

Original Research Article

Predicting cosolvents, surfactants and electrolytes as potential transdermal delivery enhancers of pantoprazole

Chika J Mbah, Chinwe M Onah*, Sardauna H Monde

Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria

*For correspondence: **Email:** onah.chinwe@unn.edu.ng; **Tel:** +2347034195701

Sent for review: 4 March 2025

Revised accepted: 21 July 2025

Abstract

Purpose: To predict cosolvents, surfactants, and electrolytes as potential enhancers of pantoprazole transdermal delivery by examining their effects on the drug's coefficient of partition.

Methods: At room temperature, the shake flask method was used in a chloroform-water system. The percent concentrations (% w/v) utilized in the study range from 0.0 - 25.0; 0.0 - 0.5 and 0.0 - 1.0 for cosolvents (glycerol, ethanol, propylene glycol, and polyethylene glycol 400); surfactants (Tween 20, Tween 80, sodium lauryl sulfate, and cetrimide); and electrolytes (NaCl, KCl, MgCl₂, CaCl₂, CdCl₂, Na₂SO₄, K₂SO₄, MgSO₄, AlCl₃, and CoCl₃), respectively. Established mathematical equations were utilized to calculate transdermal parameters.

Results: Cosolvents, surfactants, and electrolytes reduced the logarithm partition coefficient of pantoprazole in comparison with control (distilled water). A significant difference ($p < 0.05$) occurred in the partition coefficient data of the drug between control and the vehicles/electrolytes investigated. Linear relationship was established between the logarithm partition coefficient and the logarithm estimated permeability coefficient of pantoprazole.

Conclusion: Cosolvents, surfactants and electrolytes used are not to be considered potential transdermal delivery enhancers of pantoprazole.

Keywords: Pantoprazole, Partition coefficient, Transdermal delivery, Cosolvents, Surfactants, Electrolytes

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

Tropical Journal of Pharmaceutical Research is indexed by Scopus, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Pantoprazole is (RS) – 6 - (Difluoromethoxy) – 2 – ((3,4–dimethoxy - 2 - pyridinyl) - methyl sulfinyl) -1H-benzimidazole. After absorption, this substituted benzimidazole builds up in the parietal cells in the acidic environment. Clinically, it is used to treat disorders including duodenal ulcers, reflux esophagitis, gastric ulcers and symptomatic gastro-esophageal reflux syndrome (such as heartburn and acid regurgitation) where a decrease in stomach acid output is necessary

[1]. Additionally, non-steroidal anti-inflammatory drug-induced gastrointestinal lesions are prevented with its help. Pantoprazole is soluble in ethanol, dimethylsulfoxide (DMSO), and dimethylformamide (DMF); however, it is insoluble in water. The sodium salt is soluble in water and ethanol. The pK_a values are 3.94 (pyridine) and 8.23 (benzimidazole), respectively.

The mechanism of action prevents both basal and induced gastric acid secretion by specifically inhibiting the gastric H⁺, K⁺ - adenosine

triphosphatase enzyme (the proton pump), which is in charge of the stomach's parietal cells secreting gastric acid [2]. Thus, it belongs to the class of drugs referred to as proton pump inhibitors. Its mechanism of action is primarily inert at higher pH levels and is most effective in an acidic environment ($\text{pH} < 3$). Following oral treatment, the main side effects include headache, flushed dry skin, and gastrointestinal discomfort (diarrhea, flatulence, nausea, and stomach pain) [3,4]. This creates a need for an alternative route of administration that will diminish these drawbacks and transdermal route is such an alternative route.

Transdermal delivery will lessen the side effects seen with oral route. Transdermal delivery route also has the advantages of being non-invasive, improving patient compliance, being used when there is significant first-pass metabolism, providing drug release for long time, being self-administering, and being generally inexpensive. Drug's pharmacokinetics, which include a short elimination half-life (1.1 h) and first-pass metabolism that results in 77 % absolute bioavailability, strongly support this alternate route. Studies have been reported on transdermal delivery of pantoprazole [5,6]. Pantoprazole was the drug of choice among other proton pump inhibitors (omeprazole, rabeprazole, lansoprazole, etc.) in the present study because it has greater efficacy in treating oesophageal reflux disease, improved tolerability, better pharmacokinetic profile, and lower risk of drug interactions. The oral dosage form of pantoprazole contains surfactants (polysorbate 80, sodium lauryl sulfate) and a cosolvent (polyethylene glycol) among inactive ingredients. Propylene glycol, polyethylene glycol 400, sodium lauryl sulfate and polysorbate 80 are usually used in pharmaceutical or cosmetic formulations for different purposes, including enhancement of dermal permeation [7,8]. Electrolytes have been reported to influence the partition coefficients of therapeutic agents [9,10]. The purpose of this study was to assess how cosolvents, surfactants, and electrolytes affect the partition coefficient of pantoprazole. It was anticipated that by comprehending how these substances affect the partition coefficient, some insight would be gained into their potential as transdermal delivery enhancers of pantoprazole. Enhancers for transdermal delivery are frequently needed in transdermal formulations to, among other things, lower the dosage of the drug and its side effects.

Dermal coefficient of permeability is dependent on the molecular weight and partition coefficient of chemical compounds [11]. Additionally, partition coefficient may be used to assess how

well chemical substances are absorbed through the skin [12]. Thus, by examining the partitioning properties of medications in various vehicles and in the presence of electrolytes, the current study examined cosolvents, surfactants, and electrolytes as possible transdermal delivery enhancers of pantoprazole.

EXPERIMENTAL

Materials

Pantoprazole (Kim-Zee Pharmacy, Nigeria), cosolvents- glycerol, ethanol, propylene glycol, and polyethylene glycol 400 (Sigma-Aldrich, USA), surfactants - Tween 20, Tween 80, sodium lauryl sulfate, and cetrimide (Sigma-Aldrich, USA), and electrolytes - sodium chloride, potassium chloride, magnesium chloride, calcium chloride, cadmium chloride, sodium sulfate, potassium sulfate, magnesium sulfate, aluminum chloride, and cobalt chloride (Fischer Scientific, USA). UV/Vis spectrophotometer (6705 UV/Vis Spectrophotometer, JENWAY).

Preparation of standard solution of pantoprazole [10]

In a 100 mL volumetric flask, 10 mg of pantoprazole reference standard was weighed, dissolved in methanol, and diluted to volume using methanol (stock A, 100 $\mu\text{g/mL}$).

An aliquot of stock A was diluted to 100 mL with methanol in a volumetric flask (stock B, 10 $\mu\text{g/mL}$). Stock B was scanned within UV range to obtain the maximum absorption wavelength (λ_{max}). A 10 mL volumetric flask was filled with aliquots (1 – 5 $\mu\text{g/mL}$) of standard stock solution B, which were then diluted with methanol to volume and used for calibration curve measurement.

Preparation of cosolvent, surfactant, and electrolyte solutions

Various concentrations (10 - 25 %w/v) of cosolvents (ethanol, glycerol, propylene glycol, and polyethylene glycol 400) were prepared in distilled water. Similarly, distilled water was used to prepare surfactants (Tween 20, Tween 80, cetrimide, and sodium lauryl sulphate) at concentrations of 0.1 to 0.5 %w/v. Electrolytes (sodium sulphate (Na_2SO_4), sodium chloride (NaCl), potassium sulphate (K_2SO_4), potassium chloride (KCl), calcium chloride (CaCl_2), aluminum chloride (AlCl_3), cobalt chloride (CoCl_3), magnesium sulphate (MgSO_4), magnesium chloride (MgCl_2), and cadmium

chloride (CdCl_2) were prepared at concentrations of 0.1 - 1 %w/v in distilled water.

Partition coefficient measurement

Shaking flask method was used to evaluate the partition coefficient in a room-temperature chloroform-water system [10]. In a vial with 1 mL of pantoprazole solution (100 $\mu\text{g/mL}$), 4 mL of distilled water and 5 mL of chloroform were added to prepare the control. In sample analysis, the same procedure for control preparation was followed except that 4 mL of various concentrations of cosolvents, surfactants and electrolytes, respectively, were substituted for distilled water.

The vials were capped and shaken for 2 h to achieve equilibration. Each of the vial contents was transferred into a separatory funnel and allowed 15 min for the two layers to separate. A UV/VIS spectrophotometer set to a maximum wavelength of 284 nm was used to analyze the aqueous phase. The calibration graph was used to determine the drug concentration in the aqueous layer. Equation 1 was used to calculate the drug's coefficient of partition [13].

$$P = C_1 - C_w / C_w \{V_w / V_o\} \dots\dots\dots (1)$$

Where P = coefficient of partition; C_1 = pantoprazole's total concentration; C_w = pantoprazole's concentration in aqueous phase; V_w = aqueous phase's volume; V_o = organic phase's volume. The determination was done in triplicate.

Statistical analysis

One-way analysis of variance (ANOVA) was utilized in the analysis of the partition coefficient data of pantoprazole. P -value < 0.05 was considered significant.

RESULTS

Within the concentration range of 1 – 5 $\mu\text{g/mL}$, the curve that was produced by plotting

absorbance values against drug concentrations was linear. The plot is presented in Figure 1.

Statistical outcomes

In each of the cosolvents studied, the null hypothesis was rejected at $p = 0.05$ because the decrease in the partition coefficient data when compared to the control was significantly different. The decrease was greatest with polyethylene glycol 400 cosolvent. Similar inference would be drawn with each of the surfactants investigated. The decrease was greatest with Tween 80 surfactant. Likewise, with electrolytes examined, the null hypothesis was rejected at $p = 0.05$ because the partition coefficient decrease was significantly different when compared with the control. The greatest decrease was noted in aluminum chloride. Statistically, amongst the cosolvents, surfactants, and electrolytes investigated in the present study, the most significant difference at $p = 0.05$ was observed with surfactants.

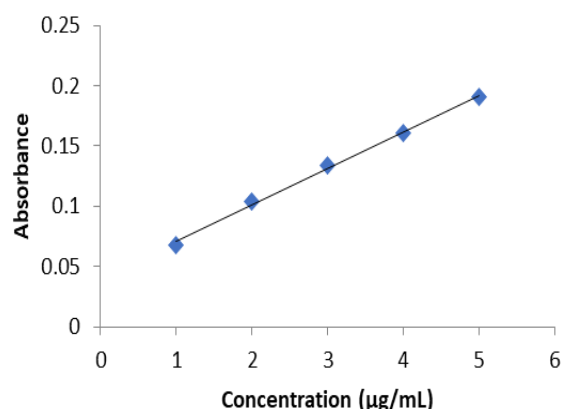


Figure 1: Calibration graph of pantoprazole

Influence of cosolvents

The influence of cosolvents on the partition coefficient of pantoprazole was evaluated. The cosolvent-partition coefficient data are given in Table 1, and the plot (logarithm partition coefficient of pantoprazole versus concentrations of cosolvents) is shown in Figure 2.

Table 1: Cosolvents' effect on partition coefficient of pantoprazole, mean $\pm$ SD

Concentration (% w/v)	Logarithm partition coefficient			
	Glycerol	Ethanol	Propylene glycol	Polyethylene glycol 400
0	2.031 $\pm$ 0.0021	2.031 $\pm$ 0.0021	2.031 $\pm$ 0.0021	2.031 $\pm$ 0.0021
10	1.805 $\pm$ 0.0079	1.562 $\pm$ 0.0015	1.521 $\pm$ 0.0086	1.396 $\pm$ 0.0047
15	1.690 $\pm$ 0.0036	1.426 $\pm$ 0.0051	1.289 $\pm$ 0.0045	1.182 $\pm$ 0.0033
20	1.530 $\pm$ 0.0042	1.272 $\pm$ 0.0024	1.162 $\pm$ 0.0035	0.894 $\pm$ 0.0026
25	1.364 $\pm$ 0.0026	1.135 $\pm$ 0.0062	1.034 $\pm$ 0.0075	0.717 $\pm$ 0.0042

SD = Standard deviation; n = triplicate determination

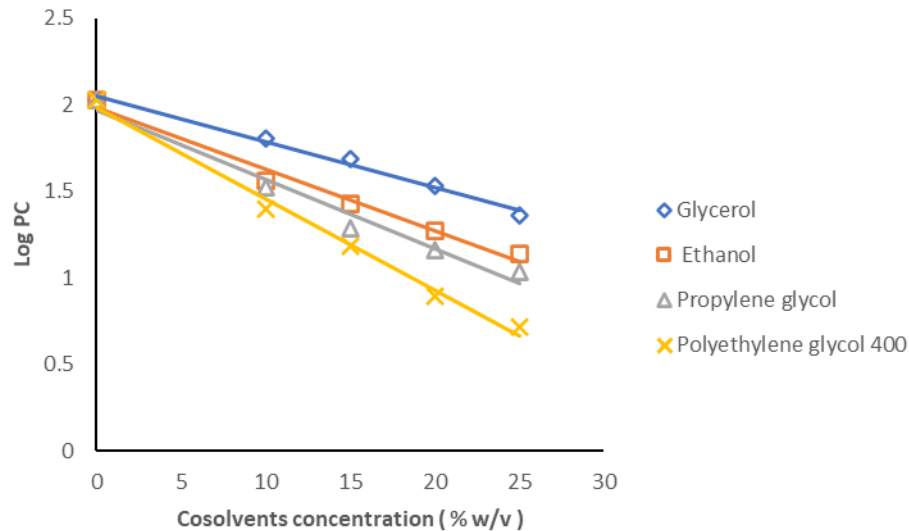


Figure 2: Plot of pantoprazole's logarithm partition coefficient against cosolvent concentration

Influence of surfactant

Likewise, the study examined the effect of surfactants on the partition coefficient of pantoprazole. The surfactant-partition coefficient data are given in Table 2, and the plot (logarithm of partition coefficient versus concentrations of surfactants) is shown in Figure 3.

Dermal permeability coefficient

Using an equation previously reported [11], the dermal permeability coefficient of pantoprazole through the skin was estimated using the logarithm of observed partition coefficient values.

$$\text{Log } k_p (\text{cm/h}) = -2.7 + 0.17 \log P - 0.0061 \text{ MW} \quad (3)$$

Table 2: Surfactants' effect on the coefficient of partition of pantoprazole (mean $\pm$ SD)

Concentration (%w/v)	Logarithm coefficient of partition			
	Tween 20	Tween 80	Sodium lauryl sulfate	Cetrimide
0	2.031 $\pm$ 0.0021	2.031 $\pm$ 0.0021	2.031 $\pm$ 0.0021	2.031 $\pm$ 0.0021
0.1	1.762 $\pm$ 0.0037	1.689 $\pm$ 0.0057	1.804 $\pm$ 0.0078	1.865 $\pm$ 0.0032
0.2	1.513 $\pm$ 0.0025	1.429 $\pm$ 0.0051	1.615 $\pm$ 0.0031	1.646 $\pm$ 0.0074
0.4	1.128 $\pm$ 0.0045	0.769 $\pm$ 0.0049	1.363 $\pm$ 0.0025	1.422 $\pm$ 0.0021
0.5	0.912 $\pm$ 0.0040	0.524 $\pm$ 0.0035	1.182 $\pm$ 0.0015	1.268 $\pm$ 0.0047

SD = Standard deviation; n = triplicate determination

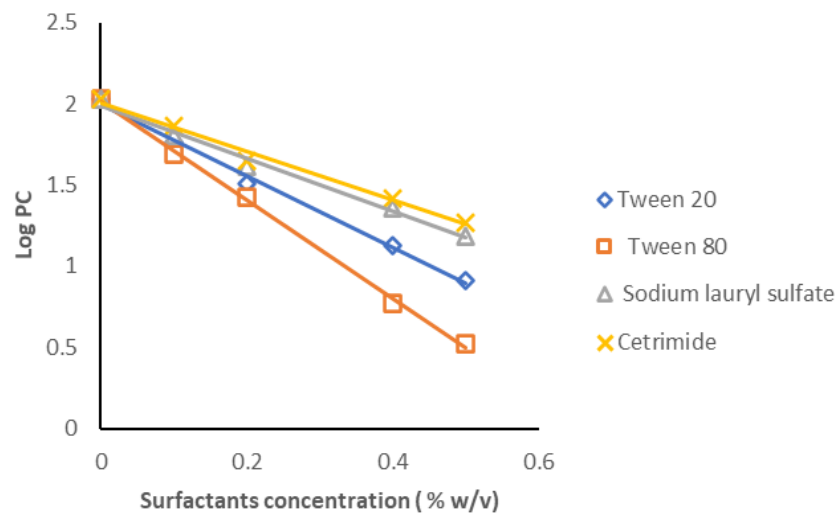


Figure 3: Plot of pantoprazole's logarithm coefficient of partition against concentration of surfactant

Where $\log k_p$ is pantoprazole's logarithm dermal permeability coefficient of pantoprazole; $\log P$ is the observed pantoprazole's logarithm coefficient of partition; MW is pantoprazole's molecular weight.

Correlation between the two parameters was demonstrated by plotting the logarithm observed coefficient of partition versus estimated dermal permeability coefficient using data obtained from glycerol (representing cosolvents) and Tween 20 (representing surfactant). The plots are given in Figure 4 and Figure 5 for glycerol and Tween 20, respectively.

Effect of electrolytes on the partition coefficient of pantoprazole

The electrolyte-partition coefficient is presented in Table 3. Due to non-linearity of the data, the plot was not generated.

DISCUSSION

Regression analysis of the plot gave equation of regression $A = 0.0303C + 0.0407$ with 0.9987 as the coefficient of correlation. Beer's law was obeyed, considering the graph's linearity and the coefficient of correlation. To explain the cosolvent-coefficient of partition profile of pantoprazole, logarithm coefficient of partition against cosolvent concentrations was plotted and a linear relationship was observed. Likewise, the surfactant-partition coefficient profile of pantoprazole was explained by plotting logarithm of partition coefficient versus surfactant concentrations and a linear relationship was obtained. The rate at which pantoprazole penetrates the skin may be predicted and quantitatively understood through an estimated permeability coefficient.

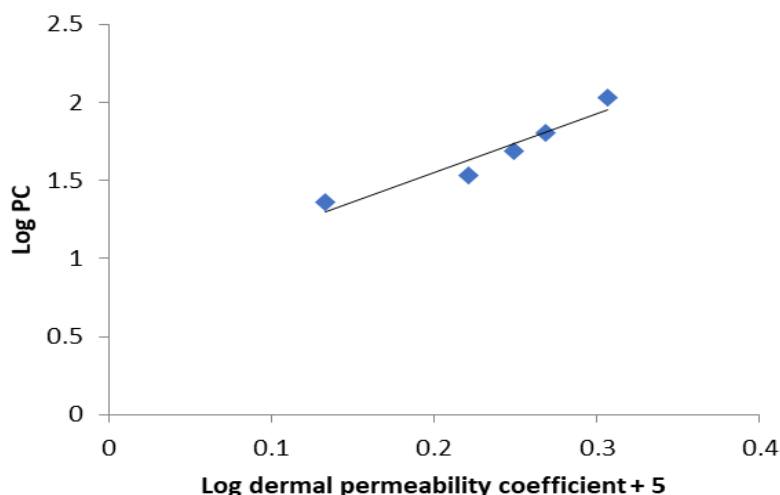


Figure 4: Log partition coefficient versus estimated dermal permeability coefficient of pantoprazole

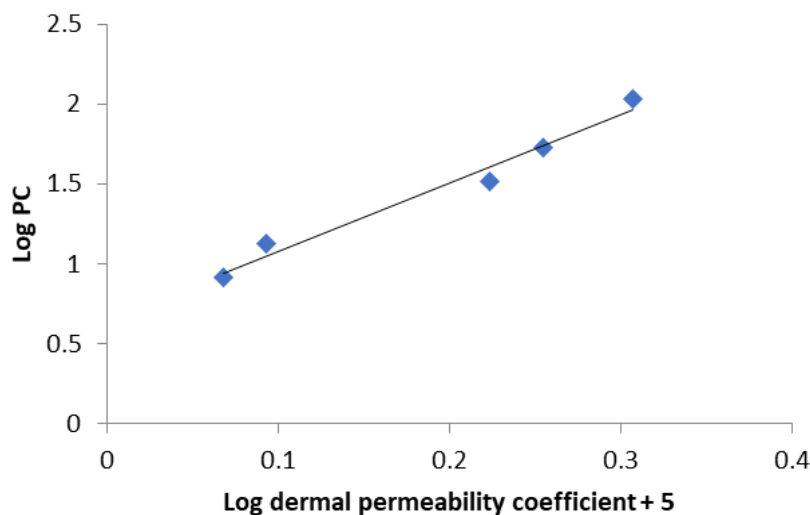


Figure 5: Log coefficient of partition versus pantoprazole's estimated dermal permeability coefficient

Table 3: Electrolytes' effect on the partition coefficient of pantoprazole, mean $\pm$ SD

Concentration (%w/v)	Logarithm coefficient of partition									
	<i>NaCl</i>	<i>KCl</i>	<i>MgCl₂</i>	<i>CaCl₂</i>	<i>CdCl₂</i>	<i>Na₂SO₄</i>	<i>K₂SO₄</i>	<i>MgSO₄</i>	<i>AlCl₃</i>	<i>CoCl₃</i>
0.0	2.031 $\pm$ 0.0021	2.031 $\pm$ 0.0021	2.031 $\pm$ 0.0021	2.031 $\pm$ 0.0021	2.031 $\pm$ 0.0021	2.031 $\pm$ 0.0021	2.031 $\pm$ 0.0021	2.031 $\pm$ 0.0021	2.031 $\pm$ 0.0021	2.031 $\pm$ 0.0021
0.1	1.458 $\pm$ 0.0058	1.694 $\pm$ 0.0033	1.491 $\pm$ 0.0054	1.637 $\pm$ 0.0075	1.435 $\pm$ 0.0057	1.626 $\pm$ 0.0073	1.857 $\pm$ 0.0027	1.653 $\pm$ 0.0085	1.426 $\pm$ 0.0042	1.455 $\pm$ 0.0083
0.2	1.131 $\pm$ 0.0056	1.548 $\pm$ 0.0038	1.434 $\pm$ 0.0066	1.492 $\pm$ 0.0012	1.259 $\pm$ 0.0033	1.598 $\pm$ 0.0048	1.758 $\pm$ 0.0053	1.613 $\pm$ 0.0048	1.197 $\pm$ 0.0051	1.221 $\pm$ 0.0026
0.4	1.087 $\pm$ 0.0010	1.417 $\pm$ 0.0043	1.378 $\pm$ 0.0051	1.417 $\pm$ 0.0047	1.133 $\pm$ 0.0037	1.491 $\pm$ 0.0054	1.583 $\pm$ 0.0045	1.451 $\pm$ 0.0017	0.981 $\pm$ 0.0025	1.005 $\pm$ 0.0035
0.5	1.043 $\pm$ 0.0039	1.386 $\pm$ 0.0016	1.297 $\pm$ 0.0040	1.372 $\pm$ 0.0065	1.009 $\pm$ 0.0063	1.416 $\pm$ 0.0023	1.529 $\pm$ 0.0061	1.303 $\pm$ 0.0052	0.854 $\pm$ 0.0062	0.868 $\pm$ 0.0044
1.0	0.953 $\pm$ 0.0024	1.303 $\pm$ 0.0020	1.244 $\pm$ 0.0032	1.175 $\pm$ 0.0036	0.894 $\pm$ 0.0015	1.316 $\pm$ 0.0025	1.421 $\pm$ 0.0031	1.214 $\pm$ 0.0035	0.726 $\pm$ 0.0037	0.742 $\pm$ 0.0018

SD = Standard deviation; n = triplicate determination

Since Potts' equation deals with unionized permeants in an aqueous formulation, the parameter also represents the skin permeability of unionized pantoprazole. Plotting the experimental logarithm coefficient of partition against the logarithm estimated permeability coefficient yielded correlation coefficients of 0.9559 (glycerol) and 0.9873 (Tween 20), indicating that coefficient of partition is an essential parameter to estimate dermal permeability coefficient. According to previous report [14] permeability coefficient is a valuable parameter in the evaluation of transdermal delivery of chemical substances via the skin.

Equation 4 was used to quantify the activation energy involved in the drug's partitioning into the chloroform-buffer system thermodynamically using a cubic equation (Equation 3) that relates activation energy (E_a) and Logarithm coefficient of partition [15].

$$E_a = 16.724 + 2.884 (\log P) - (-4.175 (\log P)^2 + 0.802 (\log P)^3) \dots\dots\dots (4)$$

The reduction in E_a value for the drug's solubilization in cosolvents at highest concentrations studied (25 %w/v) is in order of polyethylene glycol 400 (21.25) < propylene glycol (25.07) < ethanol (26.56) < glycerol (30.48) < control (46.54). Similarly, the decrease in E_a value for the solubilization of pantoprazole in surfactants at the highest concentrations studied (0.5 % w/v) is in the order of Tween 80 (19.53) < Tween 20 (23.45) < sodium lauryl sulfate (27.31) < cetrimide (28.75) < control (46.54). The results suggest that it is preferable to use polyethylene glycol 400 or Tween 80 rather than distilled water (control) where there is need for a transdermal formulation.

With monovalent salts (NaCl and KCl, respectively), partition coefficient of pantoprazole decreased with increasing concentrations (0.1 - 1.0 %w/v) of both salts. Potassium chloride (KCl) seemed to have produced less decrease in the drug's coefficient of partition at the maximum concentration (1.0 %w/v) examined. Atomic size of the two cations (Na^+ and K^+ , respectively) will provide the explanation for the results. The sodium ion (Na^+), being smaller in size than potassium ion (K^+), would have found it easier to interact with the molecules of pantoprazole, thus making it less lipophilic, because of increased aqueous solubility of the drug. With the divalent salts (MgCl_2 , CaCl_2 and CdCl_2 , respectively), the partition coefficient of pantoprazole was observed to decrease with increasing concentrations (0.1 - 1.0 %w/v) of the three salts. Cadmium chloride (CdCl_2) seemed to have

produced the greatest decrease in the drug's coefficient of partition at the maximum concentration (1.0 %w/v) studied. Complexation of the drug with these cations might be used to advance the results observed. The cadmium ion (Cd^{2+}) must have had a higher affinity for coordinating with the electron-rich sites in pantoprazole molecules compared to either magnesium ion (Mg^{2+}) or calcium ion (Ca^{2+}). The strongest complex formation with pantoprazole molecules increased the drug's aqueous solubility, thus decreasing the drug's ability to be transferred into the organic layer.

Data obtained with trivalent salts (AlCl_3 and CoCl_3 , respectively) showed that aluminum ion decreased the partition coefficient of the drug more than cobalt ion at the highest concentration (1.0 %w/v) studied. The acidic nature of aluminum chloride could explain the result. Data in this study also indicated that divalent ions gave a greater decrease in the drug's coefficient of partition at the maximum salt concentration studied than monovalent ions. Valency states of the ions could be responsible for such observations. Replacing chloride ion (Cl^-) with sulfate ion (SO_4^{2-}) on cations (Na^+ , K^+ , Mg^{2+}) of the salts reduced the decreasing tendencies of these salts on the drug's coefficient of partition. Variation in the volume of sulfate ion (anion) when compared to chloride ion (anion) could be responsible for the observed results.

CONCLUSION

The coefficient of partition of compounds determines the dermal permeability coefficient. Decreasing proportionality relationship established among the logarithm coefficient of partition and logarithm estimated permeability coefficient of pantoprazole in the present study predicts that the cosolvents, surfactants and electrolytes utilized in the study may not be transdermal permeation enhancers of pantoprazole.

DECLARATIONS

Acknowledgement/Funding

The authors appreciate the Department of Pharmaceutical and Medicinal Chemistry, Nsukka, for providing the facilities used for this study.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and the liabilities pertaining to the claim relating to the content of this article will be borne by the authors. CJ Mbah conceived and designed the study, CJ Mbah, CM Onah, and Sardauna H Monde collected and analyzed the data, and CJ Mbah and CM Onah wrote the manuscript. All authors read and approved the manuscript for publication.

REFERENCES

1. Judmaier G, Koelz HR. Pantoprazole-duodenal ulcer-study group; Comparison of pantoprazole and ranitidine in the treatment of acute duodenal ulcer. *Aliment Pharmacol Ther* 1994; 8: 81-86.
2. Sachs G, Gastric H, K-ATPase as therapeutic target. *Ann Rev Pharmacol Toxicol* 1988; 28: 269-284.
3. Steinijans VW, Huber R, Hartmann M, Zech K, Bliesath H, Wurst W, Radtke HW. Lack of pantoprazole drug interactions in man: an updated review. *Internal J Clin Pharmacol Therap* 1996; 34: S31-S50.
4. Jungnickel PW. Pantoprazole: A new proton pump inhibitor. *Clinical Therapeutics* 2000; 22(11): 1268-1293.
5. Huber R, Hartmann M, Bliesath H, Lühmann R, Steinijans VW, Zech K. Pharmacokinetics of pantoprazole in man; *Internal J Clin Pharmacol Therap* 1996; 34: 185-194.
6. Shivalingam MR, Balasubramanian A, Ramalingam K. Formulation and evaluation of transdermal patches of pantoprazole sodium. *Int J App Pharm* 2021; 13(5): 287-291
7. Shen WW, Danti AG, Bruscatto FN. Effect of nonionic surfactants on percutaneous absorption of salicylic acid and sodium salicylate in the presence of dimethyl sulfoxide. *J Pharm Sci* 1976; 65: 1780-1783.
8. Toniton E. Transdermal delivery of anxiolytics. In vitro skin permeation of midazolam maleate and diazepam. *Int J Pharm* 1986; 33: 37-43.
9. Mbah CJ. Effect of electrolytes on the partition coefficient of irbesartan. *Pharmazie* 2005; 60: 345-346.
10. Mbah CJ. Studies on the effects of electrolytes and pH control on the lipophilicity of fexofenadine hydrochloride. *Bio-Res* 2008; 6(1): 301-302.
11. Potts RV, Guy RH. Predicting skin permeability. *Pharm Res* 1992; 9: 663-669.
12. Bunge AL, Cleek RL. A new method for estimating dermal absorption from chemical exposure. Effect of molecular weight and octanol-water partitioning. *Pharm Res* 1995; 12: 88-95.
13. Johansen M, Bundgaard H. Prodrugs as drug delivery systems XI. Solubility, dissolution, and partition behaviour of N-Mannich bases and N-hydroxymethyl derivatives. *Arch Pharm Chem Sci Edu* 1980; 8: 141-151.
14. Karinth S, Schaller KH, Drexler H. Is the permeability coefficient Kp a reliable tool in percutaneous absorption studies? *Arch Toxicol* 2005; 79: 155-159.
15. Roberts MS, Anderson RA, Swarbrick J, Moore DE. Percutaneous absorption of phenolic compounds: the mechanism of diffusion across the stratum corneum. *J Pharm Pharmacol* 1978; 30(8): 486-490.
16. Hwang CC, Danti AG. Percutaneous absorption of flufenamic acid in rabbits. Effect of dimethylsulfoxide and various nonionic surface active agents. *J Pharm Sci* 1983; 72: 857-860.