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Strontium-containing, carbohydrate-based polymer networks as tooth-adherent systems for the treatment of dentine hypersensitivity

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ABSTRACT

This study describes the design/physicochemical properties of strontium-containing, mucoadhesive carbohydrate polymeric platforms, designed as treatments for dentine hypersensitivity. Interactive networks were composed of strontium chloride (10% w/w), one of two base polymers (sodium carboxymethylcellulose, NaCMC or hydroxyethylcellulose, HEC), polycarbophil (PC) and, when required, polyvinylpyrrolidone (PVP). The physicochemical properties were characterised using oscillatory and flow rheometry, texture profile analysis, mucoadhesion analysis and, additionally, the strontium release properties were examined. All platforms exhibited pseudoplastic flow. Increasing polymer concentrations increased network viscoelasticity, consistency, hardness, compressibility, gel strength, adhesiveness, mucoadhesion and, retarded strontium release. Principally zero-order strontium release was observed from all platforms. Incorporation of strontium reduced the network elasticity, consistency, hardness, compressibility, gel strength and mucoadhesion; HEC-based platforms being affected to a greater extent than NaCMC platforms. NaCMC-based platforms containing 10% strontium chloride, PVP (3% w/w) and PC (3% w/w) potentially displayed the correct balance of physicochemical properties for the treatment of dentine sensitivity.

1. Introduction

Hypersensitivity or dentine sensitivity may be defined as an exaggerated response to a non-noxious stimulus (thermal, chemical, tactile or osmotic), due principally to exposure of the dentine to the oral environment (Bamise & Esan, 2011; Mantzourani & Sharma, 2013; West, Seong, & Davies, 2015). Typically, the loss of enamel and/or the covering of periodontal tissues as a consequence of chipped teeth, fractured restorations, restorative treatments and dental caries have been reported to induce dentine sensitivity (Addy, 1990). There are a limited number of reports detailing the incidence of dentine sensitivity, due at least in part to the lack of routine screening for this clinical problem by dentists (unless prompted to do so by patients) (Mantzourani & Sharma, 2013). As a result, reports of the prevalence of dentine sensitivity vary considerably. For example, Addy (Addy, 1990) reported that the condition occurred in 8–30% of the adult dentate population whereas Chabanski et al. reported a prevalence of dentine sensitivity of 84%, with no identified bias towards gender (Chabanski, Gillam, Bulman, & Newman, 1996).

The most widely accepted theory to explain the mechanism of dentine hypersensitivity involves the transmission of pain producing stimuli to the pulp by rapid movement of the fluid in the dentinal tubules (hydrodynamics) (Bamise & Esan, 2011; Mantzourani & Sharma, 2013). Exposure of external stimuli may cause expansion or contraction of the fluid contained within the capillaries of the dentine. (Absi, Addy, & Adams, 1987).

Treatment of dentine sensitivity typically involves the topical application of a desensitising agent which ideally should be non-irritant to the pulp, painless on application, easy to apply, non-staining and consistently effective for prolonged periods of time (Chabanski et al., 1996; Mantzourani & Sharma, 2013; West et al., 2015). The treatments of dentine sensitivity include the use of chemical agents, notably strontium chloride, calcium hydroxide and silver nitrate (Bamise & Esan, 2011; Curtis, West, & Su, 2010; Rosenthal, 1990; Wang et al., 2010), which aim to block the dentinal tubules, thereby reducing the movement of dentinal fluid. Whilst this may be performed by the application of a film-forming lacquer (applied by a dental practitioner), application by the patient is preferred, normally using toothpastes and gels. Clinically, the efficacy of strontium chloride has been shown in a series of studies (Arnold, Prange, & Naumova, 2015; Blitzer, 1967; Seong et al., 2013; Shapiro, Kaslick, & Chasens, 1970; Shapiro, Kaslick, Chasens, & Weinstei, 1970; West et al., 2013, 2015), however, recently, a

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meta analyses reported by Bae et al. questioned the efficacy of strontium-containing toothpastes (Bae, Kim, & Myung, 2015). It is proposed however that this reflects, at least in part, differences in the formulation platforms used in these clinical studies and reveals one potential area of weakness, namely the formulation of platforms that optimise the delivery of chemical agent (*e.g.* strontium) to the affected tooth and hence enhance clinical efficacy.

Akin to drug delivery platforms designed for the treatment of local disorders (Jones, Irwin, Woolfson, Djokic, & Adams, 1999; Jones, Woolfson, Brown, Coulter, McClelland, & Irwin, 2000), the clinical efficacy of platforms designed for the prevention/treatment of dentine hypersensitivity is dependent on the retention of the platform at the tooth surface (Martens & Surmont, 1991). Mucoadhesive topically applied platforms may be useful in that they maintain the formulation at the applied site for longer periods of time. To date, mucoadhesive platforms have not been specifically designed for application to the tooth surface for the prevention/treatment of hypersensitivity. Therefore, given this scenario, this study specifically describes a bioactive, mucoadhesive platform that is designed for the prevention/treatment of dentine hypersensitivity. In particular, this study describes the design and characterisation of carbohydrate-based platforms in which, by manipulation of the concentrations and ratios within the binary/ternary polymer platforms, compositions may be produced that offer wide ranges of mechanical, viscoelastic, flow, mucoadhesion and strontium release properties that are relevant to this clinical application. Key to performance of these platforms is the use of two cellulose polymers, hydroxyethylcellulose and sodium carboxymethylcellulose. This study additionally seeks to utilise the interaction between strontium ions and the polymeric matrix to design platforms with unique and clinically appropriate physicochemical properties. In addition to the aforementioned, this study is unique in the comprehensive nature of the characterisation of such systems, the latter using a wide range of analytical techniques that provide information directly relevant to the clinical performance of the platforms. As such the authors believe that this study will conceptually redefine the design and characterisation of platforms for application to the tooth surface.

2. Materials and methods

2.1. Chemicals

Hydroxyethylcellulose (Natrosol® HHX, average molecular weight 1.3×10^6 g mol^{-1}, degree of polymerisation 4800) and Sodium Carboxymethylcellulose (Aqualon® High Viscosity, molecular weight 700,000 g ml^{-1}, degree of polymerisation 3200) were gifts from Aqualon Ltd, Warrington, England.

Poly(vinylpyrrolidone) (Kollidon® 90F) was a gift from BASF, Ludwigshafen, Germany.

Polycarbophil (Noveon® AA1) – was a gift from B.F. Goodrich, Cleveland, OH, USA.

Crude porcine gastric mucin was purchased from Sigma Chemical Company, (Poole, Dorset, England).

Strontium Chloride ($SrCl_2{\cdot}6H_20$) was purchased from Taresh Chemicals, Banbridge, Co. Antrim, Northern Ireland.

All other chemicals were purchased from BDH Laboratory Supplies (Poole, England) and were of AnalaR, or equivalent quality.

2.2. Manufacture of polymeric platforms

Semi-solid platforms were formulated by initially dissolving Hydroxyethylcellulose (HEC, 3% w/w) or Sodium Carboxymethylcellulose (NaCMC, 5% w/w) in the required amount of phosphate buffered saline (PBS, pH 7.2) using a Heidolph mechanical stirrer (2000 rpm). Polycarbophil (PC, 1 and 3% w/w), and, when required Polyvinylpyrrolidone (PVP, 3% w/w), were introduced into the formulation by thorough mixing with a spatula on an ointment slab. Finally, strontium chloride (10% w/w, as the hexahydrate) was mixed into each pre-formulated gel again using a spatula and an ointment slab to ensure homogeneity of the semi-solid systems. Prior to analysis all platforms were stored at 4 °C for 72 h.

2.3. Oscillatory rheological analysis

The viscoelastic properties of all semi-solid systems were investigated at 37 ± 0.1 °C over a frequency range from 0.01-1.00 Hz using a TA systems AR2000 rheometer (TA Instruments, Surrey, England) in association with a 2, 4 or 6 cm parallel plate geometry and a sample gap of 1000 μm as previously reported (Jones, Laverty, & Andrews, 2015). A stress sweep was performed initially to determine the linear viscoelastic region from which the strain values for subsequent analysis were identified (6×10^{-3} and 1×10^{-2} for platforms devoid of and containing strontium chloride, respectively). In all cases, analysis of five replicates was performed. The storage modulus (Gí), loss modulus (Gíí), dynamic viscosity (η') and the loss tangent (tan δ) were then determined using Rheology Advantage software provided by T.A. Instruments, (Surrey, England).

Modelling of the relationship between modulus and frequency was performed using a power law model, as described below:

$$G = kf^n \quad (1)$$

where G′ refers to the storage modulus, k refers to the Gel Strength, f refers to the oscillatory frequency and n is a rheological exponent (Jones, Laverty, Morris, & Andrews, 2016).

2.4. Continuous shear rheology

The flow properties of all formulations were analysed at 37 ± 0.1 °C using a TA systems AR2000 rheometer (TA Instruments, Surrey, England). All samples were analysed using either a 2 or 4 cm parallel plate geometry over the stress range 100–1000 Pa at a fixed gap width of 1000 μm. Samples were subjected to an upward and downward stress sweep with a predefined step time period of 60 s. The relationship between shear stress and shear rate was modelled using the Ostwald-Waele equation, as previously reported by the authors (equation 1) (Jones, Browne, & Woolfson, 1997).

$$\sigma = k\dot{\gamma} \quad (2)$$

Where σ refers to the shear stress (Pa), $\dot{\gamma}$ refers to the shear rate (s^{-1}) and k refers to the consistency (Pa.s^n)

2.5. Texture profile analysis

Formulation hardness, compressibility and adhesiveness were determined using a TA-XT2 Texture Analyser (Stable Micro Systems, Surrey, England) in texture profile analysis mode (Jones, Woolfson, Brown, & O'Neill, 1997; Jones, Woolfson, Djokic, & Coulter, 1996). Formulations (16 g) were packed into McCartney bottles and stored in a vacuum oven for circa 1 h to remove entrapped air. A solid, cylindrical, polycarbonate analytical probe (1 cm diameter, 5 cm length) was then twice depressed into each sample to a defined depth (15 mm), at a defined rate (10 mm s^{-1}), with a defined delay period (15 s), between the beginning of the second and the end of the first compression. Five replicates of each sample were performed at ambient temperature and the formulation hardness (N) and compressibility (N mm) were determined from resultant relationship between force and distance.

2.6. In vitro *assessment of mucoadhesion*

Mucoadhesion testing was conducted using a TA XT2 Texture Analyser in adhesion mode as previously reported by the authors (Jones et al., 2000; Jones, Woolfson, & Brown, 1997). In brief, 400 mg mucin discs were manufactured using a 13 mm IR press using a force of 10 t for a period of one minute. The resultant discs were then attached to the end of a 10 mm diameter polycarbonate probe *via* double-sided adhesive tape. Samples to be analysed were transferred into a circular mould with mucoadhesion being determined at 37 °C. Before testing, the disc was pre-wetted with 5% mucin solution for 1 min, following which any excess was removed *via* blotting. The mucin disc was allowed to contact the sample and a downward force of 0.1N was applied to the gel sample and held for 30 s before being removed at a speed of 10 mm s^{-1}. The resultant detachment force (mucoadhesive bond strength) was measured and the results expressed as the mean ± standard deviation of at least five replicates.

2.7. In vitro *strontium release*

The *in vitro* drug release properties of gel formulations were examined under sink conditions using a Caleva 7ST dissolution apparatus in conjunction with paddle stirrers. In this semi-solid systems (5 g) were loaded into small circular plastic moulds and situated at the bottom of the dissolution tanks, which contained 1 l of Phosphate Buffered Saline (pH 7.4, 37 °C). The release medium was continuously stirred at 50 rpm using paddle stirrers positioned at 25 ± 2 mm from the surface of the samples. Samples were removed at pre-defined intervals and the concentration of strontium ions in solution determined using Atomic Absorption spectroscopy. The calibration curve utilised was linear over the range from 5 to 70 ppm (Abs λ = 460.7 nm). In all cases six replicate measurements were performed.

2.8. *Statistical analysis*

The effect of oscillatory frequency (0.01–1 Hz), concentration of PVP (0–3%w/w) and PC (1–3%w/w), the nature of the base polymer (NaCMC or HEC) and the presence of Strontium Chloride (10%w/w, as the hexahydrate) on the dynamic properties (G′, G″, η′, tan δ) of all formulations were examined using a four-way repeated measures Analysis of Variance (ANOVA). The effects of the above factors on gel consistency, textural properties (hardness, compressibility and adhesiveness) and mucoadhesive bond strength were assessed using a four-way ANOVA. The effects of increasing polymer concentration (PVP (0–3%w/w)), PC (1–3%w/w) and the nature of the base polymer (HEC (3%w/w) or NaCMC (5% w/w)) on the percentage release of Sr^{2+} ions were analysed using a three-way repeated measures ANOVA. Post hoc comparisons of the means of individual factors were performed using Tukey's HSD test. In all analyses, at least five replicates were performed and in all cases, $p < 0.05$ denoted significance (Jones, 2002).

3. Results and discussion

Dentine sensitivity is a widely encountered clinical complaint which occurs upon exposure to non-noxious stimuli (Mantzourani & Sharma, 2013; West et al., 2015). Typically, this condition may be a result of exposure of the tooth root surface following periodontal surgery or gingival recession. Moreover, dentine sensitivity may occur following severe abrasion and subsequently exposure of dentine (Sehmi & Olley, 2015). Strontium chloride has been widely used for the treatment of dentine sensitivity and has been reported to function in two ways, firstly, as a protein precipitate and, secondly, to occlude dentinal tubules (Mantzourani & Sharma, 2013; West et al., 2015). Although several types of mouthwashes and dentifrices have been employed in the delivery of this desensitising agent, there are issues regarding the retention of the dosage form at the tooth surface. Topically applied mucoadhesive platforms are an ideal method of treating dentine sensitivity due to their ability to adhere to the tooth for extended periods of time, to control the delivery of desensitising agents and hence to improve clinical efficacy. The use of mucoadhesive platforms within the oral cavity has been previously reported in several studies. For example, Jones et al. reported the successful clinical use of mucoadhesive platforms for the treatment of periodontal disease and gingivitis (Jones et al., 1999, 2000) whereas Castan et al. described the formulation and characterisation of buccal bioadhesive films (composed of sodium carboxymethylcellulose and chitosan) containing doxepin designed for the treatment of odontalgia (Castan, Ruiz, Clares, & Morales, 2015). Other studies that have described the use of mucoadhesive platforms include hot melt extruded films of poly(ethylene oxide) and hydroxypropylmethylcelluose for the enhanced bioavailability of domperidone (Palem, Dudhipala, Battu, Repka, & Yamsani, 2016), hydroxypropylcellulose and poly(ethylene oxide) hot melt extruded films containing miconazole for the treatment of oral candidiasis (Chen et al., 2014) and mucoadhesive gel-forming psyllium patches containing chlorhexidine designed for the treatment of infection within the oral cavity (Cavallari, Brigidi, & Fini, 2015). However, this current study is one of the first studies that has specifically described the design of therapeutic platforms for the treatment of abnormal tooth pathologies and/or has employed mucoadhesion to the tooth surface for the successful delivery of therapeutic agents. Furthermore, the methods used to characterise these platforms have provided a comprehensive description of their physicochemical properties; properties that are relevant to their *in vivo* performance (Jones et al., 1999, 2000).

3.1. *Oscillatory rheological analysis*

The frequency dependence of the storage modulus, loss modulus, loss tangent and the dynamic viscosity for all platforms containing 5% w/w NaCMC or HEC (3% w/w) and various concentrations of PVP, PC and strontium chloride are shown in Fig. 1/Tables 1 and 2, respectively. Increasing the oscillatory frequency significantly increased the storage moduli and loss moduli of all platforms. Conversely the dynamic viscosity significantly decreased as a function of increasing oscillatory frequency. Furthermore, platforms containing 5% w/w NaCMC exhibited loss tangent values that were significantly increased as a function of frequency, whereas in the HEC-containing systems the loss tangent decreased as a function of increasing oscillatory frequency. In general, the storage modulus of each platform exceeded the loss modulus across the entire frequency range (*i.e.* loss tangent (tan δ) < 1) and is indicative of the behaviour of viscoelastic gel systems (Jones, Brown, & Woolfson, 2001; Winter & Chambon, 1986). The range of oscillatory frequencies examined in this manuscript is similar to those that exist within the oral cavity (Chu, Chandrasekharan, Amidon, Weiner, & Goldberg, 1991; Stanley & Taylor, 1993) and therefore, it may be assumed that the polymeric platforms described in this study will exhibit predominantly elastic properties in clinical use.

The effects of increasing polymer concentration (PC and PVP) and the addition of strontium chloride on the dynamic properties of NaCMC-based platforms are shown in Fig. 1 and Table 1, whereas these effects on the dynamic properties of HEC-based platforms are described in Table 2. Typically, increasing the concentration of PC from 1 to 3% and/or PVP from 0 to 3% w/w/w significantly increased the storage modulus, loss modulus and the dynamic viscosity in both NaCMC-based and HEC-based platforms. In accordance with previous publications, the observed changes to

Table 1
The effects of concentrations of poly(vinylpyrrolidone, PVP), polycarbophil and strontium chloride and oscillatory frequency on the loss modulus (G″), loss tangent (tan δ) and dynamic viscosity (η') of candidate platforms containing NaCMC (5% w/w).

Concentration of components (% w/w)			Oscillatory Frequency (Hz)	Mean (±standard deviation) Viscoelastic Parameters		
PVP	Polycarbophil	Strontium Chloride		G″ (Pa)	tan δ	η′ (Pa.s)
0	1	0	0.114	170.7 ± 6.1	>1	238.5 ± 9.5
0	1	0	0.531	278.4 ± 10.0	0.41 ± 0.01	82.8 ± 5.0
0	1	0	0.948	333.0 ± 16.5	0.42 ± 0.02	55.2 ± 1.8
0	1	10	0.114	148.8 ± 5.9	0.37 ± 0.01	206.4 ± 9.4
0	1	10	0.531	242.8 ± 13.6	0.42 ± 0.01	71.9 ± 3.5
0	1	10	0.948	290.3 ± 13.8	0.43 ± 0.01	48.3 ± 1.9
0	3	0	0.114	255.5 ± 8.3	0.33 ± 0.01	351.1 ± 12.8
0	3	0	0.531	386.7 ± 21.2	0.36 ± 0.00	115.5 ± 6.0
0	3	0	0.948	449.9 ± 17.8	0.37 ± 0.01	75.7 ± 3.4
0	3	10	0.114	182.6 ± 9.0	0.34 ± 0.01	251.9 ± 10.0
0	3	10	0.531	302.3 ± 12.2	0.40 ± 0.01	90.0 ± 3.8
0	3	10	0.948	365.9 ± 11.8	0.42 ± 0.02	60.4 ± 3.5
3	1	0	0.114	269.8 ± 9.3	0.37 ± 0.01	374.1 ± 13.9
3	1	0	0.531	436.3 ± 18.4	0.38 ± 0.02	129.6 ± 6.2
3	1	0	0.948	526.5 ± 20.0	0.36 ± 0.01	87.8 ± 4.8
3	1	10	0.114	224.1 ± 7.2	0.36 ± 0.00	310.9 ± 14.2
3	1	10	0.531	313.8 ± 11.2	0.41 ± 0.02	92.2 ± 5.9
3	1	10	0.948	355.6 ± 17.1	0.41 ± 0.02	59.6 ± 2.9
3	3	0	0.114	327.4 ± 12.9	0.36 ± 0.00	454.8 ± 17.3
3	3	0	0.531	510.4 ± 16.2	0.38 ± 0.01	155.1 ± 7.1
3	3	0	0.948	602.7 ± 19.5	0.38 ± 0.02	100.4 ± 3.1
3	3	10	0.114	304.7 ± 14.9	0.41 ± 0.01	419.8 ± 21.4
3	3	10	0.531	474.9 ± 18.5	0.43 ± 0.02	141.1 ± 5.0
3	3	10	0.948	562.6 ± 18.9	0.43 ± 0.02	91.3 ± 4.3

Table 2
The effects of concentrations of poly(vinylpyrrolidone, PVP), polycarbophil and strontium chloride ($SrCl_2$) and oscillatory frequency on the storage modulus (G′), loss modulus (G″), loss tangent (tan δ) and dynamic viscosity (η′) of candidate platforms containing HEC.

Concentration of components (% w/w)			Oscillatory Frequency (Hz)	Mean (±standard deviation) Viscoelastic Parameters			
PVP	Polycarbophil	$SrCl_2$		G'(kPa)	G″ (Pa)	tan δ	η′ (Pa.s)
0	1	0	0.114	0.58 ± 0.02	259.7 ± 9.0	0.45 ± 0.02	358.1 ± 20.1
0	1	0	0.531	0.86 ± 0.03	320.6 ± 17.8	0.37 ± 0.01	97.2 ± 7.8
0	1	0	0.948	1.00 ± 0.03	339.2 ± 16.4	0.34 ± 0.01	56.8 ± 2.9
0	1	10	0.114	0.17 ± 0.00	109.8 ± 6.8	0.65 ± 0.03	153.4 ± 8.2
0	1	10	0.531	0.31 ± 0.01	159.6 ± 5.9	0.52 ± 0.02	47.6 ± 2.9
0	1	10	0.948	0.37 ± 0.01	175.9 ± 9.2	0.48 ± 0.02	29.4 ± 1.4
0	3	0	0.114	1.09 ± 0.04	445.9 ± 13.0	0.41 ± 0.02	619.1 ± 26.3
0	3	0	0.531	1.35 ± 0.05	490.7 ± 19.2	0.36 ± 0.01	147.8 ± 8.0
0	3	0	0.948	1.47 ± 0.05	504.4 ± 21.6	0.34 ± 0.01	85.1 ± 4.6
0	3	10	0.114	0.20 ± 0.01	112.8 ± 8.1	0.57 ± 0.02	156.2 ± 7.2
0	3	10	0.531	0.33 ± 0.01	160.5 ± 7.8	0.48 ± 0.02	48.0 ± 2.1
0	3	10	0.948	0.04 ± 0.02	178.8 ± 8.9	0.45 ± 0.02	29.8 ± 1.2
3	1	0	0.114	0.68 ± 0.03	277.0 ± 9.3	0.41 ± 0.02	382.9 ± 16.8
3	1	0	0.531	1.03 ± 0.04	378.4 ± 19.0	0.37 ± 0.01	113.5 ± 6.8
3	1	0	0.948	1.37 ± 0.06	418.9 ± 22.6	0.31 ± 0.02	69.9 ± 2.7
3	1	10	0.114	0.30 ± 0.01	210.4 ± 12.8	0.71 ± 0.03	293.6 ± 11.8
3	1	10	0.531	0.57 ± 0.03	295.3 ± 16.3	0.52 ± 0.02	89.2 ± 6.1
3	1	10	0.948	0.70 ± 0.03	327.6 ± 17.1	0.47 ± 0.02	55.3 ± 2.8
3	3	0	0.114	1.68 ± 0.07	570.8 ± 26.3	0.34 ± 0.01	790.3 ± 28.9
3	3	0	0.531	2.49 ± 0.10	814.1 ± 46.8	0.33 ± 0.01	247.0 ± 12.9
3	3	0	0.948	2.95 ± 0.11	930.2 ± 38.8	0.32 ± 0.01	154.6 ± 6.8
3	3	10	0.114	0.21 ± 0.01	334.0 ± 14.6	0.62 ± 0.03	465.9 ± 20.8
3	3	10	0.531	0.98 ± 0.04	478.3 ± 21.9	0.49 ± 0.02	144.7 ± 7.2
3	3	10	0.948	1.21 ± 0.05	529.4 ± 21.0	0.44 ± 0.02	90.2 ± 5.8

the viscoelastic properties of the platforms may be accredited to enhanced polymer–polymer interactions (Jones et al., 2001; Liu, Yu, & Zhou, 2013). Statistically, an interaction between the concentrations of PC and PVP was observed within the ANOVA. In this increasing the concentration of PC from 1 to 3% had a statistically greater effect on the modulus of platforms containing 3% w/w PVP than in those platforms devoid of PVP. In platforms containing NaCMC/PVP and in those containing HEC/PVP, these polymers were dissolved in the vehicle and thus, in these the mass of available vehicle for interaction with the other components (PC and strontium chloride) was reduced in comparison to platforms devoid of PVP. These observed differences are due, in part, to differences in inter-polymer interactions leading to differences in network properties (Chun, Cho, & Choi, 2002; Jones, Lawlor, & Woolfson, 2002). The enhanced effect of adding PC into the binary platforms on the observed viscoelastic properties is accordingly due to the physical dispersion of this polymer in a swelling-inhibited state. In the presence of mono-polymeric platforms (NaCMC or HEC), PC may undergo a greater degree of swelling and, whilst this will enhance the modulus of this system, the extent of this enhancement in modulus is less than for the binary (NaCMC/PVP) platforms. Therefore, the effects of physically dispersing PC on the overall modulus of the platforms was greater than in platforms whenever PC was swollen.

Table 3
The effects of strontium on the dynamic (oscillatory) properties of polymeric platforms.

Concentration of Components (% w/w)				Oscillatory Frequency (Hz)	Mean (±standard deviation) Viscoelastic Parameters			
NaCMC	HEC	PVP	Strontium Chloride		Storage Modulus (Pa)	Loss Modulus (Pa)	Loss tangent	Dynamic Viscosity (Pa.s)
0	3	0	0	0.114	149.1 ± 6.9	128.6 ± 6.1	0.86 ± 0.04	179.3 ± 8.0
0	3	0	0	0.530	307.1 ± 12.1	199.2 ± 8.2	0.65 ± 0.02	60.2 ± 3.2
0	3	0	0	0.948	385.5 ± 12.8	223.1 ± 9.6	0.58 ± 0.02	37.7 ± 1.9
0	3	0	10	0.114	157.4 ± 6.2	134.2 ± 6.5	0.80 ± 0.03	186.7 ± 8.4
0	3	0	10	0.530	318.0 ± 13.2	184.3 ± 8.3	0.58 ± 0.02	55.4 ± 3.4
0	3	0	10	0.948	383.4 ± 13.9	195.3 ± 7.9	0.51 ± 0.02	32.7 ± 1.7
5	0	0	0	0.114	162.2 ± 5.0	85.7 ± 3.9	0.53 ± 0.03	118.5 ± 6.0
5	0	0	0	0.530	262.7 ± 11.3	153.8 ± 7.3	0.58 ±0.03	45.7 ± 1.8
5	0	0	0	0.948	320.3 ± 14.3	192.0 ± 7.2	0.60 ± 0.03	32.1 ± 1.4
5	0	0	10	0.114	98.4 ± 6.9	78.5 ± 4.1	0.79 ± 0.03	108.8 ± 6.1
5	0	0	10	0.530	191.8 ± 8.3	158.8 ± 6.7	0.83 ± 0.03	47.8 ± 1.8
5	0	0	10	0.948	252.1 ± 12.1	202.6 ± 8.9	0.81 ± 0.04	34.1 ± 1.3
5	0	3	10	0.114	209.5 ± 11.0	117.1 ± 5.2	0.56 ± 0.02	163.6 ± 7.5
5	0	3	10	0.530	350.0 ± 13.7	175.1 ± 8.6	0.50 ± 0.02	52.5 ± 2.8
5	0	3	10	0.948	418.4 ± 14.0	199.2 ± 8.8	0.48 ± 0.02	33.4 ± 1.2

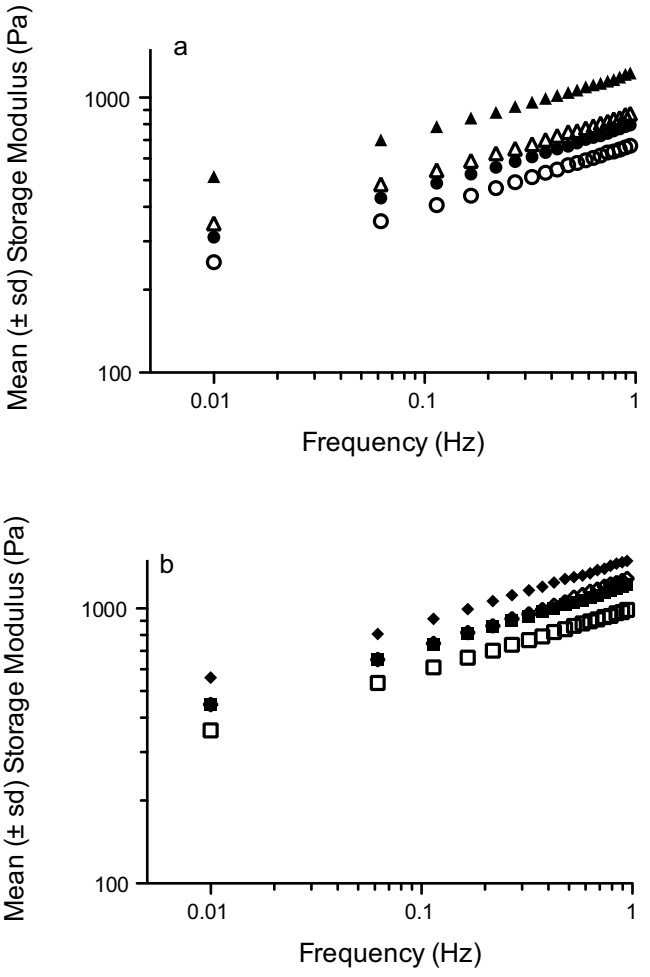

Fig. 1. The effects of polycarbophil (1, 3% w/w, PC), polyvinylpyrrolidone (0, 3% w/w, PVP) and Strontium Chloride (0, 10% w/w, SC) on the storage modulus of platforms composed of sodium carboxymethylcellulose (5% w/w). Standard deviation values (from 5 replicates) are not included for clarity however the coefficient of variation was less than 0.05 in all cases. Symbols: Closed and Open symbols refer to platforms devoid of and containing strontium chloride, respectively.
In Fig. 1a, circles refer to platforms containing 5% w/w NaCMC and 1% w/w PC whereas triangles refer to platforms containing 5% w/w NaCMC and 3% w/w PC.
In Fig. 1b, squares refer to platforms containing 5% w/w NaCMC, 3% w/w PVP and 1% w/w PC whereas diamonds refer to platforms containing 5% w/w NaCMC, 3% w/w PVP and 3% w/w PC.

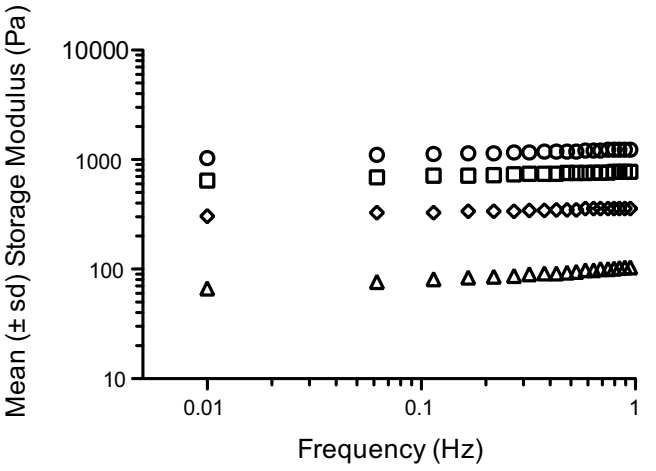

Fig. 2. The effects of molar ratio of strontium to polycarbophil on the storage modulus of binary platforms containing 10% w/w strontium chloride. Standard deviation values (from five replicates) are displayed. Symbols: circles refer to platforms with a molar ratio of Strontium Chloride: Polycarbophil of 0:1, squares refer to platforms with a molar ratio of Strontium Chloride: Polycarbophil of 0.01:1, squares refer to platforms with a molar ratio of Strontium Chloride: Polycarbophil of 0.1:1, triangles refer to platforms with a molar ratio of Strontium Chloride: Polycarbophil of 0.5:1.

Strontium chloride has been previously reported to display desensitising effects at a concentration of 10% w/w (Uchida, Wakano, Fukuyama, Miki, Iwayama, & Okada, 1980; West et al., 2015). Interestingly, the addition of 10% w/w strontium chloride to all formulations significantly decreased the storage modulus, loss modulus and the dynamic viscosity and increased the loss tangent. Clarifications of the interactions of strontium ions with NaCMC and PC are shown in Fig. 2 and Table 3. Incorporation of strontium chloride into PC gels significantly reduced the resultant modulus, the effect being enhanced as the ratio of Sr^{2+}: PC increased (Fig. 2).

In a similar fashion, the viscoelastic properties of NaCMC gels were compromised by the presence of strontium ions (10% w/w strontium chloride), confirming the interaction of strontium ions with NaCMC and the subsequent reduction in the expanded state of this polymer (Table 3). The inclusion of PVP (3%) suppressed the detrimental effects of strontium on the rheological properties of NaCMC platforms; this being attributed to both the modulus-enhancing effects of PVP on the rheological properties of NaCMC and a reduction in the interaction of Sr^{2+} with NaCMC due to competition from PVP. PVP has been previously reported to interact with

Table 4
The effects of concentrations of poly(vinylpyrrolidone), polycarbophil and strontium chloride on the gel strength, and consistency of candidate platforms containing either sodium carboxymethylcellulose (5% w/w, NaCMC) or hydroxyethylcellulose (3% w/w, HEC).

Concentration of Components (% w/w)					Mean (±standard deviation) Rheological Parameters	
NaCMC	HEC	Polyvinylpyrrolidone	Polycarbophil	Strontium Chloride	Gel Strength (kPa)[a]	Consistency (Pa s^n)[b]
5	0	0	1	0	0.80 ± 0.03	465.0 ± 18.1
5	0	0	1	10	0.67 ± 0.03	402.7 ± 16.1
5	0	0	3	0	1.22 ± 0.05	597.2 ± 25.1
5	0	0	3	10	0.87 ± 0.04	488.2 ± 21.8
5	0	3	1	0	1.38 ± 0.05	663.4 ± 28.7
5	0	3	1	10	1.00 ± 0.04	571.8 ± 16.1
5	0	3	3	0	1.50 ± 0.06	962.4 ± 32.9
5	0	3	3	10	1.29 ± 0.05	755.8 ± 28.7
0	3	0	1	0	1.01 ± 0.04	540.1 ± 31.2
0	3	0	1	10	0.38 ± 0.02	259.1 ± 19.2
0	3	0	3	0	1.51 ± 0.07	782.5 ± 31.0
0	3	0	3	10	0.41 ± 0.02	335.8 ± 16.9
0	3	3	1	0	1.36 ± 0.06	643.3 ± 28.2
0	3	3	1	10	0.73 ± 0.03	381.1 ± 17,2
0	3	3	3	0	2.88 ± 0.12	1377.3 ± 52.8
0	3	3	3	10	1.27 ± 0.08	593.4 ± 30.1

[a] Determined from Oscillatory Analysis using the power law model.
[b] Determined from flow rheometry using the Ostwald de Waele equation.

a range of hydrophilic polymers, including cellulose derivatives (Chun et al., 2002; Hao, Chan, Shen, & Heng, 2004; Jones et al., 2002; Mayo_Pedrosa, Alvarez-Lorenzo, & Conchiero, 2004). As expected, strontium chloride (10% w/w) did not affect the dynamic rheological properties of HEC. The incorporation of strontium chloride into binary and ternary polymeric platforms containing HEC exhibited significantly reduced storage and loss moduli and dynamic viscosities in comparison to the strontium-devoid systems. This effect is accredited to the directed interaction of Sr^{2+} with PC and the effects of this interaction on polymer chain expansion and particle aggregation.

3.2. Gel strength, compressional and flow rheological properties

The mechanical and flow rheological properties of implants for the oral cavity are important determinants on clinical performance, directly affecting the ease of administration to the oral cavity and the subsequent rheological structure following recovery from the applied stresses. The effects of PVP, PC and strontium chloride on the gel strength (derived using equation 1 from the data generated from oscillatory analysis), compressional (hardness and compressibility) and flow properties of the various polymeric platforms are presented in Tables 4 and 5. Increasing PC and PVP concentrations significantly increased gel strength and consistency. The rheological exponents of all platforms were similar and approached 0, indicative of pseudoplastic flow. Conversely, the presence of strontium chloride significantly decreased the gel strength, consistency, hardness and compressibility of both platform types (HEC and NaCMC). Akin to their dynamic properties, the effect of strontium chloride on the reductions in the aforementioned mechanical and rheological parameters were greater for platforms based on HEC than those based on NaCMC, this disparity accounting for a statistical interaction in the ANOVA. Modification in the various polymeric parameters generated biomaterial platforms that exhibited wide ranges of hardness, compressibility, gel strength and flow properties. The observed properties may be accredited to a number of phenomenon, including increased polymer–polymer interactions between HEC or NaCMC and PVP and PC and, given its cross-linked nature, the (swollen) state of dispersed PC within the platforms.

3.3. Conceiving the effects of strontium on the viscoelastic, rheological and mechanical properties

From the rheological and mechanical data, the effects of strontium ions on the binary and ternary polymeric platforms may be conceived. The concentrations of the base polymers were chosen to ensure broad similarity of their rheological properties. Previously (Fig. 2 and Table 3), it was previously shown that the presence of strontium ions significantly compromised the viscoelastic properties of monopolymeric NaCMC but not monopolymeric HEC platforms. Given the anionic nature of NaCMC and the cationic nature of strontium ions, these rheological observations may be attributed to shielding of the charge on the polymer chains by strontium, with the associated negative effects on polymer–polymer interactions and chain expansion. Addition of PC, an anionic polymer significantly increased the rheological and mechanical properties, with HEC based systems exhibiting greater elasticity, due to a greater interaction of this polymer with PC. Addition of strontium ions to these binary polymeric systems, significantly reduced the viscoelastic, rheological and mechanical properties. For HEC-based systems, the reduction in these properties is resultant from the interaction of strontium ions with PC, resulting in reduced polymer chain expansion, aggregation of PC particles and disruption of interactions between HEC and PC. PC enhanced the rheological structure of NaCMC gels but not to the same degree as with HEC. Accordingly, it may be assumed that there is both more limited interaction between the two polymers, as reported previously (Jones et al., 2001). In the presence of strontium ions it is proposed that there is preferential interaction of Sr^{2+} with NaCMC due to its availability in a swollen state and thus, whilst there is a reduction in the viscoelastic, rheological and mechanical properties, this is more limited than for the comparator HEC-based system in which Sr^{2+} exclusively interacts with PC. In ternary systems, the inclusion of PVP enhanced the aforementioned properties of NaCMC/PC and HEC/PC platforms, again due to its interactions with NaCMC and HEC. The inclusion of strontium into these systems had a greater detrimental effect on the properties of HEC-based systems than NaCMC-based systems. This effect is particularly manifest in the presence of 3% PVP and 3% PC. In this the extent of the interaction of PVP with HEC is greater than when 1% w/w PVP is used. The extent of interaction of HEC with PC is reduced and therefore

Table 5
The effects of concentrations of poly(vinylpyrrolidone, PVP), polycarbophil and strontium chloride on the hardness, compressibility, adhesiveness and mucoadhesion of candidate platforms designed for the treatment of dentine hypersensitivity.

Concentration of components (% w/w)				Mean (±standard deviation) of measured parameters:			
NaCMC (5% w/w) or HEC (3% w/w)	Polyvinylpyrrolidone	Polycarbophil	Strontium Chloride	Hardness (N)	Adhesiveness (N.mm)	Compressibility (N.mm)	Mucoadhesive Bond Strength (N)
NaCMC	0	1	0	0.60 ± 0.02	3.13 ± 0.08	6.08 ± 0.12	0.13 ± 0.01
NaCMC	0	1	10	0.51 ± 0.04	2.71 ± 0.08	5.17 ± 0.35	0.11 ± 0.01
NaCMC	0	3	0	0.91 ± 0.04	3.50 ± 0.27	8.06 ± 0.09	0.22 ± 0.01
NaCMC	0	3	10	0.76 ± 0.01	2.95 ± 0.09	6.14 ± 0.07	0.14 ± 0.01
NaCMC	3	1	0	0.87 ± 0.03	5.10 ± 0.03	7.41 ± 0.36	0.15 ± 0.01
NaCMC	3	1	10	0.78 ± 0.03	4.46 ± 0.11	6.70 ± 0.18	0.14 ± 0.01
NaCMC	3	3	0	1.19 ± 0.16	9.95 ± 0.11	20.58 ± 0.17	0.25 ± 0.01
NaCMC	3	3	10	0.98 ± 0.02	7.76 ± 0.10	9.82 ± 0.35	0.17 ± 0.01
HEC	0	1	0	0.71 ± 0.09	3.54 ± 0.75	6.55 ± 0.34	0.15 ± 0.01
HEC	0	1	10	0.43 ± 0.02	2.32 ± 0.16	3.57 ± 0.14	0.08 ± 0.01
HEC	0	3	0	1.23 ± 0.25	3.82 ± 0.05	12.45 ± 0.49	0.21 ± 0.01
HEC	0	3	10	0.55 ± 0.08	2.54 ± 0.85	4.46 ± 0.86	0.13 ± 0.01
HEC	3	1	0	0.91 ± 0.03	5.97 ± 0.23	8.38 ± 0.28	0.19 ± 0.01
HEC	3	1	10	0.74 ± 0.02	4.12 ± 0.18	6.08 ± 0.12	0.15 ± 0.01
HEC	3	3	0	2.28 ± 0.05	18.30 ± 1.27	16.76 ± 0.94	0.24 ± 0.02
HEC	3	3	10	0.92 ± 0.03	7.44 ± 0.11	9.32 ± 0.10	0.18 ± 0.01

there is a greater capacity for strontium ions to interact with PC and to inhibit polymer chain expansion and promote PC aggregation. The lesser effects of strontium ions on the viscoelastic, rheological and mechanical properties of NaCMC/PVP/PC ternary platforms are due to the proportionally greater interaction of strontium with NaCMC, thereby reducing the deleterious interactions of this ion with polycarbophil.

3.4. Adhesiveness and mucoadhesive properties

Mucoadhesive platforms have been successfully used for the improved treatment of disorders of the oral cavity, notably infection, inflammation, oral cancer and pain. For example, Tonglairoum et al. described the use of chitosan-coated poly(vinylpyrrolidone)/cyclodextrin sandwiches containing clotrimazole for the treatment of oral candidiasis (Tonglairoum et al., 2015) whereas a study by Abdelbary et al. reported the use of a proniosomal, mucoadhesive gel containing lornoxicam for the treatment of dental pain (Abdelbary & Aburahma, 2015). The platforms described in this study have been designed to offer simultaneous prolonged retention on the surface of the tooth and controlled delivery of strontium to enhance the treatment of dentine hypersensitivity. The adhesive properties of the platforms were measured using texture profile analysis (adhesiveness) and the force required to overcome the polymeric platform/mucin bond following application of a linear, vertical force (Table 5). A wide range of adhesiveness and mucoadhesive properties (the latter defined as the mucoadhesive bond strength) were exhibited and, akin to their effects on the mechanical and rheological properties, were dependent on the concentrations of PC and PVP and the nature of the base polymer (HEC or NaCMC). The presence of strontium chloride significantly decreased both the adhesiveness and the mucoadhesive properties. The two parameters measured have been reported to be relevant to the *in vitro* performance of platforms designed for application to and retention within the oral cavity (Jones et al., 1999, 2000). Both methods measure the interaction of the platforms with a substrate (and the force/work required to overcome this interaction) and there is a strong correlation between the results obtained from these two methods ($r > 0.9$). However, the use of the two methods has particular relevance for this study given the nature of the site of application. In the native state the tooth surface is hydrophobic, however, this is clinically modified by the presence of mucin (Lund, 2015; Tiznado-Orozco et al., 2015). The methods used to assess the adhesive properties therefore reflect adhesion to a hydrophobic surface (adhesiveness) and to a mucin-coated surface (mucoadhesion). In combination the data provided from both methods provide a comprehensive description of both the adhesive properties and offer an insight into the *in vivo* behaviour of these platforms (notably as a function of salivary content within the oral cavity). In related studies (Jones et al., 1999, 2000) the relationship between both the adhesiveness and mucoadhesion and retention were noted. The adhesive properties exhibited by the strontium-containing platforms described in this study, despite being lower than their strontium-devoid counterparts, were comparable to those reported to offer retention at the site of administration within the oral cavity and, accordingly, the current HEC-based or NaCMC-based platforms would be expected to behave similarly within a clinical environment.

3.5. Strontium release from the polymeric platforms

Prior to consideration of strontium release from the various platforms, it is appropriate to comment on the conditions employed to characterise the strontium release *in vitro*. Ideally the conditions employed *in vitro* should attempt to represent the clinical environment and therefore, it may be possible to predict possible clinical performance of the platforms. However, to date, a model does not exist that predicts *in vivo* bioactive release within the oral cavity based on *in vitro* release data. The particular application described in this manuscript presents particular methodological challenges. The platform is applied directly to the tooth surface and therefore the release of the bioactive agent will occur directly to the required site. Biologically, the release of the active agent will be facilitated by diffusion of salivary fluids/other liquids into the dosage form and diffusion of the bioactive agent into the aqueous interface between tooth surface and bioactive platform. The low fluid volume at the interface between the platform and the tooth surface, the relatively low (and variable) volume of saliva produced daily and the consumption of liquids during the day all add to the complexity of relating *in vitro* to *in vivo* strontium release. Accordingly, in this study strontium release from the platforms was studied under sink conditions (Wang, Abrahamsson, Lindfors, & Brasseur, 2015), thereby allowing the mechanism of drug release from the platform to be characterised (Ritger & Peppas, 1987). The pH of the buffer was aligned to that of saliva from healthy patients (Buzalaf, Hannas, & Kato, 2012).

Key to the success of the proposed implantable platforms is the controlled release of strontium following application to the

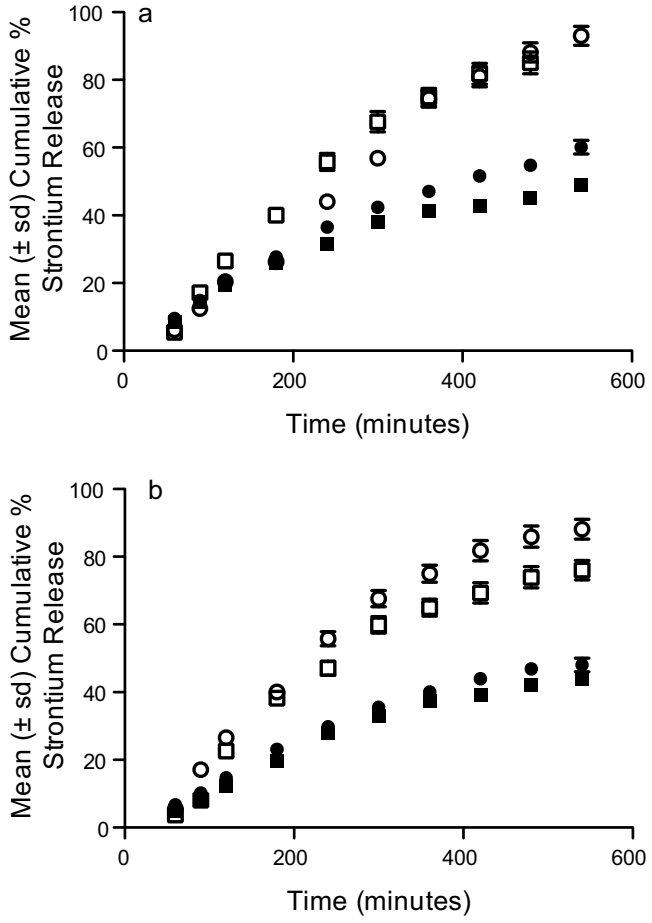

Fig. 3. The effect of polymeric composition on the release of strontium from the polymeric platforms containing 10% w/w strontium chloride.
In Fig. 3a closed circles refer to platforms containing NaCMC (5% w/w) and 1% w/w PC, closed squares refer to platforms containing NaCMC (5% w/w) and 3% w/w PC, open circles refer to platforms containing HEC (3% w/w) and 1% w/w PC and open squares refer to platforms containing HEC (3% w/w) and 3% w/w PC
In Fig. 3b closed circles refer to platforms containing NaCMC (5% w/w), 3% PVP and 1% w/w PC, closed squares refer to platforms containing NaCMC (5% w/w), 3% w/w PVP and 3% w/w PC, open circles refer to platforms containing HEC (3% w/w), 3% w/w PVP and 1% w/w polycarbophil and open squares refer to platforms containing HEC (3% w/w), 3% w/w PVP and 3% w/w polycarbophil

tooth surface. When combined with the prolonged period of retention offered by the mucoadhesive platforms, controlled delivery of strontium to the dentinal tubules will enhance efficacy and will increase the times between successive applications. Strontium release from the various platforms are presented in Fig. 3a and b. Modelling of the release kinetics of strontium from the platforms using a power-law method (Peppas, 1985) revealed release exponents that were statistically similar to 1 for HEC-based systems and *circa* 0.9 for the NaCMC-based counterparts. In effect the systems offered zero-order release of strontium, the swelling properties and erosion of the hydrophilic platforms being similar thereby providing a constant diffusion gradient of strontium from the polymeric platform into the dissolution fluid. The release of strontium from the various platforms was therefore more dependent on swelling/erosion than on diffusion (Peppas & Sahlin, 1989). In platforms containing NaCMC, increasing PC concentration decreased the rate of release. In HEC-based systems, the effect of PC on the release of strontium was significant only in the presence of PVP. These results illustrate the wide range of release rates that may be engineered from these platforms. The faster release rates associated with HEC-based platforms than from their NaCMC-based counterparts correlate with their lower elasticity (storage modulus, gel strength). A correlation was observed between the elasticity/gel strength and the observed release rates. For example, increasing the PC concentration from 1 to 3% w/w in strontium chloride containing HEC-based platforms was associated with a modest increase in elasticity and statistically similar release kinetics. Conversely, as the elasticity of NaCMC platforms was elevated by increasing the PC concentration from 1 to 3% w/w, there was an associated reduction in the release kinetics.

4. Conclusions

This study describes the design and physicochemical properties of strontium-containing, mucoadhesive polymeric platforms designed for the enhanced treatment of dentine hypersensitivity. Polymeric networks were designed composed of NaCMC or HEC, PC and, optionally PVP and 10% w/w strontium chloride. Increasing polymer concentration significantly increased elasticity, dynamic viscosity, gel strength, hardness, compressibility, adhesiveness and mucoadhesion. All platforms exhibited pseudoplastic flow. Incorporation of strontium chloride decreased the magnitude of the aforementioned parameters, due to the interaction of strontium ions with the anionic polymeric component(s). The release of strontium from the NaCMC-based and HEC-based platforms was essentially zero-order, the release from Na-CMC platforms being slower than from their HEC-based counterparts. The relevance of the methods used to characterise the polymeric platforms to clinical performance allows the preferable candidates for potential clinical evaluation to be identified. The preferred packaging for these platforms is the standard ointment tube, thus allowing platforms with a wide range of hardness and compressibility to be administered. Without an obvious restriction on the flow properties of the platforms from the packaging, platforms may be selected that offer high elasticity, adhesiveness and mucoadhesion. Furthermore, the choice of NaCMC as the base-polymer is more appropriate given the greater resistance to strontium-associated reductions in the rheological properties and is more clinically appropriate given the combination of enhanced mucoadhesive and strontium-controlled release properties. In this respect, it is suggested that NaCMC-based platforms containing 10% strontium chloride, PVP (3% w/w) and PC (3% w/w) will offer particular promise in this regard and serve as a novel strategy for the treatment of dentine hypersensitivity by means of the simultaneous prolonged retention at the tooth surface and hence blockage of fluid flow and strontium delivery to the dentinal tubules.

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