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Mechanical Characterization and Drug Permeation Properties of Tetracaine-loaded Bioadhesive Films for Percutaneous Local Anesthesia

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ABSTRACT In the development of bioadhesive patch devices for percutaneous local anesthesia, the tensile properties of the films produced after the casting of the gel intermediates is of key importance to the clinical compliance of the product, and its effective delivery of the local anesthetic agent. A range of bioadhesive patches were formulated and their mechanical and in vitro permeation properties determined. Altering formulation significantly altered the mechanical properties of films. The tensile properties of the films could be modified to allow concomitant benefits in the mechanical and drug permeation properties of the films, ensuring that patches not only exerted clinically beneficial effects, but are also mechanically robust. Tetracaine was found to plasticize films and while this effect was weak, it was significant both statistically and potentially also in the effect it has on the clinical use of these devices. Drug release from tetracaine patches demonstrate the same trends as found previously across polydimethylsiloxane films. By altering the formulation of the patch device, the drug release from the device to the skin is readily and accurately controlled, and was not solely a function of the *stratum corneum* barrier properties but additionally of the formulation.

KEYWORDS Tetracaine, Percutaneous absorption, Percutaneous local anesthesia, Texture analyzer, Tensile testing

INTRODUCTION

Percutaneous local anesthesia is the effect that occurs when a suitable therapeutic agent penetrates the intact, healthy *stratum corneum* barrier and desensitizes the underlying nociceptors by reversibly blocking conduction in the peripheral nervous system (Woolfson and McCafferty, 1993a). Of the formulations and products available for the clinical provision of percutaneous local

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anesthesia, those based on the amethocaine (tetracaine) phase change system (Woolfson and McCafferty, 1993b) demonstrate the greatest clinical efficacy, in terms of onset time and duration of the resultant anesthesia, (Russell & Doyle, 1997; Lawson & Morton, 1998).

Commercially, the only available formulations for percutaneous local anesthesia are creams and gels, such as EMLA® Cream and Ametop™ Gel. However, Woolfson and co-workers described the formulation and development of an integrated bioadhesive patch device for percutaneous local anesthesia (Woolfson et al., 1998). This device offered a similar clinical profile to tetracaine gels (McCafferty et al., 2000) but contained substantially less drug.

The patch device is constructed from a bioadhesive gel, which is cast to form a dried film. A patch is constructed from the resulting film by securing it to a backing material via an intermediate adhesive layer (Woolfson et al., 1998). The properties of the final patch depend on the nature of the dried bioadhesive film, particularly the synergy between its effective release of tetracaine and clinical compatibility when applied to the skin surface. Of particular interest is the plasticization of films and the corresponding modification of mechanical properties, illustrated in Fig. 1. Therefore, the aims of this study were to determine the effect of varying film composition exerted upon the mechanical performance of bioadhesive films, and how this impacted upon the drug release of patches manufactured from these films.

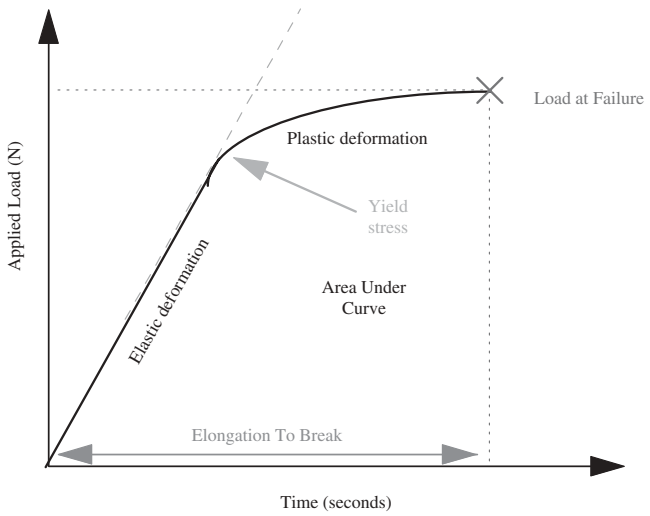


FIGURE 1 **A Typical Load-time Profile Observed in the Tensile Testing of Polymeric Films, Listing Derived Parameters. (Modified from Parikh et al., 1993.)**

MATERIALS AND METHODS

Materials

Amethocaine (tetracaine) free base U.S.P. was supplied by Smith & Nephew, Hull, U.K. (Poly)methylvinyl ether/maleic anhydride was obtained as Gantrez AN-139 Co-polymer from ISP, Manchester, UK. 4-(Butylamino) benzoic acid and procaine hydrochloride were purchased from Sigma-Aldrich, Poole, U.K. Hydroxyethylcellulose (Natrosol) Grade 250 HHX-Pharm was obtained from Aqualon, Salford, U.K. Water was reagent Grade 1 and all other chemicals used were of HPLC, or equivalent, grade. Co-Tran™ transfer adhesive, pharmaceutical grade, type 9871, 6" × 10 yard roll, low relative adhesion release liner, type 9747, color white, 6" × 10 yard roll and Scotchpak™ backing layer, types 1009 and 1109, 6" × 50 yard roll were obtained from 3M, St. Pauls, Mass., U.S.A. Ametop™ gel was a gift from Smith & Nephew, Ltd., and was used as supplied.

Instrumentation

Penetration experiments were performed using modified Franz-type diffusion cells, model FDC-400, flat flange, 15 mm orifice diameter. Cells were mounted in triplicate on an FDCD-3 diffusion cell drive console, providing synchronous stirring at 600 rpm (Crown Glass Inc., Somerville, NJ). Temperature maintenance was via water circulation at 37°C (Techne TE-8J circulating water bath) through the diffusion cell water jackets.

HPLC analysis was carried out was as described by Woolfson et al., 1990a, via a Spherisorb S5 ODS2 Analytical HPLC column, 25 cm (Phase Separations Ltd., Deeside, Wales), "WISP" Autoinjector (Waters Associates, Harrow, U.K), Integrator (model 3390A, Hewlett-Packard, Workingham, U.K.), pump (model 302, fitted with 802 manometric module, Gilson Ltd., Villiers-le-bel, France), and a variable wavelength detector (LBK, Bromma, Sweden). For experiments with a Silastic® membrane, UV analysis was performed via a Helios B UV spectrophotometer (Helios Ltd., U.K.)

Film tensile properties were determined with a SMS Texture Analyzer (model TA-XT2, Stable Micro Systems, Haslemere, U.K.), and appropriate attachments, in the tension mode.

Production of Gels and Casting of Films

The 26 gels formulated in this study were produced according to the method described by Woolfson et al. (1998), and are listed in Table 1. Briefly, this method involved preheating water to 95–99°C and adding PMVE/MA. This was stirred until a clear solution was obtained. The pH of this solution is approximately 2.5, and it was adjusted to the desired pH upon cooling to room temperature. Appropriate concentrations of glycerol and HEC were added as required. The gel was heated to 40°C and tetracaine free base added and mixed thoroughly into the matrix. The gel was made up to weight with water upon cooling. Films were obtained by pouring the gels onto the release liner and drying in a constant air flow. Patches were constructed by attaching the transfer adhesive to the tetracaine film. The Scotchpak™ backing layer was then attached to the adhesive, producing the final patch device. Patches are listed within certain specific groupings (i.e., different concentrations of adhesive, drug, etc.), and as such several of the formulations are the same, and are repeated in this table. These are gels 2, 8, 20 and 23–the formulation previously proposed as the "lead" formulation (Woolfson et al., 1998). In all cases, gels were cast onto the patch release liner with the aid of a perspex template. All films cast were dried under a constant air stream for 24 h at ambient temperature.

TABLE 1 **Formulations Examined in this Study**

	FORMULATION OF GELS (as % w/w in casting gel)				
Gel number	PMVE/MA	HEC	Glycerol	Casting gel pH	Tetracaine base
1	1	1.5	—	9	1
2	2	1.5	—	9	1
3	3	1.5	—	9	1
4	4	1.5	—	9	1
5	5	1.5	—	9	1
6	2	0.5	—	9	1
7	2	1	—	9	1
8	2	1.5	—	9	1
9	2	2	—	9	1
10	2	2.5	—	9	1
11	2	1.5	0.5	9	1
12	2	1.5	1	9	1
13	2	1.5	1.5	9	1
14	2	1.5	2	9	1
15	2	1.5	2.5	9	1
16	2	1.5	—	5	1
17	2	1.5	—	6	1
18	2	1.5	—	7	1
19	2	1.5	—	8	1
20	2	1.5	—	9	1
21	2	1.5	—	10	1
22	2	1.5	—	9	0.5
23	2	1.5	—	9	1
24	2	1.5	—	9	1.5
25	2	1.5	—	9	2
26	2	1.5	—	9	2.5
27	2	1.5	—	9	3
28	2	1.5	—	9	5
29	2	1.5	—	9	10
30	2	1.5	—	9	—

Characterization of Bioadhesive Film Properties

Tensile measurements were made with a TA-XT2 Texture Analyzer. Rubber-faced grips were attached to the baseplate and the crosshead of the instrument. The upper grip was located above the lower grip so as to leave a gap of exactly 5 mm. The tensile strength of films was measured according to ASTM method D882-91 (ASTM, 1992). Strips of film (70 mm × 10 mm) were cut from the dried film with a scalpel. The samples were placed between, and perpendicular to, the tensile grips which were tightened to ensure that the film did not slip out of the grips during the test. The film was positioned so that at least 1 mm was held securely in each grip and that exactly 5 mm of film was placed between the grips. The test was then begun, with the crosshead moving upwards at a speed of 0.5 mm/s. The distance the crosshead moved upwards depended upon the particular film under examination and was determined for each sample in preliminary investigations. The distances used ranged from 10 mm to 50 mm. Tensile parameters are calculated from load-time profiles, as shown in Fig. 1.

Residual film water content was measured by weight difference using a vacuum oven (Vacutherm Oven, Heraeus Instruments, Germany) at 110°C for 24 h. Film thickness was measured with a micrometer screw gauge (Philip Harris Ltd., England) (n = 6 in both experiments).

The In Vitro Percutaneous Absorption of Tetracaine from Bioadhesive Patches

Patches were constructed as described by Woolfson et al. (1998). Porcine skin was obtained locally. Subcutaneous fat was carefully removed by dissection and the skin was cut into pieces of suitable size for mounting in the diffusion cells. Samples thus prepared were stored at −18°C until required. Percutaneous absorption experiments and subsequent analysis were carried out using excised porcine skin mounted in Franz-type diffusion cells at 37°C, as described previously (Woolfson et al., 1990a, 1992). This involved the "prewetting" of formulations due to the bioadhesive nature of the drug delivery devices. The "lead" tetracaine formulation (as proposed by Woolfson et al., 1998) was analyzed over a 24 h period using both porcine skin and a polydimethylsiloxane (Silastic®) membrane, in order to more fully and realistically characterize the percutaneous absorption characteristics of tetracaine. Sampling was carried out at frequent intervals during the experiments, particularly at the beginning of the experiment, and then after 4, 8, 16, and 24 h. A wider range of formulations (Table 1) were examined over a 2 h time period (with sampling every 15 min), in order to determine the amount of drug absorbed over this short but clinically relevant period (Woolfson & McCafferty, 1993a; McCafferty et al., 2000). All experiments were carried out in at least triplicate. Phosphate buffered saline (pH 7.4) was employed as the receptor phase. Analysis was by reverse-phase HPLC. The steady-state flux of tetracaine (amount per unit area per time) across membranes and, where appropriate, lag times, were obtained by extrapolation of the linear plot to the time axis. Further, in order to provide a suitable reference to previous studies, a polydimethylsiloxane (Silastic®) membrane was also used to characterize percutaneous absorption (Woolfson et al., 1998).

Controls

Patches without tetracaine were formulated by the method described previously (Woolfson et al., 1998) and used as control samples (Table 1, gel number 30). These patches were examined by the same methods as drug-loaded patches.

The impermeability of the patch release liner and backing materials was also examined. The release liner or backing layer was placed across the opening of the Franz cell. Permeability of these patches to tetracaine was assessed by placing the patch with the highest drug loading (10% w/w tetracaine base) on top of the barrier material.

Statistical Analysis

Where appropriate, formulations were compared statistically by an ANOVA test followed by the Fisher Exact Test ($p < 0.05$). Main effects plots were produced (Minitab, v. 13.1) to plot the mean value of each parameter in order to graphically see the effect of different formulation parameters on mechanical and drug release properties of formulations.

RESULTS AND DISCUSSION

Tensile Characterization of Tetracaine Films

Altering casting gel pH and glycerol content produced the most substantial changes in the properties of films subsequently cast (Fig. 2). At casting gel pH values of 5, 6, and 7, the resulting films exhibited hard and tough characteristics, including a substantial plastic region after the yield point. Such materials exhibit a high elastic modulus, high tensile strength, and high elongation of break (Tables 1 and 2). As the pH increased, these properties gradually changed. At pH 8, the elongation to break shortened and the tensile strength began to increase. The elastic modulus provided no significant trend as casting gel pH was increased. At pH 9 and 10, films produced tensile curves that were representative of increasingly harder and more brittle materials. In these films, the plastic region of the curve had virtually disappeared by comparison with the other materials examined. Nothing more than minor changes were observed in the film water content and film thickness (Table 3)

Increasing the pH of the casting gels increased the amount of tetracaine present in the unionized (free base) form, and the viscosity and degree of substitution of PMVE/MA, reflecting the amount of drug present in either the ionized or unionized form. The pKa of tetracaine is 8.39 (Woolfson & McCafferty, 1993a). At pH 5 to 7, the drug is mostly ionized and, as such, is freely soluble in the casting gel matrix. In this pH range, PMVE/MA is mostly in the monosodium form. As the pH is increased, the drug is increasingly present as the free base form and may potentially disrupt the physical polymer conformation in solution, ostensibly due to its decreasing aqueous solubility. However, Raman spectroscopic studies (Dennis et al., 2004) indicate that no specific chemical interactions occur in such systems. Both systems will therefore exhibit different interactions between tetracaine and the polymer blend. At lower pH values, films exhibit a substantial plastic character (Fig. 2) which gradually disappears as the pH is raised. The greater aqueous solubility of tetracaine at lower pH and interactions between the dissolved (ionized) drug and either polymeric excipient therefore contributes to the plastic nature and behavior of the films. This is emphasized by the tensile properties of films cast at pH 8, whose behavior is intermediate to both films at the lower and higher pH values measured. At basic pH, the poorly soluble solid drug [i.e., Woolfson & McCafferty (1993a) reported the solubility of tetracaine to be 250 μL/ml at 37°C] may be responsible for producing a hard and brittle formulation, as the polymer matrix becomes physically interrupted by the solid free base tetracaine dispersed through it. Similar findings were reported by Parikh et al. (1993), who investigated the presence of microcracks in films containing dispersed silica as an anti-tack agent. They concluded that such films exhibited a high degree of internal stress and were unsuitable even for tensile testing.

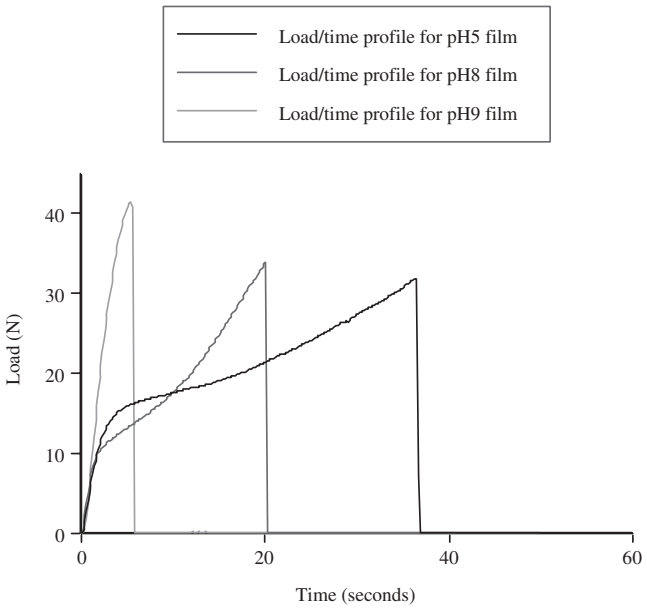


FIGURE 2 **Typical Load/time Profiles Showing the Effect of Casting Gel pH on the Tensile Properties of the Films Subsequently Cast and Dried. *Note*: Formulations Refer to Those Listed in Table 1 (Numbers 16, 19, and 20). Each Formulation Contains 2% w/w PMVE/MA, 1.5% w/w HEC, and 15 w/w/ Tetracaine and Water (to 100% w/w).**

The effect of increased glycerol concentration in films is illustrated in Fig. 3. The first two curves represent load/time profiles of films containing no glycerol, whereas the other curves represent films with increasing amounts of glycerol. The films without glycerol exhibited hard/brittle and hard/tough characteristics. Increasing the concentration of glycerol to 2.5% w/w (in the casting gel) produced films with increasingly elongated load/time profiles which took on larger plastic deformations prior to rupture. Commonly, addition of a plasticizer to a polymeric system lowers the glass transition temperature of that system, rendering it softer and more flexible. Such a modification in

TABLE 2 **Effect of Formulation on Tensile Properties of Cast Films**

Gel number	Formulation	Tensile strength (Nmm^{-2})	Work of failue (Nmm^{-1})	Elastic modulus ($Ns^{-2}mm^{-3}$)	Elongation to break (mm)
1	1% PMVE/MA	14.23 ± 0.90	26.58 ± 3.04	14.87 ± 0.37	2.41 ± 0.15
2	2% PMVE/MA	18.23 ± 0.35	15.58 ± 1.91	24.07 ± 1.06	1.68 ± 0.18
3	3% PMVE/MA	12.88 ± 1.91	16.81 ± 2.36	19.56 ± 1.30	2.08 ± 0.34
4	4% PMVE/MA	7.79 ± 0.49	17.15 ± 1.08	19.86 ± 1.44	1.67 ± 0.30
5	5% PMVE/MA	5.06 ± 0.42	23.32 ± 2.50	16.08 ± 3.07	7.03 ± 1.63
6	0.5% HEC	8.75 ± 1.15	3.25 ± 0.79	15.67 ± 2.09	0.87 ± 0.05
7	1.0% HEC	18.31 ± 2.19	11.75 ± 1.91	23.78 ± 3.27	1.23 ± 0.06
8	1.5% HEC	18.23 ± 0.35	15.58 ± 1.91	24.07 ± 1.06	1.68 ± 0.18
9	2.0% HEC	22.75 ± 1.21	19.48 ± 3.86	30.34 ± 2.58	1.547 ± 0.15
10	2.5% HEC	22.46 ± 2.49	17.14 ± 3.38	28.21 ± 3.66	1.64 ± 0.26
2	0% Glycerol	17.93 ± 0.41	15.38 ± 1.88	24.09 ± 1.06	1.68 ± 0.18
11	0.5% Glycerol	4.73 ± 0.33	27.29 ± 1.66	1.14 ± 0.34	14.72 ± 2.10
12	1.0% Glycerol	2.50 ± 0.16	30.58 ± 0.52	0.37 ± 0.14	19.84 ± 1.27
13	1.5% Glycerol	2.02 ± 0.07	28.93 ± 1.32	0.04 ± 0.01	36.54 ± 1.33
14	2.0% Glycerol	0.64 ± 0.05	10.29 ± 0.55	0.03 ± 0.01	35.08 ± 0.25
15	2.5% Glycerol	1.54 ± 0.07	18.77 ± 1.56	0.04 ± 0.01	38.74 ± 0.46
16	pH 5	14.93 ± 1.03	160.73 ± 33.74	8.58 ± 0.77	16.58 ± 1.82
17	pH 6	16.35 ± 4.15	159.35 ± 28.76	3.84 ± 1.43	19.31 ± 4.04
18	pH 7	13.21 ± 3.13	165.82 ± 32.13	3.76 ± 0.48	19.65 ± 3.62
19	pH 8	16.33 ± 1.43	75.46 ± 26.10	4.34 ± 0.21	7.75 ± 0.82
20	pH 9	18.23 ± 0.35	15.58 ± 1.91	24.07 ± 1.06	1.68 ± 0.18
21	pH 10	6.65 ± 1.13	14.93 ± 1.45	9.34 ± 5.01	1.78 ± 0.16
30	0% Tetracaine	35.86 ± 0.81	30.77 ± 3.76	17.04 ± 0.78	1.15 ± 0.09
22	0.5% Tetracaine	17.39 ± 2.66	13.77 ± 1.73	15.59 ± 0.26	1.25 ± 0.24
23	1.0% Tetracaine	18.23 ± 0.35	15.58 ± 1.91	24.07 ± 1.06	1.68 ± 0.18
24	1.5% Tetracaine	25.48 ± 4.37	16.70 ± 1.90	33.26 ± 2.53	1.20 ± 0.07
25	2.0% Tetracaine	7.46 ± 0.78	15.41 ± 4.10	28.32 ± 8.75	4.39 ± 0.46
26	2.5% Tetracaine	4.01 ± 0.23	17.15 ± 2.38	20.63 ± 4.93	5.63 ± 0.62
27	3.0% Tetracaine	7.98 ± 0.63	17.56 ± 2.59	17.26 ± 2.91	2.84 ± 0.42
28	5.0% Tetracaine	5.52 ± 0.50	7.18 ± 1.03	10.67 ± 0.20	2.12 ± 0.34
29	10.0% Tetracaine	0.53 ± 0.20	0.47 ± 0.10	5.88 ± 3.70	2.20 ± 0.17

Note: Formulation refers to the concentration (% w/w) in the original casting gel. Where it is not specified in this column, each formulation additionally contains 2% PMVE/MA, 1.5% HEC, and 1% tetracaine base, buffered at pH 9. Formulations 2, 8, 20, and 23 are the same, and are listed above for clarity and continuity of each formulation parameter.

properties is essential for topical patch devices, where the inherent rigidity of a particular device may make it difficult to apply, potentially limiting its applications. Other researchers have observed similar effects with the addition of plasticizers to polymeric systems (Arwidsson et al., 1991; Parikh et al., 1993), and such a modification was clearly achieved by the addition of glycerol to the tetracaine patches. However, addition of tetracaine base to the polymeric gel also produced films that were significantly softer and more flexible than comparable formulations without tetracaine. All the systems illustrated in Fig. 3 were formulated at pH 9, where tetracaine is predominately present as an insoluble solid. Although this system has been shown to lessen the plastic nature of the films (Fig. 2), comparison with films omitting tetracaine exhibit significantly higher tensile strength. Films containing no glycerol were significantly thinner and had a higher water content than films with glycerol. However, no significant differences were observed between films containing glycerol at the concentration range examined.

Altering the drug loading of formulations had a less well-defined effect on the tensile properties of films than altering either gel pH or glycerol concentration. Addition of 0.5% to 2.5% w/w tetracaine to the casting gel resulted in films that exhibited significantly lower tensile strength, work of failure and elastic modulus

TABLE 3 **Effect of Formulation on Film Thickness and Water Content of Cast Films**

Gel number	Formulation	Film thickness (mm)	Water content (%)
1	1% PMVE/MA	0.15 ± 0.01	26.20 ± 1.83
2	2% PMVE/MA	0.22 ± 0.02	23.98 ± 1.64
3	3% PMVE/MA	0.27 ± 0.03	23.35 ± 1.05
4	4% PMVE/MA	0.34 ± 0.04	23.24 ± 0.81
5	5% PMVE/MA	0.36 ± 0.04	22.93 ± 0.40
6	0.5% HEC	0.18 ± 0.02	32.38 ± 1.56
7	1.0% HEC	0.19 ± 0.01	30.01 ± 3.25
8	1.5% HEC	0.22 ± 0.02	23.98 ± 1.6
9	2.0% HEC	0.29 ± 0.03	25.83 ± 1.45
10	2.5% HEC	0.30 ± 0.02	24.24 ± 1.61
11	0.5% Glycerol	0.25 ± 0.03	16.28 ± 1.57
12	1.0% Glycerol	0.20 ± 0.01	15.91 ± 2.03
13	1.5% Glycerol	0.21 ± 0.01	15.45 ± 0.54
14	2.0% Glycerol	0.24 ± 0.01	10.91 ± 1.63
15	2.5% Glycerol	0.26 ± 0.01	9.54 ± 4.07
16	pH 5	0.20 ± 0.02	29.000 ± 1.11
17	pH 6	0.224 ± 0.04	26.80 ± 1.06
18	pH 7	0.27 ± 0.04	27.80 ± 1.107
19	pH 8	0.19 ± 0.01	27.00 ± 0.70
20	pH 9	0.22 ± 0.02	23.98 ± 1.64
21	pH 10	0.183 ± 0.02	27.76 ± 1.94
22	0.5% Tetracaine	0.13 ± 0.02	29.90 ± 1.38
23	1.0% Tetracaine	0.22 ± 0.02	23.98 ± 1.64
24	1.5% Tetracaine	0.22 ± 0.03	24.89 ± 0.74
25	2.0% Tetracaine	0.22 ± 0.02	25.88 ± 0.99
26	2.5% Tetracaine	0.31 ± 0.01	25.91 ± 1.27
27	3.0% Tetracaine	0.31 ± 0.02	25.59 ± 0.46
28	5.0% Tetracaine	0.38 ± 0.02	19.32 ± 1.09
29	10.0% Tetracaine	0.71 ± 0.04	19.58 ± 1.11

Note: Formulation refers to the concentration in the original casting gel. Where it is not specified in this column, each formulation additionally contains 2% PMVE/MA, 1.5% HEC, and 1% tetracaine base, buffered at pH 9.

than films without tetracaine. The elongation to break was also significantly greater when 1.0% or more tetracaine was added to the film. However, the results followed no discernible trend until drug loading was raised to at least 5% w/w, which resulted in weak films with low tensile strength and a short elongation to break. Below this concentration, drug loading altered the tensile properties of the materials significantly. Therefore, in low concentrations, addition of tetracaine base to polymer vehicles buffered at pH 9 or above resulted in less brittle and softer films. These changes in tensile properties were not as substantial as changes encountered with the addition of glycerol, but were statistically significant.

Modifying formulations by altering the concentration of either PMVE/MA or HEC did not result in any distinct trends. By comparison with films containing high concentrations of glycerol or tetracaine, these films exhibited hard and tough tensile properties and were predominately elastic in character. This is the case for all these films, except those with 4% or 5% PMVE/MA, and 0.5% HEC, which demonstrated a significant decrease in tensile strength and an increase in elongation to break, indicating a more substantial plastic nature. The ratio of PMVE/MA to tetracaine may alter the interactive effect between both chemicals, with higher concentrations of PMVE/MA tolerating the drug loading so as to produce a system with a greater plastic character. Increasing the concentrations of tetracaine, PMVE/MA, and HEC resulted in significant increases in film thickness and concomitant decreases in film water content.

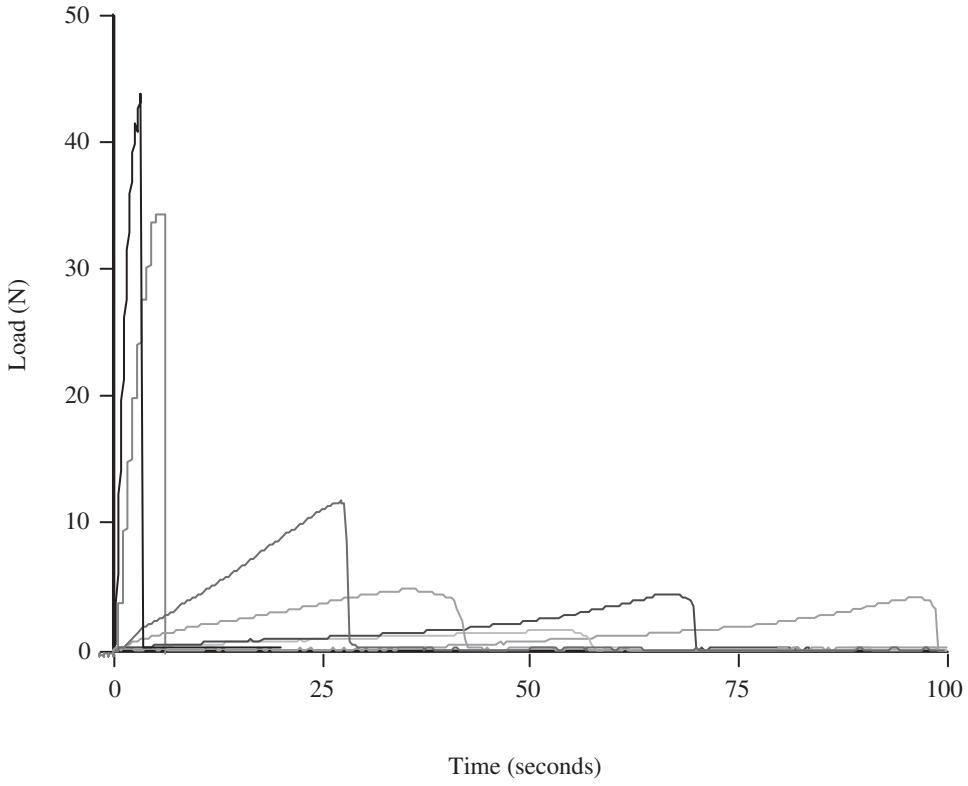


FIGURE 3 **Typical Load/time Profiles Showing the Effect of Addition of 1% Tetracaine to Casting Gel and the Effect of Various Concentrations of Glycerol on the Tensile Properties of the Films Subsequently Cast and Dried.**

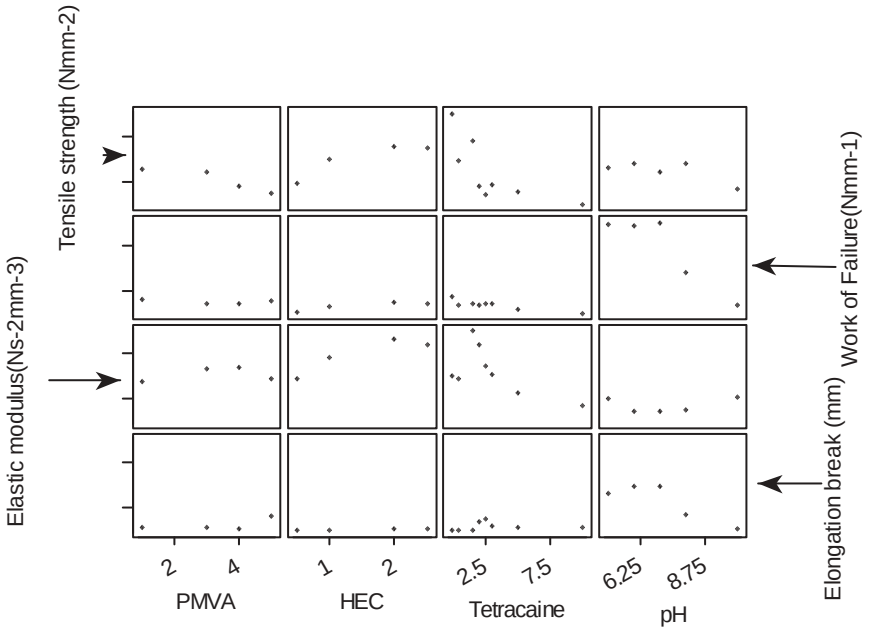


FIGURE 4 **Main Effects Plot for Film Mechanical Properties. The Data Is Presented with Some Data Removed, as the Original Dataset Is Unbalanced (i.e., It Contains a Large Number of Formulations with 1.5% w/w HEC and 1% w/w Tetracaine). Omission of These Points Allows the True Trends to Be Observed.**

In summary, Fig. 4 shows the main effects of formulation on film mechanical properties. While omitting several formulations for clarity, due to an unbalanced formulation set, it demonstrates that altering pH and drug loading significantly influenced film properties, whereas variations in HEC and PMVE/MA

concentrations exerted smaller effects on film mechanical properties.

In Vitro Percutaneous Absorption of Tetracaine

It is common practice to carry out measurements of percutaneous absorption for at least 24 h in order to characterize fully the absorption of an exogenous species. However, in this and a number of previous studies (Woolfson et al., 1992; Woolfson & McCafferty, 1993b; Woolfson et al., 1998), a much shorter experimental duration of 2–4 h is employed. This reflects the clinical window of interest and how it compares to other formulations previously evaluated, both in the laboratory and the clinic (McCafferty et al., 1989; Woolfson et al., 1990b; McCafferty et al., 1997; McCafferty et al., 2000). The present study examines all the formulations manufactured under such clinically relevant timescales, but also investigates the percutaneous absorption of tetracaine from the "lead" patch formulation (as proposed previously by Woolfson et al., 1998) over a 24 h period. Neonatal porcine skin has been shown by other researchers to provide a particularly good comparison with human skin in terms of percutaneous drug delivery (Wester & Noonan, 1980; Woolfson et al., 1992). It was used in this study to reflect the largest area of clinical usage, in topical pediatric anesthesia.

Issues of fresh vs. frozen skin (human or animal) are of huge importance to in vitro or ex vivo studies. In order to produce a consistent series of results, frozen skin from the same animal sources was used where possible. While differences may be apparent in fresh vs. frozen experiments, frozen skin was used in these experiments due to ready availability of such tissue. Further, as this is a comparative formulation study, it may be argued that "relative" values (i.e., the comparison between adjacent formulations) are more important than the "absolute" values. By contrast, if the experiments in this study compared the percutaneous absorption of, for example, a range of exogenous chemicals with different physicochemical parameters that affect absorption (i.e., log *P*, molecular weight), then the issue of using frozen skin would be more pertinent as the freezing of skin may alter its barrier properties.

TABLE 4 Parameters for Moisture-activated Bioadhesive Films Calculated from the Linear, Steady-state, Region—Penetration Through Porcine Skin. All Concentrations Are Expressed as % w/w in Original Casting Gel

Gel number	Formulation	Flux ($\mu g/cm^2/min$) $\times 10^{-3}$
1	1% PMVE/MA	1.70 ± 0.32
2	2% PMVE/MA	1.03 ± 0.23
3	3% PMVE/MA	0.78 ± 0.01
4	4% PMVE/MA	0.46 ± 0.16
5	5% PMVE/MA	0.37 ± 0.02
6	0.5% HEC	2.29 ± 0.32
7	1.0% HEC	1.50 ± 0.30
8	1.5% HEC	1.03 ± 0.23
9	2.0% HEC	0.46 ± 0.02
10	2.5% HEC	0.49 ± 0.11
16	pH 5	0.66 ± 0.04
17	pH 6	0.74 ± 0.12
18	pH 7	0.85 ± 0.08
19	pH 8	0.98 ± 0.13
20	pH 9	1.03 ± 0.23
21	pH 10	1.67 ± 0.26
22	0.5% Tetracaine Base	0.61 ± 0.14
23	1.0% Tetracaine Base	1.03 ± 0.23
24	1.5% Tetracaine Base	1.10 ± 0.36
25	2.0% Tetracaine Base	1.39 ± 0.61
26	2.5% Tetracaine Base	2.77 ± 1.61
27	5.0% Tetracaine Base	4.58 ± 8.06
28	10% Tetracaine Base	24.42 ± 8.62

Note: The concentrations listed in the first column refer to the parameters being investigated. Unless otherwise stated, these gels contain 2% PMVE/MA, 1.5% HEC, 0% glycerol, 1% tetracaine base, and are buffered at pH 9.

The flux of tetracaine absorption through porcine skin is summarized in Table 4, and illustrated in Fig. 5. Lag time data (calculated by the method of Flynn et al., 1974) were found to be inconsistent and followed no discernable trend from short (2 h) experiments, suggesting that the steady-state might not have been achieved. This may be due to the frequency of sampling, and the impact it has on receptor compartment sink conditions. While a 2 h experiment demonstrates clear differences in formulations and has significant clinical and toxicological benefits (i.e., Woolfson et al., 1998; McCafferty et al., 2000), it may be too short to allow an accurate measure to be made of the lag time, nor to establish clearly steady-state kinetics. This is also reflected in the flux of the 10% w/w tetracaine formulation which is unrealistically high (Table 4). Therefore, the 2 h experiments do act

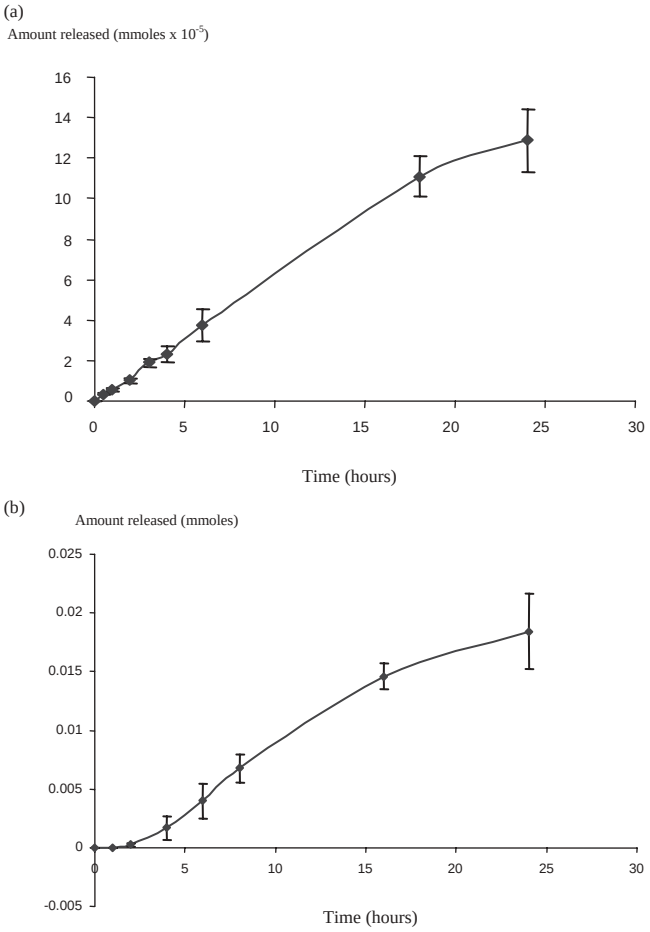


FIGURE 5 **Release Profile of Tetracaine Patch Across (a) Porcine Skin and (b) a Polydimethylsiloxane (Silastic®) Membrane.**

as a rapid and excellent way to compare the effects of formulation on drug delivery and potential clinical efficiacy, but they do not allow the derivation of important information concerning the mechanics of percutaneous absorption.

Figure 6 shows the main effects plots for the formulations examined in this study. Figure 6a indicates clearly that tetracaine loading exerts the main influence on flux. However, when all formulations containing 1% w/w tetracaine are removed (Fig. 6b), the main effects plot indicates that formulations with high pH, low PMVE/MA, and low HEC concentrations are most likely to yield the highest flux. It should be noted that, in Fig. 6, variables that produce an unbalanced design (i.e., 2% PMVE/MA, 1.5% HEC, 1% tetracaine, pH 9) must be omitted from the graphs, and their effects inferred from interpolation (i.e., Fig. 6b).

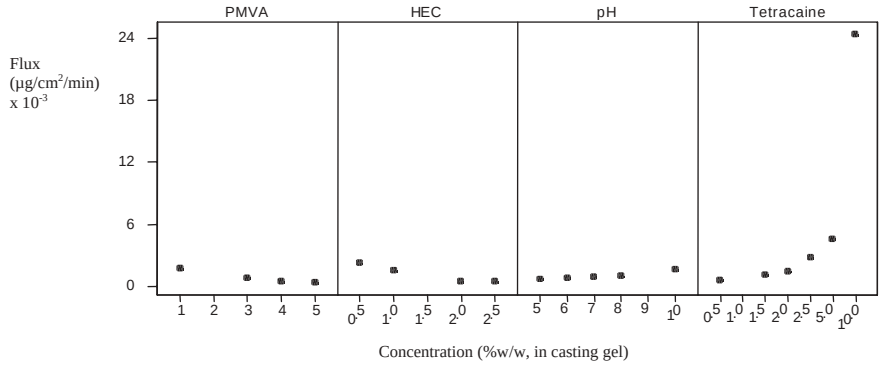
Increasing the concentrations of both PMVE/MA and HEC resulted in decreases in flux. Flux increased as casting gel pH was raised. Raising drug loading increased flux. These decreases are statistically significant between 1% PMVE/MA and all other concentrations of PMVE/MA, between 2% and 4%, and between 2% and 5% PMVE/MA. Increasing the concentration of HEC in the casting gel significantly decreased flux in all cases, except between formulations containing 2% and 2.5% HEC.

Changing casting gel pH significantly affected flux between gels cast at pH 5, and gels cast at pH 8, 9, and 10. Casting gels at pH 6 demonstrated significantly lower flux to gels cast at pH 8 and 9. Further, casting gels with pH values of 6 and 10, 8 and 9, 8 and 10, and 9 and 10 exhibited significantly different fluxes to each other. No significant differences were found between other gel formulations. Significant differences were recorded between the lag times of most of the patches cast at the different pHs. These findings are similar to those reported by Woolfson et al. (1998), where the pH of tetracaine-loaded bioadhesive patches was found to be directly related to the amount of drug delivered across a polydimethylsiloxane membrane, and the proportion of tetracaine present as the lipophilic free base. Despite the clear trends illustrated in this study, the selection of the optimum casting gel pH is mitigated by the clinical response and, in particular, the potential irritation associated with formulations buffered above pH 8.

Drug loading significantly affected flux when patches cast from gels containing 10% tetracaine base were compared with all other formulations and when patches containing 5% tetracaine base were compared with patches containing 0.5%, 1%, 1.5%, 2%, and 2.5%. No significant differences in flux were observed between any other formulations. Tetracaine penetration through excised porcine skin resulted in similar trends to membrane transport across polydimethylsiloxane (Silastic®), described previously (Woolfson et al., 1992, 1998).

Statistical analysis of the mechanical characterization and flux data indicated very few significant correlations between mechanical characteristics and flux. Linear correlations are apparent between tensile properties and flux when concentrations of PMVE/MA and HEC are altered (where r^2 = 67.7–92.0%). It would further suggest that the tensile properties of the other materials employed in patch construction, while varying significantly in their tensile properties, do not exert as significant an effect upon drug release as HEC.

(a) Effect of formulation on flux.



(b) Effect of formulation on flux, omitting formulations containing 1% w/w tetracaine or where tetracaine concentration is varied.

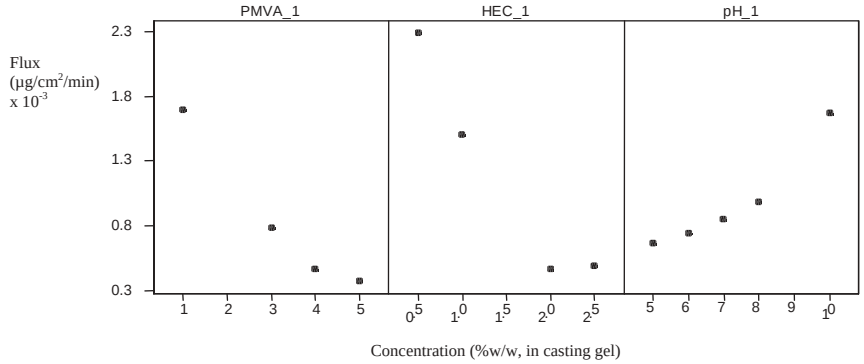


FIGURE 6 **Main Effects Plots for the Effect of Altering Formulation Parameters on Flux Across Porcine Skin. *Note*: The Abscissa Is Non-linear for the Tetracaine Plot, and the Effect Observed Is not Exponential.**

Altering patch formulation by, for example changing the casting gel pH, will also exert changes that are non-linear in nature. These include the nature (i.e., ionized or unionized) of tetracaine in gels across the pH range examined in this study, or changes in the physico-chemical properties of PMVE/MA at different pH values which yield two maxima (at pH 5 and pH 8) which correspond to the ionization respectively, one and then both carboxylic acid groups on the PMVE/MA monomer. Non-linear correlations were made for these parameters, but were found to be inconsistent.

CONCLUSIONS

Altering the formulation of a patch device was found to have a significant effect upon its mechanical performance and the percutaneous absorption of tetracaine. The tensile properties of the films could be modified to allow concomitant benefits in the mechanical and drug release properties of the films, ensuring that patches not only exerted clinically beneficial effects, but are also mechanically robust. Tetracaine was found to plasticize films and while this effect was weak, it was significant both statistically and potentially also in the effect it has on the clinical use of these films (Woolfson et al., 1998).

Drug release from tetracaine patches demonstrate the same trends as found previously across polydimethylsiloxane films (Woolfson et al., 1998). By altering the formulation of the patch device, the drug release from the device to the skin could therefore be accurately controlled, and was not solely a function of the *stratum corneum* barrier properties but additionally of the formulation. Therefore, the moisture-activated bioadhesive patch devices demonstrated comparable flux to tetracaine-loaded gel formulations, due to their

use of the tetracaine phase-change system and the formation of a saturated aqueous diffusion layer between the formulation and the membrane (Woolfson & McCafferty, 1993).

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