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## Permeability Enhancement Study of Azithromycin: Effect of Co-Solvents and Surfactants

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**Abstract** Azithromycin an antibiotic drug has a half-life of 50-60 hours and a bioavailability of 37-42 %, it undergoes appreciable first pass metabolism, has very poor aqueous solubility with an expected poor skin permeability. The aim of present work was to evaluate the effect of permeability enhancers: Tween 80, Tween 20, Sodium lauryl sulphate, propylene glycol and polyethylene glycol on the drug permeability profile using Franz diffusion glass cell. The flux and enhancement ratio calculation of azithromycin were studied. The results indicated that the steady state flux ( $J_{ss}$ ) increased linearly with increasing donor (enhancer) concentration. The observed steady state flux value was higher with 4 % sodium lauryl sulphate (27.30  $\mu\text{g}/\text{cm}/\text{hr}$ ) and least for 4% Tween 80 and aqueous suspension of azithromycin (control). Skin permeability of azithromycin was well enhanced in the presence of co-solvents and surfactants.

**Keywords** azithromycin; permeability enhancers; flux, bioavailability

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### Introduction

Over the years, the pharmaceutical technologists had been battling with some serious drug delivery problems including aqueous solubility [1-4] and skin permeability of drugs [5]. A recent development is that transdermal route has become one of the most interesting and innovative focus for research in drug delivery, though the skin barrier property had made it difficult for some transdermally delivered agents especially polar none-aqueous soluble drugs including azithromycin [6]. The skin penetration enhancement technique has been used to promote drug diffusion through the stratum corneum and epidermis [7] and this is achieved by the use of penetration enhancers [8-10]. The penetration enhancers are usually surfactants, and co-surfactants added to formulations to solubilise lipophilic active principles. They have the potential to alter lipid integrity within the stratum corneum [11]. These enhancers are known to disrupt the skin barrier [12]. Permeation enhancers include lyophilic solvents such as propylene glycol, polyethylene glycol, and acetonitrile. We equally have anionic sodium lauryl sulphate as a potent penetration enhancer. The present study highlights the drug release kinetics from the rate limiting barrier (skin) as the concentration of solvents used were varied.

### Materials and Methods

Azithromycin was a gift sample from National Agency for Food and Drug Administration and Control (NAFDAC) laboratories Nigeria. Tween 20, Tween 80, Polyethylene glycol (PEG-400), Polypropylene glycol was obtained from Jochem Chemical Industries Port Harcourt, Nigeria. All chemicals were of analytical grade and were used as such without further Processing.



**Equipment:** Pye-Unicam UV-Spectrophotometer (Germany).

### Permeability Study

#### Determination of Standard Calibration Curve (Beer's Calibration Curve)

A 0.2, 0.4, 0.6, 0.8, 1.0, and 1.6 mg azithromycin were weighed and transferred into 100 ml volumetric flask and made up to volume with analytical grade methanol to afford the following concentrations, 2, 4, 6, 8, 10, 12, 14 and 16 µg/ml. The absorbance of each concentration was determined spectrophotometrically at a pre-scanned wavelength (205 nm), and a calibration curve was plotted as absorbance against concentration.

#### Preparation of Rat Skin

Animal use and handling were carried out in line with the animal use and ethics committee guideline of the University of Port Harcourt (2005). A 300 g male albino rat was weighed and euthenized using chloroform. The dorsal abdominal region was depilated and the skin surgically removed. The epidermis was separated using heat separation technique, which involves soaking the skin in water at 60 °C for 60 seconds. All fatty matter was removed and the transparent epidermis stored in a refrigerator before use.

#### In-Vitro Skin Permeability Studies

These studies were carried out using a modified Franz diffusion glass cell with a diffusional cell area of 2.54 cm<sup>2</sup>. The diffusion cells were connected with a circulating water bath, and the temperature maintained at 37 °C. Phosphate buffer saline was used as receiver fluid (25 ml). The fluid receiver compartment was externally driven by a Teflon-coated magnetic bar. The thawed transparent epidermis was placed between the receiver and donor compartment with the stratum corneum of the skin facing upwards as the donor compartment was clamped. A 1 ml of 4% Sodium lauryl sulphate, Tween 80, 20% Polyethylene glycol and propylene glycol containing 10 mg of azithromycin each was applied on the surface of the skin facing the donor compartment which was covered with glass lid for equilibration. Samples were withdrawn from the sampling arm of the cell. An equal volume of fresh phosphate buffer at 37 °C was replaced immediately. The amount of drug permeated into the fluid was determined using UV Spectrophotometer at 205 nm.

#### Calculations

The speed of the drug passage through the skin in cm/hr is termed permeability coefficient. The coefficient of permeability (Kp) was estimated from the slope graph of the % of drug transported against time.  $K_p = \text{slope} \times V_d/S$ . Where  $V_d$  = volume of donor solution,

$S$  = surface area of the tissue.

Flux (J) is the amount of drug passing through a unit cross-sectional barrier in a unit time.

$$\text{Flux (J)} = K_p \times C_d.$$

Where  $C_d$  = concentration of donor solution. Enhancement ratio was used to calculate the effect of permeation enhancer on diffusion and permeation of azithromycin. It is calculated as

$$ER = \frac{\text{Permeability co-efficient of drug with enhancer}}{\text{Permeability co-efficient of drug alone (in water)}}$$

### Results

**Table 1:** Permeability coefficient (Kp) of azithromycin with different enhancers

Enhancer	Control (H <sub>2</sub> O)	4 % Tween 80	20 % PG	20 % PEG	4 % NaLSO <sub>4</sub>
KP (cm/hr)	0.11	0.14	0.30	1.5	2.73

PEG = polyethylene glycol, PG = propylene glycol and NaLSO<sub>4</sub> = sodium lauryl sulphate



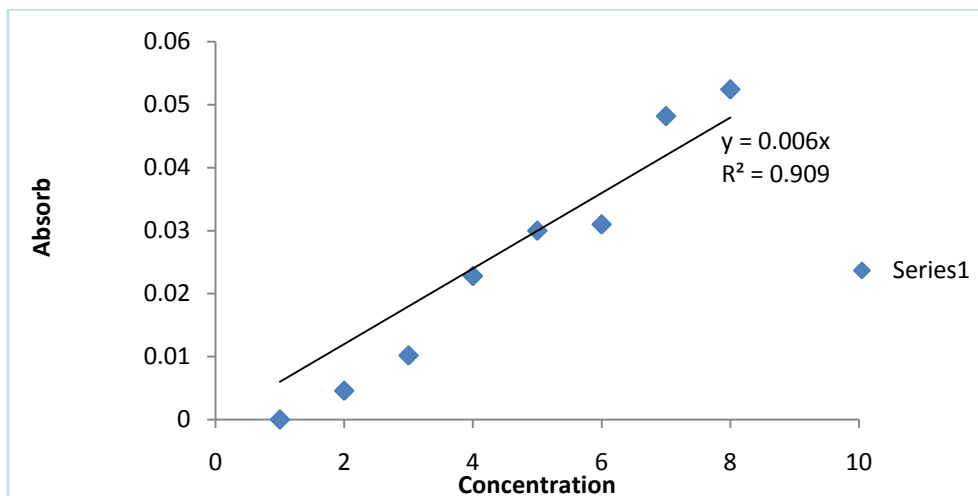


Figure 1: Standard calibration curve of azithromycin

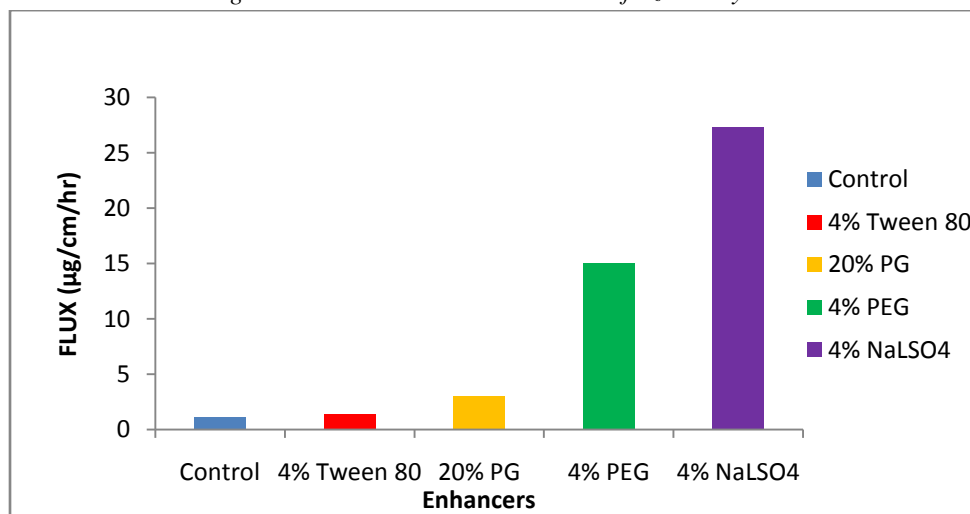


Figure 2: Bar graph showing flux of Azithromycin with different enhancers

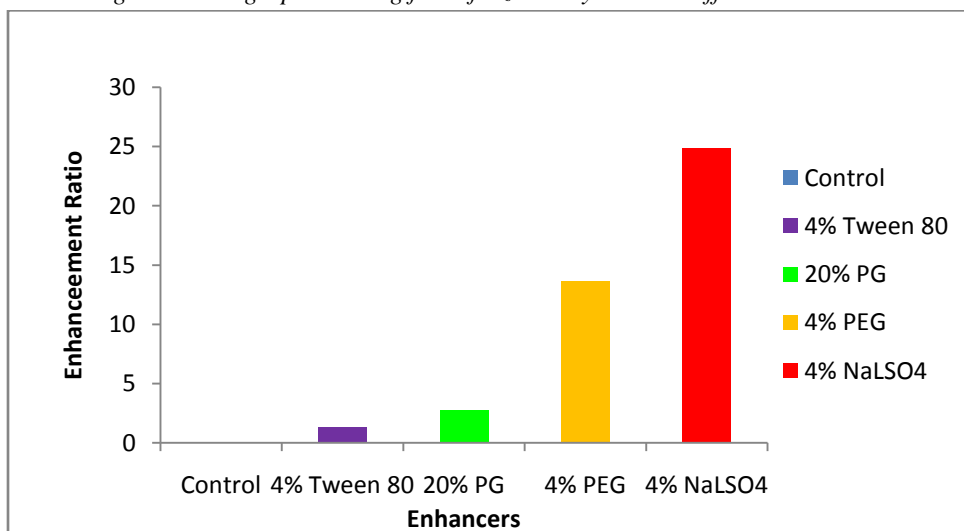


Figure 3: Bar graph showing enhancement ratio of Azithromycin with different enhancers



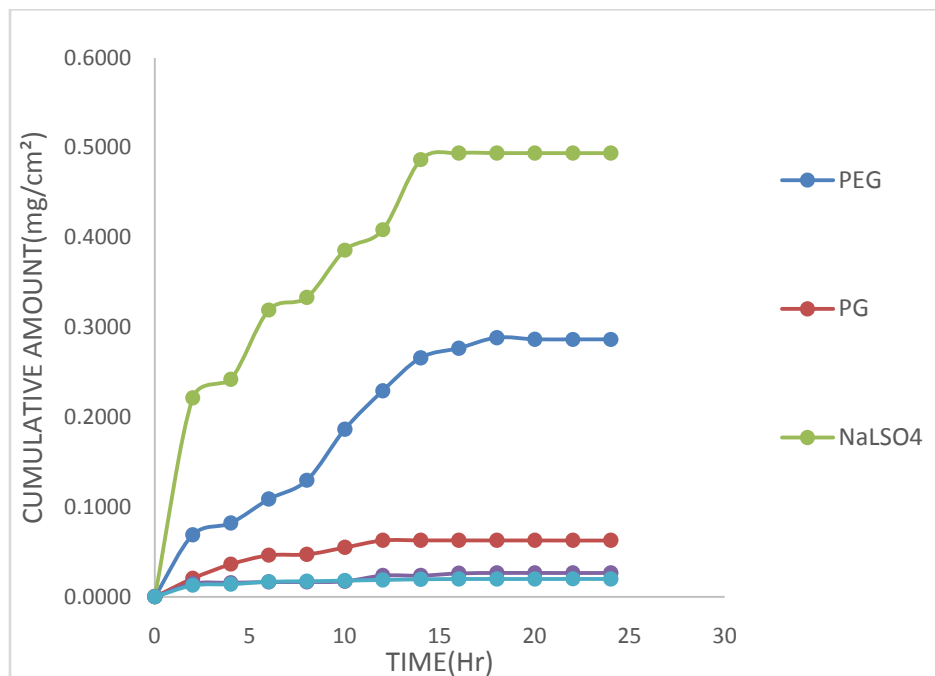


Figure 4: In-vitro diffusion of pure azithromycin with different enhancers (cumulative amount versus time) in hours using Franz diffusion cell fitted with rat skin.

### Discussion

Azithromycin, an antimicrobial agent has been chosen for this research work due to the half-life of 50-60 hours, the drug is known to undergo first-pass metabolism and also has very poor aqueous solubility. The present study aims to evaluate the permeability profile of azithromycin for topical or transdermal delivery. The theoretical value of the partition coefficient of azithromycin in octanol/water system is within the range of 2.9-3 which is favourable criteria for topical or transdermal drug delivery. The permeability coefficient, flux, and enhancement ratio of azithromycin was studied for the different enhancer. It was observed that Sodium lauryl sulphate gave high drug release as compared to the other enhancers. The value for sodium lauryl sulphate was 2.73 cm/h, 27.3  $\mu$ /cm/h and 24.81 respectively. The observed overall best permeability effect of sodium lauryl sulphate was due to its ability to induce protein denaturation as well as modification of lipid components of the stratum corneum thereby opening up permeation channels and producing higher permeation with high flux which increased linearly with the increase in the concentration of enhancer. (Table 1 and figure 2.0, 3.0 and 4.0.).

### Conclusion

Azithromycin, a poorly aqueous soluble drug skin permeability was well enhanced in the presence of co-solvents and surfactants in a concentration dependent manner.

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**Author Contributions**

Ezealisiji Kenneth Maduabuchi designed, supervised and carried out the experimental studies in this research work and also edited the manuscript.

Ukwueze Stanley Ejike carried out the experimental studies in this research work and also analysed the result.

Ishmael F. Jaja co-supervised the experimental and Laboratory work and drafted the manuscript.

**Conflict of Interest**

The authors declare no conflict of interest.

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