BPS 2110 Intro to Biopharm
Mid Term 1 Answers 2019

1. Complete the following table describing the general types of pharmaceutical companies. (**8 points**)

	Approx Size (or number of employees)	Primary operation or function
Ethical	Very large (100,000's)	Discover and develop new molecular entities
Generic	Very large to medium (100,000's to 10,000's)	Manufacture products not covered by patent
Biotech	Small (10's to 1000's)	-exploit academic discoveries (turn ideas into products)
CRO	Medium to small (10,000's to 100's)	Provide specialty services (testing, synthesis, research etc)

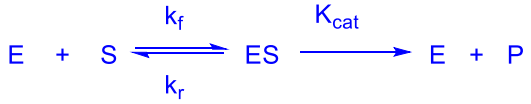
2. PAINS are a major problem during drug discovery.
   a) What does the acronym PAINS stand for? (**1 Point**)
   Pan Assay INterference compoundS
   b) Why are PAINS a problem? (**2 Points**)
   - they give positive results in virtually any biological test.
   - This tends to clutter up search results and slow down drug discovery
   c) List two types of chemical behavior that PAINS generally have in common. (**2 Points**)
   Choose any 2 of following: (2)
   - Redox (oxidation or reduction)
   - Detergents
   - Strong acids or bases
   - Strong nucleophile or electrophile
   - Photoreactive
   - Chelator
   - Highly lipophilic
   - Bright color

3. List three (3) different types of excipients and for each give one key function they provide in drug formulation. (**6 Points**)
   Choose any 3 of following. Need name + function:
   Stabilizer – protect from chemical degredation (oxygen)
   Preservative – prevent mold or bacterial growth
   Fillers – ensure consistent dosing
   Disintegrants – speeds dissolution by breaking pill apart in presence of water
   Binders – hold pill ingredients together
   Lubricants – ease of manufacture, prevent sticking to machinery
   Flavors – mask taste (bitter or sweet)
   Colors – safety, helps identify pills

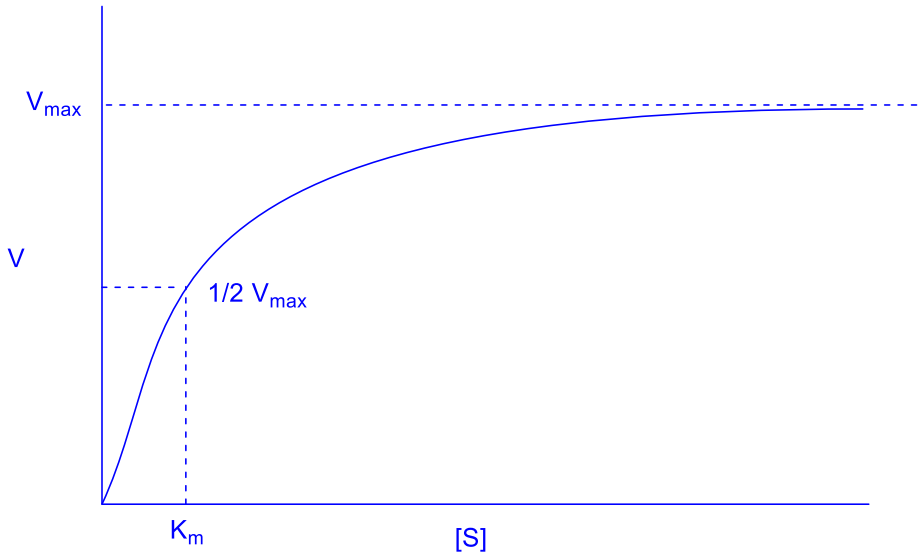
4. Name the four general types of secondary protein structure and describe how each is represented on a ribbon diagram. (**8 Points**)

a) α-helix – appears as a coiled ribbon with arrow pointing toward C-terminus. In some structures may be a cylinder
b) β-sheet (strand) – flat ribbon with arrow pointing toward C-terminus.
c) Loop – thin tube, spaghetti like
d) Turn – tight shift in direction on a loop (approx 180°)

5. The Michaelis-Menton equation is used to describe enzyme performance.
   a) What is the chemical equation used to describe enzyme function in terms of enzyme and substrate (be sure to include all parameters)? (**2 Points**)



   b) Draw a general kinetics plot (graph) that is used to describe enzyme behavior (be sure to label the axes and key points on the graph). (**4 Points**)



Lineweaver-Burke was also accepted

   c) What equation can be derived from the graph in part b? (**2 Points**)

$$V = \frac{dP}{dt} = \frac{V_{max}[S]}{Km + [S]}$$

Lineweaver-Burke was also accepted

   d) Three key parameters are used when describing Michaelis-Menton kinetics. For each of the following parameters, describe what they are (definition), and how they can be used **(5 Points**)
      i. K_{cat}

- turnover rate
- larger Kcat = faster (easier) reaction
- measure of efficiency of reaction of ES complex

(2)

      ii. K_m

- [S] at ½ V_{max}

(1)

iii. K_d

- Ratio k_r/k_f
- Measures tightness of binding between enzyme and substrate
- Small k_d = tight binding

a) How is the ratio Kcat/Km used? Give an example (**2 Points**)

- index of enzyme efficiency
- specificity constant
- high ratio = efficient enzyme

6. LogP and LogD are common measurements used in the pharmaceutical industry.
   a) What do these parameters measure? (**1 Point**)
   Lipophilicity
   b) What is the equation used to measure LogP, and what conditions are required to use this equation? (**2 Points**)

$$LogP = Log\left(\frac{[Drug]_{octanol}}{[Drug]_{water}}\right)$$

Must measure at pH at which the drug is neutral

   c) What are the two biggest disadvantages of using LogP? (**2 Points**)

- Each molecule requires different buffer (pH)
- Measurements may not be at physiological conditions (pH 7.4)

   d) What is the key difference between LogP and LogD? (**1 Point**)

- LogD is measured at a defined pH (most common is 7.4)

   e) What are the two methods used to measure LogP and LogD (brief description of each)? (**4 Points**)

Method A:

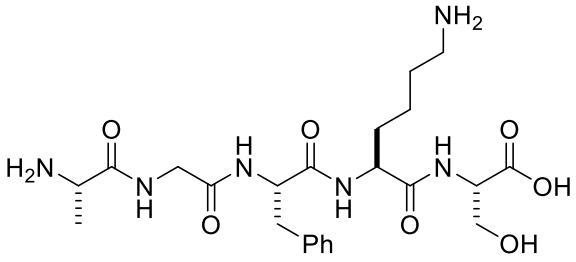
1- Make solution of drug in water (or octanol)
2- Add equal volume of octanol (or water)
3- Mix, then allow layers to separate
4- Measure concentration of drug in 1 or both layers

Method B:

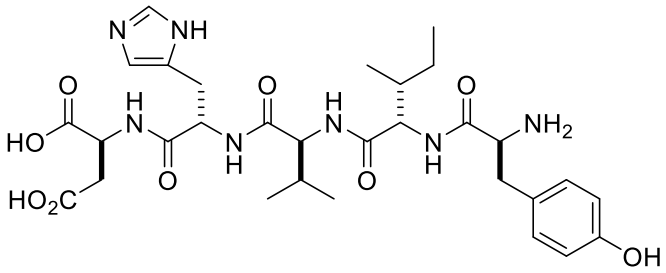
1- Run sample through special HPCLC column
2- Retention time used to calculate LogP or LogD

7. What is the amino acid sequence of the following peptides? (**4 Points**)

a)



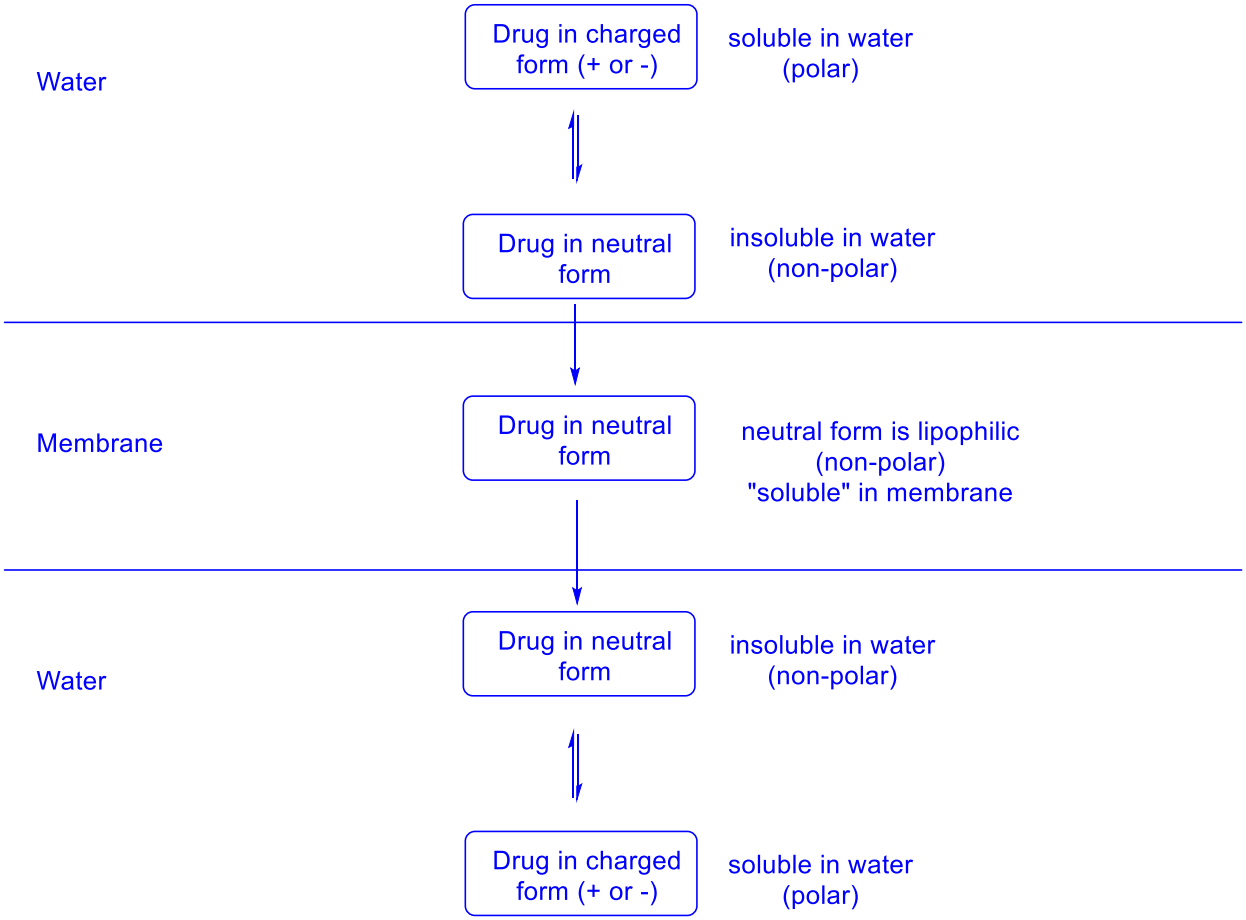
Alanine-Glycine-Phenylalanine-Lysine-Serine

b) 

Tyrosine-Isoleucine-Valine-Histidine-Aspartic Acid
(list N term to C term)

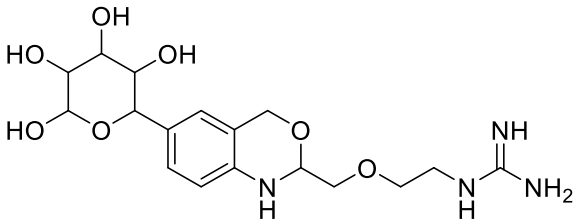
8. Most drugs approved for use in humans are acids or bases, which helps them enter cells. Use a diagram to show why acids or bases generally can be transported into and out of cells. (**5 Points**)

Charged molecules are soluble in water, but have difficulty passing through membranes
Neutral molecules are insoluble in water, but easily pass through membranes
Acids and bases exist in equilibrium between protonated and non-protonated forms. This creates an equilibrium between charged and neutral forms, which allows them to pass through both environments.



9. Predict whether the following compounds are likely to be orally bioavailable or not, and provide a brief justification for each. (**6 Points**)

a)

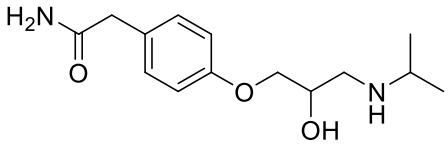


MW = 398.4
MlogP = 4.8

H-bond donors = 9
H-bond acceptors = 11

likely not bioavailable, violates three rules

b)

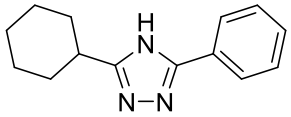


MW = 266.3
$LogD_{7.4}$ = 0.58

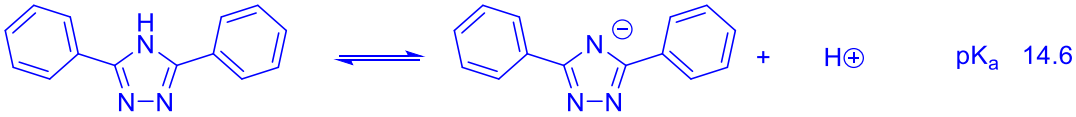
H-bond donors = 4
H-bond acceptors = 5

likely bioavailable, only violates one rule

10. The following molecule was once considered as a drug candidate by a large pharmaceutical company



a) Write the pK_a expression for the drug acting as an **acid** and identify an appropriate pK_a value using the table provided. (**3 Points**)



pK_a 14.6

b) Write the pK_a expression for the drug acting as a **base** and identify an appropriate pK_a value using the table provided. (**3 Points**)

pK_a -2.5

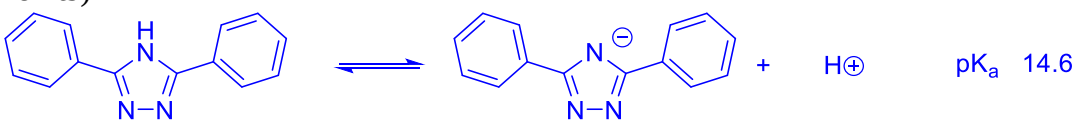
c) Use your pK_a data to predict whether the group will act as an acid or base when used as a drug. (**2 Points**)

Group will act as an acid

The pKa of the group, acting as a base (part b) is outside the range of allowed for water (-1.5 to 15.7). this expression can be ignored (the drug can only be in the non-protonated form)

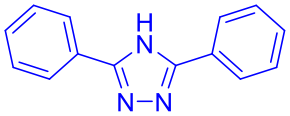
The pKa for the group acting as an acid (part a) is inside this range, and is therefore relevant for this in water solution

d) Use your pKa data to predict whether the molecule is likely to be soluble at pH 7.4. (**2 Points**)



pK_a 14.6

pH is less than pKa. At pH 7.4 the molecule will be in the protonated state.



Drug is neutral and likely insoluble in water.