Rational formulation design for cosmetic and pharmaceutical actives

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Introduction

In order to deliver an active ingredient it is crucial to circumvent the skin's innate barrier function. A rational approach to formulation design is therefore required. The physicochemical properties of the active ingredient and excipients are critical considerations when attempting to deliver active substances transdermally or to the superficial layers of the skin.

Two model actives, ibuprofen (IBU) and retinyl palmitate (RPL), were used in the work presented here. For IBU to be topically effective in treatment of musculoskeletal injury it must be delivered to the tissue below the epidermis. The cosmetic active RPL is eventually converted enzymatically to retinoic acid in the epidermis or dermis and therefore must be retained in the upper layers of the skin. Historically, the emphasis has been on monitoring the disposition of the active to the neglect of the vehicle. The focus of this work is to elucidate the roles of excipients for delivery of IBU and RPL.

Table 1 Physiochemical properties of IBU

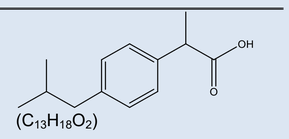
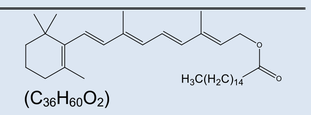
Chemical structure	 ($C_{13}H_{18}O_2$)
Molecular mass	206.3 g mol^{-1}
Solubility parameter	10.36 (cal cm^{-3})$^{1/2}$
Hansen solubility parameter	17.5 (δ_d), 2.5 (δ_p), 6.5 (δ_h)
Melting rage	75 – 77 °C
Log P	4.0

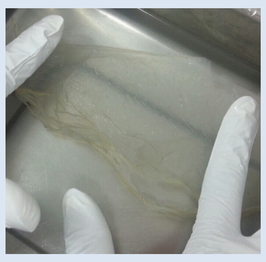
Table 2 Physiochemical properties of RPL

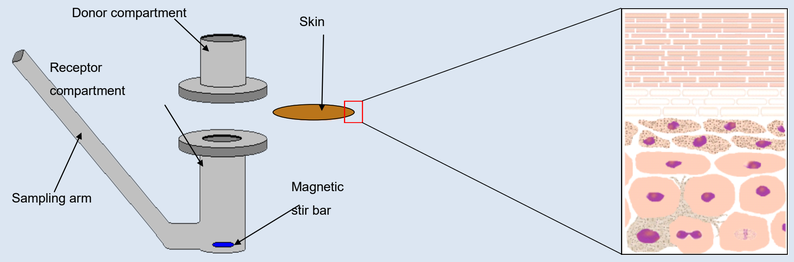
Chemical structure	 ($C_{36}H_{60}O_2$)
Molecular mass	524.9 g mol^{-1}
Solubility parameter	8.29 (cal cm^{-3})$^{1/2}$
Hansen solubility parameter	16.9 (δ_d), 4.8 (δ_p), 10.1 (δ_h)
Melting rage	25 – 27 °C
Log P	7.3

Methods

Human epidermis prepared by heat separation was mounted in Franz cells. Cells were placed in a thermostatic water bath to ensure a skin surface temperature of 32 ± 1 °C. Volatile formulations containing IBU 5% (w/w) were prepared such that after the evaporation of isopropyl alcohol the residual phase was 80% of the saturated solubility. RPL is a liquid at 32 °C and was formulated at 1% (w/w) with the appropriate vehicle.

A finite dose of formulation, **3.6 µL** per cell (~135 µg IBU), was applied to the surface of the skin and the receptor fluid sampled over 48 h. For RPL a finite dose of **10 µL** (~90 µg RPL) was used per cell and permeation was conducted over 24 h. A mass balance study was performed for each model active and selected vehicles. One way ANOVA was used to determine statistical significance.





Results

Ibuprofen

The permeation of IBU and vehicles; propylene glycol (PG), dipropylene glycol (DPG) and tripropylene glycol (TPG) are shown in Figure 1 and Figure 2 respectively.

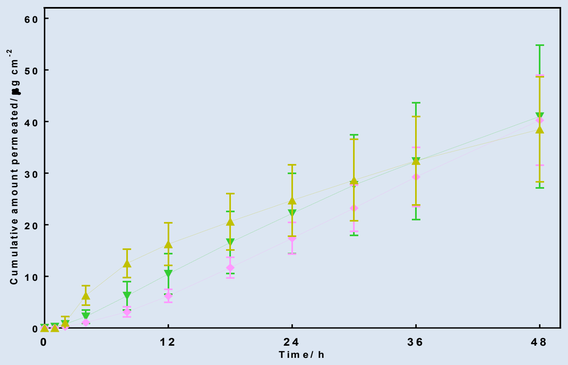


Figure 1 Permeation profile of IBU after application of liquid spray and commercial formulations to heat separated human epidermis, PG (▲), DPG (▼) and TPG (◆), (mean ± SD, n = 5).

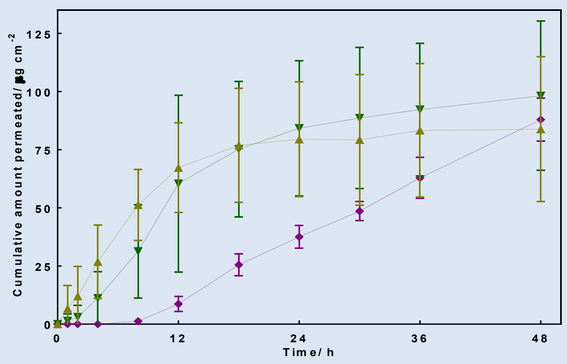


Figure 2 Permeation profiles of vehicles after application of liquid spray to heat separated human epidermis, PG (▲), DPG (▼) and TPG (◆), (mean ± SD, n = 5).

The permeation of IBU through human skin was comparable for each of the formulations after 48 h. However, significantly more IBU was delivered from the PG formulation between 4 and 8 h when compared with DPG and TPG ($p < 0.05$). The permeation profiles of PG and DPG are similar and there is clear evidence of vehicle depletion as indicated by the appearance of a plateau. This is not the case for TPG and permeation was steady after 12 h. IBU and vehicle flux profiles were estimated by differentiation of permeation data shown in Figure 3 and Figure 4 respectively.

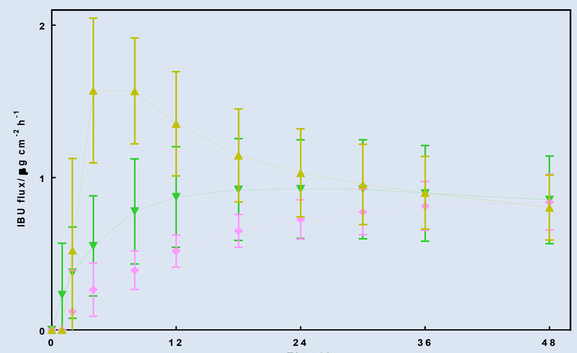


Figure 3 Estimated flux profile for IBU through human epidermis, calculated by differentiation of cumulative amount permeated, PG (▲), DPG (▼) and TPG (◆), (mean ± SD, n = 5).

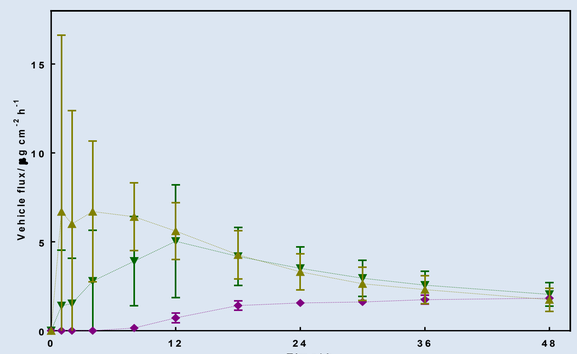


Figure 4 Estimated flux profiles for vehicles through human epidermis, calculated by differentiation of cumulative amount permeated, PG (▲), DPG (▼) and TPG (◆), (mean ± SD, n = 5).

For PG the IBU flux increased for 4 h before a decline was observed suggesting less IBU was available for transport. A comparatively higher flux was observed for the DPG formulation up to 18 h. Flux values remained constant until 30 h after which a slight decline was evident, indicating that IBU depletion occurs later than it does for PG. For TPG there is no evidence that IBU has been depleted form the formulation as the flux increased over the 48 h period. Comparing the vehicle flux profile it is clear for PG and DPG the peak vehicle flux occurs before the peak IBU flux. The shape of the flux profiles are similar for both the vehicle and IBU and this suggests that higher vehicle flux resulted in higher IBU flux.

Retinyl palmitate

The results from the mass balance study of RPL is shown in Figure 5. The skin deposition of vehicles dicprylyl carbonate (DCC) and (Transcutol®) TC were also determined shown in Figure 6 and Figure 7 respectively.

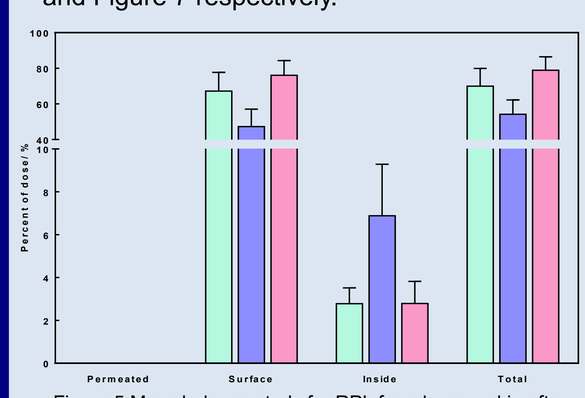


Figure 5 Mass balance study for RPL from human skin after 24 h permeation experiments, DCC ( ), DCC3:1 ( ) and DCC1:1 ( ), (mean ± SD, n ≥ 5).

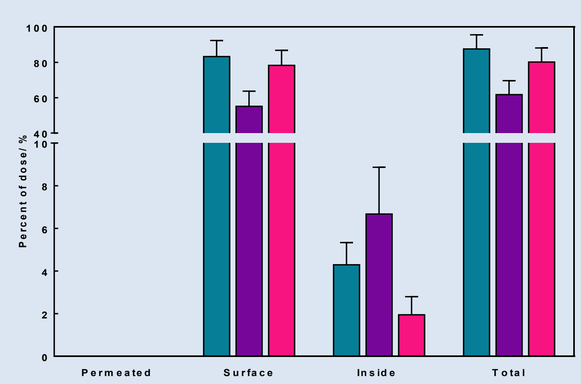


Figure 6 Mass balance study for DCC from human skin after 24 h permeation experiments, DCC ( ), DCC3:1 ( ) and DCC1:1 ( ), (mean ± SD, n ≥ 5).

RPL was not detected in the receptor fluid at any of the sampling time points. RPL did not permeate through human skin after the application of the neat DCC formulation nor from DCC and TC binary vehicle formulations over a 24 h period. The mass balance study shows that the majority of the dose remained on the surface. The binary formulation of DCC:TC (3:1) significantly enhanced the penetration of RPL when compared with DCC:TC (1:1) and DCC alone ($p < 0.05$). This is also the case for the distribution of DCC in the skin.

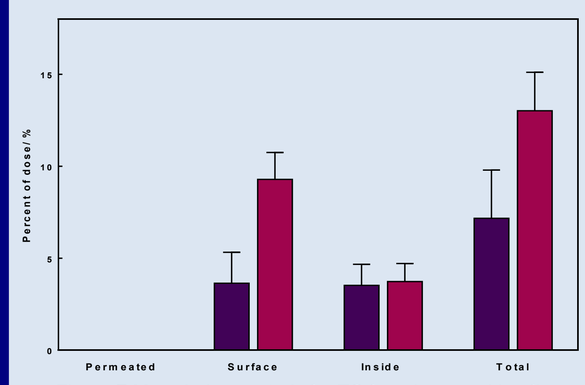


Figure 7 Mass balance study for TC from human skin after 24 h permeation experiments DCC3:1 ( ) and DCC1:1 ( ), (mean ± SD, n ≥ 5).

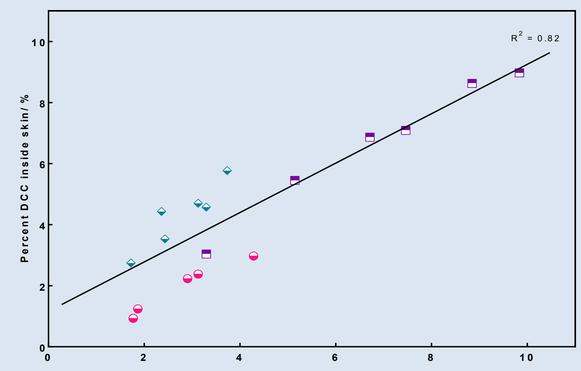


Figure 8 Correlation between the percent of RPL and DCC from extracted from inside human skin after 24 h permeation experiments, DCC ( ), DCC3:1 ( ) and DCC1:1 ( ), (mean ± SD, n ≥ 5).

About ~4% TC was extracted from the skin for both formulations but a significantly higher percent of TC was recovered from the surface after application of DCC:TC (1:1). Mass balance studies show that the penetration of RPL was closely related to the penetration of DCC. Figure 8 shows a good correlation ($R^2 = 0.82$) between RPL and DCC penetration. No correlation was observed between the percent of RPL and TC extracted from the skin. There is also no correlation between the percent of DCC and TC extracted . However, it is possible that the potentiation of DCC penetration by TC occurred in the earlier stages of the experiment.

Conclusion

PG and DPG penetrate the skin rapidly and drive IBU skin penetration. With a reduction in the glycol delivery, there is a corresponding decrease in IBU delivery. PG and DPG are effectively 'pulling' IBU through the skin. This effect is less pronounced with TPG and as a result IBU delivery is slower but more consistent. For RPL, DCC is the major vehicle constituent in the binary systems mediating skin delivery. DCC is also retained within the epidermis and may serve as reservoir for RP. Finally we propose that DCC and TC can work synergistically to enhance delivery of RP to the skin when mixed at a 3:1 ratio. The residence time and distribution of TC in human subjects will be the focus of future work.

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