



**TRANSDERMAL DELIVERY OF METOCLOPRAMIDE USING EUCALYPTUS OIL AND SHEAR BUTTER**

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**ABSTRACT**

The study investigated the effects of eucalyptus oil and shea butter on the physicochemical and bioadhesion properties as well as on the *ex vivo* drug release of metoclopramide from transdermal patch. Metoclopramide patches were formulated using hydroxypropyl methylcellulose (HPMC) in combination with varied proportions of shea butter and eucalyptus oil (10 - 30 %w/w of HPMC). The prepared patches were evaluated for their physicochemical properties such as thickness, folding endurance, moisture and drug contents as well as their bioadhesion properties and *ex vivo* drug release across treated rat skin. The patches were also characterized using Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) in order to investigate any interaction between the excipients and drug in the formulation process. The patches had thickness ranging from 0.53 - 0.70 mm and folding endurance of 300 - 310. Moisture and drug contents increased with increasing concentrations of the oil or shea butter with values ranging from 21 - 53 % and 86 - 88 %, respectively for eucalyptus oil patches and 5.0 - 10 % and 98 - 99 %, respectively for shea butter patches. Patches bioadhesion ranged from 0.01029 - 0.02283 kN and decreased with increasing concentrations of the eucalyptus oil or shea butter ( $p \leq 0.0413$ ). The shea butter patches showed better *ex vivo* release profile with significant difference ( $p \leq 0.0324$ ). FT-IR spectra and DSC thermograms showed no observable interaction between the excipients and metoclopramide. Metoclopramide patches produced with shea butter were superior in their physicochemical properties and drug release while those formulated with eucalyptus oil exhibited superior bioadhesion properties.

**KEYWORDS:** Bioadhesion, Metoclopramide, Oil, Shear butter, Permeation enhancer.

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**INTRODUCTION**

Different methods and approaches have been used to alter the barrier properties of the skin in formulating drugs for transdermal delivery. One of the long-standing methods is by adding permeation enhancers in the formulation for enhancing percutaneous absorption [1] or by the use of skin penetration techniques [2,3]. Permeation enhancers (PE) are substances that act to promote drug

movement across skin barrier and have various mechanisms of enhancement. Different classes of chemicals used as PEs include sulphoxides, alcohol, amides, surfactants [4,5], terpenes, fats and oils [6,7]. Fats and oils are subgroup of triglyceride lipids and the most commonly used lipid excipients. While fats are solid at room temperature, oils on the other hand are liquid at

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room temperature which are either volatile or non-volatile.

Eucalyptus oil is a volatile essential oil extracted from the leaves of its natural plant by steam distillation. It is a natural source of terpenes (a constituent of volatile oil) which consist of 1,8-cineole, eucalyptol and moderate amount of mono terpenes. The terpenes in eucalyptus oil have been reported to enhance percutaneous absorption of drugs by modifying the solvent nature of the *stratum corneum*, thus improving drug partitioning into the tissue [8].

Shea butter is an off-white or ivory-colored solid fat extracted from the nut of the African shea tree (*Vitellaria paradoxa*). It is edible and is used in food preparation in Africa. Shea butter is a triglyceride (fat) containing mainly stearic acid and oleic acid. It melts at body temperature and absorbs rapidly into the skin. It has a viscosity of 83.92 cSt at 40 °C [9]. Shea butter is used in the cosmetics preparation as skin moisturizers, lip gloss, emulsion and hair conditioners (for dry and brittle hair).

Metoclopramide is an antiemetic used in the management of nausea and vomiting associated with motion sickness, early stage of pregnancy and cancer chemotherapy [10]. Its oral dosage form has an unpredictable bioavailability ranging from 32 - 100 % resulting from hepatic metabolism and adverse effects like restlessness, drowsiness, fatigue and extrapyramidal side effects at high doses [11,12]. Since nausea and vomiting mitigates the use of oral dosage form of metoclopramide, other routes of administration such as parenteral and rectal have been used. But these routes are invasive and have resulted in low patient acceptance [13]. The physicochemical properties of metoclopramide such as solubility in water (0.02 g/100 ml at 25 °C), melting point (146.5 - 148 °C), stability pH (2 - 9), partition coefficient (2.667), molecular weight (354.3 Daltons) coupled with its variable oral bioavailability, makes it an ideal candidate for transdermal drug delivery [14].

Transdermal delivery of metoclopramide could be an alternative route of administration but the skin barrier against drug penetration remains a major challenge. Hence the inclusion of a permeation or penetration enhancer such as oil in its formulation may significantly improve the penetration of drug molecules across the skin barrier. An earlier study investigating the effects of arachis and eucalyptus oils on insulin release from transdermal patches in diabetic rat models revealed an improved *in vivo* release of insulin from the patches [7]. Some authors have worked on the transdermal delivery of metoclopramide over the years with the aim of

improving drug release from the transdermal formulation and they have been more or less successful [15-17]. Therefore, this work aims at investigating the effects of eucalyptus oil and shea butter on the physicochemical and bioadhesion properties of formulated metoclopramide transdermal patches as well as their effect on drug release from the transdermal patches.

## MATERIALS AND METHODS

### Materials

Hydroxypropyl methylcellulose (HPMC) and Tween 80 were products of Sigma Aldrich, Germany. Metoclopramide injections (Wuhan Grand Pharmaceuticals, China), eucalyptus oil BP (Bell's Healthcare, UK). Shea butter was purchased from a local market in Benin City, Nigeria. Other chemicals used were of reagent grade and were used without further purification.

### Preparation of metoclopramide transdermal patches

Metoclopramide transdermal patches were prepared according to the formula in Table 1 by solvent casting method. Metoclopramide was added into a mix of varying ratios of oil or shea butter and the plasticizer (Tween-80). The mixture was added to an aqueous mixture of the polymer (HPMC) and mixed intimately by stirring for 5 min. The mixture was then casted on a petri-dish and air-dried for 48 h. Thereafter, air dried patches were removed from the petri dish, cut into a 2 × 1 cm<sup>2</sup> patch size to contain the equivalent dose of 5.0 mg/patch and stored in-between foils to retain their flatness in an airtight container. This was done for patches TD1 - TD6. While patch TD0 (containing only HPMC and metoclopramide) served as the control patch.

### Evaluation of transdermal patches

#### Weight

Three patches from each batch were weighed individually using a digital balance and the average weight of the patches was obtained and standard deviation calculated.

#### Thickness

The thickness of the various batches of patches was determined using a micrometer screw gauge at different spots on the surface of the patch and the average thickness was recorded.

#### Folding endurance

This was done by a repeated folding and opening of the patches at the same point until there was

breakage or crack. The results were expressed as number of repeated folds before breakage [18].

### Moisture content

Three patches from the various batches were individually weighed and placed in a desiccator containing activated silica gel as desiccant. The patches were then withdrawn at different time intervals up to 48 h and weighed again to check for moisture loss till no further loss in weight was observed. The average weight was recorded and the moisture content was then calculated as the difference between initial and final weights and expressed as a percentage [19].

### Moisture uptake

Three patches from the various batches were weighed individually and kept in a desiccator containing saturated solution of sodium chloride to maintain a relative humidity of 78 %. After 48 h, the patches were reweighed, the average weight was recorded and the moisture uptake was calculated as the difference between initial and final weights and expressed as a percentage [19].

### Drug content

A patch from each batch was placed in a 50 ml beaker containing 20 ml phosphate buffer solution (pH 6.4) and shaken intermittently until complete dissolution. One milliliter of this solution was further diluted in 9 ml of phosphate buffer (pH 6.4). The solution was filtered and metoclopramide content was then determined spectrophotometrically at  $\lambda_{\max}$  of 273 nm using UV/Visible spectrophotometer (T70 PG Instrument Ltd, USA).

### Bioadhesion

This test was carried out for each batch of patches using a version of the modified method of Eraga and colleagues [19]. The apparatus used consists of a burette clamped to a retort stand. Below the burette, a wooden rectangular block sliced at an angle of 30° was used as a support to position a glass slide at the same angle (30°) with a treated rat skin glued to the glass slide.

An excised dorsal skin section of a male albino rat weighing 250 g was earlier obtained from a freshly slaughtered animal in the animal house of the Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Benin, Benin City. The excised skin was treated by soaking in 5.0 % NaOH solution for 30 min to remove the hair from the skin and further defatted by soaking in acetone for 1.0 h.

A patch was placed on the exposed surface of the skin for a period of 15 min, to allow for patch-skin interaction and hydration. The burette was filled

with water and then allowed to flow over the patch on the skin at a constant lamina flow rate until the patch detached from the rat skin. Using Equation 1, the sum total of the force needed to detach the patch was used as a measure of bioadhesion.

$$Force = mg \quad \dots \quad 1$$

Where m = total mass in kg of water used as calculated from the volume of water collected at the base of the setup and g = acceleration due to gravity (9.8 m/s<sup>2</sup>)

### Ex- vivo permeation of metoclopramide across rat skin

This study was carried out using a dissolution apparatus (Caleva ST7, UK) modified in place of a Franz Diffusion Cell. The treated rat skin from the bioadhesion studies was soaked in phosphate buffer (pH 6.4) overnight to equilibrate. A patch was placed firmly on the treated skin, wrapped once and tied to ensure adhesion throughout the experiment. The tied skin-patch was placed in the basket unit of a dissolution apparatus acting as the donor compartment. The donor unit was lowered into the dissolution medium (acting as the receptor compartment) containing 500 ml of phosphate buffer pH 6.4 maintained at 32 ± 0.5 °C and stirred at 50 rpm. Aliquots of 5 ml were withdrawn from the receptor compartment at various time intervals up to 12 h, replacing with equal volume of the receptor medium. Withdrawn samples were then analysed spectrophotometrically at 273 nm.

### Compatibility studies

#### Fourier transform infra-red (FTIR) spectroscopy

A patch was crushed in tiny pieces and about 5.0 mg of the particles was blended with dried potassium bromide (KBr) powder to 200 mg, and compressed into a tablet using a hydraulic press. The compressed tablet was then scanned at an IR range of 4000 - 750 cm<sup>-1</sup>. (Perkin Elmer, Beaconsfield Bucks, UK).

#### Differential scanning calorimetry (DSC)

A 5.0 mg of a crushed patch was weighed and sealed in a flat-bottom aluminum pan. Heating was carried out over a temperature range of 30 to 400°C under nitrogen at a constant flow rate of 70 ml/min and heating at an increasing rate of 10°C/min using Netzsch DSC 204F1 Phoenix apparatus, GmbH, Germany. The thermograms obtained for metoclopramide and the patch was compared.

### Data analysis

The experimental data were expressed as mean of three determinations  $\pm$  standard deviation (SD). Statistical analysis was performed using IBM SPSS Version 21. Differences between mean were determined using one-way analysis of variance (ANOVA) at 5.0 % level of significance.

## RESULTS

### Physicochemical properties of the transdermal patches

Table 2 shows some physicochemical properties of the formulated patches. The values of the weights of the patches varied between 0.21 to 0.22 g while patch thickness values ranged from 0.51 to 0.71 mm. There were no significant differences ( $p > 0.05$ ) in the weights of the patches within and among the batches while this was also the case with the patches thickness within the batches but not among the batches. The folding endurance of the patches ranged from 300 to 310 number of folds with slight variation among the patches while the moisture content or moisture loss values of the patches which ranged from 5.0 to 53 % showed significant difference ( $p < 0.05$ ) among batches especially when batch TD3 with highest moisture content is compared with the control batch TD0 which showed the least moisture content. Moisture uptake was highest in the control TD0 batch of patches but with no pattern or variable uptake values for TD1-TD6 patches. The drug content of the different batches of the patches was within 86 to 99 %, with some level of significant variations ( $p < 0.05$ ) among the batches.

### Bioadhesive property of the transdermal patches

The bioadhesion values ranged from 0.01029 - 0.02283 kN with adhesion of the patches decreasing with increasing concentrations of eucalyptus oil or shea butter. Though the reduction in bioadhesion was not significant between some batches but the reduction was significant ( $p \leq 0.0413$ ) between all the batches and the control batch TD0 with the highest bioadhesion value (Figure 1).

### Ex vivo permeation of metoclopramide across rat skin

All the patches showed an enhanced drug flux across the rat skin with the addition of eucalyptus oil or shea butter in their formulations (Figure 2). Addition of eucalyptus oil or shea butter resulted in increased permeation of metoclopramide across the rat skin. The increase in drug flux across the rat

skin from the patches containing eucalyptus oil or shea butter was also significant ( $p \leq 0.0324$ ) in comparison with the control TD0 batch of patches.

### Compatibility FT-IR analysis

The FT-IR analysis revealed no change in the spectra of the different patch formulations when compared with the spectra of metoclopramide (Figure 3). The FT-IR of metoclopramide showed the presence of -OH stretching bands at wavenumber of 3300 - 3600  $\text{cm}^{-1}$  while -C-CH stretching of -CH<sub>2</sub> and -CH<sub>3</sub> occurred at 2950-2840  $\text{cm}^{-1}$ . The spectra of the patches also expressed additional spectra patterns that indicate functional groups typically present in oils and polymers used in making the transdermal patches. There was no observable chemical interaction between the oil or shea butter and metoclopramide, thus transdermal patches containing eucalyptus oil or shea butter are stable dosage forms for metoclopramide.

### DSC analysis

The DSC thermograms (Figure 4) of the various patches containing excipients showed no obvious changes when compared with the thermogram of metoclopramide. The thermogram showed an endothermic trough in the various formulations at 90 °C indicating evaporation of moisture from the sample followed by a broad trough showing the melting of metoclopramide at 147.3 °C. However, the broad trough indicates that there are other constituents as the metoclopramide used in this study was obtained from the injectable solution. The DSC of the formulation TD3 and TD6 showed similar spectra patterns with the eucalyptus oil and shea butter masking the metoclopramide in the formulations. Peaks and troughs above 300 °C represent degradations at high temperatures.

## DISCUSSION

Metoclopramide transdermal patches incorporated with eucalyptus oil and shea butter as permeation enhancers have been formulated and evaluated for their physicochemical, bioadhesion and drug release properties in this study. While the incorporated eucalyptus oil and shea butter affected more or less the physicochemical parameters of the patches, there were significant reduction in their bioadhesion with increase in the oil or shea butter and also a significantly enhanced drug release from the patches with the eucalyptus oil or shea butter.

Among the physical parameters of the formulated

**Table 1:** Formula for preparation of metoclopramide transdermal patches

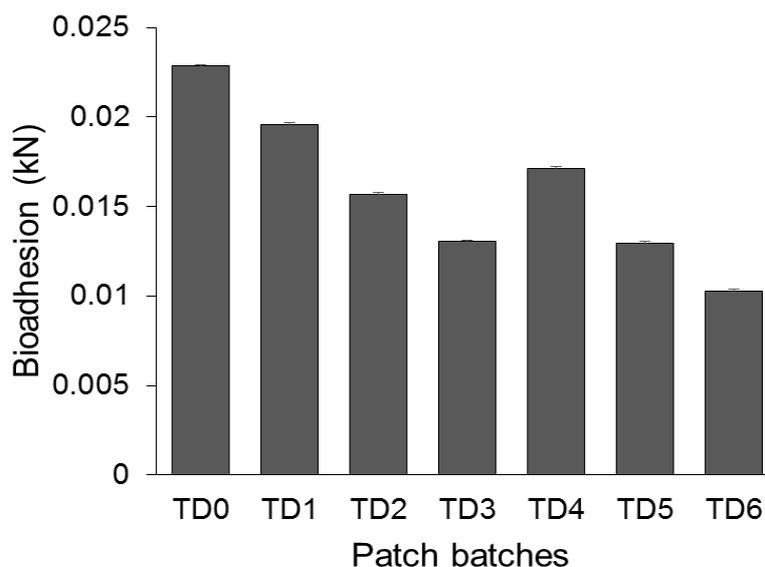
Batches	Metoclopramide (mg)	Tween 80 (ml)	HPMC (mg) [%]	Eucalyptus oil (ml)[%]	Shea butter (ml)[%]
TD0	95	2.0	200 [100]	-	-
TD1	95	2.0	180[90]	0.2[10]	-
TD2	95	2.0	160[80]	0.4[20]	-
TD3	95	2.0	140[70]	0.6[30]	-
TD4	95	2.0	180[90]	-	0.2 [10]
TD5	95	2.0	160[80]	-	0.4 [20]
TD6	95	2.0	140[70]	-	0.6 [30]

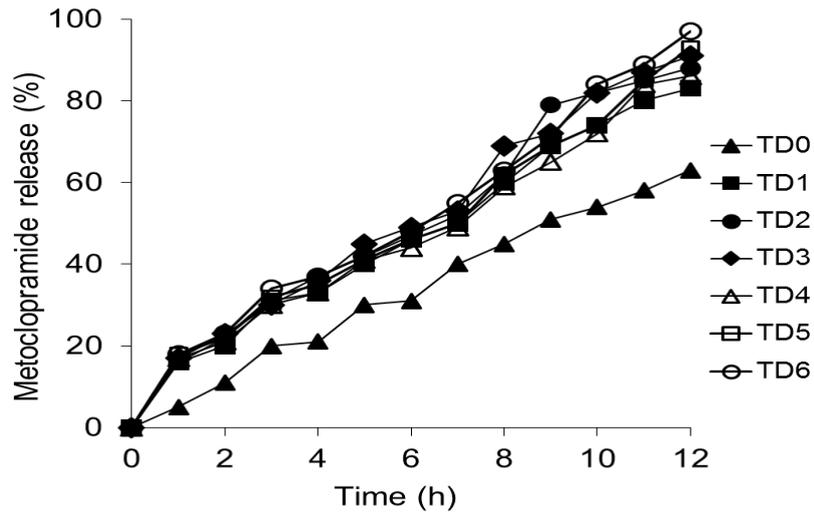
**Legend:** TD0; Control, TD1; 10 %, TD2; 20 %, TD3; 30 % eucalyptus oil and TD4; 10 %, TD5; 20 %, TD6; 30 % shea butter

**Table 2:** Some physicochemical parameters of the transdermal patches (n = 3)

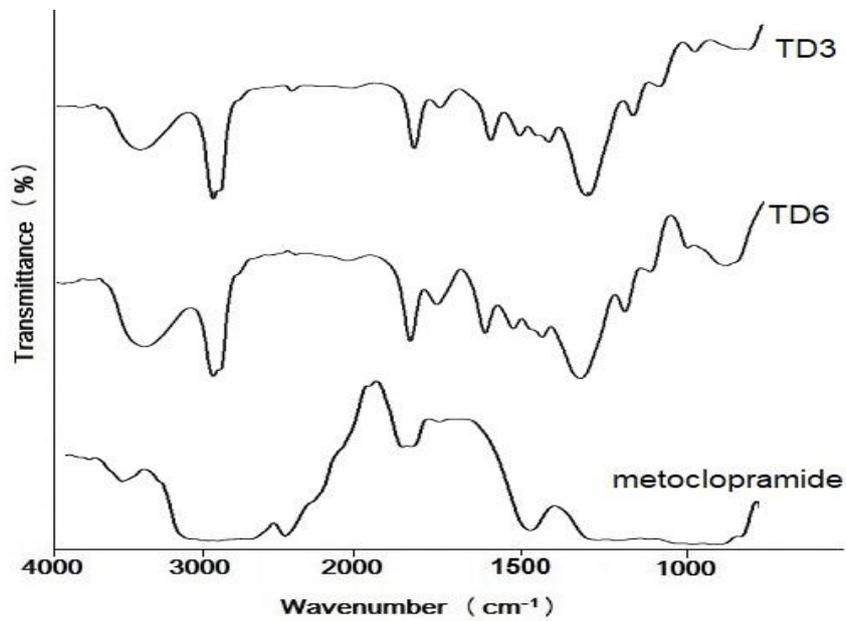
Batches	Weight (g)	Thickness (mm)	Folding endurance (n)	Moisture content (%)	Moisture uptake (%)	Drug content (%)
TD0	0.22 ± 0.00	0.71 ± 0.01	300 ± 0.57	2 ± 0.00	110 ± 0.005	98 ± 0.00
TD1	0.21 ± 0.02	0.51 ± 0.28	307 ± 1.15	21 ± 0.01	24 ± 0.000	88 ± 0.00
TD2	0.21 ± 0.02	0.70 ± 0.00	310 ± 0.00	32 ± 0.00	58 ± 0.005	88 ± 1.15
TD3	0.22 ± 0.02	0.70 ± 0.00	305 ± 1.15	53 ± 0.00	20 ± 0.000	86 ± 0.00
TD4	0.21 ± 0.02	0.53 ± 0.02	303 ± 2.00	5.0 ± 0.03	15 ± 0.000	98 ± 0.00
TD5	0.21 ± 0.02	0.70 ± 0.00	301 ± 40.10	8.0 ± 0.01	10 ± 0.190	98 ± 0.00
TD6	0.21 ± 0.02	0.56 ± 0.02	302 ± 1.10	10 ± 0.02	26 ± 0.000	99 ± 0.00

Values ± standard deviation

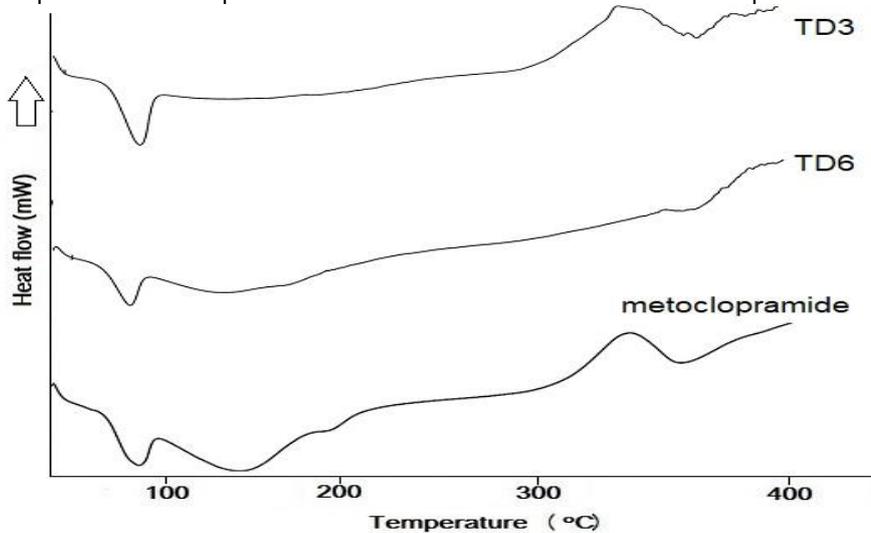
**Figure 1:** Bioadhesion values of the different batches of the metoclopramide transdermal patches.



**Figure 2:** *Ex vivo* drug release of metoclopramide from the different batches of the metoclopramide transdermal patches.



**Figure 3:** FTIR spectra of metoclopramide and some of the formulated transdermal patches.



**Figure 4:** DSC thermograms of metoclopramide and some of the formulated transdermal patches.

patches, the non-significant variations noticed in the patches' weights may be an indication of a uniformly dispersed formulation excipients [20] while the significant variations in patch thickness among the batches may be the result of variable viscosities of the oil and shea butter. Also, the high folding endurance exhibited by the patches implies that they would not easily break and would maintain their integrity when applied on skin and during skin folding over prolonged use [20,21].

In addition, the percentage moisture content or the amount of moisture lost by the patches depended on the formulation, with patches containing eucalyptus oil showing a higher moisture loss when compared to patches with shea butter. This result could have a 2-fold implication, on one hand, these patches would be supple after formulation hence their higher folding endurance and on the other hand, they could also lose their suppleness easily when in use due to drying as their eucalyptus oil content could be lost due to its volatile nature. A reasonable amount of moisture in the patch would prevent the patch from drying and ensures it remains supple and smooth during use. Moreover, the eucalyptus oil batches of patches (TD1-TD3) showed higher moisture uptake when compared with the shea butter batches (TD4-TD6) where the uptake was significantly retarded. These levels of moisture uptake showed no pattern in such a way as to link them to the moisture contents or the amounts of eucalyptus oil or shea butter in the patches but to infer that the patches may have achieved varied levels of dryness in their drying process. The very high moisture uptake of the control (TD0) batch of patches could be due to the hygroscopic property of HPMC which enabled moisture absorption from its surroundings.

Furthermore, the variation in drug content shown by the patches is not exactly known except to assume that during drying, the metoclopramide may have partitioned to varying degree due to differences in viscosities of the cast solutions as well as the proportion of the oily phase to the aqueous phase in the formulation. Metoclopramide being freely soluble in water [14], may have partitioned more in the aqueous phase resulting in an uneven distribution of the drug in the casted patch during drying. The result actually showed that patches containing shea butter had above 98 % drug content due to stable viscosity during casting while eucalyptus oil patches lost over 10 % of their metoclopramide content. Besides their drug contents been generally uniform, the loss is actually unexpected and the exact reason cannot be

immediately explained though some authors have reported similar results [21,22].

The reduction in the bioadhesion of the patches with the increase in the amounts of eucalyptus oil and shea butter is similar to a previous work where arachis and eucalyptus oils as permeation enhancer in insulin patches caused a reduction in bioadhesive strength of the patches with their increasing concentrations [7]. This reduction was due to the fact that oils have lubricating effect and interferes negatively with surface bonding of bioadhesive molecules. Patches containing eucalyptus oil showed higher bioadhesive strength over those of shea butter oil. Additionally, the viscosity of the oil and shea butter contributed to the thickness of the patches and in turn reduced the bioadhesive strength of the patches [23]. Eucalyptus oil being a less viscous oil would produce patches with higher bioadhesive strength than those patches containing shea butter. TD0 which is the control patch (containing only HPMC and metoclopramide) showed the highest adhesive strength.

The drug release results of the patches showed an enhanced drug flux across the rat skin that was significant for both the eucalyptus oil and shea butter patches when compared with the control patches. This being the case, there were insignificant variations ( $p > 0.05$ ) in drug permeation among patches containing 30 and 20 % of the oil or shea butter. There was however, a significant difference ( $p < 0.05$ ) among the 30 and 10 % concentrations of the eucalyptus oil and shea butter. Permeation followed the rank order: 30 % > 20 % > 10 % concentrations. The result of permeation of metoclopramide between eucalyptus oil and shea butter was significantly different ( $p < 0.05$ ) as shea butter gave a better permeation than eucalyptus oil. This difference in permeation maybe attributable to the varying viscosities and volatility between eucalyptus oil and shea butter. Highly viscous oil will result in the formation of thicker patch and increase the retention of metoclopramide in the patch and in turn decrease the release rate. Shea butter is non-volatile with a viscosity of 83.92 cStat 40 °C [9]. The high viscosity of shea butter indicates that it contains more solid fats and will have a high resistance to flow. While eucalyptus oil with a lower viscosity of 30.00 cStat 40 °C [24] and having a lesser resistant to flow, achieved a lesser permeation of the drug through the treated rat skin. This could be due to the fact that eucalyptus oil is more likely to evaporate rather than diffuse and hence, instead of driving the drug through the skin,

it would tend to pull the drug away from the skin as the skin temperature warms up the patch.

## CONCLUSION

Transdermal patches of metoclopramide formulated using eucalyptus oil and shea butter as permeation enhancers exhibited comparable physicochemical and bioadhesion properties as well as in their ability to enhance drug release from the transdermal formulations. However, patches produced with shea butter showed better physicochemical and permeation enhancing properties against those produced with eucalyptus oil which showed better bioadhesion.

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