Original Article:

Evaluation of Transdermal Formulations of Metoclopramide Prepared Using Arachis Oil and Liquid Paraffin as Permeation Enhancers

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ABSTRACT

Background: The study aimed to evaluate the effect of arachis oil and liquid paraffin on metoclopramide release from transdermal films.

Objectives: Batches of metoclopramide films were prepared with hydroxypropyl methyl cellulose (HPMC), arachis oil or liquid paraffin and Tween 80 as plasticizer. The films were evaluated for their physiochemical properties, *in vitro* and *ex vivo* drug release and drug release kinetics. Drug-excipient interactions were investigated using Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared (FTIR) spectroscopy.

Methods: The transdermal films had a weight range of 0.22-0.24 g, folding endurance of 300-306, percentage moisture content and uptake of 2%-10% and 19%-110%, respectively and drug content of 98%-104%. There was similar condition *in vitro* release profile for the films but their *ex vivo* profiles exhibited variable drug release with the P3 (30% arachis oil) giving the highest drug (almost 100%) release.

Results: The release kinetics of metoclopramide followed the first order and Korsemeyer-Peppas models more closely as seen in their correlation coefficients (R^2) of 0.9832 and 0.9560, respectively. Drug-excipient compatibility studies showed no interactions between excipients and metoclopramide.

Conclusion: The formulated transdermal films showed controlled drug release over a period of 12 h. Arachis oil and liquid paraffin showed similar permeation enhancing ability. These enhanced permeation properties of the films could be helpful in the development of alternative route for metoclopramide administration in the management of emesis with improved patient acceptance.

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1. Introductionn

Metoclopramide is a widely used and effective antiemetic in the management of nausea and vomiting (emesis), which is a major problem in cases of the early stage of pregnancy, motion sickness, and as a side effect associated with cancer chemotherapy [1]. The oral formulation of metoclopramide has variable bioavailability (32%-100%) because of its hepatic first-pass metabolism [2]. Administration through the oral route can be irritating and induce vomiting before it can even be absorbed. Furthermore, parenteral and rectal routes are less acceptable and result in low patient acceptance [3]. Conventional dosage forms of metoclopramide produce adverse effects like restlessness, drowsiness, fatigue, and extrapyramidal side effects at high doses [4].

Therefore, formulating metoclopramide film for transdermal delivery will be an acceptable and alternative route to the oral and parenteral routes. A major challenge in the transdermal delivery of metoclopramide is the diffusion of the drug through the stratum corneum of the skin which is the rate-limiting barrier in transdermal permeation [5]. Several approaches have been used to alter these barrier properties, one of which is the use of permeation enhancers (PEs) through possible channels for percutaneous penetration of drug molecules [6].

Lipid excipients have gained interest in the delivery of drugs because of their ability to improve solubility, absorption, and consequently bioavailability of the drug [7]. Many lipids are amphiphilic having a lipophilic portion (fatty acid) and a hydrophilic portion. Oils, a subgroup of triglyceride lipids, are the most commonly used lipid excipients. Natural oils such as vegetable oils and mineral oils are safe to use, available, non-allergic, and compatible with drugs and excipients [8]. Arachis oil is a natural vegetable oil locally known as peanut oil or groundnut oil. It is limpid, light-colored oil that has a delicate flavor and scent. It has a high unsaturated fatty acid content which includes oleic acid (46.8% as olein), linoleic acid (33.4% as linolein), and palmitic acid (10.0% as palmi% tin) [9]. Arachis oil can be directly applied to the skin or be used in pharmaceutical formulation since it is easily absorbed into the skin. It is also used as a solvent in drug formulation for sustained release in injections and vehicles for topical preparation. An earlier study using arachis oil at different concentrations as a penetration enhancer showed that it improved diffusion of insulin across treated rat skin [10].

Liquid paraffin is a mixture of highly refined paraffinic and naphthenic liquid hydrocarbons obtained from mineral crude oils. It is a transparent, colorless, almost odorless oily liquid. It is insoluble in water, sparingly soluble in ethanol, and soluble in ether. Some authors have reported that liquid paraffin can enhance the percutaneous penetration of glycerol by synergistically improving tissue optical transmittance on the skin [11, 12].

This study aimed to develop a transdermal formulation of metoclopramide using different ratios of natural and mineral oils and to study the modulating effect of the different oils on the *in vitro* and *ex vivo* release of metoclopramide from transdermal films.

2. Materials and Methods

Study materials

Study materials are hydroxypropyl methylcellulose (HPMC, E5 LV) and polysorbate 80 (Tween 80) (Sigma Aldrich, Germany), metoclopramide injection (Wuhan Grand Pharmaceuticals, China), liquid paraffin (New Healthway, Nigeria), and arachis oil (PZ Cussons, Nigeria).

Study Methods

Preparation of transdermal film

Using the formula in Table 1, the estimated amounts of the HPMC, polysorbate 80 (Tween 80), and oils were used to cast various batches of the films onto Petri dishes using the solvent casting method [13]. For each batch, an aqueous dispersion of HPMC powder was prepared in 200 mL heated distilled water in a beaker and left for an hour for complete swelling of the polymer. A dispersion containing the amount of metoclopramide and the volume of polysorbate 80 in 200 mL of distilled water and another dispersion containing the arachis oil or liquid paraffin in 100 mL of distilled water, were both added to the aqueous dispersion of HPMC and mixed vigorously using a hot plate magnetic mixer at 400 rpm until a uniform dispersion was gotten. The resulting dispersion was cast on a glass Petri dish and air dried at room temperature for 48 h. Thereafter, the air-dried films were removed from the petri dish, cut into a 2×1 cm^2 film size to contain the desired dose of 5 mg/film, and stored in-between aluminum foils as a backing layer to retain their flatness in an airtight container.

Table 1. Formula for preparation of metoclopramide transdermal films

Batches	Metoclopramide (mg)	Tween 80 (ml)	Hydroxypropyl Methyl-cellulose % (g)	Arachis oil % (mL)	Liquid paraffin % (mL)
P0	95	2.0	100 (2.0)	-	-
P1	95	2.0	90 (1.8)	10 (0.2)	-
P2	95	2.0	80 (1.6)	20 (0.4)	-
P3	95	2.0	70 (1.4)	30 (0.6)	-
P4	95	2.0	90 (1.8)	-	10 (0.2)
P5	95	2.0	80 (1.6)	-	20 (0.4)
P6	95	2.0	70 (1.4)	-	30 (0.6)

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Evaluation of metoclopramide films

Physicochemical properties

Weight variation and thickness

Ten films of 2×1 cm^2 from each batch were weighed individually using a digital balance and the average weight of the films was recorded. The thickness of the various films was measured using a micrometer screw gauge at different spots on the surface of the film and the average thickness was recorded.

Folding endurance

This was done by repeated folding and opening of the films at the same point until breakage or crack occurred. The results were expressed as the number of repeated folds before breakage [14].

Percentage of moisture content

Three films from the various batches were individually weighed and placed in a desiccator containing activated silica gel as a desiccant. The films 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 a difference between initial and final weight and expressed as a percentage [15].

Moisture uptake

Three films from the various batches were weighed individually and kept in a desiccator containing a saturated solution of sodium chloride (74% relative humidity). After 48 h, the films were reweighed, the average weight was recorded and the moisture uptake was then calculated as a difference between initial and final weight and expressed as a percentage [15].

Drug content

A film from each batch was cut into pieces and placed in a 50-mL beaker containing 20 mL phosphate buffer (pH 6.8) and shaken intermittently until complete dissolution. One milliliter of this solution was then further diluted in 9 mL of phosphate buffer (pH 6.8). The solution was filtered and metoclopramide content was then determined spectrophotometrically at a maximum wavelength of 273 nm.

In vitro release studies

A film from each batch was evaluated using the USP paddle over disk dissolution apparatus prescribed for transdermal drug delivery systems [16]. The dissolution test apparatus was thermostated at 36±0.5°C and stirred at 50 rpm. The film was placed on a glass Petri dish using cyanoacrylate adhesive and was placed at the bottom of the vessel containing 500 mL of phosphate buffer pH 6.8 allowing the drug release from only the upper surface. At various time intervals of 1, 2, 3, 4, 5, and 6 h, aliquots of 5 mL of sample were withdrawn and replaced with an equal volume of the dissolution medium each time. The withdrawn samples were then filtered and analyzed spectrophotometrically at 273 nm against the blank phosphate buffer (pH 6.8). The cumulative percentage of the released drug was calculated.

In vitro release kinetics

The data obtained from *in vitro* release studies were subjected to various release models namely; zero order,

first order, Higuchi, and Korsmeyer-Peppas to obtain the drug release kinetics from films.

Ex vivo permeation studies

This study was carried out using a dissolution apparatus modified in place of Franz diffusion cell. A treated rat skin was used as the diffusion membrane. The dorsal section of a full-thickness skin of an adult albino rat that is highly vascularized was trimmed off and soaked in 5.0% NaOH for 10 min to remove the hair from the skin and thereafter defatted by soaking in acetone for 1.0 h [17]. After defatting, it was soaked in phosphate buffer (pH 6.8) overnight to equilibrate. The films were wrapped and tied firmly in a piece of the treated skin membrane to ensure adhesion throughout the experiment, forming the donor unit. The unit was introduced into the basket of a dissolution apparatus acting as the receptor compartment containing 500 mL of the dissolution medium (phosphate buffer) maintained at a temperature of 36±0.5°C. The stirrer was operated at 50 rpm and aliquots of 5 mL of sample were withdrawn from the receptor compartment at hourly intervals up to 12 h while replacing with an equal volume of the receptor medium. Withdrawn samples were then analyzed spectrophotometrically at λmax of 273 nm. Targeted flux is the amount of drug permeated per centimeter square area which is required to maintain a therapeutic level [8]. The target flux (JTarget) of a 2×1 cm film was calculated using Equation 1 [18].

(1) $JTarget = CssCLTBW/A$

Where A is the surface area of the 2×1 cm film (i.e., 3.46 cm^2 with a mean diameter of 2.1 cm), BW is the standard human body weight of 60 kg, Css is the metoclopramide concentration at the therapeutic level (0.15 µg/L) and CLT is the total clearance (0.55 L/h). The calculated target flux value for metoclopramide was 1.43 $µg/cm^2/h$.

Drug flux of a 2×1 cm film was calculated by dividing the slope of the linear portion of the *ex vivo* drug permeation curve by the area of the exposed skin surface (3.46 cm^2). The drug flux values obtained were compared to the target flux in each batch.

Compatibility studies

The physicochemical compatibility between metoclopramide and the oils used in the films was studied by using differential scanning calorimetry (Netzsch DSC 204F1 Phoenix Apparatus, GmbH, Germany) and Fourier transform infra-red (FTIR) spectroscopy (Perkin Elmer, Beaconsfield Bucks, UK). Films from the P3 and P6 batches were used for both analyses. For the DSC analysis, 5.0 mg of the crushed film was weighed, sealed in a flat-bottom aluminum pan, and heated over a temperature range of 30°C-400°C while nitrogen was used as the purge gas at a flow rate of 70 mL/min at a constantly increasing rate of 10°C/min. The thermograms obtained for metoclopramide and oils were compared. FTIR analysis was done by crushing a piece of film and then blending about 5.0 mg of the crushed film with potassium bromide (KBr) powder to give a 200 mg powder mixture. The mixture was compressed into a tablet using a hydraulic press and then scanned at an IR range of 4000-750 cm^{-1}.

Statistical analysis

All experiments were conducted at least in triplicate and the results were expressed as a Mean±SD of replicate determinations. Statistical analysis was carried

Table 2. Some physicochemical parameters of metoclopramide transdermal films

Batches	Mean±SD					
	Weight (g)	Thickness (mm)	Folding endurance (n)	Drug content (%)	Moisture content (%)	Moisture uptake (%)
P0	0.22±0.00	0.71±0.01	300±0.57	98±0.00	2±0.00	110±0.005
P1	0.23±0.00	0.53±0.05	300±0.57	98±0.00	5±0.00	27±0.000
P2	0.22±0.01	0.51±0.28	305±0.00	99±0.57	5±0.00	37±0.005
P3	0.24±0.01	0.50±0.00	301±1.15	104±0.00	10±0.00	19±0.005
P4	0.22±0.02	0.66±0.05	310±0.00	99±0.00	7±0.00	115±0.005
P5	0.23±0.02	0.58±0.10	305±3.46	98±0.00	5±0 02	45±0.005
P6	0.23±0.02	0.55±0.05	306±2.08	100±0.00	10±0.00	65±0.005

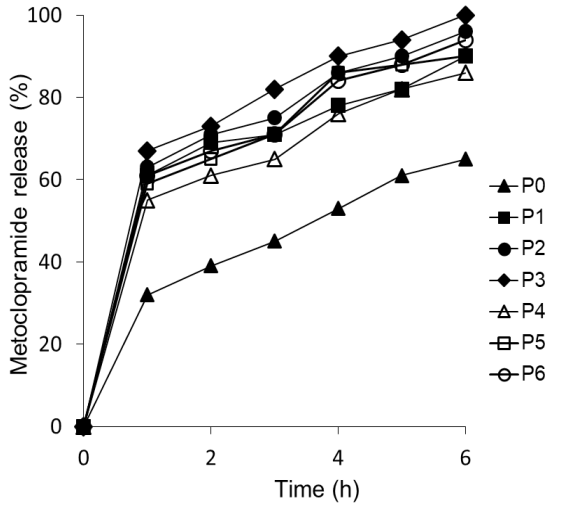

Figure 1. *In vitro* drug release of metoclopramide from the different batches of the transdermal films

out using Microsoft Excel v. 2013. Differences between means were determined by 1-way analysis of variance (ANOVA) at $P<0.05$ as significant.

3. Results

Physicochemical characterization of films

The results of the physicochemical characterization of the films are shown in Table 2. The weights and thicknesses ranged from 0.22 to 0.24 g and 0.50 to 0.71 mm, respectively. The thickness decreased, as the proportion of HPMC decreased; however, this decrease was not significantly different ($P>0.05$). Folding endurance values were high and also did not vary among the films ($P>0.05$). Drug content was uniform among all formulations and ranged from 98%-104%. The results of moisture content and uptake of the films showed variation among the batches with films of the P0 (control) and P4 showing the highest moisture uptake.

In vitro release

The *in vitro* release profiles of the various batches of the films are shown in Figure 1. Batch P0 (control) films gave the least release within 6 h when compared with the films containing arachis oil or liquid paraffin. Batch P3 (30% arachis oil) films exhibited the highest amount of drug release (100%), which was followed by P2 (20% arachis oil) and then P6 (30% liquid paraffin) films. Generally, the arachis oil films released more drugs than the liquid paraffin films within the 6 h of testing. Drug release from all the films was significantly different from that of P0 (control) films. Also, drug release increased with an increase in the concentration of arachis oil or liquid paraffin in the film.

In vitro release kinetics

The kinetic studies were used to determine the model that best represents metoclopramide release from the films. Correlation coefficients (R^2 values) are presented in Table 3 which showed that the drug release from the films seems to follow the first-order kinetic model as seen in their correlation coefficients (R^2) of 0.9253 to 0.9832 with their mechanism of drug release most consistent with the Korsmeyer-Peppas model with correlation coefficients (R^2) of 0.9248 to 0.9560. The n values obtained with the Korsmeyer-Peppas Equation (0.224 to 0.440) indicate that the drug release mechanism was by Fickian diffusion ($n<0.45$).

Ex vivo permeation studies

The results of the *ex vivo* drug permeation studies from the transdermal films are shown in Figure 2 and pre-

Table 3. Correlation coefficient (R^2) of the *in vitro* release studies

Batches	Correlation Coefficient (R^2)			
	Zero-order	First-order	Higuchi	Korsmeyer-Peppas (n)
P0	0.8861	0.9832	0.8861	0.9372 (0.440)
P1	0.6848	0.9253	0.6848	0.9383 (0.224)
P2	0.7230	0.9290	0.7230	0.9560 (0.252)
P3	0.7123	0.9740	0.7123	0.9492 (0.241)
P4	0.7545	0.9672	0.7542	0.9248 (0.284)
P5	0.7386	0.9370	0.7386	0.9369 (0.288)
P6	0.7420	0.9374	0.7420	0.9254 (0.274)

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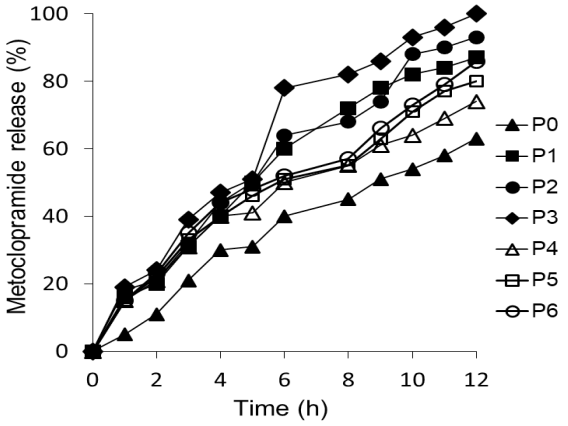

Figure 2. *Ex vivo* drug release of metoclopramide from the different batches of the transdermal films

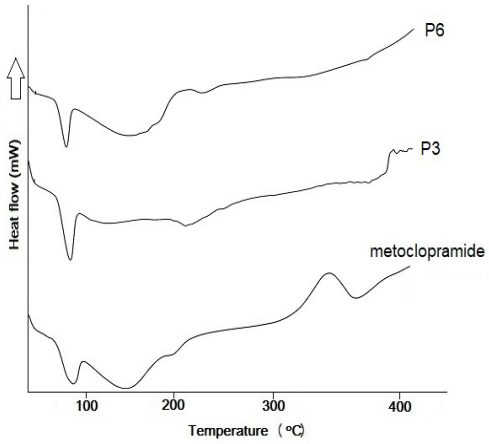

Figure 3. DSC thermograms of metoclopramide and the formulated transdermal films

sented in Table 4. The films containing varied ratios of the arachis oil and liquid paraffin increased the diffusion of metoclopramide across the treated rat skin to varying degrees within 12 h. Again, the arachis oil batches of films gave higher drug permeation/diffusion results with P3 films giving a maximum drug diffusion of 100% followed by P2 and P1 with 93% and 87% drug diffusion, respectively. Batch P6 (30% liquid paraffin) films gave the highest diffusion among the liquid paraffin films with 86% of drug diffusion across the treated rat skin. P0 (control) films gave the least diffusion with 63% of drug diffused. All the batches of films gave drug flux values ranging from 1.40 to 2.44 µg/cm^2/h (Table 4), with only P0 (control) films not meeting the targeted flux of 1.43 µg/cm^2/h.

Compatibility studies

The DSC thermogram (Figure 3) of the various films containing individual excipients showed no obvious changes when compared with the thermograms of metoclopramide. The thermogram showed an endothermic trough in the various formulations at 90°C, indicating evaporation of moisture and oils from the sample followed by a broad trough representing a mixture of constituents. There was a broad trough around 140°C-150°C, indicating the melting point of metoclopramide. The trough was broad probably because the metoclopramide was already in solution form before its incorporation into the film. There was no obvious change in the peaks and troughs indicating that the films containing the oils were all compatible with the drug.

The FTIR spectra of the films (Figure 4) show additional spectra patterns that indicate functional groups typically present in oils and polymers used in making the metoclopramide transdermal films, including the OH (3444 - 3396 cm^{-1}) and C=O (1647 - 1327 cm^{-1}) bands which were prominent. There was no observable interaction between the oils and the metoclopramide.

Table 4. A comparison of the *in vitro* drug release, *ex vivo* skin permeation, and drug flux of the metoclopramide transdermal films

Batches	Drug released (%)	Drug diffused (%)	Drug flux (µg/cm^2/h)
P0	65	63	1.40
P1	90	87	2.15
P2	96	91	2.11
P3	100	100	2.44
P4	86	83	1.92
P5	90	88	2.09
P6	94	93	2.23

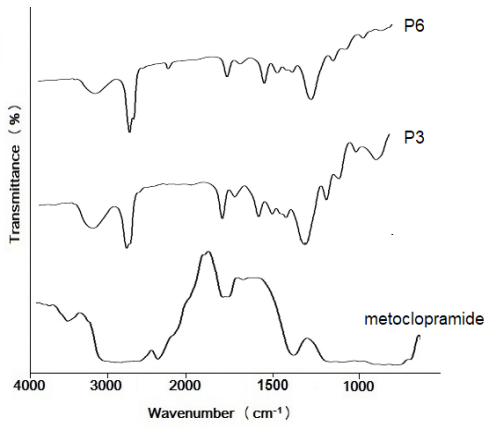

Figure 4. FTIR spectra of metoclopramide and the formulated transdermal films

4. Discussion

The permeation enhancing effect of arachis oil and liquid paraffin was investigated in metoclopramide transdermal formulations. A fundamental property that should be exhibited by the transdermal film is flexibility. Usually, the folding endurance of films is a reflection of the flexibility that was high and did not vary among the films (P>0.05) for the formulated films in this study. These high values indicate that the films would not break easily when applied on the skin and during skin folding over prolonged use. Also, when these folding endurance values are compared with the thickness of the films, it is seen the thinner films are more flexible. Natural oils have been reported to enhance the flexibility of films and patches, especially when they were uniformly dispersed in the films or patches resulting in high folding endurance values of the dosage forms [8, 16, 19]. Another vital property of films is its moisture content and uptake. Films must have a moisture content to keep it supple before use and can maintain the moisture content by uptake during. It prevents the film from drying and ensures its stability and smoothness. These properties play a key role in drug release from the transdermal films [20]. The high moisture uptake of the P0 and P4 films could be due to HPMC hygroscopicity which enables it to absorb moisture from the surrounding [16].

Additionally, the *in vitro* release of drug from the formulated films appears to be concentration-dependent since the increase in the concentration of either arachis oil or liquid paraffin in the formulations resulted in increased drug release. The enhanced drug release of the P3 and P6 films may be attributed to the effective emulsification of the drugs resulting from the interaction between the oils and the plasticizer. Furthermore, since metoclopramide is more soluble in the oily phase than in the aqueous phase, there may be a possible synergistic interference with differential solubility among the different solvents.

On the other hand, the *ex vivo* permeation of drugs from the films did not correspond exactly with the *in vitro* pattern of release. The enhanced or increased diffusion/permeation drug, especially with the films formulated with arachis oil (P1-P3) may have occurred due to the lipid content of the films as natural vegetable oils like arachis oil are composed mainly of fatty acids. Fatty acids are endogenous constituents of the rat skin which consists of an aliphatic hydrocarbon chain (non-polar) at one end and a carboxyl (polar) group at the other end. They are mainly those secreted by the sebaceous glands with C16-C18 carbon chains and those found in the stratum corneum with more C20 carbon chains [21, 22]. Fatty acids from natural oils (lipophilic substances) are released when these oils are metabolized within the skin and they increase the skin's permeability by disordering the ordered lipids (alkyl chains) within the skin to enhance the diffusivity and partitioning of an API across the skin barrier [23]. Therefore, formulating metoclopramide in a microemulsion system containing lipid excipients as penetration enhancers increase its permeation through the barrier layers of the skin from the aqueous phase through the oily phase and subsequently enhance bioavailability. Liquid paraffin is the mineral oil of hydrocarbon chain units that also enhance percutaneous penetration invariably employing the same mechanism as arachis oil.

5. Conclusions

Transdermal films of metoclopramide were successfully formulated using a natural (arachis oil) and mineral (liquid paraffin) oil as permeation enhancers. Films containing liquid paraffin exhibited similar permeation as those of arachis oil. Incorporating the oils into transdermal film formulation facilitated or increased diffusion of metoclopramide *in vitro* across treated rat skin.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization, Methodology: Matthew I. Arhewoh; Supervision, Data collection: Sylvester O. Eraga; Investigation, Writing – original draft: Ogochukwu A. Meko; Writing – review & editing: All authors.

Conflict of interest

The authors declared no conflict of interest.

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