DEVELOPMENT AND VALIDATION OF A PHARMACOKINETIC MODEL USING LINEAR SYSTEM ANALYSIS FOR THE PREDICTION OF MEDICAMENTS DISTRIBUTION IN THE HUMAN BODY

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The pharmacokinetic modeling can predict the concentration of drug in different tissues of the human body. The development of mathematical models is an important tool to verify the appropriateness of certain procedures performed in medication administration. The objective of this work is to develop a pharmacokinetic model able to predict the plasma concentration of drug in the body after various forms of infusion. Two approaches were used. Initially, in the one-compartment approach it was considered that the drug enters the body directly into the blood compartment, which represents the entire human body. The model was built by using block diagrams and the solution was obtained using the Laplace Transform. The model was validated by comparing its results to literature data, with very good agreement. The model made possible to compare constant infusion of drug in the body with the periodic infusion. The analysis of the results generated by the model showed that the concentrations achieved by these methods are not the same. The presented model enabled to simulate periodic infusions, what was not possible in the previous models found in the literature. Two-compartment analysis allowed to simulate the interruption of the treatment. It was also possible to compare a daily infusion of medicament with a half dosage given each twelve hours and it was verified that de stady state terapeutic concentration was not reached.

Keywords:*Pharmacokinetic model, biomedical engineering, linear system.*

1. NOMENCLATURE

C	concentration
Cl	clearence
$D(t)$	drug dosage in function of time
$G(s)$	transfer function
k	mass transfer coefficient
m	mass
$M(s)$	mass in Laplace Domain
s	Laplace Transform Domain
t	time
V	volume

Subscripts

0	initial
$1/2$	half life
a	absortion
ap	apparent
i	index
max	maximum
p	plasmatic
re	renal
te	total elimination

2. INTRODUCTION

Pharmacokinetic models can be extremely useful in treatment optimization. The pharmacokinetic modeling allows to predict drug concentration in serveral organs and tissues of the human body. These kind of model allow to simulates both therapeutic dosage as over dosage of drugs.

The type of pharmacokinetic model to be used depends on the result that is desired. For an intravenous injection, that analyses the plasma, a one-compartiment model can be used. One-compartment models are used when analysis of the plasma drug concentration is enough for the obtainment of the desired results. An example of this application is the evaluation of the minimum concentration that presents therapeutic values and of the maximum concentration that does not cause toxic effects to the body. One-compartment analysis and its applications can be found in the books of Bauer (2008), Rosenbaum (2011), Jambhekar and Brenn (2009) and Makoid *et al.* (1999).

In extravascular administration a two-compartiment model is used. In this model one compartiment represents the plasma and other represents the site of administration.

The aim of this work is create a model which can be used for other types of infusions, like multiple intravenous infusions, periodic infusions and multiple oral doses.

3. MODEL DESCRIPTION

3.1 One-compartment analysis

The one-compartment model considers the plasma a homogeneous compartment. In this analysis is made the assumption that the entire drug which enters the body will be present in the blood. So is considered an apparent volume of distribution, representing how the drug distributes itself for all over the body, organs and tissues.

A large volume of distribution indicates that tissue absorbs the drug in large quantities. Otherwise, when the tissue does not absorb and there is a great part of drug in the blood, the volume of distribution appears smaller. The differential equation that governs the model is given by:

$$V_{ap}\frac{dC_p}{dt} = D(t) - Cl_{re}C_p \tag{1}$$

The terms V_{ap}, C_p, $D(t)$ and Cl_{re} represent the apparent volume of distribution, the plasma concentration, the drug dosage in function of time and the renal clearance respectively.

The analitical solution of the Eq. (1) is Eq. (2):

$$C_p(t) = C_{p0}e^{\left(\frac{-Cl_{re}}{V_p}\right)t} \tag{2}$$

The term Cl_{re} refers to the sum of all routes of drug elimination of the organism and the term C_{p0} refers to the initial amount of drug present in the blood. The plasma cleaning is done by several mechanisms, each with an elimination constant. Thus, the constant total clearance k_{te} may be defined as the sum of all constants of elimination, by means of Eq. (3):

$$k_{te} = \sum_i k_i = \frac{1}{V_{ap}}\sum_i Cl_i = \frac{Cl_p}{V_{ap}} \tag{3}$$

with i = renal, metabolic, respiratory and intestinal.

Thus is obtained Eq. (4), analogous to Eq. (2), considering all routes of elimination and not only the renal clearance.

$$C_p(t) = C_{p0}e^{-k_{te}t} \tag{4}$$

A way to obtain the constant total elimination k_{te} is through the biological half-life, defined as the time that the drug concentration drops to half its initial value. Thus, from Eq. (4), making $C_p(t) = 0.5C_{p0}$ the half life is obtained:

$$t_{1/2} = \frac{0.693}{k_{te}} \tag{5}$$

Equations (1), (2), (3) and (4) refers to conditions in which there is already an initial amount of drug in the blood, taken as the initial concentration C_{p0}. The assumption used is that this initial concentration is a result of the infusion. The proposed model enables the infusion of medicament in a time dependent dosage $D(t)$ as shown in Eq. (6):

$$V_{ap}\frac{dC_p}{dt} = D(t) - Cl_{re}C_p \tag{6}$$

It can be considered that $k_{te} = \dfrac{Cl_{re}}{V_{ap}}$ and the Eq. (7) can be obtained, in terms of C_p and k_{te}.

$$\frac{dC_p}{dt} = \frac{D(t)}{V_{ap}} - k_{te}C_p \tag{7}$$

3.2 Two-compartment analysis

In the two-compartment model the compartments used were: the central one, it refers to the site where the drug is administered and the plasma one, it refers to where the drug will be diffused after the administration.

In this model, analogously to what happens in the one-compartment, it is considered that the drug is removed in the plasma compartment. It is implied the fact that the drug is filtered in the kidneys when using the variable k_{te}.

With the assumption that it is a single dose of medicament $D(t)$ (a single tablet, inhalation or transdermal patch), there will be an initial quantity of mass m_{i0} in the compartment m_{i0}.

Mass balance for the central and plasma compartments are shown in Eq. (8) and (9):

$$\frac{dm_i}{dt} = D(t) - k_a m_i \tag{8}$$

$$\frac{dm_p}{dt} = k_a m_i - k_{te} m_p \tag{9}$$

The analytical solution of the mass balance for the central compartment (Eq. (8)) is shown in Eq. (10) and analytic solution for the plasma compartment (Eq. (9)) is shown in Eq. (11) to initial conditions $m_i(0) = m_{i0}$ and $m_p(0)$ =0 mg.

$$m_i(t) = m_{i0}e^{-k_a t} \tag{10}$$

$$m_p(t) = m_{i0}\left(\frac{k_a}{k_a - k_{te}}\right)\left(e^{-k_{te}t} - e^{-k_a t}\right) \tag{11}$$

4. MODEL SOLUTION

The behavior of the body subject to an infusion of drugs can be represented as a system, and this is characterized by producing an output to certain stimulus in the input as verified by Nise (2010).

According to Haykin and Van Venn (1999), a system can be defined as an agent that transforms one or more signals in other types of signals. Therefore, in the pharmacokinetic system, the input is the dose and the output is the concentration.

To obtain the concentration from the transfer function the Laplace Transform was utilized.

4.1 One-compartment solution

It is possible to obtain a transfer function in the s-domain relating the input to the output infusion concentration, both in the transformed domain. The basic equation governing the pharmacokinetics of drug distribution in the body is given by Eq. (1) that describes the elimination of the drug given starting concentration. Transfer Function tool is useful if a variable dosage is used, making possible to calculate the concentration in the compartments. Applying the Laplace transform to Eq. (7), that considers the total elimination of the organism (k_{te}), the system will be changed from time domain to s domain as shown in the Eq. (12):

$$sC_p(s) + k_{te}C_p(s) = \frac{D(s)}{V_{ap}} \tag{12}$$

From Eq. (12) the Eq. (13) can be obtained, which allows to calculate plasma concentration for several dosage inputs. The system output $C(s)$ can be obtained from Eq. (14). The block diagram of the system is shown in Fig. 1.

$$G(s) = \frac{C_p(s)}{D(s)} = \left(\frac{1}{V_{ap}}\right)\left(\frac{1}{s + k_{te}}\right) \tag{13}$$

$$C_p(s) = D(s)\left(\frac{1}{V_{ap}}\right)\left(\frac{1}{s + k_{te}}\right) \tag{14}$$

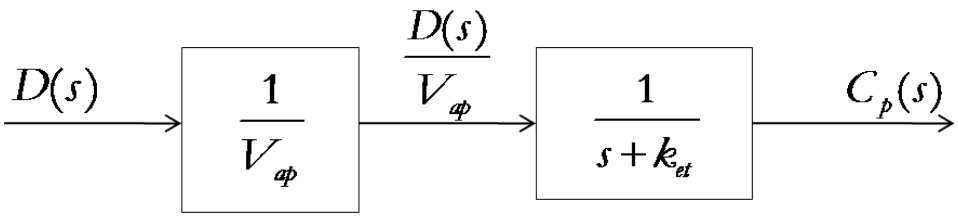


Figure 1. Block Diagram of the One-compartiment Model

4.2 Two-compartiment solution

In this analysis the mass was utilized instead of the volume. Equations (15) and (16) show the mass balance for the proposed compartiments. Transfer functions of those equations are given by Eq. (17) and Eq. (18) respectively. So, from Eq.(19) and Eq. (20) the mass present in these compartments can be calculed. The system block diagram is shown in Fig.

2.

$$sM_i(s) = D(s) - k_a M_i(s) \tag{15}$$

$$sM_p(s) = k_a M_i(s) - k_{te} M_p(s) \tag{16}$$

$$G_i(s) = \frac{M_i(s)}{D(s)} = \frac{1}{s + k_a} \tag{17}$$

$$G_p(s) = \frac{M_p(s)}{k_a M_i(s)} = \frac{1}{s + k_{te}} \tag{18}$$

$$M_i(s) = D(s)\frac{1}{s + k_a} \tag{19}$$

$$M_p(s) = k_a M_i(s)\frac{1}{s + k_{te}} \tag{20}$$

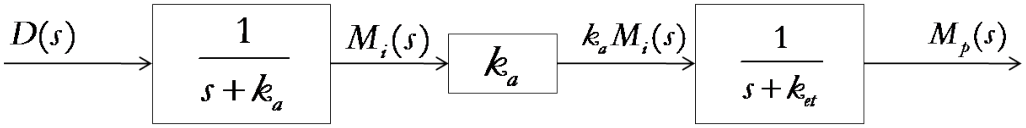


Figure 2. Block Diagram of the Two-Compartment Model

5. MODEL RESULTS

In this section the model results will be presented.

5.1 One-Compartment Validation

From Eq. (14) and the block diagram shown in Fig. 1, the simulation was performed for intravenous morphine with pharmacokinetic parameters of individuals presented in Hoskin *et al.* (1989). Table (1) shows pharmacokinetic data of each individual. The dose of $D = 10$ mg intravenous injection was applied for 2 minutes. Figure 3 shows the concentrations obtained.

Table 1. Pharmacokinetic data of each individual.

Patient	$t_{1/2}$ (h)	C_{max} (ng/ml)	V_{ap} (ml)
1	1,5	276	3623
2	2,5	314	3184
3	1,5	574	1742
4	1,7	274	3649

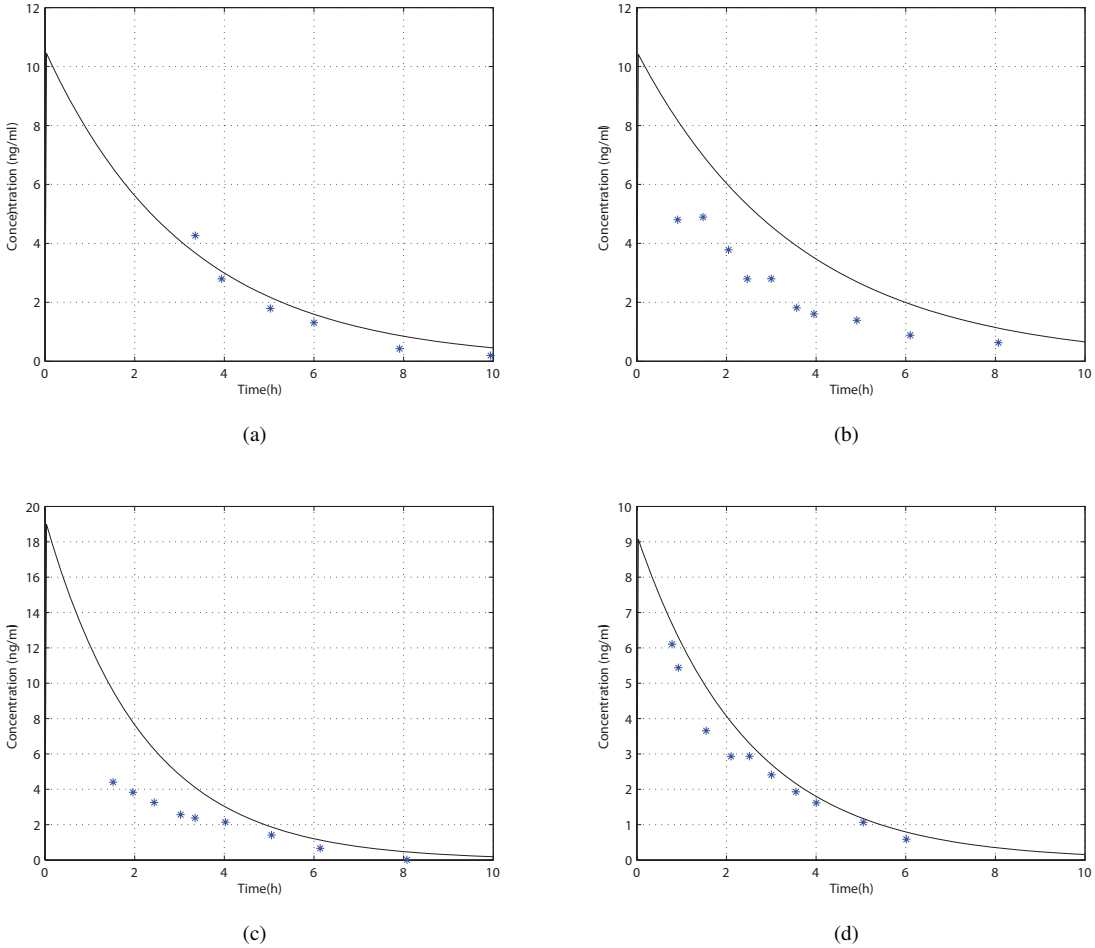


Figure 3. Morphine plasma concentrations for patients 1, 2, 3 and 4.

The model results was also compared to data present in the model of Granero *et al.* (1993). The plasma concentration for these simulation is shown in Fig. 4.

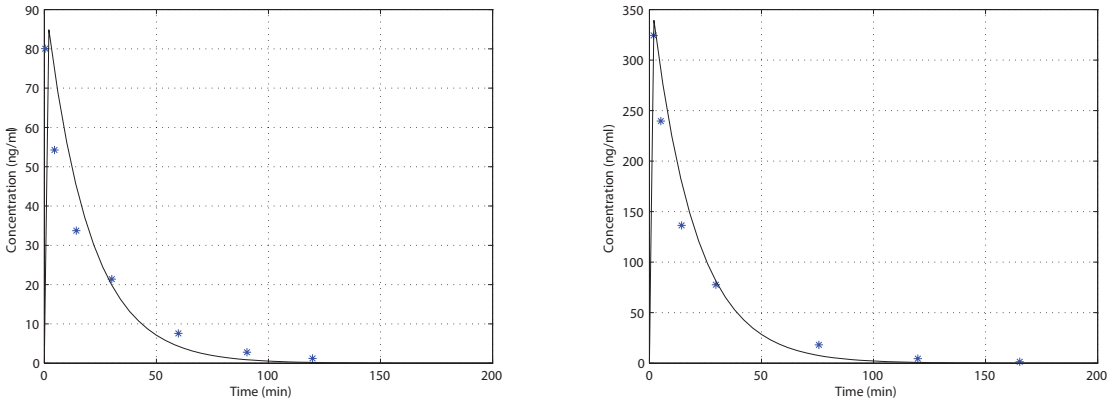


Figure 4. Comparison between the plasma concentration calculated by the model and measured experimentally (*) for a 5 mg and a 20 mg intravenous injection respectively

5.2 Two-Compartment Validation

Using Eq. (19) and Eq. (20), it is possible to obtain the mass present in each compartment after infusion of the drug.

The focus of the analysis is the plasma concentration, whereas the central compartment serves to simulate the absorption of the drug depending on the manner in which it is infused. Thus one has the Eq. (21):

$$C_p = \frac{M_p}{V_{ap}} \tag{21}$$

The comparison between the results obtained by the model and those measured experimentally are shown in the Fig. 5 and Fig. 6.

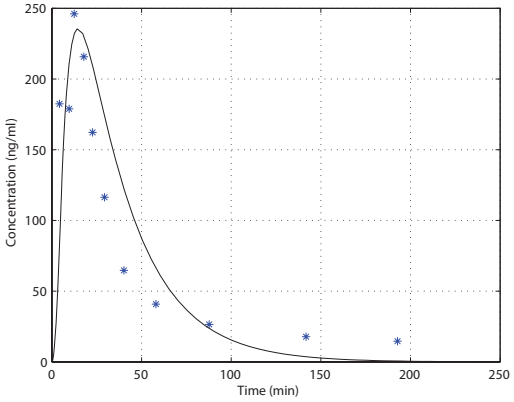


Figure 5. Comparison between the plasma concentration calculated by the model and measured experimentally (*) by Hunault *et al.* (2010).

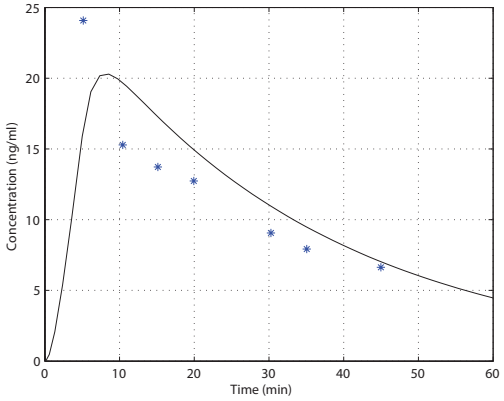


Figure 6. Comparison between the plasma concentration calculated by the model and measured experimentally (*) by Foulds *et al.* (2003).

5.3 Comparison between intravenous injection and constant infusion in the One-Compartment model

Once validated, the model permitted some simulations under new conditions.

Bauer (2008) proposed that a constant dose of 5 mg/h can be administered with periodic infusions of 30 mg each six hours. The results presented by the model showed that the concentration achieved by this dosing regimen was not the same. Simulation for these situations are shown in the Fig. 8

Figure 7(a) shows the plasma concentration for a 5 mg/h constant infusion, in Fig. 7(b) the same dosage is given with periodic infusions of 30 mg each six hours. Trying to get the steady state concentration, it was simulated an alternative situation with an intravenous dosage of 30 mg each hour as can be verified in the Fig. 7(c). The therapeutic steady state concentration was obtained with a periodic infusion of 300 mg each hour as shown in the Fig. 7(d).

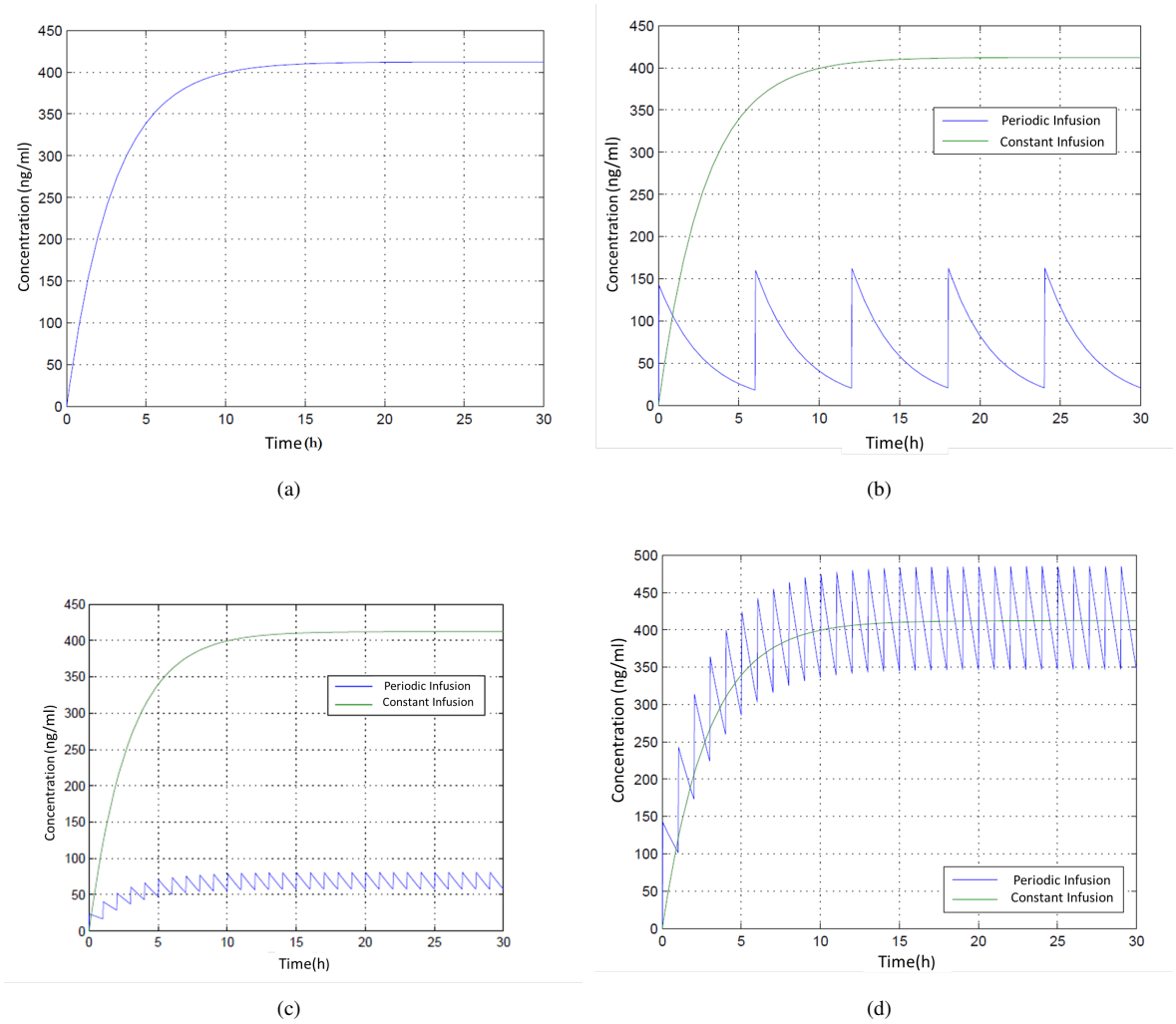


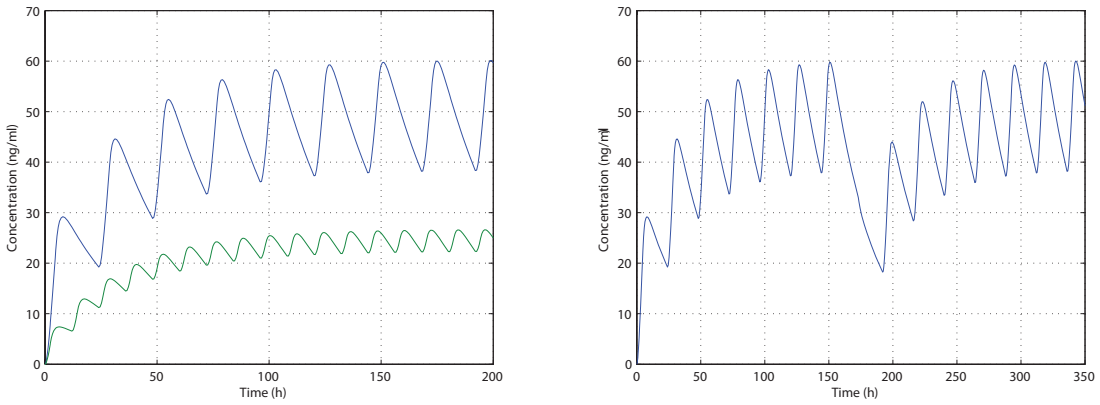
Figure 7. Comparison between constant and periodic infusion of morphine. Fig. 7(a) refers to a constant infusion of 5 mg/h. Fig. 7(b) refers to the same dosage given periodically and constant, Fig. 7(c) and Fig. 7(d) refers to an attempt to achieve the steady state concentration.

5.4 Comparison between daily infusion of a drug infusion and every twelve hours.

The daily dosage of paroxetine must be 4 mg. This condition was simulated and compared to an periodic infusion of 2 mg every twelve hours. It can verified in Fig. 8(a) that the concentration at steady state was not the same. Another situation analyzed was treatment interruption. It was verified that once the treatment is stopped the steady state concentration will be reached again only after seven days of continous treatment as can be seen in Fig. 8(b). With use of this model it can be concluded that some procedures proposed in the literature reach the expected values of concentration.

6. CONCLUSIONS

The utilization of this model verified that some procedures recommended in the literature and commonly used do not achieve the desired concentrations. Thus it can be emphasize the importance of using the proposed model order to obtain



(a) (b)

Figure 8. Oral administration of paroxetin.

results that other models are not able to do. The model allowed the simulation of different forms of infusion once it utilizes linear time invariant systems that provides a great dynamism to the model. Furthermore tentatives using the model can be done to achieve therapeutic concentrations recommended in the literature.

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