IONIZATION AND DISSOCIATION OF DRUGS

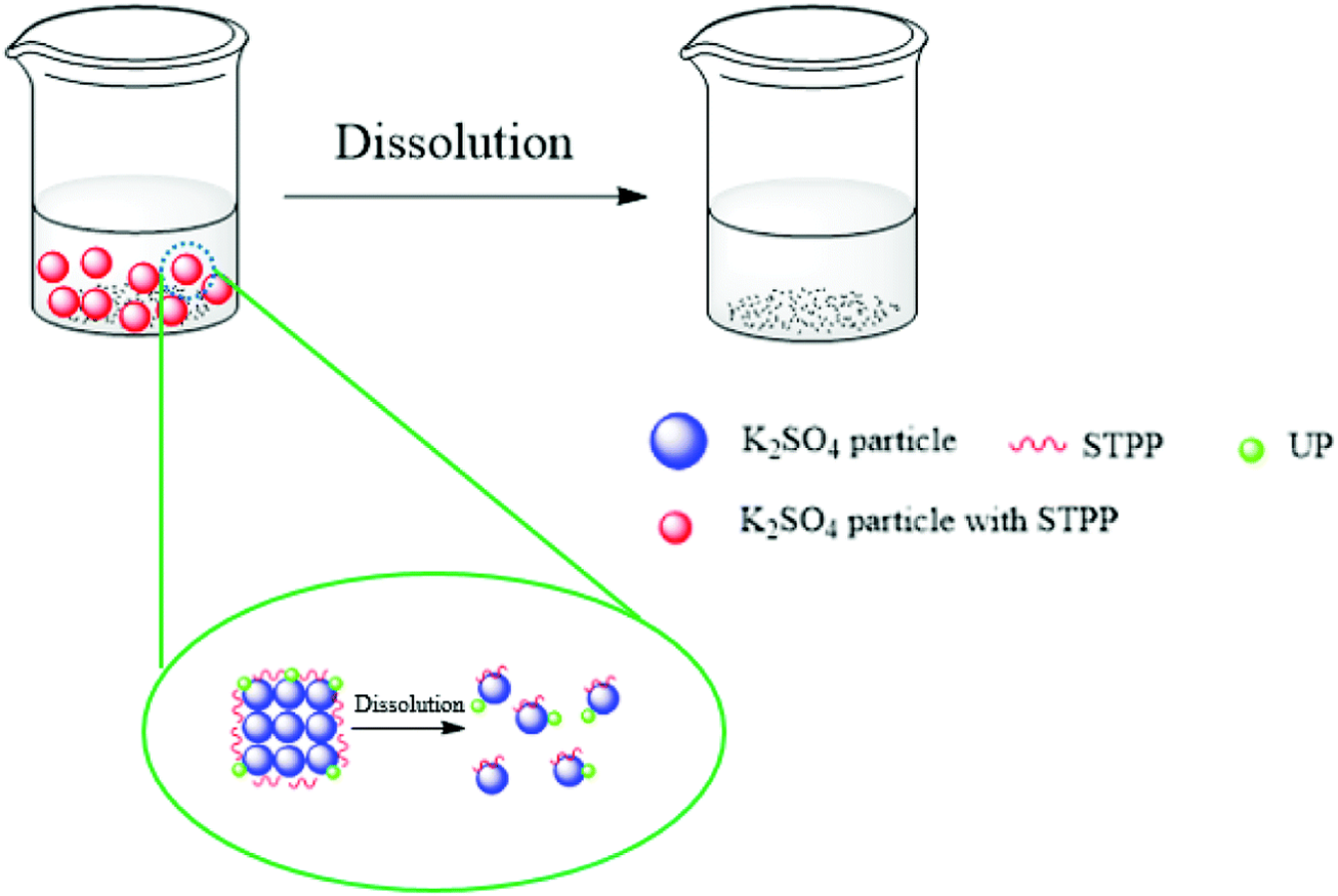
DEFINITION OF SOLUBILITY

Solubility is the ability of a solid, liquid, or gaseous chemical substance (referred to as the *solute*) to dissolve in *solvent* (usually a liquid) and form a *solution*. The solubility of a substance fundamentally depends on the solvent used, as well as temperature and pressure. The solubility of a substance in a particular solvent is measured by the concentration of the saturated solution. A solution is considered saturated when adding additional solute no longer increases the concentration of the solution.

The degree of solubility ranges widely depending on the substances, from infinitely soluble (fully miscible), such as ethanol in water, to poorly soluble, such as silver chloride in water. The term "insoluble" is often applied to poorly soluble compounds. Under certain conditions, the equilibrium solubility can be exceeded, yielding a supersaturated solution.

Solubility does not depend on particle size; given enough time, even large particles will eventually dissolve.

DISSOLUTION



NOYES AND WHITNEY EQUATION

The rate of change in concentration of dissolved material with time it directly proportional to the concentration difference between the two sides of diffusion layer

$$\text{i.e.} \quad \frac{dc}{dt} = k\,(C_s - C_b)$$

Where, dc/dt - Dissolution rate of drug.

k - Rate constant

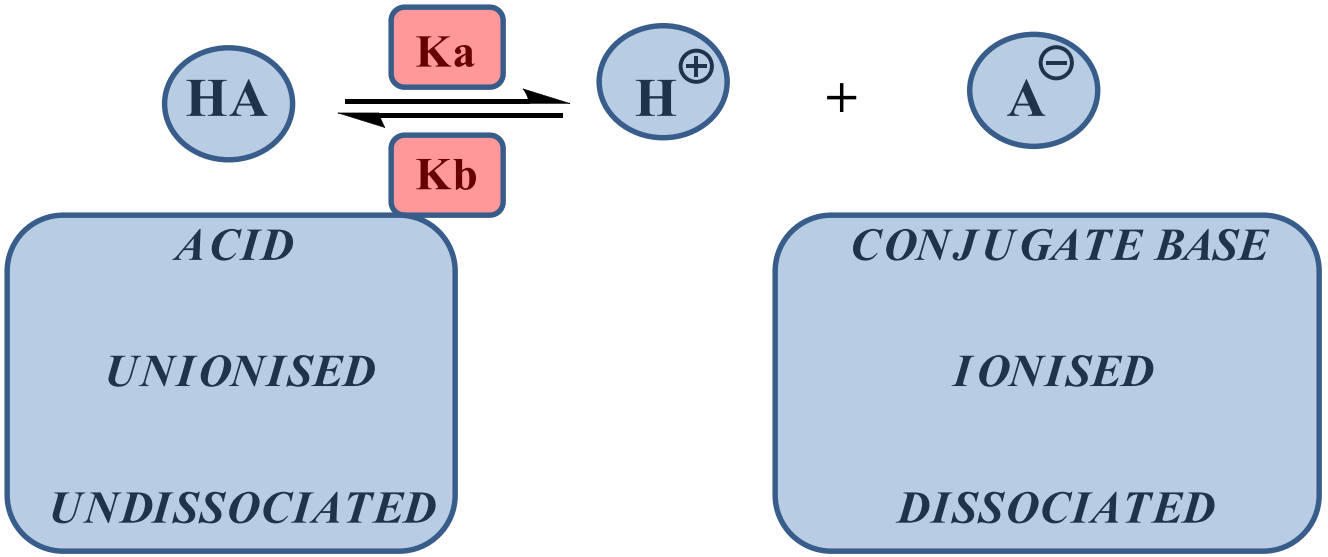
Cs - Concentration of solution at solid surface

Cь - Bulk of the solution

Ionisation and dissociation

- <u>ACIDS ARE PROTON DONORS</u>

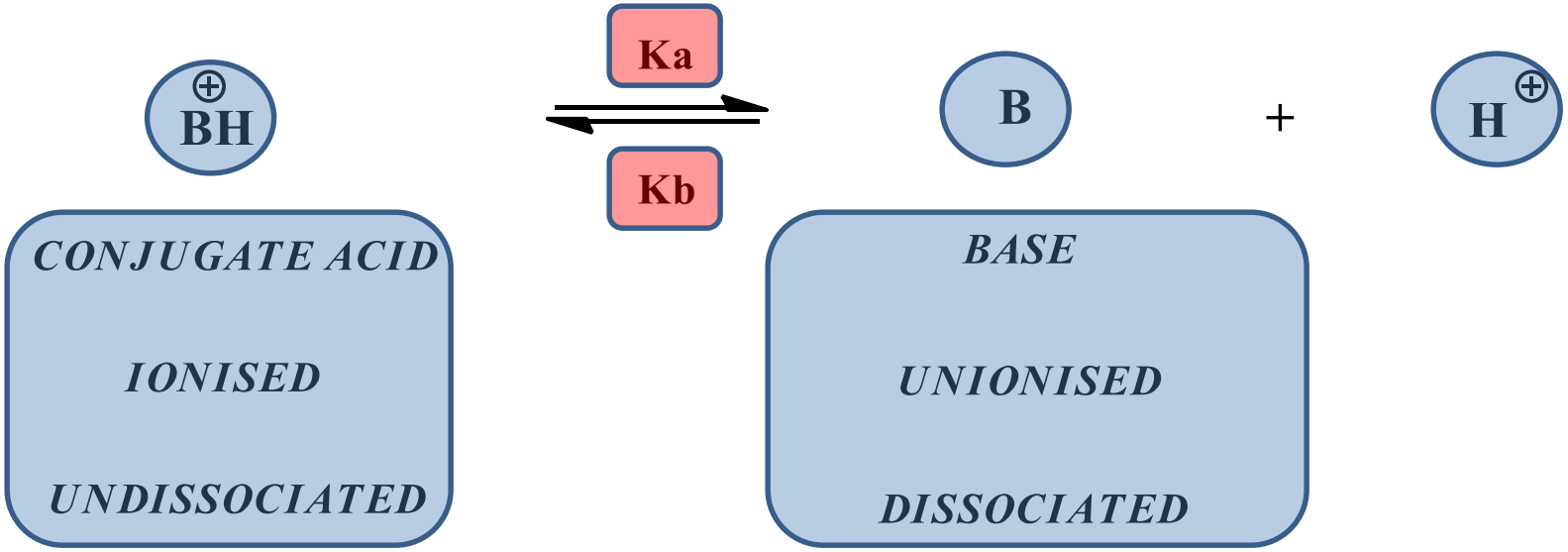
  acid is a substance that can dissociate to give H^+ and a negative ion (anion) which is called a conjugate base:



Ionisation and dissociation

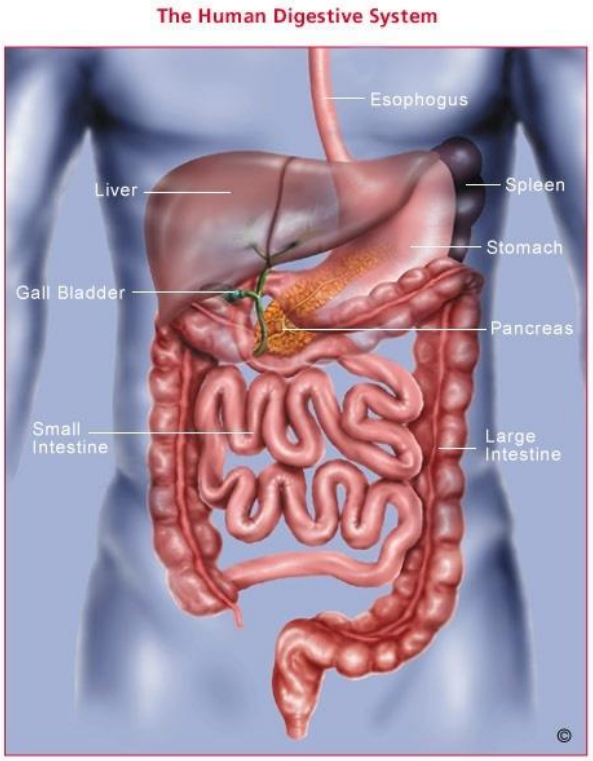
- <u>BASES ARE PROTON ACCEPTORS</u>

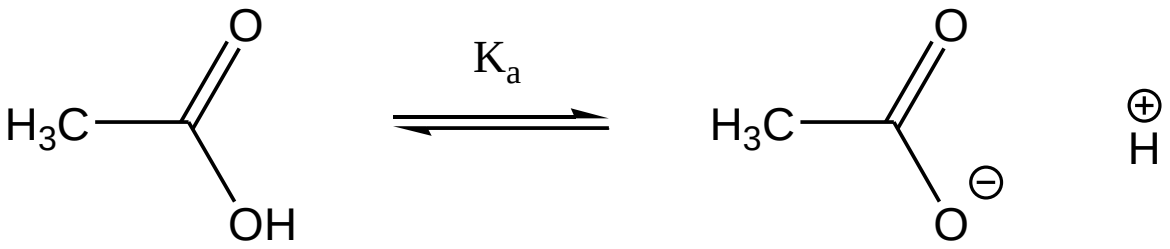
  Bases can accept a proton to form the positively charged cation (conjugate acid of the base):



pH in different body compartments

Plasma	7.35 – 7.45
Buccal cavity	6.2 – 7.2
Stomach	1.0 – 3.0
Duodenum	4.8 – 8.2
Jejunum & ileum	7.5 – 8.0
Colon	7.0 – 7.5





$$K_a = \frac{[CH_3COO^-][H^+]}{[CH_3COOH]}$$

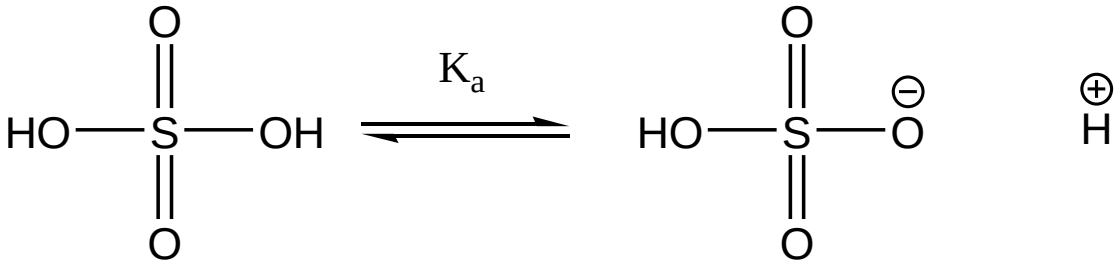
K_a for CH_3CO_2H is approximately 10^{-5}

$$K_a = \frac{1}{10^5}$$

i.e. only 1 molecule in 100,000 is DISSOCIATED (ionised).

$-\log_{10}K_a = pK_a$

So pKa for acetic acid is 5

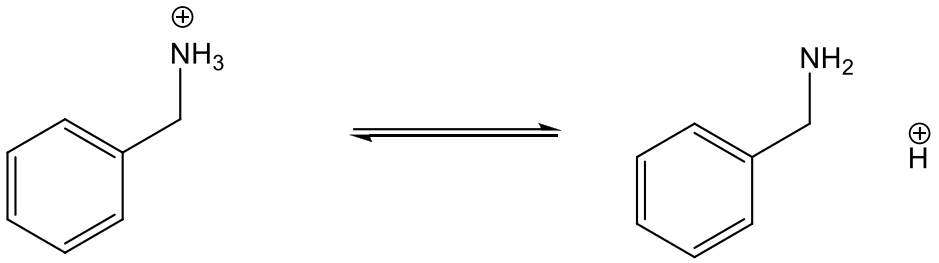


$$K_a = \frac{[HSO_4^-][H^+]}{[H_2SO_4]}$$

K_a for H_2SO_4 is approximately 10^5 $K_a = \frac{10^5}{1}$

i.e. 100,000 molecules are DISSOCIATED (ionised) for every one undissociated.

The pKa of H_2SO_4 is therefore -5



$$K_a = \frac{[PhCH_2NH_2][H^+]}{[PhCH_2NH_3^+]}$$

K_a for $PhCH_2NH_3^+$ is approximately 10^{-9} (pKa = 9) $\quad K_a = \frac{1}{10^9}$

i.e. only 1 molecule in 1,000,000,000 is DISSOCIATED (UNIONISED).

A weak conjugate acid does not easily donate its proton
(1 molecule in 1,000,000,000 donates a proton)

Therefore a strong base willingly accepts a proton
(1,000,000,000 molecules accept a proton for every one)

Ionization and dissociation of drugs-2

pKa is a different term than pH

pH is simply a measure of the $[H^+]$ concentration in a given solution

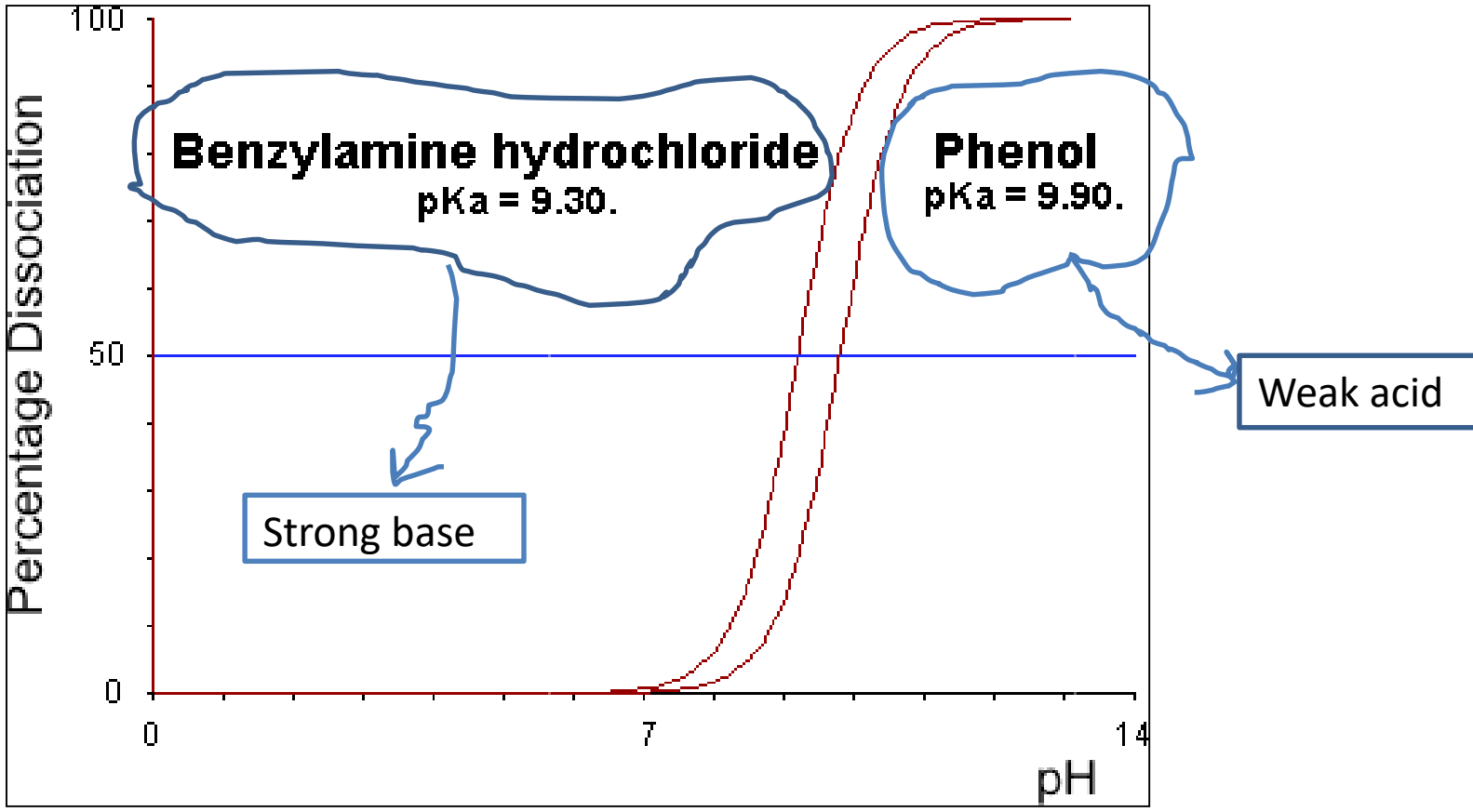
pH = 1 .....the environment is acidic

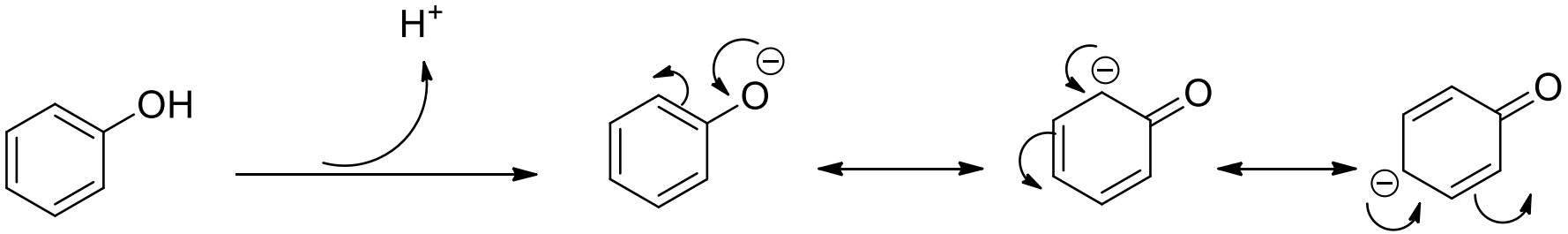
pK_a = 1 DOES NOT mean an acidic molecule

pH = 14 .....the environment is basic

pK_a = 1 DOES NOT mean a basic molecule

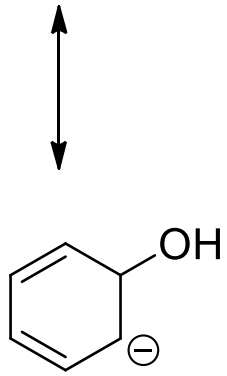
You can't tell from the pK_a value whether the species in question is acidic or basic





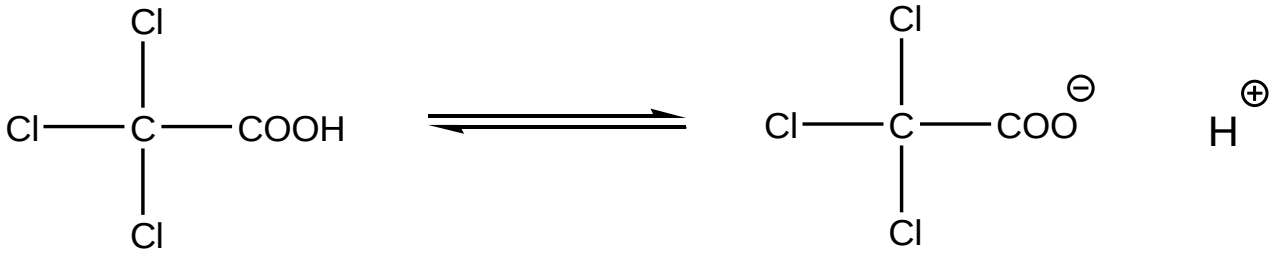
Phenoxide anion is stable by resonance
this means that phenol can give stable anion upon donating its proton

"act as an acid"

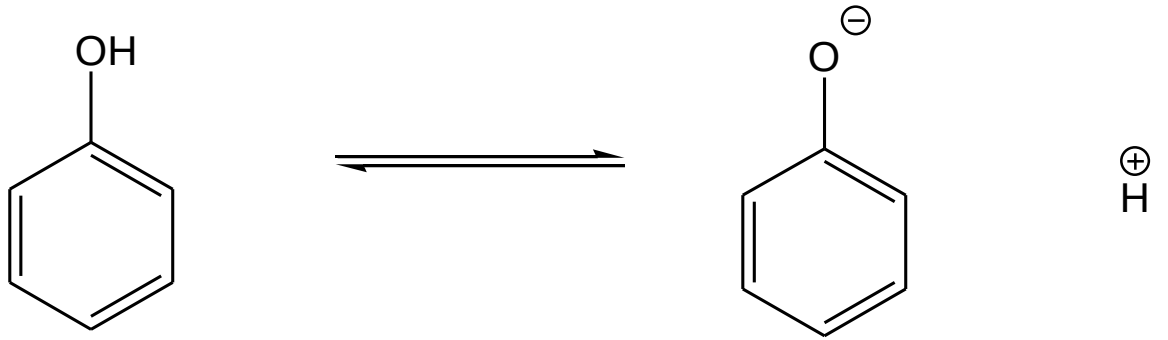


Factors affecting the strength of acid

- The more stable conjugate base (anion) formed, the stronger the acid will be.
- So any factor will stabilize the anion will increase the acidity of the group, such as resonance and induction stabilization.
- Stable negative charge results from lowering the electron density on the atom



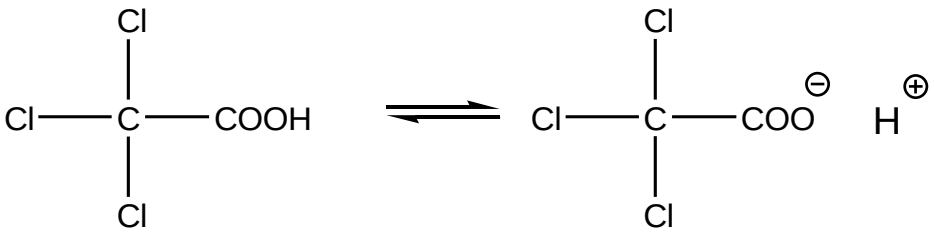
pKa = 0.9



pKa = 10.0

Which one is the stronger acid?

Considering Ka values relates ratio of products to reactants

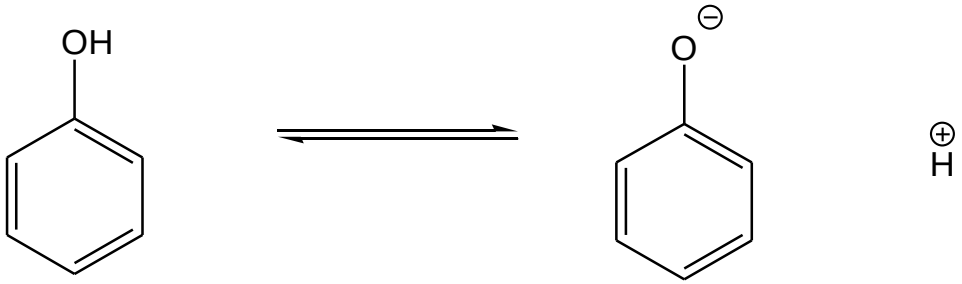


pKa = 0.9

Ka = $10^{-0.9}$

$$K_a = \frac{[Cl_3COO^-][H^+]}{[Cl_3COOH]}$$

$$K_a = \frac{1}{10^{0.9}}$$



pKa = 10.0

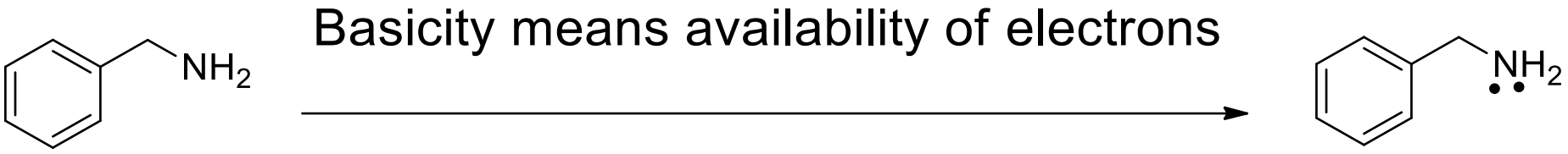
Ka = 10^{-10}

$$K_a = \frac{[PhO^-][H^+]}{[PhOH]}$$

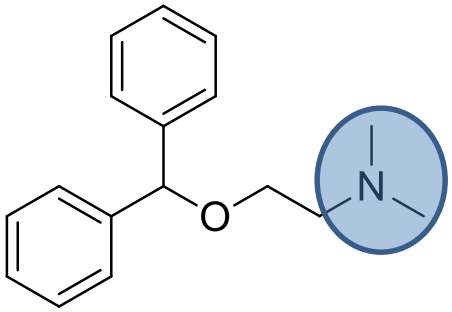
$$K_a = \frac{1}{10^{10}}$$

Phenols are weaker acids than acetates

Ionization and dissociation of drugs-3

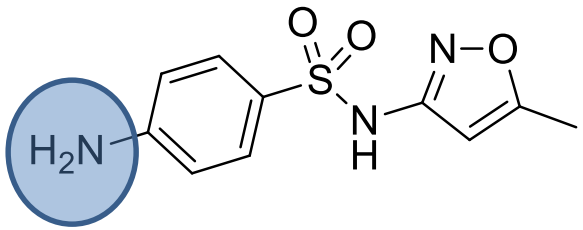


- If the atom has an available lone pair of electrons, it can act as a base…
- The availability of these electrons will determine the strength of the base
- As a result of that, aromatic amino group is much weaker base than aliphatic one



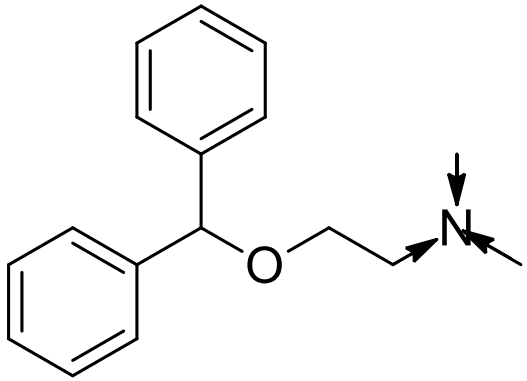
Diphenhydramine
Antihistaminic agent

Aliphatic amine.....strong base..... Pka of 10.6

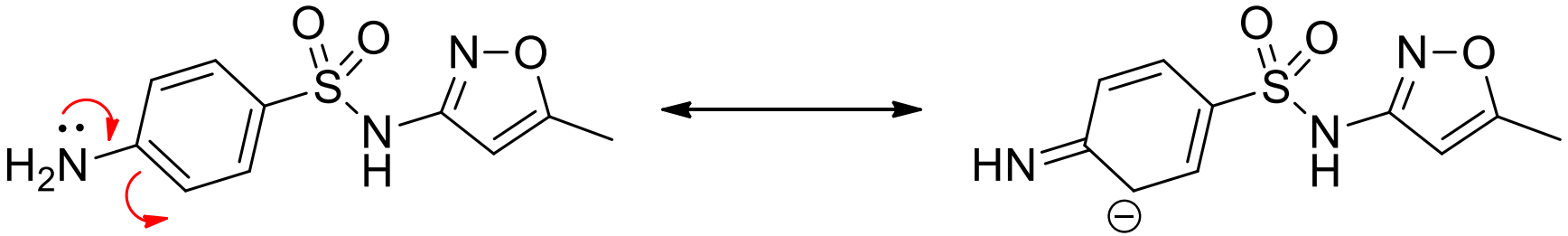


Sulfamethoxazole
Antibacterial agent

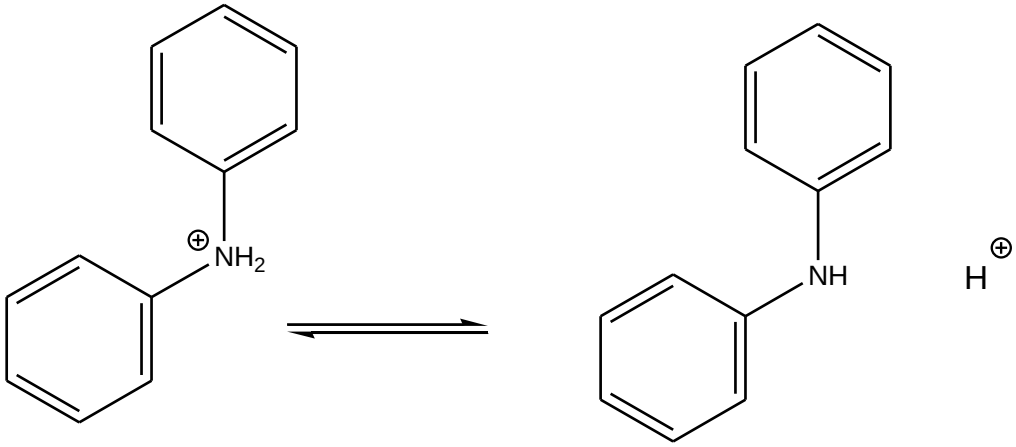
Aromatic amine..... weaker base..... Pka of 4.6



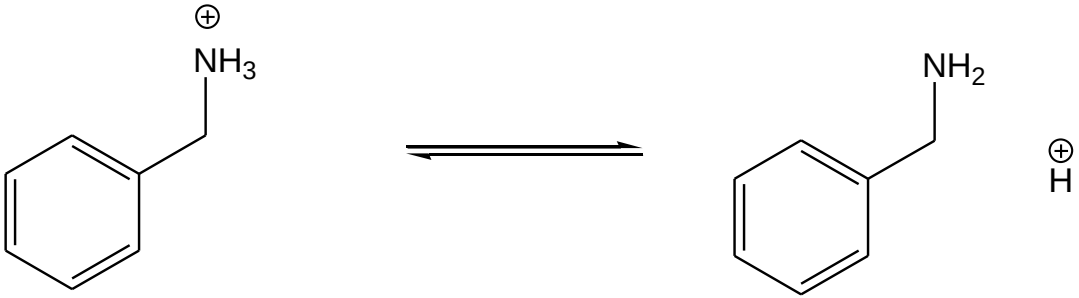
tertiary amine: methyl groups compared to phenyl group are better donating groups by induction
(more available lone pair of electrons)



the lone pair of electrons are not available....delocalized through the phenyl group
(stable by resonance)

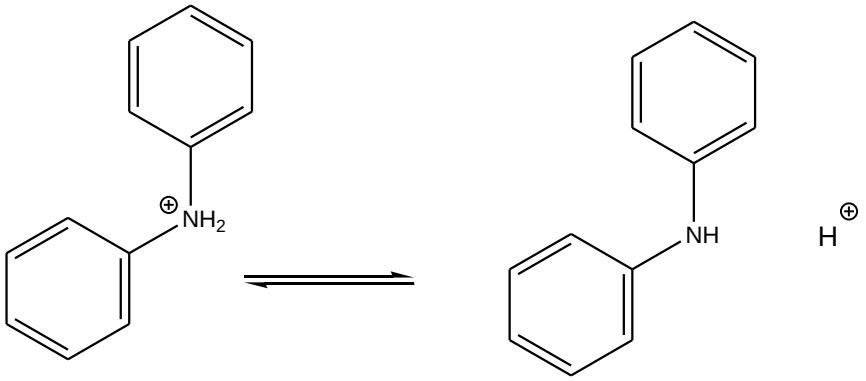


pKa = 0.5



pKa = 9.0

Which one is the stronger base?

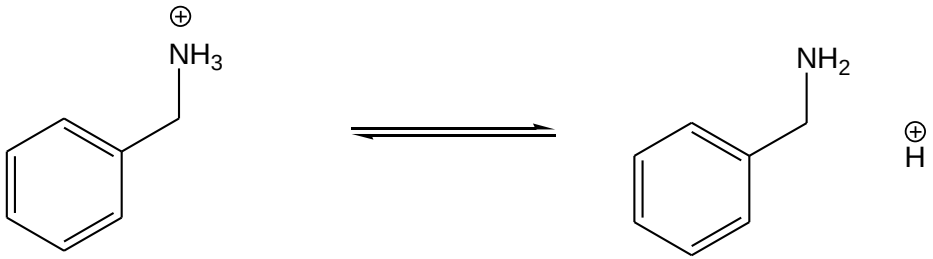


pKa = 0.5

Ka = $10^{-0.5}$

$$K_a = \frac{[Ph_2NH][H^+]}{[Ph_2NH_2^+]}$$

$$K_a = \frac{1}{10^{0.5}}$$



pKa = 9.0

Ka = 10^{-9}

$$K_a = \frac{[PhCH_2NH_2][H^+]}{[PhCH_2NH_3^+]}$$

$$K_a = \frac{1}{10^{9}}$$

Aromatic amines are weaker bases than aliphatic amines

- **We can quantify how pH changes the ratio of dissociated to undissociated species as follows:**

$$pH - pK_a = \log_{10} \frac{[Dissociated]}{[Undissociated]}$$

$10^{(pH-pKa)} = \frac{[Dissociated]}{[Undissociated]}$	$antilog(pH - pK_a) = \frac{[Dissociated]}{[Undissociated]}$

$$\frac{[Dissociated]}{[Undissociated]}$$

- For acidic drugs, this ratio describes the % ionization.

- For basic drugs, this ratio describes the % unionized form to the ionized form.

*

Effect of ionization on pharmacokinetic and pharmacodynamic profile

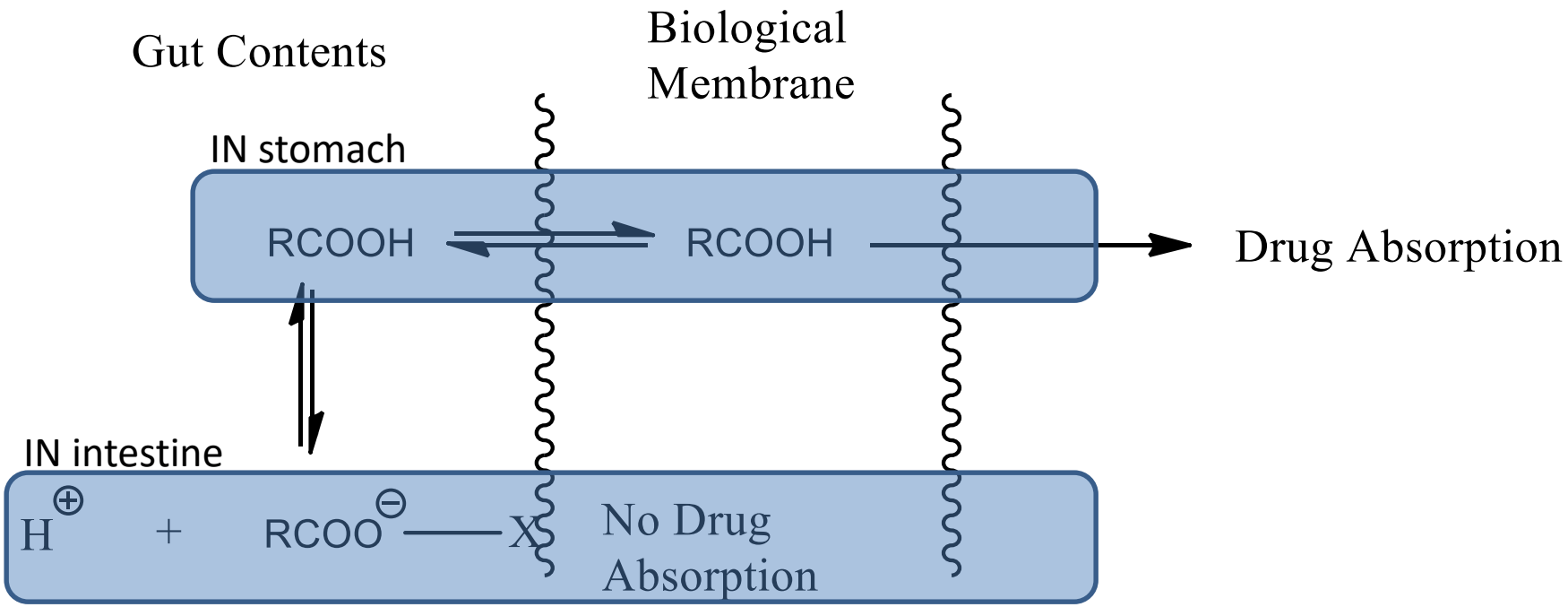
What is the importance of studying the pKa values for Acidic and basic drugs?

- only the unionised form of a drug can partition across biological membranes (providing the unionized form is lipophilic)

- the ionised form tends to be more water soluble [required for drug administration and distribution in plasma]

PARTITIONING OF ACIDS AND BASE

For acidic drugs, with a pKa of 4.0, the ionization state will be as follows

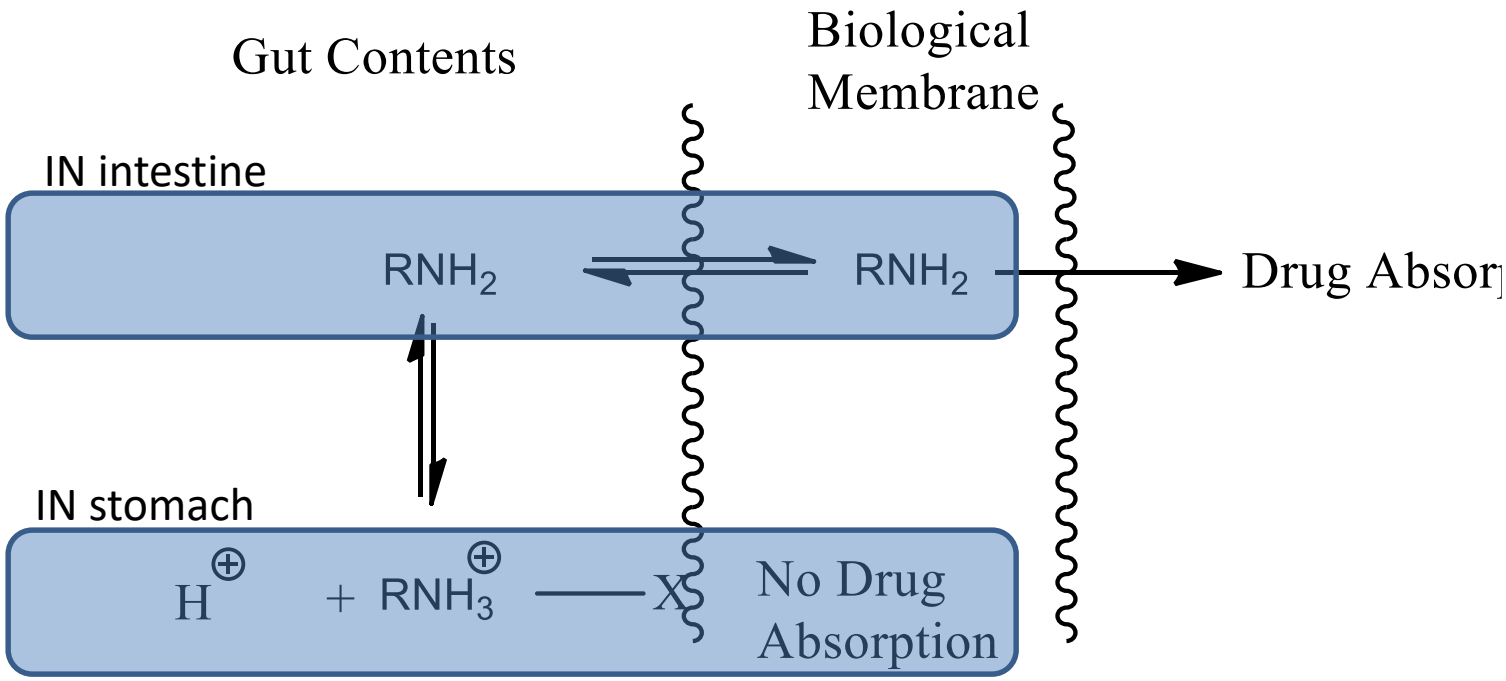


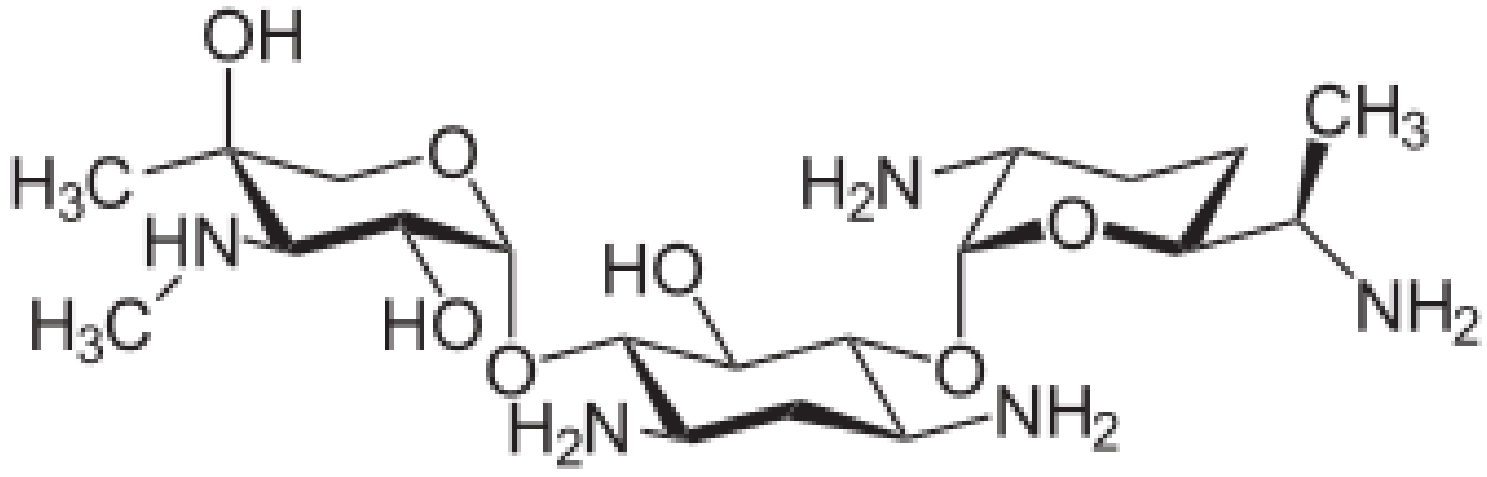
PARTITIONING OF ACIDS AND BASE

- If the pH shifts the balance towards the unionized form, the drug would be absorbed.
- If the pH shifts the balance towards the ionized form, the drug would not be absorbed.
- Assume the pH of the stomach is 2.0 and the pH of the small intestine is 8.0. Where would you expect absorption to take place from?

PARTITIONING OF ACIDS AND BASE

For basic drugs, the ionization will be as follows



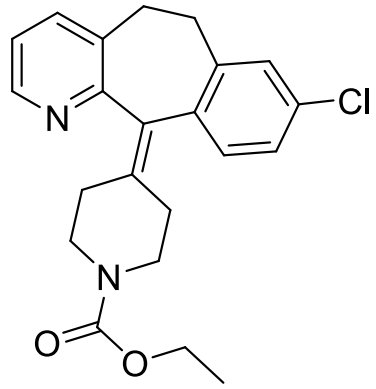


Gentamicin

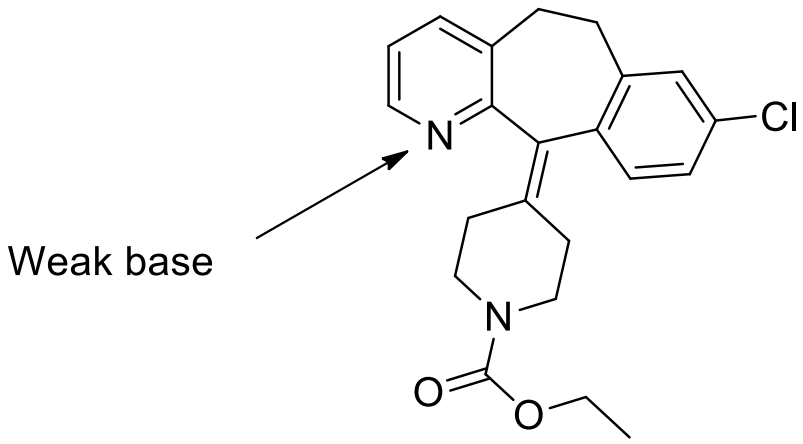
So we should expect that this compound will not be readily absorbed though the lipophilic membranes although it is in the unionized form

Practice question

- **Loratadine is an orally available drug, it has a pKa of 5, answer the followings according to its structure:**



  - **Is it basic, acidic or neutral compound?**
  - **Calculate the % ionization:**
    - **In stomach (pH = 2):**
    - **In intestine (pH = 8):**
  - **Based on your calculation, from where do you think loratadine will be absorbed?**



$$pH - pK_a = \log_{10} \frac{[Dissociated]}{[Undissociated]}$$

$$\frac{[Dissociated]}{[Undissociated]} = \frac{[Unionized]}{[Ionized]}$$ (for basic compounds)

$$\frac{[Unionized]}{[Ionized]} = 10^{-3}$$

% ionization = 99.9% (under stomach pH)

Under intestinal pH:

$$\frac{[Unionized]}{[Ionized]} = 10^3$$

% ionization = 0.1%

So loratadine will be mainly in unionized form

It will be better absorbed from intestinal membrane not from stomach

*

Effect of ionization on drug lipophilicity

Ionization and lipophilicity

- When the drug become ionized, this will increase its water solubility because there will be a better solvation by ionic-dipole interaction between ionized drug and water molecule.

- So, once the drug get ionized it will have lower logP than the unionized from (more polar).

Ionization and lipophilicity

- Because most drugs are ionizable at different body pH ranges, the % ionization must be taken into consideration when we are about to synthesize or develop certain drug.

- Lipophilicity will determine from where the drug will be absorbed and what target tissue will reach.

Partition coefficient *P*

$$P = [C_o]/[C_w]$$

$$\text{Log}P = \text{Log}[C_o]/[C_w].$$

This equation does not determine the effect of ionization on the lipophilicity of drugs

Partitioning of acids and base

- $\boldsymbol{P_{app}}$ can be used to predict the behaviour of a compound at all pH values, as long as we know P.
- For acids, at pH values below the pKa, $\boldsymbol{P_{app}}$ = P
- At pH values above the pKa the value of $\boldsymbol{P_{app}}$ decreases because the species is ionizing and moving into the aqueous layer.

$$P_{app} = \frac{P}{1+10^{pH-pKa}}$$

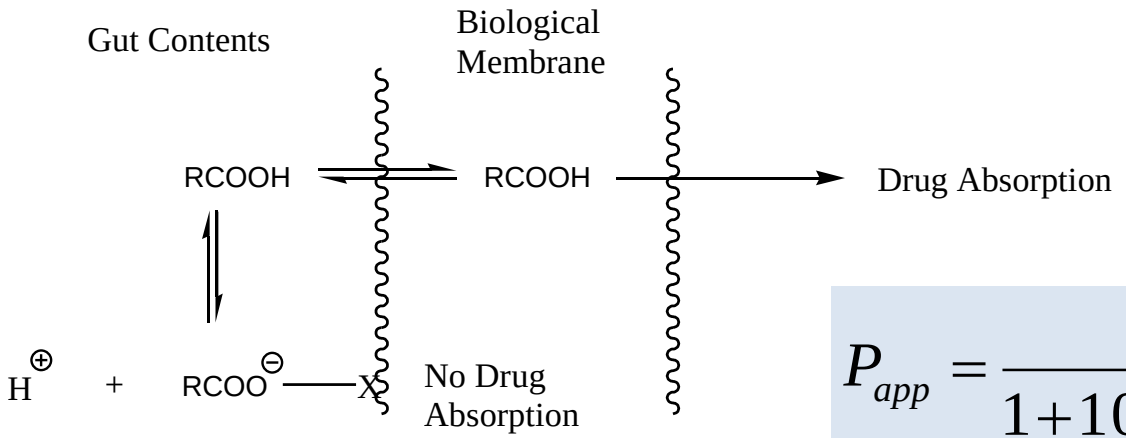
Partitioning of acids and base

- For bases, the equation becomes:

$$P_{app} = \frac{P}{1+10^{pKa-pH}}$$

PARTITIONING OF ACIDS AND BASE

Consider drugs that are acids, for example RCOOH, which has a pKa of 4.0, and a Partition coefficient of 200.



$$P_{app} = \frac{P}{1+10^{pH-pKa}}$$

- P_{app} becomes 198 in the stomach suggesting that absorption will take place
- pH 8.0 in the small intestine, the calculated P_{app} suggests no absorption.
- This equation allows to predict that an acidic drug whose unionized form has a very low partition coefficient would not be absorbed.

Oral administration and absorption

- If a drug is to be absorbed through the mucosal membranes that line the gut, then it must be in its lipophilic unionised form to partition out of the aqueous medium.

- The partition co-efficient of the unionised form will also determine how much is absorbed.

- The absorption phase of the dose-response curve is therefore heavily influenced by the pKa and log P of a drug.

Oral administration and absorption

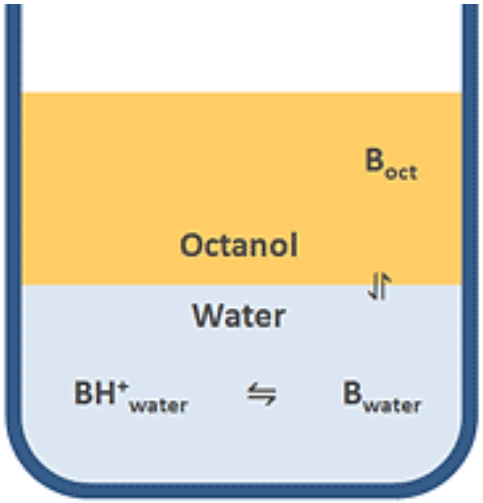
Orally administered drugs must have:

- **logP < 5.**
- **No more than 10 hydrogen bond acceptors.**
- **No more than 5 hydrogen bond donors.**
- **A molecular weight less than 500 Dalton**.

These points are called " Lipinski's rule of five"

- Not more than 7 rotatable bonds.

$$pK_a = \log \frac{[BH^+_{water}]}{[H^+][B_{water}]}$$

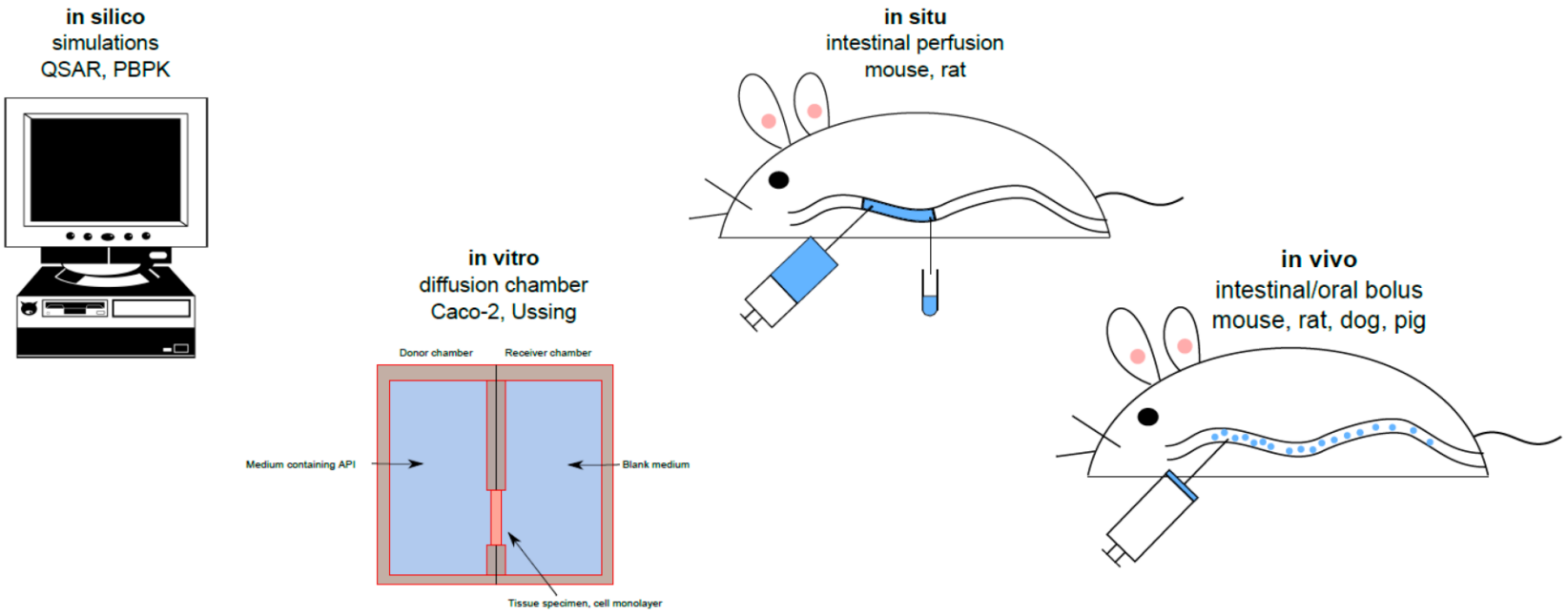


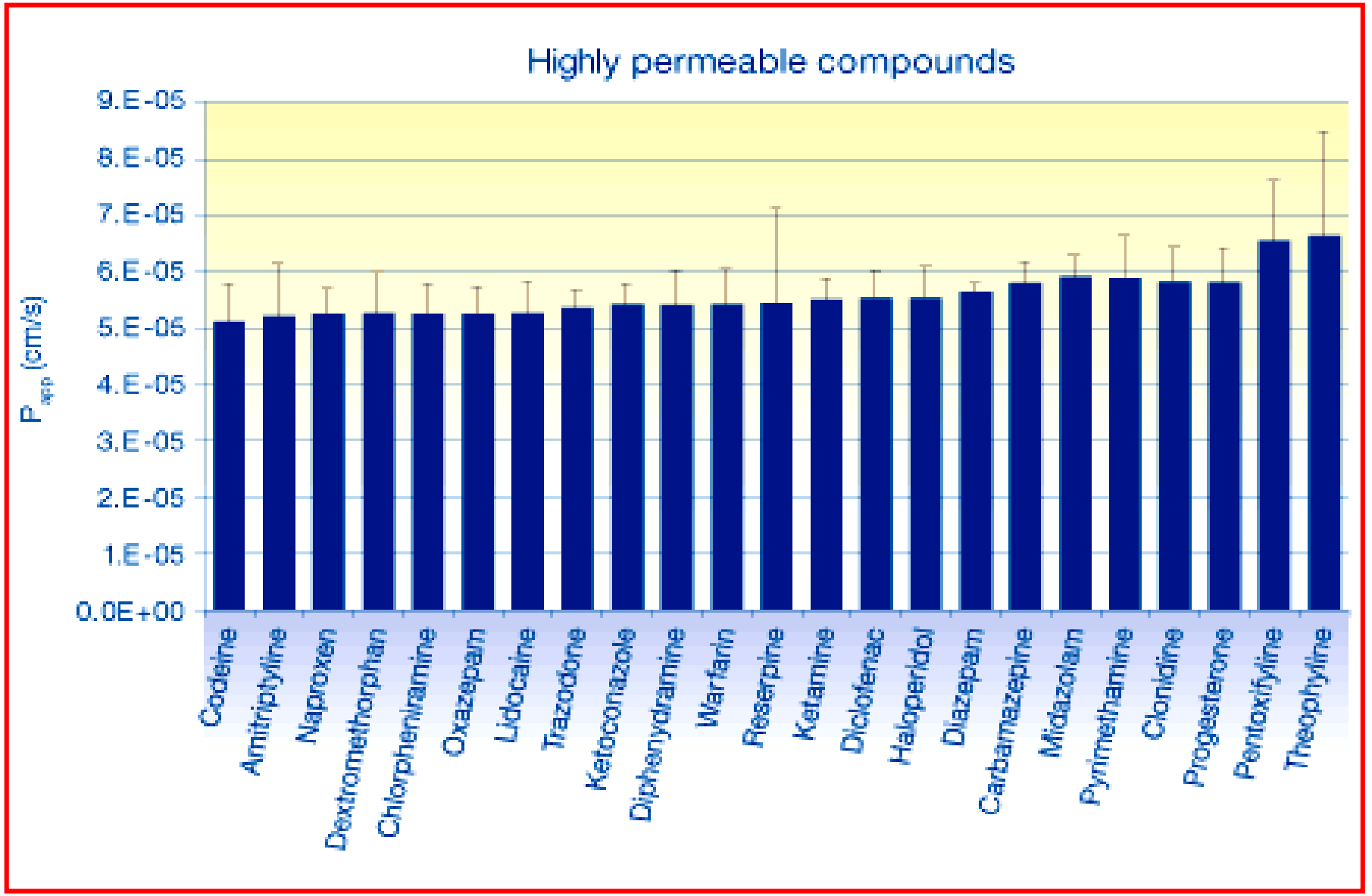
$$\log P = \log \frac{[B_{oct}]}{[B_{water}]}$$

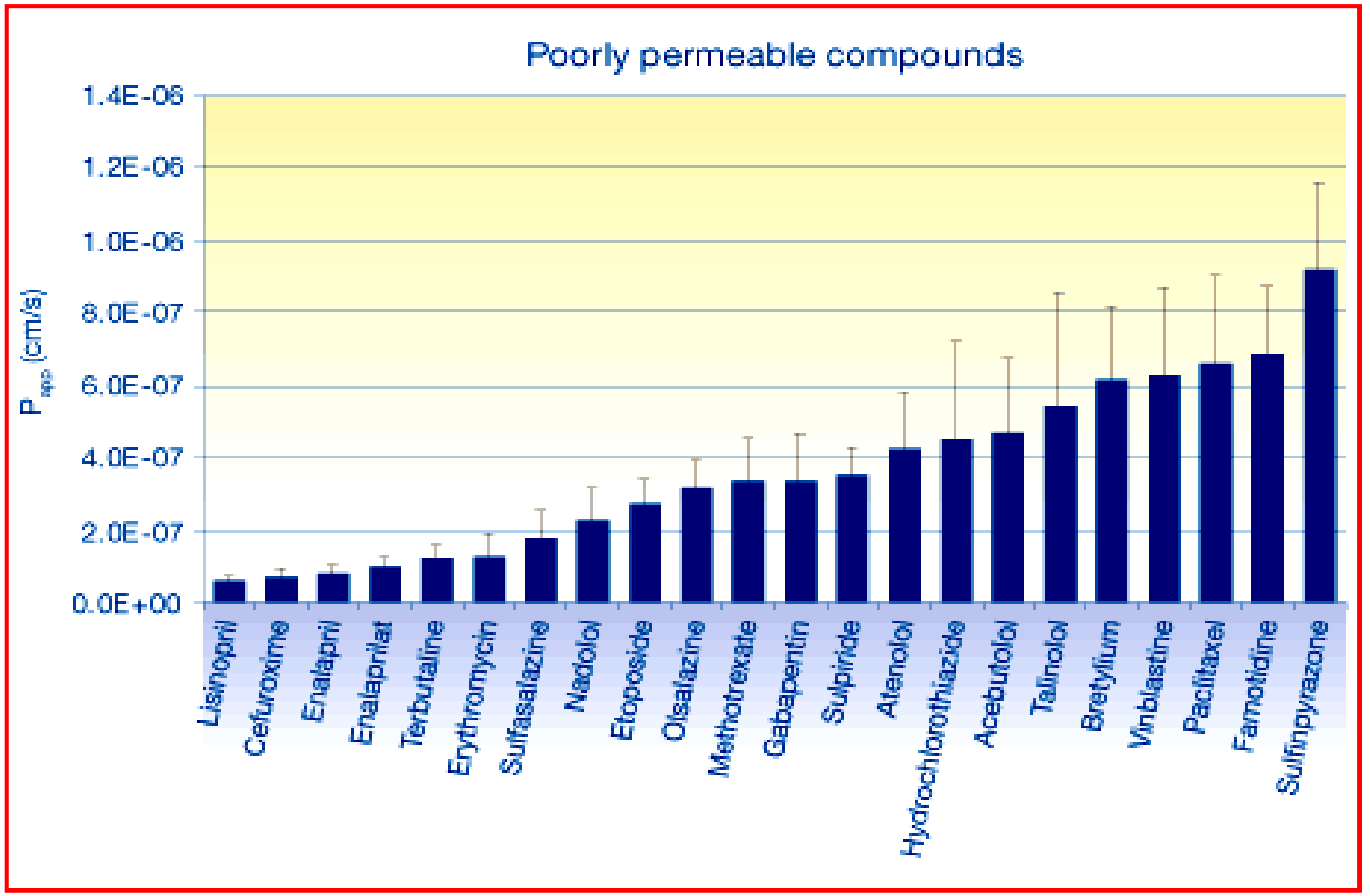
Drug permeability

1. *in silico* predictive methods
2. Caco-2 and MDCK cell culture models
3. PAMPA (parallel artificial membrane permeability assay)
4. *in vivo* brain-to-plasma ratio determination (rat/mouse)
5. brain binding assays (rat/mouse)

Rank order of GI absorption models




Highly permeable compounds
P_{app} (cm/s)
9.E-05
8.E-05
7.E-05
6.E-05
5.E-05
4.E-05
3.E-05
2.E-05
1.E-05
0.0E+00
Codeine
Amitriptyline
Naproxen
Dextromethorphan
Chlorpheniramine
Oxazepam
Lidocaine
Trazodone
Ketoconazole
Diphenydramine
Warfarin
Reserpine
Ketamine
Diclofenac
Haloperidol
Diazepam
Carbamazepine
Midazolam
Pyrimethamine
Clonidine
Progesterone
Pentoxifylline
Theophylline


Poorly permeable compounds
1.4E-06
1.2E-06
1.0E-06
8.0E-07
6.0E-07
4.0E-07
2.0E-07
0.0E+00
P_{app} (cm/s)
Lisinopril
Cefuroxime
Enalapril
Enalaprilat
Terbutaline
Erythromycin
Sulfasalazine
Nadolol
Etoposide
Olsalazine
Methotrexate
Gabapentin
Sulpiride
Atenolol
Hydrochlorothiazide
Acebutolol
Talinolol
Bretylium
Vinblastine
Paclitaxel
Famotidine
Sulfinpyrazone

Applications of drug ionization

Remember the followings

For acids:

1. *a high pka* means the species is predominantly unionised, is a bad proton donor, and a weak acid

2. *a low pka* means the species is predominantly ionised, is a good proton donor, and a strong acid

pH < pKa by 2 units, 99% unionised

pH > pKa by 2 units, 99% ionised

For bases:

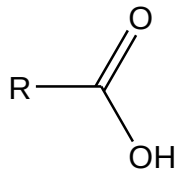
1. *a high pka* means the species is predominantly ionised, is a good proton acceptor, and a strong base

2. *a low pka* means the species is predominantly unionised, is a bad proton acceptor, and a weak base

pH < pKa by 2 units, 99% ionised

pH > pKa by 2 units, 99% unionised

Common acidic functional groups in pharmaceutical chemistry and their pKa values



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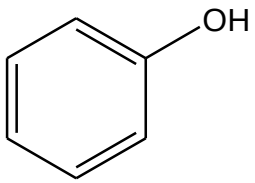

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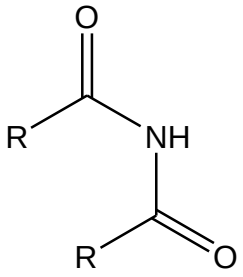

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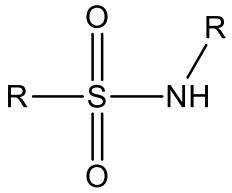

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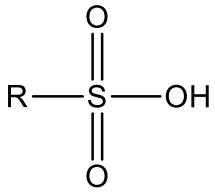

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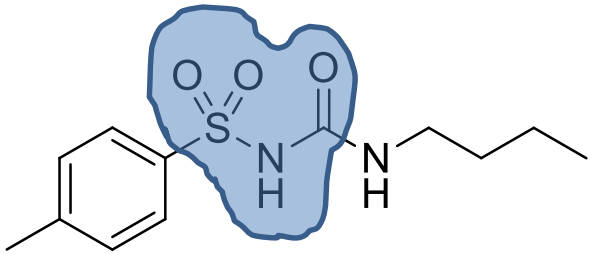
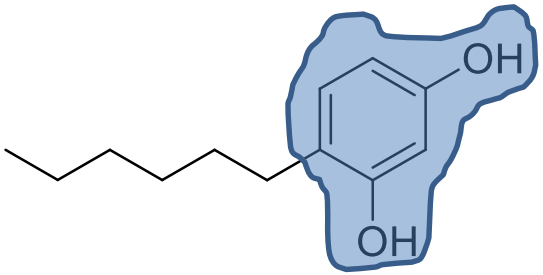
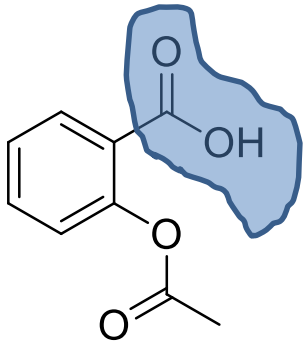
Examples of acidic drugs



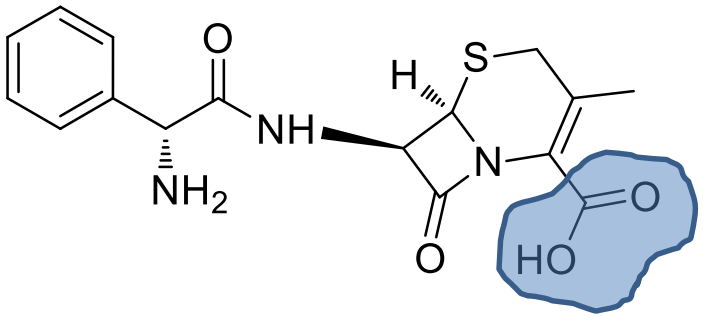
Tolbutamide
hypoglycemic agent



4-hexylresorcinol
topical anesthetic

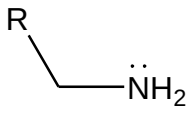


Aspirin
NSAID



Cephalexin
Antibacterial agent

Common basic functional groups in pharmaceutical chemistry and their pKa values



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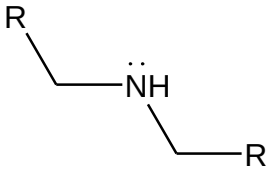

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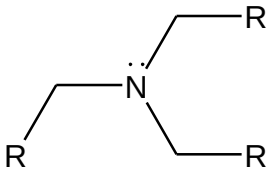

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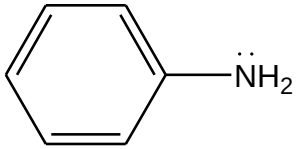

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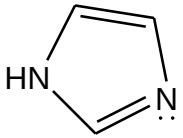

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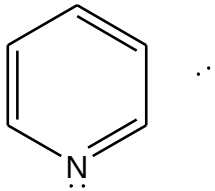
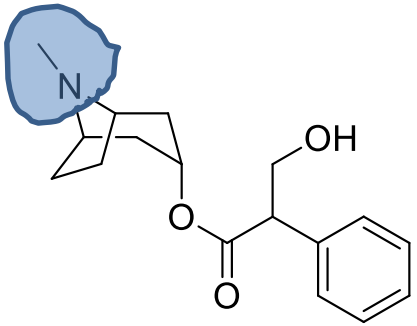
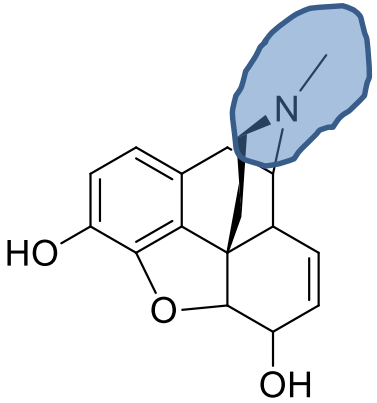


5.2

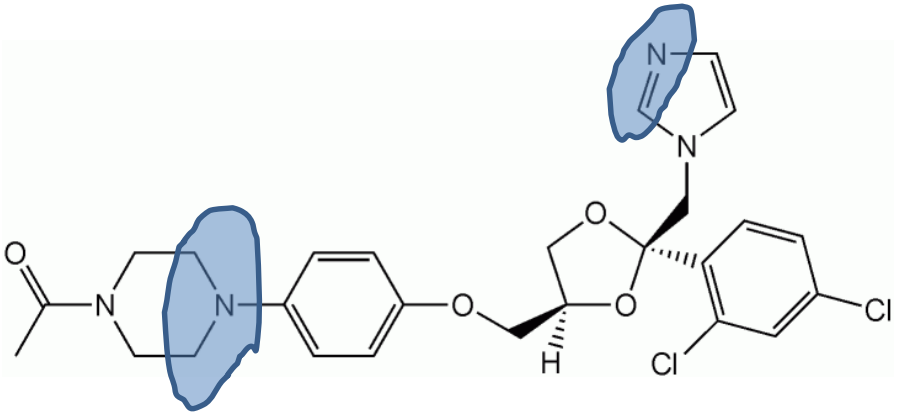
Examples of basic drugs



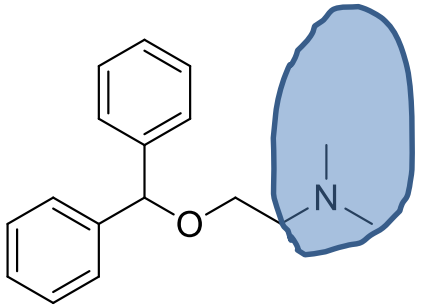
Atropine
Anticholinergic agent



Morphine
opioid analgesic

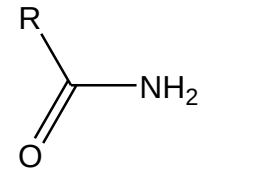


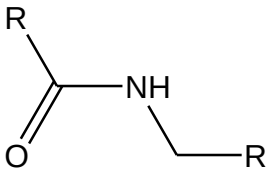
Ketoconazole
Antifungal agent

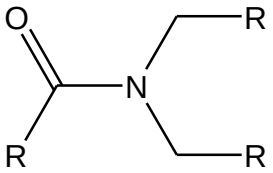


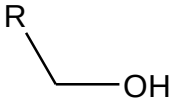
Diphenhydramine
Antihistaminic agent

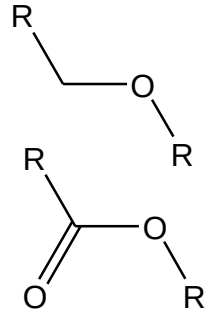
Common neutral functional groups in pharmaceutical chemistry

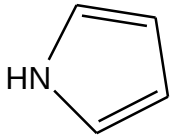


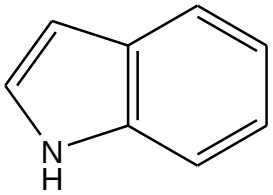






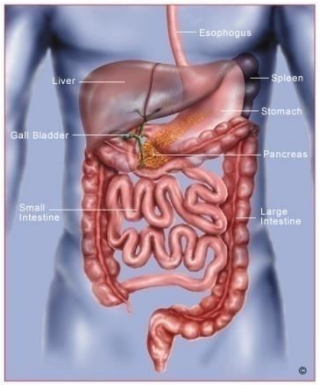


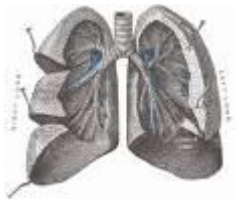




Molecular properties and routes of administration

- Oral
- rectal
- vaginal
- topical
- parenteral
- Respiratory



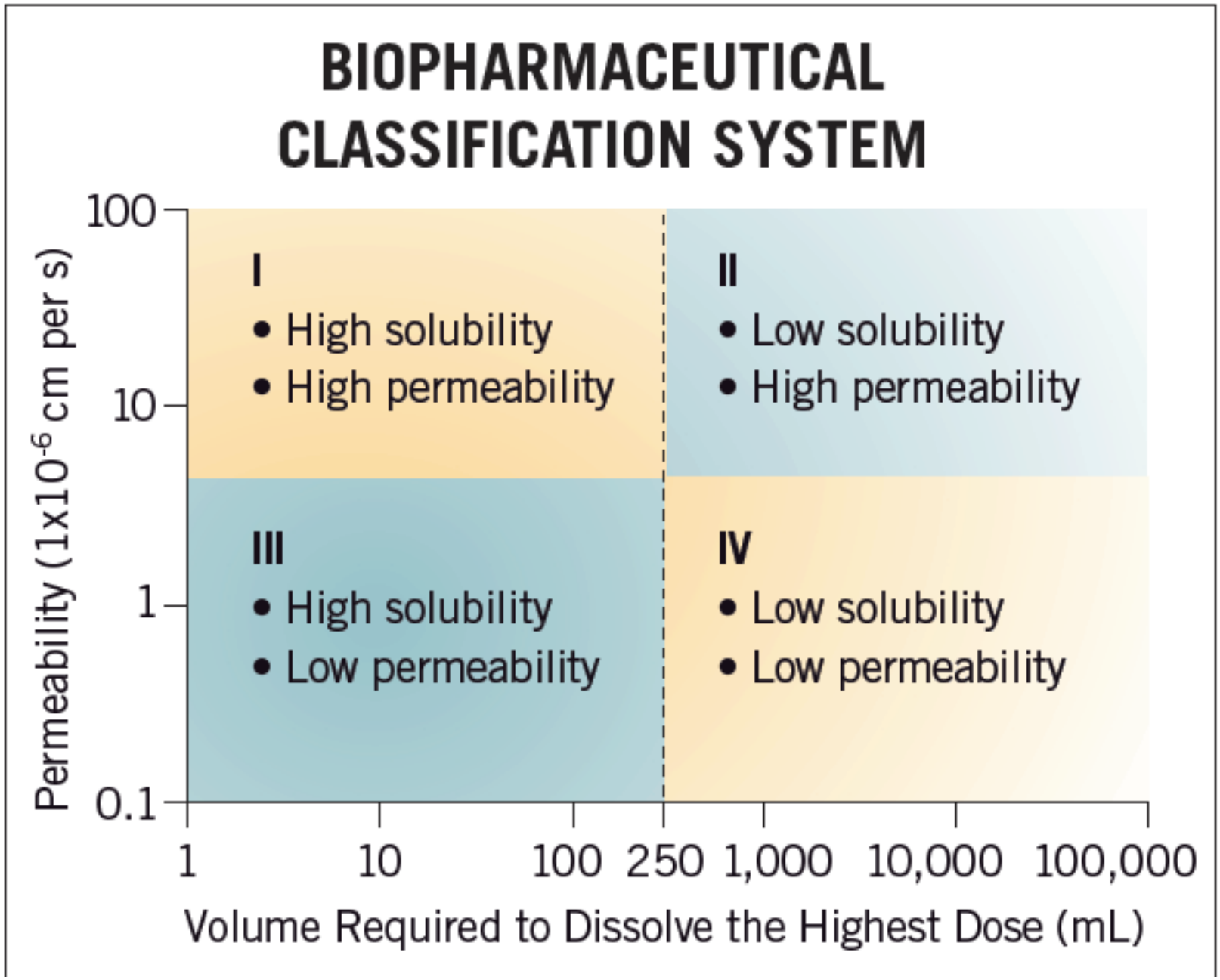


- The molecular properties of the drug must be determined before any route can be considered, but other factors are important

Factors to consider when choosing a route of administration

- molecular properties of the drug
- physiological nature of the route
- patient compliance
- onset of action
- the condition being treated
- systemic or local effect (side effects)
- metabolism

BIOPHARMACEUTICAL CLASSIFICATION SISTEM


BIOPHARMACEUTICAL
CLASSIFICATION SYSTEM
Permeability (1x10-6 cm per s)
100
10
1
0.1
I
• High solubility
• High permeability
II
• Low solubility
• High permeability
III
• High solubility
• Low permeability
IV
• Low solubility
• Low permeability
1
10
100
250
1,000
10,000
100,000
Volume Required to Dissolve the Highest Dose (mL)

- Although class I compounds are expected to have excellent oral absorption, given their high solubility and high permeability, additional absorption barriers may exist beyond the scope of the BCS
- For example, **luminal complexation and degradation** can significantly limit the amount of drug available for absorption.
- Even after the drug crosses the intestinal membrane, it may be **metabolized within the enterocytes/hepatocytes** and/or pumped out of the cells due to efflux mechanisms.

BCS CLASS I:

Exemple:

Abacavir, Acetaminophen, Acyclovir, Amitryptyline, Antipyrine, Atropine, Bucspirone, Caffeine, Captopril, Chloroquine, Chlorpheniramine, Cyclophosphamide, Desipramine, Diazepam, Dilitiazem, Diphenhydramine, Disopyramide, Doxepin, Doxycycline, Enlapril, Ephedrine, Ergonovine, Ethambutol, fluoxetine, Glucose, Imipramine, Ketorolac, Ketoprofen, Labetolol, Levodopa, Levofloxacin, Meperidine, Metoprolol, Metronidazole, Midazolam, Minocycline, Misoprostol, Nifedipine, Phenobarbital, Phenylalamine, Prednisolone, Primaquine, Promazine, Propranolol, Quinidine, Rosiglitazone, Theophylline, Verapamil, Zidovudine. Risperidone.

BCS CLASS II: POOR SOLUBILITY AND HIGH PERMEABILITY

- By definition, poor solubility and/or slow dissolution are the rate-limiting steps for oral absorption of BCS class II compounds
- For compounds with a very large dose-to-solubility ratio, poor solubility is likely to be the rate-limiting step for absorption.
- In other words, the compounds may dissolve quickly enough to reach their equilibrium solubility, but the solubility is too low to establish a wide enough concentration gradient to drive passive diffusion

Formulations designed to overcome solubility or dissolution rate problems:

- Salt formation
- Particle size reduction
- Metastable forms
- Solid dispersion
- Complexation
- Lipid based formulations
- Precipitation inhibitors

Exemple:

Amiodarone, Atorvastatin, Azithromycine, Carbamazepine, Carvedilol, Chlorpromazine, Cyclosporine, Danazol, Dapsone, Diclofenac, Digoxine, Flurbiprofen, Glyburide, Griseofulvin, Ibuprofen, Indinavir, Indomethacin, Itraconazole, Ketoconazole, Lansoprazole, Lovastatin, Mebendazole, Mefenamic acid, Nifedinpine, Naproxen, Nelfinavir, Ofloxacin, Oxaprozin, Phenazopyridine, Phenytoin, Piroxicam, Raloxifene, Ritonavir, Saquinavir, Sirolimus, Spironolactone, Tacrolimus, Talmolol, Tamoxifen, Terfenadine, Warfarin

BCS CLASS III: HIGH SOLUBILITY AND LOW PERMEABILITY

- Since passive diffusion is the rate-limiting step for oral absorption of BCS class III compounds, the most effective way to improve absorption and bioavailability of this class of compounds is to increase the membrane permeability
- Approaches to improve permeability:
  - Prodrugs
  - Permeation enhancers

Exemple:

Acyclovir, Amiloride, Amoxicillin, Atenolol, Atropine, Bisphosphonates, Cefazolin, Cetrizine, Cimetidine, Cloxacillin, Dicloxacillin, Erythromycin, Famotidine, Fexofenadine, Gancilcair, Lisinopril, Metformin, Nadolol, Neomycin B, Pravastatin, Penicillins, Ranitidine, Tetracyline, Trimethoprim, Valsartan, Zalcitabinne.

BCS CLASS IV: LOW SOLUBILITY AND LOW PERMEABILITY

- Class IV compounds exhibit both poor solubility and poor permeability, and they pose tremendous challenges to formulation development
- As a result, a substantial investment in dosage form development with no guarantee of success should be expected
- A combination of class II and class III technologies could be used to formulate class IV compounds, although the success rate is not expected to be high

Exemple:

Amphotericin B, Chlorthalidone, Chlorothiazide, Colistin, Ciprofloxacin, Furosemide, Hydrochlorothiazide, Mebandazole, Methotrexate, Neomycin. Taxol.

BIOPHARMACEUTICS CLASSIFICATION SYSTEM

INTRODUCTION

- The biopharmaceutics classification system is guidance for Predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. The fundamental basis for the BCs was established by Dr. Gordon Amidon.

DEFINITION

- The Biopharmaceutical Classification System is a scientific framework for classifying a drug substance based on its aqueous solubility & intestinal permeability & dissolution rate.

OBJECTIVE OF THE BCS

- To improve the efficiency of the drug development and review process by recommending a strategy for identifying expendable clinical bioequivalence test.
- To recommend a class of immediate-release (IR) solid oral dosage forms for which bioequivalence may be assessed based on in vitro dissolution tests.
- To recommend methods for classification according to dosage form dissolution along with the solubility– permeability characteristics of the drug product.

CLASSIFICATIAON

- According to the BCS, drug substances are classified as follows:

A.	**CLASS I**
1.	High Permeability and high Solubility.
2.	These are well absorbed and their absorption rate is usually higher than excretion.
3.	Example - Metoprolol.
B.	**CLASS II**
1.	High Permeability and Low Solubility.
2.	Bioavailability is limited by their solvation rate.
3.	Example- Glibenclmide.

B.	**CLASS III**
1.	Low Permeability and High Solublity.
2.	The absorption is limited by the permeation rate but drug is solvated very fast.
3.	Example- Cimetidine.
C.	**CLASS IV**
1.	Low Permeability And High Solubility.
2.	Poor bioavailability and Not well absorbed over the intestinal mucosa.
3.	Example- Hydrochlorothiazide.

PARAMETERS OF DRUGS CLASSIFIED IN BCS

The drugs are classified inn BCS on the basis of following parameters:

1. SOLUBILITY

- The Maximum Amount of solute dissolved in a given solvent under standard conditions of temperature, pressure and pH.
- Solubility is the ability of the drug to be solution after dissolution.
- The higher single unit dose is completely soluble in 250 ml at pH 1- 6.8 (37°C).

2. PERMEABILITY

- Permeability of the drug to pass the biological membrane which is the lipophilic.
- Permeability is indirectly based on the extent of absorption of a drug substance.
- Drug substance is considered to be highly permeable, when the extent of absorption in human determined to be 90% or more of administered drug or compare to in vivo reference dose.

DISSOLUTION

- A drug product is considered to be RAPIDLY DISSOLVING when > 85% of the labeled amount of drug substance dissolves within 30 minutes using USP dissolution apparatus I or II in a volume of 900 ml or less in the following media:

1.0.1 N HCl or simulated gastric fluid (pH 1.2) without enzyme.

2. pH 4.5 buffer & pH 6.8 buffer.

3. Simulated intestinal fluid without enzyme.

APPLICATIONS OF BIOPHARMACEUTICS

- To predict in vivo performance of drug product using solubility and permeability measurements.
- Aid in earliest stages of drug discovery research.
- For research scientist to decide upon which drug delivery technology to follow or develop.
- Also for the regulation of bioequivalence of the drug product during scale up and post approval.

- Biopharmaceutical classification system aims to provide regulatory tools for replacing certain bio-equivalence studies by accurate in vivo dissolution tests.
- The in vivo pharmacokinetics of drug depends largely on the solubility and permeability.
- Many laboratories are engaged to find better means to estimates in vivo behavior of the drug after oral administration by using simple in vitro dissolution tests