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Physical characterisation and component release of poly(vinyl alcohol)–tetrahydroxyborate hydrogels and their applicability as potential topical drug delivery systems

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ABSTRACT

Poly(vinyl alcohol)–tetrahydroxyborate (PVA–THB) hydrogels are dilatant formulations with potential for topical wound management. To support this contention, the physical properties, rheological behaviour and component release of candidate formulations were investigated. Oscillatory rheometry and texture profile analysis were used at room temperature and 37 °C. Results showed that it was possible to control the rheological and textural properties by altering component concentration and modifying the type of PVA polymer used. Hydrogels made using PVA grades with higher degrees of hydrolysis displayed favourable characteristics from a wound healing perspective. *In vitro* release of borate and PVA were assessed in order to evaluate potential clinical dosing of free species originating from the hydrogel structure. Component diffusion was influenced by both concentration and molecular weight, where relevant, with up to 5% free PVA cumulative release observed after 30 min. The results of this study demonstrated the importance of poly(vinyl alcohol) selection for ensuring appropriate gel formation in PVA–THB hydrogels. The benefits of higher degrees of hydrolysis, in particular, included lower excipient release and reduced bioadhesion. The unique physical characteristics of these hydrogels make them an appealing delivery vehicle for chronic and acute wound management purposes.

1. Introduction

Acute laceration and chronic ulceration are traumatic sites of impairment to the normal barrier function and structure of skin. Excellent accessibility means that localised drug delivery intended to alleviate pain and improve wound healing are relatively straightforward. Typical drug candidates include local anaesthetics, antibiotics and growth factors. Despite obvious advantages of the topical drug delivery approach within wound management, proprietary formulations are lacking. For example, local anaesthesia of lacerations is rarely induced topically, with infiltration being the established method (Capellan and Hollander, 2003; Singer and Dagum, 2008).

An effective topical formulation for wound management must accommodate the irregularities of the site and achieve intimate contact with exposed tissue. The ideal formulation should be sufficiently fluid in nature to fill the shape of the wound and have sufficient cohesive properties to allow it to be removed intact. In practice, few pharmaceutical materials display these attributes. Chemically cross-linked gels generally display good elasticity and sufficient cohesive integrity, but do not flow appreciably into the wound bed. In contrast, physically bonded gels, while displaying the necessary flow, have poor cohesive integrity and are difficult to remove unless washed or cleaned away.

Hydrogels are of particular interest in wound management because of their low toxicity and potential for extended drug release (Nanjawade et al., 2007; Peppas et al., 2000a,b, 2006). In addition, many hydrogels act to absorb wound exudate preventing maceration in cases where this is excessive, or can hydrate wounds that are otherwise dry, maintaining a moist wound environment. Control of wound exudate is accepted as an important aspect of overall wound management. One promising family of hydrogels are those based on poly(vinyl alcohol) (PVA), complexed with one of a range of cross-linkers, such as tetrahydroxyborate (THB) anions (Beltman and Lyklema, 1974; Eliseev et al., 2000; Roy et al., 1957; Shibayama et al., 1993). Complexation of PVA with THB anions at sufficient

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Nomenclature

PVA	poly(vinyl alcohol)
THB	tetrahydroxyborate anion
G'	storage modulus
G''	loss modulus
13–23;	98 PVA poly(vinyl alcohol), average molecular weight 13,000–23,000; degree of hydrolysis 98%
31–50;	88 PVA poly(vinyl alcohol), average molecular weight 31,000–50,000, degree of hydrolysis 88%
31–50;	98 PVA poly(vinyl alcohol), average molecular weight 31,000–50,000, degree of hydrolysis 98%
M_W	average molecular weight

concentration leads to hydrogel formation, a process studied by a number of groups (Ide et al., 1998; Keita et al., 1995; Koike et al., 1995; Nemoto et al., 1996; Pezron et al., 1988a,b, 1989a,b; Takada et al., 1998). The mechanism of interaction has been elucidated using magnetic resonance studies (Bowcher and Dawber, 1989; Dawber and Green, 1986) and results reveal that a THB anion can interact with two distinct *cis*-diol groups on PVA. First, THB anions interact with available *cis*-diol groups, leading to mono-diol complexation and formation of a charged poly(electrolyte) structure. Intra- and inter-chain electrostatic repulsion causes an expansion in polymeric volume. This leads to a more favourable conformation and formation of the second *cis*-diol interaction, leading to a di-diol complex. It is this (*cis*-diol)–TBH–(*cis*-diol) complexation, occurring both intramolecularly and intermolecularly, that gives rise to the formation of a hydrogel system.

Results from formulation studies have shown that the concentration of THB anions has a larger effect on hydrogel formation than the PVA concentration (Pezron et al., 1988a, 1989a). Sodium ions formed from the dissociation of sodium tetraborate, which is the common source of aqueous THB, assist the second step of the complexation reaction by attenuating the overall negative charge on the polyelectrolyte chain. Cross-links form closer together and the cross-link density increases (Keita et al., 1995).

The physical properties of PVA–THB hydrogels can be attributed to the reversible nature of the TBA-mediated cross-links. Light scattering observations show that they have a finite life-time (t_{life}) and the length of observation determines the type of response (Lin et al., 2005). If observation is long (low frequency), then cross-links have sufficient time to dissociate and the system behaves like a viscous fluid ($t > t_{life}$, $G'' > G'$; where G' represents the storage modulus, or solid like response, and G'' the loss modulus, or liquid like response). In contrast, if observation is short (high frequency), then they do not have enough time to dissociate and the system behaves like an elastic solid ($t < t_{life}$, $G' > G''$). It has been suggested that the frequency over which fluid-like structure exists decreases with increasing concentration of PVA (Lin et al., 2005).

The rheology of PVA–THB hydrogels indicates significant potential as a drug delivery platform in topical wound care. Although there has been much basic rheological study undertaken (Koga et al., 1999; Koike et al., 1995; Lin et al., 2005; Nemoto et al., 1996; Takada et al., 1998), there is relatively little information on how these systems behave in a topical context. Our group have considered the possibility of using a PVA–THB hydrogel as a potential topical local anaesthetic hydrogel (Loughlin et al., 2008). To investigate the factors that influence the physical and rheological characteristics of PVA–THB hydrogels, texture profile analysis and oscillatory rheometry were used to characterise formulations containing various quantities of PVA and sodium tetraborate at concentrations above the gelation point. A further aim of this study was to evaluate the effect of excipient concentration and PVA grade. Tests were conducted at room temperature and 37 °C, as the PVA–THB interaction is known to be temperature sensitive (Koga et al., 1999). The adhesiveness of candidate hydrogel formulations and commercially available alternatives were compared. A concern during the therapeutic use of any topical formulation applied to a site where the barrier function of the *stratum corneum* is comprised, is absorption of free excipients. Therefore, excipient release was evaluated as a function of polymer grade and excipient concentration.

2. Materials and methods

2.1. Materials

Three grades of poly(vinyl alcohol) (PVA) were used in this study, namely 13,000–23,000 M_W, 98% hydrolysed (13–23; 98 PVA); 31,000–50,000 M_W, 87–89% hydrolysed (31–50; 88 PVA) and 31,000–50,000 M_W, 98% hydrolysed (31–50; 98 PVA). All were obtained from Sigma–Aldrich, Dorset, UK. Sodium tetrahydroxyborate decahydrate (borax), sodium chloride and newborn calf serum (USA origin, sterile filtered, cell culture grade) were also obtained from Sigma–Aldrich, UK. Pharmaceutical grade PVA was obtained from Merck KGaA, Darmstadt, Germany and comprised 4–88 (31,000), 5–88 (37,000), 8–88 (67,000), 26–88 (160,000), 40–88 (205,000) and 28–99 (145,000). The first identifier in the notation refers to the viscosity of a 4% solution, the second refers to the degree of hydrolysis, and approximate molecular weight is shown in parenthesis. Hydrosorb®, Aquaflo®, Intrasite®, Intrasite-C® and Aquaform® were purchased from AAH Pharmaceuticals, Belfast, UK. Porcine skin was obtained from a local abattoir and either used immediately or stored frozen at −20 °C until use. All other reagents and solvents were of appropriate laboratory standard, obtained from commercial sources and used without further purification.

2.2. Preparation and texture analysis

PVA (20%, w/w) and sodium tetrahydroxyborate (5%, w/v) stock solutions were prepared in deionised water. Hydrogels were formed by mixing appropriate proportions of both solutions for approximately 30 min, with periodic stirring. Corrections for mass loss due to evaporation were made using deionised water to bring the formulation back to its original weight. Hydrogels were stored in sealed poly(propylene) containers (44 mm diameter, 55 mm depth; Sarstedt, Wexford, Ireland) at room temperature for 48 h. This permitted thermal equilibrium throughout the hydrogel and elimination of air bubbles prior to testing.

Textural properties of PVA–THB hydrogels were evaluated using a TA-XT2 Texture Analyser (Stable Micro Systems, Halsmere, UK) in texture profile analysis (TPA) mode. A tubular probe (10 mm diameter, 40 mm in length) was compressed twice into each sample to a depth of 15 mm at a rate of 10 mm s^{-1} with a 15 s delay between compressions. Hardness and compressibility were derived from the force–time plots produced using texture profile analysis. Hardness was defined as the force necessary to produce a given deformation and determined by the force maximum of the first positive curve of the force–time plot. Compressibility was defined as the work required to deform the product during the first compression of the probe and determined by the area under the first positive curve of the force–time plot.

2.3. Adhesiveness testing

Dermal adhesive properties of hydrogels were evaluated at room temperature (25 °C) using the Texture Analyser in adhesive mode. Excised porcine skin was cut along the subcutaneous–dermal interface to separate the subcutaneous fat. The epidermal side of the skin was then attached to a 1.0 cm × 1.0 cm Perspex®