

A mathematical approach to analyze Oral, IV, and Injection based therapies for enzyme kinetics and drug delivery

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Malfunctions in human physiological mechanisms often result in the administration of drugs to restore or maintain normal physiological functions. The therapeutic enzymes used in pharmacotherapy play a pivotal role in pharmacotherapy. Several methods associated with drug intake, can be analyzed through enzyme kinetics using mathematical modelling. Here we have used mathematical modeling and enzyme kinetics to evaluate the effectiveness and safety of various drug intake modes, including oral, intravenous (IV), and intramuscular or subcutaneous (IM/SC) modes. The dynamic behavior and convergence criteria of each route is also analyzed through numerical computation and simulation to minimize adverse effects. Asymptotically steady results were achieved with varying intake administration with respect to time, providing insight into the time-dependent impact of pharmacologic side effects and guiding informed therapeutic decisions. This approach promotes a predictive framework for improving drug adherence-related dosing patterns or merely supports the design of simplified and safer dosage regimens, reducing toxicity, and enhancing personalized pharmacotherapy.

Keywords: Biochemical analysis, Drug administration, Enzyme kinetics, Non-linear equations, Pharmacokinetics

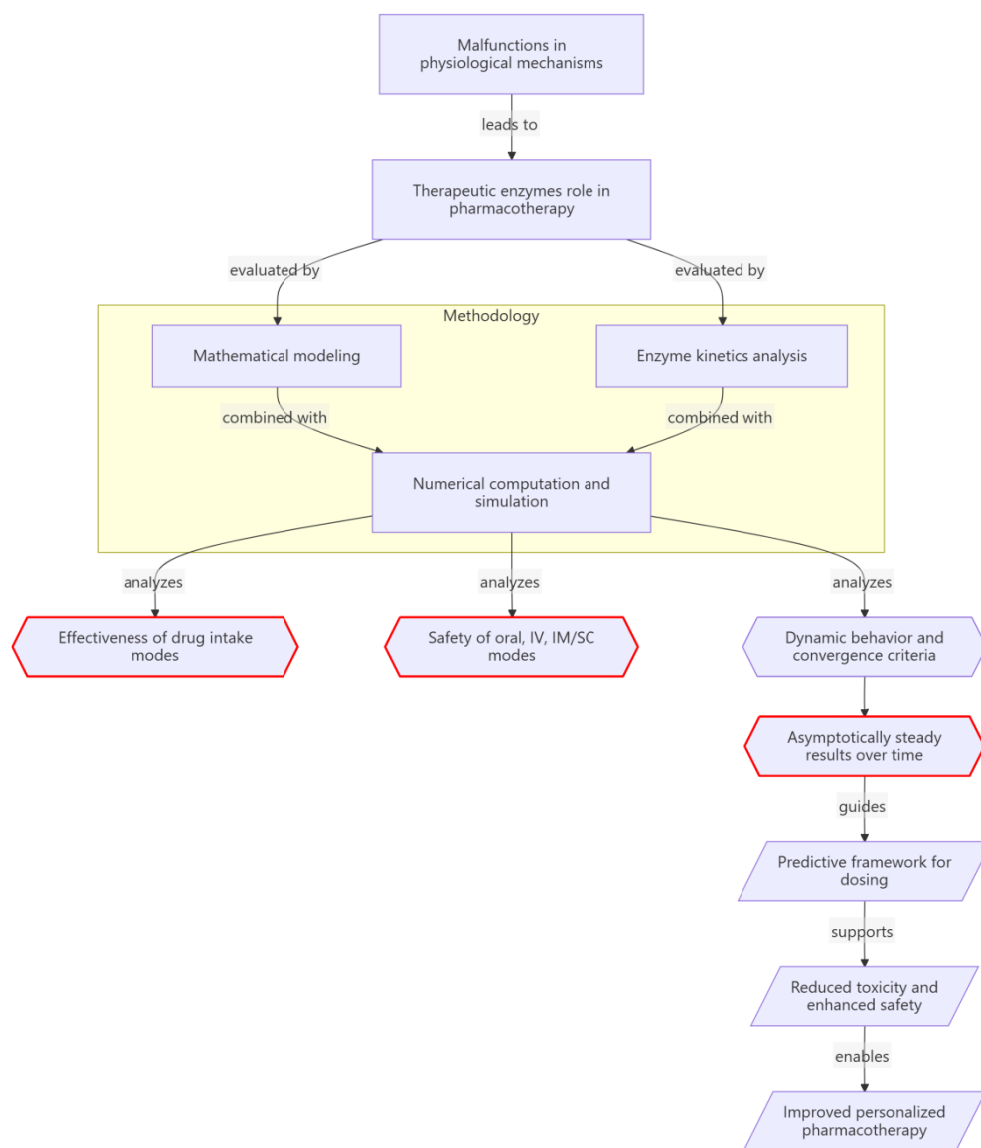
The human body is a remarkable and intricate system where each part has a specific function, and they all work together to maintain equilibrium. When there is a disturbance in the normal functioning of any part, it can lead to symptoms and diseases, ranging from minor suffer to serious medical conditions¹. For example, if the pancreas doesn't produce enough insulin, it can result in diabetes². Similarly, a blockage in the coronary arteries can lead to a heart attack³.

Pharmacokinetics provides Preventive measures, timely diagnosis, and appropriate treatment which are crucial for managing such health issues by optimal intake of drugs for its proper functioning. Drug consumption can interrupt microorganisms (germs) that enter our bodies by destroying abnormal cells or by replenishing them with cells of vitamins or hormones. Several methods for drug intake do exist, each with its own route of administration and implications for how quickly the drug takes effect and how it is distributed in the body. The common types of drug intake includes Oral Administration, where drugs are swallowed and absorbed through the digestive system into the bloodstream. Secondly, in Intravenous (IV) Administration; Drugs are injected directly into the bloodstream through a vein, and the

third one is Administration which refer to several methods such as Intramuscular (IM), Subcutaneous (SC), Intradermal, and many more. Each method has its advantages and disadvantages, such as speed of absorption, ease of use, and potential side effects. Hence it is very important to use the correct method prescribed by a healthcare professional, to ensure proper dosage and effectiveness of the medication.

At any given time, enzymes may behave as a drug for the human body or sometimes drugs interact with the inbuilt enzymes in our body. Enzymes reacts with drugs in a human body either by binding and acting on their targets with exceptional specificity along with affinity, or by changing several target molecules into the intended products. These qualities have led to the creation of numerous enzyme medications to treat a variety of illnesses⁴. In fact the field of cancer investigation has the use of enzyme therapeutics⁵. Understanding the complexity of pharmacokinetics, particularly the processes of drug Absorption, Distribution, Metabolism, and Excretion (ADME), is predominate for effective drug development and therapeutic outcomes⁶. These kind of dynamic mechanisms is indispensable for optimizing drug efficacy, minimizing adverse effects, and ultimately improving patient outcomes⁷. The metabolism of drugs, primarily generated by enzymes within the

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Graphical abstract

liver and other tissues, serves as a crucial factor of drug bioavailability and activity⁸. Similarly, enzymes have also come forth as viable therapy agents for a variety of pathologies, ranging from cancer or cardiovascular disorders to metabolic inadequacies.

Enzyme-based therapies have the capacity to change a broad variety of target molecules in order to alter physiological metabolism⁹. Because of their high specificity, enzymes can distinguish among medications with comparable structures¹⁰. They also have a remarkable catalytic ability that speeds up the desired chemical reactions. Under extremely mild pH and temperature surroundings, physiological reactions are catalysed in aqueous solutions¹¹. Numerous medications have been created with the

intention of targeting malfunctioning enzymes due to the requirement of its better functioning¹².

Using enzymes as healthful medicines directly is another strategy. They were originally applied around the close of the 1800s, when pepsin and other enzymes were utilized to treat dyspepsia¹³. The Food and Drug Administration (FDA) approved plasminogen activator Alteplase, the first recombinant enzyme medication, for acute ischemic stroke in 1987¹⁴. Between 2019 and 2024, the industrial market for enzyme-based medications has developed at a compound yearly growth rate¹⁵. Fick's code and the law of mass action are used to illustrate mathematical models that explain how drugs are dispersed among persons who intake them orally and intravenously^{16,17}.

Method of drug intake associated with enzymes can be analyzed through Enzyme kinetics using Mathematical modelling. To manage the enzyme reaction indrug intake and predict the best intake mode of the drug with fewer adverse effects. This analysis aims to conduct a sensitive analysis of the derived system of oral, IV, and intramuscular or subcutaneous (IM/SC) based routes along with their convergence criteria and stability. The impact of the side effects of drugs is also analyzed. Followed by the asymptotically stable solutions to the model with varying intake administration with respect to time using MATLAB software.

Materials and Methods

The method to intake any drug can be analysed through Enzyme kinetics using Mathematical modelling, which help predicting best intake mode of drug which results to the less side effects of it by blocking or distorting the active site. The mathematical construction of drug intake in our human body is modelled using ordinary differential equations. At any given time, enzymes may behave as a drug for the human body or sometimes drugs interact with the inbuilt enzymes in our body to overcome the symptoms of disease by blocking or distorting the active site. Here the drug binds with enzyme to form in between intermediate complex and releases the product apart from free enzyme. After that, the free enzyme might be used in another process to generate a different reactant whereas product is consumed by body as per requirement.

Here the system is written as:



where es is complex intermediate component.

The model has three parameters a_1 , a_2 , and a_3 .

Model variables are $s=[s]$, $e=[e]$, $c=[es]$, and $p=[p]$ in standardized concentrations to be 1 milligram. The mechanism illustrates the combining process of drug s and the proclamation of product p . “ e ” is unrestricted enzyme, “ c ” is the intermediate complex and k is the rate of drug consumption by body. a_1 , a_2 , and a_3 denote the measure of the rate of reaction of all processes. Note that drug involvement in reaction is revokable but product release cannot. The law of mass action along with desirable analysis are castoff to transform into a mathematical model with three forms

as per the mode of drug intake, each with its own route of administration and implications¹⁸.

The First mode is oral Administration:

MODEL – I:

$$\frac{ds}{dt} = -a_1 es + a_2 c \quad \dots (2a)$$

$$\frac{de}{dt} = -a_1 es + (a_2 + a_3) c \quad \dots (2b)$$

$$\frac{dc}{dt} = a_1 es - (a_2 + a_3) c \quad \dots (2c)$$

$$\frac{dp}{dt} = a_3 c - k \quad \dots (2d)$$

Where a_1 is the measure of the forward rate of complex formation c , a_2 is measure of backward rate, a_3 is product formation rate and enzyme proclamation, also c is intermediate component. System stability, Boundedness, equilibrium existence and stability analysis of this system is evidenced¹⁹.

The second mode is Intravenous (IV) Administration in which Drugs (Enzymes) are injected directly into the bloodstream through a vein with a constant speed. On introducing a constant rate alpha α as the constant speed at which drug is introduced to body and a constant rate k at which drug is consumed by body, we get the revised system as:

MODEL – II:

$$\frac{ds}{dt} = -a_1 es + a_2 c + \alpha \quad \dots (3a)$$

$$\frac{de}{dt} = -a_1 es + (a_2 + a_3) c \quad \dots (3b)$$

$$\frac{dc}{dt} = a_1 es - (a_2 + a_3) c \quad \dots (3c)$$

$$\frac{dp}{dt} = a_3 c - k \quad \dots (3d)$$

Where Constant rate at which drug is following into body is $\alpha=0.005$. a_1 is the measure of the forward rate of complex formation c , a_2 is measure of backward rate, a_3 is product formation rate and enzyme proclamation, also c is intermediate component. System stability, Boundedness, equilibrium existence and stability analysis of this system is also valid.

The third mode is intramuscular or subcutaneous (IM/SC), Intradermal, and many more. Here drug distort the active site and then get back to initial which can be demonstrated using normal distribution mathematically. Introducing the parameters mean and standard deviation for normal function as μ and σ and

a constant rate k at which drug is consumed by body. we get the modified system as:

MODEL – III:

$$\frac{ds}{dt} = -a_1 es + a_2 c + \frac{1}{\sigma\sqrt{2\pi}} \exp\left(-\frac{1}{2}\left(\frac{t-\mu}{\sigma}\right)^2\right) \quad \dots (4a)$$

$$\frac{de}{dt} = -a_1 es + (a_2 + a_3)c \quad \dots (4b)$$

$$\frac{dc}{dt} = a_1 es - (a_2 + a_3)c \quad \dots (4c)$$

$$\frac{dp}{dt} = a_3 c - k \quad \dots (4d)$$

Where we have considered parametric values $\mu=5$ and $\sigma=70$, a_1 is the measure of the forward rate of complex formation c , a_2 is measure of backward rate, a_3 is product formation rate and enzyme proclamation, also c is intermediate component. System stability, Boundedness, equilibrium existence and stability analysis of this system is also valid.

Mathematical analysis on the side effects of drug intake

It's well known that usage of drugs more than the body tolerance level and requirement leads to side effects on human body. This side effect can lead to a highly dangerous consequences beginning from drowsiness to organ damage and death or else it may give positive results too.

Case – I: If side Effect is beneficiary for body

The mother of anti-oxidant “Glutathione” is a well-known drug used in all three oral, IV and intramuscular or subcutaneous (IM/SC) administration for Liver disease. But its side effect is proved to be actually Skin Brightening which is a demanding product in beauty industries.

Case – II: Side effect of drug has adverse effect on human body

The widely used drug “CORTICOSTEROID” available in all three forms of intake for the humans suffering from severe back pain, Inflammation and Arthritis. But it has many major side effects, naming few as Cataract, osteoporosis, severe down Immune, myopathy etc.

In order to cope with the drug requirement ideally its mandatory to study the risk factor scale of it. Here we will analyze the accuracy and behavior of all three mode of administration, namely Oral, IV and intramuscular or subcutaneous (IM/SC) by keeping drug requirement to be identical (Figs. 1-3).

While compiling the behavior or time consumption of all three intakes it's to be noted that parametric values are set at the condition at which minimum time consumption is obtained. (Refer sensitive analysis for

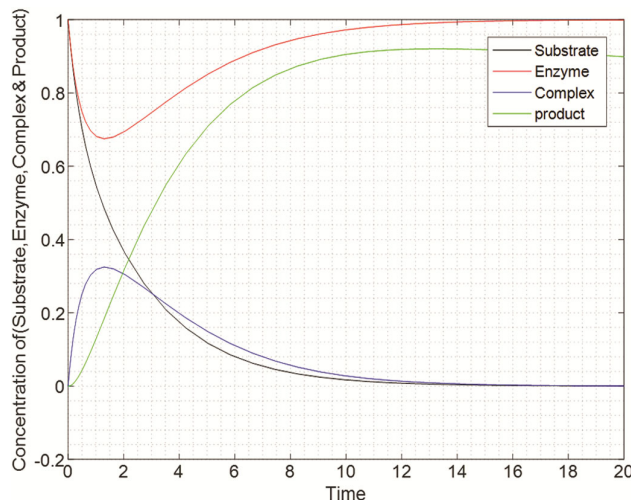


Fig. 1 — Time v/s quantity relation in oral Administration

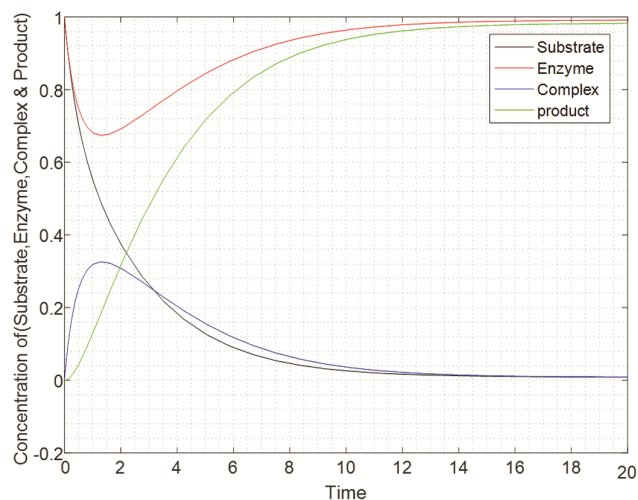


Fig. 2 — Time v/s quantity relation in IV Administration

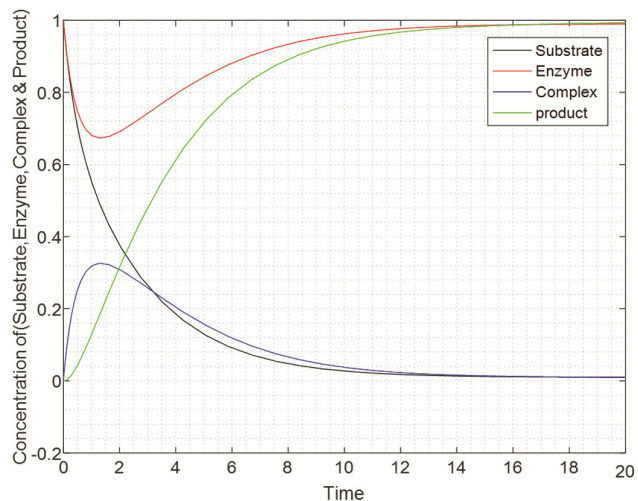


Fig. 3 — Time v/s quantity relation in IM/SC Administration

more details). Also, the drug used by body for recovery is kept ideal in all three administrations. With these initial conditions its noticed that oral administration couldn't satisfy the required quantity of drug and hence it is less effective. Discussing about IV administration and intramuscular or subcutaneous (IM/SC) administration its distinguished that although almost similar level of requirement is attained in both the cases but the better relation between enzyme and drug is cultivated into (IM/SC) mode as compared to IV.

Sensitive analysis

For all three models we have considered the initial conditions to be equal for all quantities. (As $e(0)=s(0)=1\text{ mg}$). Also the drug consumption rate is identical for all three models. The corresponding parametric values can be measured one by one keeping any one of them fixed as follows:

MODEL – I: Oral Administration

Model – I, keeping Constraint (parameter) a_1 constant, parameter a_2 lesser than a_1 and a_3 superior than a_1 we deduce that minimum time consumption is attain and so ranked 1. Considering constraint a_3 identical and a_2 larger along with a_3 shorter gives time consumption at maximum, thus ranked 5 (Table 1).

MODEL – II: IV administration with Parameter $\alpha=0.005$ & $k=0.005$

Similarly in *Model – II*, minimum time consumption is noticed if a_1 is identical with a_2 bigger and a_3 smaller and positioned first. However maximum time consumption is under the condition, a_3 indistinguishable along with a_2 least and a_1 highest results to last position (Table 2).

MODEL – III: IM/SC Administration with parameter $k=0.005$, $\mu=5$ and $\sigma=70$

Whereas for *Model – III*, minutest time consumption is noticed if a_1 is identical with a_2 reduced and a_3 better and positioned first. However extreme time consumption is under two conditions, $a_1 < a_2 < a_3$ and $a_3 < a_2 < a_1$ which results to last position (Table 3).

It is important to note down that in all the three models we have avoided negative parametric values as it results to the failure. The grades are assumed here on the time consumption rate of drug in a human body. Similarly, other possibilities are ranked accordingly in all three models.

Results and Discussion

The accuracy of rate of reaction for drug-enzyme reaction in all three models with respective hypothesis are studied as follows:

Table 1 — Relation between constraints of Model-I

Sr. No.	Constraint a_1	Constraint a_2	Constraint a_3	Behavior	Rank according to time consumption
1	Fixed	>	<	$a_3 < a_1 < a_2$	4
2	Fixed	<	>	$a_2 < a_1 < a_3$	1
3	<	Fixed	>	$a_1 < a_2 < a_3$	3
4	>	Fixed	<	$a_3 < a_2 < a_1$	3
5	<	>	Fixed	$a_1 < a_3 < a_2$	5
6	>	<	Fixed	$a_2 < a_3 < a_1$	2

Table 2 — Relation between constraints of Model-II

Sr. No.	Constraint a_1	Constraint a_2	Constraint a_3	Behavior	Rank according to time consumption
1	Fixed	>	<	$a_3 < a_1 < a_2$	1
2	Fixed	<	>	$a_2 < a_1 < a_3$	4
3	<	Fixed	>	$a_1 < a_2 < a_3$	3
4	>	Fixed	<	$a_3 < a_2 < a_1$	3
5	<	>	Fixed	$a_1 < a_3 < a_2$	2
6	>	<	Fixed	$a_2 < a_3 < a_1$	5

Table 3 — Relation between constraints of Model-III

Sr. No.	Constraint a_1	Constraint a_2	Constraint a_3	Behavior	Rank according to time consumption
1	Fixed	>	<	$a_3 < a_1 < a_2$	3
2	Fixed	<	>	$a_2 < a_1 < a_3$	1
3	<	Fixed	>	$a_1 < a_2 < a_3$	5
4	>	Fixed	<	$a_3 < a_2 < a_1$	5
5	<	>	Fixed	$a_1 < a_3 < a_2$	4
6	>	<	Fixed	$a_2 < a_3 < a_1$	2

In Model – I, the least time passage for product generation is for assumption $a_2 < a_1 < a_3$, taking constraints to be constant the study of change in drug and enzyme concentration is as follows:

Case-I: As shown below in (Fig. 4) initial quantity of enzyme is identical to drug ($e(0)=s(0)=1.0\text{mg}$).

Case-II: As given in (Fig. 5) initial quantity of enzyme is larger than substrate ($e(0)=1.0\text{mg}$ and $s(0)=0.8\text{mg}$).

Case-III: As mentioned in (Fig. 6) initial quantity of enzyme is fewer than substrate ($e(0)=0.8\text{mg}$ and $s(0)=1\text{mg}$).

In Model – II, as the least time passage for ideal product is under assumption $a_3 < a_1 < a_2$, considering the constraints to be constant and the change in drug and enzyme concentration is as follows:

Case-I: According to (Fig. 7) the initial quantity of enzyme is identical to drug ($e(0)=s(0)=1.0\text{mg}$).

Case-II: For (Fig. 8) initial quantity of enzyme is higher than substrate ($e(0)=1.0\text{mg}$ and $s(0)=0.8\text{mg}$).

Case-III: As per the visibility in (Fig. 9) initial quantity of enzyme is rarer than substrate ($e(0)=0.8\text{mg}$ and $s(0)=1\text{mg}$).

In Model – III, As the tiniest time interval used for ideal product formation is for $a_2 < a_1 < a_3$, Considering the constraints to be constant and the change in drug and enzyme concentration is as follows:

Case-I: As revealed in (Fig. 10) the initial quantity of enzyme is identical to drug ($e(0)=s(0)=1.0\text{mg}$).

Case-II: As displayed in (Fig. 11) initial quantity of enzyme is higher than substrate ($e(0)=1.0\text{mg}$ and $s(0)=0.8\text{mg}$).

Case-III: As presented in (Fig. 12) initial quantity of enzyme is fewer than substrate ($e(0)=0.8\text{mg}$ and $s(0)=1\text{mg}$).

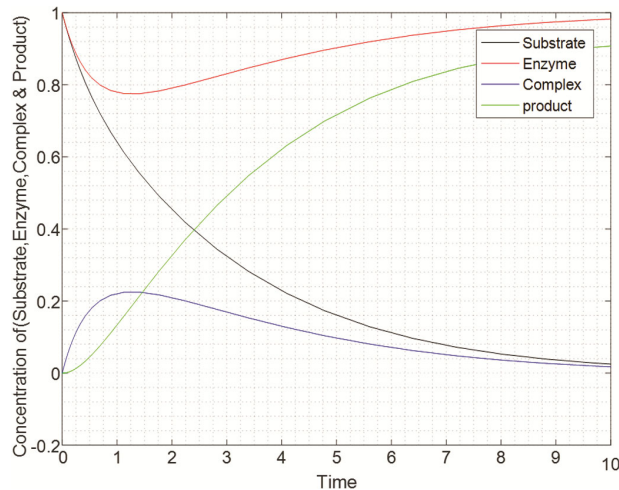


Fig. 4 — Time – Quantity relation

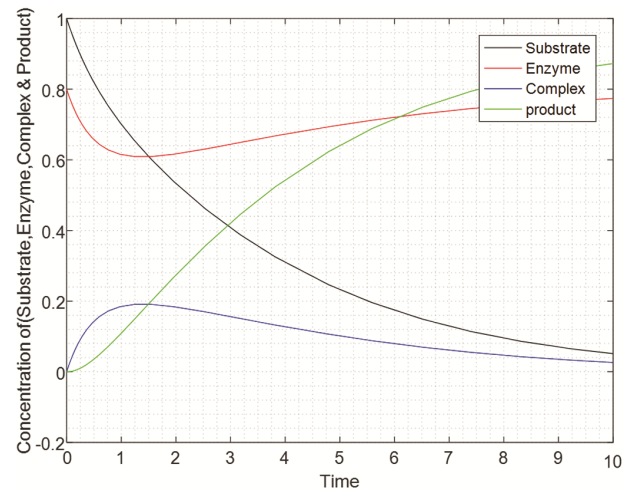


Fig. 6 — Time – Quantity relation

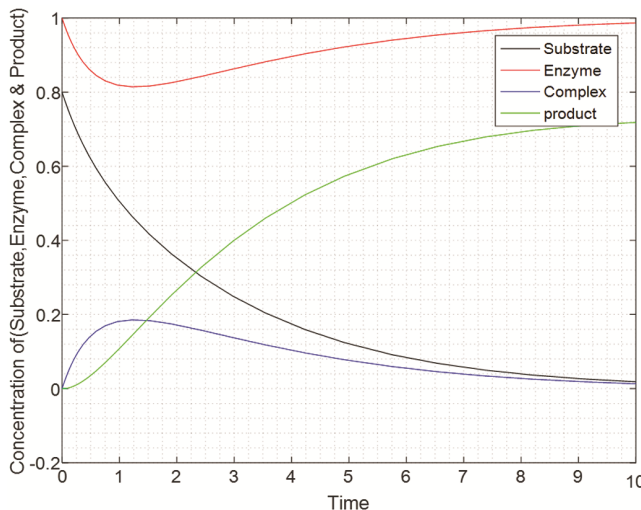


Fig. 5 — Time – Quantity relation

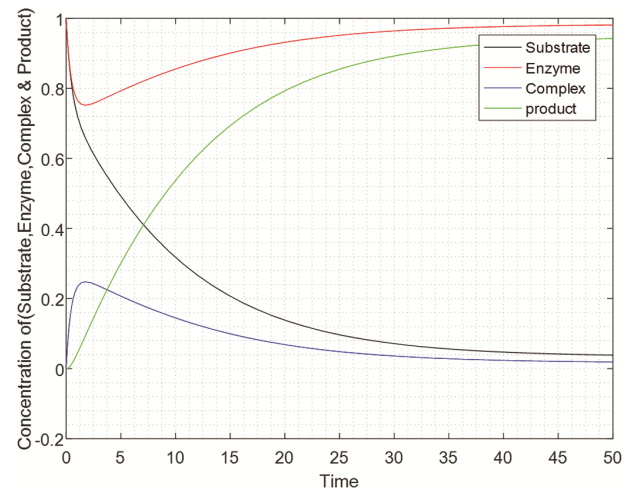


Fig. 7 — Time – Quantity relation

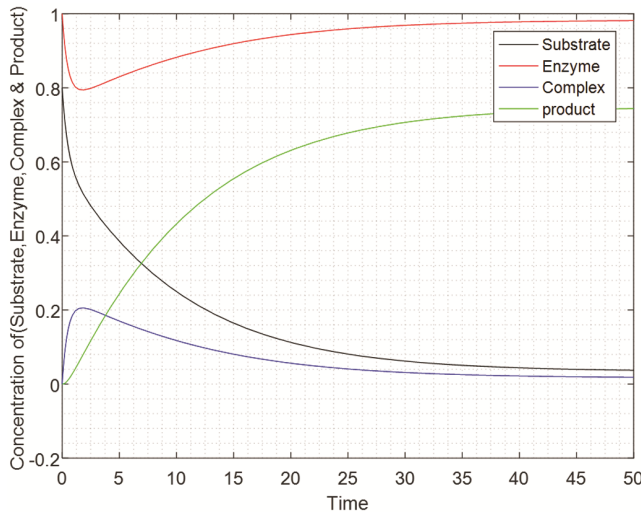


Fig. 8 — Time – Quantity relation

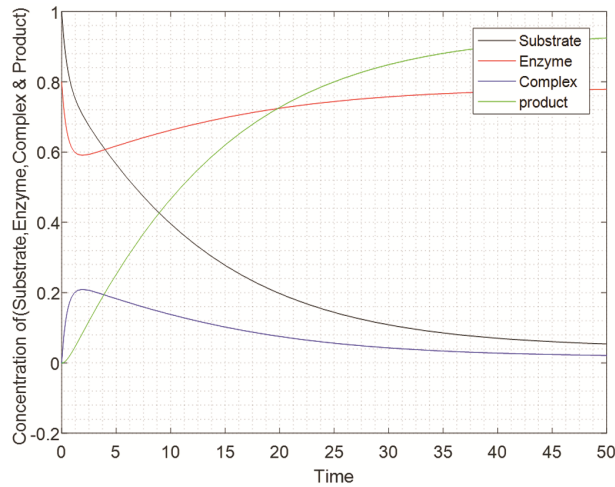


Fig. 9 — Time – Quantity relation

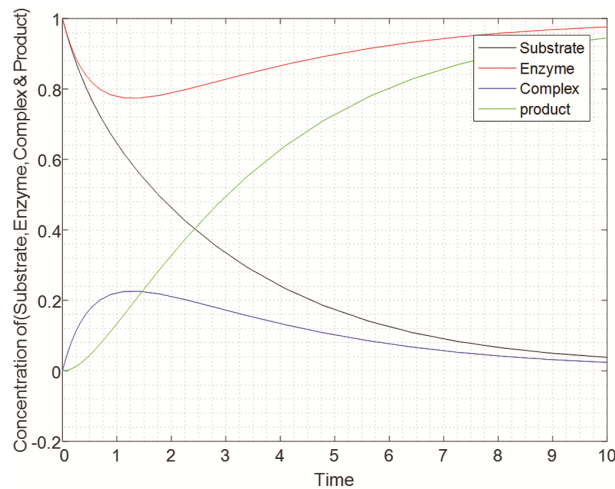


Fig. 10 — Time – Quantity relation

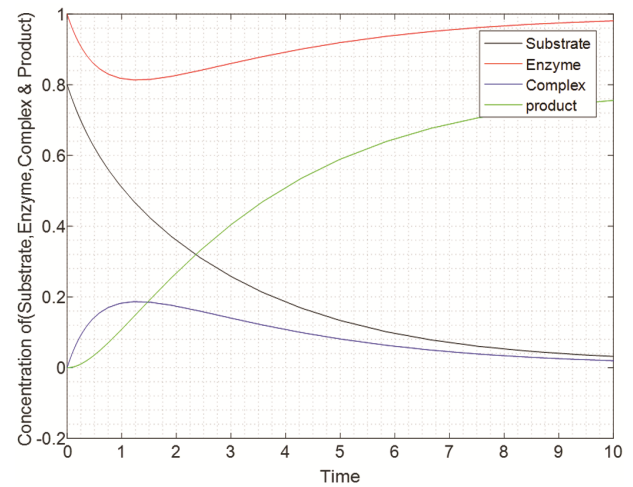


Fig. 11 — Time – Quantity relation

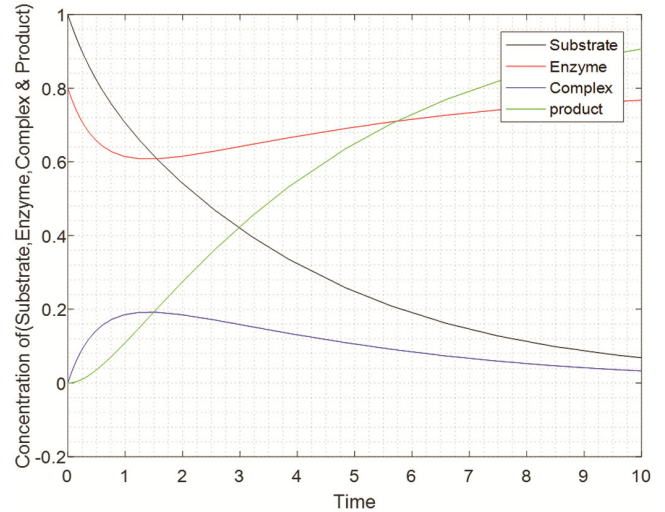


Fig. 12 — Time – Quantity relation

Conclusion

It's revealed all three drug administration modes exhibit distinct behaviours onto body. While analyzing the effects of drug intake onto body its observed that same amount of drug intake results most effective in IM/SC administration. Whereas IV intake is better if we want constant results in body with less adverse effects and if body have tolerating power high moreover, Oral administration is less effective and hence should be avoided in emergency cases. Additionally, the stability study conducted under fixed initial conditions revealed that fluctuations in the rate of constants a_1, a_2 and a_3 disturbs the period of ideal product development but much variability not seen in different mode of intakes. All three models have least time usage in

ideal product development for almost same parametric value. In model – I, Best results on body are observed under the parametric assumption $a_2 < a_1 < a_3$ and least in the assumption $a_1 < a_3 < a_2$. In model – II, Best results on body are observed under the parametric assumption $a_3 < a_1 < a_2$ and least in the assumption $a_2 < a_3 < a_1$. In model – III, Best results on body are observed under the parametric assumption $a_2 < a_1 < a_3$ and least in the assumption $a_1 < a_2 < a_3$ and $a_3 < a_2 < a_1$. Hence it can be proved that numerical change in the rate of change or parametric values behaves different in all the three drug intake administrations. It's also discovered that change in enzyme or substrate concentration do leads to dynamic change in ideal product formation differently into different modes. It follows that for optimal product production, the quantity of the enzyme must be utmost equal to the quantity of the substrate after restricting the initial conditions. However, it takes longer for the product to develop when the concentration of the enzyme is greater than that of the substrate. The models have broad applicability for different drug dispersion issues that crop up in research on narcotics. Furthermore, the models extend the characteristics of drug dispersion to include parameter flexibility and the effect of drug infusion via various pathways. Numerous applications of the study can be found in drug switch, drug prescription, and other relevant pharmacological research issues.

Conflict of interest

All authors declare no conflict of interest.

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