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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.