Available online at www.sciencedirect.com

ScienceDirect

APCBEE Procedia 9 (2014) 151 – 158

Procedia APCBEE

www.elsevier.com/locate/procedia

2013 5th International Conference on Chemical, Biological and Environmental Engineering (ICBEE 2013)
2013 2nd International Conference on Civil Engineering (ICCEN 2013)

Pharmacokinetics Study of Metformin - Mathematical Modelling and Simulation

Sukankana Chakraborty[a], Kriti Arora[a], Prakash Kumar Sharma[a], Arijit Nath[b] and Chiranjib Bhattacharjee[b,*]

[a]*Department of Biotechnology, Heritage Institute of Technology, Kolkata -700107, West Bengal, India*
[b]*Department of Chemical Engineering, Jadavpur University, Kolkata – 700032, West Bengal, India*

Abstract

In the present investigation, a deterministic mathematical model of the pharmacokinetics of Metformin was developed using the first principle of chemical engineering (mass balance). The mathematical model developed with precision, can predict the concentration time history of the drug interest in stomach, liver, intestine, and the peripheral areas. According to this model, after administration, the drug is dissolved in the stomach following first order kinetics. The intestinal absorption of Metformin is majorly mediated by plasma membrane monoamine transporter. In liver Metformin takes part in various metabolic pathways which subsequently aid the adsorption of the drug in different cellular systems. No intermediate metabolites of Metformin have been identified till now. The major route for elimination of Metformin is through tubular secretion, in an unchanged form in the urine. The outcome of the predicted data closely matches the experimental finding, extracted after a meticulous scrutiny of the accessible literature, and results of clinical trials. The model is highly realistic and pragmatic in its practice.

Selection and peer review under responsibility of Asia-Pacific Chemical, Biological & Environmental Engineering Society

Keywords: Metformin, Pharmacokinetics, Mathematical model

* Corresponding author.
E-mail address: cbhattacharyya@chemical.jdvu.ac.in.

Selection and peer review under responsibility of Asia-Pacific Chemical, Biological & Environmental Engineering Society
doi:10.1016/j.apcbee.2014.01.027

1. Introduction

Pharmacokinetics is the study of the course of a drug in its metabolised form in different body fluids and tissues, followed by establishing mathematical relationships, required for developing the necessary models for processes such as absorption, distribution, metabolism and excretion of the drug. The pharmacokinetic processes determine the drug concentration in various organs of the body [1]. The pharmacokinetic analysis of the drug aids in deciding the correct dosage of the drug to be prescribed and hence, is widely put to use in the field of drug designing and molecular modelling for the development of efficient therapeutic drugs. Much work is being done on developing the mathematical model to understand the metabolism of the drug, with the purpose of making realistic clinical predictions [2-5].

Metformin (dimethylbiguanide) is widely used in the treatment of Type II diabetes mellitus or non-insulin-dependent diabetes mellitus (NIDDM). Diabetes mellitus is a metabolic disorder characterized particularly by elevated glucose concentration in the blood. This occurs mostly due to insulin resistance or deficiency of insulin, causing high blood glucose level. The development of this chronic disease is a confluence of genetic factors and lifestyle choices. Metformin has been widely used as a blood glucose controlling agent in Type II diabetes mellitus since 1957 [6, 7].

In the present investigation, a deterministic mathematical model of pharmacokinetics of Metformin is developed using the first principle of chemical engineering (mass balance). The mathematical model is potential to predict the concentration time history of the drug interest in different organs, such as, stomach, liver, intestine, tissue and the kidney. In the initial investigations of the available literature, it is found that Metformin stimulates and controls a wide range of metabolic reactions in various parts of the body, primarily the liver, gastrointestinal tract, blood and tissues. Hence the pharmacokinetic study of Metformin was carried out framed on the compartment model. This is the first attempt to the best of our knowledge to develop the mathematical model of pharmacokinetics of Metformin. The developed mathematical model is highly realistic and the simulated results have been justified with the already published results extracted from accessible literature and results of clinical trials.

2. Mathematical Modelling

The mathematical modelling of pharmacokinetics of Metformin has been developed taking into account the following assumptions:

- Drug flow rate is unidirectional from oral cavity to excretory system.
- In the stomach dissolution of Metformin by gastro-intestinal juices follows the 1st order kinetics.
- Metformin acts as the substrate for the Organic Cation Transporter (OCTN2) in the intestine, and the mechanism follows Michaelis-Menten reaction kinetics. Formation of Metformin from Metformin~OCTN2 is instantaneous.
- Metformin facilitates phosphorylation of 5'-AMP activated protein kinase (AMPK) mediated by its binding to the SLC22A1/SLC22A3 in the hepatic cells. This mechanism also follows Michaelis-Menten reaction kinetics. Formation of Metformin from Metformin~SLC22A1/ Metformin~SLC22A3 is instantaneous.
- Accumulation of Metformin and associated biochemical reactions in the brain are considered negligible.
- Kidney is the only system responsible for excretion.

The schematic diagram of the proposed process is described in Fig 1.

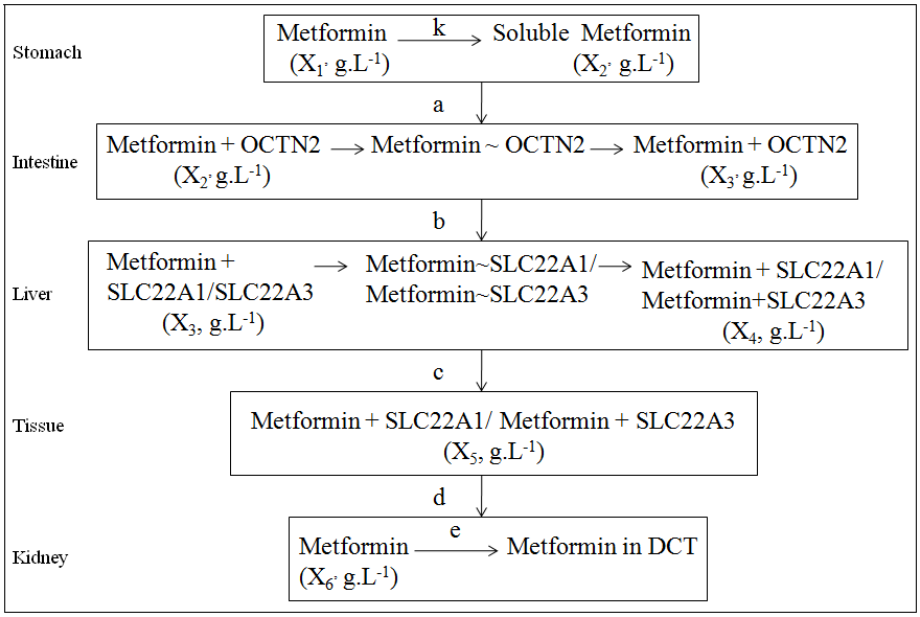

Fig. 1. Schematic diagram of pharmacokinetics of Metformin

Different mass balance equations of the proposed process are described below.

$$\frac{dX_1}{dt} = -kX_1 \tag{1}$$

$$\frac{dX_2}{dt} = kX_1 - aX_2 \tag{2}$$

$$\frac{dX_3}{dt} = \frac{v_{max_3} X_2}{K_{m_3} + X_2} - bX_3 \tag{3}$$

$$\frac{dX_4}{dt} = \frac{v_{max_3} X_3}{K_{m_3} + X_3} - cX_4 \tag{4}$$

$$\frac{dX_5}{dt} = cX_4 - dX_5 \tag{5}$$

$$\frac{dX_6}{dt} = dX_5 - e0.1 \tag{6}$$

At t = 0,

$$\begin{bmatrix} X_1 = X_{1_0} \\ X_2 = 0 \\ X_3 = 0 \\ X_4 = 0 \\ X_5 = 0 \\ X_6 = 0 \end{bmatrix} \quad (7)$$

Since, no literature data of kinetic parameters are available of the proposed process**,** some adjustable parameters have been considered for simulation purposes. The values, and magnitudes of the kinetic parameters are described in table 1. In the present investigation three different initial concentrations of Metformin, such as 0.3 $g.L^{-1}$, 0.4 $g.L^{-1}$, and 0.5 $g.L^{-1}$ have been considered for simulation purposes. The **v**alidity of the model has been checked by some already published research findings. The model equations 1-6 have been solved using 4th order Runge-Kutta method with the aid of MATLAB 7.0 using the stated initial conditions.

Table 1. List of parameters used in model.

Parameter	Value	Parameter	Value
Linear blood flow rate from stomach to intestine (a), h^{-1}	0.1	Dissolution rate of Metformin in stomach (k), h^{-1}	1.0
Linear blood flow rate from intestine to liver (b), h^{-1}	0.25	Michaelis-Menten constant of eq. 3 $\left(K_{m_3}\right)$, $g.L^{-1}$	4
Linear blood flow rate from liver to tissue (c), h^{-1}	0.5	Michaelis-Menten constant of eq. 4 $\left(K_{m_5}\right)$, $g.L^{-1}$	4.5
Linear blood flow rate from tissue to kidney (d), h^{-1}	1.0	Reaction rate constant in intestine $\left(v_{\max_3}\right)$, $g.L^{-1}.h^{-1}$	1.0
Linear blood filtration rate in kidney (e), h^{-1}	0.1	Reaction rate constant in liver $\left(v_{\max_5}\right)$, $g.L^{-1}.h^{-1}$	0.75

3. Results and Discussion

The above mentioned deterministic mathematical model has been developed to elucidate the pharmacokinetics of Metformin. Metformin is a multi-dose drug administered either orally or intravenously. It is generally prescribed twice a day; therefore it follows the flip-flop kinetics. However, the amount of drug given to a patient must never exceed 3 $g.day^{-1}$. In the present mathematical model, it is considered that the drug is administrated by orally. In Fig 2 time history concentration of Metformin in stomach for different initial doses are represented. According to this model, after administration, Metformin is dissolved in the

stomach following first order kinetics. It is observed that the concentration of Metformin for initial concentration 0.5 $g.L^{-1}$ reaches zero within an hour, showing agreement with available clinical data [8]. The drug is poorly absorbed in the stomach; however, it is known to induce a duodenum-gastric reflux which passes onto the duodenum about 20% of the amount of drug that has been absorbed in the stomach [9].

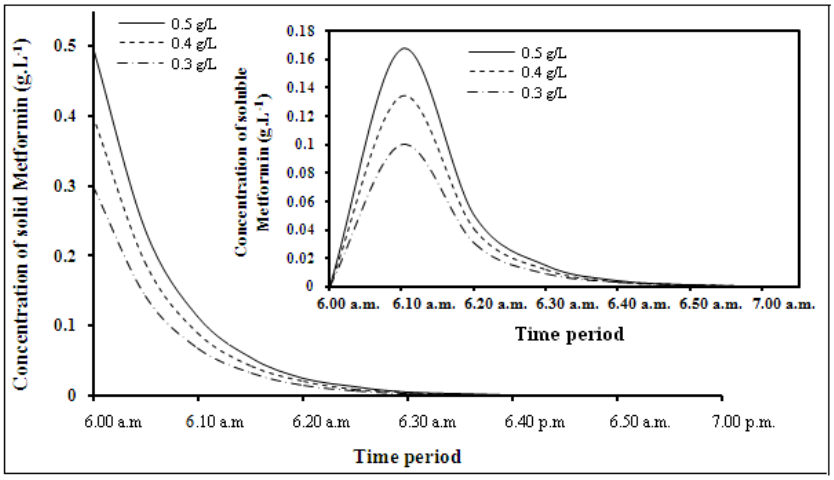

Fig. 2. Time history concentration of solid Metformin in stomach for different initial concentrations of Metformin. (inset: Time history concentration of soluble Metformin in stomach for different initial concentrations of Metformin.)

In Fig. 3, time history concentration of Metformin~OCTN2 in intestine for different initial doses are represented. The concentration of the drug in the intestine increases with time and reaches 80% of the given initial concentration of the drug, which is in coherence with the available scientific data. The jejunum, and ileum are responsible for about 10.8% and 8.8% of the absorption of Metformin respectively [9]. Similar type of time history concentration of Metformin has been plotted for evening time (data not shown).

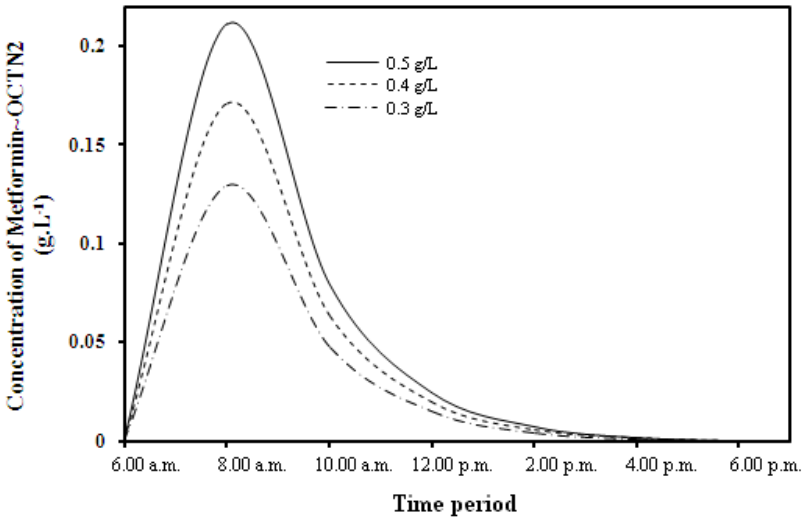

Fig. 3. Time history concentration of Metformin~OCTN2 in intestine for different initial concentration of Metformin.

In Fig. 4, time history concentration of Metformin~SLC22A1/ Metformin~SLC22A3 in liver for different initial doses are represented.

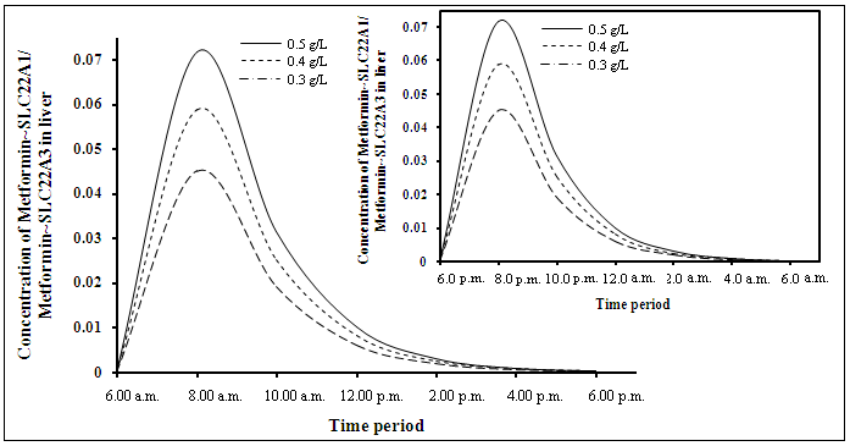

Fig. 4. Time history concentration Metformin~SLC22A1/ Metformin~SLC22A3 in liver for different initial concentration of Metformin (Morning time). (inset: Time history concentration Metformin~SLC22A1/ Metformin~SLC22A3 in liver for different initial concentration of Metformin (Evening time))

Fig. 4 also shows an increasing trend for concentration of the drug with time in the liver. The drug flows to the liver where it activates AMP-activated protein kinase (AMPK), a liver enzyme which plays a significant role in insulin signaling. The relative decrease in the slope of the graph implies a slower rate of absorption of the drug suggesting an enzymatic reaction involved which activates AMPK (AMP-activated protein kinase) in hepatocytes and hence helps inhibit production of glucose and also increase insulin sensitivity [10]**.** Similar type of time history concentration of Metformin for evening time has been manifested in the same figure.

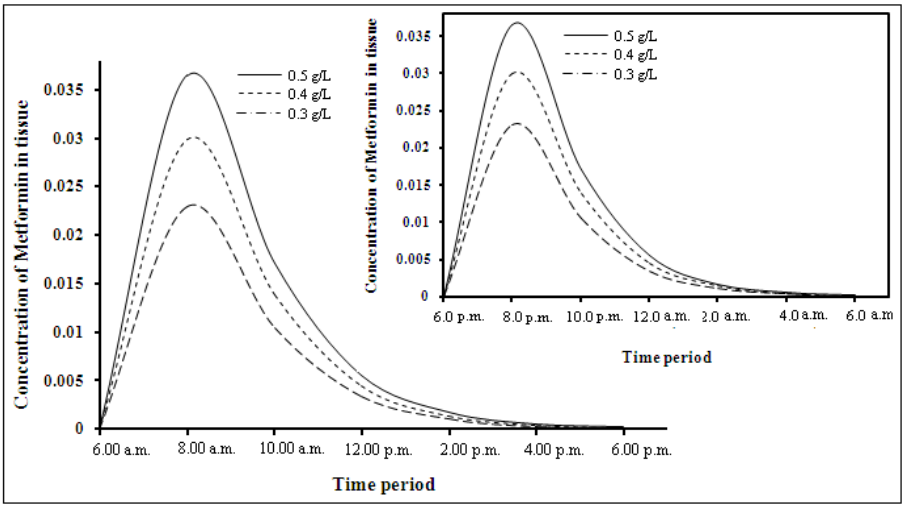

Fig. 5. Time history concentration of Metformin in tissue for different initial concentration of Metformin (Morning time). (inset: Time history concentration of Metformin in tissue for different initial concentration of Metformin (Evening time))

In Fig. 5 concentration of Metformin in tissue is plotted with time parameter. The concentration peaks after a time interval of approximately 2 hours following the administration of the drug. This information conforms to the data as obtained in clinical trials suggesting that maximum plasma concentration (C_{max}) is reached in roughly 2 hours for all subjects. It may be further concluded that the plasma protein binding of metformin is negligible, as revealed by its very high apparent volume of distribution (300–1000 L after a single dose). In the course of clinical trials of Metformin, even at maximum doses it was observed that the Metformin plasma levels did not exceed 5 mcg.mL^{-1}[11]. Similar type of time history concentration of Metformin for evening time has been manifested in the same figure.

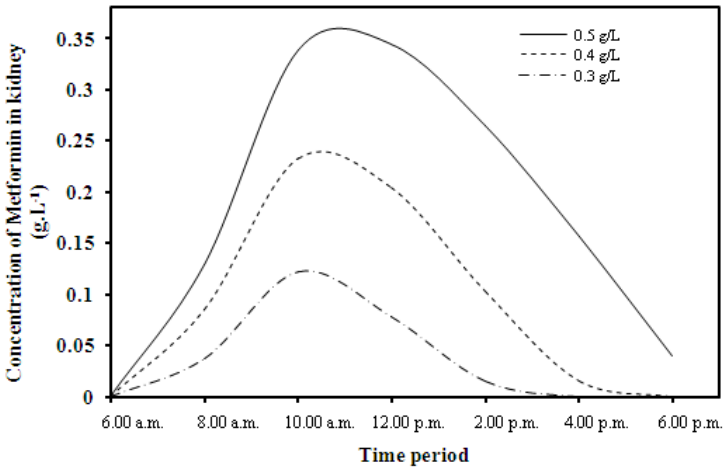

Fig. 6. Time history concentration of Metformin in kidney for different initial concentration of Metformin.

In Fig 6 concentration of Metformin in kidney has been plotted with time parameter, showing accumulation of the drug in the kidney. Research shows that Metformin is not metabolized, since no distinct intermediates are known to be formed. Poor absorption of the drug may be deduced from available clinical data suggesting that nearly 70% of the administered dose is excreted in the urine unchanged in form. It is cleared from the body by tubular secretion. The half-life of elimination is also observed to be roughly 6.5 hours which is confirmed by the corresponding data obtained from the referred scientific literature.[12] According to the data obtained at clinical trials, the renal clearance of Metformin is estimated to be 510 +/- 120 mL.min^{-1}, suggesting that Metformin is eliminated by glomerular filtration and tubular secretion [13]. Similar type of time history concentration of Metformin has been plotted for evening time (data not shown).

Although the concentrations of Metformin in different organs are indirect parameter depends on the selected direct parameters, such as, initial concentration of Metformin, linear blood flow rate and intracellular enzymatic reactions. From the above findings it may be concluded that the above mentioned mathematical model can adequately describe the time history concentration of Metformin in every organ. The successful prediction of this indirect parameter depends on the proper selection of the direct parameters, and the processes of key interest, which is the unique property of the proposed mathematical model. The mathematical model may be used as a unique tool in the field of pharmaceutical technology.

Acknowledgements

Arijit Nath would like to acknowledge the Council of Scientific and Industrial Research (CSIR), New Delhi, India for providing the required research fellowship.

References

[1] Shargel L, Wu-Pong S, Yu A B C (2005). Applied Biopharmaceutics and Pharmacokinetics. New York: Appleton & Lange Reviews/McGraw-Hill.

[2] Danhof M, Lange E C M de, Della Pasqua O E, Ploeger B A, Voskuyl R A. Mechanism-based pharmacokineticpharmacodynamic (PK-PD) modeling in translational drug research. *Trends Pharmacol Sci* 2008, 29:186-191.

[3] Ratner RE: Type 2 diabetes mellitus: the grand overview. Diabet Med 1998, **14:**54-57.

[4] Choi YH, Kim SG, Lee MG Dose-independent pharmacokinetics of metformin in rats: hepatic and gastrointestinal first-pass effects. J Pharm Sci 2006, 95: 2543–2552.

[5] Lin Sun, Ezra Kwok, Bhushan Gopaluni, Omid Vahidi. Pharmacokinetic-Pharmacodynamic Modeling of Metformin for the Treatment of Type II Diabetes Mellitus. *The Open Biomedical Engineering Journal* 2011, 5*:*1-7.

[6] Rodbard HW, Jellinger PS, Davidson JA, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. Endocr Pract. 2009;15:540–59.

[7] Chen L, Pawlikowski B, Schlessinger A, More SS, Stryke D, Johns SJ, et al. Role of organic cation transporter 3 (SLC22A3) and its missense variants in the pharmacologic action of metformin. Pharmacogenetics Genom. 2010;2011:687–99.

[8] Vahidi O, Kwok K E, Gopaluni R B, Sun L, Development of a physiological model for patients with type 2 Diabetes mellitus, *Proc Am Control Conf*, 2010.

[9] Vidon N, Chaussade S, Noel M, Franchisseur C, Huchet B, Bernier JJ.Diabetes Res Clin Pract. 1988 Feb 19;4(3):223-9

[10] Gong Li, Goswami Srijib, Giacomini Kathleen M, Altman Russ B, Klein Teri E. "Metformin pathways: pharmacokinetics and pharmacodynamics" Pharmacogenetics and genomics (2012).

[11] Bailey CJ, Turner RC, Metformin. *N Engl J Med*. 1996, 334:574–9.

[12] Raj S. Padwal, Raniah Q. Gabr, Arya M. Sharma, Lee-Ann Langkaas, Dan W. Birch, Shahzeer Karmali, Dion R. Brocks, Diabetes Care. 2011 June; 34(6): 1295–1300.

[13] Garry G G, Jeroen P, Manit A, Richard O D, Matthew P D, Janna K D, Timothy J F, Jerry R G, Louise C G, Carl M K, John E R, Peter T, Kenneth M W. Clinical Pharmacokinetics of Metformin. *Clin Pharmacokinet.* 2011, 50:81-98.