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Research Article

Prediction of Skin Permeability of Praziquantel: pH-Permeability Relationship

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Abstract

Skin permeability of drugs determines the rate and extent these agents cross the tissue and be absorbed into the systemic circulation to reach their sites of action. Praziquantel, is clinically used for the treatment of all types of schistosomiasis.

The purpose of the present study was to predict the probable pH effect on the permeability of praziquantel through the skin using data obtained from the effect of pH on the partition coefficient of praziquantel.

The partition coefficient was determined by shake-flask method at room temperature using chloroform-buffer system. A highly effective mathematical model equation was used to estimate the permeability coefficient. The maximum flux through the skin was obtained by multiplying the estimated permeability coefficient and aqueous solubility of the drug. A cubic equation that defined relationship between activation energy and logarithm of partition coefficient was utilized to calculate the activation energy involved in the partitioning of the drug in chloroform-buffer system. The diffusion coefficient through the membrane was estimated using an equation relating permeability coefficient, skin-vehicle partition coefficient and the average thickness of the stratum corneum. The results show pH of the buffer solutions to have varying effect on the partition coefficient of the drug. A non-linear curve was observed when logarithm of partition coefficient was plotted against the pH of buffer solution. The results obtained from the study also showed that the estimated permeability coefficient increased 2.5- fold at pH 2.0 and 3.2-fold at pH 8.0 respectively when compared to distilled water. This leads to the conclusion that the skin permeability of praziquantel is most favoured at slightly high basic pH value (pH 8.0).

Keywords: Praziquantel; Partition Coefficient; pH; Skin Permeability Coefficient

Introduction

Drug delivery through the skin has become a good alternative to oral or parenteral route of drug administration. This route of drug delivery is noninvasive and easy to use, avoids first pass metabolism, provides steady plasma level, increases patient compliance, reduces inter and intra variability in patients and increases therapeutic index with simultaneous decrease in side effects [1-3]. Studies have shown that transdermal delivery of chemical substances can be influenced by physical and biochemical approaches, chemical permeation enhancers and pH control [4-6].

Although the skin is composed of two layers namely the epidermis (about 100 µm thick), the dermis (about 500 to 3000 µm thick), it is the outermost layer of the epidermis, about 10 to 40 µm thick called the stratum corneum that provides the major barrier to the absorption of chemical substances deposited on the skin surface into the systemic circulation.

To assess the feasibility of skin permeation scientists often times go on to predict and understand skin permeability from the standpoint of physicochemical parameters of the drug compound because most experiments carried out using animal and cadaver skin could be expensive, cumbersome and could have extensive biovariation of skin properties in both humans and animals.

Schistosomiasis is a parasitic protozoal disease caused by flatworms of the genus Schistosoma.

Praziquantel (Figure 1) is chemically defined as 2-(Cyclohexanecarbonyl-3,6,7,11b-tetrahydro-1H-pyrazino[2,1a] isoquinolin-4-one). It is clinically used as the drug of choice in the treatment of schistosomiasis [7,8]. Praziquantel (PZQ) following oral administration has low and variable systemic bioavailability despite almost complete gastrointestinal absorption because it undergoes extensive metabolism by cytochrome P450 [9]. It has plasma half-life between 1h and 3h. The low and variable bioavailability, short half-life and gastrointestinal side effects are possible reasons why transdermal delivery could be an alternative route of administering praziquantel. Furthermore, schistosomiasis being a debilitating chronic tropical disease, transdermal delivery route could have an advantage in terms of patient compliance over the current oral route.

Transdermal delivery of praziquantel has been studied in different solvents [10]. As praziquantel has ionizable group in its molecular structure, pH control invariably will affect its skin permeability. Literature survey has revealed little or no information on the effect of pH control on skin permeability of praziquantel. Therefore, in the present study, we investigated the effect of pH control on the skin permeability of praziquantel using a mathematical

model that relates partition coefficient to permeability coefficient.

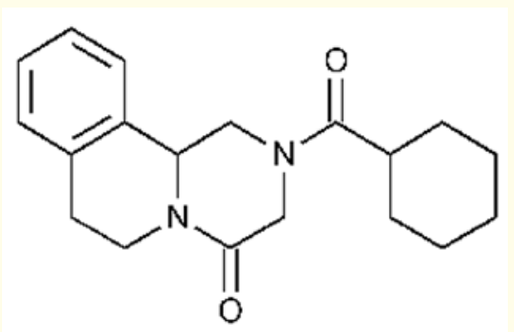

Figure 1: Chemical structure of praziquantel.

Partition coefficient has been reported as a reliable descriptor to evaluate dermal absorption (skin permeability) of chemical compounds [11]. Other reports indicate that the permeability coefficient can be used quantitatively to determine the rate of penetration of chemical compounds into the skin [12,13]. Potts and Guy [14] have shown that dermal permeability coefficient depends on the partition coefficient and molecular weight of a chemical compound. Furthermore, dermal permeability coefficient has been shown as an easy parameter in determining the usage and effectiveness of topical drugs [15].

Against this background, the present study investigated the effect of pH on the partition coefficient of praziquantel, while envisaging that the data collected would allow the effect of pH on skin (dermal) permeability of praziquantel to be predicted.

Materials and Methods

Materials

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

Methods

Preparation of 0.1M buffer solutions

1. Hydrochloric acid buffer pH 2.0: Prepared using hydro chloric acid and potassium chloride.
2. Biphthalate buffer pH 4.0 - 5.0:
   (a) pH 4.0: Prepared using potassium biphthalate and hydrochloric acid.
   (b) pH 5.0: Prepared using potassium biphthalate and sodium hydroxide.
3. Phosphate buffer pH 6.0-7.0: Prepared using monobasic potassium phosphate and sodium hydroxide.
4. Borate buffer pH 8.0-10.0: Prepared using boric acid and sodium hydroxide.

Preparation of standard solution

Praziquantel stock solution (20.0 µg/ml) was prepared in methanol. Aliquots (2.0 - 10.0 µg/ml) of the standard stock solution were pipetted into a 10 ml volumetric flask and diluted to volume with methanol.

Partition coefficient measurement

The partition coefficient of praziquantel was determined in a chloroform-buffer system. To 5 ml of chloroform (saturated with different buffer solutions) containing 400 µg of praziquantel in a vial was added 5 ml of aqueous buffer solution (saturated with chloroform). The vials were capped and agitated at room temperature for 2h to achieve complete equilibration. The phases were allowed to separate in a separating funnel. The praziquantel content was analyzed spectrophotometrically using UV/VIS spectrophotometric method (Perkin Elmer Lambda 35 UV-VIS spectrophotometer) at a maximum wavelength of 263 nm. The drug concentration was obtained from a pre-constructed calibration graph. The partition coefficient of praziquantel was calculated using equation 1 [16].

$$P = C_o V_w / C_w V_o, \quad \text{---Equation. 1}$$

where P is the partition coefficient; C_o is the concentration of praziquantel in organic phase; C_w is the concentration of praziquantel in aqueous phase; V_w is the volume of the aqueous phase; V_o is the volume of organic phase.

Results and Discussion

The calibration graph of praziquantel was linear in the concentration range of 2.0 - 10.0 µg/ml. Absorbance versus concentration relationship is described by regression equation:

A = 0.0729C + 0.0063 (r = 0.99858).

The linearity of the graph obtained in the calibration of the standard praziquantel shows that Beer's law was obeyed. To evaluate pH- partition coefficient profile of praziquantel, logarithm apparent (observed) partition coefficient was plotted against pH as shown in figure 2. A non-linear graph was obtained.

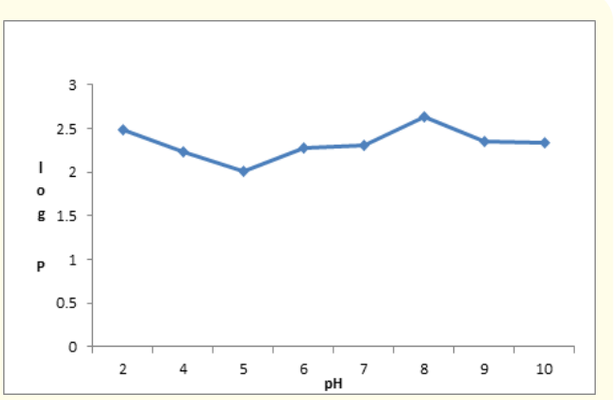

Figure 2: Plot of pH versus logarithm partition coefficient.

The pH- partition coefficient profile would allow the dissociation constant (pK_a) of praziquantel to be determined. This physicochemical parameter will contribute in predicting the effect of pH on skin permeability. To obtain the pK_a of the drug, a plot of apparent partition coefficient versus product of apparent partition coefficient and hydrogen ion concentration was constructed using equation 2 [17]. A linear graph was observed and from the slope of the graph, a value of 7.69 for pK_a (-log K_a) was calculated while a value of 213.202 (log P: 2.33) for Pm was also calculated from the intercept.

$$P_{app} = \frac{P_m - [H_3O^+]P_{app}}{K_a} \quad \text{---Equation. 2}$$

where P_{app} is the apparent (observed) partition coefficient of praziquantel, P_m is the partition coefficient of the free form (unionized), K_a is the dissociation (ionization) constant.

In order to estimate activation energy involved in the partitioning of the drug into chloroform-buffer system, a cubic equation (equation 3) that defined relationship between activation energy and logarithm partition coefficient was utilized [18]. The results are presented in table 1.

$$E_m = 16.724 + 2.884(\log P) - [-4.175 (\log P)^2 + 0.802 (\log P)^3$$

---Equation. 3

When the logarithm partition coefficient values were plotted against estimated activation energy values, a linear relationship (Figure 3) occurred and the correlation coefficient was 0.99798. Activation energy has been reported to have linear relationships with the partition coefficients for a series of phenolic compounds [18].

pH	log P	kp (cm/h)	Jss (µg/cm²/h)	Ea (Kcal/mol)	D (cm²/h)
2.03	2.485	0.00138	0.552	61.98	3.45×10^{-6}
4.01	2.228	0.00090	0.360	52.74	2.25×10^{-6}
5.04	2.012	0.00064	0.256	45.96	1.60×10^{-6}
6.02	2.277	0.00098	0.392	54.40	2.45×10^{-6}
7.06	2.312	0.0010	0.400	55.62	2.50×10^{-6}
8.04	2.625	0.00173	0.692	67.57	4.33×10^{-6}
9.05	2.349	0.00111	0.444	56.93	2.78×10^{-6}
10.03	2.332	0.00107	0.428	56.33	2.68×10^{-6}
Water	1.926	0.00055	0.220	43.49	1.38×10^{-6}

Table 1: Partition coefficient and calculated skin permeability parameters of praziquantel.

To estimate the permeability coefficient, Potts equation (equation 4) was used.

$$\log k_p(\text{cm/h}) = -2.72 + 0.71 (\log P) - 0.0061 (MW) \quad \text{---Equation. 4}$$

The results are given in table 1. From the results, the maximum estimated permeability coefficient occurred at pH 8.0.

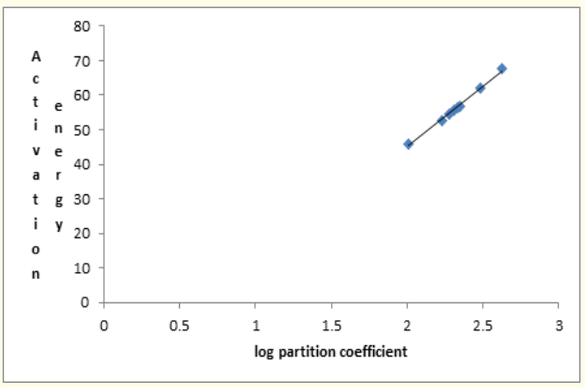

Figure 3: Plot of logarithm partition coefficient versus activation energy.

To correlate experimental partition coefficient with estimated permeability coefficient, logarithm partition coefficient was plotted against logarithm estimated permeability coefficient. A linear relationship (Figure 4) was observed with correlation coefficient of 0.99989. At very acidic pH (pH2.0) and slightly basic pH (pH 8.0) respectively, the estimated permeability coefficient was found to have maximum value. The estimated permeability coefficient would enable us to predict and understand quantitatively the penetration rate of praziquantel into the skin. The parameter will also represent skin permeability of unionized praziquantel since Pott's equation deals with unionized permeants in an aqueous formulation. Therefore, the aqueous phase would have to be acidic or basic to suppress ionization of praziquantel and that will be a function of the pKa of the drug.

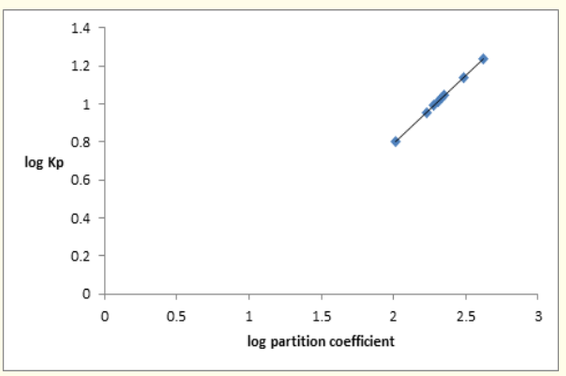

Figure 4: Plot of logarithm partition coefficient versus logarithm permeability coefficient.

The estimated maximum flux through the skin was obtained by taking the estimated permeability coefficient and multiplying it by the aqueous solubility of the drug. The results are given in table 1. Flux at steady-state is one of the parameters to evaluate dermal percutaneous absorption. However, previous report [19] has suggested that permeability coefficient is a more reliable parameter than maximum flux to evaluate dermal percutaneous absorption. The diffusion coefficient in the skin membrane was also estimated using the following relationship:

$k_p = KD/h$ ---Equation. 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 stratum corneum. K is defined as C_s/C_v, where C_s is the aqueous solubility of the drug and C_v is the drug concentration in the vehicle.

An average of 2.5×10^{-3} cm skin thickness was used in the study. The results are presented in table 1. The results indicate that diffusivity occurred more at acidic pH (pH 2.0) and slightly basic pH (pH 8.0) respectively. The parameter would allow us to estimate the maximum flux of the combination of unionized and ionized species by combining estimated permeability generated when logD (Table 1) replaces logP in Pott's equation with the aqueous solubility of the drug. As previous study [20] has shown that diffusion coefficients of alcohols in hydrated skin were ten times more than that observed in dry skin, the results of the present investigation suggest that buffer solution would be a better carrier vehicle than organic solvent (ethylene glycol monophenyl ether) as previously reported by Xin-Sheng Zheng., *et al* [10]. Although the present study has indicated that praziquantel skin permeability could be enhanced by pH control of vehicle in contact with the skin, differences could occur when *in vivo* studies are investigated where factors such as ion pairs, active processes may be involved in maintaining the pH value of the skin.

Conclusion

Skin permeability of praziquantel is strongly pH-dependent with maximum permeability coefficient observed at slightly high basic pH (pH 8.0). Both ionized and nonunionized species could have contributed to the total skin permeability of praziquantel. As permeability coefficient is very good descriptor to predict the transdermal delivery of chemical compounds, the results then suggest that pH 8.0 is the preferred pH to be employed in the formulation of transdermal dosage forms containing praziquantel.

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