Drug Processing Cheat Sheet

Why is drug delivery important?

How the drug is delivered determines how effective the pharmaceutical product is → inadequate delivery means you have an inadequate product that is not yielding the desired therapeutic effects.

Match the pharmacokinetics vocabulary word to its definition.

	Word Bank	
Absorption	Absorption Phase	ADME
Area Under the Curve (AUC)	Bioavailability	Buccal
Clearance	Cmax	Distribution
Duodenal	Duration of Action	Elimination Phase
Excretion	First Pass Metabolism	Intravenous
Lag Time	Liberation	Metabolism
Minimum Toxic Concentration	Oral	Pharmacodynamics
Pharmacokinetics	Pharmacokinetic Models	Sublingual
Subtherapeutic Window	Therapeutic Window	tmax
Toxic Window	Toxicity	Transdermal

Pharmacodynamics	What the drug does to the body
Pharmacokinetics	What the body does to the drug
Liberation	Drug release into active form
Absorption	Uptake of drug
ADME	ABCDs of Pharmacokinetics
Distribution	Transfer of drug in the body
Metabolism	Breakdown of drug into metabolites, resulting in drug deactivation

Excretion	Removal of drug and metabolites
Pharmacokinetic Models	Depict drug concentration in blood plasma over time
Cmax	Maximum concentration of drug in the blood
Toxic Window	High conc. range where patient may experience toxic effects
Therapeutic Window	Low concentration range where treatment is not effective
Subtherapeutic Window	Median conc. range where treatment is non-toxic and effective
Duration of Action	Length of time that the drug is effective
tmax	Time it takes plasma concentration to reach Cmax
Absorption Phase	Time post-ingestion where drug is taken up into the bloodstream
Elimination Phase	Time post-ingestion where drug is removed from bloodstream
Lag Time	Time between drug dosing and increase in plasma concentration
Bioavailability	Fraction of drug that yields a therapeutic effect in the body
Area Under the Curve	Used to calculate bioavailability
Intravenous	This drug delivery yields a very high bioavailability (100%)
Oral	This type of drug delivery yields a very low bioavailability (<1%)
First Pass Metabolism	Liver processing that eliminates majority of orally delivered drug
Toxicity	Damage the drug can cause to the organism
Minimum Toxic Conc.	Threshold for drug toxicity
Clearance	Volume of fluid that is completely freed of drug per unit time
Transdermal	Drug delivery through the skin
Duodenal	Drug delivery through the intestine
Buccal	Drug delivery through the cheek
Sublingual	Drug delivery under the tongue

Calculating AUC and Assessing Drug Candidates

You are a preclinical researcher at a large pharmaceutical company. You are experimenting with different formulations in order to enhance the delivery of drug molecule Y. High doses of molecule Y are associated with not super fun side effects, so you want to keep the maximum plasma concentration of molecule Y below 1000 $\frac{\mu g}{mL}$. You hypothesize that lipid encapsulation of molecule Y can increase its bioavailability and duration of action while maintaining a drug concentration within the therapeutic window. You test this hypothesis by delivering a single intraduodenal bolus injection of molecule Y into Sprague-Dawley rats and monitoring their plasma concentration of molecule Y over 24 hours. The following formulations were tested:

Active Product Ingredient (API): free molecule Y (no encapsulation)
200 nm Solid Nanoparticle: large droplets of molecule Y in lipid
100 nm Solid Nanoparticle: medium droplets of molecule Y in lipid
10 nm Solid Nanoparticle: small droplets of molecule Y in lipid

The solid Nanoparticles were developed by homogenizing and emulsifying free molecule Y within a lipid carrier and sorting the droplets by size.

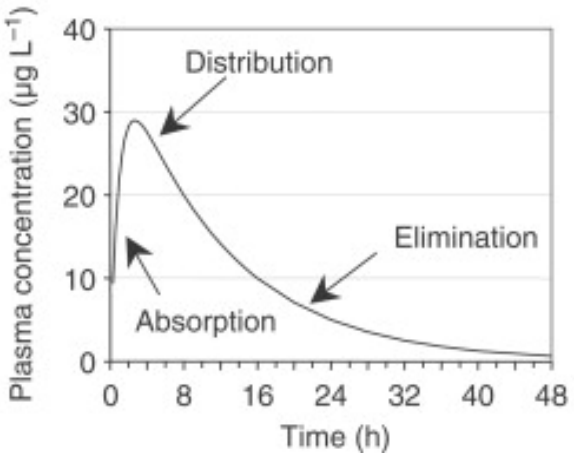
The results of this experiment can be found on the Module 9 Data Sheet posted on the Cell Team Website.

Assume that molecule Y has no subtherapeutic threshold unless specified otherwise.

1. The pharmaceutical company hopes to deliver molecule Y orally. Why are you testing its performance through an intraduodenal injection?

Rats can't swallow pills! So preclinical testing for oral medication is done by injecting the drug product into the small intestine, where the drug will undergo the same metabolic processing as orally administered medication. This allows researchers to adequately assess the toxicity of potential medications before the drug candidate moves into human clinical trials.

2. Calculate the average and standard error plasma concentration of molecule Y for each experimental condition at each time point. Plot average plasma concentration of molecule Y over time for each experimental condition.
    a. What do you notice about the shape of the pharmacokinetic model? Is the absorption phase or elimination phase longer?



Generally, PK models have a short absorption phase, reaching Cmax in the first few hours after dosing, and a long elimination phase as the drug is metabolized into its inactive form and slowly excreted from the body.

    b. You may notice that the error for this dataset is quite large. Why do you think there is such a large difference in the plasma concentration of molecule Y between the individual rats?

Drug processing is prone to inter-subject variability. Individual organisms undergo different rates of drug metabolism and have significant differences in their ability to uptake drug. The three different rats that underwent each experimental treatment likely processed the drugs differently, resulting in different concentrations of drug over time. This inter-subject variability is why pharmaceuticals are tested on a large number of organisms (on the order of thousands) before they are deemed effective and safe for human use.

3. Calculate the average area under the curve (AUC) for each formulation.

   Hint: Dust off your Calculus knowledge and break out Trapezoidal rule

$$\Delta AUC_{1-2} = \frac{C_1 + C_2}{2} \text{x } (t_2 - t_1)$$

   a. Rank the formulations from highest bioavailability to lowest bioavailability

Highest: 100 nm Nanoparticle (9597 $\frac{\mu g\ hour}{mL}$)

API (9491 $\frac{\mu g\ hour}{mL}$)

200 nm Nanoparticle (8363 $\frac{\mu g\ hour}{mL}$)

Lowest: 10 nm Nanoparticle (2446 $\frac{\mu g\ hour}{mL}$)

4. Based on your calculations and plots, which nanoparticle formulation would you recommend for future experimentation?

100 nm Nanoparticle

   a. Why might you hesitate to recommend the API formulation of molecule Y for future studies?

In some of the tested rats, the concentration of Molecule Y in Rat Plasma surpassed the minimum toxic concentration, which can result in some not very fun side effects. This may make you hesitate in using this dose of molecule Y as free API in future studies. However, you may consider studying free molecule Y at a lower oral dose to assess its effectiveness and safety.

b. If the subtherapeutic threshold for molecule Y is 500 $\frac{\mu g}{mL}$, would you change your nanoparticle formulation recommendation?

   Note: You don't need to do any calculations to answer this question - just examine the duration of action given this subtherapeutic threshold.

You can answer this question by looking at the duration of action (DOA) if the subtherapeutic threshold for molecule Y is 500 $\frac{\mu g}{mL}$. I chose to estimate the DOA by looking at the average drug concentration data for each of the four experimental groups and counting the number of hours for which the concentration was above 500 $\frac{\mu g}{mL}$. I found that free API had the highest DOA (6 hours from t = 3 to t = 9) and the 100 nm Nanoparticle formulation had the second highest DOA (4 hours from t = 5 to t = 9). Given the high Cmax of the free API formulation, I would still recommend continuing research with the 100 nm Nanoparticle formulation. However, it is important to note that one limitation of the current formulation is its shorter DOA.