Tropical Journal of Pharmaceutical Research December 2021; 20 (12): 2463-2468
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v20i12.1

Original Research Article

Theoretical study on percutaneous absorption of olmesartan medoxomil: The pH control effect

Chika J Mbah, Chinwe M Onah*, Queendalyn E Asogwa
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*

Sent for review: 2 April 2021 *Revised accepted: 23 November 2021*

Abstract

Purpose: *To predict the percutaneous absorption of olmesartan medoxomil using dermal parameters obtained under pH control.*
Methods: *Partition coefficient of olmesartan medoxomil was determined in a chloroform-buffer system by shake flask method at room temperature. The test was carried out under different pH conditions. Established mathematical equations were utilized to calculate percutaneous absorption parameters, including the permeability coefficient of the drug through the skin, maximum flux through the skin, activation energy involved in the partitioning of the drug in the chloroform-buffer system, and diffusion coefficient of the drug through skin.*
Results: *At pH 2.0, the drug gave the highest logarithm partition coefficient when compared to other pH values investigated as well as distilled water (control). The mean logarithm partition coefficient of the drug (4.36 ± 0.06) at pH 2.0 compared well to the mean logarithm partition coefficient of the drug (4.15 ± 0.07) in distilled water at 95 % level. Statistical analysis indicated that null hypothesis was rejected at this confidence level. Test of significance was not carried out on the other parameters including maximum flux, activation energy and diffusion coefficient data because they were estimated from the experimental partition coefficient.*
Conclusion: *Percutaneous absorption of olmesartan medoxomil using dermal parameters obtained under pH control can be predicted. As the rate of penetration into the skin is quantitatively assessed by the use of permeability coefficient, the results predict significant percutaneous absorption of olmesartan medoxomil.*

Keywords: *Percutaneous absorption, pH control, Olmesartan medoxomil, Skin penetration, Activation energy*

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

INTRODUCTION

Drug delivery through the skin (transdermal delivery or percutaneous absorption) has become a good alternative to the oral or parenteral route of drug administration. This route of drug delivery avoids the first- pass metabolism, is noninvasive and easy to use, increases patient compliance, provides steady plasma level, increases therapeutic index with a simultaneous decrease in side effects and reduces inter and intra variability in patients [1].

The barrier property of the skin in drug delivery has been overcome by several approaches including the pH control [2]. The permeability coefficient is one of the principal parameters in estimating the percutaneous absorption of drugs [3]. Partition coefficient and molecular weight of chemical substances influence dermal permeability coefficient of a chemical compound [4].

Dermal absorption of compounds has been used to evaluate partition coefficient [5]. Olmesartan medoxomil, 2,3dihydroxy-2-butenyl 4-[1-hydroxy-1-methylethy]-2-propyl-1-[p(o-1H-tetrazol-5-ylphenyl) benzyl] imidazole-5-carboxylate, cyclic 2,3-carbonate is used clinically to treat hypertension.

First-pass metabolism and high potency make the drug a potential candidate for percutaneous absorption. Furthermore, as hypertension is a chronic disease, the percutaneous absorption route could provide patient compliance over the current oral route. Ionizable group present in olmesartan medoxomil suggest that pH control could influence olmesartan medoxomil percutaneous absorption. Literature search has revealed little or no information on how percutaneous absorption of olmesartan medoxomil could be affected by pH control. In this context, the present study attempts to predict the influence of pH control on the percutaneous absorption of olmesartan medoxomil using calculated partitioning parameters of the drug in different buffer solutions.

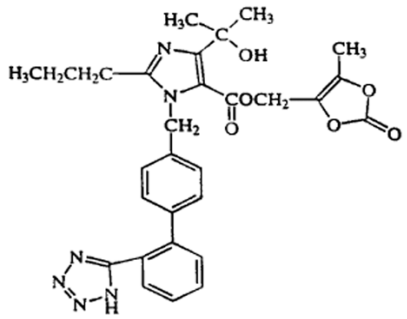

Figure 1: Chemical structure of olmesartan medoxomil

EXPERIMENTAL

Materials

Olmesartan medoxomil (Sun Pharmaceutical Ltd, Nigeria), boric acid, glacial acetic acid, hydrochloric acid, monobasic potassium phosphate, potassium biphthalate, sodium acetate, sodium hydroxide, and chloroform (Fisher Scientific, USA). Other chemicals were of analytical reagent grade.

Preparation of standard solution

Stock solution: Olmesartan medoxomil was prepared in methanol (50.0 µg/ml). Working standard solutions: Aliquots (5.0 - 25.0 µg/ml) of the standard stock solution were transferred into a 10 ml volumetric flask and diluted to volume with methanol.

Preparation of 0.1 M buffer solutions

1. Hydrochloric acid buffer solution of pH 2.0 was prepared using hydrochloric acid and potassium chloride.

2. Biphthalate buffer solution of pH 3.0-4.0 was prepared using potassium biphthalate and hydrochloric acid. Biphthalate buffer solution of pH 5.0 was prepared using potassium biphthalate and sodium hydroxide.

3. Phosphate buffer solution of pH 6.0-7.0 was prepared using monobasic potassium phosphate and sodium hydroxide.

4. Borate buffer solution of pH 8.0-10.0 was prepared using boric acid and sodium hydroxide.

Partition coefficient measurement

Olmesartan medoxomil partition coefficient was determined in a chloroform-buffer system. A 500 µg of olmesartan medoxomil was transferred to a vial containing 5 ml of chloroform (previously saturated with different buffer solutions). This was followed by the addition of 5 ml aqueous buffer solution (previously saturated with chloroform) to the vial. The vials were capped and agitated for 2h at room temperature to achieve complete equilibration. The phases were allowed to separate in a separating funnel. The aqueous layer containing olmesartan medoxomil was analyzed spectrophotometrically using UV/VIS spectrophotometric method (Perkin Elmer Lambda 35 UV-VIS spectrophotometer) at a maximum wavelength of 250 nm. The drug concentration was obtained from a pre-constructed calibration graph. The partition coefficient of olmesartan medoxomil was calculated using Eq 1 [6].

$$P = (C_1 - C_W)/C_W(V_W/V_O) \quad \ldots\ldots\ldots\ldots (1)$$

where C_1 = total concentration of olmesartan medoxomil, C_W = concentration of Olmesartan medoxomil in the aqueous phase, Vw = volume

of the aqueous phase, Vo = volume of the organic phase.

Statistical analysis

The data obtained at pH 2.0 was compared to the control (distilled water) data at a 95 percent confidence level. The statistical analysis result showed that the null hypothesis was rejected. Thus, there exists a significant difference between percutaneous absorption of olmesartan medoxomil expected from a formulation adjusted to acidic pH (pH 2.0) when compared to the aqueous formulation of the drug.

RESULTS

At concentration range of 5.0 - 25.0 µg/ml, the calibration graph of olmesartan medoxomil was found to be linear. To define the pH- partition coefficient profile of olmesartan medoxomil, logarithm apparent (observed) partition coefficient was plotted against pH and the result is shown in Figure 2. A linear relationship was obtained.

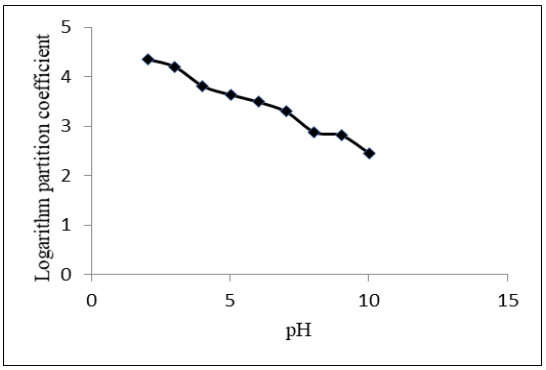

Figure 2: A plot of pH versus partition coefficient

The results of activation energy (E_a) involved in the partitioning of the drug into the chloroform-buffer system, was estimated using a cubic equation relating activation energy and logarithm partition coefficient are presented in Table 1.

The result of plotting logarithm partition coefficient values (obtained within the pH range studied) against estimated activation energy values, gave a parabolic relationship (Figure 3).

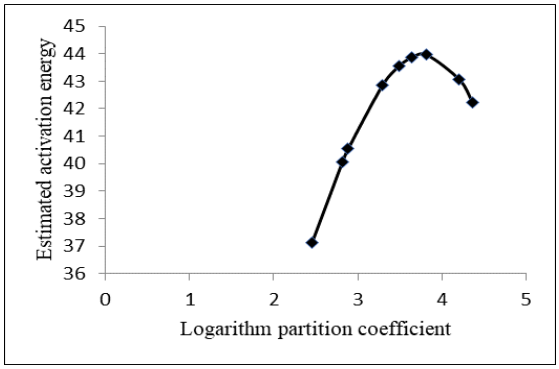

Figure 3: Logarithm partition coefficient versus estimated activation energy

However, a plot of logarithm partition coefficient values within the pH range of 5.0-10.0 versus estimated activation energy gave a linear graph (Figure 4) with 0.9841 as the correlation coefficient.

The results of estimating permeability coefficient, using Potts equation are given in Table 1 and the results showed that the maximum estimated permeability coefficient occurred at pH 2.0. Furthermore, the result of plotting logarithm partition coefficient versus the logarithm estimated permeability coefficient is given in Figure 5. A linear relationship was observed with a correlation coefficient of 0.9999.

The results of estimated maximum flux as well as the diffusion coefficient in the skin are also given in Table 1.

Table 1: Partition coefficient and calculated skin permeability parameters of olmesartan medoxomil

pH	log P	k_p(cm/h)	J_{ss}(µg/cm/h)	E_a(kcal/mol)	D(cm^2/h)
2.03	4.359 ± 0.0263	0.000929	0.00353	42.198	1.02×10^{-10}
3.01	4.202 ± 0.0110	0.000718	0.00273	43.056	1.13×10^{-10}
4.02	3.813± 0.0325	0.000380	0.00144	43.960	1.46×10^{-10}
5.04	3.638± 0.0366	0.000286	0.00109	43.856	1.64×10^{-10}
6.03	3.493± 0.0532	0.000225	0.00086	43.557	1.81×10^{-10}
7.02	3.297± 0.0760	0.000164	0.00062	42.873	2.07×10^{-10}
8.04	2.886± 0.0644	0.000084	0.00032	40.543	2.73×10^{-10}
9.03	2.818± 0.0585	0.000075	0.00029	40.058	2.85×10^{-10}
10.02	2.458± 0.0349	0.000042	0.00016	37.127	3.66×10^{-10}
Water	4.145± 0.0709	0.000655	0.00249	43.293	1.17×10^{-10}

Data are mean ± standard deviation

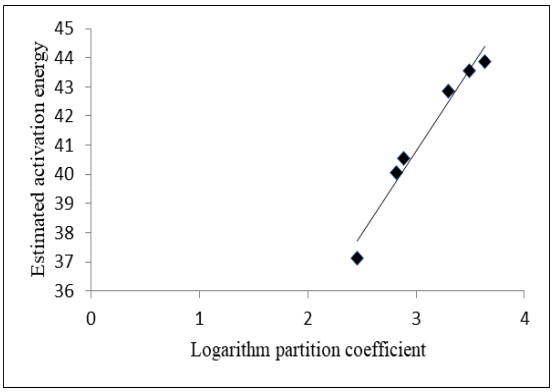

Figure 4: Logarithm partition coefficient versus estimated activation energy

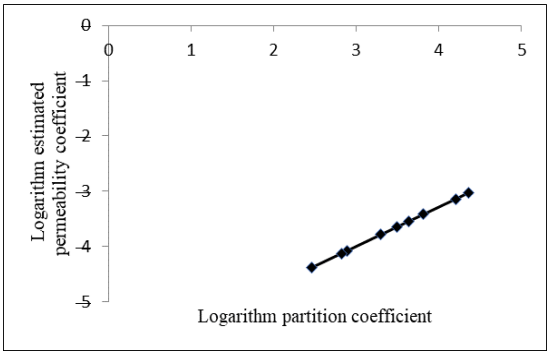

Figure 5: Logarithm partition coefficient versus logarithm estimated permeability coefficient

DISCUSSION

The regression equation A = 0.022 C + 0.018) of the calibration plot defined the absorbance versus concentration relationship. The linearity of the graph and the correlation coefficient (r = 0.9970) showed that Beer's law was obeyed. The partition coefficient results showed that the drug partitioned least into the organic phase at a pH value of 10.0 suggesting the highest ionization at this pH value. The pH- partition coefficient profile permitted the dissociation constant of olmesartan medoxomil to be evaluated. This physicochemical parameter will contribute to predicting the skin permeability ability of the drug. To obtain the dissociation constant (pKa), apparent partition coefficient versus the product of apparent partition coefficient and hydrogen ion concentration was plotted based on Eq 2 [7].

$P_{app} = (P_m - [H_3O^+])P_{app}/K_a$…….. (2)

where P_{app} is the apparent (observed) partition coefficient of olmesartan medoxomil, P_m is the partition coefficient of the free form (unionized), $[H_3O^+]$ is hydroxonium ion concentration, K_a is the dissociation (ionization) constant.

A linear graph was observed within the pH range of 4-8 and from the slope of the graph, a value of 3.83 for pKa (-log Ka) was calculated while a value of 2453.81 (log P: 3.39) for P_m was also calculated from the intercept. Although linear graphs were also obtained when other pH ranges (for example 3-6; 3-8 and 5– 8, respectively) were used in constructing the plots, however the pH range 4-8 was the most preferred plot because the values of the parameters were closer to literature values (4.27 and 4.437 for pKa and logarithm partition coefficient respectively) when compared to other pH ranges.

Thermodynamically, the activation energy (E_a) involved in the partitioning of the drug into the chloroform-buffer system was estimated using a cubic equation (equation 3) relating activation energy and logarithm partition coefficient, as in Eq 3 [8].

$Ea = 16.724 + 2.884(\log P) – [- 4.175 (\log P)^2 + 0.802 (\log P)^3$……..(3)

The decrease in Ea value at pH 2.0 when compared to water, suggests that it is more preferable to use buffer solution (pH 2.0) for a dermal formulation of the drug rather than water. The linear plot (Figure 4) obtained when logarithm partition coefficient versus estimated activation energy was in agreement with a previous study which reported that activation energy has linear relationships with the partition coefficients for a series of phenolic compounds [8].

In estimating the permeability coefficient, Potts equation (Eq 4) was used.

$\log kp(cm/h) = -2.72 + 0.71 (\log P) – 0.0061 (MW)$ ……(4)

where kp is permeability coefficient, P experimental partition coefficient and MW is the molecular weight of olmesartan medoxomil. An estimated permeability coefficient is needed to predict and understand quantitatively the penetration rate of olmesartan medoxomil into the skin. The parameter will also represent skin permeability of unionized olmesartan medoxomil since Pott's equation deals with unionized permeants in an aqueous formulation. The results of the partition coefficient study showed that olmesartan medoxomil was most unionized at pH 2.0.

The correlation coefficient of 0.9999 obtained by plotting the experimental logarithm partition coefficient versus logarithm estimated

permeability coefficient indicated that the partition coefficient is a very good parameter to estimate the permeability coefficient.

The skin maximum flux was estimated by the product of aqueous solubility of the drug and the estimated permeability coefficient. Aqueous solubility value of 3.8µg/ml was used [9]. Flux at steady-state is one of the parameters to evaluate dermal percutaneous absorption. The diffusion coefficient in the skin was estimated using Eq 5.

kp =KD/h……. (5)

where K is the partition coefficient between the skin and the vehicle (in this case buffer solution), D is the diffusion coefficient, h is the thickness of the SC, K is defined as Cs/Cv where Cs is the aqueous solubility of the drug, Cv is drug concentration in the vehicle.

An average of 2.5×10^{-3} cm skin thickness [10] was used in the study. The results indicate that diffusivity occurred most at acidic pH (pH 2.0). The parameter permits the estimation of the maximum flux of the combination of unionized and ionized species.

CONCLUSION

Most of the estimated permeability coefficient values obtained in the present study suggest that olmesartan medoxomil is significantly absorbed through the skin. The permeability coefficient obtained at pH 2.0, is about 6.9-fold higher when compared to the coefficient of scopolamine (the first transdermal patch for treating motion sickness). Finally, as permeability coefficient is the most commonly used descriptor to represent the diffusion of compounds and is also a more reliable parameter than maximum flux to evaluate dermal percutaneous absorption, the findings of this study suggest that pH control affects the potential percutaneous absorption of olmesartan medoxomil.

DECLARATIONS

Acknowledgement

The authors are grateful to the Department of Pharmaceutical and Medicinal Chemistry, University of Nigeria, Nsukka, for providing the facilities used for the 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 all liabilities about claims relating to the content of this article will be borne by the authors. Prof CJ Mbah conceived and designed the study, Prof CJ Mbah, Dr CM Onah and Queendalyn E Asogwa collected and analyzed the data, Prof CJ Mbah and Dr CM Onah wrote the manuscript as well. All authors read and approved the manuscript for publication.

REFERENCES

1. *Ezealisiji MK, Mbah CJ, Osadebe PO, Krause R. Pharmacokinetics studies of mirtazapine loaded nanoemulsion and its evaluation as transdermal delivery system. J Chem Pharm Res 2017; 9(3): 74-84.*
2. *Mbah CJ, Harry P, Ezealisiji MK. Prediction of skin permeability of praziquantel: pH-permeability relationship. Ac Scient Pharm Sci 2018; 2 (5): 36-39.*
3. *Karinth S, Schaller KH, Drexler H. Is permeability coefficient Kp a reliable tool in percutaneous absorption studies. Arch. Toxicol 2005; 79: 155-159.*
4. *Potts RV, Guy RH. Predicting Skin Permeability. Pharma Res 1992; 9(5): 663-669.*
5. *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(1): 88-95.*
6. *Johansen M, Bundgaard H. Prodrugs as drug delivery systems XI. Solubility, dissolution and partition behaviour of N-Mannich bases and N-hydroxymethyl derivatives. Arch Pharma Chem Sci Edu 1980; 8(a): 141-151.*
7. *Hasegawa J, Fujita T, Hayashi Y, Twamoto K, Watanabe J. pKa determination of verapamil by liquid-liquid partition. J Pharm Sci 1984; 73(4): 442-445.*
8. *Robert MS., et al. Percutaneous absorption of phenolic compounds: the mechanism of diffusion across the stratum corneum. J Pharm Pharmacol 1978; 30(8): 486-490.*
9. *Abbas1 Z, Nanjunda Swamy NG. Physicochemical characterization of olmesartan medoxomil: polymer solid*

dispersions by hot melt extrusion for dissolution rate enhancement. Egypt Pharm J 2017; 16(3): 157-167.

10. *Bartzatt R. Determination of Dermal Permeability Coefficient (Kp) by Utilizing Multiple Descriptors in Artificial Neural Network Analysis and Multiple Regression Analysis. J Sci Res Rep 2014; 3(22): 2884-2899.*