Strathmore UNIVERSITY

STRATHMORE INSTITUTE OF MATHEMATICAL SCIENCES (SIMS)

MASTER OF SCIENCE IN BIOMATHEMATICS

END OF SEMESTER EXAMINATION

BMA 8204-BIOMEDICAL MATHEMATICS

Date: 1st September, 2022 Duration: $2\frac{1}{2}$ Hours

Answer **Question ONE** and any other **two** questions.

Question I (20 marks)

1. (a) Define pharmacology and hence differentiate between pharmacokinetics and pharmacodynamics.(**3 Marks**)

   (b) What is an enzyme in chemical reaction and what do you understand by enzyme kinetics (**4 Marks**)

   (c) Assume that the reaction catalyzed by an enzyme follows Michaelis-Menten kinetics. If at a substrate concentration of 100 nM, the reaction proceeds at 98% of the maximum reaction velocity (V_{max}), what is the Michaelis constant (K_m) for this substrate. K_m is the substrate concentration needed to reach 50% of V_{max}. (**4 Marks**)

   (d) consider the chemical reaction represented by the following chemical notation:

$$D + E \rightleftharpoons_{k_2}^{k_1} C \longrightarrow^{k_3} P + E$$

   (i) Discuss the difference between law of mass action and law of mass conservation in modeling. (**2 Marks**)

   (ii) Use the law of mass action to formulate the ODEs representing the reaction represented by the chemical notation above. (**4 Marks**)

(e) Differentiate between dug efficacy and drug potency. What is the implication of a higher Therapeutic index in medication? (**3 Marks**)

Question 2 (20 marks)

2. (a) Why is the study of pharmacokinetics important? (**2 marks**)

(b) When a drug is orally administered, it dissolves and releases the medications into the gastrointestinal tract. The medications diffuse from there into the blood and the bloodstream takes medications to the site where it has therapeutic effect. The flow of drugs within the body is modelled by treating the different parts of the body as compartments and then tracking the medication as it enters and leaves each compartment. Figure 2 below shows the flow of a drug administered orally.

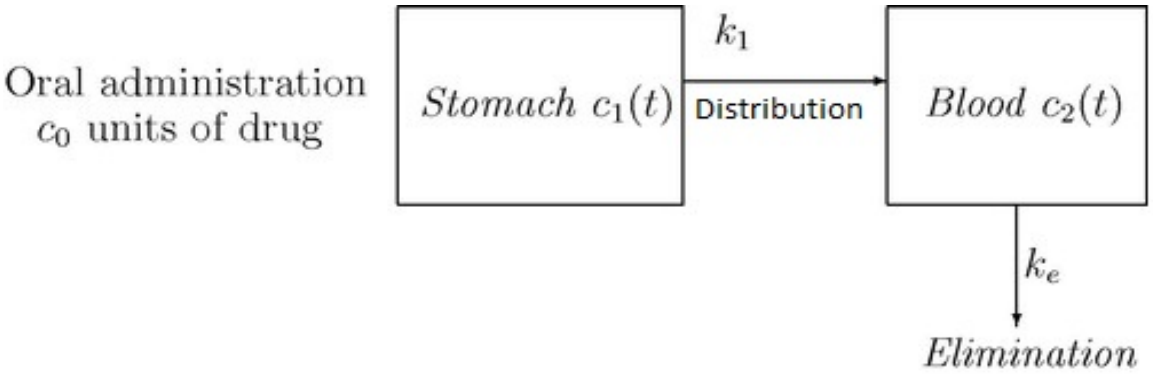

Figure 1: Simple process of drug administration through stomach and blood.

Where $c_1(t)$ and $c_2(t)$ denote the concentration of drug in stomach or GI tract and blood stream compartments respectively. Let $c_0 = c_1(0)$ be the initial concentration of drug dosage. Also let k_1 and k_e be the rates of drug distribution and drug elimination respectively.

(i) Formulate the mathematical models describing the the rate of change of drug concentration in the stomach and blood plasma respectively assuming $c_2(0) = 0$. (**4 marks**)

(ii) Using the initial condition, show that the solution to the model formulated in (i) above is given by: ((**9 marks**)

$$\begin{aligned} c_1(t) &= c_0 e^{-k_1 t} \\ c_2(t) &= \frac{c_0 k_1}{k_1 - k_e}(e^{-k_e t} - e^{-k_1 t}); \qquad k_1 \neq K_e \end{aligned}$$

(iii) Why is elimination half-life critical in developing a dosing strategy?? Express the concentration of the drug in the stomach $c_2(t)$ in terms of half-life of the drug. ((**5 marks**)

Question 3 (20 marks)

3. Consider a chemical reaction denoting metabolism of a certain drug which is represented by the following flow diagram: Where, S represents drug concentration in plasma, E is the drug

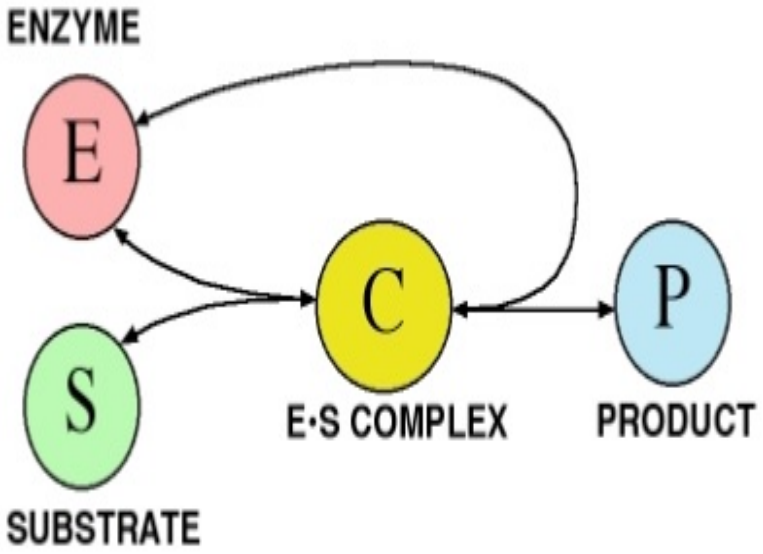

Figure 2: Simple process of drug administration through stomach and blood

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binding enzyme, C is the bound complex compound and P is the product.

(i) Represent the process using chemical notation (**2 Marks**)

(ii) Discuss k_1,k_2 and k_3 in relation to drug metabolism process above. (**2 marks**)

(iii) Show that the rate of drug metabolism v is given by: (**6 Marks**)

$$v = \frac{V_{max}S}{K_m + S}$$

(iv) Discuss K_m and V_{max} as represented in the model in (iii) above? . (**2 marks**)

(v) A lower numerical value of the Michaelis constant (K_m) indicates a higher enzyme affinity for the drug. Discuss. (**2 marks**)

(vi) Plot the equation in (iii) and indicate the type of kinetics/kinetic order in the graph. (**3 marks**)

(vii) Assume that the reaction catalyzed by an enzyme follows Michaelis-Menten kinetics. The substrate concentration (K_m, Michaelis constant) needed to reach 50% of the maximum reaction velocity (V_{max}) is $25\mu M$. What substrate concentration is required to obtain at least 95% of the maximum reaction velocity? (**3 marks**)

Question 4 (20 marks)

4. (a) For an enzyme-catalyzed reaction obeying Michaelis-Menten kinetics, $V_{max} = 0.5$ mol/sec and $K_m = 10$ mM.

(i) What is the rate of the reaction when the concentration of the substrate, $[S] = 20$ mM?. (**4 marks**)

(ii) Draw a Michaelis-Menten plot of the reaction kinetics, labeling the axes and giving values for the two points where you know V (from above). (**4 marks**)

(b) Consider the graph in Figure 3 showing drug dose-response relationship.

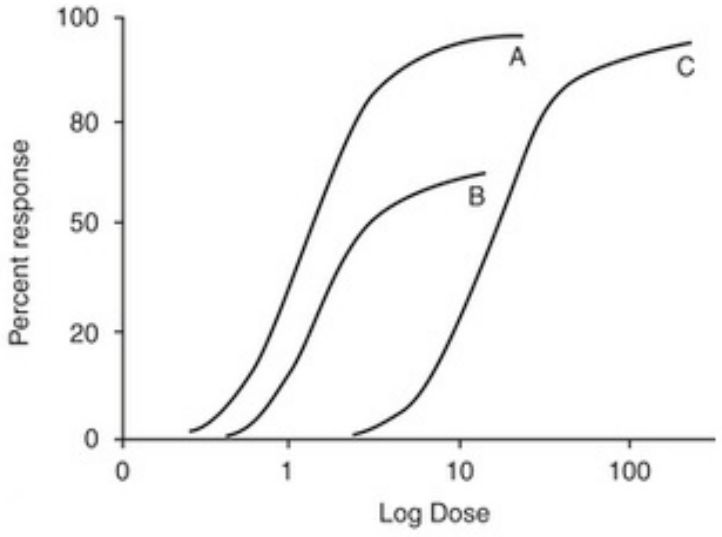

Figure 3: Drug Potency and Efficacy

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(i) Use Figure 3 to discuss the potency and efficacious of drugs A, B and C. (**4 marks**)

(ii) Why is drug potency important and what determines drug potency? (**4 marks**)

(c) Differentiate between Therapeutic window (TW) and therapeutic index (TI) of a drug. How is TI related to drug toxicity? (**4 marks**)