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Research paper

Modulation of gel formation and drug-release characteristics of lidocaine-loaded poly(vinyl alcohol)-tetraborate hydrogel systems using scavenger polyol sugars

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Abstract

Polyol sugars, displaying a plurality of hydroxyl groups, were shown to modulate tetrahydroxyborate (borate) cross-linking in lidocaine hydrochloride containing poly(vinyl alcohol) semi-solid hydrogels. Without polyol, demixing of borate cross-linked PVA hydrogels into two distinct phases was noticeable upon lidocaine hydrochloride addition, preventing further use as a topical system. D-Mannitol incorporation was found to be particularly suitable in circumventing network constriction induced by ionic and pH effects upon adding the hydrochloride salt of lidocaine. A test formulation (4% w/v lidocaine HCl, 2% w/v D-mannitol, 10% w/v PVA and 2.5% w/v THB) was shown to constitute an effective delivery system, which was characterised by an initial burst release and a drug release mechanism dependent on temperature, changing from a diffusion-controlled system to one with the properties of a reservoir system. The novel flow properties and innocuous adhesion of PVA–tetrahydroxyborate hydrogels support their application for drug delivery to exposed epithelial surfaces, such as lacerated wounds. Furthermore, addition of a polyol, such as D-mannitol, allows incorporation of soluble salt forms of active therapeutic agents by modulation of cross-linking density.

Keywords: Poly(vinyl alcohol); Borate; Hydrogel; Lidocaine hydrochloride; Mannitol; Polyol; Topical delivery

1. Introduction

Poly (vinyl alcohol) (PVA) is a water-soluble polymer that forms ion complexes with a range of charged secondary diazo dyes and metal ions, such as Congo Red [1], borate [2], vanadate [3] and cupric ions [4]. Of these ion complexes, the PVA–tetrahydroxyborate (THB) polymer–ion complex is biomedically superior to other cross-linked networks, especially in terms of compatibility and acceptability. Complexes based on vanadate, for example, display appreciable toxicity to living tissue. The mechanism of PVA–THB complex formation has been elucidated previously through ^{13}C and ^{11}B nuclear magnetic resonance [5,6], with the underlying means of network formation believed to be a di-diol complexation formed between two adjacent diol groups from PVA on one hand and the THB ion on the other [7]. The cross-link reaction is shown in Fig. 1. It is a two-step procedure, whereby an initial mono-diol complexation (Fig. 1(a)) produces a poly(electrolyte), which as a result of electrostatic repulsion, causes the expansion of individual polymer chains and produces a sterically favourable environment for the proceeding di-diol complexation reaction (Fig. 1(b)) to occur [8].

Both inter- and intra-molecular cross-links occur as a result of the di-diol complexation reaction. Once sufficient

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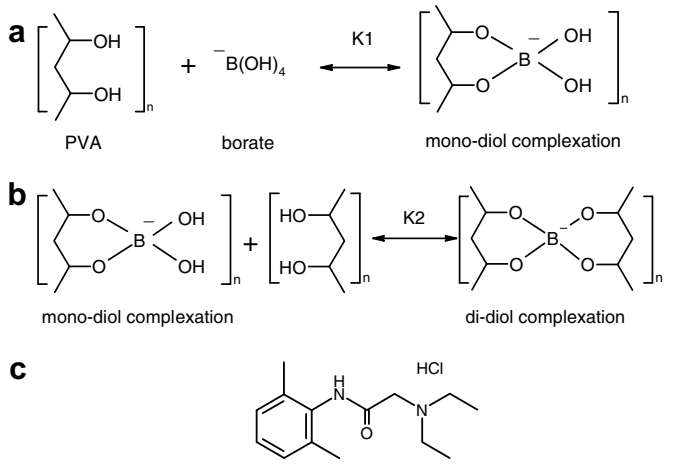


Fig. 1. Two-step mechanism of PVA complexation with aqueous THB anions, leading to an initial (a) mono-diol complexation and then followed by (b) di-diol complexation. (c) Structure of lidocaine hydrochloride.

inter-molecular cross-links exist, the network takes on the form of a gel system, a process reliant on the concentration of THB ions and, to a lesser extent, the concentration of PVA [9,10]. THB ions are produced through the aqueous dissociation of sodium tetraborate decahydrate (borax) to give equimolar portions of boric acid, THB ions and sodium ions. Their participation in the formation of cross-links induces anionic electrostatic repulsion between chains [10]. The sodium cations attenuate the overall negative charge on the nascent poly(electrolyte) and in so doing, permit PVA–THB cross-links to reside closer together. This effectively increases the cross-link density [11]. The overall situation, as described by Lin et al., is that the final conformation of the polymer chains results from a balance between their excluded volume, electrostatic repulsion between charged complexes bound to the polymeric chains and the shielding effect of free sodium ions associated with the charged complexes [12].

PVA–THB hydrogels are of particular interest to topical drug delivery, given their unique and characteristic flow properties that have been studied extensively through dynamic viscoelastic measurements [12–16]. These properties have been attributed to the finite lifetime (t_{life}) of the thermo-reversible, THB-mediated, cross-link. Therefore, viscoelastic properties can be explained in terms of the complex modulus (G): if the length of an observation is long (low frequency), the cross-links have sufficient time to dissociate ($t > t_{life}$) and the system behaves like a viscous liquid ($G'' > G'$). In contrast, if the length of an observation is short (high frequency), the cross-links have insufficient time to dissociate ($t < t_{life}$) and the system behaves like an elastic solid ($G' > G''$) [12,17,18]. Indeed, they begin to resemble the nature of cross-links found in elastic, covalently bonded, hydrogels, such as glutaraldehyde–PVA hydrogels, which display no appreciable flow due to the significant structural integrity maintained by cross-links with an infinite life-time [12].

One novel application of PVA–THB hydrogels is as a drug delivery system to sites of laceration as often encountered in Accident and Emergency medicine. Obviously, the repair of such lacerations must be as painless as possible and this can be achieved by using effective local anaesthesia. The use of topical anaesthetic formulations has been shown to be effective in this regard, with most tested prospectively in randomised controlled trials within North America. The formulation receiving most interest has been a combination of tetracaine, adrenaline and cocaine (TAC), which has been shown to be an effective alternative to lignocaine infiltration in the repair of children's lacerations [19,20]. A number of other topical anaesthetics sharing similarities to TAC have been developed and shown also to be as effective [21–23]. Although these formulations provide some measure of anaesthesia, they do not reside well in a wound and must be removed afterwards with a saline wash. Thus, one aspiration of this current work is to make use of the unique flow properties of PVA–THB hydrogels as a way to administer local anaesthesia to sites of laceration. These particular hydrogels demonstrate viscoelastic properties under conditions of differing rates of shear, behaving like a putty or solid when handled allowing it to be moulded into the outline of a wound. However, when left, the material acts like a viscous liquid and flows slowly, over a period of about 10 min, and fills the wound cavity, maximising drug absorption. Importantly, the gel remains as a cohesive mass when it is extricated from the wound site and preliminary results indicate that it is non-adhesive, can be removed intact and does not cause further tissue trauma.

The hydrochloride salt of lidocaine, as shown in Fig. 1(c), is an obvious choice for topical administration because it has a quick onset of action and a long duration of action. However, direct incorporation into PVA–THB hydrogels must account for its potential effects on network stability. Addition of lidocaine HCl to PVA–THB hydrogels increases the total free ion concentration within the gel and in so doing, has a profound effect on their internal structure [11,24]. The initial poly(electrolyte) formed between THB and PVA moderates further complexation by way of electrostatic repulsion of free THB away from sites of potential cross-linking. However, this effect can be attenuated by the shielding effect of exogenous free ions, such as those arising from inclusion of the salt form of a drug substance [25]. Therefore, these free ions reverse any reductions in the complexation constant and if the additional ionic strength is sufficient, electrostatic repulsion is reduced. This means that further THB access to the poly(electrolyte) is no longer restrained, the system cross-links prodigiously and demixes into a two-phase system that is of no practical use for topical delivery.

The aim of this work is to investigate the incorporation of the hydrochloride salt of a model amide-type local anaesthetic (lidocaine HCl) into PVA–THB hydrogels

and to modify gelation using poly-functionalised sugar alcohols. The complexation of THB by polyols has been studied extensively [1]. Penn et al. showed that D-sorbitol and D-mannitol (ligands) forms monoesters (one ligand) and diesters (two ligands) with THB ions, with the diester complex being more energetically favourable [26]. Additionally, no ligand was seen to contain more than one THB ion, which is a consequence of electrostatic forces preventing more than one THB ion attaching to each D-mannitol/D-sorbitol molecule. Furthermore, Penn et al. showed that the diol carbons involved in the monoester/diester affected the stability of the resultant complex [26]. Through modelling studies, it was shown that the 3,4-diol carbons give rise to the most favourable complex, because on formation, the free hydroxyl groups appear orientated towards the centre and so stabilise the complex [26]. D-Mannitol, for example, has a strong affinity for THB ions and if added to PVA–THB hydrogels has been shown to cause the system to fluidize [10]. This comes about as a result of D-mannitol binding up free THB ions and removing THB ions from PVA molecules. The latter process causes the network to fluidize, with excess THB ions being bound by D-mannitol. Similarly, THB ions bound to PVA diol functionalities are sequestered by D-mannitol. Therefore, D-mannitol will potentially enhance the solubility of lidocaine HCl (through a reduction in pH by binding of free THB ions – Lewis base) and prevent demixing brought about by the lidocaine anions (through reduction in available THB ions). With this in mind, an objective of this work is to evaluate the combined effects of polyol sugars and lidocaine HCl on the physical properties of PVA–THB hydrogels and to produce an optimised formulation that would be suited to topical delivery. An additional objective is to study the release of lidocaine HCl into a model receiver phase and to evaluate the effect of temperature on the release kinetics.

2. Materials and methods

2.1. Materials

Poly(vinyl alcohol) (PVA) (98–99% hydrolyzed, MW = 31,000–50,000), sodium tetraborate decahydrate (borax), lidocaine HCl, xylitol, meso-erythritol, maltitol, D-mannitol, D-sorbitol, dulcitol, 1,2-propandiol, glycerol, propan-2-ol and D-mannitol were purchased from Sigma–Aldrich Company Ltd. (Gillingham, Dorset, UK). All reagents and solvents were of appropriate laboratory standard and used without further purification.

2.2. Preparation and pH measurements of PVA–THB hydrogels

PVA–THB hydrogels (10% w/w PVA and 2.5% w/w borax) were prepared by combining equal volumes of separate stock solutions (20% w/w PVA and 5% w/w borax) prepared in de-ionised water. Gels were stored for 48 h at room temperature to allow complete gelation prior to evaluation. Excipients, such as lidocaine HCl and D-mannitol, were added to the sodium tetraborate solution prior to addition to the PVA solution.

The pH of gel formulations were recorded using a Sensorex® spear-tip electrode (S175CD, Sensys Ltd, Stevenage), which is designed to penetrate and measure the pH of semi-solid systems. Measurements of pH in borax solutions (5% w/v), following successive additions of D-mannitol (5.0×10^{-3} mol), were recorded using the same electrode apparatus.

2.3. Texture analysis

Evaluation of the mechanical properties of PVA–THB hydrogels was performed using a TA-XT2 Texture Analyzer (Stable Micro Systems, Haslmere, UK) in texture profile analysis (TPA) mode. Formulations were placed in poly(propylene) containers (44 mm diameter × 55 mm depth) (Sarstedt©, Wexford, Republic of Ireland) with any air bubbles in the gels removed upon standing at ambient temperature (about 6.0 h) prior to investigation. The tubular probe (10.0 mm in diameter and 150.0 mm in length) was compressed twice into each sample to a depth of 15.0 mm at a rate of 10.0 mm s^{-1}, with a 15.0 s delay between compressions. Four replicate measurements were made in each case at ambient temperature.

Hardness and compressibility, which have previously been used to define the mechanical properties of hydrogels, were derived from the force–time plots produced by the TPA analysis [27]. Hardness, the force required to achieve a given deformation, was determined by the force maximum of the first positive curve of the force–time plot. Compressibility, the work required to deform the product during the first compression of the probe, was determined by the area under the first positive curve of the force–time plot [27].

2.4. Viscosity analysis

The viscosity of PVA–THB hydrogels was determined at a constant shear force using the falling sphere technique and applying the Stoke's equation, as shown in Eq. (1);

$$\eta = \frac{2(\Delta P)ga^2}{9v} \quad (1)$$

where η is the viscosity at constant shear force, ΔP is the difference in density between the sphere and the gel, g is the acceleration due to gravity (9.807 m s^{-1}), a is the radius of the sphere and v is the experimentally derived velocity of the sphere through the test gel. Constant velocity was derived from the time required for the metallic sphere to travel a defined distance into the gel. To ensure measurements were taken upon attaining terminal velocity, the defined distance was measured from a point when the sphere had depressed 2.0 cm into the gel and was stopped 5.0 cm before the sphere had reached the bottom of the

container. The viscosity was determined for each hydrogel and subsequently repeated for replicate samples ($n = 4$).

2.5. Comparison of polyol affinity for THB ions

The following polyols were used in this investigation: maltitol, dulcitol, D-mannitol, D-sorbitol, xylitol, meso-erythritol, 1,2-propanediol and glycerol. Additionally, the effect of propan-2-ol was also investigated. The affinity of each polyol for THB was estimated using direct titrimetry and by analysis of gel characteristics. In the former method, incremental additions (1.0 ml) of a 0.5 M solution of polyol were added to 100.0 ml of 5% w/v Borax solution and the pH recorded. The reduction in free THB and subsequent percentage reduction per 5.0×10^{-3} mol of polyol were calculated using Eq. (2);

$$10^{(\mathrm{pH}-\mathrm{p}K_a)}[H_3BO_3]_0 = [B(OH)_4^-]_f \quad (2)$$

where $[H_3BO_3]_0$ is the concentration of boric acid, $[B(OH)_4^-]_f$ is the concentration of free THB ions and pK_a is the pK_a of boric acid (derived from the initial pH of the 5% w/v borax solution). The equation assumes that boric acid concentration does not change with addition of the polyol and that only mono-THB ions occur at the concentration of borax used in the analysis (i.e. no THB aggregates exist). These assumptions are consistent with work of other researchers [28,29].

Additionally, the effect of the polyols on the concentration of free THB ions within the hydrogel was estimated using changes in the pH of the gel after addition of a defined polyol. Standard hydrogels of 10% w/w PVA and 2.5% borax were produced containing each polyol at a concentration of 0.1 M. The pH of each gel was measured upon equilibration, with each measurement performed for four samples ($n = 4$). Similarly, the changes in gel hardness arising from variations in free THB induced by polyol addition were determined using texture profile analysis, as described above. As before, four replicate measurements were made in each case at ambient temperature ($n = 4$).

2.6. In vitro release studies

One-dimensional drug release was evaluated using cell culture inserts (Nunc®, No. 137508, Rochester, USA) normally used to provide a surface intended for cell attachment and growth studies. The integral poly(carbonate) membrane has a pore size of 8 μm and facilitates transport of soluble material, normally from the underlying reservoir through to cells growing on the top surface. In this work, however, the arrangement is reversed, with the membrane allowing soluble payloads to pass through into a reservoir below, as shown in Fig. 2. Inserts were used as the gel-loaded donor phase suspended in an aqueous receiver phase. Cell inserts were modified to become free standing by raising the standard base by 1.0 cm in height, which also ensured effective stirring under the receiver side of the permeable membrane. The hydrogel (4.00 g) was added to the inserts and its height and weight within the insert recorded prior to, and after, *in vitro* release investigations.

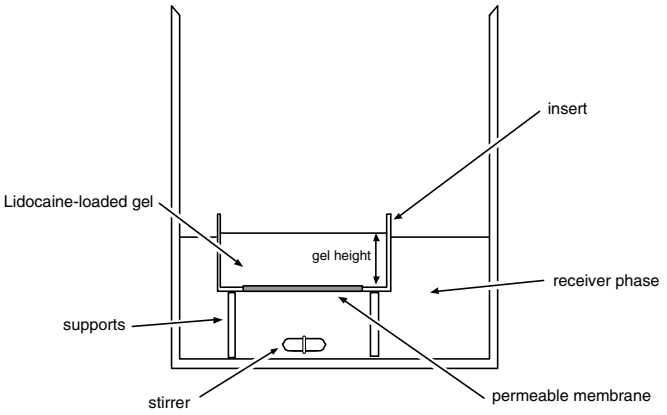


Fig. 2. Cross-sectional representation of apparatus used to determine lidocaine release from test formulations. The hydrogel is loaded into a plastic insert, which is suspended above a stirred and thermostatically controlled receiver phase. This insert has a poly(carbonate) membrane perforated with 8 μm pores. The height of the gel above the membrane, both before and after the analysis duration, was recorded.

Lidocaine release experiments commenced once gel-loaded inserts were placed in 100 ml of receiver phase, which was stirred at 250 rpm. A phosphate buffer (BP 1999, pH 6.8) was used as the receiver phase to mimic the slightly acidic environment of an infected/inflamed wound [30]. Sink conditions were maintained throughout the release experiment by ensuring that the total drug concentration possible in the receiver phase never exceeded 10% of its solubility in this compartment. At defined time intervals, 5.0 ml of receiver phase was removed, replaced by fresh buffer and lidocaine concentration determined spectrophotometrically at 265 nm (Carey® 50 scan UV–Visible spectrophotometer). *In vitro* release studies were carried out at ambient temperatures (25 °C), 37 and 50 °C. Once complete, the gel height and weight were measured again. Each release experiment was performed three times ($n = 3$).

2.7. Data treatment and statistical analysis

To elucidate the drug-release mechanism as a function of temperature, the drug-release data were fitted to the exponential equation described by Peppas and shown in Eq. (3) [31];

$$\frac{M_t}{M_\infty} = kt^n \quad (3)$$

where M_t is the amount of drug released at time t, M_∞ is total amount of drug in the system, M_t/M_∞ is the fraction of drug released at time t, k is the kinetic constant that incorporates the properties of the polymeric system and the drug and n is the diffusional exponent of the drug release, used to characterise the drug transport mechanism. Therefore, calculation of the release exponent n allows for

the determination of the mechanism of diffusion in the polymeric systems. Only the region of the first 60% of drug release with discernable stability in the profile was used to determine n. The initial region of high flux was, therefore, excluded from the determination of n.

The effects of D-mannitol and lidocaine HCl on the hardness, compressibility and viscosity of PVA–THB hydrogels were evaluated using a two-way analysis of variance (ANOVA) with a 5×7 factorial design. Post-hoc analysis, namely Tukey's test, was employed for comparison of the means of the individual groups. Additionally, the effect of each polyol on hardness of standard hydrogels was evaluated using ANOVA with a 1×7 factorial design, with Tukey's test again being employed for post-hoc analysis. $P < 0.05$ denoted significance for all statistical comparisons.

3. Results

The effect of D-mannitol on the physical appearance of lidocaine HCl-loaded PVA–THB hydrogels is shown in Fig. 3(a), (b) and (c). A formulation containing 10% w/w PVA and 2.5% w/w THB was chosen for this investigation because it possessed high degrees of hardness, compressibility and viscosity and could accommodate any reductions in the physical properties brought about by D-mannitol or lidocaine HCl addition. From examination of the results, it is clear that D-mannitol increased the solubility of lidocaine HCl, as shown by the clear gel region seen in the upper right-hand corner of the phase diagram (Fig. 3(a)). Additionally, D-mannitol prevents the demixing effect seen in PVA–THB hydrogels brought about by lidocaine HCl concentrations that exceed 3.0% w/w. Furthermore, it is an important finding that as temperature increased from ambient temperature through 37 to 50 °C, the solubility of lidocaine HCl was reduced progressively. This is evident in the progressive movement of the opaque-clear interface region that eventually encompasses all lidocaine HCl concentrations, as seen in Fig. 3(c).

Table 1 shows the effect of each polyol on free THB concentration, pH and hardness of the test hydrogel (10% w/w PVA and 2.5% w/w THB). The overwhelming trend was that affinity for THB increased as the number of hydroxyl groups per molecule increased. There was a clear increase in the percentage reduction of free THB (as seen by the reduction in pH) and hardness as this structural feature was incremented. In fact, each sequential reduction in hydroxyl group number per molecule, that is, going from 6 to 5 to 4 and so on, resulted in significant increases in hardness of the hydrogel, as shown in Fig. 4. For example, the hydrogel containing 0.1 M erythritol (four hydroxyl groups per molecule) was shown to have significantly greater hardness ($p < 0.001$) and compressibility ($p < 0.001$) than the hydrogel loaded with 0.1 M xylitol (five hydroxyl groups per molecule). If the number of hydroxyl groups per molecule was kept constant, as in dulcitol, D-mannitol and D-sorbitol, no significant differences in hardness were observed. Furthermore, the effect of hydroxyl groups per molecule on hardness was shown to be inversely related to affinity of the polyol for THB ions. This was illustrated by the decreasing trend in THB affinity as the number of hydroxyl groups per molecule was decreased. Additionally, hydrogels loaded with 0.1 M propan-2-ol and 1,2-propandiol, with one and two hydroxyl groups per molecule, respectively, were shown to have no effect on the hardness of the hydrogel when compared to the hydrogel containing no polyol.

The effect of D-mannitol and lidocaine HCl incorporation on the pH of PVA–THB hydrogel, containing 10% w/w PVA and 2.5% w/w THB, is shown in Fig. 5(a). It is clear that both D-mannitol and, to a lesser extent, lidocaine HCl reduce the pH of this particular hydrogel formulation. Importantly, increasing D-mannitol caused a linear reduction in pH. This can be compared to the effect of D-mannitol on the pH of a 5% w/v sodium tetraborate solution, as shown in Fig. 5(b), which again displayed inverse proportionality between pH and D-mannitol concentration.

The effects of D-mannitol and lidocaine HCl incorporation on compressibility, hardness and viscosity are shown in Fig. 6(a), (b) and (c), respectively. Again, the concentrations of PVA and THB were kept constant (10% w/w PVA and 2.5% w/w THB). In the absence of lidocaine HCl, increasing D-mannitol by 0.5% w/w increments caused a significant reduction between steps in the hardness and compressibility of PVA–THB hydrogels up to a total concentration of 2.5% w/w D-mannitol. For example, the hydrogel containing 0.0% w/w lidocaine HCl and 1.5% w/w D-mannitol was shown to possess significantly greater hardness ($p < 0.001$) and compressibility ($p < 0.001$) than the hydrogel containing 0.0% w/w lidocaine HCl and 2.0% w/w D-mannitol. However, increasing D-mannitol by 0.5% w/w between 2.5% w/v and 3.0% w/v did not produce a significant effect on hardness and compressibility. The trend seen in hardness and compressibility was also evident for viscosity changes. Although once D-mannitol exceeded 2.0% w/v, no further significant reduction was seen. Furthermore, from the statistical analysis (two-way analysis of variance), it was clear there existed an interaction between lidocaine and D-mannitol in that the effect of adding both into the same gel was not simply an additive reduction in the physical properties. A saturation point was evident, where at certain concentrations of D-mannitol, adding lidocaine HCl had no effect on the physical properties of the hydrogel. With respect to hardness and compressibility, increasing lidocaine HCl by 2% w/w (up to 4%) caused a significant reduction in the hardness and compressibility of the hydrogels when the concentration of D-mannitol was greater or equal to 1.5% w/v. For example, the hydrogel containing 1.0% w/w lidocaine HCl and 1.0% w/w D-mannitol was shown to possess significantly greater hardness ($p < 0.001$) and compressibility ($p < 0.001$) than the hydrogel containing 3.0% w/w lidocaine HCl and 1.0% w/w D-mannitol. However, when the concentration of D-mannitol was greater than 1.5% w/w

(saturation point) varying lidocaine HCl concentration from 0% to 4% w/w did not have a significant effect on the hardness and compressibility. This trend was also apparent with respect to viscosity, whereupon further addition of lidocaine HCl had no significant effect.

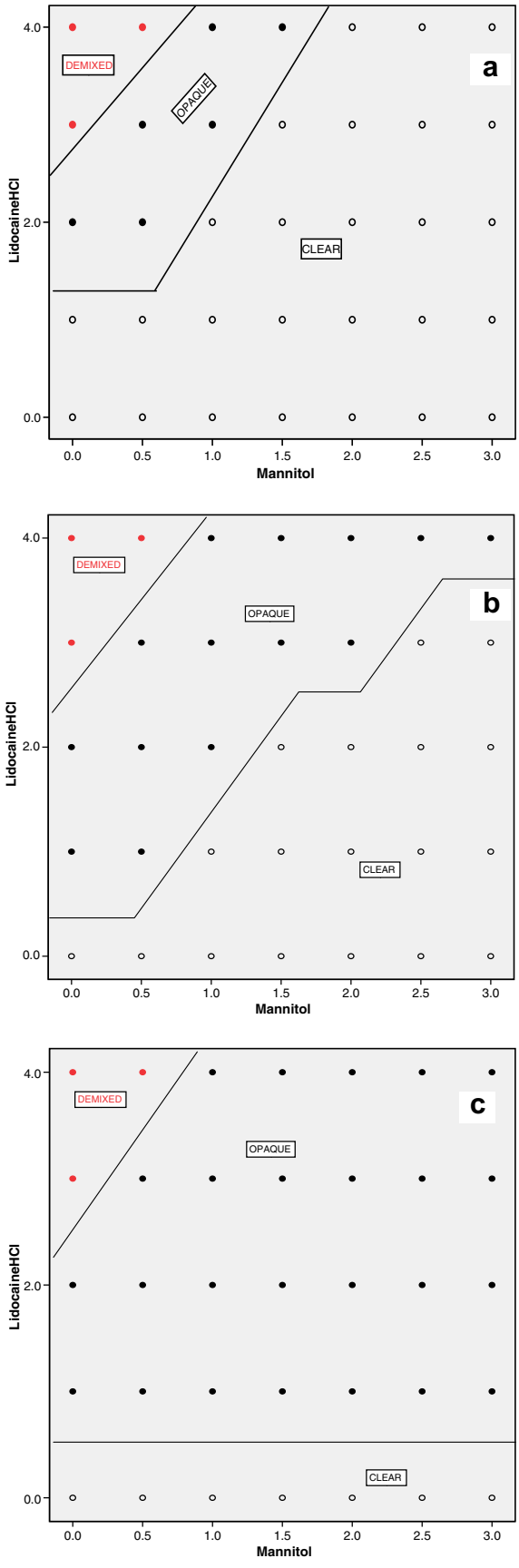


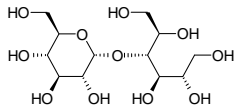
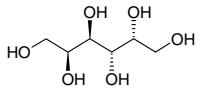
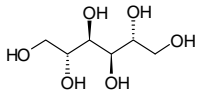
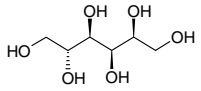
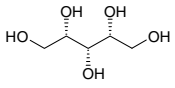
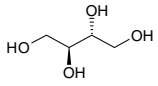
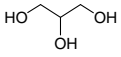
Fig. 3. Solubility phase diagrams obtained at (a) room temperature (25 °C), (b) 37 °C and (c) 50 °C. Regions of demixing are shown in red and indicate where the hydrogel has separated into a two-phase system, generally comprising a hard rubber-like mass suspended in a low viscosity aqueous solution. Opaque regions were white in appearance, indicative of lidocaine base present above its saturation solubility limit. Clear regions were colourless, transparent and homogeneous. Solid lines are included in the diagrams for illustrative purposes to indicate interfacial regions. *X* axis is concentration of D-mannitol in % w/w and *Y* axis is lidocaine HCl concentration in % w/v.

The *in vitro* release profiles are shown in Fig. 7. In this part of the study, the loadings of lidocaine HCl (4.0% w/w), D-mannitol (2.0% w/v), sodium tetraborate (2.5% w/v) and PVA (10.0% w/v) were kept constant, with temperature being the only changing variable. The loading of lidocaine chosen was the highest investigated in this study and the one most likely to induce rapid anaesthesia during clinical application. It was evident that increasing temperature not only caused an increase in the release rate of lidocaine HCl, but also altered the mechanism by which the drug vacates the system. As can be seen in Table 2, the mean time taken for 60% of drug to be released ($t_{60\%}$) decreased to 210 min for release at 50 °C. Interestingly, the release exponent, as calculated using the natural log plots of the drug-release studies and applying Eq. (1), also increased as temperature was increased. These results indicated a change in drug release mechanism, where diffusion was the predominant mechanism when the temperature was low, changing steadily to one approaching zero-order kinetics as the temperature rose. Indeed, the profile at 50 °C showed evidence of the lidocaine release approaching linearity for the first 60% of lidocaine HCl release with respect to time.

4. Discussion

PVA–THB polymeric matrices are of particular interest to topical drug delivery. They offer a unique set of characteristic flow properties that make them an attractive delivery vehicle for therapeutic agents, such as local anaesthetics, into cavernous wounds. Their low bioadhesive strength and cohesive integrity ensure that the system can be removed as an intact piece and without inflicting further trauma. The formulation of local anaesthetics, such as lidocaine HCl, into various polymeric matrixes and subsequent release have been studied extensively [32,33]. However, pharmaceutical evaluation of drug release is problematic as PVA–THB hydrogels display limited dissolution upon direct exposure to a reservoir phase. This would not mimic the restricted dissolution seen following application to a site of trauma. To circumvent this problem, tissue culture inserts were adapted to form part of a novel dissolution apparatus. The choice of membrane was one that did not impede drug transport from the formulation, but also prevented appreciable dissolution of the gel system.

Table 1
Effect of polyol structure on free THB concentration, pH and hardness of a test PVA–THB hydrogel (10% w/w PVA and 2.5% w/w THB)

Polyol	% Reduction in free THB/0.0005 mol	pH of hydrogel with 0.1 M polyol	Hardness (N)
Malititol, $C_{12}H_{24}O_{11}$ 	7.25 ± 1.59	7.63 ± 0.019	2.79 ± 0.14
Dulitol, $C_6H_{14}O_6$ 	7.46 ± 1.41	7.67 ± 0.015	3.87 ± 0.38
D-Mannitol, $C_6H_{14}O_6$ 	7.47 ± 1.10	7.74 ± 0.023	4.07 ± 0.25
D-Sorbitol, $C_6H_{14}O_6$ 	6.87 ± 1.25	7.79 ± 0.02	4.37 ± 0.31
Xylitol, $C_5H_{12}O_5$ 	4.97 ± 1.21	7.95 ± 0.038	5.18 ± 0.31
Meso-erythritol, $C_4H_{10}O_4$ 	4.97 ± 1.17	8.10 ± 0.01	9.01 ± 0.45
1,2-Propandiol, $C_3H_8O_2$ 	2.08 ± 0.78	8.39 ± 0.02	14.10 ± 0.5
Propan-2-ol, $C_3H_8O_1$ 	0.51 ± 1.09	8.393 ± 0.012	14.30 ± 0.65
Glycerol, $C_3H_8O_3$ 	3.36 ± 1.34	8.17 ± 0.022	11.06 ± 0.62
No polyol	–	8.41 ± 0.51	14.58 ± 0.89

A direct incorporation of salt forms into PVA–THB systems is not possible without some form of modulation of the PVA and THB interaction, which is mediated by ionic and pH-induced effects. As seen in Fig. 3, without the action of D-mannitol, lidocaine HCl compatibility is poor, giving a system that displays either a precipitate or a complete demixing of the hydrogel phases. An important finding of this work has been to show that polyol sugars, exemplified by D-mannitol, are able to modify these cross-linking dynamics and to diminish ionic-induced net-

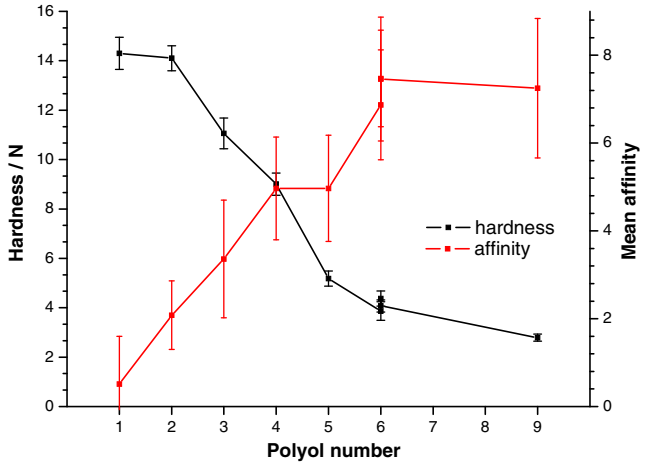


Fig. 4. The relationship between polyol number (number of hydroxyl groups on modulator) and hardness of the resulting gel and affinity. Affinity is defined as % $[THB\ ions]_f$ 0.0005 mol^{-1} and is the percentage reduction in free THB ions for every 0.0005 mol polyol, as explained in Eq. (4).

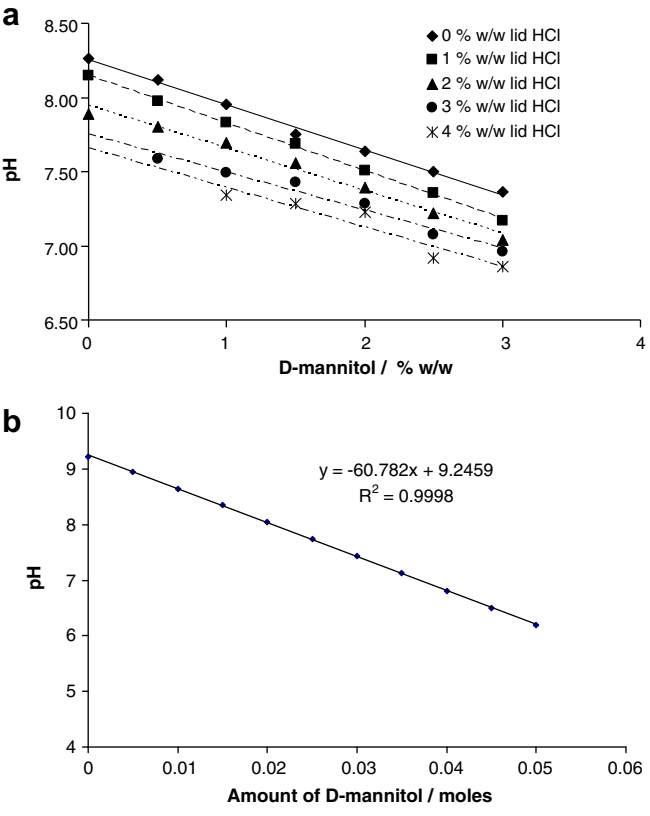


Fig. 5. (a) The effect of D-mannitol and lidocaine HCl concentration on the pH of a PVA–THB hydrogel (10% w/w PVA and 2.5% w/w THB). (b) The effect of D-mannitol concentration on the pH of 5% w/v sodium tetraborate solution. Results are plotted as means ($n = 3$) – error bars were negligible and are not shown.

work collapse and drug precipitation. Indeed, it was shown that an incorporation of up to and exceeding 4.0% w/v lidocaine HCl in a homogeneous gel was possible.

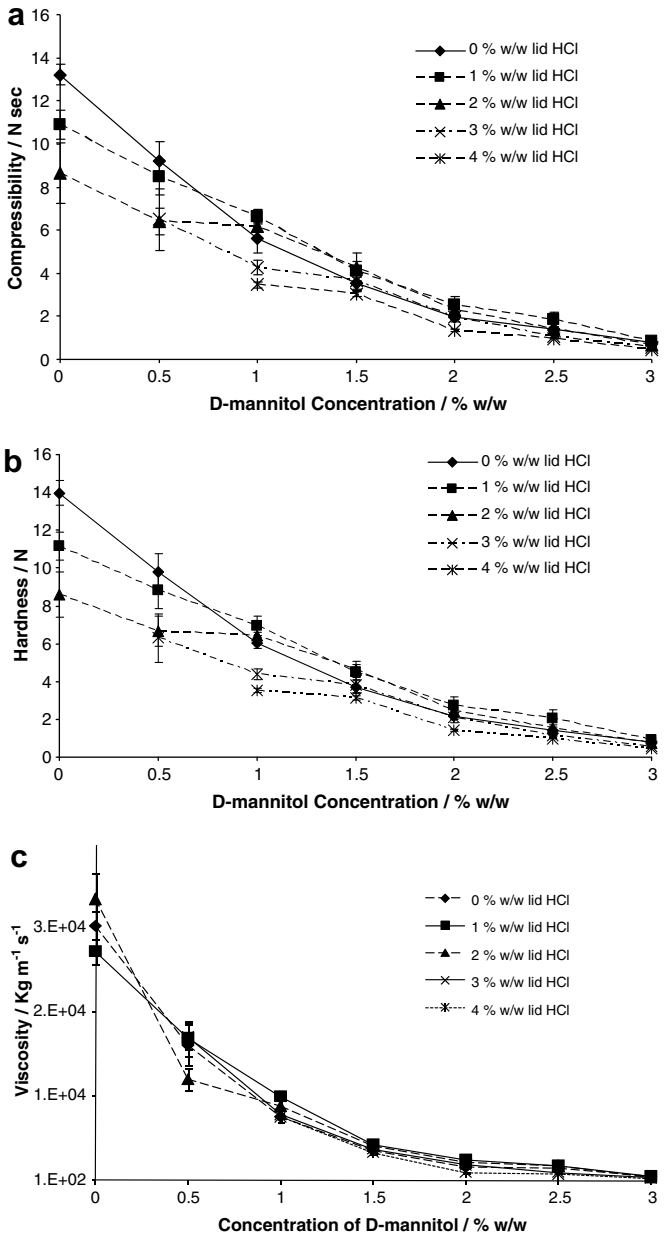


Fig. 6. The effect of D-mannitol and lidocaine HCl concentration on the (a) compressibility, (b) hardness and (c) viscosity of PVA–THB hydrogels (10% w/w PVA and 2.5% w/w THB). Results are plotted as means ± standard deviation ($n = 4$).

Lidocaine HCl is an ideal candidate local anaesthetic drug for inclusion in topical vehicles. It dissolves in water to form an acidic solution, as shown below.

$$LD.H^+Cl^- \rightarrow LD.H^+ + Cl^-$$
$$LD.H^+ \rightleftarrows LD + H^+ \quad pK_a = 7.9$$

The conjugate acid $LD.H^+$ will dissociate to form the relatively insoluble lidocaine base LD (solubility = 0.015 mol L^{-1}). The formation of the lidocaine base and any subsequent precipitation can be related to the initial lidocaine HCl concentration and pK_a by Eq. (4) [32];

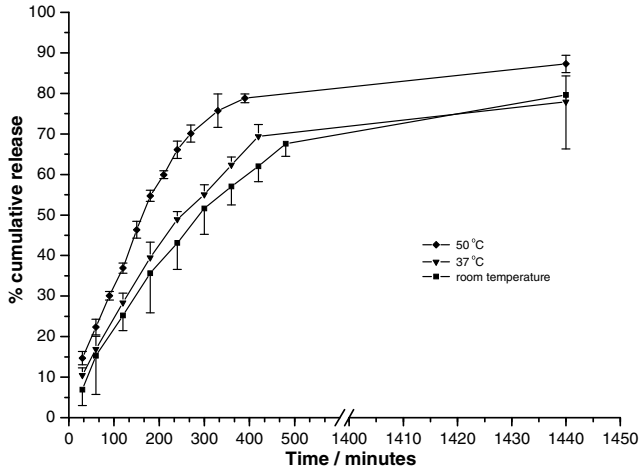


Fig. 7. Cumulative release of lidocaine HCl (4.0% w/w loading) from PVA–THB hydrogels through 8.0 μm pore cell inserts runs at three temperatures, where room temperature was 26 °C. Results are plotted as means ± standard deviation ($n = 3$; positive and negative error bars are plotted when appropriate to enhance clarity) and axis break runs from 600 to 1400 min.

Table 2
Time to achieve 60% release ($t_{60\%}$) and corresponding release exponent as calculated using Eq. (1)

Temperature (°C)	$t_{60\%}$/(min)	Release exponent
Ambient	390.48 ± 14.79	0.668 ± 0.095
37	336.59 ± 4.30	0.711 ± 0.025
50	238.42 ± 2.06	0.825 ± 0.012

$$\mathrm{pH_p} = \mathrm{p}K_\mathrm{a} - \mathrm{Log}_{10}\left(\frac{S - S_0}{S_0}\right) \quad (4)$$

where $\mathrm{pH_p}$ is the pH above which the drug begins to precipitate from solution as the free base, $\mathrm{p}K_\mathrm{a}$ is the $\mathrm{p}K_\mathrm{a}$ of lidocaine HCl (= 7.9), S_0 is the solubility of lidocaine base (0.015 mol L^{-1}) and S is the concentration of lidocaine HCl dissolved in solution. According to Eq. (4), homogeneous solutions are favoured at low pH and dissolved drug is only found as the free base above pH 7.9. Therefore, given the inherent alkalinity of PVA–THB hydrogels, producing a solution of lidocaine HCl at therapeutic concentrations in such gels is potentially unattainable.

The increased solubility of lidocaine HCl in PVA–THB hydrogels, brought about by D-mannitol, as shown in Fig. 3, is a result of D-mannitol binding up free THB ions in the aqueous environment of the gel [34]. By binding up THB ions, D-mannitol decreases the pH of the hydrogel and subsequently enhances the solubility of lidocaine HCl. It can be seen from Table 1 that the determining factor of THB affinity among the polyols is the number of hydroxyl groups per molecule. The more available hydroxyl groups, the greater the possible association and formation of a monoester and the more likely will be the formation of an energetically favourable complex, as seen with THB and diol carbons 3 and 4 of D-mannitol. Additionally, isomers such as dulcitol, D-sorbitol and D-mannitol have similar affinities for THB because they have an equivalent density of hydroxyl groups on an open chain structure. This is confirmed by the effect of 0.1 M dulcitol, D-mannitol or D-sorbitol on the hardness of a tested PVA–THB hydrogel, as no significant difference was shown (Fig. 3). Malititol, with the largest hydroxyl density per molecule, has been shown to have the greatest affinity for THB ions. It should be borne in mind, however, that malititol is a disaccharide and it is conceivable that two THB ions could bind to each ligand. Although malititol has a greater affinity for THB ions overall, there is no advantage to using it as its larger molecular mass, necessitates a greater mass to be included in the formulation in order to achieve the same binding as an equivalent amount of D-mannitol. Following on from this, D-mannitol was chosen as the polyol of choice, because of its affinity, ready availability and regulated pharmaceutical status (mannitol BP).

By binding up free THB ions, D-mannitol effectively drives the pH of the aqueous environment down, as confirmed in Fig. 5(a), which results in the increased solubility of lidocaine HCl. Furthermore, demixing, as brought about by high lidocaine HCl concentrations ($\geqslant$3.0% w/w), is actively inhibited by D-mannitol, an effect that can be explained in terms of the complexation constant between PVA and THB ions. It should be remembered that demixing is brought about by an increase in the complexation constant with PVA due to an increase in ionic strength. The increase in ionic strength, as a result of added lidocaine HCl, lessens the repulsive effect of the poly(electrolyte) network, which in turn causes an increase in complexation constant and a resultant increase in the PVA–THB cross-linking. This increase in cross-link density results in phase separation and demixing [25,34]. It follows, therefore, that if D-mannitol can mop up free THB ions, the latter are not available for binding and constriction of the network is avoided. It is important to note that, in the absence of D-mannitol, only lidocaine HCL concentrations $\geqslant$3.0% w/w cause demixing in the tested hydrogel. At lidocaine HCl concentrations less than 3% w/w, lidocaine-H^+ cations are not produced in significant amounts (conjugate acid) because the environmental pH of the hydrogels are greater than 7.9 (i.e. greater than the $\mathrm{p}K\mathrm{a} = 7.9$ of lidocaine HCl).

This study has shown that the solubility of lidocaine HCl in PVA–THB systems decreased as the temperature was increased, as shown in Fig. 3(a). This is an important finding and can be attributed to the breakdown of the internal structure of PVA–THB hydrogels upon heating, whereupon the density of di-diol cross-links reduce and the available free THB ions increase. This increase in free THB ions (lewis base) enhances the deprotonation of lidocaine-H^+, which in turn increases the concentration of lidocaine base. The end result is a precipitate formed once the

saturation solubility of the lidocaine base is exceeded (0.015 mol L^{-1}).

It is well described in the literature that D-mannitol has a greater affinity for THB ions relative to PVA, which means that D-mannitol will progressively compete and remove THB ions from PVA–THB hydrogels, causing the system to fluidise [34]. The progressive reduction in the cross-link density of PVA–THB hydrogels by increasing D-mannitol concentration is evident from the texture and viscosity analyses. Physical characterisation showed that increasing D-mannitol in 0.5% increments up to a final concentration of 2.5% w/w for texture analysis and up to 2% w/w for viscosity determination produced significant reductions in both (Fig. 6). This reduction in the physical properties of the hydrogel can be attributed to the successive sequestering by D-mannitol of both free THB and THB bond to PVA molecules. This binding of THB ions to D-mannitol appears to reach some form of saturation point at high concentrations of D-mannitol. For example, there is no significant reduction in viscosity through increasing D-mannitol from 2% to 3% w/w. This saturation effect is explained in terms of the logarithmic reduction in THB ions as D-mannitol is increased. Effectively, at high concentrations of D-mannitol (>2.0% w/w), further increases cause a small change in the percentage of bound THB ions. D-Mannitol causes a linear reduction in pH, which, according to the Henderson–Hasselbalch equation, causes a log reduction in free THB ions. Therefore, at high D-mannitol concentration (>2% w/w), there is only a small amount of free THB ions and adding additional D-mannitol will have a minimal effect on the integrity of the gel. However, although it is clear from the physical analysis that increasing D-mannitol progressively reduces THB ions bound to PVA, it is not clear what percentage of THB ions is bound to PVA or D-mannitol. In order to elucidate the relative binding proportions, more sophisticated analysis, such as ^{11}B NMR, would be required. Furthermore, at low levels of D-mannitol, increasing lidocaine HCl by 2% w/w increments significantly reduces the physical properties of PVA–THB hydrogels. This can be attributed to the production of H_3O^+ ions by the conjugate acid LD.H^+. The H_3O^+ ions react with the THB ions (Lewis base) to produce boric acid which results in a net reduction in the free THB ions. The reduction in free THB ions produces a reduction in the bound THB ions, which in turn causes a reduction in the physical properties of the system. This effect is limited by high levels of D-mannitol, because at such conditions free THB ions are at a low concentration.

The investigation of drug release was carried out on a formulation judged to possess favourable flow characteristics for topical drug delivery. Over the three temperatures tested, similar patterns were observed, namely, an initial region of high flux followed by a stable phase of release. The initial high flux can be attributed to an initial burst effect, known to occur over a short period of time, being unpredictable and often occurring in hydrogels as a result of higher surface concentrations brought about by migration of the drug to the surface [35]. Ongoing flux took about 60 min to reach a more stable profile. It was interesting to note that the duration of initial anomalous flux was temperature-dependent, with higher temperatures producing a more stable profile after a shorter duration, indicating that this initial phase cannot simply be explained in terms of a burst effect. Effects arising from system swelling and forming an equilibrium with the surrounding environment may be attributive. In any event, the large release of lidocaine at the beginning of the release profile could be construed as beneficial, because the initial high levels will offer a quick and effective local aesthetic effect to a target wound site.

The region of stable flux (up to a maximum of 60% of drug released) was used to determine the mechanism of diffusion by calculation of the release exponent, which was seen to approach 1.0 as the environmental temperature increased. This temperature-induced alteration in the release mechanism can be explained on the basis of the concentration of free THB ions, which increase as the temperature is increased. The increase in THB ion concentration produces an increase in the deprotonation of LD.H^+ to lidocaine base, which results in a precipitate once the saturation solubility of lidocaine base is exceeded. This nascent precipitate acts as a drug reservoir that constantly replaces the soluble lidocaine that diffuses out of the system. Indeed, the hydrogel can be observed to turn opalescent in appearance when warmed. As a result of the reservoir effect, a constant diffusion gradient can be maintained effectively whilst the precipitate is present. This effect was most evident for the release at 50 °C ($n = 0.83$), where the precipitate was still observed throughout the hydrogel even after 60% of the drug had been released. In contrast, cooler temperatures resulted in both diminutions in precipitate and the release exponent until, at ambient temperature ($n = 0.66$), no precipitate was evident. As a consequence, the hydrogel at ambient temperature contains drug completely dissolved in a hydrophilic matrix. Therefore, it is not surprising that diffusion through this system approaches a square root of time relationship ($n = 0.5$), as this relationship is often seen in polymer matrixes where the drug is completely dissolved throughout.

In conclusion, D-mannitol was shown to be an effective and requisite excipient for formulating lidocaine HCL into PVA–THB hydrogels. D-Mannitol was shown to circumvent network constriction induced by ionic effects upon adding a HCl salt of a drug substance. A test formulation (4% w/v lidocaine, 2% w/v D-mannitol, 10% w/v PVA and 2.5% w/v THB) was shown to constitute an effective delivery system, which was characterised by an initial burst release and a drug release mechanism dependent on temperature, changing from a diffusion-controlled system to one with the properties of a reservoir system. The novel flow properties and innocuous adhesion of PVA–THB hydrogels support their application for drug delivery to

exposed epithelial surfaces, such as lacerated wounds. In particular, this work shows that incorporation of local anaesthetics into PVA–THB hydrogels can now be achieved, something that was not possible without the use of polyol modulators.

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