Research Article

Int J. Pharm. Drug. Anal, Vol: 11, Issue: 2, 2023; 50-53

International Journal of Pharmaceutics and Drug Analysis

Content Available at www.ijpda.com ISSN: 2348:8948

PREDICTION OF PASSIVE MEMBRANE PERMEABILITY OF LINAGLIPTIN

Chika J. Mbah, Chinwe M. Onah*, Chibuike F. Iloabuchi

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

Received: 08 Mar 2023 Revised: 22 Mar 2023 Accepted: 26 June 2023

Abstract

Linagliptin is a highly selective inhibitor of dipeptidyl peptidase-4 and therefore clinically utilized to treat adults with type 2 diabetes mellitus. The objective of this study was to predict how the ions normally found in extracellular or intracellular fluids within the body system will influence the linagliptin's rate of passive diffusion across a cell membrane. The methodology involved measuring linagliptin partition coefficient in a chloroform-water system containing the salts at 25 °C by the shake flask method. The results indicate that at the highest concentration (0.5 M) of the salts studied, sodium chloride was found to give the highest partition coefficient value when compared to the control. In conclusion, physiological ions would have little or no effect on the drug's molecular state within extracellular or intracellular fluid as the salts failed to significantly alter the partition coefficient of the drug, hence will not alter passive membrane permeability of linagliptin.

Keywords: Linagliptin, partition coefficient, salts (electrolytes), passive diffusion.

***Corresponding Author**

CM Onah
Department of Pharmaceutical and Medicinal Chemistry
Faculty of Pharmaceutical Sciences,
University of Nigeria Nsukka 410001,
Enugu State, Nigeria.
Tel.:+2347034195701

DOI: https://doi.org/10.47957/ijpda.v11i2.540

Produced and Published by

South Asian Academic Publications

Introduction

Linagliptin, chemically defined as 8-[(3R)-3-Amino-1-piperidinyl]-7-(2-butynyl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]-1H-purine-2,6-dione has a chemical structure as shown in Figure 1. Linagliptin is a highly selective dipeptidyl peptidase-4 inhibitor clinically indicated for once daily use to treat adults with type 2 diabetes mellitus. Its mechanism of action entails lowering blood glucose levels by inhibiting the enzyme DPP-4, thus preventing incretin hormones degradation [1]. The incretin hormones are glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). Incretins are secreted at a low basal level throughout the day, however levels are observed to rise immediately after meal intake. The hormones are involved in the physiological regulation of glucose homeostasis. The selective targeting of DPP-4 by linagliptin potentially causes a more physiologically based control of fasting blood glucose as well as glucose-dependent postpradial glucose excursions mediated by glucose effect on insulin and glucagon secretion.

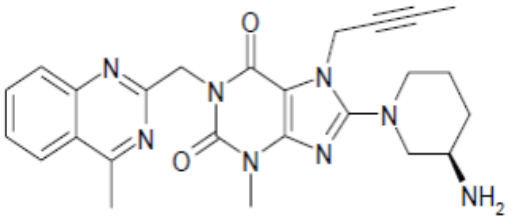


Figure 1 Chemical structure of linagliptin

The drug is very slightly soluble in acetone, water and isopropanol, soluble in methanol and sparingly soluble in ethanol. Linagliptin is a basic drug with pKa of about 9-10, partition co-efficient (log P = 1.7, free base) and distribution coefficient (log D, pH 7.4 = 0.4).

The pharmacokinetics of the drug indicates that it is rapidly absorbed following oral administration, and has absolute bioavailability of 30 % [2]. Unlike other DPP-4 inhibitors, most of the absorbed drug is excreted unchanged through non-renal route [3]. with about 84.7 % eliminated through bile and the gut (faeces) and 5.4 % excreted in urine [4].

The body water is distributed into two main compartments namely extracellular and intracellular compartments [5]. The cell membranes separate these compartments from each other. The plasma volume, interstitial fluid, and transcellular fluid make up the extracellular fluid. Electrolytes necessary for fluid balance (sodium, chloride ions); acid-base balance (potassium, bicarbonate ions); energy (phosphate ions); osmotic

pressure (sodium, chloride ions); enzymatic activities (magnesium ions); blood clotting and bone integrity (calcium ions);are found both in extracellular and intracellular fluids. The rate of passive diffusion across a cell membrane has been reported to be proportional to the partition coefficient of the drug between the external medium (aqueous environment) and the lipophilic cell membrane; the diffusion coefficient of the drug through the membrane, and the drug's concentration gradient across the membrane [6]. The membrane permeability controls the uptake and efflux of drugs in relevant compartments. To predict passive membrane permeability, lipophilicity is the most critical parameter to be investigated [7]. The logarithm partition coefficient (log P) of a chemical substance between an aqueous and organic phase, (usually water and octanol) is the parameter which determines the lipophilicity of a chemical substance [8]. Since most drugs pass at least one cellular membrane to reach the site of action, it becomes important to know how electrolytes present in biological fluids compartments affect the lipophilicities of active chemical substance (drug) molecules. Linagliptin was the drug of choice in the present study amongst DPP-4 inhibitors, because it is the only drug in this class that most of the absorbed drug is excreted unchanged through non-renal route.

Thus, in an attempt to verify if biological fluid ions affect the lipophilicity of linagliptin and hence its excretion, the present study, investigated the influence of electrolytes (salts) on the partition coefficient of linagliptin.

Experimental

UV/Vis spectrophotometer (Jenway 6305, England), linagliptin (Sreeven Pharma Pvt, India), the salts (sodium chloride, sodium sulfate, potassium chloride, calcium chloride, cobalt chloride. potassium sulfate, magnesium sulfate, aluminium sulfate) were purchased from Fischer Scientific, (USA). All other chemicals were of analytical grade and double distilled water was utilized in the analysis.

General procedures

The standard solution of linagliptin was prepared by accurately weighing 10 mg of the reference drug and transferred to a 100 ml volumetric flask, dissolved in methanol and diluted to volume with methanol (stock solution A). Stock B flasks solution was prepared by diluting 1 ml of stock A to 10 ml with methanol in a volumetric flask. Working standard solutions (1.0, 2.0, 3.0, 4.0, 5.0 µg/ml) were prepared in volumetric from stock B solution.

The salt solutions were obtained by preparing a stock of one molar (1M) solution of each salt in double distilled water. Working salt solutions (0.05, 0.1, 0.2, 0.3, 0.4, 0.5 M) were prepared by diluting the stock solution.

Linagliptin partition coefficient was measured in a chloroform-water system. To 5 ml of saturated chloroform in a vial containing 50 µg/ml of linagliptin was added 4 ml of distilled water (control) or saturated aqueous solution of each of the salts studied. The vials were capped and agitated at room temperature for 2 h to obtain complete equilibration. The mixture was transferred to a separating funnel and the phases were allowed to equilibrate for about 15 min and separate. The aqueous phase was analyzed at a maximum wavelength of 292 nm using UV/Vis spectrophotometer. Linagliptin concentration was obtained from a pre-constructed calibration graph. The partition coefficient of the drug was calculated using equation 1 [8].

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

Where P is the partition coefficient; C_1= the total concentration of linagliptin; C_w = the concentration of linagliptin in aqueous phase; V_w = the volume of the aqueous phase; V_o = the volume of organic phase.

Results and Discussion

A plot of absorbance versus concentration, gave a linear graph. The regression analysis of the plot gave an equation: Abs = 0.05996C-0.00762. The linearity (defined by the correlation coefficient of 0.9992) of the plot between absorbance and concentrations of the drug shows that Beer-Lambert law was obeyed.

The results obtained from the partition coefficient analysis are presented in Table 1.

Table 1: Partition coefficient of linagliptin

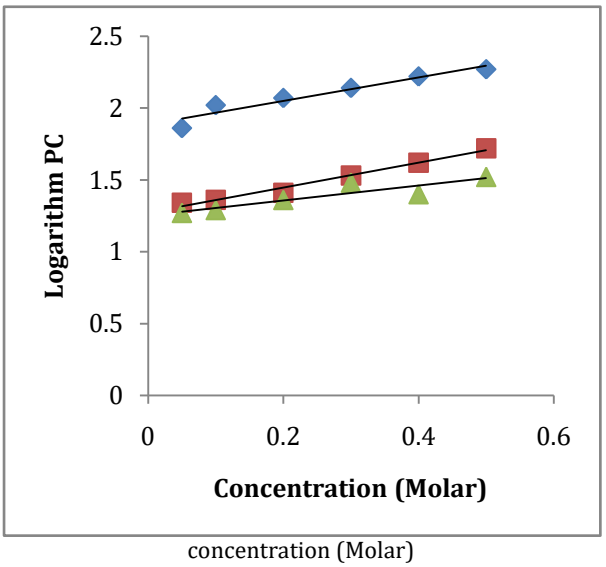
Conc. (M)	Logarithm partition coefficient, mean±SD (SD= Standard deviation)							
	NaCl	KCl	$CaCl_2$	$CoCl_3$	Na_2SO_4	K_2SO_4	$MgSO_4$	$Al_2(SO4)_3$
0.0	1.68±0.015	1.68±0.015	1.68±0.015	1.68±0.015	1.68±0.015	1.68±0.015	1.68±0.015	1.68±0.015
0.05	1.86±0.020	1.34±0.031	1.27±0.030	1.22±0.032	1.45±0.031	1.38±0.032	1.32±0.025	1.14±0.035
0.10	2.02±0.035	1.36±0.026	1.29±0.035	1.25±0.026	1.66±0.035	1.42±0.025	1.37±0.035	1.25±0.032
0.20	2.07±0.016	1.41±0.024	1.36±0.025	1.28±0.030	1.78±0.033	1.46±0.023	1.42±0.036	1.32±0.041
0.30	2.14±0.031	1.53±0.035	1.48±0.045	1.32±0.033	1.89±0.040	1.58±0.033	1.53±0.041	1.38±0.044
0.40	2.22±0.026	1.62±0.026	1.40±0.041	1.38±0.029	1.97±0.036	1.65±0.036	1.59±0.045	1.45±0.042

0.5 0	2.27±0.009	1.72±0.031	1.52±0.046	1.43±0.034	2.18±0.021	1.81±0.034	1.70±0.031	1.52±0.047

The results indicate that the partition coefficient of linagliptin increased as the concentrations of the electrolytes (salts) were being increased. At the highest concentration level (0.5 molar) studied, cobalt (Co^{3+}) ion produced the least partition coefficient value of the drug. With the chloride anion (Cl^-), it was observed the order of increase in the partition coefficient of linagliptin is $Na^+ > K^+ > Ca^{2+} > Co^{3+}$. Similarly with sulfate anion (SO_4^{2-}), it was also noted that the order of increase in the partition coefficient of linagliptin is $Na^+ > K^+ > Mg^{2+} > Al^{3+}$. However, with the same cation (for example Na^+ion), the order of increase in the partition coefficient of the drug is $Cl^- > SO_4^{2-}$. Partition coefficient is extensively utilized to predict the bioactivity of drugs as it exhibits interesting superficial similarity with lipids [10].

The correlation between experimental partition coefficient and the concentration of the salts was expressed by plotting logarithm partition coefficient of the drug versus concentration of salts (Figures 2 and 3 respectively) and linear relationships were observed. The correlation coefficients of these linear plots are 0.9612, 0.8811, 0.9048, 0.9771, 0.9831, 0.9951 for sodium chloride, potassium chloride, calcium chloride, sodium sulfate, potassium sulfate and magnesium sulfate respectively. Furthermore, the correlation coefficients (plots not presented) of cobalt chloride and aluminum chloride were found to be 0.9949 and 0.9859 respectively.

Figure 2: Plot of logarithm partition coefficient versus concentration (Molar)



□-------□ NaCl
□-----□ KCl
Δ------Δ $CaCl_2$

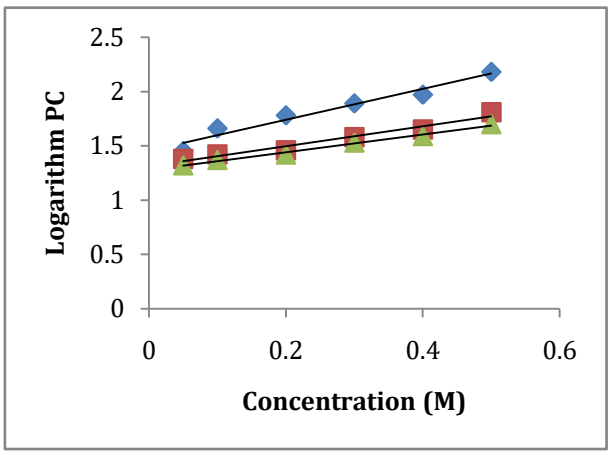


Figure 3: Plot of logarithm partition coefficient versus concentration (Molar)

□-------□ Na_2SO_4
□-----□ K_2SO_4
Δ------Δ $MgSO_4$

Sodium, potassium and magnesium ions that increased the partition coefficient of the drug at the highest concentration studied (0.5 molar) when compared to the control, may have the tendency to enhance the membrane permeability of linagliptin in relevant compartments. This will probably occur because the drug will have more of its unionized form in both the extracellular and intracellular fluids.

The reverse effect on the membrane permeability of linagliptin may be expected from calcium, cobalt, aluminum ions as a result of their decrease in partition coefficient of the drug when
compared to the control. In general, the ions influence on the drug's partition coefficient could be explained in terms of ionic charges and sizes of these ions. Calcium, cobalt, aluminum ions when compared to sodium potassium, magnesium ions, have the greatest charges and largest ionic sizes (invariably largest ionic volumes) and these properties must have contributed to their

strongest interaction with the drug. Likewise, ionic charge and size might be responsible for the difference observed with sulfate ion and chloride ions on the partition coefficient of the drug.

Conclusion

The partition coefficient values of linagliptin were not significantly altered by the salts (electrolytes) investigated, implying that physiological ions would have little or no effect on the drug's molecular state in either the extracellular fluid or intracellular fluid, and therefore will have no effect on passive membrane permeability of linagliptin. Furthermore, the study reveals that linagliptin can be concomitantly administered with inorganic drugs like antacids or antiemetics, without the therapeutic effect of linagliptin being altered.

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

Funding
No Funding

Author contribution
All authors are contributed equally

Ethical Considerations
Not Applicable

References

1. Boer GA, Holst JJ. Incretin hormones and type 2 diabetes-Mechanistic insights and therapeutic approaches. Biology. 2020;9(12): 473-478.
2. Retlich S, Duval V, Ring A. Pharmacokinetics and pharmacodynamics of single rising intravenous dose (0.5 mg-0 mg) and determination of absolute bioavailability of dipeptidyl peptidase-4 inhibitor linagliptin (B 1 1356) in healthymale patients. Clinical Pharmacokinetics. 2010;49: 829-840.
3. Deeks ED. Linagliptin. Drugs. 2012;72(13): 1793-1824.
4. Blech S, Ldwig-Schwellinger E, Grafe-Mody EU. The metabolism and disposition of the oral dipeptidyl peptidase-4 inhibitor, linagliptin in humans. Drug Metabolism Disposition. 2010;38(4): 667-678.
5. Agrò FE, Vennari M. Physiology of Body Fluid Compartments and Body Fluid Movements. In: Agrò FE Body Fluid Management. Milano, Italy, Springer, 2013, pp. 1-25.
6. Wolak DJ, Thorne RG. Diffusion of macromolecules in the brain: implications for drug delivery. Molecular pharmaceutics. 2013;10(5): 1492-1504.
7. Liu X, Testa B, Fahr A. Lipophilicity and its relationship with passive drug permeation. Pharmaceutical research. 2011;28(5): 962-77.
8. Shuo S, Shu-zhi L, Mao-bo D, Ke-ya G, Lihua S, Zu-guang Y. Determination of equilibrium solubility and apparent oil/water partition coefficient of artesunate. Chinese Journal of Experimental Traditional Medical Formulae. 2013;19: 9-12.
9. Johansen M, Bundgaard H. Prodrugs as drug delivery systems XI. Solubility, dissolution and partition behaviour of n-mannich bases and n-hydroxymethyl derivatives. Archives Pharmaceutical Chemistry Science Education 1980;8: 141-151.
10. Pallicer JM, Rosés M, Ràfols C, Bosch E, Pascual R, Adriana PA. Evaluation of log Po/w values of drugs from some molecular structure calculation software. ADMET & DMPK 2014;2(2): 107-114.