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Research Article

## Development of Transdermal Patches for the Delivery of Chlorpheniramine in Infants using Hypromellose and Cassava Starch Composite Polymers

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### ABSTRACT

**Background:** Chlorpheniramine is an antihistamine that is used in the treatment of rhinitis and other allergies. **Objectives:** The objectives of this research was to develop and evaluate transdermal patches for improved delivery of chlorpheniramine in infants using hypromellose and cassava starch composite polymers. **Methods:** Chlorpheniramine transdermal patches were formulated by solvent casting method using varying amounts of hypromellose (hydroxypropyl methylcellulose), cassava starch and polyethylene glycol 4000. The formulated transdermal patches were characterized by Fourier Transform Infra-red Spectroscopy (FT-IR), folding endurance, elongation breaking test, percentage moisture uptake/loss and *ex vivo* permeation studies. **Results:** The spectra showed no chemical interaction between the ingredients. The transdermal patches showed elastic qualities and high folding endurance. Patches with consistently high moisture uptake (around 40%) were observed to contain high concentration of cassava starch while those with higher amounts of HPMC lost more water (around 35%). The *ex vivo* study showed efficient permeation and flux for the target purpose. **Conclusion:** Transdermal patches may be used to deliver low dose chlorpheniramine drug through the skin possibly soft and thin infant skin.

**Keywords:** Transdermal; permeation; flux; allergy; chlorpheniramine

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### INTRODUCTION

Chlorpheniramine is a first generation, oral sedating antihistamine (H1-blocker) of the alkylamine class used in the treatment of rhinitis and other allergies. It is an anticholinergic antihistamine. The half-life in children is around 13 h <sup>1</sup>, whereas in adults it is approximately 20 h and is mainly eliminated after metabolism to monodesmethyl and didesmethyl compounds <sup>2</sup>. The drug is largely inactivated in the liver and the metabolites excreted in the urine. The continuous treatment of infants of these allergies may require frequent administration of chlorpheniramine and transdermal administration would provide a convenient, safer and more effective route with bypass of first-pass metabolism in liver.

Transdermal drug delivery systems are self-contained, discrete dosage forms which are actually patches <sup>3</sup> that when applied to the intact skin, deliver any loaded drug through

the skin at a controlled rate to the systemic circulation <sup>4</sup>. This set-up allows a pre-calculated amount of drug to be delivered at pre-designed and reproducible rate through the skin <sup>3</sup>. Transdermal drug administration is non-invasive and therefore avoids any interference with body barrier or disruption of physiological barriers such as the skin. Influx of drug into the human blood system can be promptly interrupted simply by removal of the patch if toxicity is observed in any form such as reactions or discomfort. This mode of drug administration improves compliance.

Chlorpheniramine is a low dose drug and the skin of infants is sufficiently tender, thin and weak to encourage passage of low dose drugs which explains the rationale for engaging in this study.

The objective of this research is to prepare, optimize and characterize transdermal patches for the delivery of

chlorpheniramine in infants using hypromellose and cassava starch composite polymers.

## MATERIALS AND METHODS

### Materials

Chlorpheniramine (Juhel, Nigeria), HPMC (Qualikems, India), Cassava starch (extracted in Pharm Tech Lab, UNN), PEG 4000, Propylene glycol, Tween 80 (Sigma Aldrich, USA).

### Methods

#### Extraction of cassava starch

Cassava starch was extracted in Pharmaceutical Technology laboratory, University of Nigeria, Nsukka. The tubers of *Manihot utilissima* (cassava) was peeled and reduced into small pieces. The reduced pieces of cassava tubers were soaked in distilled water for 48 h. After, it was washed and soaked in 0.1 M sodium metabisulphite solution for 24 h. Thereafter, the metabisulphite solution was washed off and pieces of cassava tubers ground/ blended to a pulp. The cell debris was removed by passing the slurry through a muslin cloth of 150 µm aperture sieve size, with occasional passage of water for effective filtration. The starch was then allowed to settle and the supernatant decanted. The starch was suspended in 0.1 N potassium hydroxide solution for 12 h.

The solution was washed off completely and the starch was also suspended in 0.1 N sulphuric acid solution for 12 h. The solution was effectively removed/ washed off and the settled starch washed with distilled water to remove impurities (e.g cyanide), tested for sulphates/sulphites, and dried at 40 °C for 6 h. The extracted starch was identified using established protocols.

#### Preparation of chlorpheniramine transdermal patches

Varying concentrations of HPMC, cassava starch, and PEG 4000 were employed in the formulation of chlorpheniramine transdermal patches. Chlorpheniramine, propylene glycol and Tween 80 were used as fixed amounts. For the different batches (A-H), different quantities of the materials were weighed and measured as shown in Table 1.

The cassava starch and HPMC were mixed in a 250 ml beaker dispersed in water (heated to 60°C) and stirred to obtain mucilage. It was further diluted with 20 ml of water. Propylene glycol, PEG 4000, Tween 80 and chlorpheniramine were dispersed in 10 ml of water, stirred and then added to the mucilage. The mucilage was diluted to 50 ml by making up with water, stirred and poured into a petri dish. The formulations were allowed to dry at room temperature after which they were stored for further use.

**Table 1: Formulation of different patches**

Materials	Batch A	Batch B	Batch C	Batch D	Batch E	Batch F	Batch G	Batch H
Chlorpheniramine	176mg	176mg	176mg	176mg	176mg	176mg	176mg	176mg
Cassava starch	1000mg	200mg	200mg	600mg	600mg	200mg	466.7mg	320mg
HPMC	1600mg	2400mg	1600mg	2000mg	1600mg	2000mg	1866.7mg	2040mg
PEG 4000	200mg	200mg	1000mg	200mg	600mg	600mg	466.7mg	440mg
Propylene glycol	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml
Tween 80	0.2ml	0.2ml	0.2ml	0.2ml	0.2ml	0.2ml	0.2ml	0.2ml

### Characterization of transdermal patches

#### Fourier transform infrared spectroscopy (FT-IR)

FT-IR was used to investigate any chemical interaction between chlorpheniramine maleate and transdermal patch excipients. Sufficient quantities of pure chlorpheniramine maleate, HPMC, cassava starch, polyethylene glycol 4000 and the formulated transdermal patches were scanned over a wavelength range of 4000 to 650 cm<sup>-1</sup> at a resolution of 4cm<sup>-1</sup> in a FT-IR instrument (Agilent Technologies, USA). The system was operated in the transmission mode. Samples were placed on the sample stage and 100 N force applied for scanning.

#### Physical appearance and properties

All the formulated patches were inspected for clarity, colour, and smoothness. Also other organoleptic properties such as odour was also observed.

#### Folding endurance and percentage elongation break test

Folding endurance of patches/ films was determined manually by folding a 1cm<sup>2</sup> strip of each patch repeatedly at

the same place on the patch until a breaking point is reached.

The number of times that the patch was folded at the same place without breaking or cracking was taken as the value for the folding endurance.

The percentage elongation break was determined by recording the length just before the break point, the percentage elongation can be determined from Equation 1:

$$\text{Elongation \%} = \frac{L_1 - L_2}{L_2} \times 100 \text{-----}1$$

Where L<sub>1</sub> and L<sub>2</sub> are the final and initial lengths of each strip.

#### Percentage moisture uptake and loss of patches

The percentage moisture uptake of the patches was determined using static methods involving saturated salt solutions. For moisture uptake, weighed patches were placed in desiccators containing 100 ml of saturated solution of potassium chloride (84% relative humidity RH). At 24 h intervals for 4 days, the patches were removed and weighed.

The percentage moisture uptake was calculated as one hundred times the ratios of the difference between final and

initial weights to the initial weights of the patches (Equation 2):

$$\text{Percentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100 \text{ --- 2}$$

For percentage moisture loss, the weighed patch samples were kept in a desiccator containing 20g of anhydrous calcium chloride. At 24 h intervals for 4 days, the patches were removed and weighed repeatedly. The percentage moisture loss was calculated from the difference between initial and final weight with respect to initial weight as presented in Equation 3:

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100 \text{ ---- 3}$$

**Ex vivo skin permeation studies**

Ex vivo skin permeation studies was performed using a magnetic stirrer-beaker assembly. The patches were sandwiched between two layers of the excised skin while sealing the edges of the layers. The skin and the sandwiched patch were placed in a cylindrical basket which was suspended in a beaker containing 100ml of phosphate buffer saline (pH 7.4). The assembly was fixed in a magnetic stirrer apparatus and the receptor medium continuously stirred using magnetic beads at 50 rpm, while the temperature was maintained at 37± 1°C. Samples were withdrawn at 1 h intervals for 5 h and analyzed for drug content using spectrophotometer at 252 nm. The medium was replenished with equal volume of PBS, pH 7.4, after each sample withdrawal. The amount of drug permeated per square centimeter of patches was plotted against time.

The permeation data was analyzed by determining the flux and permeability coefficient of the drug. The flux (µg cm<sup>-2</sup> h<sup>-1</sup>) of chlorpheniramine maleate was calculated from the slope of the plot of the cumulative amount of chlorpheniramine permeated per cm<sup>2</sup> of skin at steady state

against time using linear regression analysis. The steady-state flux (J) was determined from the relationship in Equation 4:

$$J = \frac{dQ}{A dt} (\mu\text{g} / \text{cm}^2 \text{ h}) \text{----- 4}$$

Where Q indicates the quantities of substances crossing the rat skin, A is the area of the rat skin exposed and t is the time of exposure.

The permeability coefficients are obtained from the steady-state flux values using Equation 5:

$$P = J / C_0 (\text{cm} \cdot \text{h}^{-1}) \text{-----5}$$

Where P is the permeability coefficient, C<sub>0</sub> is the initial drug concentration in the donor compartment and J represents the steady-state flux obtained from Equation 4. C<sub>0</sub> is the concentration of drug in the patch.

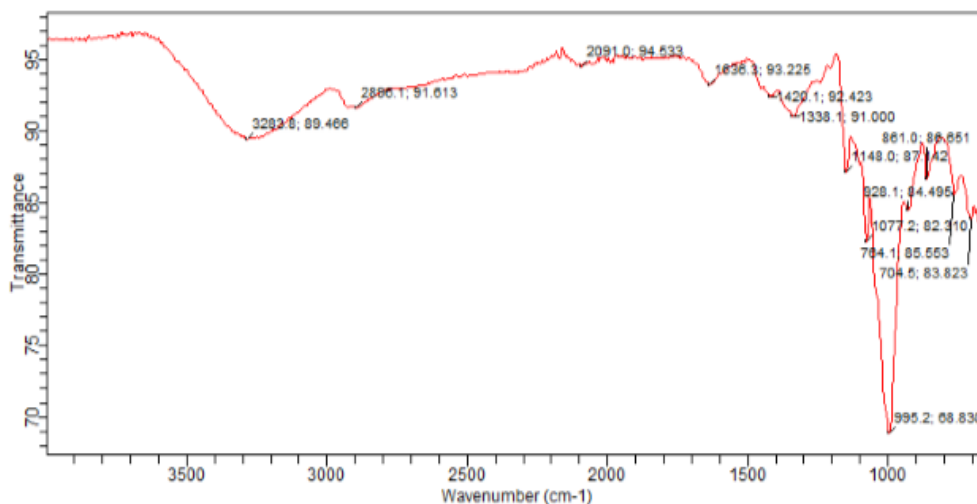
**RESULTS AND DISCUSSION**

**Organoleptic properties of the transdermal patches**

The patches were smooth, opaque and odourless. The patches possess desirable physical attributes which would facilitate its general acceptance and use.

**Fourier transform infrared spectroscopy (FT-IR)**

The FT-IR (Figs. 1-6) showed that there was no drug-excipient interaction since all the bands in the spectra represented functional groups in the individual component. The FT-IR spectra of the components showed methyl, hydroxyl and ether bond stretching while amine bond stretch was also observed for chlorpheniramine. The spectra of formulated patches were also seen to have the bands representing these functional group.



**Figure 1: FT-IR Spectra for Cassava Starch**

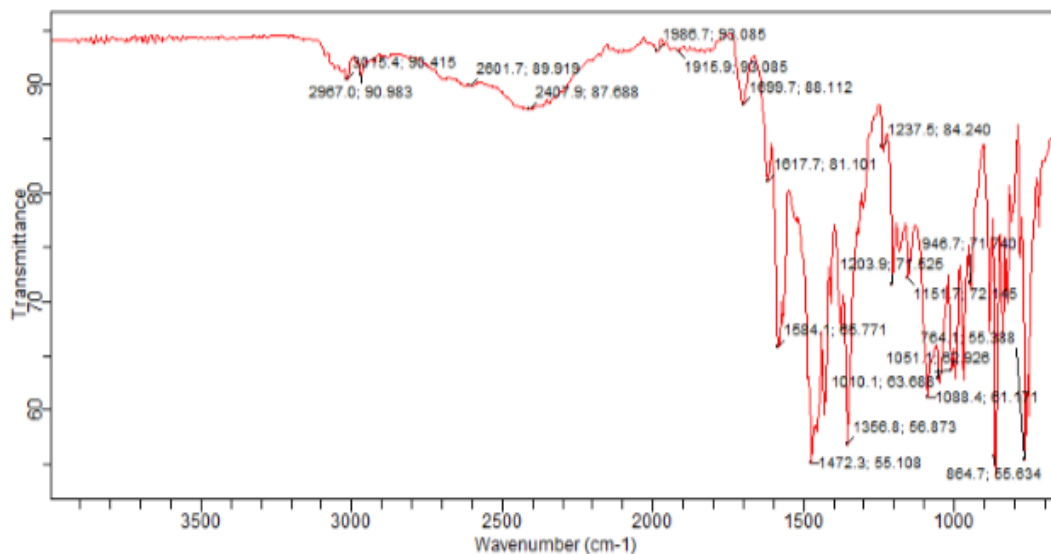


Figure 2: FT-IR Spectra for Chlorpheniramine

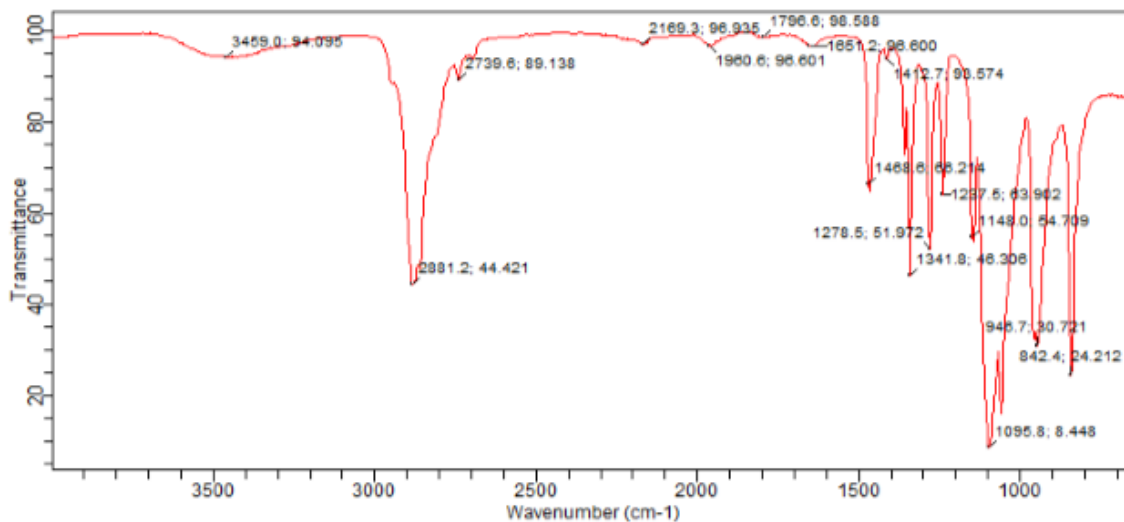


Figure 3: FT-IR Spectra for PEG 4000

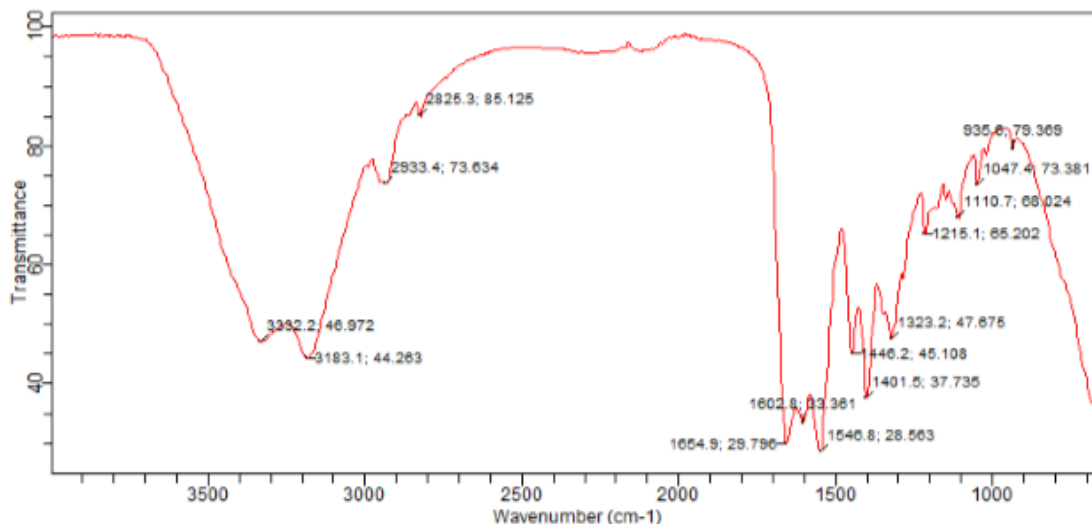


Figure 4: FT-IR Spectra for HPMC

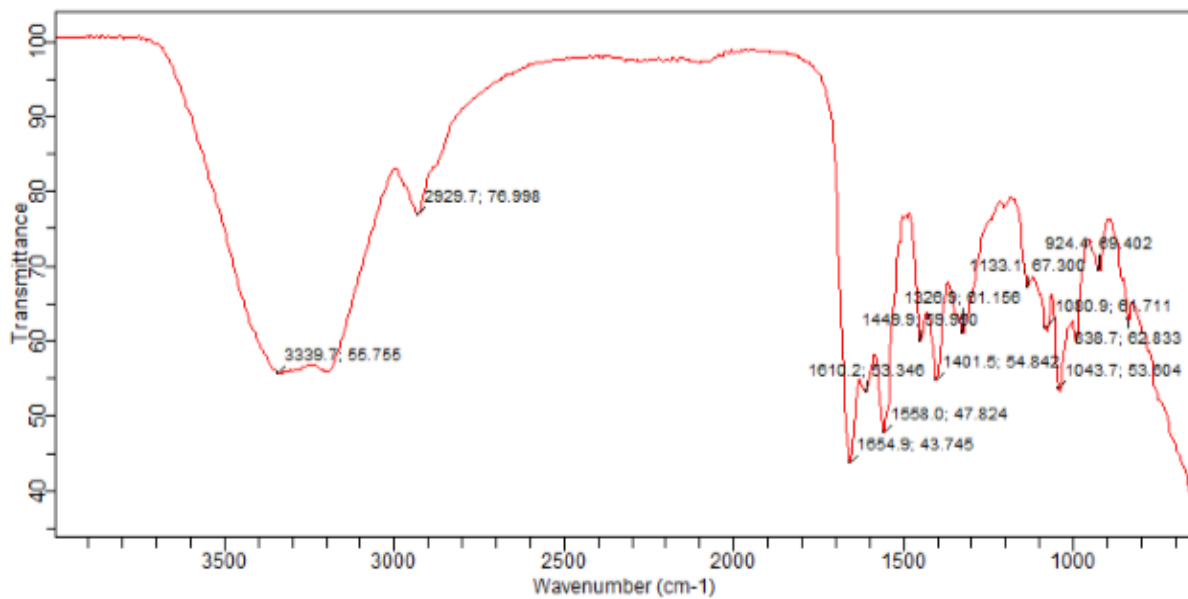


Figure 5: FT-IR Spectra for Batch A

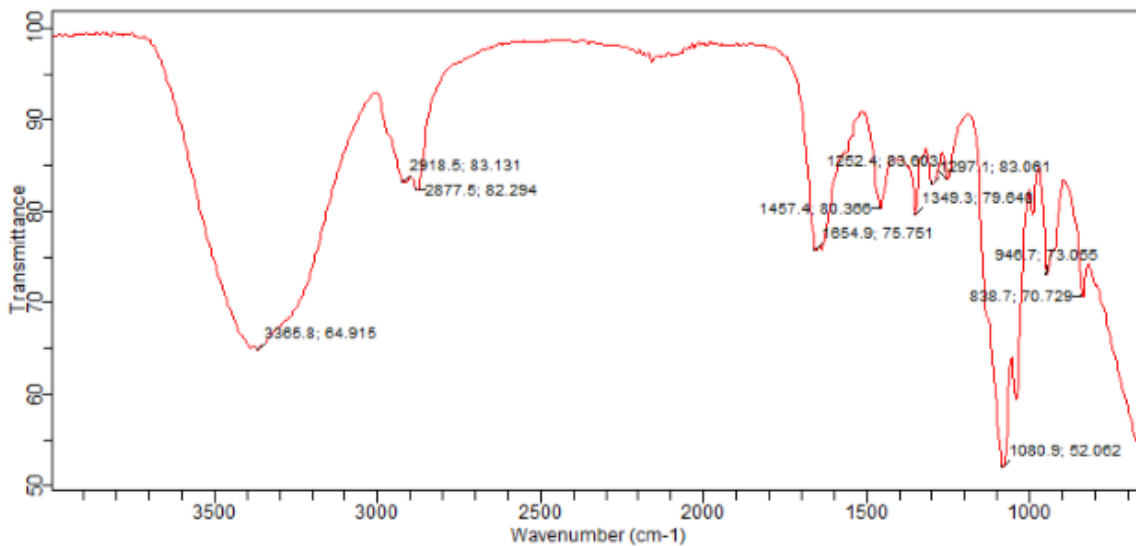


Figure 6: FT-IR Spectra for Batch F

**Folding endurance and breaking elongation**

The folding endurance of the patches were determined with patches C, E, F and G having the highest folding endurance of > 500 and patch A showing the least folding endurance of 89. Batches C, E, F and G have higher PEG concentration. This shows that differences in concentration of the constituents can affect the final mechanical property of the product. The combined effect of HPMC as film-former and PEG as plasticizer may have facilitated this flexibility attribute. Hydrophilic compounds such as polyethylene glycol has been used as plasticizers in starch-based films to improve the physico-mechanical and barrier properties of these products. The brittleness and rigidity of mixtures containing starch (after storage), usually facilitated by recrystallization of starch molecules, causes a major problem <sup>5</sup>. The biodegradable PEG plasticizer may have occupied intermolecular spaces between polymer chains, changed the 3D-molecular organization, reduced the energy required for

molecular motion and improved hydrogen bonding between chains. The results of folding endurance are presented in Table 2. The percentage elongation break test measures the ability of the formulated patches to withstand the mechanical stress of pull. The formulated patches (A-H) all showed elasticity on elongation.

**Percentage Moisture Uptake and Loss**

The percentage moisture uptake (Fig 7) with time (in days) of the formulated patches showed that patch A had the highest uptake and patch B had the least moisture uptake. Patch A with high concentration of cassava starch absorbed more moisture than other patches while batches D and B with high amounts of HPMC showed low moisture uptake probably because the HPMC had already entrapped and bonded relatively large quantities of water during production inhibiting further attraction of moisture. Moisture content would affect properties such as adhesion

and stability (especially since moisture supports microbial growth which causes degradation). Physical integrity of the product would also be affected.

For moisture loss (Fig 8), patches B, D, F and H with higher HPMC concentration showed higher moisture losses. This is because it was relatively easier for these batches to lose water under dry atmosphere than to absorb more under high relative humidity.

Percentage moisture uptake and loss were mostly around 0-40% and 15-45%, respectively. The nature and strength of bonding of all the constituents in the transdermal patches or films would affect the rate and extent of drug release from these automated devices.

Table 2: Folding endurance of the transdermal patches

Batch	Folding Endurance
A	89
B	230
C	>500
D	100
E	>500
F	>500
G	>500
H	200

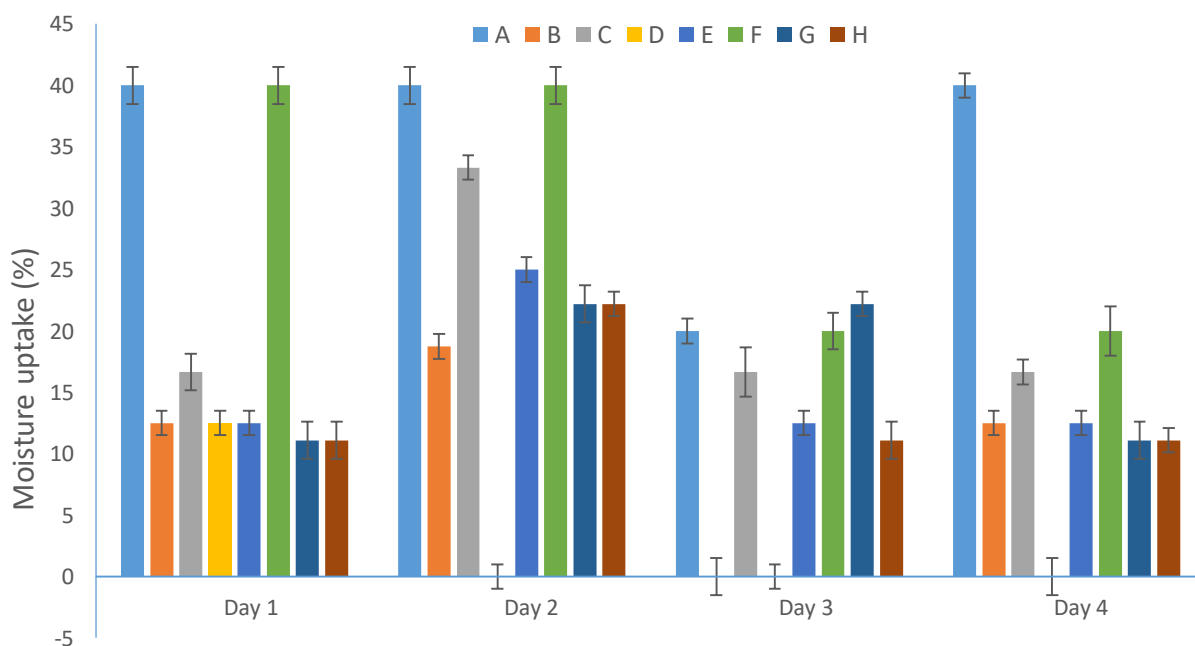


Figure 7: Moisture uptake profile of patches

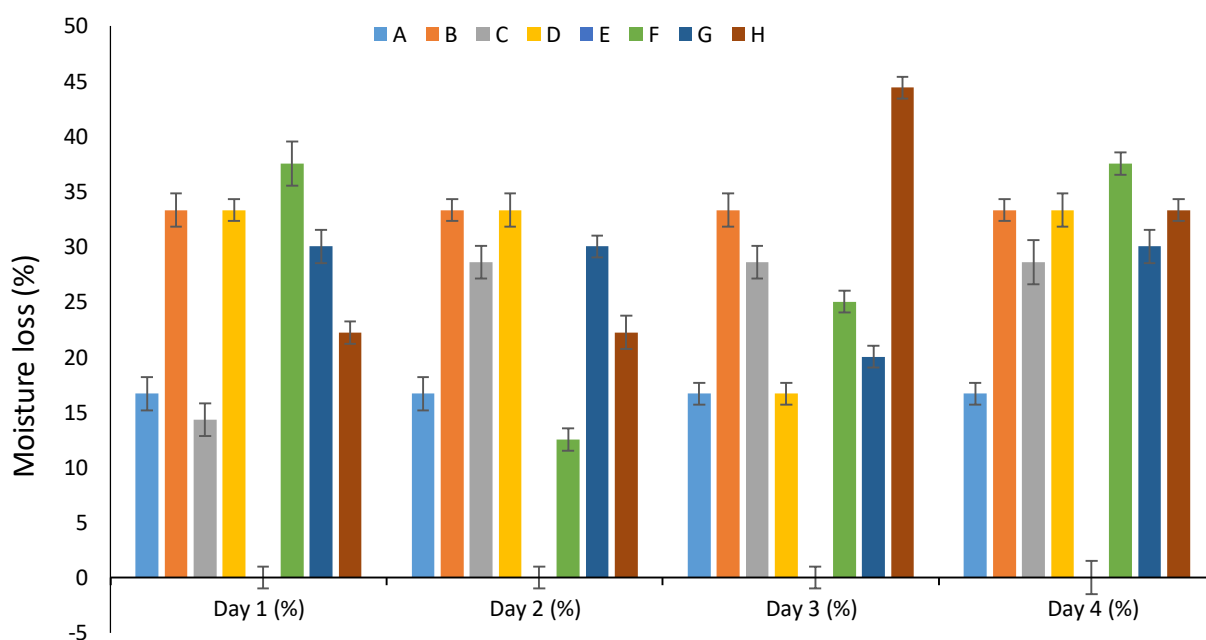


Figure 8: Moisture loss profile of transdermal patches



**Ex vivo Permeation Studies**

From the results obtained (Fig. 9), batch G showed the highest chlorpheniramine permeation through the excised rat skin. This batch is at the centre point of the design of experiment and contains the variable components as follows; cassava starch 0.47g, HPMC 1.87g and PEG 4000 0.47g. This shows the need for a balance of these components and an optimal mixture is required for maximum permeation of chlorpheniramine. Batch E showed the lowest chlorpheniramine permeation and independent variables present are cassava starch 0.6g, HPMC 1.6g and PEG 4000 0.6g. The result showed that improved permeation may be achieved if the difference between HPMC and either or both of cassava starch or/and PEG 4000 is more than 1g or a factor of 2.67. Most of the films showed a sustained, steady release and permeation of chlorpheniramine. The use of HPMC created a network that is highly hydrophilic allowing drug release. The responses obtained showed that combinations around the centre point of the centroid design space produced films with improved drug release and permeation. It has been typically observed that addition of hydrophilic component to an insoluble film-former usually improves the drug release rate <sup>6</sup>. Usually the dissolution of the aqueous soluble fraction of the film or patch facilitate drug release and permeation and may create channels or pores which decrease mean diffusion path length of the drug molecule being released into dissolution medium <sup>7</sup>.

Batches B and D with relatively high HPMC and low PEG showed a rising permeation profile probably because the

lower amount of plasticizer allowed gradually increasing release and permeation. The transdermal patches exhibited controlled drug delivery for the release and permeation of low dose of chlorpheniramine through the excised rat skin over a prolonged period of time. Furthermore the metered dose released over time showed that similar transdermal profile can be achieved for infant dose.

Flux was obtained as slope of linear relationship between amount of drug permeated per unit surface area and time. The flux and permeability coefficients are shown in Table 3.

The range of these important permeation parameters are as follows; Flux was 7.40-15.93  $\mu\text{g}/\text{cm}^2\text{h}$  and permeability coefficient was 0.000561-0.001207  $\text{cm}/\text{h}$ . These data reflect the possibility of applying the formulation for tailored infant doses. The unique nature of the modified *ex vivo* study with film/patch sandwiched between skin surfaces allowed diffusion of drug to occur from the two sides of the film/patch with increased initial drug release. The values of the steady state flux or rate of drug permeation showed that the transdermal system may be valuable in minimizing the sedating effect of the drug by only providing small gradual increments in systemic drug concentrations. The presence of polysorbates in the formulation enhances drug permeation by opening epidermal pores and tight junctions. Some surface-active agents have been shown to affect tight junction permeability <sup>8</sup>. Previous studies have shown that mixtures of hydrophilic polymers and cassava starch can form suitable film-formers for improved transdermal drug delivery <sup>9</sup> and HPMC have been effectively used to formulate transdermal films of low dose drugs <sup>9,10</sup>.

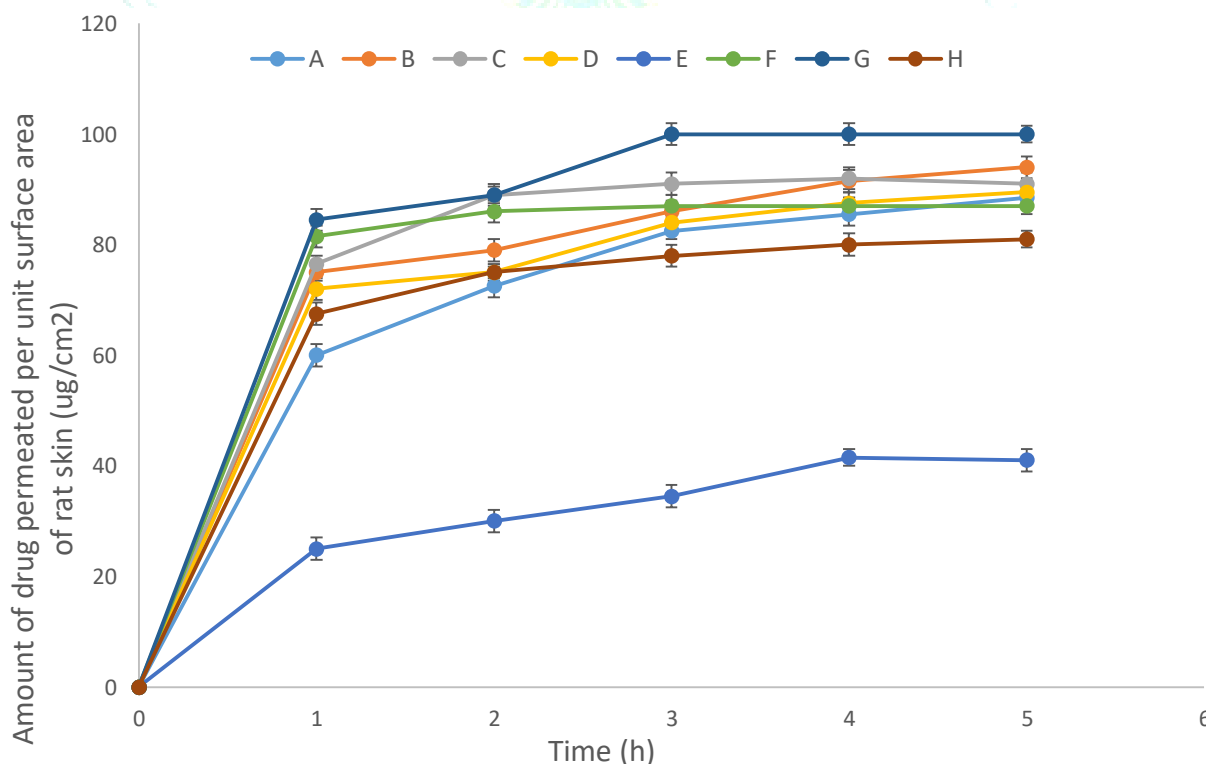


Figure 9: Chlorpheniramine permeation profile

**Table 3: Flux and Permeability Coefficient values for chlorpheniramine transdermal films**

Batches	Flux ( $\mu\text{g}/\text{cm}^2\text{h}$ )	Permeability coefficient (cm/h)
A	15.11	0.001145
B	15.04	0.001139
C	14.39	0.001090
D	14.37	0.001089
E	7.40	0.000561
F	12.93	0.000980
G	15.93	0.001207
H	12.73	0.000964

## CONCLUSION

The transdermal route has been shown to be effective, non-invasive means for the administration of Chlorpheniramine in allergy-related conditions. Hypromellose and cassava starch function effectively as film formers for the formulation of the transdermal patches. Different combinations of materials produce patches with varied physical, mechanical and drug permeation properties. Transdermal patches can be effectively used to deliver controlled doses of chlorpheniramine through the skin for systemic actions for prolonged duration and may be useful in Paediatric Medicine.

## Conflict of Interest

The authors declare that they have no conflict of interest

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