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RESEARCH ARTICLE

An evaluation of crude palm oil (CPO) and tocotrienol rich fraction (TRF) of palm oil as percutaneous permeation enhancers using full-thickness human skin

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ABSTRACT

The drawbacks associated with chemical skin permeation enhancers such as skin irritation and toxicity necessitated the research to focus on potential permeation enhancers with a perceived lower toxicity. Crude palm oil (CPO) is obtained by direct compression of the mesocarp of the fruit of the oil palm belonging to the genus *Elaeis*. In this research, CPO and tocotrienol-rich fraction (TRF) of palm oil were evaluated for the first time as skin permeation enhancers using full-thickness human skin. The *in vitro* permeation experiments were conducted using excised human skin mounted in static upright 'Franz-type' diffusion cells. The drugs selected to evaluate the enhancing effects of these palm oil derivatives were 5-fluorouracil, lidocaine and ibuprofen: compounds covering a wide range of Log *p* values. It was demonstrated that CPO and TRF were capable of enhancing the percutaneous permeation of drugs across full-thickness human skin *in vitro*. Both TRF and CPO were shown to significantly enhance the permeation of ibuprofen with flux values of 30.6 μg/cm^2 h and 23.0 μg/cm^2 h respectively, compared to the control with a flux of 16.2 μg/cm^2 h. The outcome of this research opens further scope for investigation on the transdermal penetration enhancement activity of pure compounds derived from palm oil.

Abbreviations: CPO: Crude palm oil; RPO: Refined palm oil; TRF: Tocotrienol rich fraction; TDD: Transdermal drug delivery; DMSO: dimethyl sulfoxide; GRAS: Generally recognized as safe; EFSA: European Food Safety Authority; 5FU: 5-Fluorouracil; PG: Propylene glycol; ODS: Octyl-decylsilanol; LOD: limit of detection; LOQ: limit of quantification; ICH: International Conference on Harmonization; CMC: Critical micellar concentration.

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Permeation enhancer; CPO; TRF; in vitro; diffusion cell

Introduction

Fats and oils have been used by humans as food, fuel, cosmetics and medicines since ancient times. One important member of the fat and oil family is palm oil. Palm oil is extracted from the fruit of the oil palm of which the two main species are *Elaeis guineensis* and *Elaeis oleifera* and are native to West Africa and South America respectively (Sambanthamurthi et al. 2000). Palm oil and palm kernel oil are obtained from the mesocarp and the kernel (seed) respectively of the oil palm fruit (Edem 2002). The oil obtained from the mesocarp is edible whereas the kernel oil has wide applications in the oleochemical industry (Matthäus 2007; Rupilius and Ahmad 2007). CPO is derived from the mesocarp of the oil palm fruit by direct compression whereas refined palm oil (RPO) is the commercially available palm mesocarp oil which is obtained by bleaching, deodorisation and neutralisation of CPO (Sundram et al. 2003). The composition of the vitamin E obtained from CPO is unique as it consists of 74.4% tocotrienols and 25.6% tocopherols by weight (Kua et al. 2016). Tocotrienols are not commonly found in vegetable oils in such large quantities, with the other main exceptions being rice bran and corn oil (Qureshi et al. 2000). Tocopherols and tocotrienols exist in four different isoforms namely alpha (α), beta (β), gamma (γ), and delta (δ). An important product of CPO is the TRF. As the name suggests, TRF is a palm oil derivative which contains a very high content of tocotrienols and has been shown to exhibit wide pharmacological activities such as anticancer, cardioprotective and neuroprotective effects (Qureshi et al. 1991; Sen et al. 2007; Aggarwal et al. 2010; Alayoubi et al. 2013).

The stratum corneum of the skin acts as the main protective layer and this slows down the permeation of drugs and other exogenous substances across the skin. Incorporation of permeation enhancers in transdermal formulations can significantly improve drug flux and, to date, numerous chemicals have been identified as permeation enhancers for transdermal delivery such as ethanol, DMSO (dimethyl sulfoxide) and Azone (Williams and Barry 2004; Walker and Smith 1996; Raju Y et al. 2017). However, the drawbacks associated with these and other chemical permeation enhancers make them less popular. For instance, the enhancing power of DMSO is concentration dependent and usually requires a concentration above 60% to exert an effect. Such a concentration can cause skin irritation and may denature stratum corneum proteins (Walker and Smith 1996). Similarly, Fang et al. evaluated the efficacy and safety of permeation enhancers using the drug flurbiprofen and they reported that Azone causes significant skin irritation and toxicity (Fang et al. 2003). Hence, there is a need to focus on permeation enhancers with a reduced level of toxicity.

Palm TRF has a long history of safe use as a vitamin E source and as an antioxidant (Wong and Radhakrishnan 2012).

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Table 1. Structural differences of tocotrienol derivatives.

Tocotrienol derivative	R1	R2
α-tocotrienol	CH_3	CH_3
β-tocotrienol	CH_3	H
γ-tocotrienol	H	CH_3
δ-tocotrienol	H	H

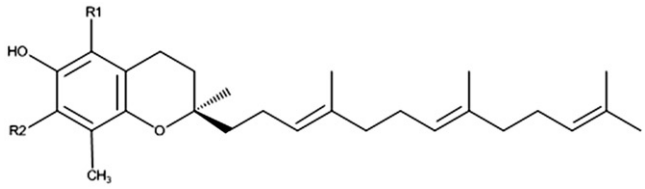

Figure 1. Structure of the tocotrienol isomers of palm oil derivatives.

Furthermore, TRF is also certified by the US FDA as generally recognized as safe (GRAS) (FDA 2009). In 2008, the European Food Safety Authority (EFSA) reported the safety of tocopherols and tocotrienols when used as sources of vitamin E in food supplements (Schauss et al. 2013). In recent years, tocotrienols (Table 1) were found to possess more potent antioxidant properties than tocopherols (Theriault et al. 1999). Moreover, the disrupting effect of the unsaturated side chain of tocotrienols (Figure 1) permits the more efficient penetration of tocotrienol into membrane lipid bilayers than that of tocopherols (Sen et al. 2010). There is potential that penetration of tocotrienol into the lipid matrix of the stratum corneum may have a similar disrupting effect leading to enhanced transdermal drug delivery (TDD). The free fatty acid value of CPO (7.42 mg/g) also suggests a possibility of TDD enhancement; free fatty acids such as oleic acid and linoleic acid are proven transdermal permeation enhancers (Fang et al. 2003; Lane 2013). The unsaponifiable matter is also notable in CPO and squalene, one of the compounds that contributes to this value, has been shown to act as an emollient and a hydrating agent (Huang et al. 2009).

Reports also show that a 5% solution of either α-tocopherol or tocotrienols (α, γ) in polyethylene glycol-400 can rapidly permeate deep into hairless murine skin following a topical application (Traber et al. 1998). Previous studies from our lab also report that the phytonutrients present in the TRF of palm oil show promising skin permeation (Sri et al. 2013). This study demonstrated that α-tocotrienol is able to permeate human skin at a much higher rate than α-tocopherol and it was proposed that this may have been due to the self-enhancing effects of the unsaturated tocotrienol molecule. Based upon the permeation demonstrated of constituents of CPO and TRF, these substances were subsequently investigated as potential skin permeation enhancers for the drugs: 5-fluorouracil, lidocaine, and ibuprofen. The model drugs were selected based on their wide range of hydrophilicity/hydrophobicity to rule out any bias based upon the drug's Log *p*. The selected drugs were having a wide range of log *p* values (5-FU: −0.78, lidocaine: 2.36, ibuprofen: 3.72). The log of partition coefficient, Log $p_{(oct/water)}$, is the most widely used parameter to explain the relative polarities of molecules. A molecule with Log $p < 0$ is generally said to be hydrophilic and usually partition readily into aqueous phase. Those molecules with Log $p > 0$ is generally regarded as hydrophobic or lipophilic and tend to partition into non-polar solvents. However, molecules with Log *p* between 1 and 3 have been shown to readily penetrate the stratum corneum (Walker and Smith 1996). In this study, the permeation enhancing the potential of CPO and TRF were evaluated using excised human skin.

Materials and methods

Materials

Lidocaine was purchased from Sigma-Aldrich (St.Louis, USA) and ibuprofen, 5-fluorouracil were sourced from Acros (Geel, Belgium). HPLC grade acetonitrile and methanol were purchased from Merck (Darmstadt, Germany). Glacial acetic acid, propylene glycol (PG), cetrimide and extra pure diethylamine were purchased from Thermo Fisher (Fairlawn, USA). All other chemicals and reagents used were of analytical grade and purified water was obtained using an ELGA Pure Lab Water System (Woodlands, Singapore).

HPLC method development and validation of 5-fluorouracil, lidocaine and ibuprofen

A Perkin Elmer 200 series HPLC system (Waltham, USA) equipped with a quaternary pump, UV/Vis detector and a variable-volume auto-sampler were used for the quantification of all drugs used in this study. An Ascentis® reverse-phase 5 μm octyl-decylsilanol (ODS) column (4.6 mm diameter × 250 mm) was employed for the method development and analysis. A stock solution of each model drug was prepared using methanol, these stock solutions were then diluted successively by serial dilutions with methanol. The calibration range of the drugs were as follows: 5-flurouracil (7.81 μg/mL– 500 μg/mL), Lidocaine (11.72 μg/mL–750 μg/mL), Ibuprofen (11.72 μg/mL– 750 μg/mL). The method used for 5-fluorouracil analysis was modified from that of Alsarra et al (Alsarra and Alarifi 2004) with analysis at a wavelength of 245 nm. The mobile phase comprised of methanol (10%) and water (90%) at a constant flow rate of 1 ml/min. The method adopted for lidocaine analysis was modified from that of Zhao et al (Zhao et al. 2008). The mobile phase used was methanol to water (80:20), which was selected based upon the best peak symmetry and shorter retention time. The detection wavelength was 235 nm and the flow rate was fixed at 1 ml/min. Diethylamine 0.5% (v/v) was added as a competing base to reduce the interaction of the silanol group with lidocaine molecules with the aim of reducing peak tailing. The mobile phase pH was adjusted to 8 using acetic acid, as pH values higher than 8 have been reported to degrade the type of column used (Cheng et al. 2000). The HPLC method used for ibuprofen analysis was modified from that of Farrar et al (Farrar et al. 2002). The mobile phase composition was methanol: water (80:20). The detection wavelength was 230 nm with a flow rate of 1 ml/min. The mobile phase pH was adjusted to 2.8 using phosphoric acid to suppress the ionisation of free silanol groups in the stationary phase which otherwise caused peak tailing. These adapted methods were subsequently validated in our laboratory as per International Conference on Harmonization (ICH) guidelines (ICH 2005). The validation parameters used included linearity, precision, accuracy, limit of detection (LOD), and limit of quantification (LOQ).

Permeant solubility study

The solubility of 5-fluorouracil, lidocaine, and ibuprofen in CPO, TRF and RPO was determined by adding an excess amount of drug to 3 ml of vehicle followed by agitation on a thermo-regulated orbital shaker (37 °C; 200 rpm) for 72 h. Samples were inspected at 12-h intervals; clear samples indicate complete dissolution and an additional 0.5 g of drug was added. Each sample was subsequently filtered using a 0.45 μm nylon syringe filter and analyzed by HPLC.

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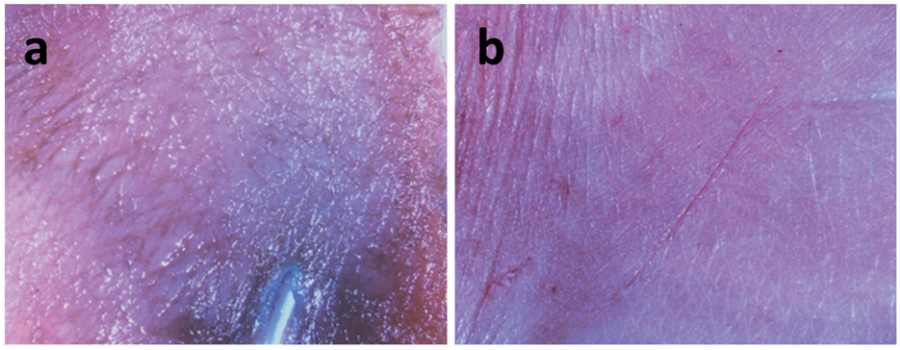

Figure 2. Microscopic view of the damaged portion of human skin with darkening around piercing (a), and a cut (b).

Table 2. HPLC validation parameters of 5-flurouracil, lidocaine and ibuprofen.

Validation parameters	5-fluorouracil	lidocaine	Ibuprofen
Capacity factor, k′	1.25	1.86	3.00
Retention time, minutes	3.75	4.65	6.10
Linearity, regression value ($n = 5$)	1.000	1.000	1.000
Limit of detection, μg/mL	0.08	0.17	0.03
Limit of quantification, μg/mL	0.26	1.44	1.21
Intraday Accuracy % RE			
Low QC sample	0.74	−1.64	0.13
Medium QC sample	0.63	2.17	0.30
High QC sample	0.67	−10.03	1.37
Interday Accuracy % RE			
Low QC sample	2.44	−0.91	0.71
Medium QC sample	2.09	2.01	1.05
High QC sample	2.71	−10.38	1.49
Intraday Precision % RSD			
Low QC sample	0.48	0.16	−1.81
Medium QC sample	2.22	0.18	1.31
High QC sample	0.48	0.39	−0.93
Interday Precision % RSD			
Low QC sample	0.13	0.89	−1.68
Medium QC sample	0.76	3.84	1.10
High QC sample	0.85	1.17	−1.08

Precision is expressed as %RSD and accuracy as %RE ($n = 5$).

Receptor phase studies

The receptor phase used in the permeation studies was phosphate buffered saline (PBS) pH 7.4 containing the cationic surfactant cetrimide. The surfactant was added to increase the solubility of the lipophilic drugs in the buffer and also for its antimicrobial properties (Arias-Moliz et al. 2010). The critical micellar concentration (CMC) of cetrimide in PBS was investigated using the surface tension method and this was subsequently confirmed using light diffraction studies with the aim of determining the appropriate concentration of cetrimide.

Determination of CMC by surface tension and light diffraction methods

PBS containing varying concentrations of cetrimide (0.25 mg/mL–10 mg/mL) was prepared in 22 ml glass vials with screw caps and allowed to equilibrate for 3 h at 37 °C. A clean glass capillary tube was immersed in each sample to the same level and the meniscus height in the capillary tube was measured. These steps were repeated for all of the cetrimide concentrations using the same capillary tube, which was rinsed and dried between each measurement. The height of the meniscus in the capillary tube was plotted (as a proxy for surface tension) against the concentration of cetrimide. The CMC was taken to be the point where there was no further decrease in the height of the meniscus (Arutchelvi and Doble 2010).

To determine the CMC by light diffraction methods, PBS containing varying concentrations of cetrimide was prepared and allowed to equilibrate for 3 h at 37 °C. These solutions were then transferred to sampling cuvettes and the hydrodynamic diameters of any colloidal particle were measured using a Malvern Zetasizer Nano ZS (Malvern, UK). Each measurement was reported as an average of 16 replicate scans. The hydrodynamic diameter was then plotted against the cetrimide concentration, and the CMC was indicated by the concentration at which there was a sharp increase in colloid diameter (Jones and Leroux 1999).

Drug stability study in receptor phase

The stability of each drug in the final receptor phase was assessed. Firstly, 500 μg/mL drug solutions of ibuprofen, lidocaine and 5-fluorouracil were prepared and these were transferred to 22 ml sample bottles which were held at two different temperatures (25 °C and 37 °C) in a water bath. Samples were withdrawn after 6, 12, 24, 48, 72, 96, 120 and 144 h and were stored at 4 °C prior to HPLC analysis.

Preparation and integrity evaluation of human skin

Human skin was obtained from consenting patients who had undergone abdominoplasty operations. Research ethics approval was obtained from the Ministry of Health Malaysia (project registration number NMRR-09–494-4158). The subcutaneous fat was removed by blunt dissection and the skin was subsequently cut into pieces of ~4 cm^2. Care was taken to avoid any damage to the skin during this process. It is possible that during the abdominoplasty and subsequent processing of the tissue unintentional damage may have occurred to the stratum corneum. Hence, a procedure to evaluate skin integrity was necessary in order to ensure that only intact skin samples were used in the permeation experiments. A visual skin integrity check was performed by observing the tissue for any obvious physical damage using a Leica EZ4 dissection microscope at 10× magnification. Any pieces of skin which exhibited any darkening, small cuts, or peeling of the epidermis were rejected (Figure 2). Only undamaged skin samples were accepted and these were subsequently wrapped in aluminium foil, sealed in a polythene bag and stored at −20 °C until future use.

Ex- vivo *skin permeation study using full-thickness human skin*

The permeation experiments were conducted using static upright 'Franz-type' glass diffusion cells (Permegear, USA). After applying silicone grease to the flanges of both the receptor and donor compartments, the cells were assembled with the skin (stratum corneum facing the donor) clamped firmly between the two compartments (Sreedharan Nair and Nair 2015; El-Say et al. 2017). The receptor compartment (volume: ~2 ml) was filled with PBS containing cetrimide and a miniature magnetic stirring rod was placed in the receptor compartment. The cells were subsequently placed on a submersible magnetic stirring block in a heated water bath. The diffusion cells were equilibrated at 37 °C for 2 h prior to the addition of the donor phase. The donor phase consisted of drug dissolved in an excess of CPO, TRF or RPO as control ($n = 4$). Samples were withdrawn (400 µL) from the receptor compartments at 3, 6, 24, 48 and 72-h intervals and replaced with an equal amount of fresh PBS containing cetrimide. Samples were stored at −20 °C prior to analysis by HPLC. Cumulative permeation profiles were constructed for each formulation and the flux was calculated (Rajesh and Sujith 2013).

Table 3. Solubility of 5-flurouracil, lidocaine and ibuprofen in TRF, CPO and RPO.

Drug	Vehicle	Saturation solubility ± SE (mg/mL)
5 Fluorouracil	TRF	0.006 ± 0.0002
	CPO	0.190 ± 0.01
	RPO	0.003 ± 0.00
Lidocaine	TRF	411.0 ± 1.59
	CPO	357.0 ± 2.10
	RPO	322.0 ± 6.56
Ibuprofen	TRF	59.9 ± 10.7
	CPO	129.0 ± 1.2
	RPO	141.0 ± 0.39

Drug solubility in all three vehicles ($n = 3$).

Drug stability study in skin extract

The stability of drugs when exposed to excised skin was assessed. Solutions of ibuprofen, lidocaine and 5-fluorouracil (500 µg/mL) in PBS containing 1.25 mg/mL cetrimide were prepared. Firstly, 20 pieces of full-thickness skin, each with an area of 4 cm^2 were minced on a white ceramic tile. All of this minced tissue was placed in a glass bottle, followed by the addition of 100 ml of receptor phase solution. The mixture was then placed on an orbital shaker for 72 h at 200 rpm. Following this, 10 ml of the filtered skin extract was added to each of the drug solution (10 ml) and incubated in a water bath at 37 °C. Samples from the drug-extract mixture were taken at 6, 12, 24, 48 and 72 h and stored at 4 °C prior to analysis by HPLC.

Statistical analysis

Statistical analysis was done using GraphPad Prism software 7.0 (La Jolla, CA). All values are expressed as mean ± standard deviation. The comparative analysis of the permeation data was done by one-way analysis of variance (ANOVA) followed by *post-hoc* Tukey-HSD (Honestly Significant Difference), $p < 0.05$ was considered significant.

Results and discussion

HPLC method development and validation of 5-fluorouracil, lidocaine and ibuprofen

The HPLC validation parameters of drugs used such as linearity, precision, accuracy, LOD and LOQ are represented in Table 2. All methods show an excellent linearity of 1.00, the capacity factor (k) was above 1 which satisfies the criteria for a good separation,

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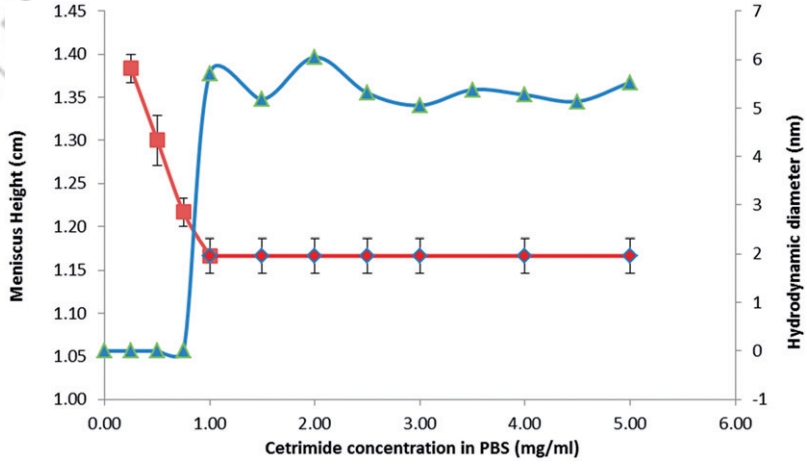

Figure 3. CMC of cetrimide in PBS by surface tension method and light diffraction method.

a '*k*' value of less than 1 is said to be poorly separated as the analyte may not have spent sufficient time on the column. LOD values of ibuprofen, 5-fluorouracil and lidocaine were 0.03 μg/mL, 0.08 μg/mL and 0.17 μg/mL respectively. Similarly, the LOQ values were 0.26 μg/mL (5-fluorouracil), 1.21 μg/mL (ibuprofen) and 1.44 μg/mL for and lidocaine. The obtained LOD values were much lower compared to some of the other reports for ibuprofen (0.67 μg/mL) (Payán et al. 2009), lidocaine (5 μg/mL) (Malenovic et al. 2005), and a comparable LOD is been reported for 5-fluorouracil (0.05 μg/mL) (Lamprecht et al. 2003). In order to investigate the precision and accuracy of the HPLC methods, three QC samples were selected which represented a high, medium and low concentration of each drug. Both intraday and interday evaluations have shown low values of %RSD and %RE for precision and accuracy respectively; this signifies optimum repeatability of these methods and closeness of the test results with the standard.

Permeant solubility and receptor phase studies

The solubility of the drugs in RPO, CPO and TRF are shown in Table 3. These solubility values were used to gauge the amount of drug that was required in the donor phase. To ensure consistency of thermodynamic activity in the donor phase, saturated vehicles were used throughout. The thermodynamic activity of a solution dictates the driving force of diffusion experienced by the solute molecules. Consequently, a higher thermodynamic activity increases the probability of the solute leaving the solution. Thus, in order to ensure a maximum and constant thermodynamic activity throughout the duration of the permeation studies, the saturation solubilities of the drugs in each vehicle were determined and subsequently used in these studies. An excess of drug was then added to the donor phase in the anticipation that it would replace any permeating drug and maintain maximal thermodynamic activity.

Throughout the permeation experiments, PBS containing cetrimide was used as the receptor phase medium. A 'rule of thumb' dictates that the final drug concentration in the receptor phase should not exceed 10% of the saturation solubility in order to ensure that permeant dissolution does not become a rate-limiting step (Sartorelli et al. 2000). Cetrimide was used as a solubility enhancer since it has been previously shown to increase the solubility of lipophilic drugs without affecting the skin's barrier properties (Morris et al. 2009). Furthermore, cetrimide has antimicrobial properties which negate the need for an additional antimicrobial agent in the receptor phase.

Table 4. Flux and enhancement ratio of ibuprofen, lidocaine and 5-fluorouracil from TRF, CPO and RPO ($n = 4$).

Drug	Vehicle	Mean flux (μg/cm2.h) ±SE	Enhancement ratio
5-fluorouracil	TRF	5.13 ± 1.29	1.30
	CPO	4.19 ± 0.47	1.06
	RPO (control)	3.94 ± 0.25	1.00
Lidocaine	TRF	38.1 ± 3.32	1.25
	CPO	33.2 ± 3.10	1.09
	RPO (control)	30.5 ± 3.61	1.00
Ibuprofen	TRF	30.6 ± 0.87	1.89
	CPO	23.0 ± 0.92	1.42
	RPO(control)	16.2 ± 0.35	1.00

CMC determination by surface tension and light diffraction methods

The CMC of cetrimide in PBS was determined using the surface tension method and the light diffraction methods; at 0.97 mg/mL and 1 mg/mL respectively (Figure 3) the results were very similar giving a high degree of confidence in the CMC value. The CMC of cetrimide in PBS was lower than that of cetrimide in water. This was not unexpected given that low CMC values of cetrimide in solutions of high electrolyte concentration (such as PBS) have been previously reported. This reduction may be due to the low repulsion experienced by the polar head of the surfactant

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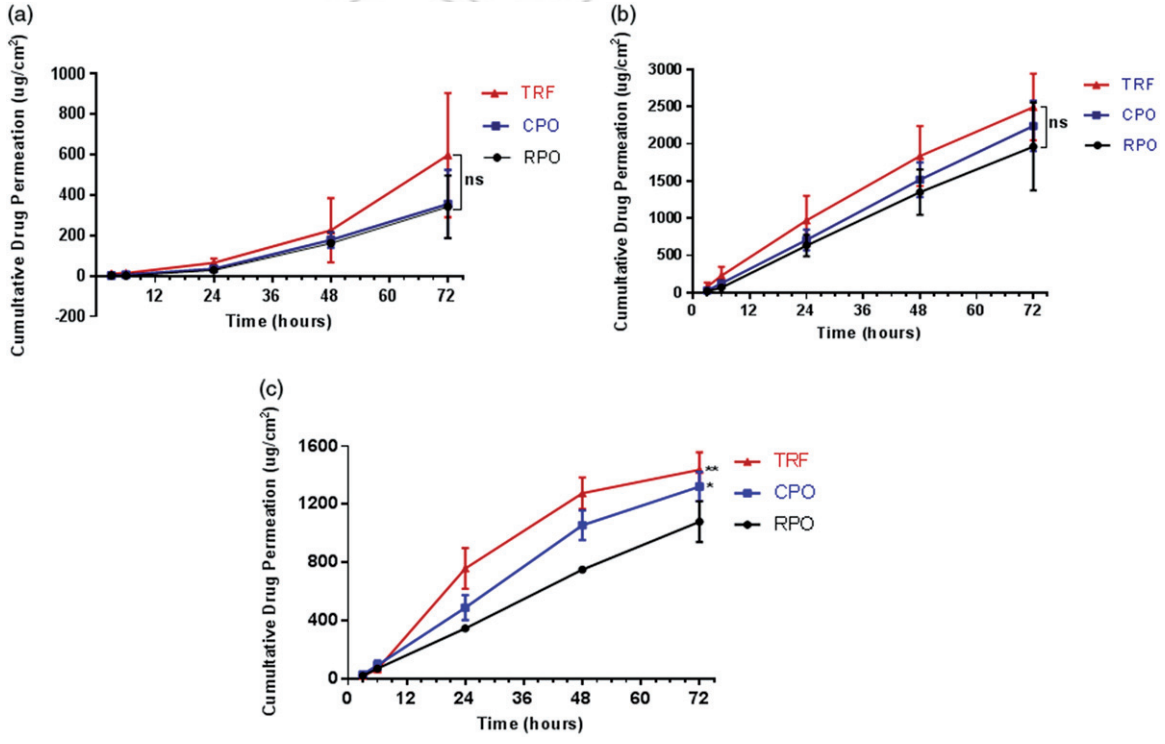

Figure 4. Comparison of cumulative drug permeated across full-thickness human skin from TRF, CPO and RPO: (a) 5-flurouracil; (b) lidocaine; (c) ibuprofen ($n = 4$; ±SD) (ns: not significant; $^*p < 0.05$; $^{**}p < 0.01$).

molecules due to the presence of excess counter ions (Wan and Poon 1969).

Drug stability study in receptor phase and in skin extract

The stability of the three drugs in PBS was assessed at 25 °C and 37 °C and the latter was selected for the permeation experiments to simulate the approximate physiological temperature of skin. Stability studies were performed at 37 °C and also at 25 °C because this was the approximate temperature at which the samples were queued in the HPLC autosampler whilst awaiting analysis. It was found that the concentration of all drug solutions remained unchanged for at least 72 h, which is in agreement with published literature for the drugs used in this study (Powell 1987; Chouhan and Bajpai 2009; Walker et al. 2011).

Drug stability in skin extract was also evaluated and it was found that 5-fluorouracil and lidocaine did not show any change in concentration throughout the entire experiment. This suggests that 5-fluorouracil and lidocaine would not have undergone any degradation as result of exposure to enzymes that may have leached from the skin into the receptor medium. Moreover, 5-fluorouracil has a low protein binding capacity (Knox et al. 2011), which could help explain the stable drug concentration when incubated with the skin extract. Conversely, lidocaine is primarily metabolized in the liver by the microsomal enzyme system and has a long physiological half-life, which could be the main reason why its concentration did not change in the skin extract (Collinsworth et al. 1974). However, it was noted that the concentration of ibuprofen fell considerably when incubated with the skin extract; a 58% reduction in concentration was seen at 72 h. However, it was noted that during HPLC analysis no additional peaks were observed in the ibuprofen chromatograms, whilst ibuprofen has been shown to be stable in human plasma for more than 120 hours (Ganesan et al. 2010). It is possible that ibuprofen has been lost as a result of binding to soluble proteins present in the skin extract; ibuprofen is known to exhibit high protein binding (up to 99%) (Knox et al. 2011).

Ex vivo *skin permeation study using full-thickness human skin*

The percutaneous permeation of 5-fluorouracil, lidocaine and ibuprofen from vehicles such as 2-pyrrolidone, propylene glycol, oleic acid and RPO was also assessed *in vitro* using the full-thickness human skin. However, it was evident that the use of RPO did not enhance the transdermal delivery of these drugs. Therefore, RPO was used as a negative control in this permeation experiments. It was found that permeation of all three drugs was highest from TRF and this was followed by CPO with the lowest flux being observed from RPO (Table 4). In the case of 5-fluorouracil and lidocaine, the flux from CPO and TRF was not significantly different to that from RPO (Figure 4(a,b)), implying that permeation was not significantly enhanced by these vehicles. However, the flux of ibuprofen from both CPO and TRF was significantly greater ($p < 0.05$) than that from RPO (Figure 4(c)). The ibuprofen flux from TRF was almost twice that from RPO, indicating that TRF has superior permeation enhancing capacity compared to RPO. This suggests that the tocotrienols, which make up around 50% of TRF, warrant further investigation as possible transdermal permeation enhancers. Aioi et al. reported that the addition of vitamin E acetate (10–30%) or squalene (10%) to lauroylsarcosine (TDD enhancer), elicited enhanced permeation of isosorbide dinitrate with a reduction in erythema compared to lauroylsarcosine used alone (Aioi et al. 1993). This further supports the use of vitamin E-containing palm oil derivatives in topical and transdermal formulations. Furthermore, the ibuprofen permeation from 2-pyrrolidone had shown a mean flux of 31.1 μg/cm^2 h (data not shown) which is equivalent to the mean flux of ibuprofen from TRF (30.6 μg/cm^2 h), presented in Table 4. This demonstrates that TRF may possess similar TDD enhancing effects as the 2-pyrrolidone, which is known to be a potent permeation enhancer (Barry 1987).

Conclusion

The results have demonstrated that CPO and TRF vehicles are capable of enhancing the percutaneous permeation of ibuprofen across the full-thickness human skin. Given that both of these vehicles are high in tocotrienols, the permeation enhancing the activity of this group of compounds in isolation should potentially be investigated.

Disclosure statement

No potential conflict of interest was reported by the authors.

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