20.201 Problem Set for Fundamentals
9 Oct 2013

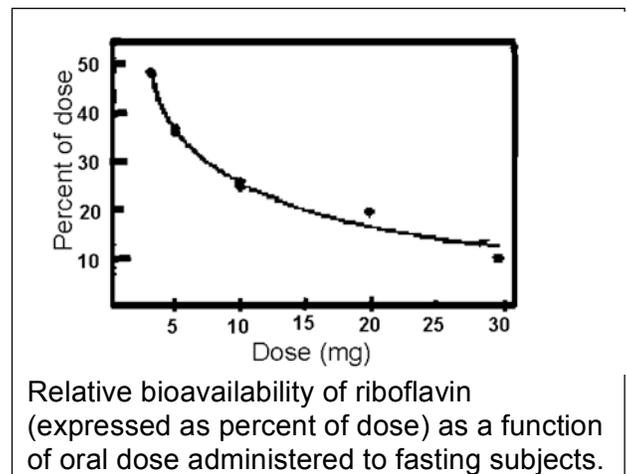**Please prepare your answers in electronic format and submit the answers before or on**
October 11. While this is not a graded problem set, you will get credit for completing the problem set and submitting it. An answer key will be posted on October 12, so no credit will be given for late submissions!

(1) Which of the following parameters will result in faster passive diffusion of a drug? Why or why not?

    ~ surface area of the absorption site
    ~ membrane thickness
    ~ partition coefficient of the drug between lipid and water<
    ~ gradient between drug concentrations on both sides of the membrane
    ~ ATP-concentration in the membrane

(2) As shown in the figure shown on the right, riboflavin (vitamin B_2) absorption is dose-dependent. Which of the following absorption mechanisms could be responsible for the absorption from the intestines? Why?

    ~ Active transport
    ~ Facilitated transport
    ~ Passive diffusion

Relative bioavailability of riboflavin (expressed as percent of dose) as a function of oral dose administered to fasting subjects.

(3) Which of the following drug formulations would lead to absorption of the drug into the general (systemic) circulation, thus bypassing the portal circulation. How?

    ~ peptide nasal spray
    ~ nitroglycerin transdermal system
    ~ intramuscular injection of penicillin G
    ~ injection into the cephalic vein of the forearm
    ~ antipyretic suppository

(4) Explain why these statements are true or false

    ~ drugs that are very lipophilic tend to distribute well into body tissues.
    ~ drugs that are predominantly ionized at physiologic pH do not readily distribute into tissues when compared to drugs that are primarily unionized. (Assuming tight membrane junctions)
    ~ drugs are generally less well distributed to highly perfused tissues.

~ the volume of distribution depends only on the degree of tissue binding.

(5) The volume of distribution in a 70 kg man is observed to be 10 liters. Indicate which one (or more) of the following statements is (are) consistent with the observation when you consider that albumin has a volume of distribution of about 7 liters.

~ highly bound to plasma proteins
~ does not pass any membranes
~ not bound to plasma proteins
~ low extraction drug

(6) Select the correct answer(s). Due to the nature of biological membranes, drugs with the following properties are more likely to cross most membrane barriers:

~ ionized and lipophilic
~ ionized and hydrophilic
~ non-ionized and lipophilic
~ non-ionized and hydrophilic

(7) The larger the volume of distribution:

~ the more sequestration may have occurred
~ the larger the plasma albumin binding
~ the higher the clearance
~ more drug is outside of the plasma

(8) The molecule shown below is acetylsalicylic acid (a.k.a., aspirin).

   a)   Please <u>derive</u> the Henderson-Hasselbalch equation using the following acid dissociation equilibrium:

$K_a = 10^{-3.5}$

$+ \quad H^+ \ (H_3O^+)$
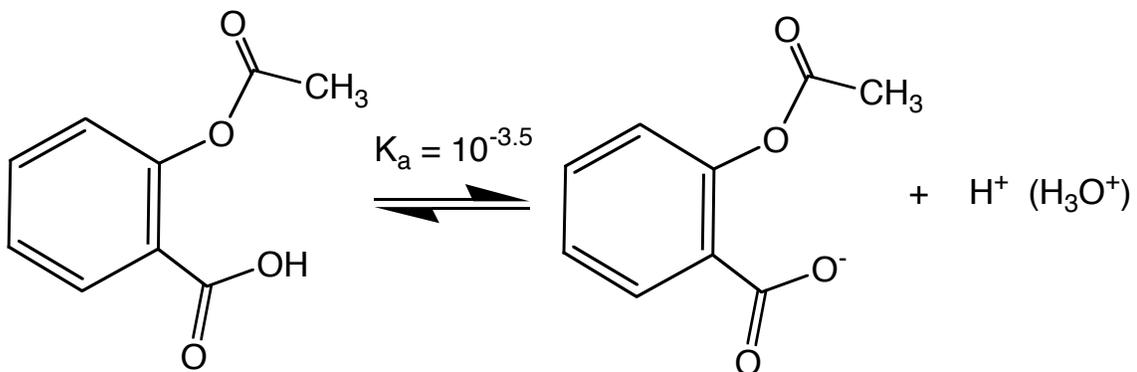
   b)   Calculate the ratio of charged (base) to uncharged (acid) forms of aspirin at pH 2 and pH 7.

   c)   Where in the body would you expect to find significant diffusion of aspirin into cells if you assume that the charged form does not diffuse across cell membranes?

(9)   Answer questions a, b and c for nicotine.

   a)   Please <u>derive</u> the Henderson-Hasselbalch equation using the following
         acid association equilibrium:

$$pK_a \sim 8$$

$$H^+$$

Nicotine

$$H^+$$

Uncharged, base   *Charged, acid form*
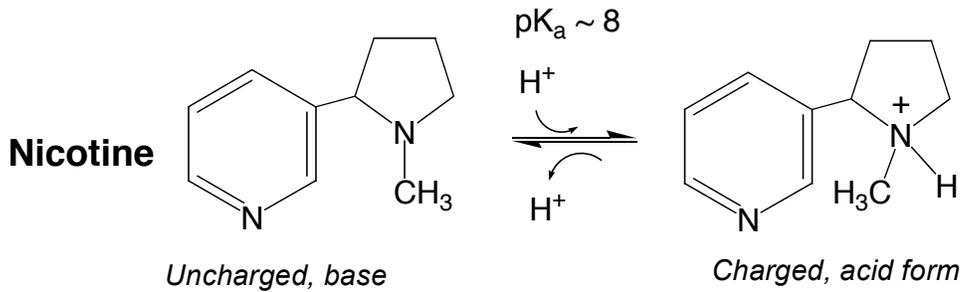
   b)   Calculate the ratio of charged (base) to uncharged (acid) forms of nicotine
         at pH 2 and pH 7.

   c)   Where in the body would you expect to find significant diffusion of nicotine
         into cells if you assume that the charged form does not diffuse across cell
         membranes?

20.201 Mechanisms of Drug Actions
Fall 2013