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Transdermal delivery enhancement of haloperidol from gel formulations by 1,8-cineole

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Abstract

The feasibility of using 10% 1,8-cineole as an enhancer for transdermal delivery of haloperidol has been examined. In-vitro transdermal delivery across full-thickness human, rabbit and hairless mouse skins was measured from three polymer gel systems, hypromellose (hydroxypropylmethylcellulose), Carbomer (Carbopol) 940 and macrogol (polyethylene glycol) using Franz cells. Values for the permeability coefficient k_p, calculated as the product (Kh)×(D/h^2) where these two factors were obtained from curve fitting of the non-steady-state equation over 24 h, were similar from the three formulations. The value of k_p from hypromellose was significantly enhanced by cineole by factors of 6.2 (4.6–8.1), 5.6 (5.0–6.2) and 3.0 (2.6–3.4) for human, rabbit and mouse, respectively (mean and 95% confidence intervals). Enhancement ratios for K: 13.3 (8.3–20), 3.1 (2.5–3.9) and 2.0 (1.5–2.6), were higher than those for D: 0.47 (0.41–0.55), 1.8 (1.6–2.1) and 1.5 (1.3–1.8). This suggested that the barrier function of the skin lipids was marginally affected and the main effect was to increase the thermodynamic activity of the drug in the barrier. The enhancement achieved in human skin suggested that delivery could be safely enhanced by terpenoids.

Introduction

Haloperidol is used to treat schizophrenia and other psychoses, mania, psychomotor agitation, excitement, violent or dangerously impulsive behaviour, including delusions, confusions and hallucination. Daily oral dosages range from 0.5 mg (anxiety and agitation) to 30 mg (resistant schizophrenia) (British National Formulary 2006). Although completely absorbed from the gastrointestinal tract, its bioavailability is limited to approximately 60% by first-pass metabolism (Forsman & Ohman 1976) and transdermal delivery can potentially overcome this drawback. Using a log P value of 4.3, MW 375.9 and an aqueous solubility of 14 mg mL^{-1} (Virtual Computational Chemistry Laboratory; http://146.107.217.178/), the maximal flux from aqueous vehicle is predicted (Potts & Guy 1992) as approximately 0.15 μg cm^{-2} h^{-1}. Since low blood levels of 2–13 ng mL^{-1} are effective in the clinical treatment of schizophrenia (Volavka et al 1992), the transdermal delivery route is of potential interest. Neuroleptic-induced catatonia and pharmacokinetic parameters in rat were determined from a matrix-diffusion-type transdermal film (Samanta et al 2003).

In general, a transdermal delivery device contains a drug dissolved or suspended in a vehicle, which is often thickened to ease handling. Skin generally has a low permeability because of the effective barrier function of the stratum corneum, and chemical enhancers can be used to increase drug delivery (Finnin & Morgan 1999). The effects of cetrimide and ascorbic acid on the in-vitro permeation of haloperidol across rat and human skin were reported by Vaddi et al (2001a, b). Volatile oils are widely and safely used as flavours and in perfumery, and the transdermal enhancing powers of their terpenoid constituents have been investigated since 1989 (Williams & Barry 1989, 1991). Eucalyptus oil was one of the most effective, with the additional benefit of low toxicity. Its main constituent (~90%) is 1,8-cineole, which was confirmed as an enhancer for several drugs (El-Kattan et al 2000). Narishetty & Panchagnula (2005) suggested that terpenes transform stratum corneum lipid packing from highly ordered orthorhombic to less ordered hexagonal patterns, a view supported by electron paramagnetic resonance spectroscopy studies of 1,8-cineole stratum corneum interactions (Anjos et al 2007). Lim et al (2006) showed enhancement of haloperidol flux across human skin by terpenoids

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from organogels of dibutyllauroylglutamide and propylene glycol. Limonene enhanced flux by a factor of 26.5 and cineole by 6.9.

We measured the permeation of haloperidol from three gels based on macrogol (polyethylene glycol; PEG), Carbomer (Carbopol) and hypromellose (hydroxypropylmethylcellulose, HPMC), which are widely used in pharmaceutical manufacturing as water-soluble bases for topical preparations (Martindale 2006). Using the most promising of these, enhancement of haloperidol delivery by incorporation of 10% 1,8-cineole was studied. Inter-specific effects were studied using three different species of skin to assess whether an animal model would be suitable for further developmental studies.

Materials and Methods

Materials

Haloperidol and hypromellose were supplied by Sigma (St Louis, MO, USA). Macrogol 6000, macrogol 400, propylene glycol, 1,8-cineole, glacial acetic acid, HLPLC grade acetonitrile and methanol were supplied by BDH Chemicals (Poole, UK). Carbomer 940 and methyl hydroxybenzoate (methylparaben) were from Winlab (Maidenhead, UK), and macrogol 4000 was from Fluka Ag (Buchs SG, Switzerland). Male HL strain hairless mice (5–8-weeks-old; 25–30 g) and male white New Zealand rabbits (3.0–3.5 kg) were obtained from the Experimental Animal Care Centre, College of Pharmacy, King Saud University, Riyadh.

Haloperidol gel formulations (0.5%)

Carbomer 940, hypromellose, and macrogol 400 mixtures were used as gel bases, using standard formulations and methods developed in-house. Gel compositions are given in Table 1. Haloperidol–propylene glycol stock solution was made by dissolving 50 mg haloperidol in 3 g heated propylene glycol containing 20 mg methyl hydroxybenzoate.

Hypromellose gel preparation

Hypromellose 1.25 g was dispersed in 4 g propylene glycol to form a gel. Haloperidol–propylene glycol solution was added dropwise with continuous stirring, the pH adjusted to 7.0 by dropwise addition of 2 M NaOH, and the weight made up to10 g with propylene glycol. For the enhancer formulation the 1,8-cineole was pre-dissolved in the haloperidol–propylene glycol.

Table 1 Haloperidol gel formulations

	Gel formulation		
	Hypromellose	Carbomer 940	Macrogol mixture
Haloperidol	0.05 g	0.05 g	0.05 g
Hypromellose	1.25 g	–	–
Carbomer 940	–	0.15 g	–
Macrogol 4000	–	–	1.25 g
Macrogol 300	–	–	2.25 g
Methyl hydroxybenzoate	0.02 g	0.02 g	0.02 g
Propylene glycol to	10.00 g	10.00 g	10.00 g

Carbomer 940 gel preparation

Carbomer 940 0.15 g was dispersed in 4 g propylene glycol and left for 6–8 h to form a gel. Haloperidol–propylene glycol solution was added dropwise with continuous stirring and the weight made up to10 g with propylene glycol.

Macrogol mixture gel preparation

Macrogol 4000 1.25 g and macrogol 300 2.25 g were melted in a porcelain dish on a heating mantle and haloperidol–propylene glycol solution added with continuous stirring. The pH was adjusted to 7.0 by NaOH and the weight made up to10 g with propylene glycol.

Diffusion studies

Skin preparation

Mice were killed by spinal dislocation and rabbits by overdose of inhaled ether. Rabbit skin was clipped as close as possible using an electric shaver (Diato Electric Machine Ind. Co., Japan) and the dorsal skin carefully removed. Subcutaneous fat was removed by blunt dissection. Skins were examined with a magnifying lens for damage or disease conditions. The freshly-prepared skin was mounted into the Franz cell without freezing. Female breast skin was obtained following surgery. Subcutaneous fat was removed and the skin stored at –20°C. It was allowed to thaw at room temperature before use.

In-vitro permeation experiments

Franz-type split diffusion cells (Crown Glass Company, Somerville, NJ, USA) were used, with a diffusional area of 5.37 cm^2 and a receptor compartment of 20 mL, filled with 0.1 M phosphate buffer solution pH 7.2, stirred (600 rev min^{-1}) by Teflon-coated followers and maintained at 37 ± 0.5°C by water circulating through a jacket. Skins were mounted with epidermal surface in contact with the donor taking care to avoid air bubble formation beneath the skin. Approximately 1 g gel (5 mg haloperidol) was distributed evenly over the skin and 0.5-mL samples taken with replacement at 3, 6, 9, 12 and 24 h.

HPLC analysis of haloperidol

HPLC binary pump model LC-10 AD (Shimadzu Corporation, Kyoto, Japan) and automatic injector (Waters Associates, Bedford, MA, USA). Stainless steel analytical adsorbasphere phenyl column (4.6-mm i.d.×150-mm length) packed with 5-μm particle size ultrasphere (Alltech Associates Inc., IL, USA) at 35°C. The mobile phase consisted of acetonitrile:methanol:0.05 M phosphate buffer:triethylamine (25:25:50:0.1, v/v) adjusted to pH 7.10 with phosphoric acid (200–250 μL). Mobile phase was degassed and filtered through 0.22-μm membrane filters type GV (Millipore, Bedford, MA, USA) and pumped at 1.5 mL min^{-1}. Injection volume was 50 μL. The variable wavelength model 10A-UV/vis detector was set at 247 nm. The assay was validated measuring the peak height of haloperidol relative to that of 4-OH propyl benzoate as internal standard. The response was linear ($r^2 > 0.999$) over haloperidol concentrations of 10–1000 ng mL^{-1}. The coefficient of variation of the gradient for experiments conducted over two weeks was 3.98%.

Data analysis

The permeability coefficient, k_p, is usually calculated from J_{ss}/c_{donor}. J_{ss} is the steady-state flux calculated from the limiting gradient of the plot of cumulative quantity in the receptor phase against time. It was evident from the steadily increasing gradient that steady state might not have been achieved in these experiments. Sink conditions were probably maintained in the receptor phase since approximately 95% of the haloperidol (pK_a 8.5) would be ionized. An alternative approach would be to calculate k_p as the product $(Kh)\times(D/h^2)$ from the non-steady state equation (Crank 1956).

The amount (Q) transferred at time (t) is given by:

$$Q = AKhC\left[\frac{Dt}{h^2} - \frac{1}{6} - \frac{2}{\pi^2}\sum_{n=1}^{\infty}\frac{(-1)^n}{n^2}\exp(-Dn^2\pi^2 t/h^2\right] \quad (1)$$

Where A is the area; K the partition coefficient between skin/vehicle; h the diffusional pathlength; C the concentration in vehicle; D the diffusion coefficient.

The quantities Kh and D/h^2 were estimated by curve fitting for n = 1 to 4 using the Origin v7.03 package (OriginLab Corp., Northampton, MA, USA). Local optimal fitting was avoided by checking consistency of the fitted values of Kh and D/h^2 from a range of starting values. Regression analyses for the assay validation and analyses of variance were done by the Minitab Release 14.20 package (Minitab Inc) and the confidence intervals for the enhancement ratios were found by Fieller's method (QuickCalcs; http://graphpad.com).

Results and Discussion

The results of the curve fitting were consistent using starting values ranging from 0.01 to 100 for Kh and D/h^2. As further checks, the fitted curve corresponded to the data points, the coefficients of variation (100×s.d./mean) associated with Kh and D/h^2 were reasonably small at 15–39% and 7–30%, respectively, and lag times calculated from $h^2/6D$ (Crank 1956) were in the region of 5–10 h in agreement with visual inspection of the cumulative amount plots, and the mean k_p for human skin in hypromellose and Carbomer was 4.1 E-4 cm h^{-1} (95% CI 3.5 to 4.7 E-4), in reasonable agreement with the value from water, 3.36 E-4 (95% CI 0.13 to 6.59 E-4) from the results of Vaddi et al (2001b).

Effect of gel base polymer on transdermal delivery

Values of k_p for rabbit from hypromellose, Carbomer 940 and macrogol formulations are shown in Table 2. One-way analysis of variance shows difference ($P < 0.05$) between all three means. The highest value (0.00105 cm h^{-1}) was from hypromellose. The enhancement in hypromellose relative to the other vehicles was 1.2 (95% CI 1.1 to 1.4) for Carbomer and 1.7 (1.4 to 2.1) for macrogols. This level of enhancement was of marginal interest per se. However, hypromellose is widely used as an emulsifier, suspender and stabilizing agent for topical preparations (Wu et al 1998). Peppas (1987) suggested that its amphiphilic nature reduced the formulation/skin interfacial tension, allowing good wetting of the skin surface and higher partitioning of drug into the skin. Lund (1994) reported that it was non-toxic and non-irritant, and Wu et al (1998) concluded that it was an effective base for percutaneous absorption of captopril. Using these results from rabbit skin as a pilot, hypromellose was therefore chosen as the gel base for formulations including the selected enhancer (1,8-cineole, 10%) for subsequent studies.

Table 2 Permeability coefficients, Kh and D/h^2 (mean; s.d.) from curve fitting

Skin	Gel	k_p (E-4) (cm h^{-1})	Kh (E-2) (cm)	D/h^2 (E-2) (h^{-1})
Human	Hypromellose	3.9 (0.6)	1.93 (0.52)	2.09 (0.23)
Human	Hypromellose + cineole	24.2 (6.5)	25.6 (9.70)	0.99 (0.16)
Human	Carbomer	4.5 (1.0)	2.76 (1.06)	1.80 (0.56)
Mouse	Hypromellose	21.7 (2.1)	10.8 (1.60)	2.02 (0.15)
Mouse	Hypromellose + cineole	65.1 (7.7)	21.8 (5.90)	3.00 (0.31)
Mouse	Carbomer	17.3 (1.6)	7.95 (1.25)	2.19 (0.21)
Rabbit	Hypromellose	10.5 (1.2)	5.63 (1.00)	2.45 (1.89)
Rabbit	Hypromellose + cineole	58.5 (3.9)	17.3 (3.00)	3.52 (0.41)
Rabbit	Carbomer	8.8 (1.3)	5.60 (1.62)	1.61 (0.20)
Rabbit	Macrogols	6.3 (1.3)	3.95 (1.54)	1.72 (0.46)

Enhancement effect of cineole (10%) on k_p

Cineole 10% was incorporated into the hypromellose gel and its effect assessed on human, rabbit and mouse skins. Two-way analysis of variance using Gel Formulation and Skin as variables showed a significant difference ($P < 0.001$) between the mean k_p values for gel (0.0012 cm h^{-1}) and gel + cineole (0.00493 cm h^{-1}). The k_p values from the three skins were all different (post hoc Bonferroni $P < 0.05$) from one another: human 0.00141, rabbit 0.00345, mouse 0.00434 cm h^{-1}. A P value of < 0.001 for the interaction term indicated a possible difference in mechanism of action of cineole on the skins.

Enhancement ratios were therefore calculated for the three species separately (QuickCalcs; http://graphpad.com) and are shown in Table 3. The enhancement in mouse skin (3.0) was significantly ($P < 0.05$) less than in human (6.2) or rabbit (5.6) skin.

For haloperidol across human skin, Almirall et al (1996) found an enhancement of 1.95 for cineole. Limonene had an enhancement ratio of 4.21.

Table 3 Enhancement ratios with 95% CIs (hypromellose:10% cineole/hypromellose)

	k_p	K	D
Human	6.2	13.3	0.47
	4.6–8.1	8.3–20.0	0.41–0.55
Mouse	3.0	2.0	1.5
	2.6–3.4	1.5–2.6	1.3–1.8
Rabbit	5.6	3.1	1.8
	5.0–6.2	2.5–3.9	1.6–2.1

Enhancement effect of cineole (10%) on K and D

Assuming that cineole has no effect on h, the enhancement ratios for K may be calculated as: (Kh from hypromellose + cineole)/(Kh from hypromellose). Those for D were found similarly.

Values are given in Table 3 and show that the enhancement of K was generally greater than that of D, in agreement with the findings of Rosado et al (2003) on the effects of vehicle on transdermal penetration. Human skin was less permeable ($P < 0.05$) than either rabbit or hairless mouse. Similar observations have been reported by Catz & Friend (1990) for levonorgestrel, Ghosh et al (1992) for metoprolol and Niazy (1996) for dihydroergotamine. In addition to species differences in the lipoidal nature of the skin, differences may potentially arise from structural differences, such as the surface density of appendageal openings, the absence of eccrine sweat glands, and the presence of small-sized hair follicles (Idson 1975). The large increase in partition (13.3) caused by cineole in human skin suggested that its main effect may have been attributable to its accumulation in the skin encouraging absorption of the drug. Our observed enhancement of D in animal skins was in line with the reduction in lag time after enhancement reported by other authors (Schaefer et al 1982; Chow et al 1984; Sugibayashi et al 1985; Stuttgen et al 1990; Bonina & Montenegro 1994).

Conclusion

Values of k_p from the three basic gel formulations were similar. Choosing hypromellose as a suitable gel for future work, k_p was significantly enhanced by incorporation of 10% cineole. In human skin, the enhancement was largely due to a tenfold increase in partition into the skin, whilst in rabbit and hairless mouse both partition into and diffusion across the skin were increased to a lesser extent. Hypromellose was a suitable base for a matrix formulation, and terpenes such as 1,8-cineole or limonene might have potential as enhancers to achieve therapeutic blood levels of haloperidol.

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