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Is Transdermal Delivery Potential Route for Sitagliptin Phosphate: The pH Control Effect

Chika J Mbah, William O Obonga, Chidinma M Ekebor*

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

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Abstract

The objective of this study is to predict transdermal delivery as a potential route for sitagliptin phosphate. The partition coefficient of sitagliptin phosphate was measured in a chloroform-buffer system using the shake flask method at room temperature, and the analysis was performed under different pH conditions. Established mathematical equations were employed to calculate transdermal parameters. The results indicate that the logarithm partition coefficient values of the drug at pH 2.0 (0.354) and pH 3.0 (0.293) were higher compared to the control (0.274). Statistical analysis revealed the rejection of the null hypothesis at a 95% confidence level when comparing the mean partition coefficient of the drug at pH 2.0 to the mean partition coefficient of the drug in distilled water (control). In conclusion, the results suggest that using permeability coefficient as a reliable parameter, an aqueous solution of pH 2.0 would be the preferred vehicle to formulate a potential transdermal dosage form of sitagliptin phosphate.

*Corresponding Author

Name: Chidinma M Ekebor
Email: bosky24.ec@gmail.com

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INTRODUCTION

The transdermal delivery route (drug delivery through the skin) presents a potentially good alternative to the oral or parenteral routes of drug administration. This route avoids first-pass metabolism, enhances patient compliance, increases the therapeutic index with a simultaneous decrese in side effects, is noninvasive and easy to use, provides steady plasma levels, and reduces inter and intra variability in patients [1]. The barrier properties of the skin in drug delivery can be overcome by various approaches ,including pH control [2][3]. Previous reports have demonstrated that dermal permeability coefficient depends on the partition coefficient and molecular weight of chemical compounds [4][5]. Additionally,studies have shown that the permeability coefficient can quantitatively determine the rate of penetration of chemical compounds into the skin [6][7].

Sitagliptin phosphate **Figure 1**, chemically defined as (R)-4-oxo-4-[3-(trifluoromethyl)-5,6-

dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine, is clinically used to treat type 2 diabetes mellitus.

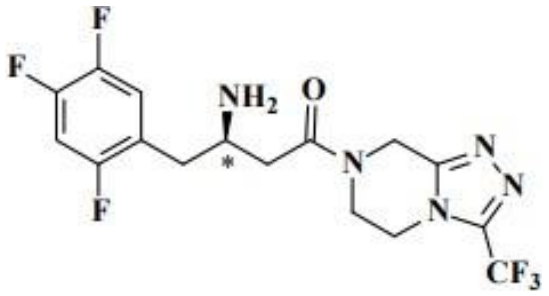

Figure 1 Chemical structure of sitagliptin

As a potent, highly selective dipeptidyl peptidase–4 (DPP-4) inhibitor, it acts by inhibiting the hydrolysis of incretin hormones [namely glucagon like peptide-1 (GLP-1) and glucose dependent insolinotropic polypeptide (GIP)] by dipeptidy peptidase 4. By preventing GLP-1 and GIP inactivation, sitagliptin increases the secretion of insulin by the beta cells of pancreas and suppresses glucagon release by the alpha cells of pancreas hence bringing blood glucose levels towards normal [8][9]. Incretin hormones are gastrointestinal tract hormones released in response to food intake. Currently, the drug exists only in solid dosage form (tablet) with relatively absolute bioavailability (87 %), however compliance could be a problem particularly with geriatric patients. Therefore, the necessity to have an alternative route of administration to overcome the compliance drawbacks as well as side effects that accompany oral administration exists. High potency, minimal protein binding, potential for better patient compliance (as type 2 diabetes mellitus is a chronic disease), lack of hypoglycaemia, and low effective concentration in the body make sitagliptin phosphate a potential candidate for transdermal delivery. Ionizable groups present in sitagliptin phosphate suggest that pH control could influence its transdermal delivery. Literature review showed little or no information on how pH control could affect transdermal delivery of sitagliptin phosphate. Thus, in the present investigation, attempts were made to predict the transdermal delivery of the drug by utilizing calculated partitioning parameters of the sitagliptin phosphate obtained under pH control (using different buffer solutions).

Experimental

2.1 UV/Vis spectrophotometer (Jenway 6305, England), sitagliptin phosphate (Getz Pharma Inc., USA.), hydrochloric acid, sodium hydroxide, potassium biphthalate, monobasic potassium phosphate, boric acid, potassium chloride ethanol and methanol (Fisher Scientific, USA). All other chemicals were of analytical grade and double distilled water was employed in the analysis.

General procedures

Preparation of standard solution of sitagliptin phosphate:

The weighed (0.05 g) pure sample of sitagliptin phosphate was transferred into a 100 ml volumetric flask, dissolved and diluted to volume with methanol (stock solution A).

A dilution of 5 ml of stock A to 50 ml with methanol in a volumetric flask gave stock solution B (50 µg/ml). Working standard solutions (5-30 µg/ml) were prepared from stock B solution and measured at maximum wavelength of 276 nm using UV/Vis spectrophotometer.

Preparation of standard buffer solutions:

Standard buffer solutions between the range of pH 2 and 10 were prepared by appropriate combinations of 0.1M solutions of the chemical substances.

They include:

1. Hydrochloric acid buffer solution (pH 2.0)- prepared using hydrochloric acid and potassium chloride.
2. Biphthalate buffer solutions (pH 3.0-4.0)- prepared using potassium biphthalate and hydrochloric acid.
3. Biphthalate buffer solution (pH 5.0)- prepared using potassium biphthalate and sodium hydroxide.
4. Phosphate buffer solution (pH 6.0)- prepared using monobasic potassium phosphate and sodium hydroxide.
5. Borate buffer solutions (pH 8.0-10.0)- prepared using boric acid and sodium hydroxide.

Partition coefficient determination:

Sitagliptin phosphate partition coefficient was determined in a chloroform-buffer system. A

500 µg of sitagliptin phosphate was transferred to a vial containing 5 ml of chloroform (previously saturated with each of the buffer solution). To this vial was added 4 ml aqueous buffer solution (previously saturated with chloroform). 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 the drug was analyzed at a maximum wavelength of 267 nm using UV/VIS spectrophotometer. The drug concentration in the aqueous layer was obtained from the calibration graph. The partition coefficient of the drug was calculated using the equation below [10]:

$$P = C_1 - C_w / C_w \{V_w/V_o\} \text{---------- equation 1}$$

where P = partition coefficient; C_1 = total concentration of sitagliptin phosphate; Cw = concentration of sitagliptin phosphate in aqueous phase; Vw = volume of the aqueous phase; Vo = volume of the organic phase. The determination was done in triplicates.

Statistical analysis: The data obtained at pH 2.0 was used in statistical analysis. It was compared to the control (distilled water) at a 95 percent confidence level.

RESULTS

The curve obtained by plotting absorbance values versus concentrations of the drug was linear within the concentration range of 5-30 µg/ml. Regression analysis of the plot gave regression equation:

$$A = 0.0062\ C + 0.0029 \text{ ---------- equation 2}$$

with 0.9938.as the correlation coefficient

The pH-partition coefficient data are presented in Table 1. To explain the pH- partition coefficient profile of sitagliptin phosphate, logarithm apparent (experimental) partition coefficient was plotted against pH and a non linear relationship was obtained. The plot is shown in **Figure 2**.

Table 1 Partition coefficient and calculated skin permeability

pH	Log P	Kp (cm/h)	Ea (Kcal/mol)
2.02	0.354±0.003	0.00000218	18.304
3.04	0.293±0.005	0.00000198	17.947
4.01	0.283±0.005	0.00000194	17.893
5.02	0.182±0.004	0.00000165	17.392
6.03	0.076±0.003	0.00000139	16.968
8.04	0.117±0.002	0.00000148	17.120
9.02	0.152±0.003	0.00000157	17.262
10.01	0.188±0.004	0.00000166	17.467
Water	0.274±0.003	0.00000192	17.844

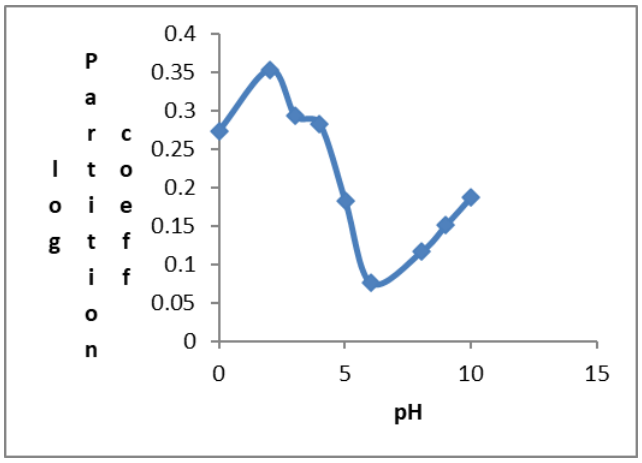

Figure 2 Logarithm of apparent partition coefficient versus pH

To predict the permeability coefficient of sitagliptin phosphate through the skin, the apparent logarithm partition coefficient values were utilized. This was achieved by applying Potts and Guy equation [4]:

$$\log k_p \text{ (cm/h)} = -2.72 + 0.71 (\log P) - 0.0061(MW), \text{ equation 3}$$

where k_p is the dermal permeability coefficient, P is the partition coefficient and MW is the molecular weight of sitagliptin phosphate monohydrate respectively. The results are presented in **Table 1**.

In order to confirm if partition coefficient is a very good parameter to estimate the permeability coefficient, a plot of the experimental (apparent) logarithm partition coefficient versus logarithm estimated permeability coefficient was carried out. A linear graph was obtained with 0.9999 as the correlation coefficient. The plot is given in **Figure 3**.

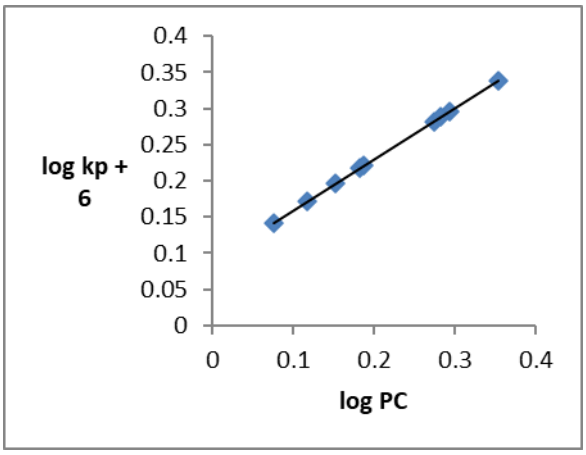

Figure 3 Experimental logarithm partition coefficient versus logarithm estimated

To estimate activation energy involved in the partitioning process, a cubic equation (equation 4) that defined relationship between activation energy and logarithm partition coefficient was employed [11].

E_a = 16.724 + 2.884(logP) – [- 4.175 (log P)2 + 0.802 (log P)3 ---equation. 4

The results are presented in **Table 1**.

Plotting logarithm partition coefficient values versus estimated activation energy values, a linear relationship (**Figure 4**) was obtained and 0.9974 as the correlation coefficient.

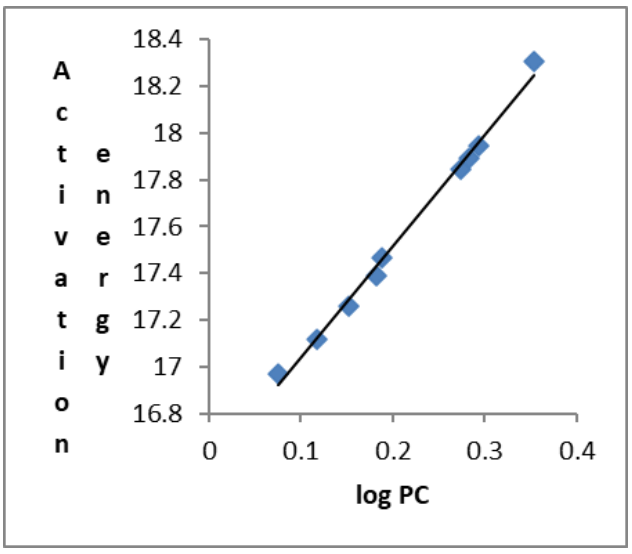

Figure 4 Activation energy versus log apparent partition coefficient

Discussion

The linearity of the calibration graph indicates that Beer's law was obeyed. The high correlation coefficient obtained for the graph confirms the linearity and accuracy of the determination.

The pH- partition coefficient profile results (**Figure 2**) could be explained in terms of the ionization properties of the drug. The initial increase in partition coefficient values within the acidic pH region (pH 2.02- 4.01) might be due to the acidic salt property of the drug. This might also explain the decrease in partition coefficient of the drug as pH was gradually being increased (pH 5.02-6.03). However, at pH 6.03, the drug seemed to have completely lost its acidic nature because at that pH the drug partitioned least into the organic phase. Then followed a gradual increase in partition coefficient of the drug within alkaline pH region (pH 8.04-10.01), The observed increase in partition coefficient of the drug might be as a result of the drug conversion to its base form. The statistical analysis result showed that the null hypothesis was rejected. Therefore, a significant difference is expected from a transdrmal formulation of the drug adjusted to acidic pH (pH 2.0) in comparison to its aqueous transdermal formulation.

The determined partition coefficient values were used to predict dermal permeability coefficient of the drug because permeability coefficient has been reported to be a useful parameter in evaluating dermal absorption of drugs [6,7,12]. The linearity of the plot of 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 estimated permeability coefficient could enable one to predict and quantitatively understand the penetration rate of the drug into the skin.

The parameter also represents skin permeability of unionized sitagliptin phosphate since Pott's equation illustrates the behavior of unionized permeants in an aqueous formulation.

The activation energy (E_a) involved in the partitioning of the drug into the chloroform-buffer system was estimated using a cubic equation (equation 4) relating activation energy and logarithm partition coefficient. The linear plot (**Figure 4**) obtained from the plot 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 [11].

Flux at steady-state (one of the parameters to evaluate transdermal delivery) and diffusion coefficient through the skin (parameter permitting the estimation of the maximum flux of the combination of unionized and ionized species) were not estimated in the present study because both depend on the aqueous solubility of the drug. The drug studied is completely soluble in water, and therefore not aqueous solubility limited. The skin maximum flux would have been estimated by the product of aqueous solubility of the drug and the estimated permeability coefficient. The diffusion coefficient through the skin would also have been estimated using equation 5: kp =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 the stratum corneum (provides the major barrier to the absorption of chemical substances deposited on the skin surface into the systemic circulation), K is defined as Cs/Cv where Cs is the aqueous solubility of the drug, Cv is drug concentration in the vehicle.

In general, prediction and understanding skin permeability from physicochemical parameters of a drug substance have assisted researchers to minimize expenditures, cumbersomeness and time on initial experiments handled using animal and cadaver skin which are subject to biovariation of skin properties in animals and humans.

CONCLUSION

Although, flux and diffusion coefficient were not estimated in this study, prediction of transdermal delivery as a potential route for sitagliptin phosphate could be successful done with permeability coefficient because the parameter has been reported to be a reliable tool in percutaneous absorption studies. Potential skin permeability of sitagliptin phosphate has been observed to be strongly pH-dependent with maximum permeability coefficient found at high acidic pH (pH 2.0). Both ionized and nonunionized species would be expected to contribute to the total skin permeability of sitagliptin phosphate. Finally, as permeability coefficient is very good descriptor to predict the transdermal delivery of chemical compounds, the results of the present study suggest that potential transdermal dosage form of sitagliptin phosphate could be formulated in a aqueous vehicle adjusted to acidic condition (pH 2.0)..

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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