phase, Figure 4.2(b). At this increased temperature a sharp increase was observed in G' and finally a fully developed hydrogel forms above 60 °C, Figure 4.2(c). These results show that gelation occurs after phase separation over a small thermal increment between these two processes. However, there is a controversy about the exact nature of phase separation and gelation. It has been suggested that phase separation is due to precipitation and occurs forming dense aggregates. It is further suggested that these aggregates go on to form a gel network as the polymer mobility of the system has been reduced and the hydrophobic methoxy groups become more exposed [18]. However, Desbrieres et al. have suggested that the gels form through hydrophobic association and followed by phase separation, and it is this that causes an increase in viscosity [11]. The observations and rheological data obtained in these studies would tend to support the former hypothesis, in which gel formation occurs following phase separation. Secondary phase separation may occur due to separation of gel network and water phase. Therefore, the final gel structure includes a polymer-rich phase, polymer poor phase, and water phase (or an extremely polymer-poor phase) [12].

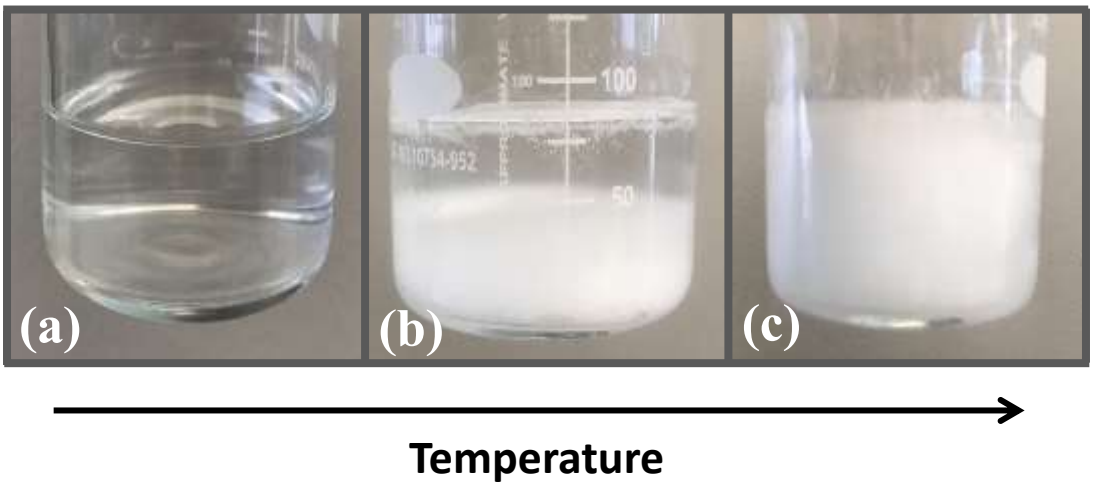

Figure 4. 2 Photographs of 2% (w/v) HPMC E4M solutions: (a) Transparent solution at 25 °C, (b) Clouding point and phase separation at 57 °C, (c) A fully developed hydrogel at ~60 °C.

4.1.2- Effect of NaCl and NaF on thermogelation of a 2% w/v HPMC E4M solution

Figure 4.3 shows the temperature dependence of the storage modulus (G')of 2% w/v E4M (HPMC) and the mixtures of 1-4% w/v NaCl and 1-3% NaF w/v during heating from 10 to 80 °C. Total volume is 100 ml (v=100). The abrupt increase of G' which is defined as the gelation temperature shifted to the left or to a lower temperature by increasing both NaCl and NaF concentrations.

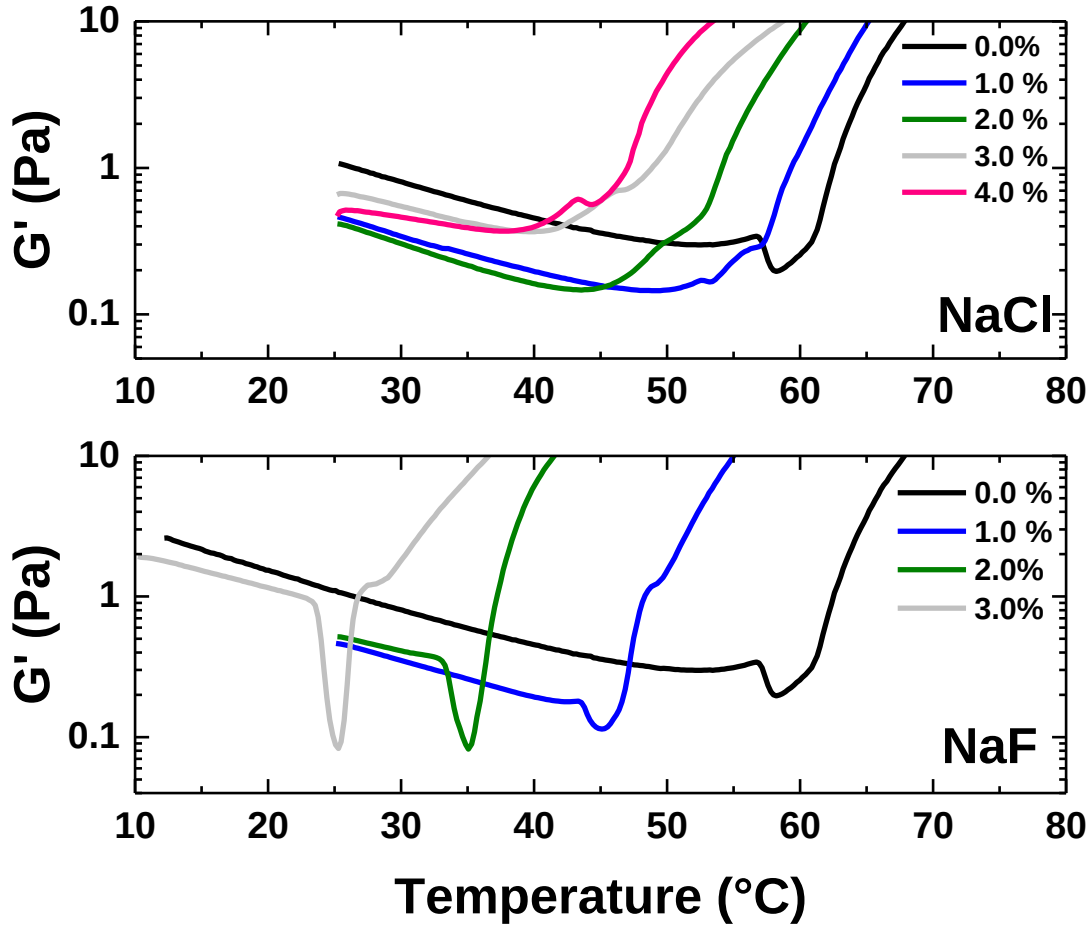

Figure 4. 3 Storage modulus (G') of 2% w/v E4M (HPMC) and the mixtures of HPMC and various concentrations of NaCl and NaF during heating from 10 to 80 °C.

Table 4. 1 Thermal gelation temperature of HPMC/NaF (n =3).

Sample	Concentration of NaF (%)			
	0	1	2	3
1	59.9	46.2	35	17.6
2	60.4	44.8	33.2	16.1
3	60.7	42.8	32	16.1
Mean	60.3	44.6	33.4	16.6
SD	0.32	1.39	1.23	0.71
%RSD	0.55	3.12	3.69	4.25

Table 4. 2 Statistical analysis of the gelation temperature of HPMC/NaCl for three independent experiments.

Sample	Concentration of NaCl (%)				
	0	1	2	3	4
1	59.9	55.5	50.3	47	44.3
2	60.4	53.3	49.6	47.8	44.4
3	60.7	54.8	50.5	46.4	43.7
Mean	60.3	54.5	50.13	47.07	44.13
SD	0.33	0.91	0.39	0.57	0.31
%RSD	0.55	1.68	0.77	1.22	0.70

Table 4. 1 shows the gelation temperature of HPMC, 1% NaCl/HPMC, 2% NaCl/HPMC, 3% NaCl/HPMC, and 4% NaCl/HPMC are 61.6, 57.1, 52.6, 47.2, and 44.2 °C, respectively, Using a one-way ANOVA, it was observed that that each value obtained for G' were all statistically significantly different from each other for HPMC 2910 samples

containing NaCl ($P < 0.05$).

The abrupt increase in G' also shifts to the lower temperature with an increasing NaF concentration. Table 4.2 shows the sol-gel temperatures of 1% NaF/HPMC, 2%

NaF/HPMC, and 3% NaF/HPMC are 49.6, 40.4, and 28.9 °C, respectively. Using a one-way ANOVA, it was observed that that each value obtained for G' were all statistically significantly different from each other for HPMC 2910 samples containing NaF ($P < 0.05$).

The results show that both NaCl and NaF belong to the "salt-out" category, attracting water molecules to surround them which leads to the disruption of water cages around the hydrophobic methoxy groups of HPMC. As a result, the methoxy groups are exposed at lower temperatures, which in turn results in a lower thermal gelation temperature (T_{Gel}). The results further demonstrate that an equivalent amount of NaF reduces the T_{Gel} of HPMC 2910 more than NaCl. The larger effect on T_{Gel} with NaF supports our hypothesis that the fluoride anion (F^-) being more electronegative than the chloride anion (Cl^-), attracts water molecules to a greater extent resulting in a higher degree of hydrophobic aggregation and ultimately gelation at lower temperature. These results show that the effect of these two salts on thermogelation of HPMC 2910 correlates well with the order of the Hofmeister series ($F^- > Cl^-$).

Figure 4.4 is a schematic representation of how NaF can affect the sol-gel transition temperature of HPMC compared to a saltfree the HPMC solution (Figure 1.4). As described earlier the addition of a gelling aid such as sodium fluoride has a comparable

effect to that of increasing the temperature, essentially resulting in the disruption of water "cages" that surround the hydrophobic methoxy groups. This effect occurs as the ability of sodium fluoride to interact with water molecules is greater than that of the HPMC polymer.

Hence, the methoxy groups are exposed at lower temperatures, enabling the hydrophobic association to occur. In short, hydrogels of HPMC that include NaF as a gelling aid are formed at lower temperatures than pure HPMC.

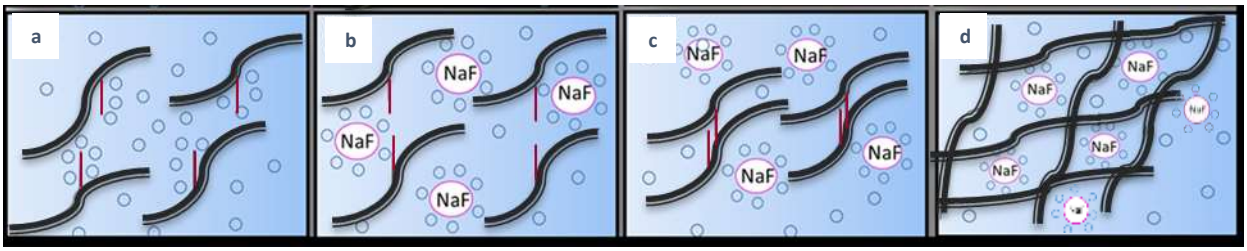

Figure 4. 4 Schematic of sol-gel transformation for aqueous solution of HPMC with NaF (a) Formation of cage like structure. (b) The pink circles represent sodium fluoride and causes disruption of water cages. (c) Hydrophobic association. (d) Formation of hydrogel.

Here, we consider a linear dependence between gelation temperature and concentration of selected additives [45]. Therefore, the following relationship between gelation temperature (T_{Gel}) and additive composition (x) can be applied:

$$T_{Gel} = T_0 - \alpha_G x$$

Where, T_0 is the gelation temperature of pure HPMC and α_G is the rate of change in gelation temperature as a function of additive composition. The parameter T_0 is strongly dependent on HPMC concentration and type of HPMC, which is related to the nature and

the quantity of the substituent groups attached to the anhydroglucose glucose ring [40]. If one considers a 2% w/vHPMC 2910 solution, α_G should be strongly dependent on the additives and their electronegativity.

Figure 4.4 exhibits a comparison between the NaF and NaCl in terms of reducing the gelation temperature of 2% w/v HPMC 2910. The thermal gelation temperature for each data point is an average of the rheological measurement, the error bar represents the standard deviation (n = 3). As expected, a decrease was observed upon increasing the concentration of both NaCl and NaF. The results were fitted using the function described in Equation 1, with an R-square value above 0.98, indicating good linearity of the data set. The gelation temperature of a pure 2% w/v HPMC solution (T_0) was found to be ~ 60 ˚C, and is considered to be independent of the nature of the additive used in the experiment. This value was found to be close to the reported values in literature for HPMC 2910 with similar concentrations [4]. A high value of α_G was obtained for NaF ($\alpha_{G-NaF} \sim 14.5$) which is greater by a factor of approximately 3.6 times that of the corresponding value obtained for NaCl ($\alpha_{G-NaCl} \sim 4.0$). This can be attributed to the relatively high electronegativity of the fluoride anion compared to the chloride.

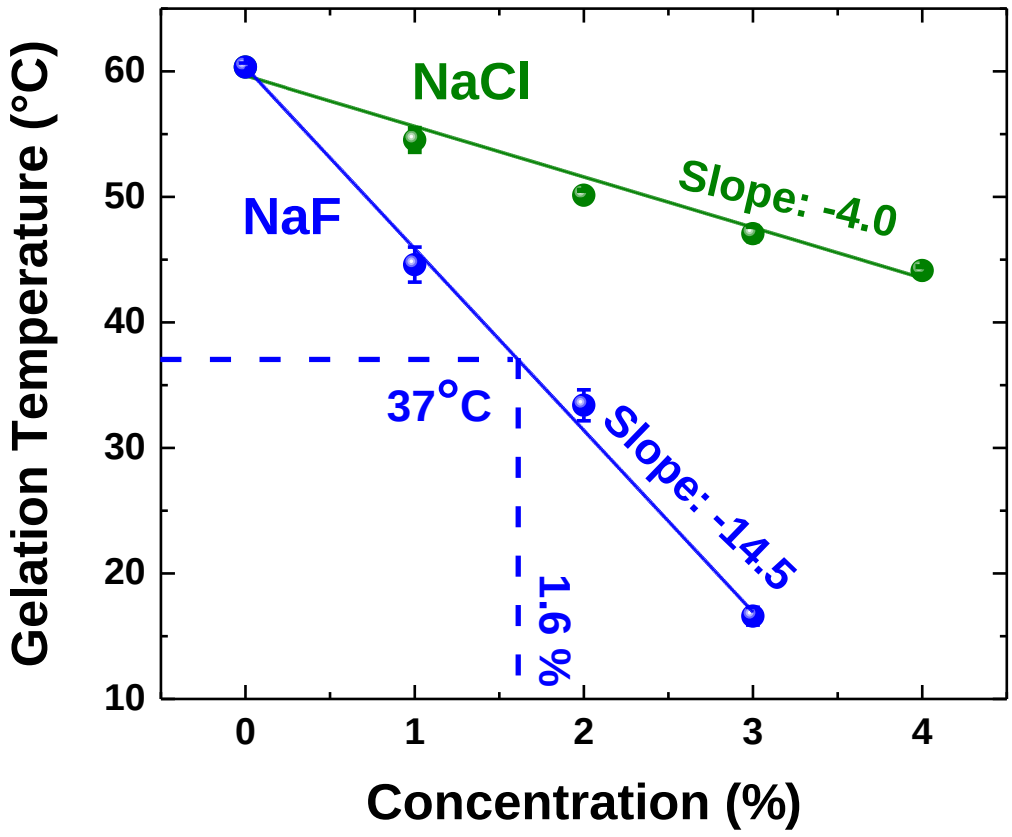

Figure 4. 5 The gelation temperature of 2% w/v E4M (HPMC) and the mixtures of HPMC and various concentrations of NaCl and NaF as a function of temperature.

As described earlier, NaF has the potential to prevent tooth decay or reverse minor decay. Therefore, a mixture of HPMC and NaF could be used as a potential application for *in situ* gelation, potentially prolong the release of fluoride to a specific site. By reducing the

gelation temperature of HPMC to body temperature, it is feasible to apply the fluoride in a low viscosity solution and apply it into a deep pit or fissure of a tooth (which is currently inaccessible with higher viscosity applications). The affected tooth area might then receive fluoride over a sustained period after the HPMC in solution subsequently gels rapidly at body temperature. It is known that the higher the contact time for fluoride on an effected tooth, the greater the extent of remineralization [7] Figure 4.6 shows that the maximum amount of fluoride is released in 40 seconds, as a solution or "sol" phase. Conversely, Figure 4.7 shows that it took 120 seconds for the complete fluoride release from the gel (with an identical formulation but above the T_{Gel}). Thus, the release rate of fluoride from the gel was found to be three times slower than that of an identical solution (below the T_{Gel}). Since this is the highest molecular weight available for Hypromellose 2910 (Methocel® E4M), then there is an extensive methoxy hydrophobic interaction for each high molecular weight HPMC polymer chain; leading to a slower rehydration and slow reversal of the sol-gel transition. In fact, it was observed that the gel remained for approximately 1 hour following complete diffusion of the NaF from the 3D gel matrix. It is conceivable that a smaller molecular weight HPMC grade (e.g. Methocel® E6) might disperse more quickly. Additionally, using the higher molecular weight HPMC 2910 grade (Methocel® E4M), it was observed that the gel still remained following complete release of fluoride into the bulk solution. In this case it is likely that there is a period that rehydration of the methoxy groups must occur before dissolution and dispersion of the gel can proceed. Again, it is likely that this dispersion of the gel following complete fluoride release would be quicker with a lower molecular weight HPMC grade.

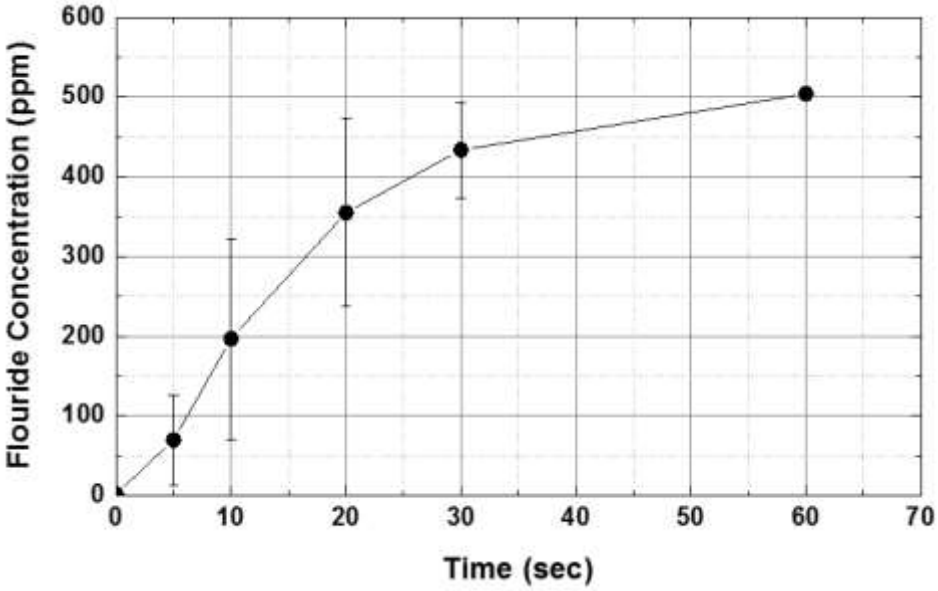

Figure 4. 6 Concentration of fluoride release as a function of time for solution.

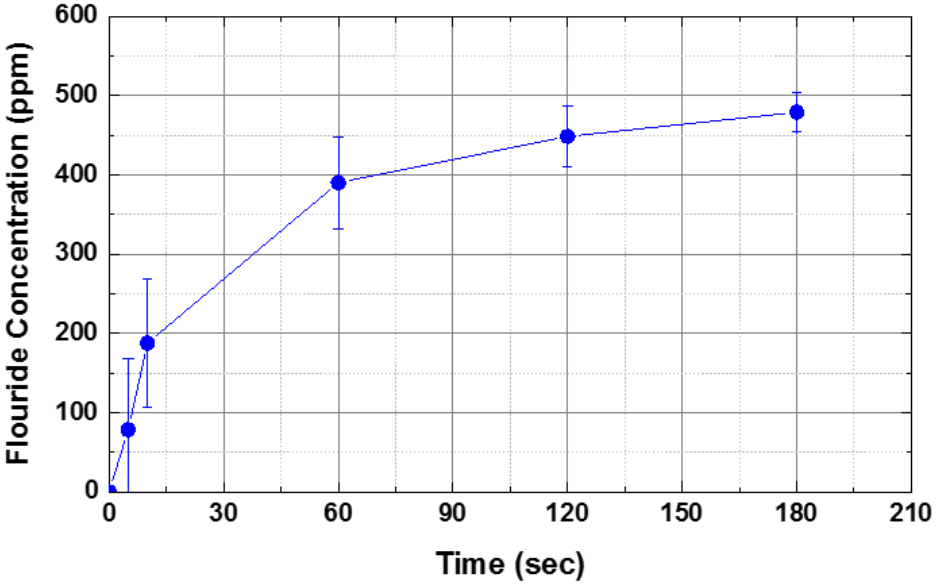

Figure 4. 7 Concentration of fluoride release as a function of time for gel.

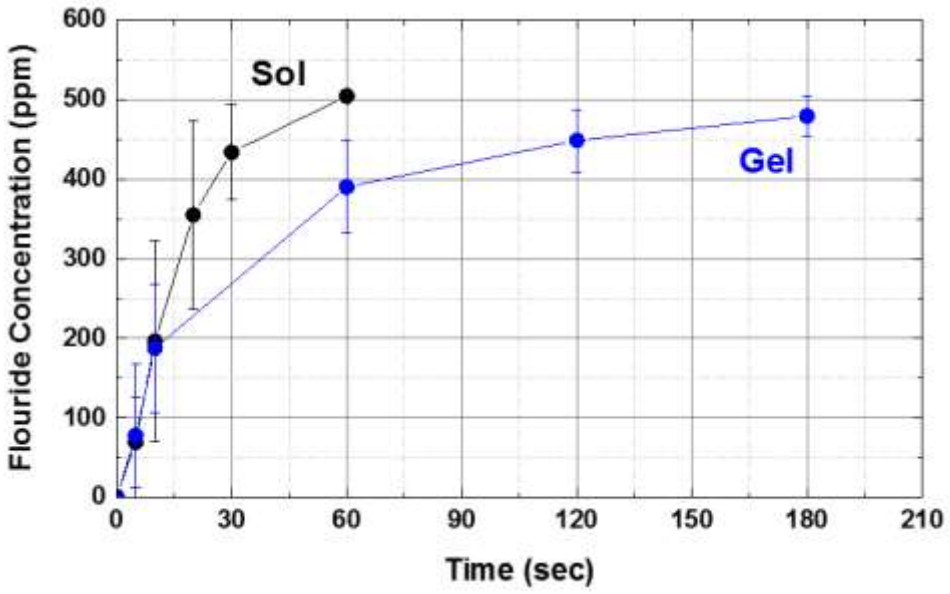

Figure 4. 8 Concentration of fluoride release as a function of time for solution and gel.

Figure 4.8 compares the rate of fluoride release from solution and gel. It is apparent that the total amount of NaF released from the gel takes a longer time compared to that of the solution formulation. However, it should be noted that a fraction of NaF is likely to be on the surface or at the periphery of the hydrogel after it is formed. This fraction is estimated to be approximately 200 ppm, since the release rate of the gel matches that of the liquid for the first 200 ppm fluoride anions detected, before deviation from this immediate release rate by the gelled formulation is seen. A similarly factor evaluation to compare these two release profiles, gave an f_2 factor of 5. This value indicates that release profiles for the same HPMC/NaF compositions were not statistically similar

CHAPTER 5.
5.1- CONCLUSIONS

The experiments presented in this study investigated the effect of NaCl and NaF in the thermal gelation temperature of HPMC 2910 using rheological analysis. It was found that the gelation temperature of HPMC 2910 reduces linearly with increasing additive concentration, when either NaCl or NaF are added as gelling aids. Although the mechanism of the gelation is the same for each gelling aid, a significant difference was observed in the rate of T_{Gel} reduction. NaF was shown to shift the T_{Gel} to a lower temperature significantly more than NaCl. This more significant shift can be attributed to the greater degree of interaction between the fluoride anion and water molecules, compared to the same interaction with water molecules and the chloride anion. Therefore, NaF as a gelling aid, is more effective in reducing the thermal gelation temperature than NaCl.

The experimental results, comparing the rate of fluoride release from a solution state to that of a gel, indicated that fluoride releases slower when it is entrapped in the gel state. In a hydrogel comprising HPMC and NaF, a fraction of NaF can be considered to be on the on the surface and at the periphery of the hydrogel network, while the bulk of the fluoride in the mixture resides inside that hydrogel network. It was determined that this portion of the fluoride, on the outside and periphery, released at the same rate of a non-gelled solution of the same composition. Furthermore, the amount of fluoride that is considered to be

inside the hydrogel matrix releases at a different rate, and over an extended period. Thus,

we can conclude that due to the transition of the solution (sol phase) containing fluoride, into the gel phase, release rate of fluoride can be prolonged. This type of fluoride delivery would enable the tooth surface more time to absorb fluoride, and thus likely making it a more effective therapy.

Chapter 6.

6.1- Applications and Future Directions

6.1.1- Dental Applications

NaF comprises fluoride anions which are effective for the prevention of tooth decay. As such, a potential advantage of using NaF as a gelling aid with HPMC is the ability to administer fluoride as an *in-situ* gelation formulation, at body temperature. Currently, fluoride is delivered to teeth by different compositions such as: mouthwash, toothpaste, pre-formed gel, varnish, and foam. The main issue with the existing fluoride applications is an extremely low effective contact time of fluoride with teeth. On the other hand, using pre-formed gels for fluoride therapy is not altogether efficient because deep fissures and pits of dental caries do not efficiently receive enough direct fluoride contact due to the relative high viscosity of a pre-formed gel. Figure 4.5 shows a schematic of the difference between fluoride delivery in the form of solution (sol) and a pre-formed gel in terms of

receiving insufficient fluoride into deep area of dental caries. With this in mind, there is likely to be therapeutic advantage with the administration of fluoride in the solution state at the initial application into deep areas of tooth decay. Following this application, a sol gel transition at body temperature would be expected to allow for improved adherence and residence time at dental surfaces, whilst simultaneously prolonging the release time of fluoride. In summary, the exploitation of the sol-gel transformation with a mixture of HPMC/NaF could be used functionally for *in situ* delivery of fluoride into deep areas of dental caries.

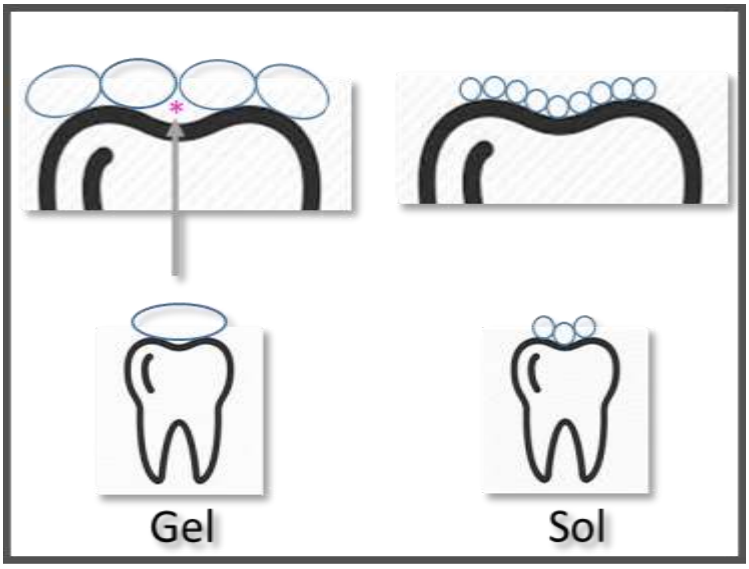

Figure 5. 1 Schematic of the fluoride delivery in the form of sol and gel. The gel form of fluoride is not effectively delivered into deep areas of the tooth while it is more efficiently delivered in sol phase.

6.1.2- Future Directions for Study

Biorelevant Fluoride Release Studies

A necessary area for further study would be the development of *in vitro* test to simulate the saliva volume which is secreted in the oral cavity. The test could also incorporate either a suitable and reproducible substrate, or actual dental material on which to deposit the sol phase. This would enable a more suitable experimental assessment means to compare formulations and their release rates. It is predicted that the fluoride release would be slower compared results obtained in a large volume of liquid media, since saliva is secreted gradually (approximately 1 mL per minute). In the fluoride release experiments conducted in these studies the gel was immersed in a large 100 mL volume. Although this was a discriminatory test, it did not faithfully reproduce the conditions in the mouth.

Rate of Thermal Gelation

Another investigation should focus on the rate of gel formation in a suitable environment (i.e. akin to the oral cavity). This type of study may be able identify an optimized formulation that formed a gel quickly still enabled suitable fluoride release. This investigation could also be used to identify suitable HPMC viscosity formulations that could be more effectively applied to the dental surface.

Bioadhesion Studies

Adhesion of a gel to the dental surface would be another factor should be considered in this study. Temperature controlled force of adhesion studies could be carried out using texture analysis to determine how well a given sol-gel transformation could adhere, and under what optimized conditions this may occur.

Platform Technology for the Delivery of other APIs

In addition, the approach of using a sol-gel transformation for dental purposes may also be useful for the delivery of other active pharmaceutical ingredients (APIs), such as antibiotics for the treatment of periodontal disease. Since the periodontal disease is caused by bacteria, both systemic and topical antibiotics are used to treat periodontal disease [31]. Therefore the sol-gel transformation could potentially be used for topical antimicrobial therapy for periodontal disease.

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Projects

Investigation of HPMC gelation temperature and the effect of various additives and their concentrations on lowering the gelation temperature.

Formulation and evaluation of fast dissolving films for drug delivery of Itraconazole to the oral cavity

Utilizing of Silver nanoparticle-based printed circuitry to control medication using a wireless system.

Papers

William J.McLain,Rkhav P. Gala, Adnan M. Hassan Sudha Ananthakrishnan, , Elnaz Sadeghi, Jason T. McConville. Formulation and evaluation of fast-dissolving films for drug delivery of Naloxone to the oral cavity. (Under preparation)

Adnan M. Hassan, Rikhav P. Gala, Sudha Ananthakrishnan, William J. McLain, Elnaz Sadeghi, Jason T. McConville. Formulation and evaluation of fast-dissolving films for drug delivery of Itraconazole to the oral cavity. (Under preparation)

Meeting Abstracts

Elnaz Sadeghi, Jason McConville. Reducing the Sol-Gel Transition of Hypromellose 2910 with Highly Electronegative Ion Containing Gelling Aids. Excipient Fest Americas Conference in San Juan, Puerto Rico, May, 2018.

Elnaz Sadeghi, Jason McConville. Reducing the Sol-Gel Transition of Hypromellose 2910 with Highly Electronegative Ion Containing Gelling Aids. Annual Association of Pharmaceutical Scientists Meeting, Washington D.C., November, 2018. (Encore Presentation).

Patent

Jason T. McConville , Rikhav P. Gala , and Elnaz Sadeghi. Thermally gelling drug dispersion system 2018