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Development and characterisation of a moisture-activated bioadhesive drug delivery system for percutaneous local anaesthesia

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Abstract

This study describes the design, formulation and characterisation of a moisture-activated device incorporating the tetracaine phase-change system for percutaneous local anaesthesia. Gel intermediates for candidate devices were formulated with various concentrations of bioadhesive polymer, viscosity builder and tetracaine at pH values from 5 to 10. Gels were cast onto a release liner, dried and a backing layer attached, thus forming a percutaneous anaesthetic patch system. Patches were characterised by in vitro measurement of tetracaine flux through a polydimethylsiloxane barrier membrane, apparent viscosities of the casting gels, patch bioadhesion to a porcine skin substrate, uniformity of drug content and chemical stability of the active agent in the system. The clinical efficacy of candidate formulations was evaluated by a volunteer trial. Patches were of a consistent appearance and exhibited a uniform thickness and drug distribution throughout the matrix. Varying formulation parameters significantly ($p < 0.05$) affected drug release, patch viscosity and, thus, clinical efficacy. Tetracaine was stable in the patch system during storage for 6 months at 4 and 25°C. Patches with lower concentrations of bioadhesive and thickener, formulated at pH 8 or above, demonstrated the highest levels of drug flux and provided optimum percutaneous anaesthetic activity. All volunteers reported complete cutaneous anaesthesia at the treated site, with a mean onset time for anaesthesia of $44 + 6.7$ min. The optimised bioadhesive patch device offered a more patient-compliant and convenient alternative to tetracaine percutaneous anaesthetic gel, particularly where large areas of skin are to be treated.

Keywords: Tetracaine; Percutaneous local anaesthesia; Poly (methylvinyl ether-maleic anhydride); Polydimethylsiloxane; Apparent viscosity; Bioadhesion

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1. Introduction

Aqueous gel compositions containing tetracaine provide effective percutaneous local anaesthesia of intact, healthy skin (Woolfson et al., 1990), thus rendering it insensitive to needle penetration challenge and other minor surface surgical procedures. The local anaesthetic must be presented to the skin surface substantially in its uncharged, lipophilic form such that it penetrates the outer, lipophilic skin barrier, the stratum corneum (Wertz and Downing, 1989), in order to reach and desensitise the underlying pain receptors within the skin structure (Monash, 1957). The concept of percutaneous local anaesthesia, strategies for ensuring efficient penetration by the local anaesthetic of the intact skin barrier and effective percutaneous anaesthetic systems have all previously been reviewed in detail (Woolfson and McCafferty, 1993a).

The efficacy of tetracaine gel as a percutaneous anaesthetic is partly due to the formation of a low melting metastable hydrate in aqueous media such that the system undergoes a phase change from a solid to oily suspension at skin temperature (Woolfson and McCafferty, 1993b). This is the basis of the commercial percutaneous local anaesthetic product, Ametop™ Gel. Tetracaine percutaneous anaesthetic systems are characterised by a relatively short onset time and prolonged duration of anaesthesia (Covino, 1986; Morton, 1996).

Although gel formulations are relatively simple to manufacture and are adaptable in use, when large skin areas are to be treated, for example, prior to the harvesting of split skin grafts, the mass of gel to be applied becomes relatively large and the procedure is somewhat inconvenient. In all cases, the gel compositions require a separate dressing in order to protect clothing. Further, tetracaine is susceptible to degradation by base hydrolysis of the ester grouping and, therefore, a tetracaine aqueous gel requires storage under cool conditions. Therefore, a patch presentation of the tetracaine phase-change system would be advantageous. However, since the presence of moisture is required to activate the phase change and since the delivery system depends on movement of lipophilic local anaesthetic base from a completely aqueous to a relatively hydrophobic environment (the stratum corneum), conventional pressure-sensitive adhesives are unsuitable. Pressure-sensitive adhesives are known to lose adhesion in the presence of moisture.

A unit-dose tetracaine composition in the form of a hydrophilic film has previously been reported (McCafferty and Woolfson, 1993). This produced effective percutaneous anaesthesia of intact human skin, comparable to that of the gel system. The film composition was non-adhesive and required presentation as an island dressing with an outer surround of pressure-sensitive adhesive. Given that the dry film had to be moisture-activated to effect drug release, this significantly impaired the efficacy of the surrounding adhesive layer and, in addition, the patch design was complex to assemble.

The present study reports on a novel type of skin patch in which a moisture-activated adhesive (bioadhesive) polymer composition is combined with the moisture-activated tetracaine release system to provide effective percutaneous anaesthesia that is clinically comparable to the commercial tetracaine product. The patch system is relatively simple to produce and, unlike pressure-sensitive compositions, the bioadhesive tetracaine patch is easily removed from the skin by peeling, leaving a negligible, water-soluble residue.

2. Materials and methods

2.1. Materials

Tetracaine USP was supplied by Smith & Nephew, Hull, UK. (Poly)methylvinyl ether/maleic anhydride (PMVE/MA) was obtained as Gantrez AN-139 Co-Polymer from ISP, Manchester, UK. 4-(Butylamino) benzoic acid (BBA) was purchased from Sigma-Aldrich, Poole, UK. Hydroxyethylcellulose (Natrosol) Grade 250 HHX Pharm (HEC) was supplied by Aqualon, Salford, UK. Water was reagent Grade 1 and other chemicals used were of AnalaR, or equivalent, quality.

White low relative adhesion fluorinated release liner type 9747 and Scotchpak® backing layer type

1109 were supplied by 3M, Borken, Germany. Perspex templates (internal well measurements 100×100 mm and various depths from 3 to 4.5 mm) were manufactured in-house.

For in vitro drug penetration studies, the barrier membrane used was polydimethylsiloxane, thickness 0.0125 cm (Silescol®, Bibby Sterilin UK).

2.2. Instrumentation

Penetration experiments were performed using modified Franz diffusion cells, FDC-400, flat flange, 15 mm orifice diameter, mounted in triplicate on an FDCD-3 diffusion cell drive console providing synchronous stirring at 600 rpm (Crown Glass, Somerville, NJ).

Temperature maintenance was via water circulation at 37°C (from Techne TE-8J circulating water bath) through diffusion cell water jackets. UV absorbance measurements were made with a Philips PU 8720 spectrophotometer (Philips, Cambridge, UK). Apparent viscosity was determined with a Brookfield Synchro-Lectric Viscometer with LV4 spindle (Brookfield Engineering, Stoughton, MA). Adhesion measurements were made with a SMS Texture Analyser (TA-XT2) in tensile mode (Stable Micro Systems, Haslemere, UK). Differential scanning calorimetry measurements were made with a Model DSC-4 (Perkin-Elmer, Beaconsfield, UK). Laminated pouches for stability testing were heat sealed (Portsdown Engineering, Fareham, UK).

2.3. Patch manufacture

2.3.1. Production of bioadhesive anaesthetic hydrogel

PMVE/MA copolymer was added to water between 95°C and 99°C with constant stirring to produce the required concentration (from 1 to 5% w/w). Upon addition and solvation, the solution initially appears cloudy but clears after stirring for approximately 15 min. The pH of this solution was approximately 2.5 and, following cooling, was raised to the required value by addition of 2 M NaOH. HEC was then added with constant stirring to give a final concentration of 1.5% w/w.

The resulting gel was, in each case, heated to 40°C and the required weight of tetracaine base added, forming oily droplets within the gel. The gel was then stirred rapidly to ensure homogeneity of drug distribution. The pH was checked and adjusted with 2 M NaOH, and water added, with stirring, to final weight. Air bubbles were removed by refrigeration at 4°C.

2.3.2. Casting of hydrogel, film formation and patch assembly

A release liner of appropriate dimensions was placed upon a glass plate, release surface uppermost. A perspex template was secured to the surface with vacuum grease and the required weight of tetracaine gel poured slowly into the template and spread evenly across the area of the template by a conventional knife casting technique. The gel was dried in a constant air flow under ambient conditions.

The dried film was removed from the template and its upper surface attached to the transfer adhesive. The backing layer was then attached to the transfer adhesive and secured firmly. The assembled patch system was finally cut to the required size, conveniently 3×4 cm. An overlapping flap of backing layer was left at one edge of the patch as a peel strip to facilitate easy removal after use.

2.4. In vitro penetration of tetracaine from patch systems through a model barrier membrane

Following the method previously described (Woolfson et al., 1992), the receiving chamber of each Franz cell was filled with 12 ml of phosphate-buffered saline (PBS, pH 7.4) and allowed to equilibrate for 1 h. The barrier membrane was polydimethylsiloxane, thickness 0.0125 cm. Each experiment was performed simultaneously in triplicate, with membranes for each triplicated run cut from the same sheet. Bioadhesive patches (1 cm square) were pre-wetted on one side with 100 μl of water for 60 s and placed, wet side down, against the barrier membrane. Samples of receiving fluid were withdrawn at 10-min intervals over a 2-h period and their tetracaine concentration was determined by UV spectrophotometry at 310 nm using a flow through system.

The steady-state flux of tetracaine, expressed as $\mu g\ cm^{-2}\ min^{-1}$ of drug appearing in the receiving fluid, was determined for each formulation from the slope of the drug concentration (μg/ml) versus time (min) plot via regression analysis for the initial linear section of the release profile. The lag times were obtained by extrapolation of the linear plot to the time axis.

2.5. Determination of apparent viscosity

The viscometer spindle was inserted into a gel sample (previously equilibrated in a sealed glass vessel for several hours) up to the level of the marked immersion groove. The viscometer was adjusted to a speed of 6 rpm and sample equilibration took approximately 45 s. The viscosity of the sample was then determined by multiplying the observed reading by the appropriate Brookfield Factor. Each sample was measured in triplicate.

2.6. Determination of film tetracaine content

Prepared tetracaine films (1×1 cm) were placed in HCl (5.0 ml, 1 M). When film dissolution was complete, the solution volume was adjusted to 100.0 ml with distilled water. A further dilution (1:25) was made with distilled water and the resulting solution analysed for tetracaine content by reverse phase, ion-pair high performance liquid chromatography, as previously described (Woolfson et al., 1992). Uniformity of film content was analysed by random selection of six 1×1 cm sections.

2.7. Bioadhesion measurements

Candidate patch systems (1 cm square) were attached to the probe of the Texture Analyser (in tensile mode) with double-sided adhesive taped and the exposed surface pre-wetted with water (100 μl, 60 s). Adhesion to neonate porcine skin was measured at a probe speed of 0.2 mm/s, with a force of 2.5 N applied for 30 s. Adhesion was recorded as the force required to detach the sample from the surface of the excised skin.

2.8. Stability testing

Patch samples were placed in heat sealed pouches and stored at a constant 4°C and 25°C for 6 months. Three samples of each patch (1 cm $\times$ 1 cm) were assayed monthly by HPLC (Woolfson et al., 1992). Concentrations of tetracaine and its degradation product (BBA) were determined from patch assays and expressed as a percentage recovery, based upon the expected concentration of tetracaine per unit area. The pouches were immediately resealed and replaced in the appropriate location. The seals of the pouches were checked by placing the sealed pouch, containing the sample, into a solution of crystal violet for 24 h, opening and inspecting for leaks.

Samples of tetracaine films (approximately 10 mg, accurately weighed) were placed into aluminium DSC sample pans and hermetically sealed to prevent the formation of a water endotherm at 100°C. A blank pan was similarly

Table 1
Characteristics of tetracaine percutaneous local anaesthetic films prepared from various weights of a standard casting gel containing 2% w/w PMVE/MA, 1.5% w/w HEC and 1% w/w tetracaine

	n	Gel weight (g) cast in 100×100 mm template		
		45	10	5
Film weight (g) after ambient drying	5	4.3642 ± 0.140	0.799 ± 0.026	0.488 ± 0.026
Water loss (%) on drying	5	90.302 ± 2.930	92.014 ± 3.007	90.248 ± 4.536
Thickness (mm) of dry film as determined by micrometer	5	0.215 ± 0.019	0.0828 ± 0.005	0.054 ± 0.005
Tetracaine concentration (mg cm^{-2})	6	4.5 ± 0.18	1.0 ± 0.03	0.5 ± 0.08

All values are $\pm$ S.D.

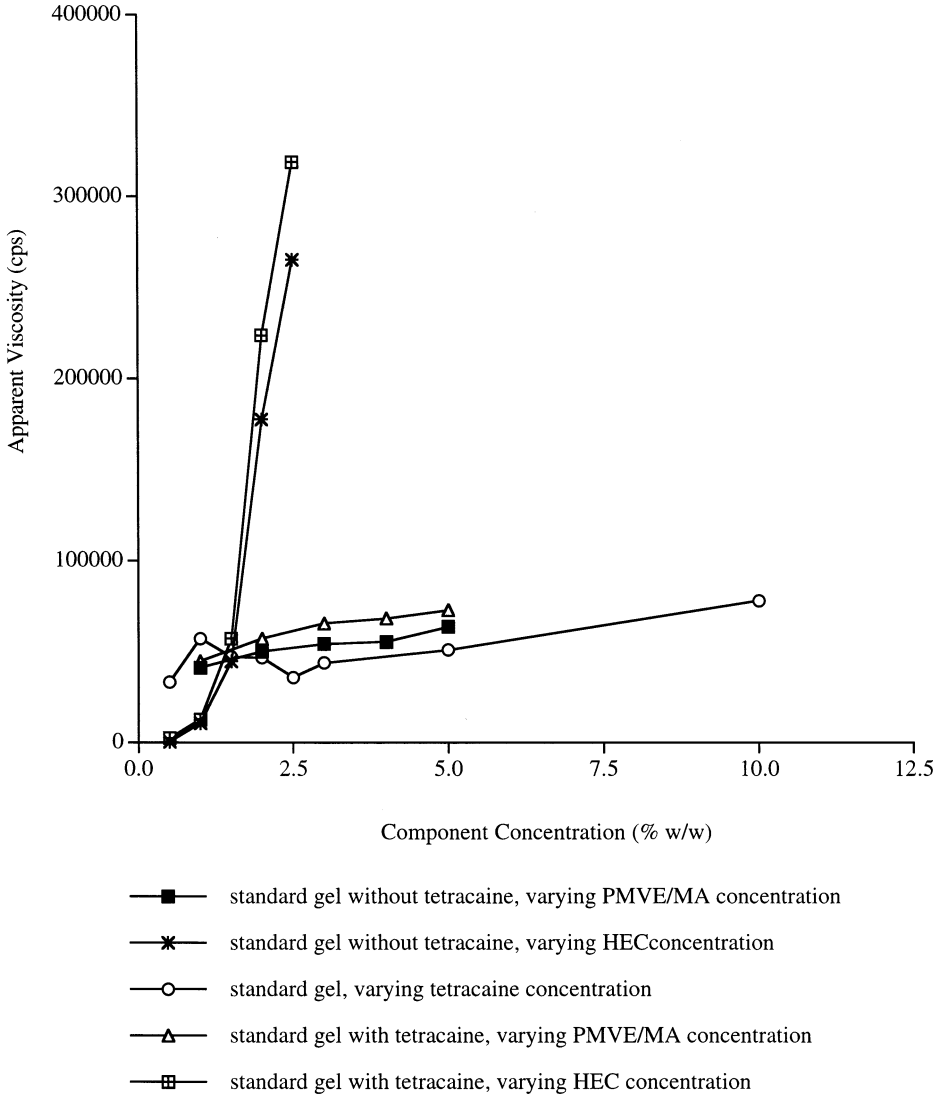

Fig. 1. Apparent viscosities of film casting gels, with and without tetracaine, with varying concentrations of either poly(methylvinyl ether-maleic anhydride) (PMVE/MA), hydroxyethylcellulose (HEC) or tetracaine. The standard gel contained 2% w/w PMVE/MA, 1.5% w/w HEC and 1% w/w tetracaine base at pH 9.

prepared and employed as an internal reference during scans. The calorimeter was calibrated with indium as a standard (melting point 156°C). Samples were scanned at 10°C min^{-1} and 0.5 mCal full sensitivity from 30°C to 200°C. The melting point of tetracaine (°C) in the dried film formulation was recorded from the DSC scans.

2.9. Volunteer trial

Adult volunteers (12) aged between 23 and 48 years of age, all of whom gave informed consent in writing, applied the patch to an area of healthy, intact skin on the forearm, at or near the anterior cubital fossa. Local ethical committee approval for the study was obtained. The patch was applied

for 30 min in each case, after which it was removed, the treated area delineated and assessed for anaesthesia by pin-prick challenge, as previously described (Woolfson et al., 1988).

2.10. Statistical analysis

Where appropriate, results were evaluated using a single factor ANOVA. Inter-comparisons of candidate formulations were made with the Fisher Exact Test, where $p < 0.05$ was taken to represent a statistically significant difference.

3. Results and discussion

3.1. Bioadhesive film formulation, patch design and characteristics

The novel aspect of the tetracaine patch system for percutaneous local anaesthesia is the combination of a water-activated drug with a water-activated bioadhesive. Formulation development was aimed at the production of an active tetracaine film, as a patch component, such that the following requirements were satisfied: pharmaceutical elegance; mechanical properties—tensile strength, plasticity and conformability to irregular surfaces; security of location at the skin site; low residue on removal (related to the internal cohesion of the film and the amount of bioadhesive polymer in the casting gel); sufficient viscosity of the casting gel such that the drug remains in homogeneous dispersion during the casting (film forming) process; optimal drug release pattern for clinical efficacy; ease and rapidity of manufacture; physical and chemical stability, the latter being related primarily to removal of mobile water from the system.

Incorporation of air bubbles into the hydrogel solutions was a regular problem associated with

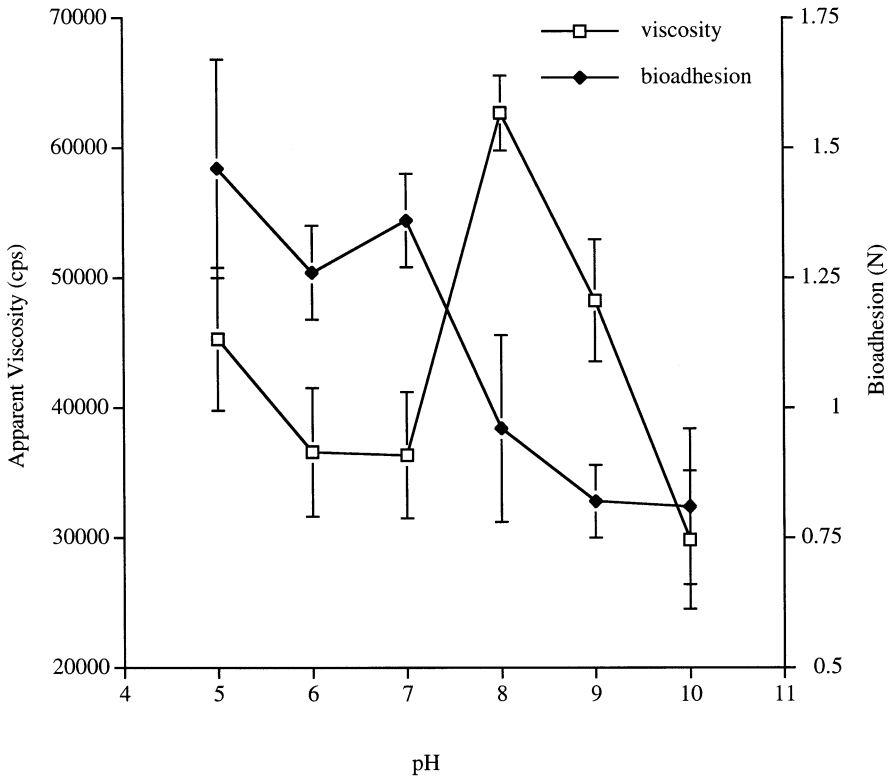

Fig. 2. Apparent viscosities of film casting gels containing 2% w/w poly(methylvinyl ether-maleic anhydride) (PMVE/MA), 1.5% w/w hydroxyethylcellulose (HEC) and 1% w/w tetracaine base from pH 5 to 10.

mechanical mixing, especially with more viscous materials. Centrifugation of the water-based systems was not possible, as suspended solid material would settle out. Therefore, refrigeration at 4°C was the preferred method of clearing gels of entrapped air. Air bubbles also occasionally became introduced to the gel during the casting process. Although this was rare and mostly associated with highly viscous materials, it was nonetheless problematic, both in terms of film appearance and subsequent characterisation. The problem was solved by placing the cast film under a slowly-drawn vacuum, forcing air bubbles to the surface of the material.

The main problems associated with film formation were the suspension of the drug in its vehicle, the total amount of solid materials present in the casting gel and the amount of solvent (water) to be rapidly removed. Various methods of film drying were initially examined. Drying at an elevated temperature was not possible because the aqueous phase-change system lowers the melting point of tetracaine base to approximately 32°C (Woolfson and McCafferty, 1993b). In this situation the drug melts, forming an oil that settles on the surface of the aqueous gel layer. Upon cooling, this results in a film where the drug component was distinct from the polymeric excipients. Therefore, a conventional drying oven could not be used to dry drug loaded films. Accelerated drying, employing either cold or hot air streams, caused channels and fissures to be cut into the gel, resulting in aesthetically unacceptable films. Therefore, films were dried at ambient temperature in a constant, slowly-flowing air stream. In this study, a 24-h standardised drying period was used for all candidate formulations. This allowed the gel layer to dry as slowly as possible and all dried films could be directly compared in subsequent studies.

The substrate that supports the gel during drying must be impermeable to both the casting solvent and tetracaine, in order to maintain the desired drug concentration in the final product. Gels that were cast directly onto the backing material adhered insufficiently when dried to produce an integrated patch device. Casting the hydrogels onto a drug-impermeable, fluorinated release, using Perspex templates and base plates, proved more successful. The dried films did not stick to the release liner, but attachment of an intermediate transfer adhesive, to which the backing material was subsequently secured, provided a convenient method of patch construction.

Table 2
In vitro drug flux and lag time determinations for moisture-activated, bioadhesive tetracaine films through a polydimethylsiloxane barrier membrane

Formulation (casting gel)[a]	Flux (mg cm^{-2} min^{-1})	Lag time (min)
PMVE/MA content (% w/w)		
1	0.301 ± 0.007	2.170 ± 2.010
2	0.168 ± 0.003	2.989 ± 2.665
3	0.130 ± 0.055	8.241 ± 1.042
4	0.127 ± 0.049	6.340 ± 0.933
5	0.077 ± 0.006	6.215 ± 0.421
HEC content (% w/w)		
0.5	0.303 ± 0.072	3.833 ± 1.468
1.0	0.188 ± 0.039	6.89 ± 4.011
1.5	0.168 ± 0.003	2.989 ± 2.665
2.0	0.109 ± 0.028	13.021 ± 1.719
2.5	0.049 ± 0.005	6.519 ± 1.514
pH		
5	0.048 ± 0.011	15.368 ± 6.857
6	0.017 ± 0.008	11.226 ± 3.611
7	0.075 ± 0.022	15.135 ± 3.083
8	0.118 ± 0.022	9.112 ± 2.011
9	0.168 ± 0.003	2.989 ± 2.665
10	0.149 ± 0.034	4.003 ± 1.767
Tetracaine content (% w/w)		
0	—	—
0.5	0.104 ± 0.013	10.210 ± 2.190
1.0	0.168 ± 0.003	2.989 ± 2.665
1.5	0.190 ± 0.025	3.040 ± 1.313
2.0	0.286 ± 0.031	3.043 ± 1.619
2.5	0.303 ± 0.048	1.524 ± 0.701
3.0	0.326 ± 0.042	2.146 ± 1.500

[a] The values listed in the first column refer to the parameters being investigated. Unless otherwise stated, gels contained 2% PMVE/MA, 1.5% HEC and 1% tetracaine base at pH 9.

Film thickness could be varied by changing the weight of gel cast. Table 1 gives the characteristics of dried films produced from various cast weights of gel. In particular, the films were extremely thin, allowing the construction of aesthetically satisfactory patches. Identical cut sections were found to be of uniform weight and reproducible drug content throughout (Table 1), indicating that the

viscosity of the casting gel was sufficient to ensure a homogeneous drug dispersion throughout the casting and drying processes. After drying, films retained approximately 10% of water bound within the cross-linked hydrogel structure.

3.2. Viscosity and in vitro drug penetration

In order to optimise film formulation, a range of bioadhesive (PMVE/MA), viscosity builder (HEC) and active agent (tetracaine) concentrations were employed. The principle underlying the development process was to match the clinical efficacy of the commercial system, where approximately 1 g of a 4% w/w tetracaine gel is applied to the treatment site prior to venepuncture and related procedures, equivalent to a topical dose of approximately 40 mg of tetracaine. The size of the treatment site is influenced by the need to cover two adjacent veins, in order to give an alternative site for the procedure. Clinical advice suggested that the minimum patch size for this purpose was 4×3 cm.

Percutaneous anaesthesia is unique in that it is relatively simple to test for clinical efficacy of candidate formulations by pin-prick, provided trained volunteers are employed. Using procedures described previously (Woolfson et al., 1988) it became apparent during initial volunteer tests that films formed from the most viscous gels were those that induced the least, or no, skin anaesthesia. Viscosity was judged in this case by a simple measurement of apparent viscosity on the Brookfield scale. The variation in viscosities of the various casting gels is shown in Fig. 1 for a standard casting gel at pH 9 comprising tetracaine

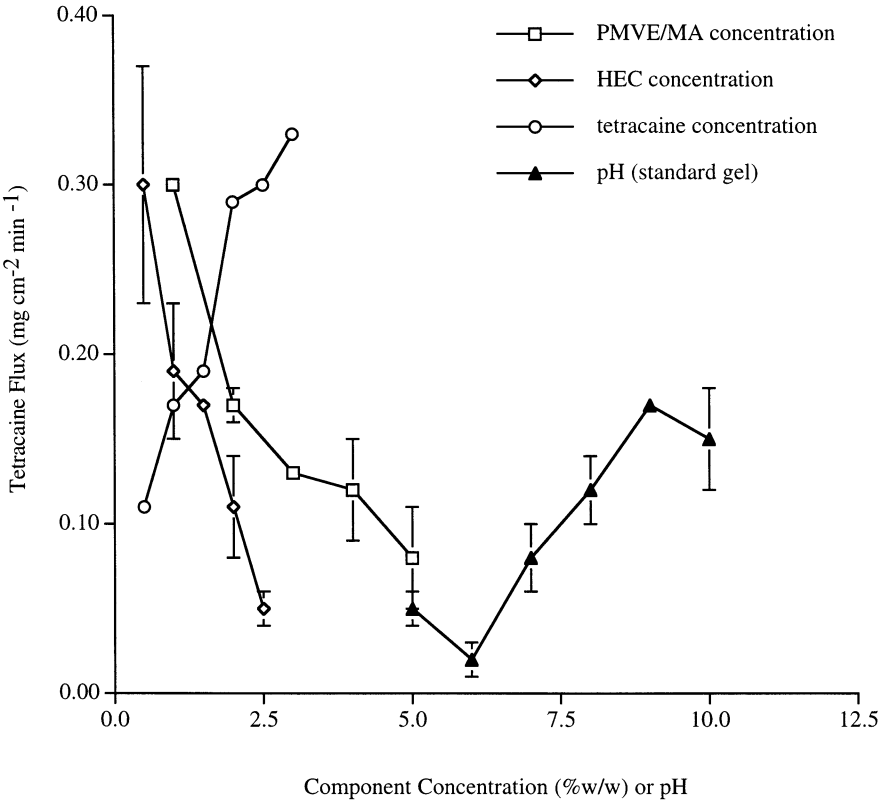

Fig. 3. Tetracaine flux values (mg cm^{-2} min^{-1}) through polydimethylsiloxane of bioadhesive films cast from gels with varying concentrations of either poly(methylvinyl ether-maleic anhydride) (PMVE/MA), hydroxyethylcellulose (HEC) or tetracaine, or with varying pH from 5 to 10. The standard gel contained 2% w/w PMVE/MA, 1.5% w/w HEC and 1% w/w tetracaine base at pH 9.

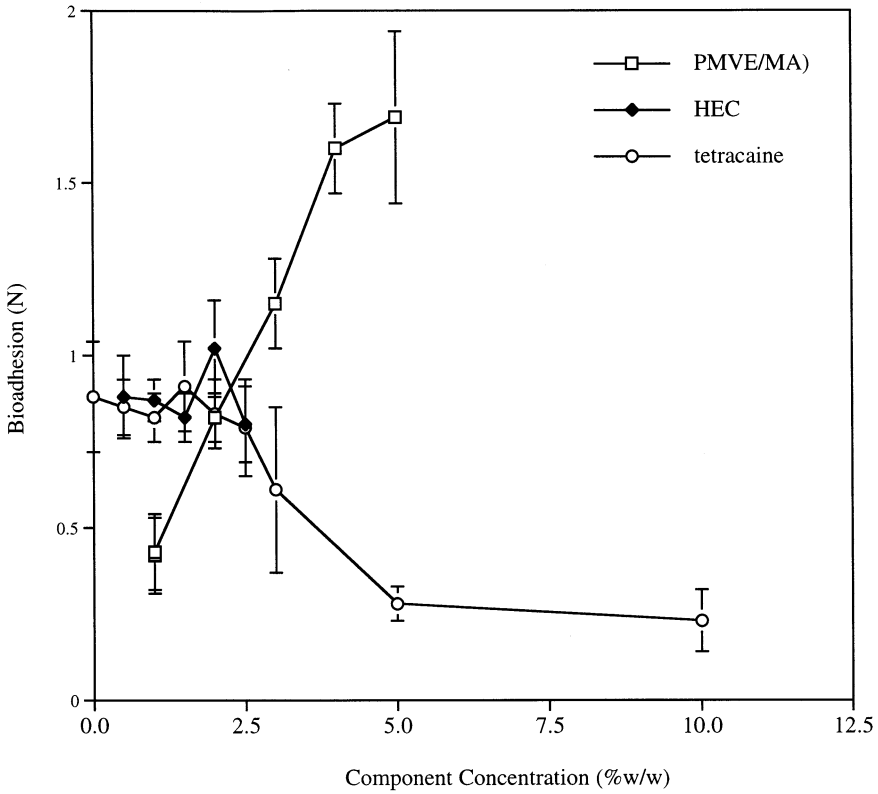

Fig. 4. Bioadhesion (expressed as force of removal of film from substrate) to neonate porcine skin of bioadhesive films cast from gels with varying concentrations of either poly(methylvinyl ether-maleic anhydride) (PMVE/MA), hydroxyethylcellulose (HEC), or tetracaine. The standard gel contained 2% w/w PMVE/MA, 1.5% w/w HEC and 1% w/w tetracaine base at pH 9.

(1% w/w), PMVE/MA (2% w/w) and HEC (1.5% w/w), with each component systematically varied while the other two were held constant at their standard values. A more complete rheological evaluation of the casting gel systems has been reported previously (Woolfson et al., 1997), with pseudoplastic gels containing $< 2.5\%$ tetracaine exhibiting little thixotropy and rapid structural reformation after pouring.

At lower drug contents, there was little effect on apparent viscosity. However, at higher tetracaine concentrations, viscosity was affected by the increased presence of suspended solid particles in the gel. Increases in PMVE/MA and HEC content produced expected increases in apparent viscosity, with a viscosity maximum due to pH variation at pH 8 (Fig. 2), as expected from the known behaviour of the PMVE/MA copolymer.

Although, in low viscosity gels, a major problem was settling out of the solid drug from the gel matrix, higher viscosity systems were clinically inactive, even when higher drug loadings were used in the casting gel. With a higher viscosity casting gel, it is likely that the micro-viscosity at the surface of the resultant water-activated film becomes the determining factor in drug release, reducing drug flux to a point where an insufficient drug concentration can be achieved at the dermal nociceptors (pain receptors) in order to produce the desired pharmacological action. Thus, tetracaine flux from a range of films prepared by varying systematically all the components of the casting gel was studied in a standard Franz diffusion cell experiment (Franz, 1978), with polydimethylsiloxane as the barrier membrane. For in vitro percutaneous drug diffusion, where lipophilicity of the penetrant is the prime determi-

nant of drug flux across the barrier, polydimethylsiloxane has been shown to correlate well with the in vivo situation and is particularly useful in the development of percutaneous local anaesthetic systems (Garrett and Chemburkar, 1968; Woolfson et al., 1988).

The data obtained for in vitro penetration of tetracaine through polydimethylsiloxane showed pronounced trends (Table 2). In every case an initial lag time was observed, followed by the steady-state appearance of tetracaine in the receptor fluid. The data were analysed by simple regression analysis, providing lag times and flux values for each formulation. The flux data showed good fit to the simple linear model, demonstrating steady-state penetration characteristics after the characteristic lag period. Drug flux remained in the linear phase during the sampling period.

The effect of altering PMVE/MA and HEC concentrations in the casting gel for drug release through polydimethylsiloxane membranes is shown in Fig. 3. Tetracaine flux values decreased and lag times increased as the concentrations of both polymer components increased. Increasing the concentration of PMVE/MA or HEC in the casting gel and, thus, in the resultant film, increased the viscosity of the gel and, consequently, the film thickness. Such an increase will raise the micro-viscosity of the water-activated film and provide a more concentrated matrix from which the drug will be released more slowly. The low flux values seen with films formed from higher viscosity casting gels containing, for example, 5% PMVE/MA, correlated with their observed lack of clinical efficacy. Indeed, such films left a tacky and unacceptable residue at the treatment site.

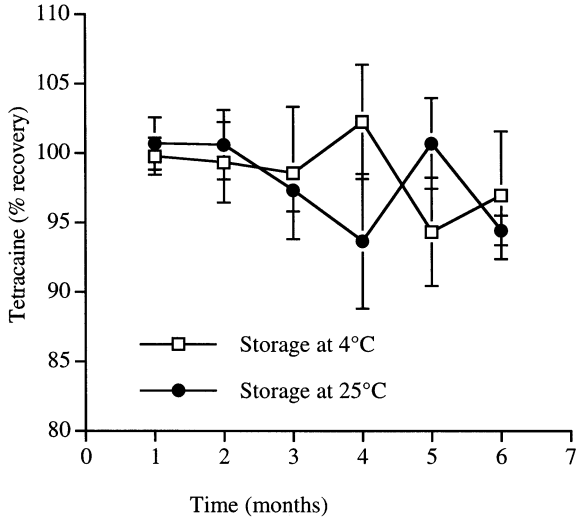

Fig. 5. Recovery (%) of tetracaine during storage at 4°C and 25°C from percutaneous anaesthetic patches in which the bioadhesive film component was cast from a gel containing 2% w/w PMVE/MA, 1.5% w/w HEC and 1% w/w tetracaine base at pH 9.

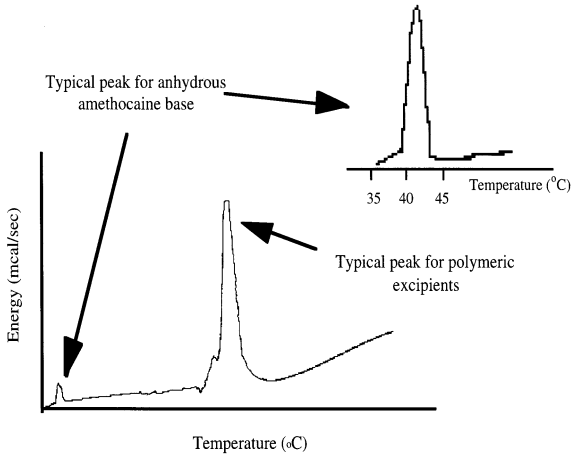

Fig. 6. Differential scanning calorimetry of a bioadhesive tetracaine film cast from a gel containing 2% w/w PMVE/MA, 1.5% w/w HEC and 1% w/w tetracaine base at pH 9.

An increase in drug loading, where other parameters were constant, resulted, as expected, in a linear increase in flux (Fig. 2). Lag times were not significantly affected since these are dependent on the diffusion coefficient of the drug and the membrane thickness. Increasing the drug loading can be considered as increasing the concentration gradient between donor and receptor phases, consequently increasing the driving force, or 'push' effect of drug from the vehicle. Providing there is no significant restraint on drug release, it is known (Ametop™ data sheet, 1996) that an application of approximately 40 mg of tetracaine from a gel formulation provides clinically effective percutaneous local anaesthesia. A tetracaine patch, 3×4 cm, provides a defined dose of 54 mg (Table 1), in a similar range allowing for variations in the area of the treated site.

The effect of altering the casting gel pH is shown in Fig. 3. Films formed from casting gels formulated at pH 5, pH 6 and pH 7 all showed similar, low flux values and long lag times, whereas the release of tetracaine from vehicles formulated at pH 8, pH 9 and pH 10 all exhibited similar, high flux values and short lag times. This effect can be explained by the amount of drug in the lipophilic, or unionised form. The pK_a of tetracaine is 8.39. Thus, at pH 5, pH 6 and pH 7 there are, respectively, 0.041%, 0.406% and 3.914% of the drug in the lipophilic, free base form. At pH 8, pH 9 and pH 10 there are, respectively, 28.946%, 80.291% and 97.604% of the drug in the unionised, lipophilic form, the ideal state for penetration of the predominately lipophilic polydimethylsiloxane barrier. Therefore, in order to provide a greater amount of tetracaine in free base form, the casting gel should preferentially be at a skin-compatible pH ≥ 8.

Statistically, analysis of flux data by single factor ANOVA and the Fisher Exact Test showed that variation in the concentration of each parameter produced significantly different ($P < 0.05$) flux values. For PMVE/MA concentration, comparisons of flux data for concentrations of 2% w/w with 3, 4 or 5% w/w all yielded significantly different (lower) fluxes, correlating with the observed reduction in clinical efficacy for those systems with higher polymer content. A similar trend was observed for HEC content. Casting gel pH and tetracaine content also significantly affected drug flux, the former through increasing the amount of local anaesthetic agent in the free base form, as observed with other local anaesthetic systems (Menczel and Goldberg, 1978; Miller et al., 1991).

3.3. Bioadhesion

The adhesion of candidate patches to neonate porcine skin was evaluated in tensile mode in order to investigate the security of attachment at the site of films formed from lower viscosity casting gels. Only lower viscosity systems had acceptable in vitro drug flux values and in vivo clinical efficacy comparable to the commercial tetracaine gel product. In producing these systems, the adhesive component (PMVE/MA) was, of necessity, reduced in concentration. Fig. 4 shows the effect of varying the casting gel composition on bioadhesion to the substrate. Increasing the concentration of PMVE/MA increased bioadhesion significantly up to PMVE/MA concentrations of 4%. Higher bioadhesive concentrations probably require a longer wetting period with a greater volume of water. However, when the method of patch application in vivo is considered, significant adhesion must occur relatively quickly. This clinical need is reflected in the test parameters chosen in this study.

Varying the concentration of HEC in the casting gel did not significantly influence bioadhesion. Increasing the casting gel pH decreased patch adhesion (Fig. 2), although changes were not consistently significant. Although film adhesion decreased as the pH of the casting gel was increased, this trend did not affect the in vivo performance of patch devices and was secondary to the need for gel formulation at or above pH 8 in order to provide an adequate amount of drug in the unionised form for rapid penetration of the skin. Given that only a short period of attachment (30–45 min) at the treatment site is required, all systems tested had adequate adhesion to securely locate the device on the skin. Further, the lower adhesion patches had the practical advantage of leaving little or no residue at the site following removal of the patch.

3.4. Stability testing

The seal on each pouch was found to be intact in every case examined. Fig. 5 shows the percentage tetracaine recovered by the assay after storage at 4°C and 25°C (ambient temperature) for 6 months. Chromatograms did not show any detectable quantities of the primary hydrolysis product, BBA. Further, there were no significant ($P < 0.05$) differences between the percentages of drug recovered after each month.

Differential scanning calorimetry (Fig. 6) showed two endotherms, with that at 41.25 ± 2.06°C corresponding to the melting point range of anhydrous tetracaine base (40–42°C). The second endotherm is due to a polymeric excipient.

The value for the tetracaine endotherm is significant in that it suggests that tetracaine base does not undergo a depression in melting point within the 'dry' film formulation, in which the remaining water content is not available to form a lower melting hydrate. Since the primary degradation route for tetracaine, a water-labile drug, is via base-catalysed hydrolysis of the ester group, this lack of interaction with water confirms the concept of improving tetracaine stability by formulation in a 'dry' carrier.

3.5. Final design and clinical efficacy

The most appropriate casting gel system that was compatible with the requirements of providing sufficient tetracaine as the free base, drug flux, clinical efficacy, sufficient adhesion and low residue following removal was that containing tetracaine (1% w/w), PMVE/MA (2% w/w), HEC (1.5%) at pH 9, with a cast weight of 45 g in a $100 \times 100 \times 3$ mm template. A plasticiser was not required, the resultant film being flexible, strong, non-adhesive when dry and easily handled in final patch construction. In a basic evaluation of clinical efficacy using trained volunteers exposed to multiple pin-prick challenge, all volunteers reported complete skin anaesthesia at the patch-treated site with a mean onset time of $44 + 6.7$ (S.D.) min from initial patch application (application time 30 min) and a duration of activity in excess of 4 h in every case. These figures correspond well with those previously reported (Woolfson et al., 1990) for the tetracaine percutaneous anaesthetic gel system, indicating that the water-activated bioadhesive tetracaine patch will offer a convenient alternative in the provision of clinically effective percutaneous local anaesthesia, particularly where a precisely defined dose and/or a larger area of skin are to be treated.

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