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First Project Deliverable

Background

Drugs can be produced in a variety of dosage forms. The dosage form used for a particular drug is determined by the properties of the drug (solubility, stability at various pH values, etc.), the area of the body being treated, and the concentration of drug that will provide the maximum therapeutic effect in a patient.

A common obstacle faced in drug design is ensuring that the blood maintains a high enough concentration of the drug's active ingredient to provide the desired therapeutic effect. In cases where the therapeutic concentration needs to be maintained for a long period of time or when the efficacy of the drug depends on a constant concentration of the drug in the blood, a modified release capsule can be used.

Modified release capsules contain a release rate controlling membrane and an internal reservoir, where the active ingredient resides (Figure 1). The membrane is typically made of a polymer that slows drug absorption into the body by acting as an additional diffusion barrier for the molecule. This aids in maintaining a more consistent blood concentration of the drug for a longer period of time. Because of this, less doses of the drug are needed to effectively treat a patient.

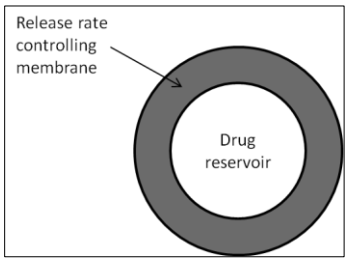

Figure 1: Modified release capsule

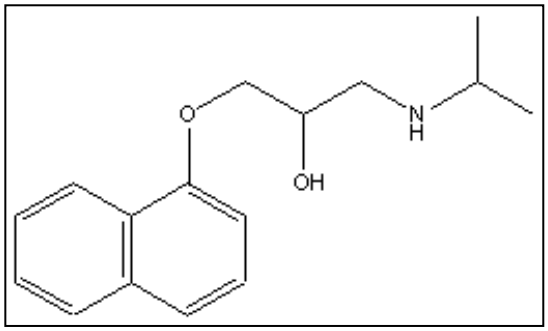

Figure 2: Inderal LA, a drug commonly used in modified release capsules. Image from www.pharmacy-and-drugs.com

Proposal

For my project, I have decided to model the concentration of a modified release drug in the blood as a function of time. In particular, I have chosen to consider Inderal LA, which is a beta blocking drug that is most commonly used to treat hypertension (Figure 2). According to dailymed.nlm.nih.gov, it is available in 60mg, 80mg, 120mg, and 160mg doses, and its release rate controlling membrane is a gelatin polymer.

The main output of my model will be the blood concentration of Inderal LA at any given time. However, the model will also be able to determine the time it takes the modified release capsule to liberate all of the drug, what the steady state drug concentration is, and the time it takes to reach the steady state concentration.

In order to produce these output parameters, many input parameters will need to be considered. A few of these parameters include time, initial mass of the active ingredient, and body temperature. A more complete list of parameters can be found in Table 1 below.

Table 1

Symbol	Parameter
t	time
m_0	initial mass of active ingredient
V_c	volume of capsule reservoir
B	thickness of gelatin membrane
L	length of the small intestine
D_{cm}	diffusion coefficient of drug in capsule membrane
D_{if}	diffusion coefficient of drug in intestinal

Symbol	Parameter
C_0	initial concentration of drug in capsule reservoir (m0/Vc)
$C_{cm}(t,r)^*$	concentration of drug in capsule membrane
$C_{ep}(t,r)^*$	concentration of drug in epithelial cells of the small intestine
$C_{bl}(t,r)^*$	concentration of drug in basal lamina of enteric blood vessels
$C_{en}(t,r)^*$	concentration of drug in endothelial cells of enteric blood vessels
r_c	radius of the capsule
r_1	inner radius of the small intestine

	fluid
D_{ep}	diffusion coefficient of drug in epithelial cells of the small intestine
D_{bl}	diffusion coefficient of drug in basal lamina of enteric blood vessels
D_{en}	diffusion coefficient of drug in endothelial cells of enteric blood vessels
k_L	rate of drug uptake/metabolism by liver
T	temperature of the body
k_e	rate of excretion into urine
k_d	rate of drug degradation in blood

r_2	radial distance from lumen of small intestine to basal lamina of enteric blood vessels
r_3	radial distance from lumen of small intestine to endothelial cells of enteric blood vessels
r_4	radial distance from lumen of small intestine to lumen of enteric blood vessels
r	radial distance drug has diffused from lumen of small intestine.
t_f	total time the capsule remains in small intestine
V_b	Total volume of blood in body
* Concentration profiles will be used to determine surface concentrations.	

A diagram of the drug's path through the body is shown in Figure 3 below.

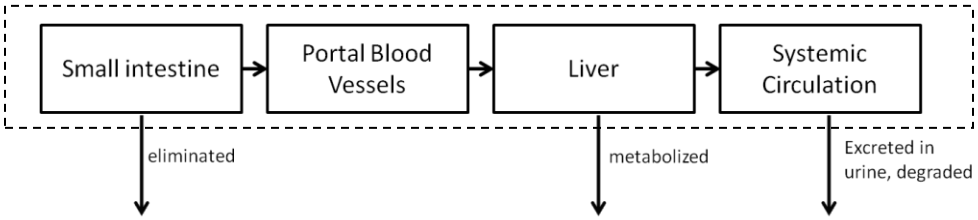

Figure 3: A simple schematic of Inderal LA's path through the body

As the diagram shows, there are many barriers the drug must pass through to reach the body's systemic circulation (the blood where the model will predict drug concentration). Also, there are additional barriers that are not shown. For example, in order for the drug to move from the small intestine into the portal blood vessels, it must first diffuse through the capsule membrane, the fluid in the small intestine, the epithelial cells lining the small intestine, the basal lamina of the enteric blood vessels, and the endothelial cells of the enteric blood vessels. After reaching the portal blood vessels, the drug must pass through the liver, where a large portion will be metabolized. Finally, the drug can enter systemic circulation, where it may also be lost to kidney filtration or natural degradation.

The parameters listed in Table 1 will be used to calculate the changing amounts of drug present in each of the compartments depicted in the Figure 3. The initial mass of the drug (m_0), volume of the capsule (V_c), thickness of the capsule membrane (B), and diffusion coefficient for the drug in the capsule membrane (D_{cm}) will allow the concentration profile of the drug to be determined in the capsule membrane. Similarly, the remaining diffusion coefficients and radii will allow concentration profiles to be determined through the intestinal fluid, intestinal epithelial cells, enteric vessel basal lamina, and enteric vessel endothelium. Once the drug has reached the lumen of the enteric vessels, it will move immediately into the portal vessels that transport the drug to the liver. From here, the changing systemic blood drug concentration will depend on the rate the liver metabolizes the drug (k_L), the rate the drug molecule degrades (k_d), and the rate that the drug is filtered into urine to be excreted (k_e). Other significant parameters that must be considered in the model include body temperature (effects rate of diffusion), volume of blood, and time.

The main fundamental principle that will be used in this project is the first law of thermodynamics: mass cannot be created or destroyed. Therefore, all of the drug mass that enters the small intestine must be maintained, whether it remains in the intestine for elimination, is metabolized by the liver, or makes it all the way to systemic circulation. This means that whatever drug is coming into the blood vessels of the systemic circulation minus whatever is metabolized, excreted, or degraded will represent the accumulation of drug in the blood. This accumulation represents the changing drug concentration in the blood, the main output parameter of the model.

This model, upon completion, will be helpful in predicting how long it takes for Inderal LA to reach its optimum blood concentration, what the steady state blood concentration is, and how long a particular dose of Inderal LA will have a therapeutic effect. It will be able to demonstrate the effect of dosage size on the length of therapeutic effect and could be easily modified to show how different capsule materials/thicknesses could affect release time and blood concentration as well. Additionally, since the model will be derived with symbolic variables, it will be easy to modify and use for other drugs that use the same method of delivery. This would be a very useful tool to have when determining what mass of drug or capsule material should be used for a particular medication.