Transdermal Permeation: Refined Palm Oil Vehicle Effects?

I Singh[1], T J Khoo[1], S Gan[2], V Cheong[3], and A P Morris[1]
[1]School of Pharmacy / [2]Faculty of Engineering University of Nottingham Malaysia Campus, 43500 Semenyih, Selangor. Malaysia.
[3]KPJ Selangor Specialist Hospital, Lot 1, Jalan Singa 20/1, Section 20, 40300 Shah Alam, Selangor. Malaysia.

INTRODUCTION

Transdermal drug delivery (TDD) is indeed a desirable means of drug administration as it provides a number of advantages (Roberts et al., 2002). However, the major drawback to TDD is the inability for most drugs to achieve clinically efficacious plasma levels and this is due to the barrier nature of the stratum corneum (SC) (Lampe et al., 1983). Hence, over the last three decades much work has been carried out to, firstly understand the nature of the skin and the fundamentals of the permeation process, and secondly, to develop different strategies to overcome the SC (Langer, 2004). In this present study, the ability of refined palm oil to acts as a permeation enhancer was evaluated. This is due to the fact that palm oil is commonly incorporated as an excipient in topical medicinal and cosmetic products (Ghazali et al., 2006) and since palm oil contains fatty acids that have been shown to act as permeation enhancers (Aungst et al., 1986) the consequence of its use should be assessed. In fact, because palm oil is generally regarded as safe (GRAS) and contains components such as squalene and the tocotrienols, that has anti-inflammatory properties (Shu-Jing et al., 2008). As such the inclusion of palm oil in transdermal patches may be beneficial as it may be useful in reducing local allergic effects at the site of application that is sometimes cited as a drawback of TDD.

MATERIALS AND METHODS

A. Donor phase study

Drug solubility in the vehicles (refined palm oil, oleic acid, 2-pyrrolidone, propylene glycol) was determined by adding excess drug to vehicles, followed by equilibration on a thermo-regulated orbital shaker set at 37°C, 200rpm for 72 hours. Each sample was then filtrated using a 0.45µm nylon syringe filter (pre-equilibrated to 37°C) and the resulting filtrate was analysed using HPLC.

B. Receptor phase studies

Phosphate buffered saline (PBS) adjusted to pH 7.4 was selected as the receptor phase to mimic the physiological condition. In order to increase ibuprofen solubility in the PBS cetrimide was added. The critical micelle concentration (CMC) was determined by the surface tension method. Cetrimide in PBS solutions (0.25-10mg/ml) were prepared in sample vials with screw caps and allowed to equilibrate for 3 hours at 37.0°C. A clean capillary tube was immersed in each sample and the solution height in the immersed capillary tube was measured. These steps were repeated for all the cetrimide solutions with the same capillary tube being rinsed and dried between every single measurement. The experiment was repeated in triplicate and the CMC was taken to be the concentration at which the curve plateau.

Figure1: Upright Franz Diffusion. The skin pieces were mounted in between the donor and the receptor phase.

Figure 2: The Franz cell setup during a permeation run. They are placed on magnetic plate stirrer and in a water bath set at 37°C.

C. Skin preparation and integrity check

Full thickness human skin was obtained from patients who had undergone abdominoplasty surgery. The skin was then processed to remove subcutaneous fat by blunt dissection. Care was taken to avoid any direct slicing or other damage to the skin during this process. The skin was then cut into pieces of about 2cm² and an integrity check was performed by observing individual skin pieces under a dissection microscope (Leica EZ4) for any obvious physical damage.

D. Skin permeation experiment design

The permeation experiments were conducted using static 'Franz-type' upright glass diffusion cells (Permegear, USA. Each drug formulation had nine replicates and each three replicates were randomly allocated 3 skin pieces from different donors (patient). The sampling intervals were fixed at 3, 6, 24, 48 and 72 hours after the formulation was added to the donor phase. A total of 400 µl of receptor phase was removed at each interval and an equal amount of fresh PBS containing cetrimide was returned to each cell.

RESULT AND DISCUSSION

A. Receptor phase studies

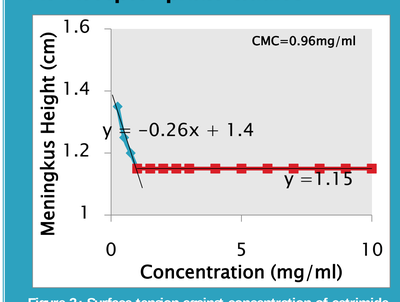

Figure 3: Surface tension against concentration of cetrimide

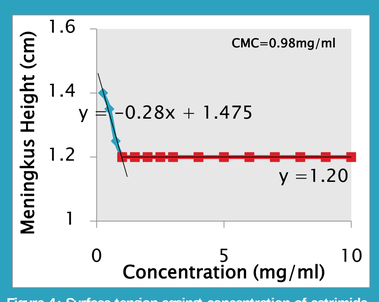

Figure 4: Surface tension against concentration of cetrimide

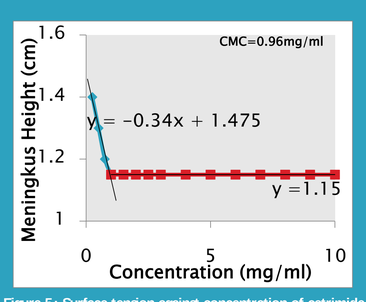

Figure 5: Surface tension against concentration of cetrimide

B. Skin integrity check

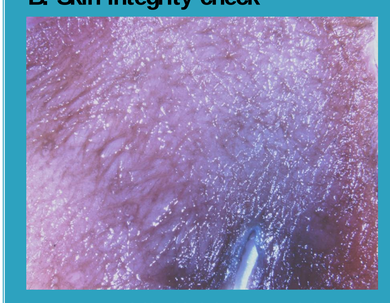

Figure 6: Damaged skin with darkening around piercing (10X)

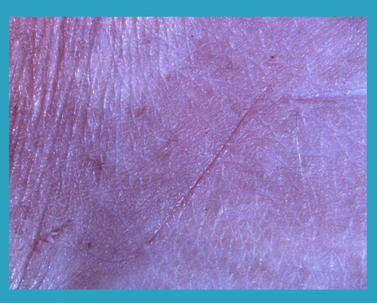

Figure 7: Damaged skin with a cut (10X)

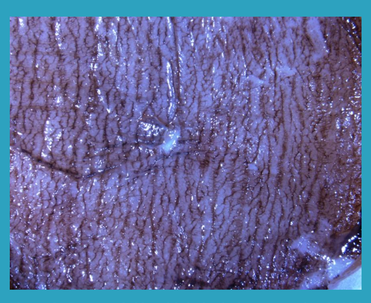

Figure 8: Damaged skin with hole during processing (10X)

C. Drug solubility in vehicle and flux across full thickness human skin

Vehicle	Vehicle Type	Solubility (mg/ml)	Lidocaine flux (µg/cm²/h)	T-Test (p value)
PO	Test	322.28 ± 6.56	24.70	0.82
PY	(+) High	778.51 ± 7.98	55.90	1.85
PG	(+) Med	751.21 ± 6.26	45.85	1.52
OA (control)	(-)	434.46 ± 4.14	30.19	Nil

Table 1: Illustrates the drug solubility in vehicle (n= 3), drug flux across skin (n= 9) and the significance of drug flux (single tailed T-test, p< 0.05) compared to negative control vehicle.

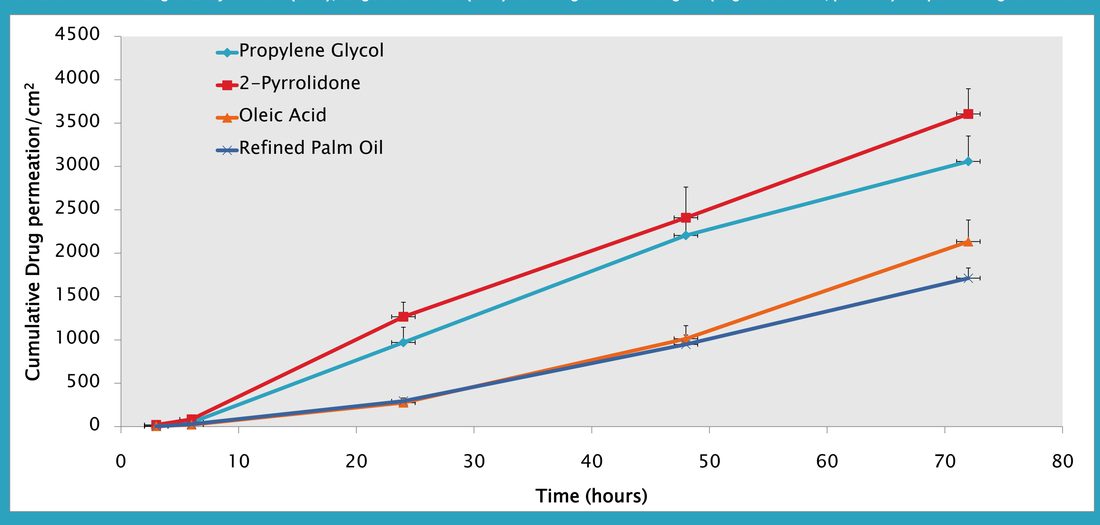

Figure 9: Depicts the permeation of ibuprofen from four vehicles (n= 9,± SE).

CONCLUSION

It was evident that the use of refined palm oil did not show any improvement in the transdermal delivery of lidocaine. As such we can conclude that refined palm oil does not have the percutaneous penetration enhancement potential for the model drug lidocaine with Log p of 2.1. However, there may be a different outcome when drugs of higher or lower polarity is used. Some chemical enhancers are polarity specific enhancers, such as the hydrophobic terpenes which enhance the permeation of non-polar drugs only. Furthermore, there remains a possibility that refined palm oil may be a concentration dependent enhancer, which only exerts its effect at lower concentrations such as with oleic acid. Further work is being planned by the authors to investigate the possibilities discussed above.

ACKNOWLEDGEMENT

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