A Rational Formulation Design Approach for Dermal Delivery of Retinyl Palmitate
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Purpose
Retinyl palmitate (RPL) is often included in cosmetic formulations with the aim of improving skin health. RPL is thought to undergo enzymatic hydrolysis in the epidermis to retinol, which is subsequently converted to retinaldehyde and finally retinoic acid. The biological activity of retinoic acid and to a lesser extent, other retinoids, increases the amount of collagen in the skin leading to remodelling of the dermis. Previous studies have shown that RPL is less irritant compared with other retinoids and thus is preferred for use in personal care products. The penetration of RPL is critical to its physiological efficacy and with a rational selection of excipients its delivery may be enhanced. The purpose of the work presented here is to determine the influence of the vehicle and its influence on the dermal delivery of RPL.

Methods
Vehicles were selected based on their solubility parameters. The molecular mass and Log P values were also determined. The selected vehicles were; isopropyl myristate (IPM), isostearyl isostearate (ISIS), polypropylene glycol 15 stearyl ether (PPG) and dicaprylyl carbonate (DCC). Transcutol® (TC) was subsequently used to prepare two binary vehicle formulations. Miscibility studies and stability studies ensured there was acceptable compatibility between RPL and the vehicles. Single and binary vehicle formulations were manufactured containing RPL 1% (w/w). In vitro permeation studies were conducted using human epidermis clamped in Franz diffusion cells. A finite dose of formulation, (~10 μL cm⁻²) was applied to the surface of each cell and receptor phase samples were removed at predetermined time points. Permeation studies were performed for 24 h followed by mass balance studies. HPLC was used for analysis of RPL and retinol. Skin penetration of the vehicle was determined by gas chromatography (GC).

Results
RPL did not permeate through human epidermis in sufficient amounts to be detected by HPLC and there was also minimal or undetectable amounts of retinol present in the receptor fluid. The mass balance studies for RPL indicated that the overwhelming majority of the dose, between 50% and 70% for each formulation remains on the surface of the skin. Less than 4% of the applied RPL dose penetrates the skin but a significantly higher percent of the dose was extracted from the skin for the DCC formulation when compared with the PPG formulation (p < 0.05). The vehicle mass balance data gave similar results; the majority of the vehicle remained on the surface of the skin, with only 1- 4% of the vehicle extracted from the skin. A significantly higher percent of DCC was extracted from the skin compared with PPG (p < 0.05). The results show a good correlation (R² = 0.99) between the percent of RPL and vehicle extracted from the skin. The binary vehicle containing DCC:TC (3:1) delivered significantly more RPL compared with DCC:TC (1:1) or DCC alone (p < 0.05). The data suggest that the RPL delivery is influenced by the lipophilic vehicle DCC to a greater extent than the hydrophilic vehicle TC. A 3:1 ratio of DCC: TC was optimal for the effects of DCC.

Conclusion
Careful selection of the vehicle is critical for maximal delivery of RPL. For these vehicles their penetration is heavily dependent on their molecular masses. Vehicles with higher molecular weights penetrate the skin to a lesser extent and thus reduce the uptake of RPL by the skin. The combined use of DCC and TC significantly increased penetration of RPL. Work is on-going to identify the disposition of TC when applied topically.