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Ibuprofen delivery into and through the skin from novel oxidized cellulose-based gels and conventional topical formulations

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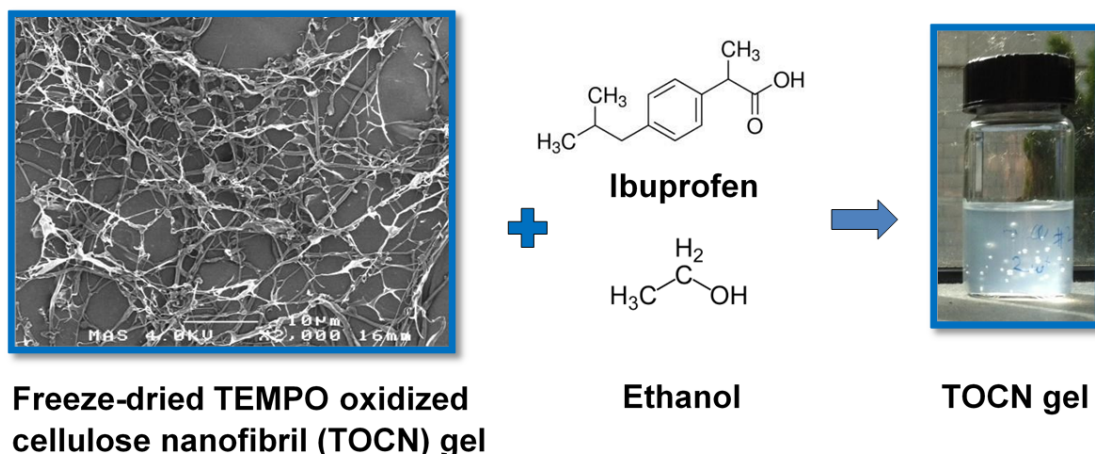
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ABSTRACT

The delivery of ibuprofen into and through the skin from novel formulations containing TEMPO-oxidized cellulose nanofibril-based (TOCN) gels was compared to that from two conventional and commercially available products. The gels were evaluated *in-vitro* (using both silicone membranes, and pig skin) and *in-vivo* in human volunteers. All gels showed consistent behaviour in a standard *in vitro* release test. The stratum corneum (SC) uptake and skin penetration of ibuprofen *in vitro* from the novel gels and the marketed formulations were generally comparable even though the drug loading in the TOCN-based vehicles was only 20% of that in the 'reference' products. *In vivo*, the new gels appeared to enhance drug uptake into the SC following a relatively short application time, again matching the performance of the commercial formulations. Taken together, the results of this research provide proof-of-concept for the idea that the sustainable, oxidised cellulose gels may provide more efficient drug delivery into and through the skin, thereby improving drug utilisation and reducing potential adverse effects when such formulations are applied chronically over large skin areas.

Graphical abstract



INTRODUCTION

Ibuprofen is a non-steroidal anti-inflammatory drug that is applied to the skin to treat the local pain and inflammation associated, for example, with arthritis and other musculo-skeletal problems (Patel et al., 2013). A number of ibuprofen gel formulations are commercially available and typically contain the drug at a concentration of 5% w/w. Common components of these formulations include an alcohol (such as ethanol, isopropanol, alone or in combination), a gel-forming polymer, such as Carbomer[®], chitosan, hydroxyethylcellulose, or hydroxypropyl cellulose, a skin penetration enhancer (e.g., propylene glycol), a compound to adjust pH (triethanolamine, sodium acetate), an antimicrobial and/or antioxidant, and water (Wisniewski and Gemborys, 1992). The composition of the formulation, not unexpectedly, can have a significant impact on the delivery of ibuprofen into the stratum corneum (SC), its subsequent transfer to the viable skin layers and, ultimately, to its ability to reach the intended subcutaneous tissue target. The literature, in fact, reports studies which show, despite most products containing 5% w/w of drug, that the uptake and delivery of ibuprofen is not always the same (Hadgraft et al., 2003; Herkenne et al., 2007a).

Cellulose is the most abundant biomass in nature and it is a material that has found multiple applications and uses involving fibres, membranes, nanocomposites and polymers. The mechanical strength, biocompatibility, hydrophilicity and optical properties of cellulose are particularly attractive features in many fields of research and development (Qiu and Hu, 2013); for example, polymeric systems integrated with cellulose have been seriously considered for applications in drug delivery, and stimuli-responsive hydrogels based on cellulose have been used to release drugs by modifying environmental factors such as temperature and pH (Prabaharan and Mano, 2006; Sannino et al., 2009). More classically, cellulose-polymer combinations have also been used to create controlled release formulations (Fang and Cathala, 2011; Tan et al., 2010). The hydrophilic properties of these hydrogels are especially attractive because of their water solubility and the fact that drug release can be sensitively modulated in response to changes in electrolyte composition as well as other factors already mentioned (e.g., temperature and pH) (Çaykara et al., 2006; Pourjavadi et al., 2007, 2006)

In this study, the performance of two over-the-counter ibuprofen gels has been compared with that of novel formulations prepared with TEMPO-oxidized cellulose nanofibrils (TOCN), which are derived from natural, renewable sources, unlike the synthetic polymers that are used in the products currently on the market. TOCN provide a non-irritant, colourless, odorless material which can be used as a thickener in pharmaceutical, personal care and cosmetic products (Crawford et al., 2012). Oxidised cellulose, in general, has found many uses in the pharmaceutical industry (Dol'berg et al., 1973; Pines and Cunningham, 1984; Kaputski et al., 1995; Zhu et al., 2004; Shimotoyodome et al., 2011; Jia et al., 2016). TOCN also have good

suspending power and tolerate alcohols and hydrophobic moieties well, thereby providing a promising material for use in aqueous formulations (Crawford et al., 2012; Dol'berg et al., 1973; Pines and Cunningham, 1984; Zhu et al., 2004). Indeed, it has been suggested that the combination of low molecular weight alcohols (ethanol, propanol) with TOCN can yield gels even in the presence of surfactants (Crawford et al., 2012). Here, the use of TOCN in hydroalcoholic formulations for topical drug delivery is demonstrated for the first time and the delivery of ibuprofen from these vehicles, relative to two products on the market, is examined.

MATERIALS & METHODS

Materials: Ibuprofen ($\geq 98\%$ GC), sodium dodecyl sulfate (ACS reagent, $\geq 99.0\%$), acetonitrile (HPLC grade, $\geq 99.9\%$), hydrochloric acid (ACS reagent, 37%), triethylamine ($\geq 99\%$) and phosphoric acid ($\geq 99\%$) were purchased from Sigma Aldrich (Gillingham, UK). Sodium chloride (99.7+%), potassium chloride (99.5+%), sodium phosphate (99+%) and potassium phosphate (99+%) were from Fisher Scientific (Leicestershire, UK).

The commercial gels, Sainsbury's Ibuprofen and Ibuleve™, were purchased from Sainsbury's Pharmacy (Bath, UK) and Diomed Developments Ltd (Hertfordshire, UK), respectively.

Artificial silicone membrane (serial number 7-4107, thickness 75 μm) was donated by Dow Corning Ltd. (Cardiff, UK).

Abdominal porcine skin (B&J Pigs Ltd, Somerset, UK) was acquired immediately post-sacrifice. After cleaning and trimming off coarse hairs, the tissue was dermatomed (Zimmer® Electric Dermatome, Warsaw, IN) to a nominal thickness of $\sim 750 \mu\text{m}$. The skin was stored at -20°C and used within three months.

Cellulose nanofibres were prepared from purified α -cellulose (Croda International Plc, East Yorkshire, U.K.) by 2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (TEMPO)-mediated NaOCl/NaBr oxidation in water, followed by mechanical dispersion as described previously (Isogai et al., 2011; Saito et al., 2006). The process, if taken to completion, would generate water-soluble poly(glucuronic acid), but here the reaction was limited to 20-25% by controlling the quantity of oxidant used (Crawford et al., 2012). The TEMPO-oxidized cellulose nanofibril (TOCN) dispersion was subsequently dialysed (MWCO 12000 dialysis membrane, diameter 16 mm, Sigma Aldrich, Gillingham, UK) in deionised water for a week (changing the medium three times each day). The resulting product was then freeze-dried and dispersed, at room temperature, overnight with stirring, in deionised water (Milli-Q water, $18.2 \text{ M}\Omega \text{ cm}^{-1}$) to form a stock solution of 2% w/w at pH 6.5. Finally, the dispersion was sonicated for 30 minutes (Vibra Cell Sonicator (Sigma Aldrich, Gillingham, UK) at a 50%, 1Hz duty cycle and at 2 W cm^{-2}) using an ultra-high intensity tip of 3 mm diameter.

Formulation of TOCN gels: Hydroalcoholic, ibuprofen-containing TOCN gels were prepared from the aqueous stock dispersion. The drug was first dissolved in ethanol and the cellulose dispersion was then added. Five 1% w/w ibuprofen formulations, differing in the amount of TOCN, were prepared and compared with Sainsbury's Gel and Ibuleve™ in the experiments described below. The compositions of the TOCN formulations and of the commercial products are in Table 1.

Table 1: Components (in %w/w) of the ibuprofen gel formulations studied.

Formulation	Ibuprofen	Aqueous TOCN dispersion ^a	Ethanol	SDS	Propylene glycol
A	1.0	60	37	-	2.0
B	1.0	60	39	-	-
C	1.0	60	39	-	-
D	1.0	60	39	-	-
E	1.0	60	39	0.07	-
Sainsbury's Gel	5.0	hydroxyethylcellulose, sodium hydroxide, benzyl alcohol, isopropyl alcohol, purified water			
Ibuleve™	5.0	industrial methylated spirit, carbomer, propylene glycol, diethylamine, purified water			

^a For formulations A, B and E, the aqueous dispersion was prepared at a concentration of 1.8% w/w TOCN; for formulations C and D, 1.2% w/w and 0.6% w/w TOCN were used, respectively.

Formulation viscosities were determined using a Bohlin C-VOR viscometer (Malvern Instruments, MA, US) equipped with CP 4/40 cone and plate (4° cone angle and 40-mm cone diameter). Experiments were performed at 25°C using approximately 5 g of formulation for each (mean of three) measurement. Shear rate ranged between 0.01 and 100 s⁻¹. Each measurement was repeated three times and the results were averaged.

Formulation pH was measured (again, in triplicate) using a pH meter (Orion 420Aplus, Thermo Scientific, US) that had been pre-calibrated with buffer solutions at pH 4, 7 and 10.

Ibuprofen analysis: Ibuprofen was quantified by high-performance liquid chromatography (Jasco, Great Dunmow, UK) using a Dionex Acclaim 120 column (C18, 5 µm, 4.6 x 150 mm, Thermo Scientific, US), with UV-vis detection at 227 nm (Waters, Milford, MA), and a mobile phase of 60:40 v/v acetonitrile/triethylamine (TEA) (0.2% v/v aqueous) adjusted to pH 2.84 with phosphoric acid. The flow rate was 1.1 mL/min and the retention time for the drug was ~6 minutes. A calibration curve over an ibuprofen concentration range of 0.05 (the limit of quantification) to 100 µg/mL was established.

In vitro ibuprofen release testing using silicone membranes: The experiments (n = 5 replicates) were conducted at 37°C in vertical Franz diffusion cells (PermeGear Inc., Bethlehem, PA) with a receptor volume of 9 - 9.5 mL (accurately measured for each case). The receptor solution was phosphate-buffered saline (0.1 M, pH 7.4). The area of exposed silicone membrane surface was ~3 cm² and the amount of gel deposited in the donor compartment of the diffusion cell was approximately 1 g. The cells were occluded with Parafilm (Bemis, Oshkosh, WI) immediately after the gel was dosed onto the membrane. At various times up to 8 hours post-initiation of the experiment, 1 mL of receptor medium was removed for drug analysis by HPLC

and replaced with 1 mL of fresh receptor solution. The cumulative amount of drug that had penetrated the membrane from each formulation as a function of time was calculated.

In vitro skin uptake and penetration of ibuprofen: Porcine skin used in these experiments was thawed and any excess hair was carefully trimmed away using scissors. As above, experiments (n = 4-6 replicates) were conducted at 37°C in vertical Franz diffusion cells with phosphate-buffered saline in the receptor phase (7 – 7.5 mL, accurately measured). Approximately 0.64 g of gel was deposited on the skin surface facing the donor compartment of the diffusion cell, which was then occluded with Parafilm™. The exposed skin surface area was ~ 2 cm². At various times up to 8 hours post-initiation of the experiment, 1 mL of receptor medium was removed for drug analysis by HPLC and replaced with 1 mL of fresh receptor solution. The cumulative amount of drug that had penetrated the membrane from each formulation as a function of time was calculated.

The pig skin was removed from the diffusion cell and pinned to a sheet of foam. Any remaining formulation on the skin surface was immediately cleaned away using tissue (Kimberly Clark, Fisher, UK) and the stratum corneum (SC) was then removed by sequential tape-stripping (Scotch Book Tape, 3M, St Paul, MN). To ensure reproducible SC removal from the skin, a circular template, from which a central hole (diameter 2 cm) had been cut out was centred over the skin to be tape-stripped. As reported previously (Herkenne et al., 2007a; Kalia et al., 2000; Russell et al., 2008), repeated tape-stripping was then undertaken with concomitant measurements of transepidermal water loss (TEWL) (Aquaflux, Biox Systems Ltd, London, UK) to determine when most (>80%) if not all the SC had been removed and to estimate the total thickness of the SC as well. This approach requires the amount of SC removed by each tape strip to be deduced from the weight difference (SE2-F, Sartorius AG Microbalance, Gottingen, Germany) in the tapes before and after SC stripping. Each tape was then rolled inside a 1.5 mL HPLC vial and ibuprofen in the SC removed was quantitatively extracted by immersing the tape in 1 mL of a 90:10 mixture of acetonitrile and 1 M hydrochloric acid, and shaking overnight. The extracted solution was filtered (0.45µm nylon filter, SMI-LabHut Ltd, Gloucestershire, UK) prior to HPLC analysis. Finally, the total SC uptake of drug, following an 8-hour treatment period, from the gel formulations tested was calculated.

In vivo skin uptake of ibuprofen: Four healthy volunteers (aged 22-30 years, two male and two female), with no history of dermatological disease, participated in this study which was approved by the Research Ethics Approval Committee for Health (REACH; EP 14/15 2) of the University of Bath. Informed consent was obtained from all subjects. The ibuprofen formulations were applied to sites on the ventral forearm inside a foam ring and were occluded with plastic Hill Top chamber (16 mm, Sarasota, FL). Self-adhesive tapes (Mefix, Mölnlycke

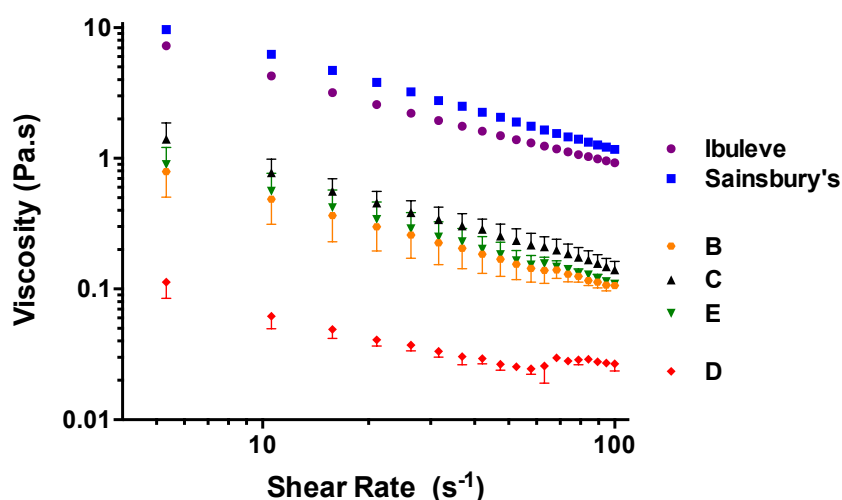
Health Care, Sweden) were used to cover the each of the treated sites to secure the chambers in place. An additional site on the forearm provided an untreated control at which no drug was applied. SC weights and TEWL measurements obtained at this site were used to determine the SC thickness of the subject (Kalia et al., 2000; Russell et al., 2008).

In this case, the treatment time was 1 hour, at the end of which, the formulations were removed, the skin surface cleaned and the SC tape-stripped (with concomitant TEWL measurements) as described above. The control, no-treatment site was tape-stripped to determine SC thickness on the forearm and to ensure that complete or nearly complete removal of the SC had been achieved where the formulations had been applied (N'Dri-Stempfer et al., 2009, 2008). Ibuprofen extraction from the tapes and its subsequent analysis were as before. The results provided profiles of drug concentration across the SC after a 1-hour treatment as well as total drug uptake into the barrier within this time period.

RESULTS & DISCUSSION

Viscosity and pH of the gel formulations: The pH values of the TOCN gels were between 4.8 and 5.3; those of Ibuleve™ and Sainsbury's Gel were 7.0 and 8.2, respectively. The viscosities of Sainsbury's Gel, Ibuleve™ and four of the TOCN formulations as a function of shear rate are shown in Figure 1. The commercial products were the most viscous, by nearly an order of magnitude. No significant difference in the viscosity of TOCN gels B, C and E was observed, even though formulation C contained only 1.2% w/w TOCN (compared to 1.8% w/w in B and E). Gel D, comprising only 0.6% w/w TOCN, was the least viscous, about 1/10th of that of B, C and E. Gel A, which contained 2% w/w propylene glycol was insufficiently semi-solid to provide useful data.

Figure 1: Viscosities of marketed and selected TOCN gels (mean \pm SD; $n = 3$).

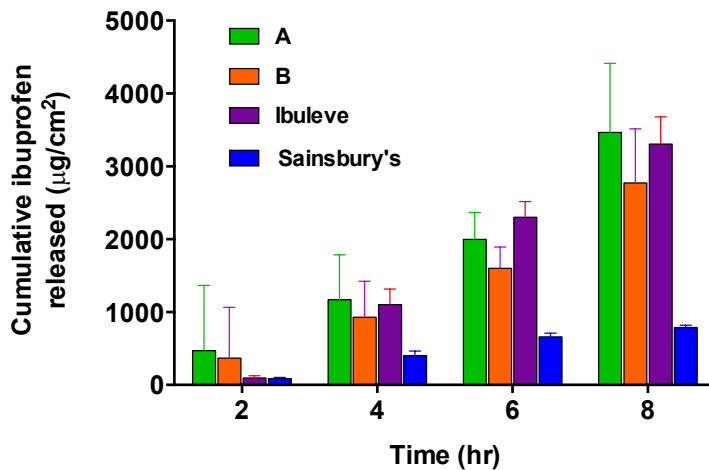


In vitro ibuprofen release across silicone membranes: The release profiles of ibuprofen from the two commercial products, and from TOCN formulations A and B, across a silicone membrane as a function of time are shown in Figure 2. Formulations A and B differ in that the former contains 2% w/w propylene glycol (and 2% less ethanol) and is significantly less viscous than the latter.

It is clear from a one-way analysis of variance, followed by Tukey's *post-hoc* test, that drug release from 4 hours onwards is significantly slower ($p < 0.05$) from Sainsbury's Gel than from the other three formulations. Interestingly, despite the very large differences in the viscosities of Ibuleve™, TOCN formulation A and TOCN formulation B (Ibuleve™ is about 10-fold more viscous than formulation B, while formulation A is essentially a liquid), the release profiles of ibuprofen from these three vehicles are indistinguishable over the same 4 – 8 hour period of time. It seems likely, therefore, that it is the relative affinity of the drug for the formulation

which controls its release kinetics rather than the rheological properties of the gel. Furthermore, it is worth noting that the predictive value of this experiment, in terms of drug delivery across the skin, is limited because a simple artificial membrane cannot simulate the complex manner in which a formulation's excipients interact with the biological matrix of the stratum corneum.

Figure 2: *Ibuprofen release profiles across a silicone membrane from four formulations (mean \pm SD; n = 3).*



In vitro skin uptake and penetration of ibuprofen: The *in vitro* performance of the TOCN and commercial gels, in terms of their ability to facilitate drug uptake into, and permeation through porcine skin, was evaluated and the results are summarised in Figure 3 and Table 2. In this case, formulation A was not studied because the presence of propylene glycol prevented gel formation.

Figure 3: *Ibuprofen permeation across porcine skin as a function of time from six gel formulations (mean \pm SD; n = 4-6). For the purposes of clarity, individual data points have been displaced slightly on the time axis.*

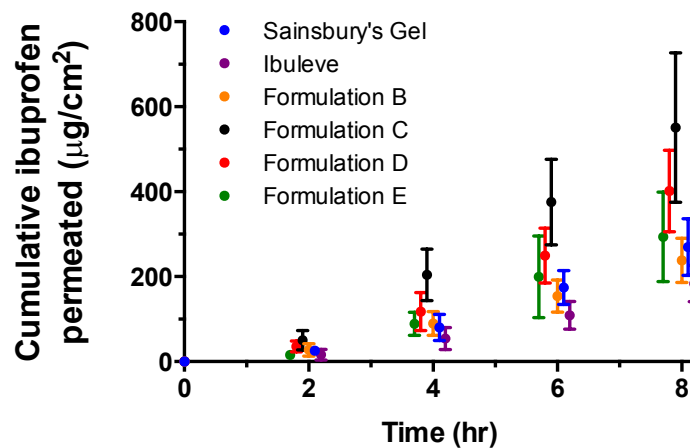


Table 2: Ibuprofen uptake into, and cumulative permeation through, porcine stratum corneum (SC) *in vitro* after application of six gels for a period of 8 hours (mean \pm SD; n = 4-6).

Formulation	Ibuprofen uptake into SC ($\mu\text{g}/\text{cm}^2$)	Ibuprofen permeation through SC ($\mu\text{g}/\text{cm}^2$)
Sainsbury's Gel	163 \pm 40	270 \pm 67
Ibuleve™	202 \pm 32	184 \pm 43
Formulation B	94 \pm 23	238 \pm 52
Formulation C	265 \pm 59	551 \pm 176
Formulation D	233 \pm 44	402 \pm 96
Formulation E	179 \pm 26	294 \pm 106

The penetration profiles of ibuprofen from all the gels was quite consistent, and the cumulative amount absorbed in 8 hours was statistically indistinguishable for Sainsbury's Gel, Ibuleve™, and formulations B, D and E (1-way ANOVA followed by Tukey's *post-hoc* test). Total drug penetration from formulation C was significantly higher ($p < 0.05$) than that from all other gels except formulation D. In terms of drug recovery from the SC at the end of the 8-hour experiment, there was a less than 3-fold variation across the six gels tested. Nonetheless, the same statistical analysis revealed that ibuprofen uptake from formulation B was significantly less ($p < 0.05$) than that from Ibuleve™ and formulations C, D and E, while drug recovery from formulation C was significantly higher than that from Sainsbury's Gel and formulations B and E.

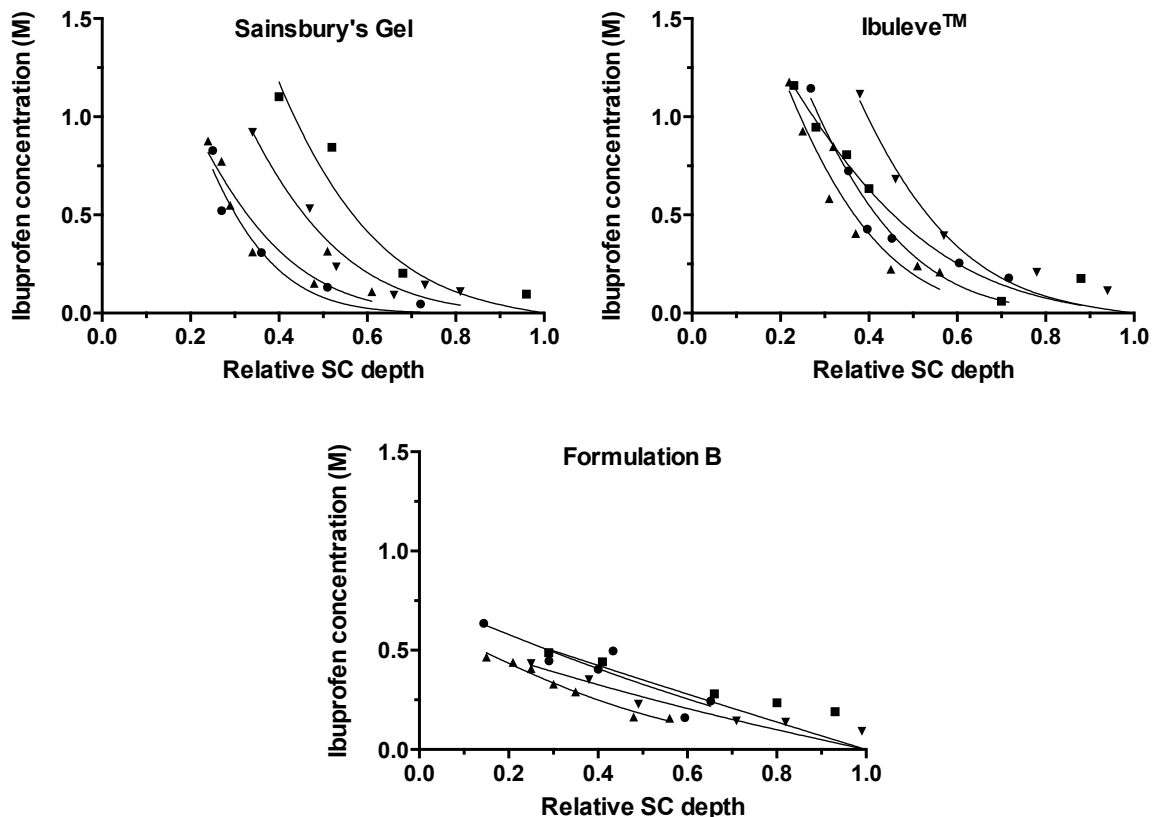
Given the variability observed, and the relatively modest number of replicate experiments performed (n = 4-6), it seems unlikely that even the statistically different results obtained would translate into a noticeable discrimination in the eventual bioavailability of the drug at its site of action after topical application to the skin. More important, however, is to draw attention to the fact that the TOCN gels investigated here performed at least as well (in terms of SC uptake and skin penetration) as the two commercial products even though the ibuprofen concentration in the new formulations was only 1% w/w, compared to 5% w/w in Sainsbury's Gel and Ibuleve™.

In previous work, diffusion profiles like those shown in Figure 3 have been fitted to the appropriate solution to Fick's 2nd law of diffusion to extract so-called partitioning and diffusivity parameters (Herkenne et al., 2007a); the former is the product of the drug's SC-formulation partition coefficient (K) and the diffusion path-length (h), while the latter is the ratio of the drug's diffusivity (D) through the SC to the diffusion path-length squared (h^2). When this approach is

applied to the data in Figure 3, the deduced values of D/h^2 for ibuprofen delivered from all six tested gels fall in the range of 0.21 to 0.28 hr^{-1} . In contrast, while the best-fit values of $K.h$ for ibuprofen are 6.9 cm for Sainsbury's Gel and 4.7 cm for Ibuleve™ (coefficients of variation are 24% and 9% of the mean values, respectively), those for the four TOCN gels range from 28 cm to 65 cm (%CVs being between 37% and 46%). The more efficient delivery of the drug from the TOCN gels appears, therefore, to be the result of enhanced partitioning into the SC rather than alteration of the diffusion barrier *per se*.

In vivo skin uptake of ibuprofen: Given the relatively consistent performance of the TOCN gels *in vitro*, only one of these formulations (B) was compared to the two commercial products in the *in vivo* experiments. Following a 1-hour application, the ibuprofen concentration profiles across the SC were deduced and the results in four subjects are shown in Figure 4. No visible evidence of any skin irritation was apparent post-treatment with any of the gels used.

Figure 4: Concentration profiles of ibuprofen across human SC *in vivo* ($n = 4$) following topical application of Sainsbury's Gel, Ibuleve™ and TOCN gel formulation B. The data are presented as a function of relative depth into the SC (where 0 represents the SC surface, and 1 indicates the interface between the SC and the underlying, viable skin layers).



While the profiles for the marketed products were quite similar, as was the total recovery of ibuprofen from the SC (Table 3), the results from Formulation B were noticeably different: in this case, the concentration profile was almost linear (suggesting that steady-state had been reached, or nearly so) and the apparent partitioning of drug into the SC was significantly less than that from the commercial gels (as reflected in the y-axis intercepts of the concentration profiles) (Herkenne et al., 2008, 2007a, 2007b).

Table 3: *Ibuprofen uptake into human stratum corneum (SC) in vivo after application of three gels for a period of 1 hour (mean \pm SD; n = 4).*

Formulation	Ibuprofen uptake into SC ($\mu\text{g}/\text{cm}^2$)
Sainsbury's Gel	83 \pm 16
Ibuleve TM	115 \pm 19
Formulation B	53 \pm 7

The more rapid diffusion of the drug from Formulation B in the first hour of application may be the result of the relatively high level of ethanol in this vehicle that facilitated the establishment of a quite linear concentration profile in a rather short period of time. That such an effect in the *in vitro* experiments was not observed, when the penetration profiles were analysed after an 8-hour exposure, might simply be due to the different time scale involved which resulted in the initial impact of the volatile solvent being missed.

While total drug uptake in to the SC in 1 hour *in vivo* from the different formulations paralleled that seen *in vitro* after 8 hours, extrapolation of the concentration profiles in Figure 4 to the SC surface suggests that the apparent partitioning of ibuprofen from Sainsbury's Gel and IbuleveTM is much greater than that from Formulation B. While this finding is at odds with the *in vitro* data, the discrepancy may be due to technical reasons associated with the surface cleaning of the formulations at the end of the experiments. It has been previously reported that the 'dry-wipe' method used here may sometimes prove somewhat less than efficient for the removal of residual formulation from the SC surface, especially for more viscous formulations, such as the two commercial products studied here (see Figure 1) (Wiedersberg et al., 2009). The result of incomplete surface cleaning, of course, is that residual formulation is also removed with the initial SC tape-strips, artificially inflating the apparent levels of drug in the outer SC, and suggesting a higher SC-vehicle partition coefficient than is actually the case. The impact of this shortcoming is less important in *in vitro* experiments of longer duration, especially when the donor compartment has been fully occluded for several hours. During this time, water moves from the receptor across the skin and into the formulation on

the SC surface, reducing the viscosity of more 'sticky' vehicles, which then become easier to efficiently clean off when the experiment terminates.

CONCLUSIONS

The potential of TOCN-based gel formulations to deliver drugs topically into and through the skin has been clearly demonstrated. When compared with two marketed products, which are available over-the-counter, the performance of the TOCN formulations, in terms of facilitating drug uptake into the SC (both *in vitro* and *in vivo*) and penetration through the skin (*in vitro*), was entirely respectable. Of particular note is the fact that the novel formulations were, in large part, as efficient as the commercially available gels despite a drug loading that was only 20% of the reference products. This would be a considerable benefit, of course, for expensive drugs, as well as reducing potential, long-term adverse effects when such formulations are used chronically over large areas of skin. The work presented here serves as an initial proof-of-concept for the idea of sustainable formulation development; however, further research would be required to optimise the gels and their development.

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FIGURES & FIGURE LEGENDS

Figure 1: Viscosities of marketed and selected TOCN gels (mean \pm SD; $n = 3$).

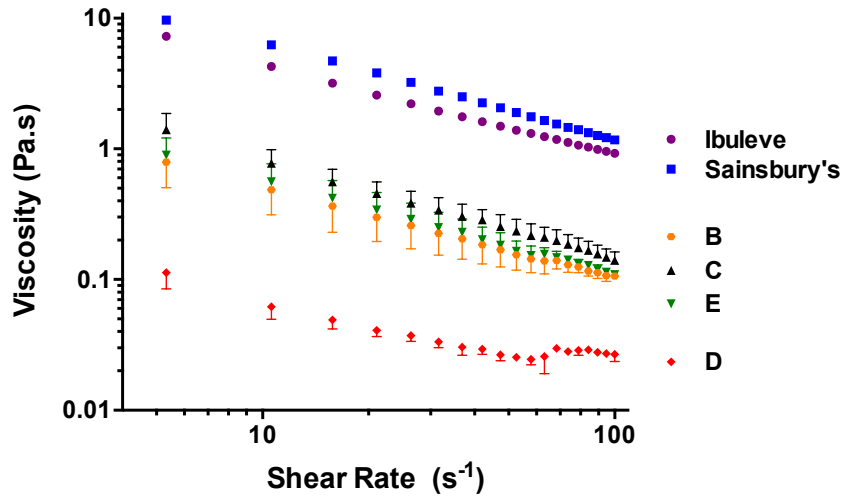


Figure 2: Ibuprofen release profiles across a silicone membrane from four formulations (mean \pm SD; $n = 3$).

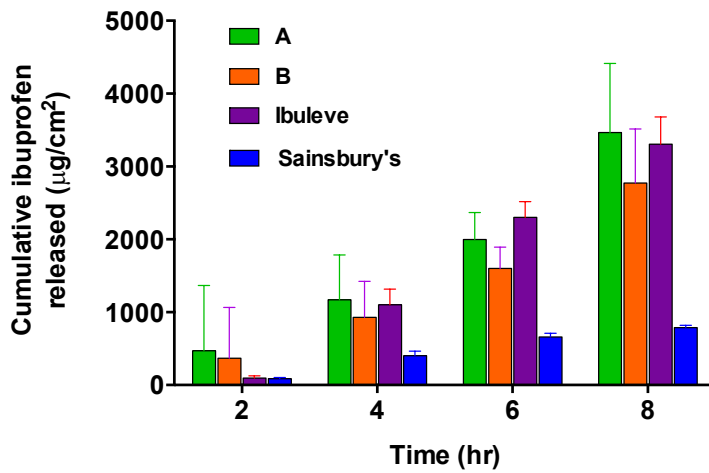


Figure 3: Ibuprofen permeation across porcine skin as a function of time from six gel formulations (mean \pm SD; $n = 4-6$). For the purposes of clarity, individual data points have been displaced slightly on the time axis.

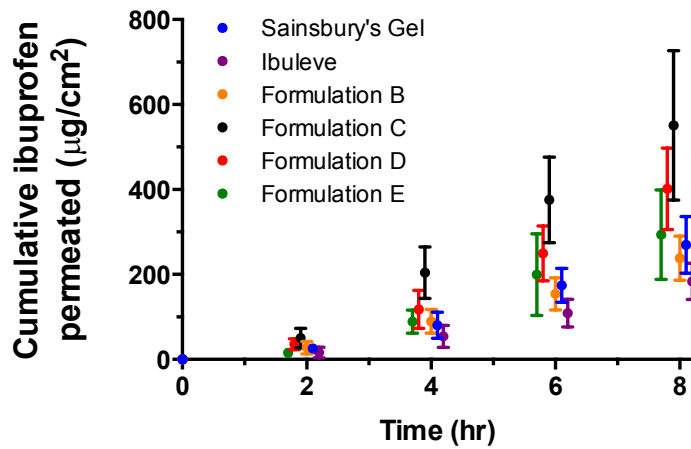
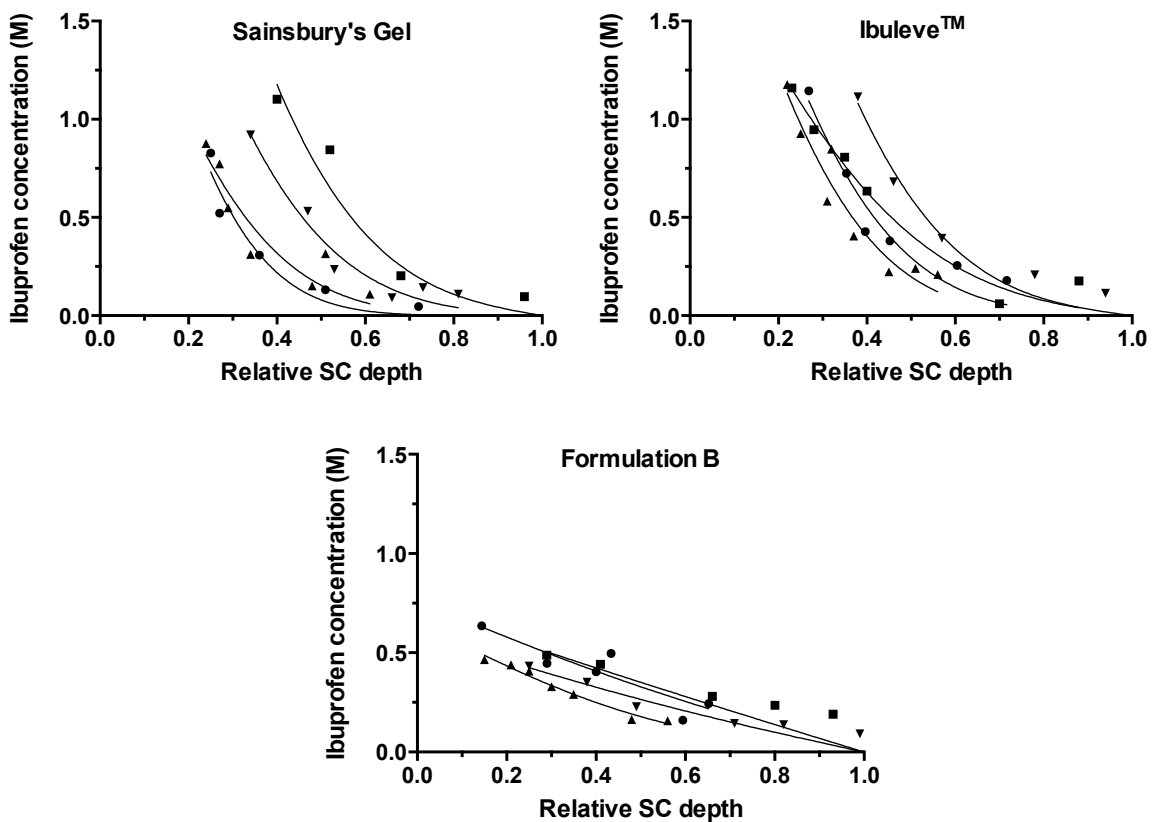


Figure 4: Concentration profiles of ibuprofen across human SC *in vivo* ($n = 4$) following topical application of Sainsbury's Gel, IbuleveTM and TOCN gel formulation B. The data are presented as a function of relative depth into the SC (where 0 represents the SC surface, and 1 indicates the interface between the SC and the underlying, viable skin layers).



TABLES

Table 1: Components (in %w/w) of the ibuprofen gel formulations studied.

Formulation	Ibuprofen	Aqueous TOCN dispersion ^a	Ethanol	SDS	Propylene glycol
A	1.0	60	37	-	2.0
B	1.0	60	39	-	-
C	1.0	60	39	-	-
D	1.0	60	39	-	-
E	1.0	60	39	0.07	-
Sainsbury's Gel	5.0	hydroxyethylcellulose, sodium hydroxide, benzyl alcohol, isopropyl alcohol, purified water			
Ibuleve™	5.0	industrial methylated spirit, carbomer, propylene glycol, diethylamine, purified water			

^a For formulations A, B and E, the aqueous dispersion was prepared at a concentration of 1.8% w/w TOCN; for formulations C and D, 1.2% w/w and 0.6% w/w TOCN were used, respectively.

Table 2: Ibuprofen uptake into, and cumulative permeation through, porcine stratum corneum (SC) *in vitro* after application of six gels for a period of 8 hours (mean ± SD; n = 4-6).

Formulation	Ibuprofen uptake into SC (µg/cm ²)	Ibuprofen permeation through SC (µg/cm ²)
Sainsbury's Gel	163 ± 40	270 ± 67
Ibuleve™	202 ± 32	184 ± 43
Formulation B	94 ± 23	238 ± 52
Formulation C	265 ± 59	551 ± 176
Formulation D	233 ± 44	402 ± 96
Formulation E	179 ± 26	294 ± 106

Table 3: Ibuprofen uptake into human stratum corneum (SC) *in vivo* after application of three gels for a period of 1 hour (mean ± SD; n = 4).

Formulation	Ibuprofen uptake into SC (µg/cm ²)
Sainsbury's Gel	83 ± 16
Ibuleve™	115 ± 19
Formulation B	53 ± 7