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RESEARCH PAPER

Topical Delivery of a Naproxen-Dithranol Co-drug: *In Vitro* Skin Penetration, Permeation, and Staining

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ABSTRACT

Purpose This work probed the topical delivery and skin-staining properties of a novel co-drug, naproxyl-dithranol (Nap-DTH), which comprises anti-inflammatory (naproxen) and anti-proliferative (dithranol) moieties.

Method Freshly excised, full-thickness porcine ear skin was dosed with saturated solutions of the compounds. After 24 h, the skin was recovered and used to prepare comparative depth profiles by the tape-stripping technique and to examine the extent of skin staining.

Results Depth profiles showed that Nap-DTH led to a 5-fold increase in drug retention in the skin compared to dithranol. The application of Nap-DTH also demonstrated improved stability, resulting in lower levels of dithranol degradation products in the skin. Furthermore, significantly less naproxen from hydrolysed Nap-DTH permeated into the receptor phase compared to naproxen when applied alone (0.08 ± 0.03 nmol cm^{-2} and 180 ± 60 nmol cm^{-2}, respectively). Moreover, the reduced staining of the skin was very apparent for Nap-DTH compared to dithranol.

Conclusions Topical delivery of Nap-DTH not only improves the delivery of naproxen and dithranol, but also reduces unwanted effects of the parent moieties, in particular the skin staining, which is a major issue concerning the use of dithranol.

KEY WORDS anti-proliferative · co-drug · ester hydrolysis · prodrug · psoriasis

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ABBREVIATIONS

HMPA	Hexamethylphosphoramide
IPM	Isopropyl myristate
LOD	limit of detection
MW	molecular weight
Nap-DTH	Naproxyl-dithranol
SC	stratum corneum
THF	Tetrahydrofuran

INTRODUCTION

Psoriasis is a chronic autoimmune inflammatory disorder of the skin, characterised by keratinocyte hyperproliferation and the accumulation of activated T-cells in the dermis and epidermis, leading to relapsing and remitting scaling. It affects approximately 2% of the world population. Of these cases of psoriasis, 10–30% also develop psoriatic arthritis (1). The cause of psoriasis is still not fully understood, but the underlying pathogenesis is thought to involve inflammation, keratinocyte hyperproliferation and altered keratinocyte differentiation (2–6).

Topical therapy remains the mainstay of treatment for the majority of patients with psoriasis, and dithranol (1,8-dihydroxy-9(10H)-anthracenone, also known as anthralin) has been used successfully to treat psoriasis for over 80 years. The precise mechanism of action remains unclear (7); however, it has been proposed that it acts on DNA replication and repair synthesis (8), mitochondrial membrane and function (9), epidermal growth factor receptor phosphorylation in keratinocytes (10), and cytosolic key enzymes associated with cell proliferation and inflammation, which lead to clearance of psoriatic plaques and hence a remission period (11). Dithranol is essentially free of systemic side effects or the skin atrophy that can

occur with other topical treatments such as steroids. However, despite its undoubted efficacy, the widespread use is limited by its propensity to cause local skin inflammation and irritation, as well as severe staining of skin and clothing. Dithranol is also chemically unstable, and readily undergoes oxidation to a range of degradation products, including danthron and dithranol dimer, which are thought to contribute to the undesired effects (12). Dithranol can be used alone, but is typically prescribed with other drugs, e.g. cyclosporine, coal tar, salicylic acid or ultraviolet irradiation (13, 14). However, the undesired effects of dithranol, and its intrinsic instability, remain a concern and lead to compliance issues.

The current work explored *in vitro* the potential value of a novel topical system based on a co-drug of dithranol and naproxen. The term co-drug (alternatively: codrug) refers to the combination of two or more therapeutically active compounds via a cleavable covalent linkage, and the potential of co-drugs in topical delivery has been recently reviewed (15). Dithranol (Fig. 1) contains two hydroxyl groups which could be utilised in the formation of ester linkages. In addition, naproxen is prescribed for patients affected by inflammatory skin conditions such as dermatitis (16) and is the treatment of choice for psoriasis arthritis (17). Naproxen possesses a carboxylic group which can utilised in the formation of an ester bond with dithranol, yielding mono-substituted naproxyl-dithranol (Nap-DTH) which has already been successfully synthesised (Fig. 1) (18). By forming Nap-DTH, it was hypothesised that the physicochemical properties of the two active parent compounds would be altered simultaneously to enhance topical drug delivery and potentially improve the stability of dithranol, thus reducing its side effects. In addition, with both parent compounds having clinical applications for psoriasis, the co-drug could offer synergistic and/or dual therapeutic actions upon *in situ* liberation.

Using porcine ear skin, the current studies investigated the stability of Nap-DTH, followed by the *in vitro* determination of skin staining, skin penetration and permeation, relative to the parent compounds.

MATERIALS AND METHODS

Materials

Dithranol was purchased from BUFA Pharmaceutical Products (Uitgeest, Holland). Naproxen, 1,8-dihydroxyanthraquinone (danthron), Hanks' balance salt and isopropyl myristate (IPM) were obtained from Sigma-Aldrich Company Ltd. (Poole, UK). All other chemicals, reagents and HPLC-grade solvents were obtained from Fisher Scientific UK (Loughborough, UK). The synthesis, physical-chemical characterisation and spectrophotometric properties of the Nap-DTH, 8-hydroxy-9-oxo-9,10-dihydroanthracen-1-yl 2-(6-methoxynaphthalen-2-yl)propanoate, are described elsewhere (18). Porcine ears were obtained from a local abattoir prior to steam cleaning, immersed in iced Hanks buffer solution and used within 3 h of slaughter.

Solubility and Stability in Isopropyl Myristate (IPM)

By trial and error, IPM was determined to be an appropriate vehicle. IPM is a commonly used excipient in topical formulations in which each of the test compounds were soluble. Saturated solutions were prepared by adding an excess amount of dithranol, naproxen or Nap-DTH to 1 mL IPM in microcentrifuge tubes, continuously rotated on a blood tube rotator in an incubator set at 32°C. After 4 h, the tubes were centrifuged at 13,000 rpm for 5 min, and the supernatants sampled and used either to dose skin or for analysis.

The stabilities of naproxen, dithranol and Nap-DTH were studied by placing 2 mL of a saturated solution in IPM of each compound into a sealable amber glass vial. All the stability samples were prepared in triplicate and were kept at three different temperature settings close to the ICH guidelines (19) for stability testing of new drug substances and products: (5±3°C; 30±3°C and an accelerated temperature of 40±2°C) and shielded from light. A 200 μL sample was taken immediately after starting and then again every 2 days over a period of 10 days. HPLC was used to determine the amount of compound present in the sample. The reduction was calculated as the difference between the

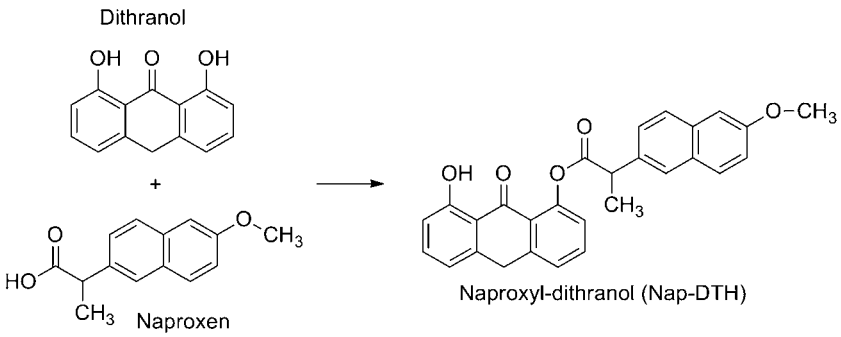

Fig. 1 Formation of Nap-DTH co-drug using a 1:1 ratio of dithranol and naproxen.

applied and the detected doses. Zero-order decomposition rates (k) of each compound were calculated from the gradient of the graph of concentration data versus time.

Preparation of Skin Membranes

Porcine ear skin has been widely used for *in vitro* skin permeation studies (20, 21) and has been shown to be the best alternative model for human skin (22–25). The excised porcine ears were washed with running cold tap water, and full thickness skin was liberated from the underlying cartilage by blunt dissection using a scalpel; hairs were removed with electric clippers. The skin was cut into 2 cm^2 sections and used immediately.

Skin Permeation

The permeation of naproxen, dithranol and the co-drug were compared to determine the amount of each drug that may potentially be taken up by the systemic circulation. The skin was mounted on the pre-greased flanged of glass Franz-type diffusion cells, with nominal diffusion areas of 0.95 cm^2 and receptor volumes of 4.5 mL. The receptor chambers were filled with de-gassed Hanks solution to maintain skin viability (21). The diffusion cells were placed in an incubator set at 32°C, and after 10 min equilibration, dosed with 300 μL of test solution. The donor and receptor phases were occluded. At appropriate timepoints, the entire receptor phases were withdrawn with dedicated pipettes. Samples of 1 mL were placed in Eppendorf tubes and centrifuged at 13000 rpm for 10 min, and the supernatants transferred to HPLC autosampler vials. Receptor phases were replaced with fresh temperature-equilibrated solution as appropriate. For each drug, four replicates were used, and two further cells dosed with IPM alone served as a control.

Comparative Skin Staining and Penetration

Diffusion cells were set up as described above. After 24 h, they were dismantled, and the remaining drug in the donor compartment was collected. Any drug residue left on the surface of the donor compartment was cleaned with a cotton bud. The surface of the skin was wiped gently with a cotton bud. The tips of the cotton buds were cut off and placed in 5 mL extraction solvent (which consisted the mobile phase: 10% water/H_3PO_4 in MeCN). At this stage, the skin colour was then compared visually, and representative images of three determinations were taken. One further cell dosed with vehicle alone served as a control.

Tape stripping was then carried out, using regular adhesive tape to consecutively strip the skin 20 times, with the strips being placed in 2 mL extraction solvent (10% water/H_3PO_4 in MeCN). The tape strips were grouped in the following manner: 1–2, 3–4, 5–7, 8–10, 11–14, 15–20. The diffusion area was excised from the surrounding skin using a scalpel and cut into small pieces (approximately 2 mm^2) and placed in 2 mL extraction solvent. Six replicates were carried out for the Nap-DTH and for both of the parent compounds, with two further cells dosed with 300 μL of IPM served as the control. All samples were occluded and constantly agitated overnight on a rocking plate at ambient temperature. Aliquots of 1 mL were then centrifuged at 13,000 rpm for 10 min prior to HPLC analysis.

High Performance Liquid Chromatography

A reverse phase HPLC method was developed to simultaneously determine dithranol, naproxen, Nap-DTH, danthron and dithranol dimer. Samples were analysed at ambient temperature using an Agilent 1100 series automated system with a quaternary solvent delivery system and UV detector set at 230 nm. The instrument was fitted with a Gemini C_{18}, 5 μm, 250×4.6 mm column (Phenomenex, Macclesfield, UK) and a Phenomenex Securityguard precolumn. The flow rate was set at 1 mL min^{-1} with an injection volume of 100 μL. A gradient elution was used, consisting of mobile phase A: de-ionised water adjusted to pH 2.2 with phosphoric acid, and mobile phase B: 100% MeCN. A and B ran for 6.5 min (6:4), changing to 1:9 over 1 min, and was run for a further 12.5 min. Calibration curves were constructed for each compound in mobile phase and each provided R^2 of >0.999. Retention times for naproxen, danthron, dithranol, dithranol dimer and Nap-DTH were 6.5, 11.7, 12.4, 16.7 and 17.3 min, respectively. The analytical limit of detection (LOD) was 0.008, 0.45, 0.09, 1.8 and 0.9 μg mL^{-1}, respectively.

Statistical Analysis

Statistical analysis was carried out using MS Excel 2007 Data Analysis Add-In programme. Significant differences and comparisons of the means were made using ANOVA (single factor). The 95% confidence interval is generally thought to be of significantly different; however, p >0.05 may sometime be accepted as significantly different especially when performing *ex vivo* skin experiments due to the inherently high variability.

RESULTS

Physicochemical Determinations

The physicochemical properties of the three test compounds are summarised in Table I. Generally, compounds with molecular weight (MW) of less than 500 are

Table I Physicochemical Properties of Nap-DTH and Its Parent Compounds, Dithranol and Naproxen

Compound	MW	ClogP[a]	Solubility[b] (mM)	k (μM day^{-1})[c]			k (% day^{-1})[d]		
				5°C	30°C	40°C	5°C	30°C	40°C
Naproxen	230	2.94 ± 0.07	30.7 ± 1.7	3.01	3.42	3.94	0.008	0.011	0.013
Dithranol	226	2.37 ± 0.45	20.8 ± 0.2	31.7	51.2	79.5	0.131	0.215	0.378
Nap-DTH	438	5.45 ± 0.47	3.2 ± 0.2	11.4	6.24	13.9	0.334	0.167	0.399

[a] ClogP was determined using ChemDraw Ultra, and the reported value is the average of three different algorithms. [b] The value of solubility in IPM is the mean ± s.d., $n = 6$. The decomposition constant (k) is the slope obtained from plotting concentration versus time in days (mean ± s.d., $n = 3$). [c] concentration of compound in μM and [d] concentration of compound as a percentage of the initial dose.

considered appropriate for skin absorption (26), and compounds with a logP≈1–3 would be expected to penetrate through normal skin most effectively. As dithranol is chemically unstable, solubility was determined by a kinetic method (shaking then assaying), rather than the thermodynamic method (shake until equilibrium is reached) (27).

Permeation Study

When naproxen was applied alone to the skin, its permeation followed a typical profile of an infinite dose application (Fig. 2A), with a steady-state flux of 1.6 nmol $cm^{-2}h^{-1}$ attained within 4 h. In comparison, when Nap-DTH and dithranol were applied to the skin, both were below LOD in the receptor phase. Although the concentration of Nap-DTH was below LOD, it was interesting to note that when Nap-DTH was dosed, naproxen was detected in the receptor phase (Fig. 2B) with a cumulative concentration of 0.08 ± 0.03 nmol cm^{-2} after 24 h.

Skin Penetration Study

The penetration of Nap-DTH, naproxen and dithranol into full thickness porcine skin 24 h after application is summarised in Fig. 3. In all cases, 80–90% of the applied doses were recovered. Figure 4 shows the molar concentrations of dithranol and naproxen liberated from Nap-DTH in different fractions of the skin. Penetration profiles for dithranol and its degradation products, danthron and dithranol dimer, were also determined (Fig. 5).

Skin Staining Comparison

The appearance of the skin 24 h after the application of 300 µL IPM solution saturated with Nap-DTH is shown in comparison with dithranol in Fig. 6. Control experiments with vehicle alone were conducted to allow better visual comparison between the changes in skin colouration with or without Nap-DTH and dithranol. It can clearly be seen that after application of Nap-DTH, the skin colour was not different compared to the untreated control. On the other hand, after dithranol application, the skin-staining effect was very noticeable, with a characteristic dark brown discolouration.

DISCUSSION

Physicochemical Determinations

Nap-DTH has a MW of 438, thus obeying the 500 Da rule. It also has a ClogP value of 5.5, indicating potential

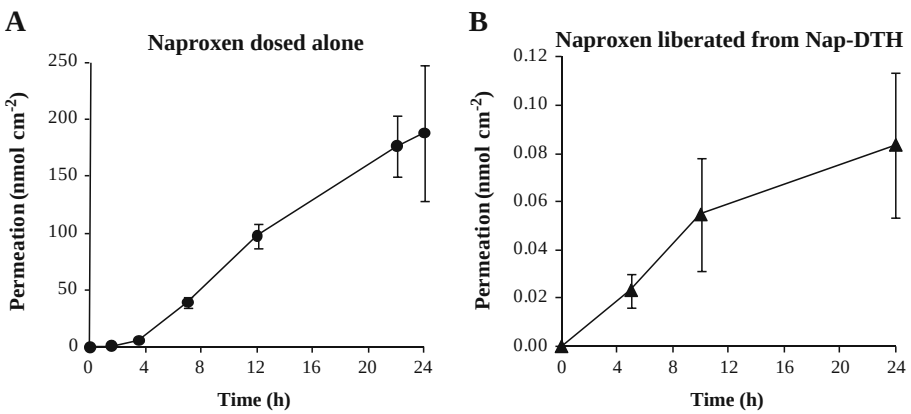

Fig. 2 Permeation profile for naproxen across porcine ear skin using IPM as the donor vehicle, whereby naproxen was **A** dosed alone, or **B** liberated due to the decomposition of Nap-DTH (mean ± s.d., $n = 6$).

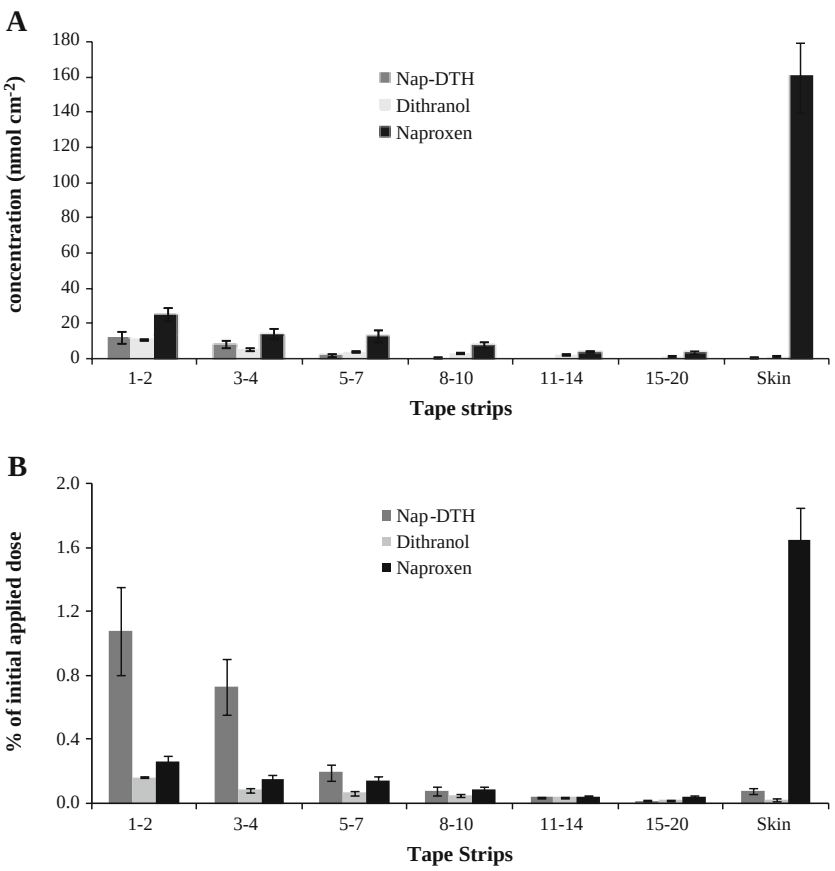

Fig. 3 Penetration profiles of Nap-DTH, naproxen and dithranol. The y-axes represent **A** the concentration obtained in nmol cm^{-2} and **B** the amount retained as a percentage of the applied saturation dose. The total concentration was calculated as the original compound less its hydrolysed components or degradation products (mean ± s.d., $n = 6$). 'Skin' on the x-axis denotes remaining skin tissue following 20 tape-strips.

retention within lipid domains and the establishment of a reservoir. However, the stratum corneum (SC) barrier of psoriatic skin is compromised, even though the epidermis is considerably thickened relative to uninvolved skin, so this criterion is not so important, and the levels of drug delivery observed using non-psoriatic skin can be considered as the minimal achievable. Highly lipophilic compounds, including tacrolimus and pimercrolimus (logP > 6, indicating low potential for topical delivery) have been shown to penetrate diseased skin sufficiently to demonstrate a therapeutic effect (28, 29). Thus, even though the ClogP of Nap-DTH is relatively high it may still be able to penetrate and result in a therapeutic concentration. Furthermore, this does not yet take into consideration the effects of co-drug cleavage and liberation of the two parent compounds *in situ*, which are expected to increase the penetration potential of the liberated drug moieties.

Dithranol is practically insoluble in water, sparingly soluble in acetone and slightly soluble in alcohol (30). A range of excipients including (but not limited to) methanol, ethanol, polyethylene glycol, Miglyol 840, glycerol, liquid paraffin and dimethicone were investigated, but dithranol and/or Nap-DTH exhibited either limited solubility or limited stability in these solvents (data not shown). However,

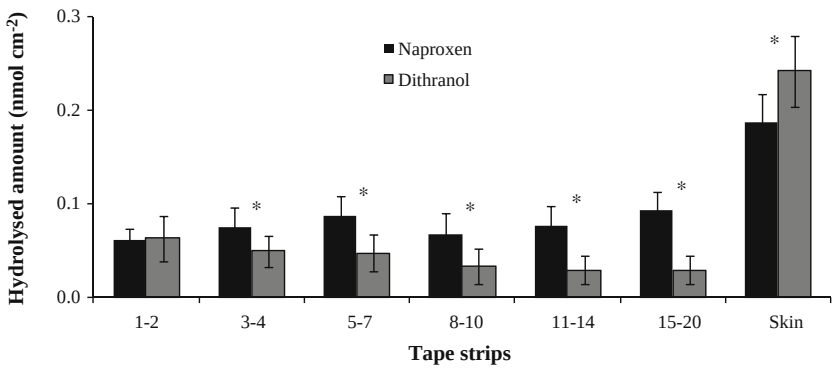

Fig. 4 Concentration of naproxen and dithranol liberated from Nap-DTH in different skin layers (mean ± s.d., $n = 6$). 'Skin' on the x-axis denotes remaining skin tissue following 20 tape-strips. * represent significant difference between naproxen and dithranol ($p < 0.05$).

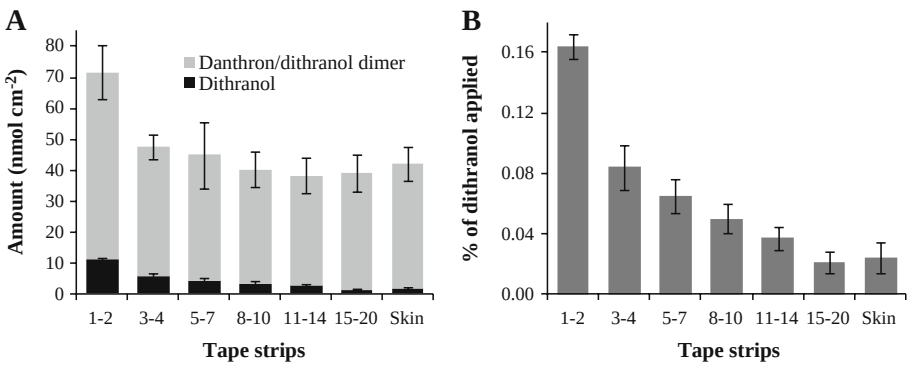

Fig. 5 Penetration profile after 24 h application of saturated dithranol in IPM (mean ± s.d., $n = 6$). **A** The amount of dithranol plus its degradation products (danthron and dithranol dimer) obtained in different skin layers (nmol). **B** The amount of active dithranol retained in different skin layers, expressed as a percentage of the initial saturation dose applied.

isopropyl myristate (IPM) was found to be suitable and was thus utilised as the donor vehicle. IPM is a non-polar aprotic solvent which is commonly used in pharmaceutical and topical formulations as a hydrophobic vehicle (31, 32). Another study reported increased pro-drug stability in IPM compared to protic solvents (33). Saturated solutions of the test compounds in IPM were used in skin experiments to maintain an equal thermodynamic activity.

All three compounds, Nap-DTH, dithranol and naproxen, were found to be stable in IPM for at least 10 days at all three temperatures (5°C, 30°C and 40°C). Even at 40°C, decomposition was no more than 0.4% of the initial concentration after 24 h (Table I). For Nap-DTH, parent compounds were below limit of detection (LOD) for the duration of the experiment. Both danthron and dithranol dimer were below LOD in the dithranol stability study.

Skin Permeation and Penetration Study

When applied to the skin alone, naproxen achieved a steady-state flux within 4 h. When it was applied as a co-drug, the released naproxen did not achieve steady state even at 24 h, indicating that a complex reaction involving the co-drug had occurred during the diffusion process. Given the stability of the co-drug in the donor vehicle and the receptor phase, hydrolysis must have been enzyme-mediated. It was unlikely to have occurred in the receptor phase, since neither dithranol nor its oxidation products were detected. Overall, the amount of naproxen permeated into the receptor phase after co-drug application was greatly reduced relative to dosing with naproxen. This is advantageous, as a greater proportion of naproxen would be retained within the skin, rather than entering the systemic circulation, and thus would have greater impact on cyclooxygenase (the biological target of many NSAIDs) within the skin.

In the skin penetration experiment, Nap-DTH was detected in all fractions of the skin, with some 2.1% (26 nmol) of the saturated dose detected in the skin layers, providing 0.07% (0.8 nmol) of naproxen and 0.05% (0.6 nmol) of dithranol within the skin. This implies that hydrolysis of the co-drug occurred in the SC, with higher levels of metabolism in the epidermis. In theory, one molecule of Nap-DTH should generate one molecule of naproxen and one molecule of dithranol upon hydrolysis. Although there was a significant difference ($p = 0.03$) between the amount of parent compounds obtained, the lower amounts of dithranol recovered from the skin layers compared to the naproxen were likely due to auto-oxidation of dithranol after release from the co-drug.

Significant differences ($p < 0.05$) were observed between the molar concentrations of liberated dithranol and naproxen obtained in different fractions of the skin (Fig. 4), with the amount of liberated naproxen being greater in the tape strips, whereas dithranol was mainly recovered in the remaining skin. The concentration difference in the tape strips could be due to the differences in tissue binding affinity between naproxen and dithranol, which in turn leads to the differences in the penetration rate of the two compounds.

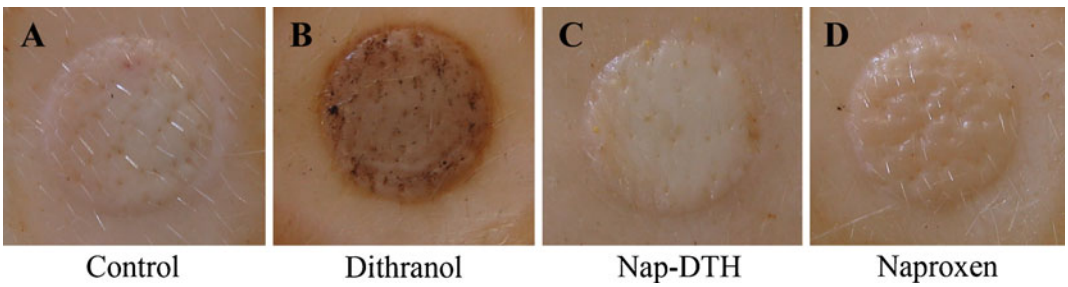

Fig. 6 Appearance of the skin after 24 h of drug application. The skin staining effect can be visually compared. **A** The control containing the vehicle alone, **B** dithranol, **C** Nap-DTH and **D** naproxen. Each image is representative of three independent replicates.

Dithranol is known to bind to the SC, and its heavy staining is a major pitfall in the clinical application of this drug (34).

The data have suggested that naproxen has a lower tissue binding affinity, as an almost constant level of naproxen was detected across all tape strips, and only a slightly higher concentration was obtained from the remaining skin. Since less naproxen was tissue-bound, we surmise that it was able to permeate through the skin to the receptor phase and be detected. On the other hand, the amount of dithranol obtained decreased with increasing depth; however, a significant amount of dithranol was retained in the remaining skin layer. It has been suggested that retarded penetration of lipophilic compounds may be explained by their hydrophobic interactions with a lipophilic component or components of the skin (35). Another study has shown similar results where the viable epidermis/dermis layer contributed to resisting the permeation of a lipophilic ester pro-drug (36). Thus, the retention of dithranol could be due to a higher tissue binding affinity compared to naproxen, which could reduce its diffusion rate from the skin into the receptor medium. The comparatively higher concentration of parent compounds obtained from the remaining skin tissue over the amount obtained from different sections of the tape strips suggests that there is a greater enzyme distribution and metabolic activity in the skin tissue underlying the SC. This is in agreement with numerous other studies demonstrating that the viable epidermis is the major location of cutaneous enzyme activity and a major site for drug metabolism (37–39). Thus, the distribution of enzyme activity can affect hydrolysis of the co-drug (18).

For comparison, a penetration study was carried out using a saturated IPM solution of the parent compounds (Fig. 3). Naproxen provided a typical depth profile for infinite dosing with a total of 2.4% (230 nmol) recovered from the tape-stripped skin layers, while a significantly higher amount was retained in the remaining skin tissue. The amount of naproxen retained (as a percentage of the saturation dose) within the skin layer was not significantly different from Nap-DTH ($p=0.7$). Although there was no enhancement of topical delivery of the co-drug compared to naproxen, co-drug administration significantly reduced the amount of naproxen reaching the receptor phase, i.e. the systemic circulation. This suggests Nap-DTH could maximise skin retention and minimise systemic absorption, thus potentially leading to a reduction in systemic side effects.

The penetration profile for dithranol shows that some 4.4% out of the total 4.8% extracted from the skin layers was inactive dithranol degradation products. Although naproxen and dithranol have similar ClogP and MW, the permeation of dithranol was very much lower than naproxen, which is thought to be due to its poor stability and extremely poor water solubility. Only some 0.4% (29.6 nmol) was the active dithranol (Fig. 5). Since danthron and dithranol dimer are not therapeutically active (34), the amounts obtained were not taken into account when producing the penetration profile in Fig. 3. Only 0.02% (1.6 nmol) of the active dithranol was retained in the viable skin layer. These data show that although a measurable amount of dithranol penetrated into the skin layers, only a very small proportion of this remained as active dithranol after 24 h in the skin. The vast majority was oxidised to the non-therapeutically active derivatives. Higher concentrations of these degradation products are more likely to lead to adverse effects, such as skin staining and irritation. With the use of Nap-DTH, the amounts of dithranol degradation products were significantly reduced. In addition, a significantly higher percentage of Nap-DTH was retained in the remaining skin layer than the amount of dithranol recovered when applied alone (0.08% and 0.02% respectively, $p<0.05$). Thus, the co-drug could potentially have a superior anti-inflammatory and anti-proliferative profile with less toxic effect as compared to the parent compounds (18).

Skin Staining Comparison

One benefit of the co-drug approach is that it offers the possibility of modulating the chromophore and therefore the colour of the overall complex. This would be a major advantage in the case of dithranol, where intense staining of skin and clothing is an unpleasant side effect of this otherwise highly efficacious drug. Also, the temporary alteration in dithranol chemistry within the co-drug could confer stability by reducing the auto-oxidation of dithranol. Spectrophotometric analysis has shown that the absorptivity of Nap-DTH is some 40% less than an equimolar solution of dithranol (19). The current study clearly shows that 24 h after the application of Nap-DTH, the skin colour was comparable to the untreated control (Fig. 6). On the other hand, after dithranol application, the skin staining effect was very noticeable, with characteristic dark brown discolouration.

Modulation of the dithranol chromophore via the attachment of the naproxen moiety resulted in a complex that has a much lower colour intensity (19). When applied to the skin, dithranol is exposed to air and undergoes auto-oxidation and polymerization. However, adopting the co-drug approach, the modulation of the chemical structure of dithranol enabled a dramatic reduction in the degradation of dithranol in the skin, thus reducing skin staining. As expected, the application of naproxen in IPM did not produce any significant colour change to skin.

CONCLUSION

The staining of skin and clothing by dithranol presents major compliance challenges for this otherwise highly

effective drug. From our study, it was found that Nap-DTH exhibited minimal skin staining effects compared to dithranol. For topical treatments of skin conditions, it is vital that the drug retains sufficiently high concentrations within the skin and preferably without permeating into the systemic circulation to minimise systemic side effects. It was found that approximately 2.6% of the permeated co-drug was hydrolysed to the parent compounds. This would appear to be a relatively small amount but could be accounted for by a reduction in enzymatic activity after excision of the skin samples used. The rate of co-drug hydrolysis is expected to be much higher *in vivo*. Despite this, a greater degree of interaction of Nap-DTH with the skin was observed. This is evident from the fact that the percentage of co-drug obtained from the skin layers was significantly higher compared to dithranol, with no dithranol degradation products observed. In addition, the amount of naproxen in the skin was comparable when liberated from the co-drug, Nap-DTH, and when naproxen was administered alone. This could suggest that the co-drug may be beneficial in reducing the auto-degradation of dithranol. Also, the amount of naproxen permeated into the receptor phase was greatly reduced with the use of the co-drug compared to naproxen alone. This could beneficially limit the proportion of the dose reaching the systemic circulation.

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Conflict of interest None declared.

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