Effect of Experimental Time on Concentration of Gentamicin Intake in the Body Compartment using Computational Approach

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ABSTRACT

In investigating the computational approach of predicting the concentration of flucloxacillin drug in the body compartments and its response to dosage over time at time interval 0:5:240, was carried out computationally using MATLAB ODE45. From the various results output, we observed that on the based day of our experimental time here called the initial condition, the amount of complete solvent in the body compartment N1 is recorded as zero (0) in content whereas the gentamicin concentration (the active mass) in the body compartment N2 records zero (0) amount as well. Furthermore, when the time ranges from five (5 mins) up to fifty five (55mins), the concentration which is the active mass that is being used up increased down the trend from a value of 7.9 unit up to a value of 12.3 unitwhen the time is fifty five (55mins), whereas the amount of substance containing the syrup mixture in the stomach compartment ranges from 94.2mg at the fifth (5^{th}) minutes, and increases down the trend up to 517.3mg at the fifty five (55mins). Furthermore, when the time ranges from one hundred and eighty five minutes (185 mins) up to two hundred and forty minutes (240mins), the concentration which is the active mass that is being used up maintain a constant value of 12.4 unit down the trend as it saturation value on convergence at the two hundred and forty minutes (240mins), whereas the amount of substance containing the syrup mixture in the stomach compartment ranges from 1486.6mg at the 185th minutes, and increases down the trend up to 1895.9mg at the 240th minutes. This observation will serve as a guide for a proper monitoring of a patient by a physician for its response to dosage and the active component of the gentamicin drug as that specific time. The full results and discussions of this investigation is well presented in this study.

KEYWORDS: livestock, cumulative density, methane gas, computational method, environment.

INTRODUCTION

Gibiansky*et al.*(2009) did a target-mediated drug disposition model: relationships with indirect response models and application to population. The paper focuseson approximation of thetarget-medicated drug disposition (TMDD) model as applied to pharmacodynamic (target kinetics) modeling. Compartmentmodeling of the transport system in the

human body plays an important role in pharmacokinetics due to local processes in each part of the compartment since it is the mathematical representation of the body or a part of the body created to study physiological or pharmacological kinetics characteristic. The study established the fact that the body is represented as a series of compartments arranged either in series or in parallel depending upon the process of transport of materials. Crooks et al. (2000) did a thorough review of pharmacokinetics in the elderly, demonstrated that the adaptation of drug dosages to obese patients is a subject of concern, particularly for drugs with a narrow therapeutic index. Obese people have larger absolute lean body masses as well as fat masses than non-obese individuals of the same age, gender and height. Cardiac performance and adipose tissue blood flow may be altered in obesity. There is uncertainty about the binding of drugs to plasma proteins in obese patients. The dosage of these drugs should he based on the ideal bodyweight (IBW). Myrna et al.(2007)proposed drug dosing adjustments in patient with chronic kidney disease which, affects renal drug elimination and other pharmacokinetic processes involved in drug disposition (e.g.; absorption, drug distribution, nonreal clearance[metabolism). Li and Nekka (2007) proposed that the adherence phenomenon is now well recognized to seriously compromise drug efficacy. Seng et al. (2007) said that statistical techniques have been traditionally used to deal with parametric variation in pharmacokinetic and pharmacodynamic models, but these require substantial data for estimates of probability distributions. Tang and Xiao (2007) provided the analytical solutions of one-compartment models with MichaelisMentea elimination kinetics for three different inputs (single intravenous dose, multiple dose both injection and constant. Matthews (2008) realized that the goal of most population pharmacokinetic and pharmacodynamicanalysesis to develop a model that adequately describes the available data that can be used for predictive purpose. Kha (2009) analyzed local

pharmacokinetic and pharmacodynamics of angiogene growth factors in myocardial tissue. This tissue was designed to examine critically whether the lack of late efficiency of local delivery of antigenic factors could be explained by a comprehensive understanding of local pharmacokinetics (PK) arid pharmacodynamics (PD) in the myocardial tissue.

Gibiansky et al. (2009) did a target-mediated drug disposition model: relationships with indirect response models and application to population. The paper focuses on approximation of the targetmedicated drug disposition (TMDD) model as applied to pharmacodynamic (target kinetics) modeling. Strougo et al (2012) reached on first dose in children: physiological insights into pharmacokinetic scaling approaches and their implications in paediatric drug development. Dose selection for "first in children" trials often relies on scaling of the pharmacokinetics from adults to children. Koch and Schropp (2012) worked on a general relationship between transit compartments models. Transit compartment model (TCM) areimportant pharmacokinetic/pharmacodynamic(PKPD) modeling, in this work we investigate the relationship between TCMs with arbitrary initial values and lifespan models (LSM) with non-constant past and constant lifespan. Weiss (2013) did Fractal structure of the liver: effect on drug elimination. Armaou (2013) released Pharmacokinetics Modeling for H.I.V. Treatment Strategies. The project focuses on modeling the dynamics associated with the uptake of medication during treatment of H.I.V. infection. Tang and Xiao (2007) provided the analytical solutions of one-compartment models with MichaelisMentea elimination kinetics for three different inputs (single intravenous dose, multiple dose both injection and constant). Gibjausky et al. (2009) did a target-mediated drug

disposition model: relationships with indirect response models and application to population. The paper focuses on approximation of the target-medicated drug disposition (TMDD) model as applied to pharmacodynamic (target kinetics) modeling.

In mathematical modeling (Amadi&Ekaka-a, 2017) the ordinary differential equation was used to study the deterministic stability and yeast interacting population undergoing changing initial condition. This same application of the ordinary differential equation is of great importance in the mathematical modeling for drugs diffusion as it constitutes an influential predictive tool for having the basic understanding of bio-transport processes in the human body especially the numerical simulation approach.

MATHEMATICAL FORMULATION

In a single compartment modeling the gentamic drug concentration in the body compartment for response to dosage of drug intake by a patient under observation, the established kinetics model (Bornelli and Coleme, 2004) uses a first order Pseudo kinetic model expressed mathematically as

$$\frac{dc}{dt} = Kc, C(0) = C_o > 0$$

Where, C represents the equilibrium concentration (mg/L)

t represents time (mins)

C_o represents the initial concentration.

The solution trajectory of this model formulation of the concentration in this model follows an exponential growth path which indication shows that the concentration of the gentamic drug intake will grow unbounded and this phenomenon in mathematically tractable but does not agree with normal procedure in pharmacokinetics in terms of initiative reasoning since the solution map will take the form $C(t) = C_0 e^{kt}$.

Thus, following (Bornelli and Coleme, 2004), for a balance law of an inflow-outflow model, we formulate as follows:

Rate of change of the concentration of a mixture of a substance,

C(t) = Rate at which concentration enters the body compartment - Rate at which concentration exits the body compartment.

This is expressed mathematically as:

$$\frac{dc(t)}{dt} = R_1 - R_2 \tag{1}$$

where $R_1 = r_1 c_1$ and $R_2 = r_2 c_2$

$$\frac{dc(t)}{dt} = r_1 c_1 - r_2 c_2 \tag{2}$$

Here
$$C_2 = \frac{\text{Amount of substance}}{\text{Volume of solvent}} = \frac{C(t)}{V_0 + V_{en} - V_L}$$
 (3)

Hence,

$$\frac{dc(t)}{dt} = r_1 c_1 - \left[\frac{C(t)}{V_0 + V_{en} - V_L} \right] r_2$$
(4)

Where V = rt, $V_{en} = r_1 t$, $V_L = r_2 t$ and on substitution into equation (4), we have

$$\frac{dc}{dt} = r_1 c_1 - \left[\frac{C(t)}{V_0 + (r_1 - r_2)t} \right] \cdot r_2$$
(5)

In this model formulation, the variables and parameters are defined as follows:

R₁ represents the inflow rates of the syrup concentration

R₂ represents the outflow rates of the syrup concentration

 C_1 represents the concentration of syrup inflow

C₂ represents the concentration of syrup outflow

V_o represents the initial volume of syrup mixture in the body compartment

V_L represents the volume of syrup mixture leaving the body compartment

 V_{en} represents the volume of syrup mixture entering the body compartment r_1 represents the rate at which the solvent is entering the body compartment r_2 represents the rate at which the solvent is leaving the body compartment C(0) represents the initial concentration of the syrup.

t represents time.

In this study, we will take a look at three different cases scenario:

Case I:
$$c_2 = 0 \frac{dc}{dt} = r_1 c, c(0) = C_0 > 0$$
 (6)

$$C(t) = C_0 e^{r_1 t}$$
 Case II: $c_1 = 0$

$$\frac{dc}{dt} = \frac{-r_2C}{V_o + rt} \tag{7}$$

Where $r = \Delta r = r_1 - r_2$

The equation can be solved analytically by separation of the variable where

$$\frac{dc}{c} = \frac{-r_2}{V_o + rt} dt \tag{8}$$

Integrating both sides

$$\int \frac{1}{c} dc = -r_2 \int \frac{1}{V_0 + rt} dt = \frac{-r_2}{r} \int \frac{r}{V_0 + rt} dt \tag{9}$$

$$Log_e C(t) = \frac{-r_2}{r} \log_e (V_0 + rt) + h \tag{10}$$

Where, h is a constant of integration

$$C(t) = e^{\left(\frac{-r_2}{r} Log_e(V_o + rt) + h\right)}$$

$$C(t) = e^{Log_e} \left(V_o + rt\right)^{-r_2/r} e^h$$

$$C(t) = \left(V_o + rt\right)^{-r_2/r} * A \qquad \qquad \text{(where A = e^h)}$$

$$C(t) = A * (V_o + rt)^{-r_2/r}$$

$$C(t) = \frac{A}{(V_o + rt)^{r_2/r}}$$
(11)

Using the initial condition $C(0) = C_o$

$$C(0) = \frac{A}{(V_o + (0).r)^{r_2/r}}$$

$$C_o = \frac{A}{\left(V_o\right)^{\frac{r_2}{r_r}}}$$

$$A = C_o \left(V_o \right)^{\frac{r_2}{r}}$$

$$C(t) = \frac{C_o(V_o)^{\frac{\gamma}{\gamma_r}}}{(V_o + tr)^{\frac{\gamma}{\gamma_r}}}$$
(12)

If $c_1 \neq 0$ and $c_2 \neq 0$

$$\frac{dc}{dt} = r_1 * c_1 - \frac{r_2 c}{V_0 + rt} \tag{13}$$

In this study we assume $r_1 = \alpha$ and $c_1 = k$ so that $r_1 * c_1 = \alpha * k$ and $r_2 = \beta$

Collecting like terms:

$$\frac{dc}{dt} + \frac{\beta c}{V_0 + rt} = \alpha k \tag{14}$$

This is a linear ODE with integrating factor

$$I.F = e^{\int p(t)dt}$$

Since the equation can be represented as

$$\frac{dy}{dx} + p(x)y = Q(x)$$
 is identified to (15)

Here.

$$\frac{dc}{dt} + p(t)c = Q(t) \tag{16}$$

Hence the integrating factor

$$I.F = e^{\int p(t)dt}$$

$$I.F = e^{\int \frac{\beta}{V_o + rt} dt}$$

$$I.F = e^{\beta / \int_{V_o + rt}^{\underline{\beta}} dt}$$

$$I.F = e^{\beta/r} \log_e (V_o + rt)$$

$$I.F = e^{\log_e} (V_o + rt)^{\beta/r}$$

Hence,
$$I.F = (V_o + rt)^{\beta/r}$$

Multiplying equation (3.7) with the integrating factor (I.F)

$$(V_o + rt)^{\beta/r} \frac{dc}{dt} + (V_o + rt)^{\beta/r} \cdot \frac{\beta}{V_o + rt} \cdot c = \alpha * k (V_o + rt)^{\beta/r}$$

$$\frac{d}{dt}\left[c\left(V_{o}+rt\right)^{\beta/r}\right] = \alpha * k\left(V_{o}+rt\right)^{\beta/r}$$

Integrating both sides:

$$\int d \left[c \left(V_o + rt \right) \right]^{\beta/r} = \alpha k \int \left(V_o + rt \right) dt$$

Solving the right hand side,

Set,
$$U = V_o + rt$$

$$du = rdt, \quad dt = \frac{du}{r}$$

$$\int d \left[c \left(V_o + rt \right)^{\beta/r} \right] = \alpha k \int U^{\beta/r} \frac{du}{r}$$

$$C(V_o + rt)^{\beta/r} = \frac{\alpha k}{r} \left(\frac{U^{\frac{\beta}{r}+1}}{\frac{\beta}{r}+1} \right) + h$$

Where, h is a constant of integration

$$C(V_o + rt)^{\beta/r} = \frac{\alpha k}{r} \left(\frac{U^{\frac{\beta+r}{r}}}{\frac{\beta+r}{r}} \right) + h$$

$$C(V_o + rt)^{\beta/r} = \left(\frac{\alpha k}{r} * \frac{U^{\frac{\beta+r}{r}}}{\frac{\beta+r}{r}}\right) + h$$

$$C(V_o + rt)^{\beta/r} = \frac{\alpha k}{\beta + r} U^{\frac{\beta + r}{r}} + h$$

$$C(V_o + rt)^{\beta/r} = \frac{\alpha k}{\beta + r} (V_o + rt)^{\frac{\beta + r}{r}} + h$$

Dividing through by $(V_o + rt)^{\beta/r}$ gives:

$$C(t) = \frac{\alpha k}{\beta + r} \frac{\left(V_o + rt\right)^{\frac{\beta + r}{r}}}{\left(V_o + rt\right)^{\beta/r}} + h \left(V_o + r\right)^{-\beta/r}$$

$$C(t) = \frac{\alpha k}{\beta + r} \left(V_o + rt \right)^{\frac{\beta + r}{r} - \frac{\beta}{r}} + \frac{h}{\left(V_o + rt \right)^{-\beta/r}}$$

$$C(t) = \frac{\alpha k}{\beta + r} \left(V_o + rt \right) + \frac{h}{\left(V_o + rt \right)^{-\beta/r}}$$

C(o) = O, initial drugs concentration in the tissue

$$O = \frac{\alpha k}{\beta + r} \left[V_o + r(0) \right] + \frac{h}{\left(V_o + rt \right)^{-\beta/r}}$$

$$O = \frac{\alpha k}{\beta + r} \left(V_{o} \right) + \frac{h}{\left(V_{o} \right)^{\beta/r}}$$

$$\frac{h}{\left(V_{o}\right)^{\beta/r}} = \frac{-\alpha k \left(V_{o}\right)}{\beta + r}$$

$$h = -\alpha k^* \frac{(V_o) \cdot (V_o)^{\beta/r}}{\beta + r}$$

Substituting into C (t),

$$C(t) = \frac{\alpha k}{\beta + r} \left(V_0 + rt \right) + \frac{1}{\left(V_o + rt \right)^{\beta/r}} \left[\frac{-\alpha k \left(V_o \right)^{\frac{r+\beta}{r}}}{\beta + r} \right]$$

$$C(t) = \frac{\alpha k}{\beta + r} \left[\left(V_o + rt \right) - \frac{\alpha k \left(V_o \right)^{\frac{r+\beta}{r}}}{\left(V_o + rt \right)^{\beta/r}} \right]$$

$$C(t) = \frac{\alpha k}{\beta + r} \left[1 - \frac{(V_o)^{\frac{r+\beta}{r}}}{(V_o + rt)^{\beta/r} (V_o + rt)} \right]$$

$$C(t) = \frac{\alpha k}{\beta + r} \left[1 - \frac{\left(V_o\right)^{\frac{r+\beta}{r}}}{\left(V_o + rt\right)^{\frac{r+\beta}{r}}} \right]$$

$$C(t) = \frac{\alpha k}{\beta + r} \left[1 - \frac{\left(V_o\right)^{\frac{r+\beta}{r}}}{\left(V_o + rt\right)^{\frac{r+\beta}{r}}} \right]$$

Therefore;

$$C(t) = \frac{\alpha k}{\beta + r} \left[1 - \left(\frac{(V_o)}{(V_o + rt)} \right)^{\frac{r+\beta}{r}} \right]$$
(17)

Hence, in studying the qualitative behavior of the drugs concentration in the compartment overtime:

as $t \to \infty$, we take the limit C(t) as $t \to \infty$ as follows

$$\lim_{t \to \infty} C(t) = \lim_{t \to \infty} \left[\frac{\alpha k}{\beta + r} \left(1 - \frac{\left(V_o\right)^{\frac{r+\beta}{r}}}{\left(V_o + rt\right)} \right) \right]$$

Thus,

$$\lim_{t \to \infty} C(t) = \frac{\alpha k}{\beta + r}$$
(18)

This limiting value quantity, is the peak concentration of gentamicin drug that will be left in the body compartment overtime, this is the basis of our study and its computational results output using MATLAB ODE45 numerical scheme is being simulated numerically and discussed as well in chapter four.

Table A: Model Parameters for various Drugs

Parameter	Paracetamol	Gentamicin	Flucloxacillin	Diclofenac	References
α	1.2	2.1	3.2	0.8	Crooks et al. (2000)
k	4.5	12.4	18	3.1	Crooks et al. (2000)
β	0.15	1.5	20	0.15	Crooks et al. (2000)
Vo	10	8.9	20	12	Crooks et al. (2000)
r	0.85	0.6	1.2	0.62	Crooks et al. (2000)
v_1	8.1	9.1	9.1	8.0	Crooks et al. (2000)
h	0.9	1.1	4.2	2.0	Crooks et al. (2000)

Table 1: Gentamicin Concentration in the Body Compartment Within the Time Interval Between 0:5:55

1.0E+003 *

0.0150	0.2027	0.0113
0.0200	0.2461	0.0118
0.0200	0.2.01	
0.0250	0.2870	0.0120
0.0300	0.3266	0.0121
0.0350	0.3654	0.0122
0.0400	0.4038	0.0123
0.0450	0.4418	0.0123
0.0500	0.4796	0.0123
0.0550	0.5173	0.0123

This study focuses on the qualitative behavior of experimental time on the absorption of the concentration of gentamic drug in a single body compartment for a time interval of 0(5)55days when all model parameter values are fixed, we denote N1 as the amount of complete solvent in the body compartment within the stipulated time interval in mg and N2 as the gentamicin concentration in the body compartment within the stipulated time interval in mol/dm³ over time. From the numerical simulated result obtained, we observed that on the based day of our experimental time here called the initial condition, the amount of complete solvent in the body compartment N1 is recorded as zero (0) in content whereas the gentamicin concentration (the active mass) in the body compartment N2 records zero (0) amount as well. Furthermore, when the time ranges from five (5 mins) up to fifty five (55mins), the concentration which is the active mass that is being used up increased down the trend from a value of 7.9 unit up to a value of 12.3 unit when the time is fifty five (55mins), whereas the amount of substance containing the syrup mixture in the stomach compartment ranges from 94.2mg at the fifth (5th) minutes, and increases down the trend up to 517.3mg at the fifty five (55mins). This observation will serve as a guide for a proper monitoring of a patient by a physician for its response to dosage and the active component of the gentamicin drug as that specific time.

Table 2: gentamicin concentration in the body compartment within the time interval between 60:5:115

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1.0e+003 *
Time (mins) N1 N2
0.0600 0.5548 0.0124
0.0650 0.5923 0.0124
0.0700 0.6297 0.0124
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0.0750	0.6671	0.0124
0.0800	0.7045	0.0124
0.0850	0.7418	0.0124
0.0900	0.7791	0.0124
0.0950	0.8164	0.0124
0.1000	0.8537	0.0124
0.1050	0.8910	0.0124
0.1100	0.9282	0.0124
0.1150	0.9655	0.0124

In the same scenario, in the studying the qualitative behavior of experimental time on the absorption of the concentration of gentamicin drug in a single body compartment for a time interval of 60(5)115days when all model parameter values are fixed, we denote N1 as the amount of complete solvent in the body compartment within the stipulated time interval in mg and N2 as the gentamicin concentration in the body compartment within the stipulated time interval in mol/dm³ over time. From the numerical simulated result obtained, we observed that on the 60thday of our experimental time, the amount of complete solvent in the body compartment N1 is recorded as 554.8 in content whereas the gentamicin concentration (the active mass) in the body compartment N2 records 12.4 in amount as well. Furthermore, whenthe time ranges from sixty five (65 mins) up to fifty five (115mins), the concentration which is the active mass that is being used up main a constant value of 12.4 unit down the trend as it saturation value onconvergence atthe fifty five (55mins), whereas the amount of substance containing the syrup mixture in the stomach compartment ranges from 554.8mg at the sixtieth (60th) minutes, and increases down the trend up to 965.5mg at the one hundred and fifteenth (115mins). This observation will serves as a guide for a proper monitoring of a patient by a physician for its response to dosage and the active component of the gentamicin drug as that specific time.

Table 3: gentamicin concentration in the body compartment within the time interval between 120:5:175

1.0e+003 *

Time (min	s) N1	N2
0.1200	1.0027	0.0124
0.1250	1.0400	0.0124
0.1300	1.0772	0.0124

0.1350	1.1144	0.0124
0.1400	1.1516	0.0124
0.1450	1.1889	0.0124
0.1500	1.2261	0.0124
0.1550	1.2633	0.0124
0.1600	1.3005	0.0124
0.1650	1.3377	0.0124
0.1700	1.3750	0.0124
0.1750	1.4122	0.0124

Furthermore, this study also extends the impact of the qualitative behavior of experimental time on the absorption of the concentration of gentamicin drug in a single body compartment for a time interval of 120(5)175days when all model parameter values are fixed, we denote N1 as the amount of complete solvent in the body compartment within the stipulated time interval in mg and N2 as the gentamicin concentration in the body compartment within the stipulated time interval in mol/dm³ over time. From the numerical simulated result obtained, we observed that on the 120th day of our experimental time, the amount of complete solvent in the body compartment N1 is recorded as 1002.7 in content whereas the gentamicin concentration (the active mass) in the body compartment N2 records 12.4 in amount as well.Furthermore, whenthe time ranges from one hundred and twenty five (125 mins) up to one hundred and seventy five (175 mins), the concentration which is the active mass that is being used up maintain a constant value of 12.4 unit down the trend as it saturation value on convergence at the one hundred and seventy five minutes (175mins), whereas the amount of substance containing the syrup mixture in the stomach compartment ranges from 1040mg at the 125th minutes, and increases down the trend up to 1412.2mg at the 175th minutes. This observation will serves as a guide for a proper monitoring of a patient by a physician for its response to dosage and the active component of the gentamicin drug as that specific time.

Table 4: gentamicin concentration in the body compartment within the time interval between 180:5:240

1.0e+003 *

Time (mi	ins) N1	N2
0.1800	1.4494	0.0124
0.1850	1.4866	0.0124
0.1900	1.5238	0.0124

0.1950	1.5610	0.0124
0.2000	1.5982	0.0124
0.2050	1.6354	0.0124
0.2100	1.6726	0.0124
0.2150	1.7098	0.0124
0.2200	1.7470	0.0124
0.2250	1.7843	0.0124
0.2300	1.8215	0.0124
0.2350	1.8587	0.0124
0.2400	1.8959	0.0124

Furthermore, this study also extends the impact of the qualitative behavior of experimental time on the absorption of the concentration of gentamicin drug in a single body compartment for a time interval of 180(5)240days when all model parameter values are fixed, we denote N1 as the amount of complete solvent in the body compartment within the stipulated time interval in mg and N2 as the gentamicin concentration in the body compartment within the stipulated time interval in mol/dm³ over time. From the numerical simulated result obtained, we observed that on the 180thday of our experimental time, the amount of complete solvent in the body compartment N1 is recorded as 1449.4 in content whereas the gentamicin concentration (the active mass) in the body compartment N2 records 12.4 in amount as well. Furthermore, when the time ranges from one hundred and eighty five minutes (185 mins) up to two hundred and forty minutes (240mins), the concentration which is the active mass that is being used up maintain a constant value of 12.4 unit down the trend as it saturation value on convergence at the two hundred and forty minutes (240mins), whereas the amount of substance containing the syrup mixture in the stomach compartment ranges from 1486.6mg at the 185th minutes, and increases down the trend up to 1895.9mg at the 240th minutes. This observation will serve as a guide for a proper monitoring of a patient by a physician for its response to dosage and the active component of the gentamicin drug as that specific t

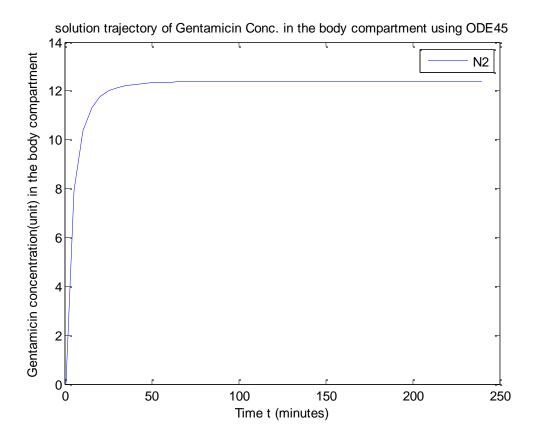


Fig1: Qualitative characteristics of the solution trajectory of Gentamicin drug concentration in the body compartment for a time interval of 0(5)240 mins

CONCLUSION

This study has utilized computation approach to predict the concentration and active mass of gentamicin drugs in the body compartment over time up to the point where it has a stable concentration being the convergent point here called the target site. This study will be useful and will serve as a guide to physicians in observing a patient with respect to its response to dosage.

RECOMMENDATION

This study will recommend further research to look at the impact of how other parameter values and changes in initial concentration will affect response to dosage in the administration of drugs to a patient under observation. Furthermore, this method should be applied in other drugs using various parameters displayed in the data source.

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