Evaluation of the Skin Percutaneous Absorption of Four Drugs

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Background

The *in vitro* human trunk skin percutaneous absorption of transdermal compounded formulations containing four active substances – Ketamine HCl, Gabapentin, Clonidine HCl and Baclofen – incorporated simultaneously in Lipoderm and also in Lipoderm ActiveMax, was evaluated using the Franz Skin Finite Dose Model. Currently, it is common practice to combine multiple active substances in pain management therapy and the four active substances were selected due to their frequent use in topical pain compounded formulations (Brown *et al.*, 2010). The Franz Skin Finite Dose Model has proven to be a valuable tool for the study of percutaneous absorption and to accurately predict *in vivo* percutaneous absorption kinetics. Therefore, the Franz Skin Finite Dose Model was selected to evaluate the total absorption, rate of absorption and the skin content of the four active substances simultaneously applied to the outer surface of the skin.

Methods

The percutaneous absorption of the four active substances was measured using *ex vivo* human trunk skin, without obvious signs of skin disease, from the posterior torso of three male donors (Black and Caucasian races). The skin samples were dermatomed, cryopreserved, sealed in a water-impermeable bag and stored at approximately -70°C, prior to skin preparation. Topical pain compounded formulations containing Ketamine HCl 5% (w/w), Gabapentin 10% (w/w), Clonidine HCl 0.2% (w/w) and Baclofen 2% (w/w), incorporated simultaneously in Lipoderm and also in Lipoderm ActiveMax, were applied to the skin sections (5 µL formulation/cm^2) and their percutaneous absorption was evaluated over a period of 48 hours. The skin sections were mounted in Franz diffusion cells (Figure 1) allowing the skin to be maintained at a temperature and humidity that match normal *in vivo* conditions. One non-dosed diffusion cell was included per donor as a blank control. A receptor solution was placed bathing the inner surface of the skin sections in order to measure the rate of appearance of the four active substances. During the exposure period, samples of the receptor solutions were removed at pre-selected times (2, 4, 8, 12, 24, 32 and 48 hours) and were analyzed for Ketamine HCl, Gabapentin, Clonidine HCl and Baclofen content using the HPLC/MS analytical method. After the last sample of the receptor solutions (collected at 48 hours), the skin sections were cleansed, tape stripped (to remove the stratum corneum) and separated into the epidermis and dermis to evaluate the skin content of the four active substances.

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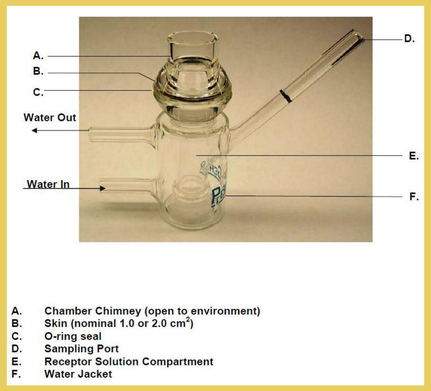

Figure 1. Franz diffusion cell

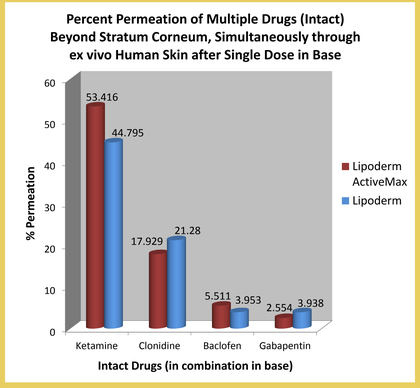

Figure 2. Percent permeation of the four active substances

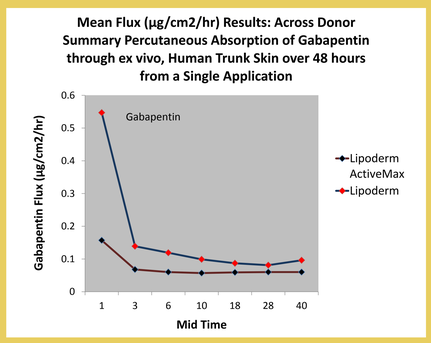

Figure 3. Gabapentin flux versus time

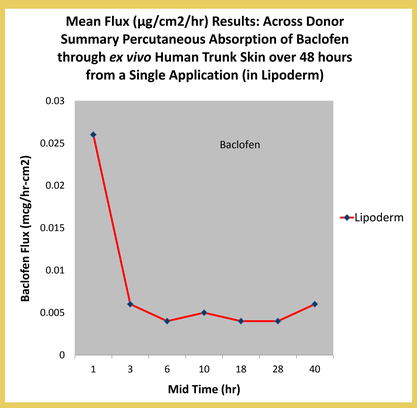

Figure 4. Baclofen flux versus time

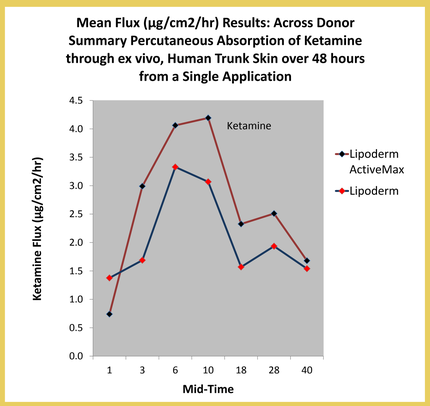

Figure 5. Ketamine flux versus time

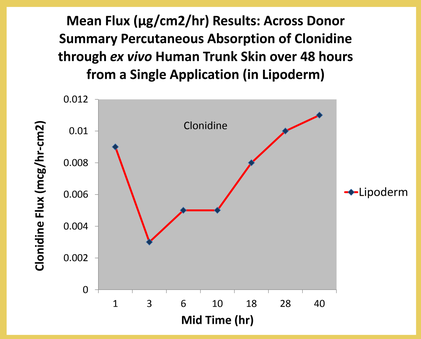

Figure 6. Clonidine flux versus time

Results and Discussion

The total absorption, rate of absorption and the skin content (distribution) of the four active substances were determined for a total of seven Lipoderm and Lipoderm ActiveMax test formulations containing Ketamine HCl 5% (w/w), Gabapentin 10% (w/w), Clonidine HCl 0.2% (w/w), Baclofen 2% (w/w) and Propylene Glycol 10% (w/w). The absorption results indicate the percutaneous absorption of the active substances through the skin whereas the distribution results indicate the percutaneous absorption into the skin. The total absorption and the skin content were determined after 48 hours from a single application of the transdermal compounded formulations in the skin sections (Figure 2). The total absorption corresponded to the total recovered in the receptor solutions and the skin content corresponded to the mass recovered in the stratum corneum, dermis and epidermis (µg/cm^2), of the four active substances. The rate of percutaneous absorption, on the other hand, is a time-averaged value and it was determined as the mean flux of the active substances, collected at the receptor solutions (µg/cm^2/h), over the 48-hour period. The absorption and distribution profiles of each active substance were similar for all seven Lipoderm and Lipoderm ActiveMax test formulations. The rate of percutaneous absorption showed a rapid penetration to a peak flux for Gabapentin and Baclofen (Figures 3 and 4) occurring approximately 1 hour after dose application, and approximately 4 hours for Ketamine HCl (Figure 5). Clonidine HCl exhibited a rapid penetration to an initial peak flux occurring 1 hour after dose application, but also a secondary peak at approximately 40 hours (Figure 6), possibly due to a depot of some of the applied dose in the epidermis, followed by a slow decline in flux thereafter. Mass accountabilities ranged from 85% to 115% of the applied doses across all test formulations (PCCA, 2013).

Conclusion

The four active substances – Ketamine HCl, Gabapentin, Clonidine HCl and Baclofen – incorporated simultaneously in Lipoderm and also in Lipoderm ActiveMax, penetrate through and into *ex vivo* human trunk skin, following topical application of the transdermal compounded formulations.

It is concluded that the transdermal bases Lipoderm and Lipoderm ActiveMax are indicated in pain management therapy for the preparation of multi-drug topical compounded formulations.

Brown, S., Erickson, B., Muller, G., Bryant-Snure, S. and Mestayer, R. (2010) 'Compounded analgesic therapy for disorders of movement: arthritis, neuropathic pain, and postpolio syndrome', *International Journal of Pharmaceutical Compounding*, 14 (3), p.182-192.

PCCA (2013) Lipoderm. Available at: http://www.pccarx.com/pcca-products/pcca-exclusives/bases/lipoderm (Accessed: 20 August 2013).