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Controlling barrier penetration via exothermic iron oxidation

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ABSTRACT

Exothermic iron oxidation is an elegant means to generate heat, with the potential to modulate barrier penetration if reaction kinetics can be controlled. This aim of this study was to gain a fundamental understanding of how these temperature change kinetics influenced barrier diffusion rate. Lidocaine transport through a hydrophilic carboxymethyl cellulose (CMC) gel was compared using two rapid iron oxidation reactions initiated by water (ExoRap$_{50}$, T_{max}—47.7 ± 0.6 °C, t_{max}—3.3 ± 0.6 min, ExoRap$_{60}$, T_{max}—60.4 ± 0.3 °C, t_{max}—9.3 ± 0.6 min) and a slower reaction initiated by oxygen (ExoSl$_{45}$ T_{max}—ca. 44 °C, t_{max} ca. 240 min). Temperature change induced by the oxygen initiated reaction (ExoSl$_{45}$) was almost double those initiated by water (over 4 h), but lidocaine diffusion was approximately 4 times higher for the latter (ExoRap$_{50}$, 555.61 ± 22.04 μg/cm^2/h; ExoRap$_{60}$, 663.1 ± 50.95 μg/cm^2/h; compared to ExoSl$_{45}$, 159.36 ± 29.44 μg/cm^2/h). The large influence of temperature change kinetics on lidocaine diffusion suggested that transport was heavily dependent on temperature induced structural changes of the barrier. CMC, like many polymers adsorbs more water when exposed to moderate increases in temperature and this appeared to be a critical determinant of lidocaine barrier diffusion rate.

1. Introduction

Introducing a small but significant change in membrane temperature is one method that can be used to promote penetration of chemicals across biological membranes (Blank et al., 1967). This strategy, commonly known as thermophoresis, has previously been shown to drive chemicals across the skin (Hull, 2002). Although controlling the exothermic chemical reaction at the membrane surface can be problematic, the iron oxidation reaction could offer an elegant means to generate heat. With a better understanding of how this oxidation reaction influences barrier temperature change kinetics bespoke systems could be engineered to control the delivery of a number of therapeutic and diagnostic agents.

The lidocaine and tetracaine thermophoresis patch (currently licensed by the Food and Drug Association, USA) utilises iron oxidation to control transmembrane penetration (Zars Pharma, 2008). This exothermic reaction generates heat by combining iron, carbon, sodium chloride, vermiculite and water in a semi-synthetic air permeable pouch (Parkin and Al-Habaibeh, 2003). The pouch is stored in an air tight packet and the heating reaction is initiated upon the breaking of the packaging and exposure of the reactants to oxygen. The multi-step exothermic iron oxidation process generates a $2Fe^{2+}$ intermediate (Eq. (2)) which is sequentially oxidised to ferrous then ferric hydroxide (FeOOH) (Eqs. (3) and (4)). The oxidation product is stabilised upon conversion to maghemite, Fe_2O_3 (Xiao et al., 2008).

$$2Fe_{(S)} \rightarrow 2Fe^{2+}_{(aq)} + 4e^- \quad (1)$$

$$O_2 + 2H_2O_{(1)} + 4e^- \rightarrow 4OH^-_{(aq)} \quad (2)$$

$$2Fe^{2+}_{(aq)}O_2 + 2H_2O_{(1)} \rightarrow 2Fe(OH)_2 \quad (3)$$

$$4Fe(OH)_2 + O_2 \rightarrow 4FeOOH + H_2O \quad (4)$$

Under standard conditions (298 K and 1 bar) the formation of Fe_2O_3 has an enthalpy of −808.1 KJ mol^{-1} (Majzlan et al., 2003). It is essential to understand the nature of an exothermic reaction under standard conditions, but it is difficult to translate this information to transmembrane penetration without knowledge of *in situ* temperature change kinetics. The temperature at the surface of the barrier will be dependent upon the reactants access to water and/or oxygen and the environment in which the reaction occurs and more work is needed to understand how the heat generated by the exothermic iron oxidation process could influence the transmembrane transport process.

In the commercial product used on the skin, the oxidation reaction occurs in a patch that is placed onto the barrier. The exposure to oxygen is controlled using a gas-permeable membrane which is integral to the patch in which the reaction mixture is held. The reac-

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tion is known to achieve a temperature of ca. 42 °C at the surface of the membrane that can be maintained for four or more hours. However, as the oxidation of iron in such patches was originally developed to soothe muscle pain there has been little previously published work that has investigated how the iron oxidation process influences the transmembrane diffusion process (Stanley et al., 2002). Although prolonged exposure to mild increases in temperature may have a positive influence on the diffusion coefficient of a molecule (according to Stokes–Einstein equation) the potential for local sensitisation, chemical degradation and permanent structural alterations of the membrane suggest that research into shorter bursts of higher temperatures may also have merit.

The aim of this study was to gain a fundamental understanding of how the exothermic oxidation of iron influenced transmembrane penetration. In order to achieve this aim a series of iron oxidation systems with very different capacities to change the temperature of a barrier were developed. The iron oxidation reaction can either be controlled by limiting the reactants access to water or oxygen. The commercial patch controls the heat generation by limiting the access of the reactants to oxygen and so in attempt to produce very different heat change kinetics a statistical experimental design was employed to understand how the principle components of iron oxidation reaction controlled heat generation when the reaction was initiated by water. The diffusion of lidocaine (a model agent used to enable comparison to previous work) through a hydrophilic barrier composed of carboxymethyl cellulose (CMC) was compared upon the application of two water initiated reactions and the commercial oxygen initiated iron reaction.

2. Materials and methods

2.1. Materials

Sodium chloride, activated charcoal, iron powder (<212 μm), carboxymethyl cellulose (CMC) sodium salt (medium viscosity, 2% aq. solution at 25 °C, 400–800 cps) were all purchased from Sigma–Aldrich (Gillingham, UK) and were used as received. Vermiculite (grade #3) was also obtained from Sigma–Aldrich but was milled to a fine powder prior to use. Methanol (MeOH) and deionised water (high performance liquid chromatography (HPLC) grade) were both purchased from Fisher Scientific (Loughborough, UK). Lidocaine base (BP grade) (2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide) was purchased from QueMaCo Ltd. chemical marketing company (Nottingham, UK). Phosphate buffered saline (PBS) tablets were purchased from Oxoid (Basingstoke, UK). Regenerated cellulose membrane (RCM) in the form of dialysis tubing (12–14 k molecular weight cut-off) was purchased from Medicell International (London, UK). Loctite® super glue gel (cyanoacrylate) was purchased from Henkel Ltd. (Cheshire, UK). Nurofen® back pain heat patches were sourced from Crookes Healthcare Ltd. (Nottingham, UK).

2.2. Iron oxidation

Iron, carbon, vermiculite, sodium chloride and water were the principle oxidation reaction components. The effect of each iron oxidation component on the temperature change kinetics was investigated using a traditional 2 level full factorial experimental design. Limits of 50 and 1000 mg (except water which ranged between 50 and 2000 μl) were used to produce 21 compositions (including five centre points) using a standard statistical design matrix. Prior to reaction initiation the mixtures were placed in glass vials and agitated using a vortex mixer to ensure even distribution of components. Water was added to the iron oxidation mixtures using a Gilson pipette (Gilson Inc., Middleton, USA) to initiate the reaction. Further oxygen entry into the reaction vessel, after exposure to the initial bolus, was limited using a gas-permeable membrane. The temperature profile measurement of the exothermic reactions was conducted inside a thermoregulated vivarium maintained at 32 °C (to mimic skin surface temperature; Exo Terra, Castleford, UK). A wire probe connected to a thermocouple (Hanna Instruments, Leighton Buzzard, UK) was attached to the basolateral surface of the exothermic reaction vessel. The data was plotted to produce time vs. temperature profiles. Three indices were taken from the temperature profiles and employed in the statistical experimental design analysis, the peak of the maximum temperature change (T_{max}), time to reach maximum temperature change (t_{max}) and the duration (DUR); defined as the time the system took to lose 3 °C from maximum temperature. In the statistical experimental design the heating profiles for each heating device were recorded only once as the error in the profile had previously been shown to be very small and the statistical model assumes the error of the system to be constant. The accuracy of the statistical model, calculated as the average percentage discrepancy in the T_{max} indices which was verified practically using six heating devices selected at random in the design space. Two iron oxidation reactions with different temperature change kinetics were selected from the statistical experimental design and their temperature change profiles were compared in detail with a commercial heat patch which employed an identical iron oxidation reaction that was initiated by oxygen. These three systems were analysed in greater detail and the T_{max}, t_{max}, area under the heat profile curve (baseline at 32 °C between 0 and 240 min) and the heat dissipation rate (assuming log linear kinetics) were compared.

2.3. Diffusion studies

A 2.5% (w/w) CMC hydrophilic matrix was prepared by the addition of CMC to water and stirring for 48 h to allow the system to hydrate. Sufficient lidocaine base was added to CMC to produce a drug sub-saturated vehicle (2.0 mg ml^{-1}) and a drug saturated suspension (10.0 mg ml^{-1}) in the hydrophilic matrix. The lidocaine loaded systems were allowed to stir for a further 24 h prior to use (lidocaine was shown to be stable in aqueous vehicles under these conditions, data not shown). The molecular weight of CMC was higher than the MWCO of the RCM and therefore the polymer would not compete with lidocaine for transport through the porous RCM. Lidocaine diffusion through the hydrophilic CMC matrix was determined using individually calibrated unjacketed upright Franz type diffusion cells (MedPharm Ltd., Guildford, UK) with an average receiver volume of 10.0 ml and an average surface area of 2.0 cm^2. RCM was employed as the barrier due to its excellent temperature resistance (Kallioinen et al., 2006; Medicell International Ltd., 2008). RCM thickness was found not to change throughout the duration of the study at any of the temperatures within the working range (data not shown). RCM was soaked for 30 min at 70 °C in DiH_2O then rinsed. RCM was either glued to the donor chamber, or sealed between the donor and receiver chamber (Fig. 1). The receiver chamber was filled with a PBS (0.15 M, pH 7.3) receiver fluid and equilibrated for 30 min at ca. 37 °C (ensuring a membrane temperature of 32 °C) inside the thermoregulated vivarium. Cells were inverted and checked for integrity by visual inspection prior to initiation of the diffusion study. The experiments were initiated by applying the hydrophilic matrix to the apical surface of the RCM and covering immediately with either the commercial oxygen initiated iron oxidation reaction or the water initiated oxidation reactions generated in-house. An identical material was used to separate both iron oxidation systems from the hydrophilic matrix to ensure consistent contact and heat transfer between the reaction and enclosure where the diffusion occurred (a variety of backings were tested and parafilm was selected as it optimised this

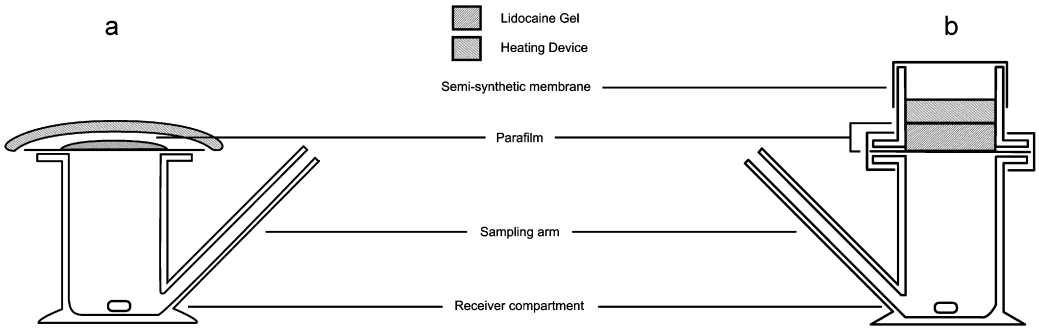

Fig. 1. Diagrammatic representation of a Franz diffusion cell assemblies used to apply two heating systems. (a) An oxygen initiated reaction; (b) a water initiated system.

process, data not shown). Lidocaine diffusion was monitored by removal of 1 ml samples at pre-determined time points from the receiver fluid that maintained contact with the basolateral surface of the RCM. Franz cell receiver volume was replenished with 1 ml thermostatically regulated receiver fluid at each time point. Samples were analysed using HPLC. The cumulative amount of drug per sample area ($\mu g/cm^{-2}$) was plotted against time (h) and steady state release was determined from the linear portion of the plot ($R^2 \geq 0.97$ over five points).

2.4. Lidocaine analysis

The quantitative determination of lidocaine base was performed using HPLC. A 250 mm × 4.60 mm 5 μm Gemini C18 (Phenomenex, UK) stationary phase was used with a 1.2 ml min^{-1} flow rate and a 20 μl injection volume. A column heater (Jones Chromatography, Hengoed, UK) was used to ensure the column was at 50 °C. A 759A UV absorbance detector (Applied Biosystems, USA) was set at a wavelength of 210 nm. A Spectra System AS1000 autosampler (Thermo separation Products, USA) and a PU-980 pump (Jasco, Essex, UK) completed the HPLC system. The mobile phase was a mixture of methanol with deionised water in a 7:3 ratio, adjusted to pH 10.0 with 1 M sodium hydroxide. The average retention time of lidocaine base was 6.9 min and calibration curves were constructed from a series of standard concentrations prepared by serial dilution. This method demonstrated a limit of detection of 0.55 μg ml^{-1} and was shown to be 'fit for purpose' in accuracy, precision and linearity as prescribed by the International Conference on Harmonisation guidelines (data not shown) (ICH, 1996).

2.5. Statistical analysis

Statistical analysis of the data was performed using Statistical Packages for the Social Sciences (SPSS) software (version 16.0; SPSS Inc., Chicago, IL, USA). Analysis of variance was used to compare the cumulative release of lidocaine from the gel (at both thermodynamic levels, 0.5 and 1) after 90 min, between the three systems with attached heat generating devices and the control. The chosen level of significance was $p \leq 0.05$.

3. Results

3.1. Iron oxidation

The statistical experimental design generated a linear mathematical model to describe how the five input variables influenced the three predefined outcomes: T_{max}, t_{max} and DUR. The mathematical equation generated by the statistical design (Table 1) was a good fit to the experimental data for two of the three model outcomes, T_{max} ($r^2 > 0.98$, ANOVA, $p < 0.0001$) and t_{max} ($r^2 > 0.96$, ANOVA, $p < 0.0001$), neither of which showed a significant lack of fit ($p = 0.3117$ and $p = 0.2851$, respectively). The correlation of the mathematical equation with the experimental data for DUR was poor ($r^2 = 0.1707$) and therefore this indices was not used in any further evaluation. Only water and carbon proved to have a significant effect on t_{max} (Fig. 2). Increasing the water available to the oxidation reaction from 50 μl to 2000 μl increased t_{max} from 3.13 to 7.13 min and increasing the carbon present in the reaction from 50 to 1000 mg increased the t_{max} from 4.00 to 6.25 min. T_{max} was a more sensitive indices with all the reaction components influencing this output. Iron was found to have the largest independent effect: an increase of 50–1000 mg changed T_{max} from 33.6 to 36.8 °C. A significant synergistic effect between iron and vermiculite and iron and sodium chloride was identified by the statistical design. The two component interaction between iron and vermiculite had the greatest impact on the temperature change kinetics. This interaction can be described in a linear manner by the observation that altering vermiculite from 50 to 1000 mg with 1000 mg of iron, decreased T_{max} by 4.9 °C from 39.3 °C to 34.4 °C, where as changing the vermiculite content from 50 to 1000 mg and keeping iron content at 50 mg only changed T_{max} by 0.3 °C. The contour plots show in detail how T_{max} changed when vermiculite and sodium chloride were set at a level of 50 mg, water was set at 50 μl and iron and carbon levels varied between 50 and 1000 mg (Fig. 3). The T_{max} recorded for the heating device with 50 mg carbon and 1000 mg iron was 47.45 °C and the t_{max} was 3.63 min. The reliability of the statistical experimental design was shown to be >80% practically by comparing the predicted and actual indices for 6 randomly selected iron oxidation reactions.

Table 1
The significance of the mathematic equation from the statistical experimental design for the three model outcomes, peak of maximum temperature change (T_{max}), time taken to reach maximum temperature (t_{max}) and time at which a 3 °C fall from T_{max} is observed (DUR).

Output	Model significance	r^2 value	Lack of fit
T_{max}	<0.0001	0.9899	0.3117
t_{max}	<0.0001	0.9640	0.2851
DUR	0.0702	0.1707	0.0644

The temperature change profiles for the two iron oxidation systems initiated by water selected for the diffusion studies was compared in detail with the commercial oxidation reaction (Fig. 4). The iron oxidation reaction, $ExoRap_{50}$, attained a T_{max} of 47.4 ± 0.3 °C, a t_{max} of 3.3 ± 0.6 min, an AUC of 1412 ± 46 min.degree and two linear regions in the exponential heat loss gradients; log linear functions of −9.5 and −3.0, respectively. $ExoRap_{60}$ attained a T_{max} of 60.4 ± 0.3 °C a t_{max} of 9.3 ± 0.6 min, AUC of 1629 ± 107 min.degree and two linear regions in the exponential regions of the heat loss profiles; log linear functions of −28.4 and −3.2, respectively. The commercial oxidation reaction initiated by oxygen ($ExoSl_{45}$) attained a T_{max} of 45 ± 0.2 °C a t_{max} of ca. 240 min,

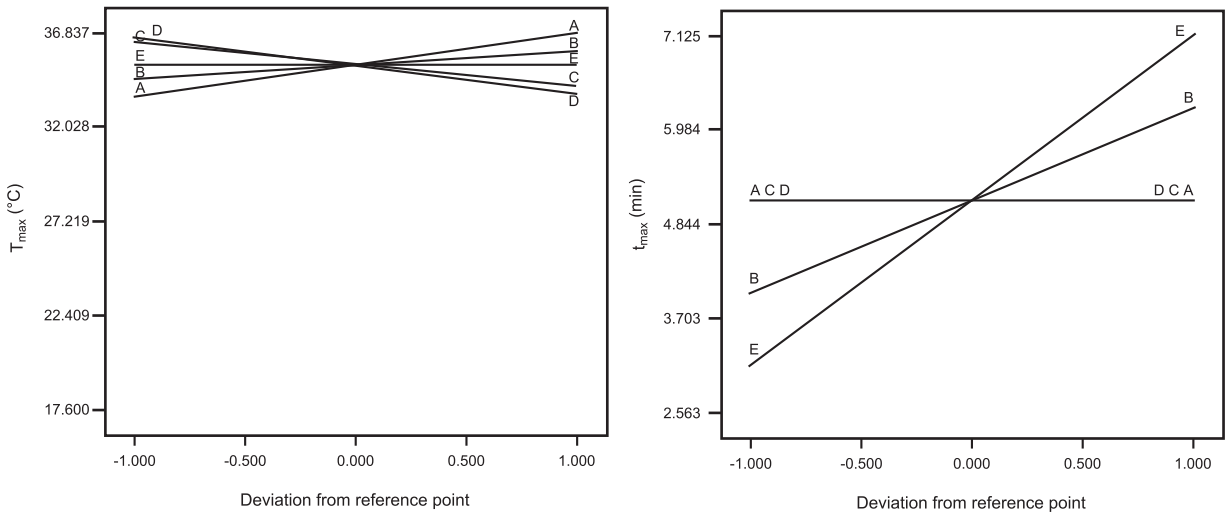

Fig. 2. Perturbation plots showing the effect of input variable levels, i.e. the concentration of heating device components (A = iron, B = carbon, C = vermiculite, D = sodium chloride and E = water) on the model outcomes; peak of maximum temperature change (T_{max}) and the time to reach maximum temperature (t_{max}) produced by a heating device.

AUC of 2604 ± 74 min.degree and no exponential loss of heat over the study period.

3.2. Diffusion studies

The rate of lidocaine penetration through the hydrophilic matrix when the drug was saturated in the system increased significantly ($p \leq 0.05$) when the water initiated iron oxidation reactions were applied to the barriers ($ExoRap_{50}$, $555.61 \pm 22.04\ \mu g/cm^2$ and $ExoRap_{60}$, $663.18 \pm 50.95\ \mu g/cm^2$) compared when no heat was applied ($485.39 \pm 31.75\ \mu g/cm^2$) (Fig. 5a). Conversely, the application of the oxygen initiated system ($ExoSl_{45}$) above the saturated lidocaine gel significantly ($p \leq 0.05$) retarded the diffusion ($159.36 \pm 29.44\ \mu g/cm^2$) compared to when not heat was applied. Lidocaine diffusion rate showed no statistically significant ($p > 0.05$) change with ($ExoRap_{50}$, $231.90 \pm 15.89\ \mu g/cm^2$ and $ExoRap_{60}$, $222.88 \pm 14.15\ \mu g/cm^2$) and without ($231.31 \pm 22.25\ \mu g/cm^2$) the application of heat when the drug was not saturated in the system (Fig. 5b). Diffusion through the sub-saturated hydrophilic gel, was significantly retarded ($p \leq 0.05$) when the $ExoSl_{45}$ reaction supplied the heat ($111.46 \pm 38.29\ \mu g/cm^2$) compared to the control, that is, when no additional heat was generated.

4. Discussion

The application of heat to the biological barriers has long been known to increase transport of small organic molecules (Blank et al., 1967). For example, Blank et al. (1967) reported that the rate of alcohol transport across the skin could be increased if the temperature of the permeability chamber in which this transport occurred was increased (Blank et al., 1967). More recently, studies have demonstrated that only 15 min of heat generated from an infra-red bulb can double the rate of nitroglycerin transport into the systemic circulation (Klemsdal et al., 1992). Not surprisingly the exothermic oxidation of iron, a classic inorganic reaction, has been previously employed to generate heat with the purpose of enhancing chemical transport across biological barriers. The study by Shomaker et al. (2000) elegantly demonstrates the effectiveness of a patch containing a controlled exothermic iron oxidation reaction, applied over an transdermal fentanyl patch, to improve drug transport into the systemic circulation (4-fold improvement) (Shomaker et al., 2000). However, the fundamental principles of how heat generated at a topical membrane influences the thermodynamic activity of a chemical, its diffusion, partition and transport kinetics has not been elucidated to date.

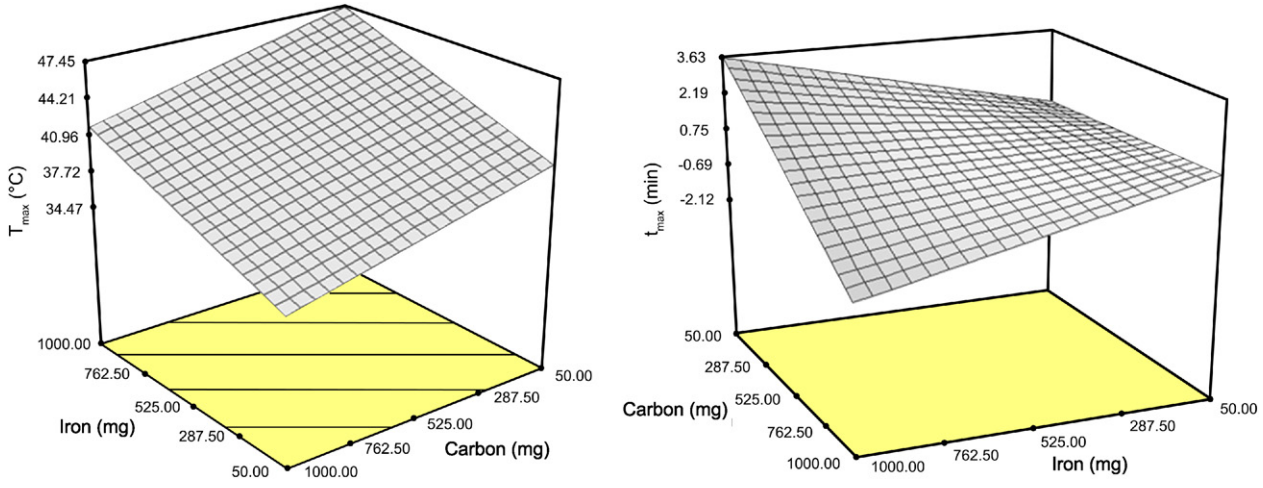

Fig. 3. A 3D surface contour map showing the predicted maximum temperature (T_{max}) and the time to reach that temperature (t_{max}) for an iron oxidation system containing iron, carbon, vermiculite (50.00 mg), sodium chloride (50.00 mg) and deionised water (50.00 μl).

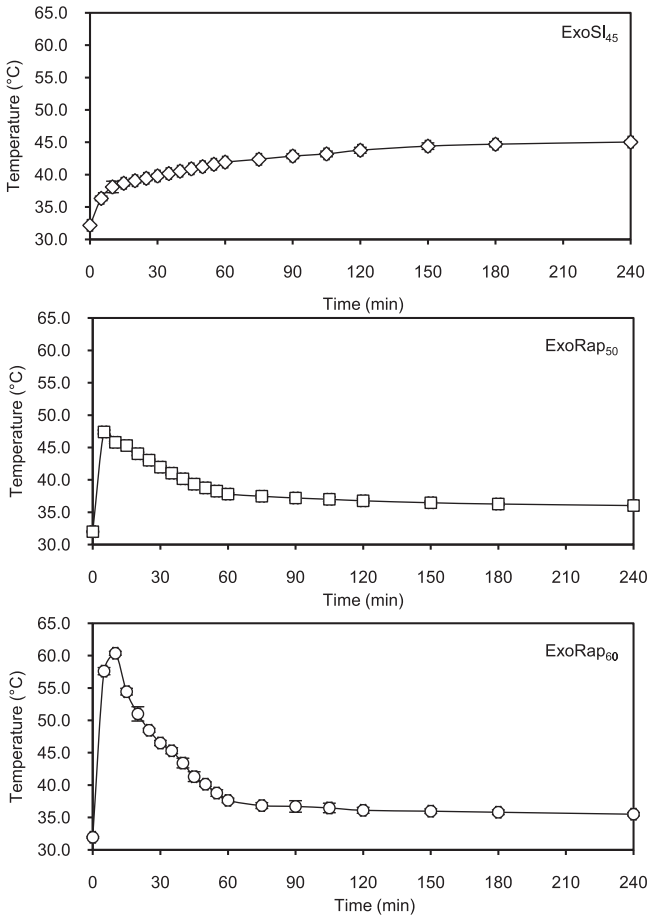

Fig. 4. Temperature profiles of three iron oxidation reactions used in the diffusion studies. A commercial oxidation reaction ($ExoSl_{45}$), and two oxidation reactions with rapid temperature change kinetics $ExoRap_{50}$ and $ExoRap_{60}$. Each point represents mean temperature ± 1 standard deviation ($n = 3$).

Key component effects of the iron oxidation reaction were investigated using a statistical experimental design that generated a sound linear model for the T_{max} and t_{max} indices. Although there is little previously published data to aid the explicit deconvolution of how the individual components of the iron oxidation system determined their contribution to the final temperature change profile, the trends in the data supported the obvious contributions of the components to the four stage reaction outlined in Eq. (1)–(4). It was not surprising that iron levels had the greatest effect on the temperature change profiles as the access to iron by the bolus supply of oxygen should be rate limiting for the oxidation reaction. Sodium chloride catalysed the oxidation process and this was probably a consequence of pH control in the reaction mixture (Roekens and Van Grieken, 1983; Raleigh et al., 2005). Iron oxidation is known to be a second order reaction with respect to pH because a hydronium ion redox reaction acts as an initiator to the iron oxidation sequence (Stumm and Lee, 1961; Morgan and Lahav, 2007). Drobot et al. (2002), suggested that organic radicals were generated on the surface of carbon when sodium chloride and water are present, but as the specific details of such a reaction have not been conclusively elucidated the specific effects of radical generation in this process remain unclear (Drobot et al., 2002). Although the availability of oxygen in the water is crucial to the oxidation process the statistical designs demonstrated that water content can also have a negative effect on the temperature generation kinetics; implied by the increase of T_{max} associated with larger volumes of water. Disproportionately large water volumes compromise the function of the insulating agent, vermiculite, during heat generation and this is explains why large volumes of water impair the efficiency of the iron oxidation reaction. The results from the statistical design suggest that the carbon, which provides the solid interface for the oxidation reaction to occur, was particularly important in the reaction. Again this was not surprising as increasing the surface area of carbon available either through increasing porosity or quantity of carbon is known to increase the rate of oxidation (Evans and Taylor, 1972; Yamashita and Shimizu, 1985). Unlike linear designs, statistical experimental designs allow two component interactions to be assessed. The interaction between

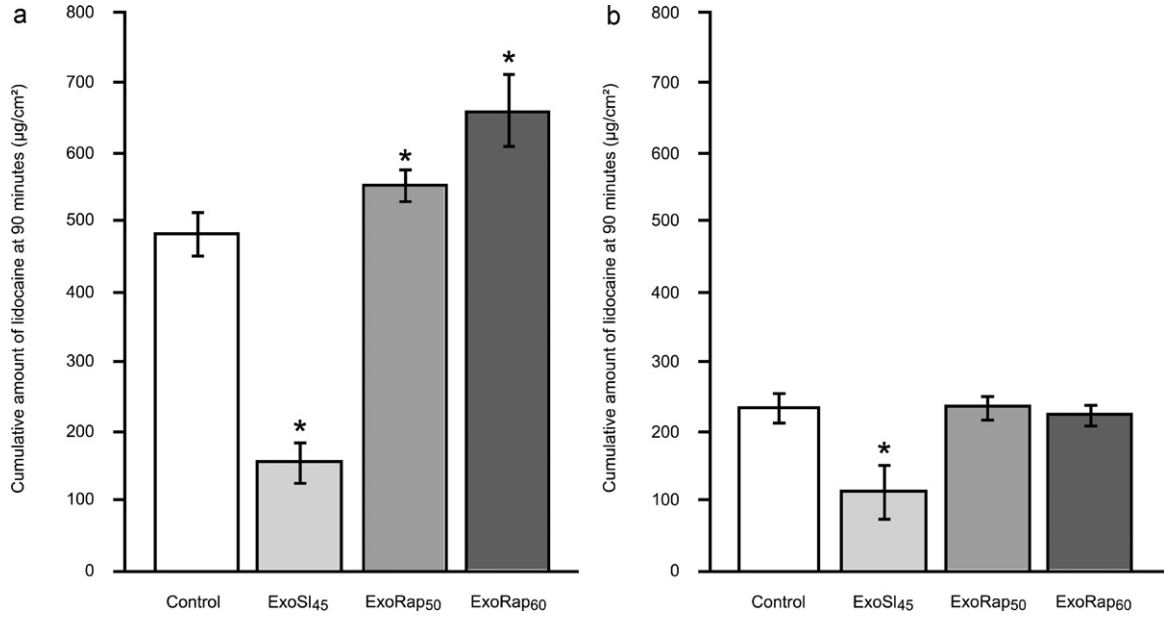

Fig. 5. The cumulative amount of lidocaine base (µg/cm^2) released from either a saturated (a) or sub-saturated (b) hydrophilic matrix during 90 min (T_{90}). A commercial oxygen initiated reaction ($ExoSl_{45}$), two water initiated oxidation reactions $ExoRap_{50}$ and $ExoRap_{60}$ applied to the drug loaded gel and a control, a drug loaded gel with no heat. Each point refers to the mean cumulative mass per area ± 1 standard deviation ($n = 5$). Asterisk (*) donates a significant difference in cumulative amount compared to the control.

iron and vermiculite demonstrates the importance of reaction insulation (previously also indicated by the negative effects of too much water) when there is a bolus exposure of oxygen. Vermiculite is particularly effective at retaining and dispersing the heat produced from the exothermic oxidation of iron (White, 1999; Potter, 2000).

The potential for irreversible skin damage, sensitisation and pain must be considered when assessing the ability of the iron oxidation reaction to induce a temperature change that could control barrier penetration in a clinical setting. The temperatures of the heating devices evaluated in this work did not exceed 65 °C and varied in temperature change kinetics. There appears to be an interesting, but as yet unexplored, relationship between temperature change kinetics and safety when previous literature is reviewed. Below 75 °C the effects of heat on the barrier properties of human skin has been shown to be reversible (Van Duzee, 1975). Therefore temperatures of this magnitude are not thought to cause lasting damage to this membrane. However, previous work conducted by Moritz and Henriques (1947) found several subjects experienced an uncomfortable sensation above 47 °C when heat was applied for a duration as short as 40 min (Moritz and Henriques, 1947). Although the use of temperatures above 100 °C for short durations (<1 s), has also been proposed as a strategy to increase the delivery of therapeutic agents *in vivo*, assessment of such extreme heating has yet to be performed (Park et al., 2008). As the potential to damage membrane proteins is a major concern at these high temperatures, although the iron oxidation reaction is undoubtedly capable of inducing significantly higher temperature changes we applied a cautionary limit of ca 65 °C in this work (Lawson et al., 1998; Silva et al., 2006).

The barrier diffusion rate of lidocaine through a gel with a thermodynamic activity of 0.5 without heat was, as predicted by the Higuchi equation, approximately half that when the drug was present with a thermodynamic activity of 1 in the absence of an oxidation reaction (Higuchi, 1960). Unusually, lidocaine solubility shows inverse proportionality with temperature (Brodin et al., 1984). Therefore, as heat was generated by the iron oxidation system it should reduce lidocaine solubility and increase drug thermodynamic activity. However, this was not observed in this work, probably due to the fact that the actual decrease in solubility that accompanied the increase in temperature was <15% (Brodin et al., 1984, solubility data not shown).

Lidocaine diffusion through the CMC gel was more rapid when the barrier experienced a short, sharp temperature change rather than the slow more extensive one driven by the oxygen controlled oxidation reaction. Hypothetically more extensive lidocaine penetration could be ascribed to iron oxidation reaction causing: an alteration of the membrane, an increase in drug thermodynamic activity or a change in the inherent molecular diffusion. As thermodynamic activity change was shown to be minimal, RCM thickness (previously been shown to be a good indices of membrane medication, Reid et al., 2008) was not modified by heat, the most plausible reason for increased lidocaine release was either enhanced molecular motion or a change in hydrophilic matrix structure. An alteration in molecular diffusion in simple aqueous vehicles has previously been suggested by Akomeah et al. (2004), but how this change applied to a hydrophilic barrier as used in the current work is unknown.

Careful analysis of the temperature profile and lidocaine diffusion through the hydrophilic matrix when the commercial iron oxidation reaction was employed can help to isolate the major effects of applying heat to CMC in this work. Applying heat over a more prolonged period generated an enhanced AUC and therefore if heat simply altered the molecular diffusion coefficient according to the Stokes–Einstein equation then more heat word result in more rapid diffusion for the commercial device. The CMC barrier is formed from numerous hydrogen bond cross links (Yang and Zhu, 2007). Hydrogen bonds are broken by heat and water ingress and therefore the most likely explanation for the prolonged temperature change kinetics leading to penetration retardation is the breakdown of the hydrophilic matrix secondary structure, uptake of water and change in barrier thickness. Although it is impossible to measure these dynamic processes *in situ* after the application of the oxidation reaction in the current experimental set up, these data provide and excellent basis for further work to detail the exact changes induced in relevant biological barriers by a local iron oxidation reaction.

5. Conclusions

The temperature change kinetics of the iron oxidation reaction is readily manipuliable and this enabled the effects of this classical inorganic reaction upon lidocaine diffusion through a model hydrophilic barrier to be assessed. A rapid oxidation reaction that resulted in a moderate temperature change over a 30 min period, initiated by a bolus of oxygen enhanced the lidocaine diffusion rate more than a slow more extensive heat generation system. The structural changes of the hydrophilic matrix appeared to be critical to diffusion rate and this needs careful consideration when attempting to apply the well know principles of thermophoresis in any clinical settings.

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