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Predicting Skin Permeation-enhancing Effect of Fixed Oils Using Saturated to Unsaturated Fatty Acid Ratio Content

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: Transdermal drug delivery is non-invasive and advantageous as it improves patient compliance.
Objective: This study evaluated the effect of varying ratios of saturated to unsaturated fatty acids in fixed oils on the permeation of ibuprofen across pig dorsal skin.
Methods: The solubility of ibuprofen in soybean oil, theobroma oil, and shea butter (fixed oils) was evaluated and *in vitro* skin permeation studies were conducted using Franz diffusion cells.
Results: A significant difference in permeability parameters, such as flux and effective skin permeability, in the different formulations was observed. Skin permeation depended on the ratio of saturated to unsaturated fatty acids. It also depended on the type and concentration of individual saturated and unsaturated fatty acids present in the fixed oils. The skin permeation of ibuprofen increased with an increasing ratio of palmitic acid (PA) to oleic acid (OA) concentrations. The highest flux was obtained in the theobroma oil formulation, with a PA:OA ratio of 0.78. The lowest flux was obtained in the shea butter formulation, with a PA:OA ratio of 0.09. The PA:OA ratio was 0.46 in the soybean oil formulation.
Conclusion: These results suggest that the ratio of saturated to unsaturated fatty acids in fixed oils could be used as a model for predicting the rate of skin permeation of drugs in oil-based formulations. Depending on the desired rate of drug permeation, different combinations of the ratio of saturated to unsaturated fatty acids can be used in formulations for transdermal delivery.
Keywords: Fixed oils, ibuprofen, saturated fatty acids, unsaturated fatty acids, transdermal delivery

INTRODUCTION

Transdermal drug delivery is a non-invasive route of administration of therapeutic agents through the skin to achieve systemic effects. This ease of administration improves patient compliance compared to the enteral and parenteral routes of drug administration. It is an alternate route of administration for drugs susceptible to hepatic first-pass metabolism or gastrointestinal tract irritation. Unlike the parenteral route, transdermal delivery systems can be designed to control the rate of drug delivery to the systemic circulation, thus maintain a steady concentration of the drug in the blood for a longer period. This also improves patient compliance as undesirable side effects of drugs, due to fluctuating serum drug concentrations are avoided (Caparica *et al.,* 2018).

Despite multiple advantages, few drugs are marketed in a transdermal dosage form. This limitation has been attributed to the stratum corneum of the skin, which causes poor permeation of most drugs (Yu, Y-Q *et al., 2021).* Reports have shown that the success of a transdermal drug delivery system depends on the ability of the drug to penetrate the skin in sufficient quantities to achieve the desired therapeutic effect (Yu, Y-Q *et al., 2021*). Thus, the major challenge in transdermal drug delivery is to find ways to modify or bypass the stratum corneum, to optimize drug delivery.

One strategy that has been used to enhance the permeation of drugs through the skin is the modification of the formulations (Trommer and Neubert, 2006). This involves optimizing drug permeation through the transdermal route by incorporating agents in the drug formulation that can alter the properties of the skin barrier (penetration enhancers) (Williams and Barry, 2004; Nino et al., 2010). The disadvantage of this method is that some penetration enhancers can cause skin irritation (Mathur *et al.,* 2010). This could be of concern when the drug is administered for a long-term (Zhai and Maibach, 2004). The development of penetration enhancers that are safe, compatible with the drug formulation, and do not cause skin irritation is a challenge (Sarango-Granda *et al.,* 2022). Fatty acids are a class of substances that have been reported to cause little or no skin irritation in topical formulations. They have also been reported to be effective penetration enhancers (Oh *et al*., 2001; Mittal *et al*., 2009). There are two main types of fatty acids: saturated and unsaturated fatty acids. They can be obtained synthetically or from a natural origin (Das and Gupta, 2021). Fatty acids can be synthesized in both saturated and unsaturated forms. However, when they are obtained from natural sources, they occur as a combination of saturated and unsaturated fatty acids (IUPAC1997; Cerone, 2021). Fixed oils are rich sources of fatty acids and are abundant in nature. These oils are commonly used in the formulation of gels for cosmetics and pharmaceuticals. Many studies have evaluated the influence of fixed oils on transdermal drug delivery. This study will investigate how the ratio of saturated to unsaturated fatty acid contents of oils used in gel formulations influences the rate at which drugs can be delivered through the skin from the formulations. Theobroma oil, soybean oil, and shea butter were used in this study. The fatty acid contents are shown in Table **1**. Ibuprofen, a non-steroidal anti-inflammatory drug, was used as the model drug.

Pain is a public health concern (Carr, 2016). It is estimated that approximately one in five adults suffers from pain globally (Goldberg and McGee, 2011). Pain contributes to mortality, morbidity, and disabilities, and overwhelms the healthcare system. Many man-hours are lost daily to pain. Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line treatments for pain. Pain relief is most effective when it is addressed before it becomes severe. Ibuprofen is one of the most commonly used NSAIDs for pain relief. Ibuprofen also has beneficial effects in patients with cystic fibrosis. It is used as an anti-inflammatory and antimicrobial agent against cystic fibrosis-associated gram-negative pathogens (Shah, 2018). Ibuprofen causes gastrointestinal irritation and is advised to be consumed with food to minimize this side effect. The transdermal delivery of ibuprofen will improve its ease of administration as it can be applied without regard to the consumption of food.

Generally, drugs are rarely administered in their pure form. They are mostly present in addition to other excipients in their dosage form. Excipients are added to modify the properties of the drug. Topically administered drugs are applied to the skin as creams, gels, lotions, or ointments. They are mostly composed of oil, water, and alcohol. The choice of oil base used in these formulations affects the potency and rate of delivery of the medication. This is due to the differences in the occlusive and skin barrier-modifying abilities of various oil bases. With the correct choice of formulation base, the desired rate and extent of drug delivery through transdermal formulations can be achieved, without the need to add another excipient as a penetration enhancer.

In this study, the solubility of ibuprofen in the fixed oils – theobroma oil, soybean oil and shea butter were presented. The effects of the type and varying ratio of saturated to unsaturated fatty acids in the fixed oils on the skin permeation of ibuprofen were also investigated.

Table 1. Fatty acid composition of the fixed oils (Claude Leray, 2014)

Fixed Oils	Saturated:Unsaturated Fatty Acid Ratio	Unsaturated Fatty Acids %			Saturated Fatty Acids %		
		Linoleic Acid	Alpha-Linolenic Acid	Oleic Acid	Palmitic Acid	Stearic Acid	Lauric Acid
Theobroma oil	1.8	3	0	32	25	38	0
Soybean oil	0.2	54	7	24	11	0	0
Shea butter	0.9	5	0	44	4	39	1

METHODOLOGY

Materials and methods

Ibuprofen, ethanol, sodium hydroxide, sodium chloride, potassium dihydrogen orthophosphate, disodium hydrogen phosphate, n-hexanol, and petroleum ether were purchased from (BDH, Poole, UK). All other reagents were of analytical grade. Soybean oil, shea butter and theobroma oil were obtained locally from the open market. Phosphate buffered saline (PBS, 0.01 M, pH 7.4) was prepared using the reagents listed in Table **2**. Franz diffusion cells for a skin permeation study were obtained from PermeGear, Inc. (Hellertown, PA, USA). They consisted of two half-cells with a diffusional area of 1.77 m^2 and a donor receptor capacity of 12 mL. Fresh skin sections from the abdominal region of male pigs were obtained from the butcher at the slaughterhouse, Department of Veterinary Medicine, University of Ibadan (Ibadan, Nigeria). Pig skin was used for the permeation study as it has been reported to be similar to human skin in permeability (Zhai and Maibach, 2004). After removing the subcutaneous fats, the skin sections were stored in a freezer at -20 ℃.

Table 2. Chemical composition of isotonic phosphate buffer

Chemical	Concentration (M)	Amount (g)
KH_2PO_4	0.0506	6.8816
K_2HPO_4	0.0494	8.5956
NaCl	0.0336	1.9757
Water		*q.s.1 liter

2.2 Solubility of ibuprofen in fixed oils

To determine the apparent solubility of ibuprofen in fixed oils, PBS/soybean oil, PBS/shea butter, and PBS/theobroma oil mixtures were prepared and placed in 10 mL capacity stoppered vials. A 15% w/w concentration of each mixture contained 15 g of fixed oil. Ibuprofen powder was mixed with each of the oil/buffer mixtures using a vortex mixer (Fisher Scientific, Hampton, NH, USA).

The mixtures were then incubated at 37 ℃ for 36 h, and centrifuged at 5000 *g* for 10 min. The supernatant was filtered through a 0.20 µm Millipore filter. The concentration of ibuprofen in each oil sample was spectrophotometrically determined at 264 nm.

Preparation of test formulations

Saturated solutions of ibuprofen in 15% soybean oil, 30% soybean oil, 15% theobroma oil, and 15% shea butter were prepared with vigorous agitation in a vortex mixer for 10 min at 80 ℃. Ethanol (60%) and phosphate buffer were used in each formulation as co-solvents due to the lipophilic nature of ibuprofen. The formulations contained 50 mg/mL ibuprofen. The mixtures were cooled to 25 ℃ and agitated until the desired viscous solutions were obtained.

Skin permeation study

An *in vitro* skin permeation study was performed using Franz diffusion cells. The pig skin samples were thawed, rinsed in PBS, and cut into sizes that covered the orifice of the donor and receptor chambers of the cells. Then, the samples were mounted on the receptor chamber, with the stratum corneum facing the donor chamber and the lower surface of the receptor chamber. Each cell had an O-ring clamp that provided a good seal around the skin. A sampling port attached to the receptor chamber enabled easy sampling of receptor fluid without interrupting the experiment.

The receptor chamber was filled with 0.1 M ethanolic PBS (40:60% v/v, pH 7.4). The chamber was allowed to attain a temperature of 35 ℃ one hour before the experiment and was maintained at this temperature by attaching it to a thermostatic water bath (Nishihata et al.1991*)*. The solutions were magnetically stirred at 150 rpm throughout the sampling period. Care was taken to prevent the formation of air bubbles on the underside of the skin during the experiment. The donor compartments were charged with 2.0 mL of the respective formulations (50.0 mg/mL ibuprofen) and were sealed with a paraffin film to provide occlusion. Samples were withdrawn at 1 hour and then subsequently at 2-hour intervals over a period of 10 hours. The samples were analyzed spectrophotometrically at 264 nm, to assess ibuprofen concentration. After each sampling, the change in the volume of the receptor solution was corrected.

Data analysis

Each experiment was performed in triplicates. Data are presented as the means of the values. Individual cell data are plotted as the concentration (Q) of the drug in the receptor chamber as a function of time (t). The fluxes (J) for each formulation were determined using linear regression analysis of the straight-line portion of the cumulative drug penetration vs. time plots. The lag times (h) were determined from the intercept of the curve along the x-axis.

The effective skin permeability (P) of each formulation was calculated by dividing the flux by the area of the skin surface (A) through which diffusion occurred and the donor compartment drug concentration (C_d). (Equation 2)

$$J = (dQ/dt) \quad \text{..... (1)}$$

where dQ/dt is the change in concentration Q with time (t).

$$P = J/AC_d \quad \text{..... (2)}$$

Where P is the effective skin permeability (P) of each formulation, A is the area of the skin surface through which diffusion occurred and (C_d), the donor compartment drug concentration.

Statistical analysis

Statistical analyses of the data were performed using the SPSS software (IBM, Armonk, NY, USA), and the results were evaluated using *Student's* *t*-test and analysis of variance. Results were considered statistically significant at $P < 0.05$.

RESULTS AND DISCUSSION

The solubility of ibuprofen in the fixed oil formulations was determined, and the results are presented in Fig. (**1**). Ibuprofen solubility was highest in theobroma oil (24.13 mg/mL), followed by soybean oil and shea butter. The permeation parameters of the ibuprofen formulations across the pig abdominal skin are listed in Table **3**. The drug fluxes from soybean oil, shea butter, and theobroma oil formulations are compared in Fig. (**2**).

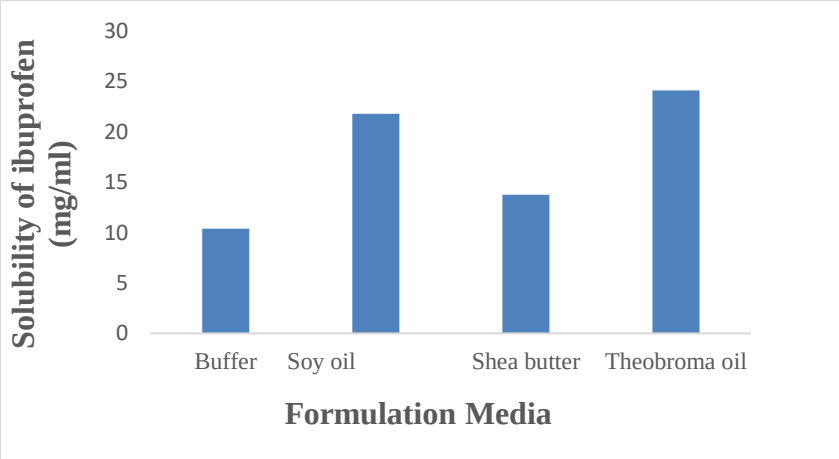

Figure 1 Solubility of ibuprofen in formulation media

Table 3 Permeation parameters of ibuprofen in 50 mg/mL fixed oil formulations across pig abdominal skin

Flux (µg/h)	Effective skin permeability (cm/h)	Flux (µg/h)
15% TBMO[a]	96.84	0.00109
15% SBO	60.72	0.000686
15% SHB[b]	56.48	0.00064
30% SBO[c]	55.57	0.00063

a Theobroma oil, b Shea butter, c Soybean oil

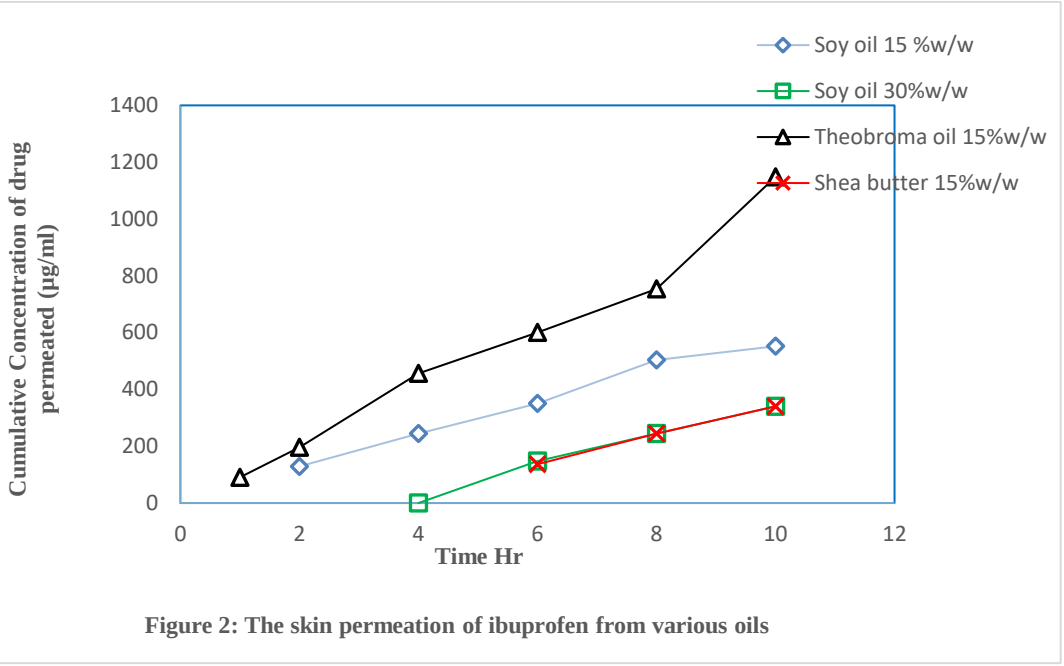

Figure 2: The skin permeation of ibuprofen from various oils

A significant difference in the permeation parameters among all the formulations was observed ($P < 0.05$). For the 15% fixed oil formulations, the drug flux and effective skin permeability of ibuprofen were highest in theobroma formulation, and lowest in the shea butter formulation. The drug flux from the 30% soybean oil formulation was lower than that from the 15% soybean oil formulation. The skin permeation of a drug when fatty acids are used as a vehicle is related to the physicochemical properties of the drug, as well as the chemical structure of the fatty acids (Mittal *et al*., 2009).

The bioavailability of a drug from a transdermal delivery system has been linked to solubility parameters, thermodynamic activity, and physicochemical interactions between the drug and its carrier/vehicle and the skin (Alomrani, *et al*., 2018; Haq *et al*., 2020; Souto *et al.*, 2022). Changes in carrier composition may alter drug solubility, which can influence its thermodynamic activity. The carrier may also alter skin integrity, thereby influencing drug flux from a formulation into the skin (Ishii *et al*., 2010). Hence, it can be deduced that the permeation profiles obtained in this study were due to both the driving force and alteration in the integrity of the skin barrier.

According to Fick's law, the flux of a drug from a formulation is proportional to its concentration in the formulation (Ceschel *et al*., 2005; Mustapha *et al*., 2011). Fig. (**2**) and Table **3** show that the solubility of ibuprofen was highest in theobroma oil. Moreover, the theobroma oil formulation exhibited the highest flux of ibuprofen (96.84 µm/h), with an effective skin permeability of 0.00109 cm/h. The lowest ibuprofen solubility was observed in the soybean oil formulation, while the 15% shea butter formulation exhibited the lowest flux (56.48 µm/h) and effective skin permeability (0.00064 cm/h).

One mode of action for permeation enhancers is to alter the barrier properties of the skin. Altering intercellular lipids or intracellular keratin increases the permeability of drugs through the stratum corneum (Kim et al., 2008). Fatty acids enhance skin permeation by altering the lipid layer of the skin, causing disorders in the layer, and allowing for more areas of penetration, less rigidity, and greater flux (Kim *et al*., 2008).

As shown in Fig. (**2**), the theobroma oil formulation enabled effective and almost instant release of ibuprofen. In the soybean oil formulation, the lag time was 1 h, which was shorter than that for the shea butter formulation. The shorter lag time for the theobroma oil formulation showed a higher diffusivity, with a 1.8 ratio of saturated to unsaturated fatty acids.

Cho and Gwak, 2004, reported that skin permeation of ketorolac tromethamine was higher in the presence of saturated fatty acids, than in that of unsaturated fatty acids. They also showed that the highest permeation of ketorolac tromethamine was obtained when oleic acid (OA) and linoleic acid were used at a concentration of 5%. Increasing the concentration of unsaturated fatty acids in the formulation did not result in any further increase in the flux.

This result corresponds with an earlier report by, Kannikannan *et al.*, (2000), that the level of unsaturation of penetration enhancers, among other chemical factors, influences the interaction of the

enhancer with the stratum corneum, and thus, influences the extent of chemical penetration enhancement achieved. The type and concentration of fatty acids used in penetration enhancement influence the extent of penetration enhancement achieved Kim et al., (2008). However, these reports were based on permeation experiments, in which either saturated or unsaturated fatty acids were used.

The results obtained in this study showed that although all carriers used in the different formulations contained fatty acids, the extent of drug flux achieved was different. This may be due to differences in the type and concentration of fatty acids they contain. The fixed oils used in this study contained both saturated and unsaturated fatty acids. This was represented by the ratio of saturated to unsaturated fatty acids in each carrier. The ratios were 0.2, 0.9, and 1.8, for soybean oil, shea butter, and theobroma oil, respectively. Hence, soybean oil contained more unsaturated fatty acids than saturated fatty acids, while theobroma oil contained more saturated fatty acids than unsaturated fatty acids. However, shea butter had almost equal contents of both types of fatty acids.

The chemical structure-related factors of fatty acids that influence skin permeation include carbon chain length, degree, and type of unsaturation and branching Mittal *et al*., 2009). The saturated fatty acids in all three fixed oils included palmitic acid (PA, 16:0, carbon chain length: no. of double bonds), lauric acid (12:0, carbon chain length: no. of double bonds), and stearic acid (18:0, carbon chain length: no. of double bonds). Saturated fatty acids increase skin permeation with increasing carbon chain length, with maximal skin permeation occurring at C-16 (PA). A parabolic relationship has been reported between the chain lengths C-12 and C-20 (Kim *et al*., 2005). Table **1** shows that the highest concentration of PA was observed in theobroma oil, while the lowest was observed in shea butter. This explains why soybean oil, with a lower ratio of saturated to unsaturated fatty acids, had a higher skin flux than shea butter. Also, the flux of ibuprofen (56.48 µg/h) in the 30% soybean oil formulation did not increase with the increase in soybean oil concentration.

Oleic acid (18:1, carbon chain length: no of double bonds) and linoleic acid (18:2 and 18:30, carbon chain length: no. of double bonds) were the unsaturated fatty acids detected in the fixed oils. Unsaturated fatty acids increase the skin permeation of drugs by increasing the chain length from C-14 to C-22 (Morimoto *et al.,* 1996). The permeation of indomethacin through rat skin was increased by unsaturated fatty acids in the following order: C20 > C22 = C18 = C16 > C14. At C18, increasing the number or positioning of the double bonds did not further enhance drug flux (Thomas *et a*l., 2003.) Thus, the skin permeation enhancing effect of unsaturated fatty acids in theobroma oil, soy oil, and shea butter is dependent on the OA content of the carriers. Oleic acid has been said to be the most popular fatty acid used to enhance skin permeation (Mittal *et al.,* 2009; Thomas *et a*l., 2003; Choi et al., 2012). The OA content was ranked as follows: theobroma oil > shea butter > soybean oil.

However, as shown in Table **3**, the flux of ibuprofen from the carriers was in the following order: theobroma oil > soybean oil > shea butter. This can be attributed to the synergism between the OA and PA balance in the carriers, which optimizes the flux of ibuprofen. Oleic acid and PA have been used as permeation enhancers to enhance transdermal drug delivery in several formulations. The OA: PA ratio in the carriers used in this study was 0.8 for theobroma oil, 0.5 for soybean oil, and 0.1 for shea butter. Determining the right balance of OA:PA may be instrumental in maximizing the use of fatty acids as skin permeation enhancers.

Formulation media/carriers that can reversibly change the skin barrier property and can effectively solubilize the desired amount of drug while minimizing the decrease in thermodynamic activity are used when a high skin penetration rate is desired Cho and Gwak, 2004).

CONCLUSION

The results of this study show that the suitability of a fixed oil as a carrier in topical drug delivery can be determined based on the saturated: unsaturated fatty acid content. It will help to streamline the choice of fatty acids as candidates for transdermal drug delivery formulations. Determining the OA: PA balance of fixed oils can be used to predict the rate of drug delivery form the oils. This has relevance when there is need to customize formulations for target populations like the geriatrics and pediatrics; and also, in disease states where the integrity of the skin has been compromised. Varying combinations of OA:PA can lead to the formulation of new penetration enhancers that can be used in the transdermal delivery of Active pharmaceutical ingredients (APIs).

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