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Physical Pharmacy

Acid-base equilibria

Learning Outcomes

On completion of this lecture students should be able to:

- Appreciate the rationale behind the pH-partition hypothesis (aka pH-partition model, pH-partition theory) of drug absorption
- Recognise and understand the application of the Henderson- Hasselbalch equation to drug ionisation
- Apply the pH-partition model to acids and bases of pharmaceutical relevance
- Calculate/predict the ionisation of weak electrolytes at biological pH using the Henderson–Hasselbalch equation
- Define partition coefficient (P) and distribution coefficient (D) and appreciate their significance in drug absorption
- Understand the relationship between logP,drug ionisation(pKa),and the pH at the site of absorption, along with their influence on drug formulation and absorption
- Appreciate the Biopharmaceutics Classification System (BCS) of drug (BCS)of drugs

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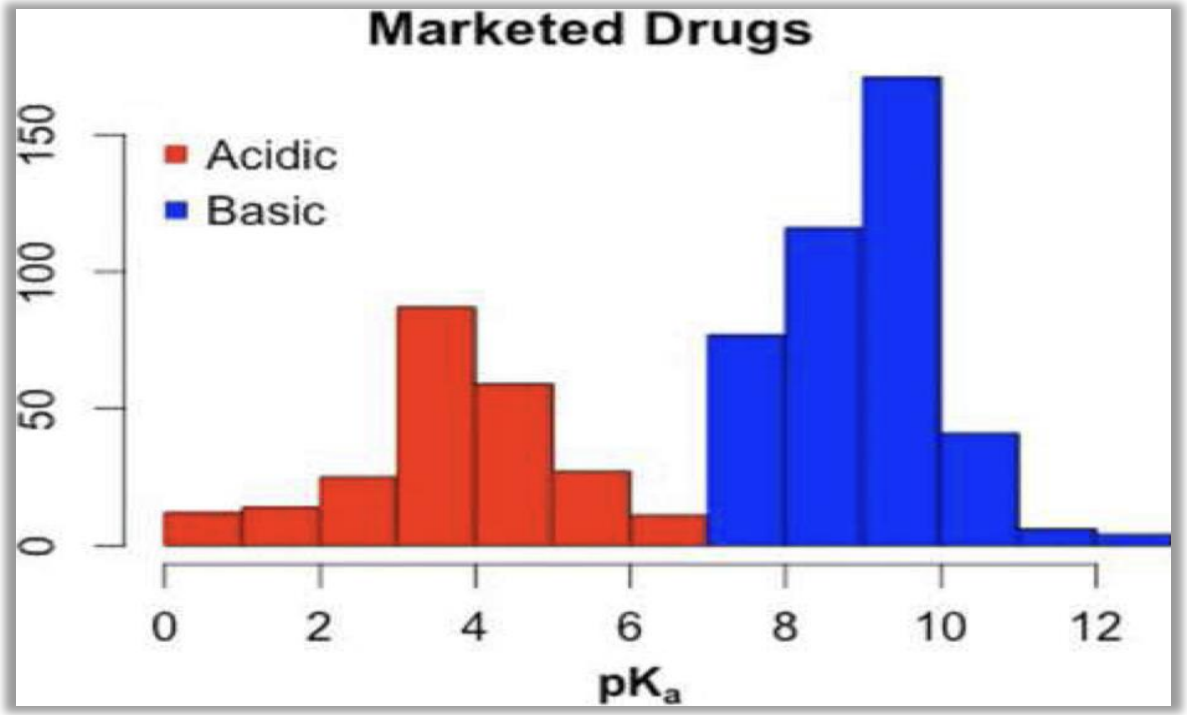
Acid-base equilibria

Why do we need to learn about acid-base equilibria?

- How is this knowledge relevant to pharmacy?



- Over 50% of all existing drugs are weak electrolytes (weak acid or base)

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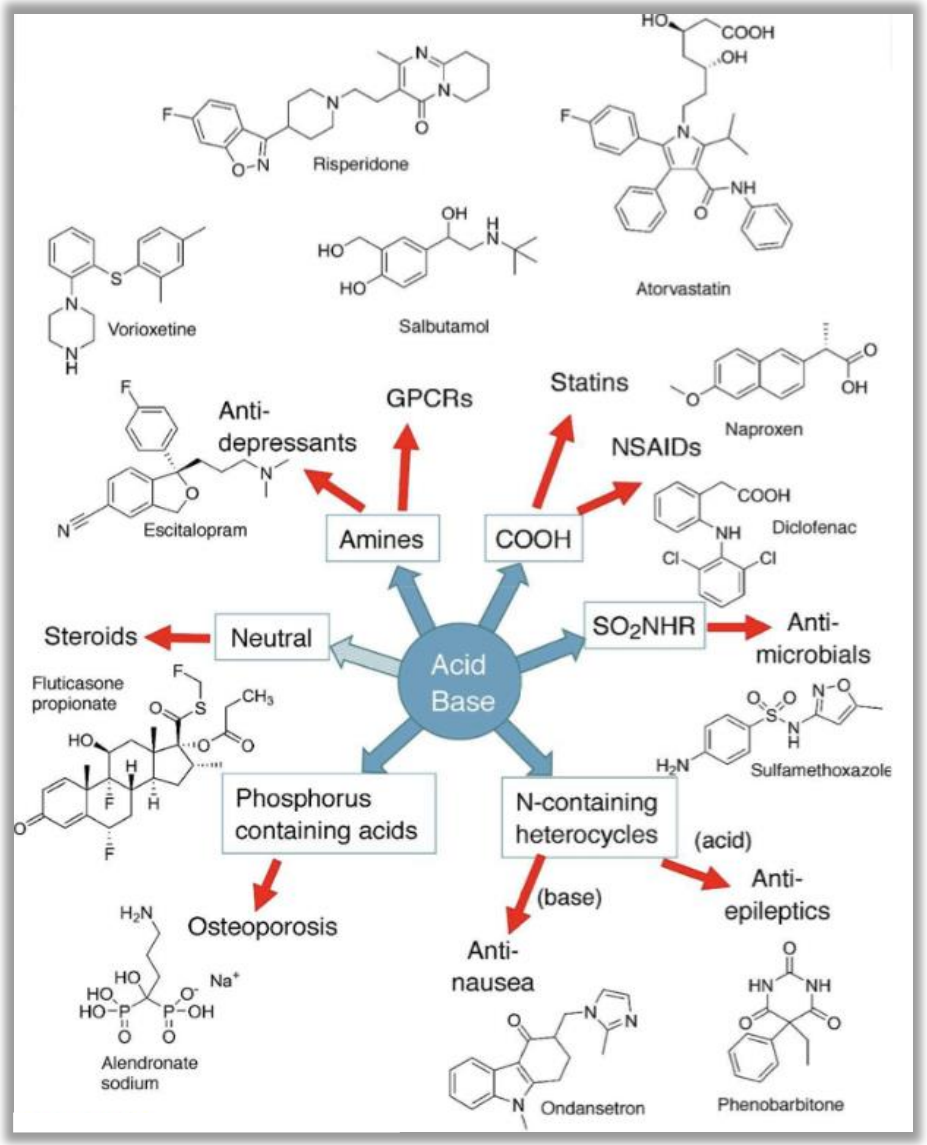
Acid-base equilibria

Think chemically!

- Examples of compounds or therapeutic drug classes and associated ionisable functional groups.

- "**Neutral**" refers to their molecular state under physiological conditions



Acid-base equilibria

Think chemically!

- Drugs are not all the same! They could be:

1. Weak acids
2. Weak bases
3. Non-ionic
4. Zwitter ionic

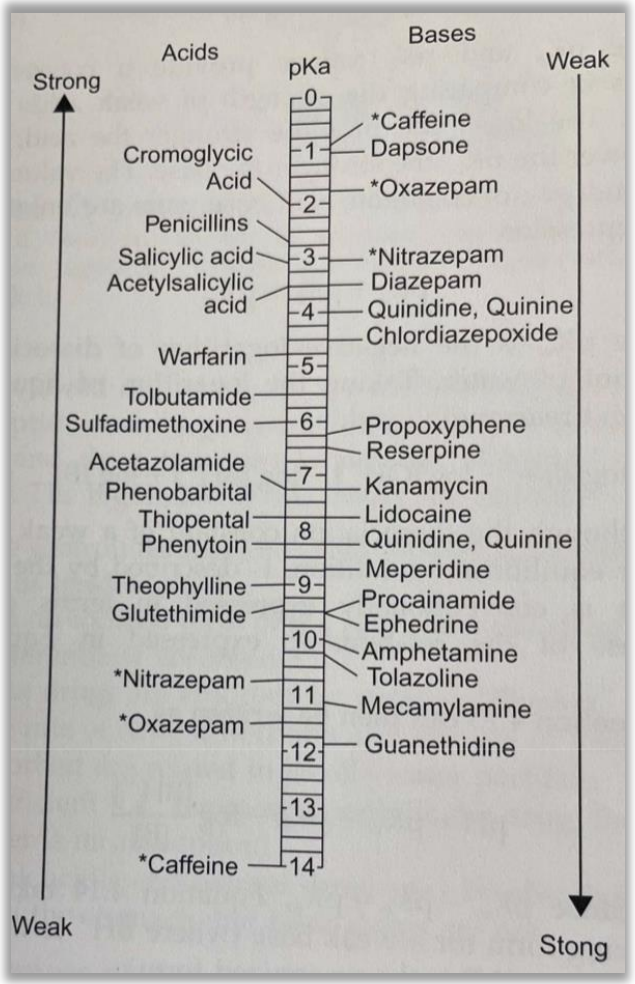


FIGURE 4.6 The pK, values of certain acidic and basic drugs. Drugs denoted with an asterisk are amphoteric

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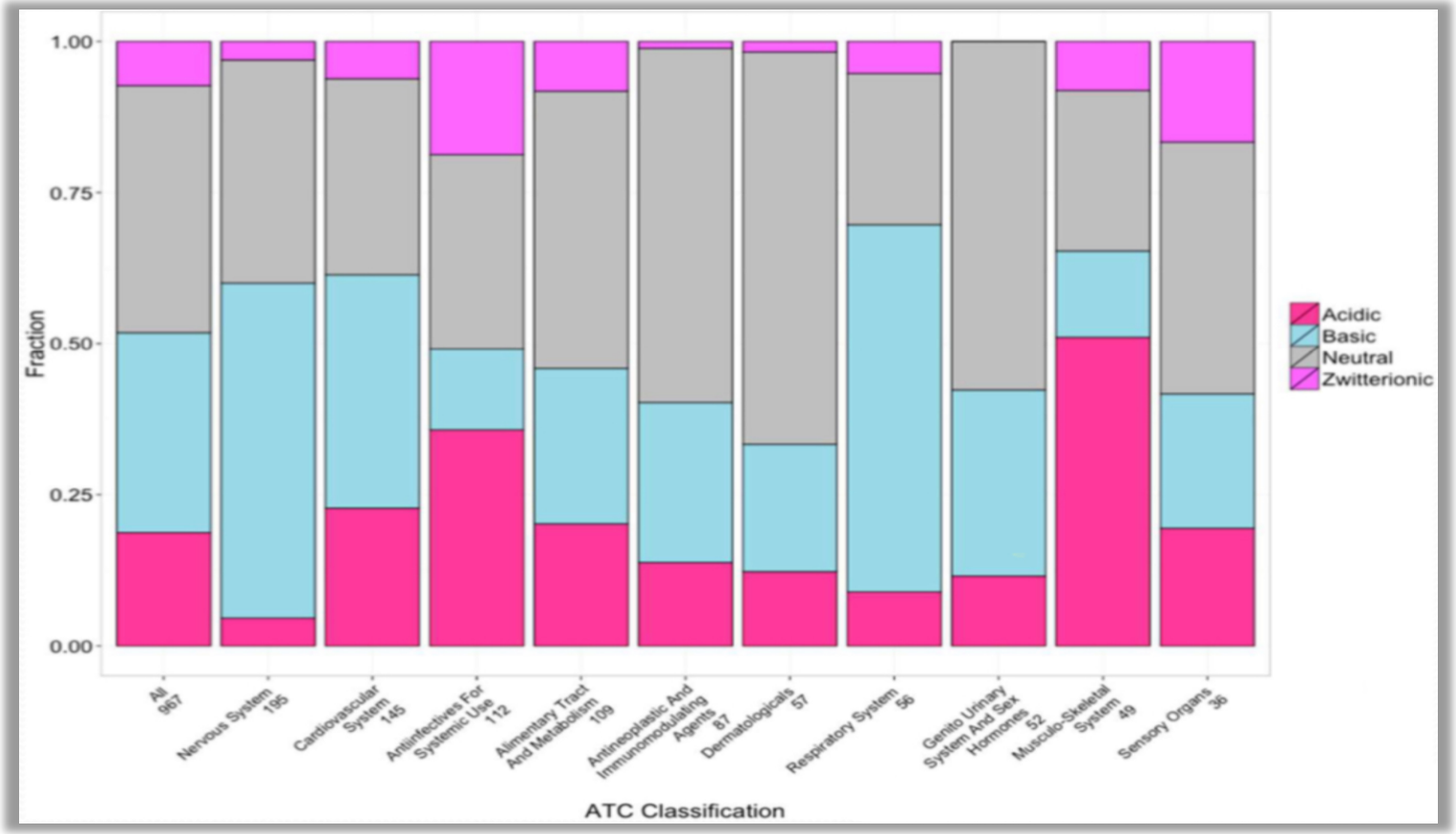
Acid-base equilibria

Distribution of acidic, basic, neutral, and zwitterionic drugs across the four most highly populated ATC target classes



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Acid-base equilibria

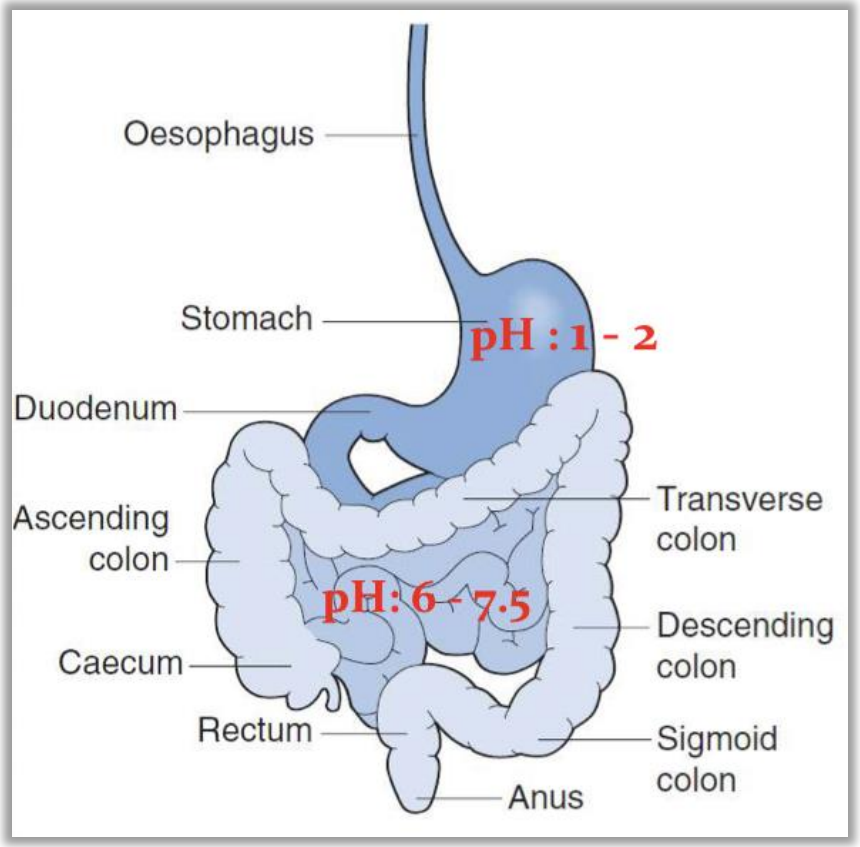
pH of GIT and Drug Absorption

- It has been established that pH of a biological fluid may affect drug solubility, Why and How?

$$AH \rightleftharpoons H^+ + A^-$$

- Is the pH constant along the digestive tract ?

- How will different (pH)s affect the drug absorption (absorption window!)



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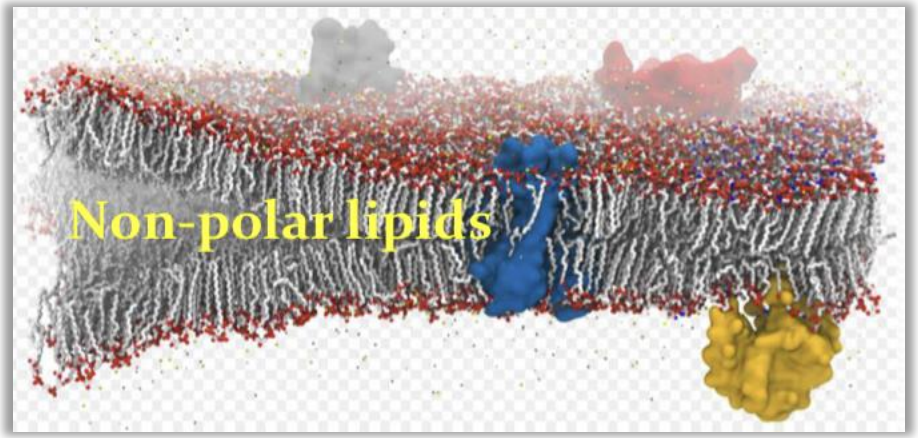
Acid-base equilibria

Cell Membrane (Absorption Barrier)

- In order for a drug to be absorbed, the drug must be in solution (dissolved) AND, must permeate through biological membranes.

$$AH \rightleftharpoons H^+ + A^-$$

- What is the nature of biological membranes?
- Ions are polar, so they do not enter the non-polar lipid regions
- Ionised for of drug is not easily absorbed.



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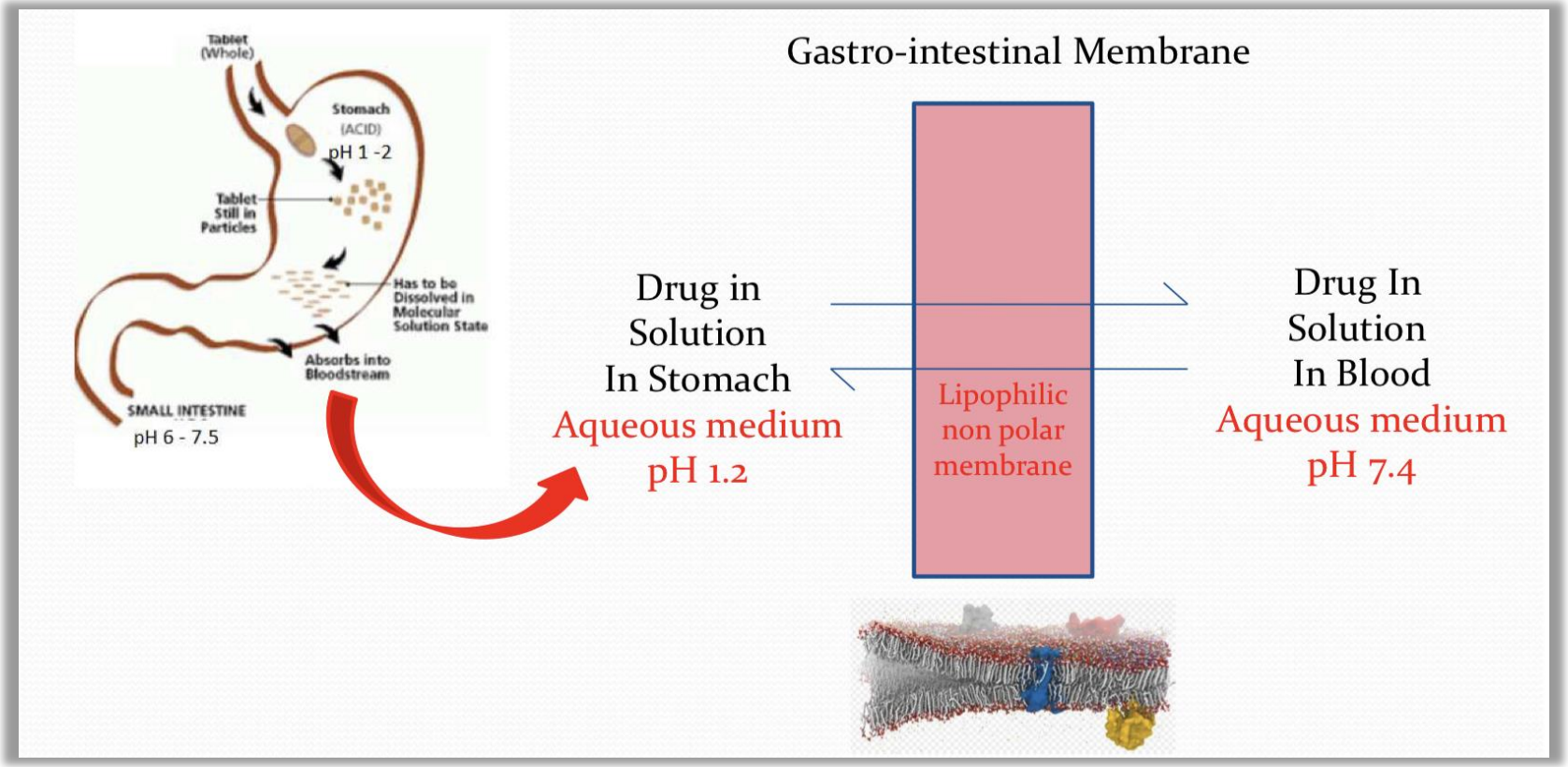
Acid-base equilibria

pH-Partition Hypothesis

- Consider the absorption of an oral drug



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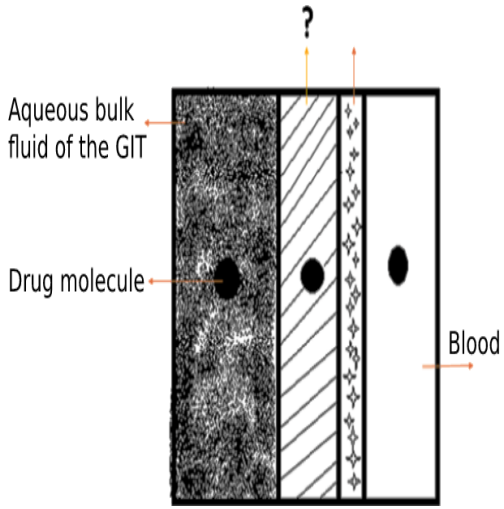
Acid-base equilibria

pH-Partition Hypothesis

- Passive diffusion is responsible for the absorption of most drugs (review Fick's first law of diffusion)
- Drugs are preferentially absorbed in the UN-ionised form across lipid membranes from the lumen of the gastrointestinal tract
- Dissociation constants (pKa), lipid solubility (logP) and pH off the surrounding environment governs the extent of drug absorption.
- The inter-relationship amongst these parameters is what we refer to as the pH partition hypothesis (theory model etc).



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Acid-base equilibria

Highlights of pH Partition Model

- The gastrointestinal membrane separates the two biological fluids (GI content fluids and blood)
- The dissolved drug partitions between the two phases (lumen and wall of GI tract)
- Assume the gastrointestinal membrane is a lipid barrier
- **Ionised molecules are hydrophilic and won't pass readily through the lipid barrier**
- **Therefore unionised molecules can be better absorbed**

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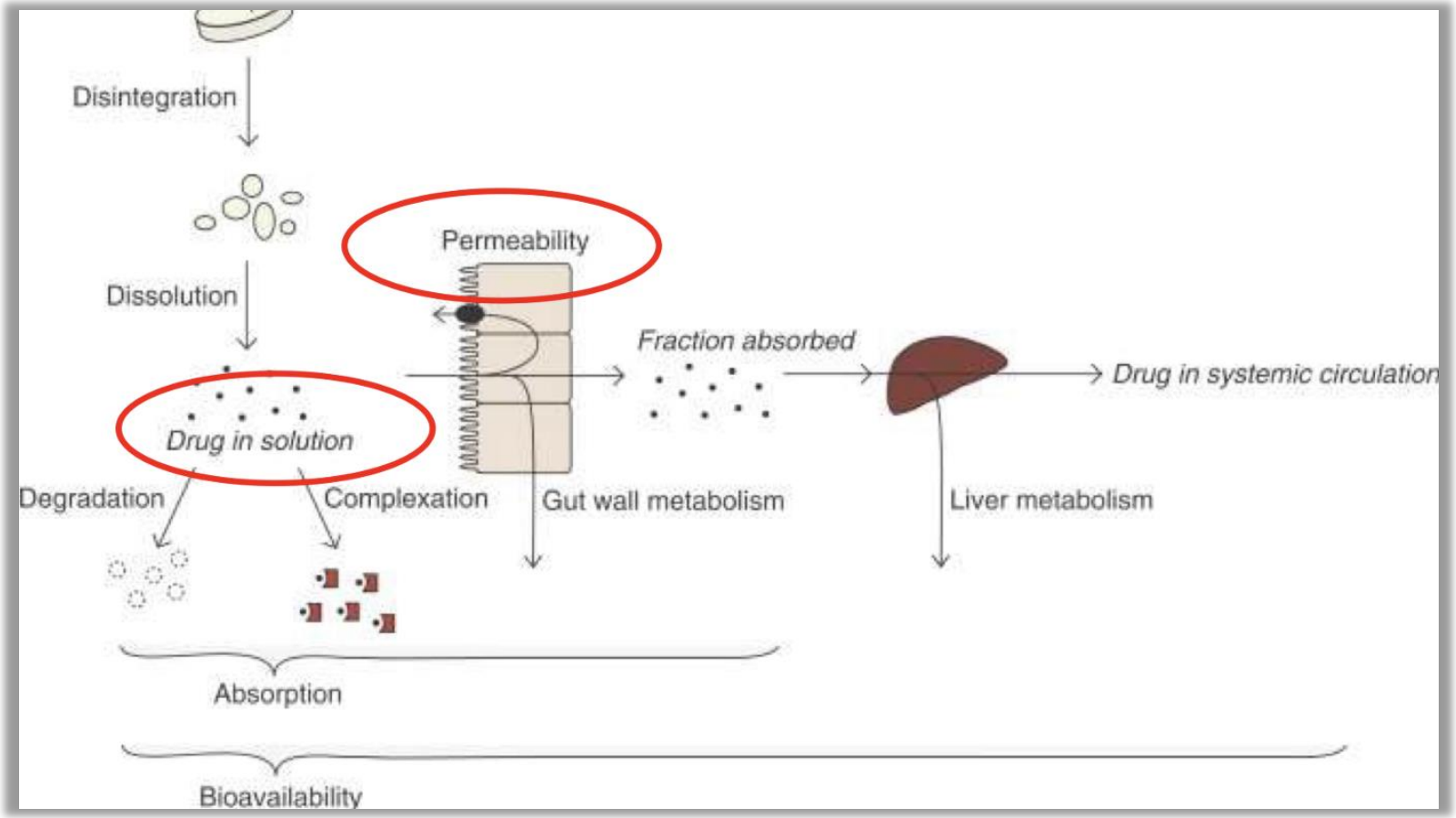
Acid-base equilibria

Two important processes that directly impact drug absorption are:



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Acid-base equilibria

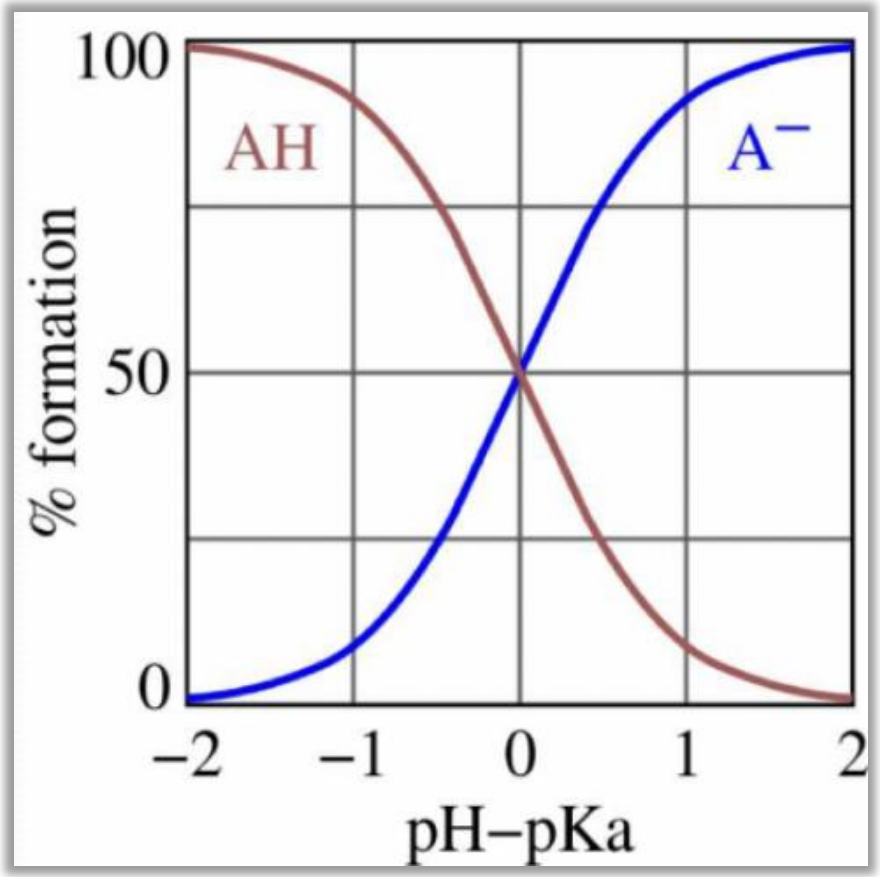
Henderson–Hasselbalch equation

- **$AH \rightleftharpoons H^+ + A^-$**
- Define its equilibrium constant.
- $Ka = (H^+)(A^-)/(AH)$
- Where [..]represents the concentration.
- Taking logarithm on both sides.
- $\log Ka = \log [H^+] + \log [A^-]/[AH]$
- **Define :**

  $pKa = -\log Ka$: $pH = -\log [H^+]$
- **We obtain**

  $pKa = pH - \log [A^-]/[AH]$
- **Or**

  $pKa = pH + \log [HA]/[A^-]$



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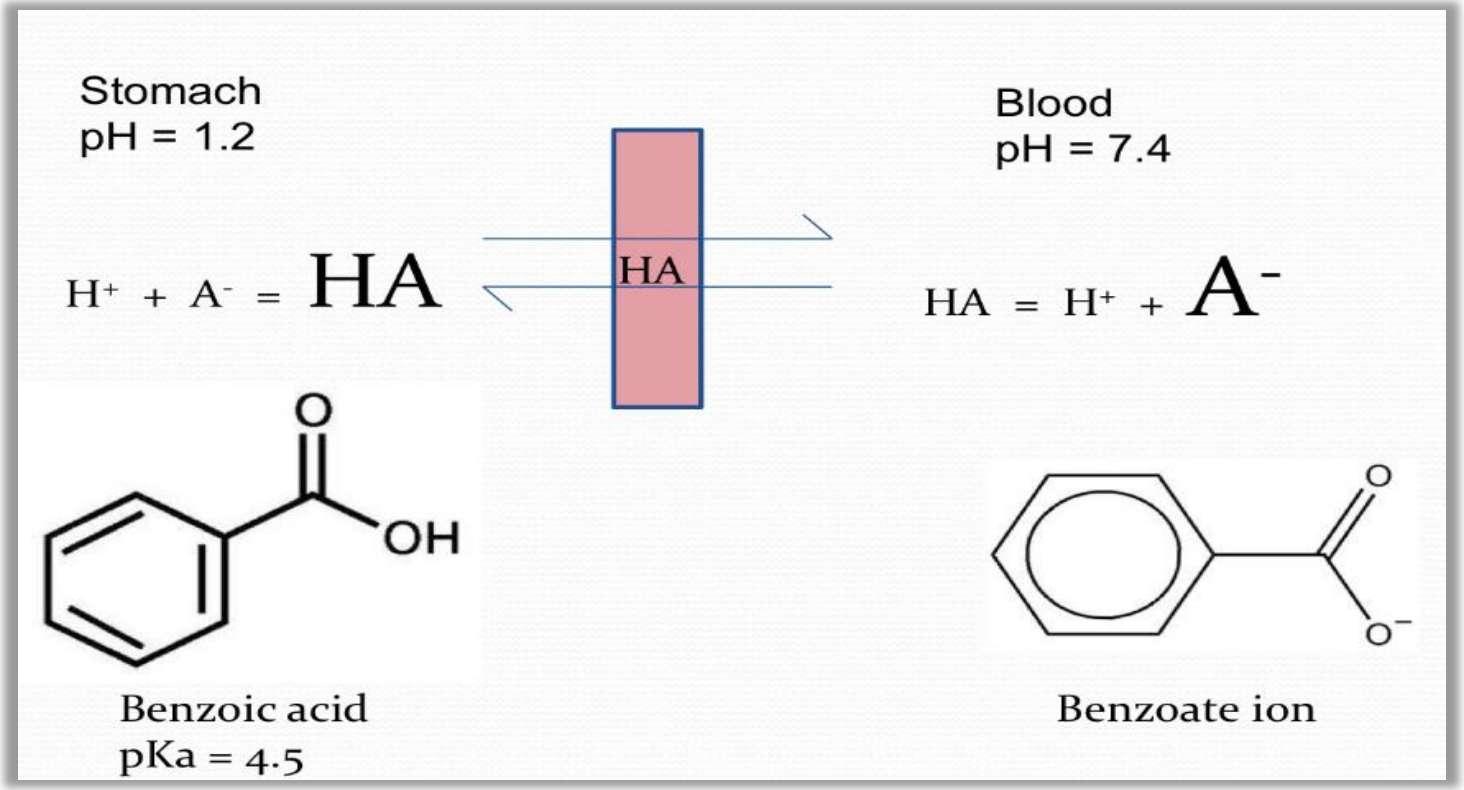
Acid-base equilibria

Absorption of Weak Acids

- Only the neutral molecule can pass through the membrane



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Acid-base equilibria

Example:

For a drug with pKa=3.4
Stomach pH = 1.2

$$log\left(\frac{[HA}{[A^-]}\right) = 3.4 - 1.2 = 2.2$$

$$\frac{[HA\,]}{[A^-]} = anti\log(2.2)$$

$$= \frac{158}{1}$$

i.e. 99.4% HA
and 0.6% A^-

In this example:
The drug is mostly in the UNIONISED HA form in the stomach

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Acid-base equilibria

Example:

$$pka = pH + \log\frac{[HA]}{[A^-]}$$

Blood pH = 7.4

$$\log\left(\frac{[HA]}{[A^-]}\right) = 3.4 - 7.4 = -4.0$$

$$\frac{[HA]}{[A^-]}\ anti\log(-4)$$

$$= \frac{1x10^{-4}}{1}$$

i.e. 0.0001% HA
and99.9999% A^-

The drug is mostly in the IONISED A^- form in the blood

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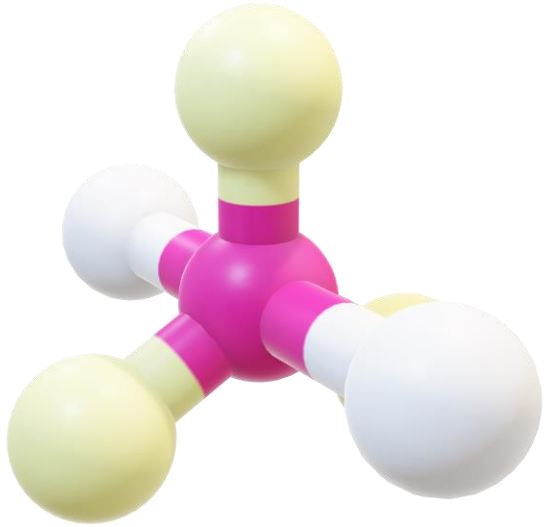
Acid-base equilibria

Absorption of Weak Acids

- Therefore, this weakly acidic drug is readily absorbed from the stomach.

- Once in the blood the drug becomes ionised, preventing it from moving back across the membrane from the blood back into the stomach.



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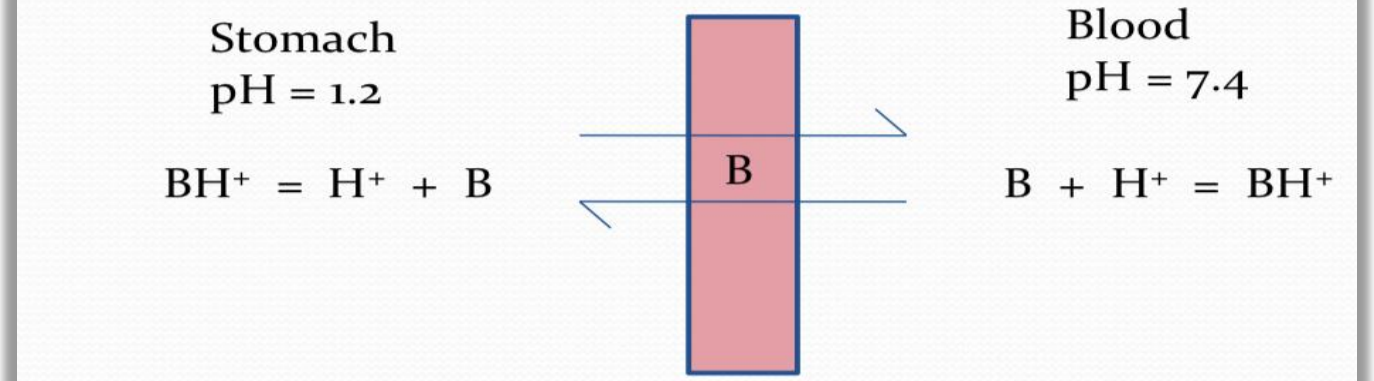
Acid-base equilibria

Absorption of Weak Bases

- The basic drug B will not be absorbed from the stomach because it will exist mainly as the IONISED BH^+ form.

- The main absorption site is likely to the small intestine where the pH will be above 5.

$$pK_a = pH - \log \frac{[B]}{[BH^+]}$$



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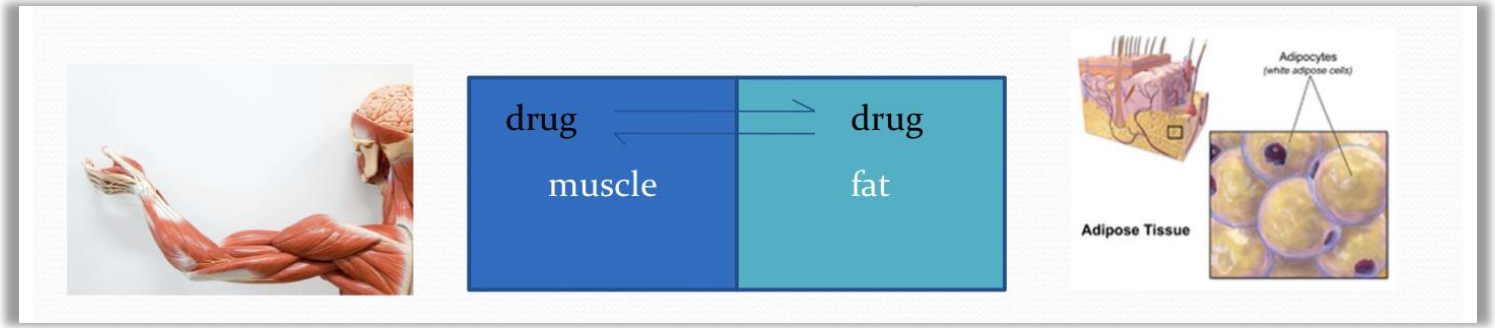
Acid-base equilibria

Partitioning of Non-Ionic Molecules

- Not all drugs are ionic, but they still undergo partitioning between different regions of the body
- This is because different parts of the body have different properties eg hydrophobic or hydrophilic
- Therefore, molecules can have different solubility in different tissues and this causes them to partition between different parts of the body



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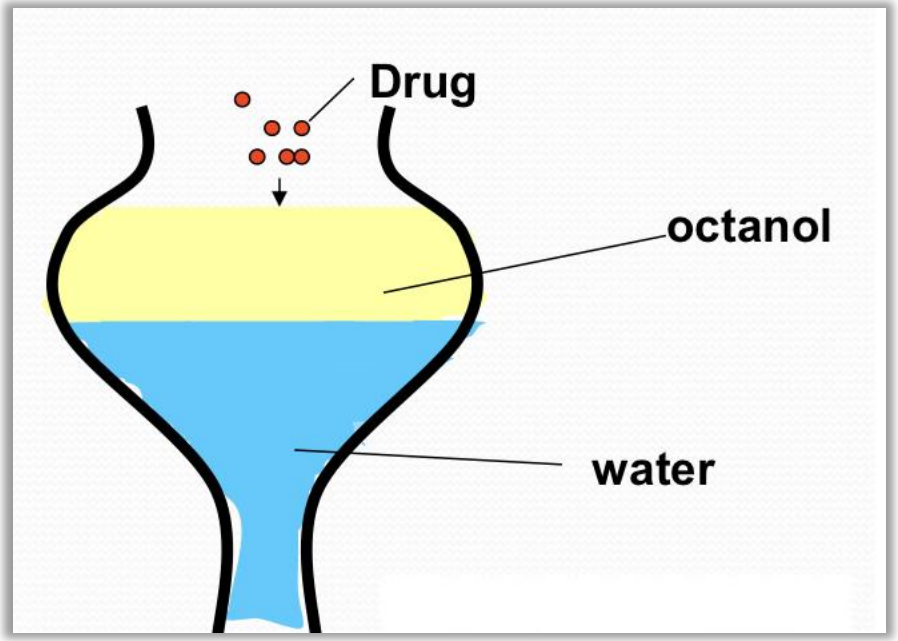
Acid-base equilibria

Partition coefficient (key concepts)

- Definition: The partition coefficient is the measure of the lipophilicity of a drug and an indication of its ability to cross the cell membrane.

- It is defined as the ratio between un-ionized to ionized drug distributed between the organic and aqueous layers at equilibrium



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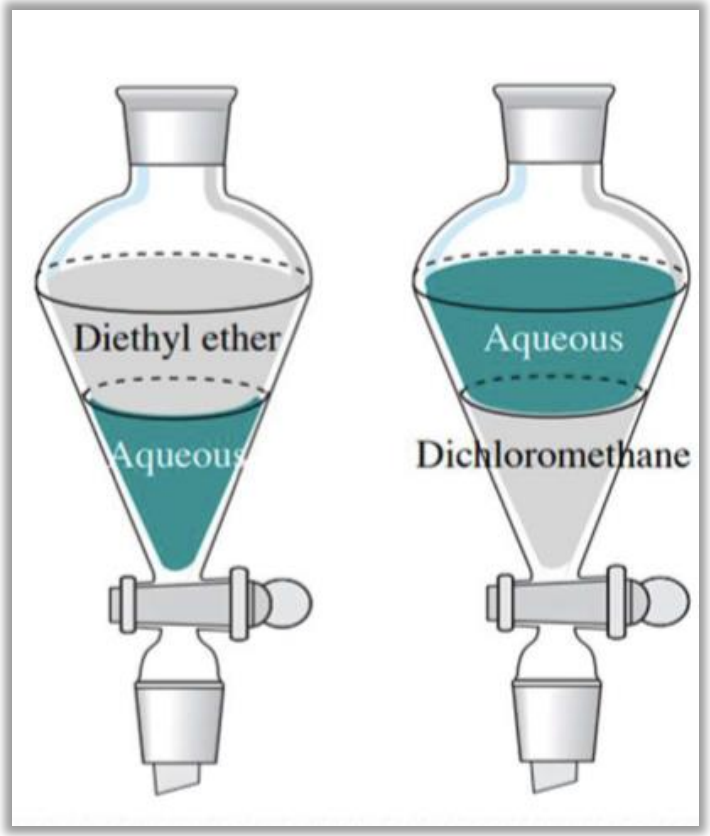
Acid-base equilibria

Partition coefficient (key concepts)

- Experimental measurement (shake-flask method):

1. Add drug to a mixture of equal volumes of lipophilic liquid (e.g. octanol) and water.
2. At equilibrium,phases separate and
3. Assayed for drug content

- **Partition coefficient (P) = $C_{oil\ (octanol)}/C_{water}$**
- **(C= concentration in either phase)**



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Acid-base equilibria

Partition Coefficient P

- The ability of a molecule to partition between two phases depends on its solubility in each phase and how easily it can diffuse between them
- We use standard solvents to define the partitioning of a molecule
- This gives us the octanol- water partition coefficient, P

P= solubility in octanol /solubility in water

- The more hydrophobic the molecule, the larger the value of **P**
- The value of P for different molecules can vary greatly therefore usually **log P** is reported and used.
- Hydrophilic drugs have negative log P values whereas lipophilic drugs have **positive log P** values

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Acid-base equilibria

Partition coefficient-application

- **log P is often quoted :**
- equal distribution of the drug in both phases : **log P = 0**
- The drug has a higher affinity for the lipid phase : **log P >0**
- The drug has a higher affinity for the aqueous phase : **log P <0**
- If the log P is too high or too low, poor bioavailability and biological activity is the likely outcome!

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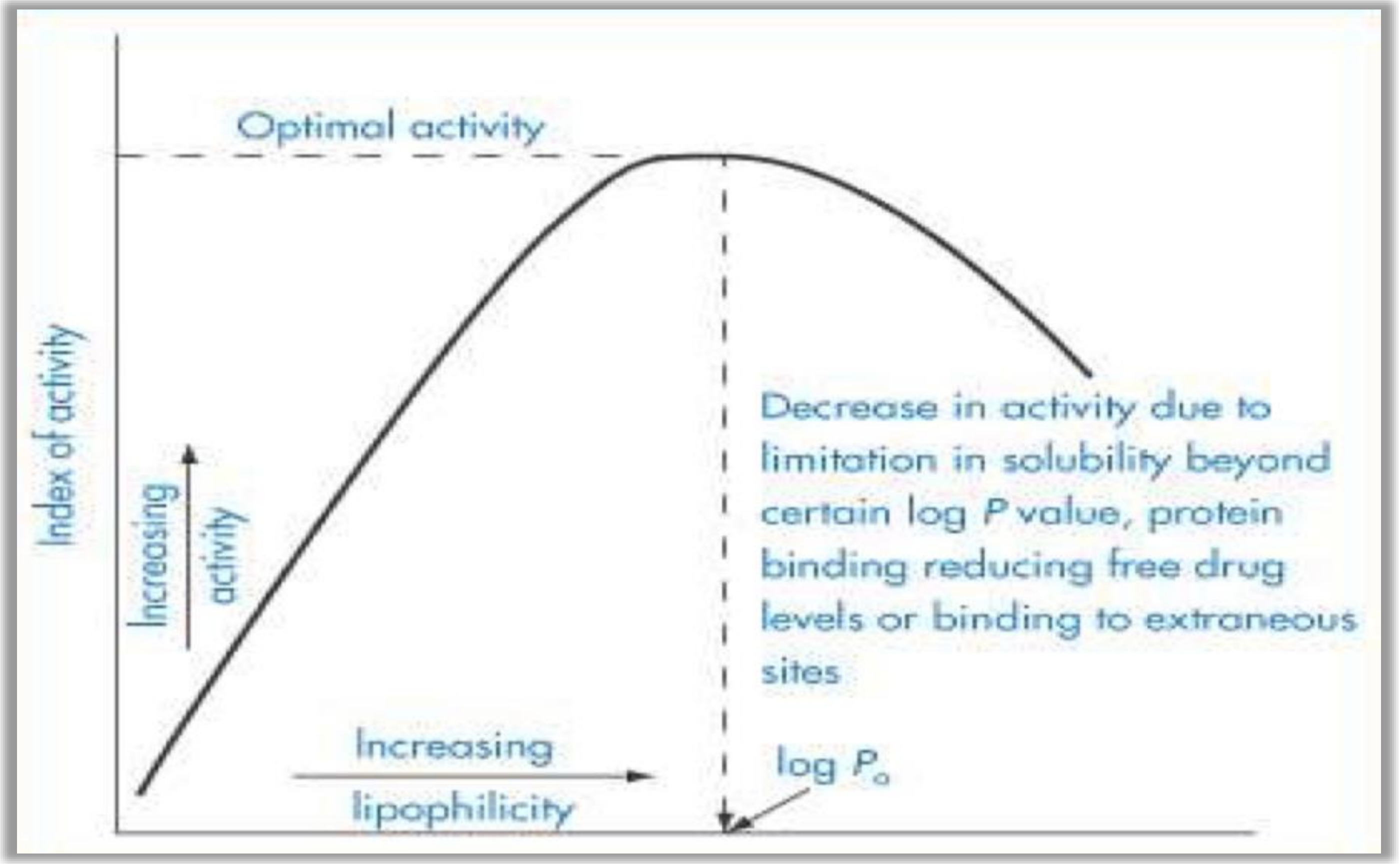
Acid-base equilibria

Partition coefficient-application

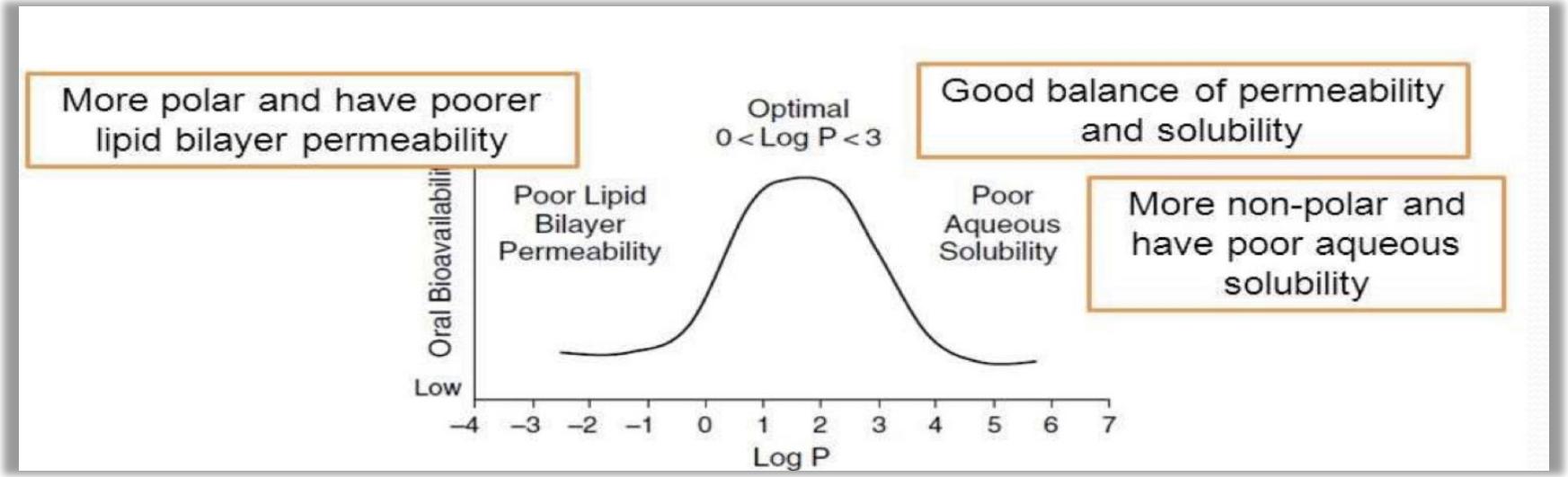


Acid-base equilibria

5.2 Lipophilicity Effects

- A general guide for optimal absorption is to have a moderate Log P(range 0-3)

- **Figure 5.1 :** Hypothetical example of how Log P can affect oral bioavailability for a compound series. , Absorption by passive diffusion permeation after oral dosing is generally considered optimal for compounds having a moderate Log P and decreases for compounds having higher and lower Log P values.



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Acid-base equilibria

TABLE 4.5 Log of P Values for Representative Drugs*

Drug	Log P
Acetylsalicylic acid (Aspirin)	1.19
Amiodarone	6.7
Benzecaine	1.89
Caffeine	0.01
Chlorpromazine	5.30
Ciprofloxacin	-1.12
Indomethacin	3.1
Lidocain	2.26
Methadone	3.9
Phenytoin	2.50
Prednisone	1.46

Acid-base equilibria

TABLE 4.4 Partition Coefficients of Four Analogues of Tetracycline (7]

Analogues of Tetracycline	Partition Coefficient*	Partition Coefficient**
Minocycline	30.0	1.1
Doxycycline	0.48	0.60
Tetracycline	0.09	0.036
Oxytetracycline	0.007	0.025

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Acid-base equilibria

Interpreting P

- The value of P for different molecules can vary greatly therefore often log P is tabulated

- Log P values tell us how a drug may partition between a cellular membrane and the biological fluid for example

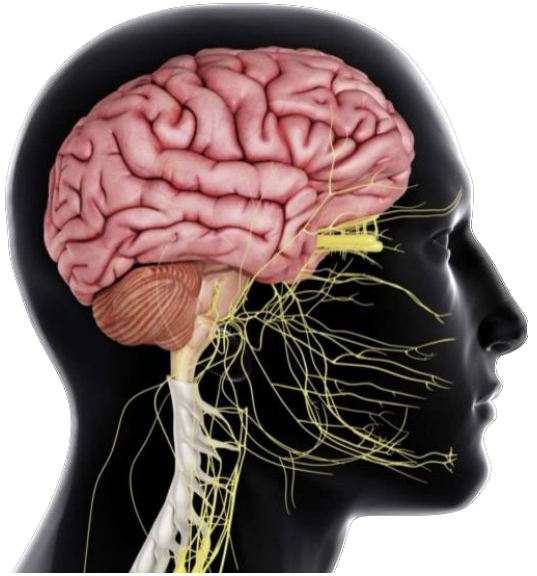
- **Studies have found:**

1. Optimum CNS penetration around Log P = 2
2. Optimum Oral absorption around Log P = 1.8
3. Optimum Intestinal absorption Log P =1.35
4. Optimum Colonic absorption LogP = 1.32
5. Optimum Sub lingual absorption Log P = 5.5
6. Optimum Percutaneous absorption log P = 2.6

Acid-base equilibria

Log P and Drug Formulation

- Low Log P (below 0) Injectable
- Medium (0-3) Oral
- High (3-4) Transdermal
- Very High (4-7) Toxic build up in fatty tissues
- **Principle of minimum hydrophobicity (CNS drug penetration):**
  - To prevent drugs penetrating the central nervous system (CNS) and causing effects such as depression, strange dreams, anaesthesia, they should have log P lower than 2.0.
  - This is not always possible (CNS side effects may result from many drugs with log P of or greater)



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Acid-base equilibria

More Log P values!

Drug	Log P	notes
Oxytetracycline	-1.12	Oral dose
Caffein	0.01	Oral dose
Aspirin	1.19	Oral dose
Lidocaine	2.26	Surface anaesthetic (s.c . injection)
Thiopental	2.8	i.v. general anaesthetic CNS side effects
Methadone	3.9	Analgesic strong CNS effects
Hydrocortisone	4.3	Intramuscular injection Aggravates neuro- psychiatric conditions

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Acid-base equilibria

Summary

- According to the pH-partition hypothesis, weak acids are more readily absorbed at low pH since HA (unionised form / more lipid soluble form) predominates
- Strong acids (pKa < 1.0) are not absorbed at low pH since A- (ionised form)predominates
- Weak bases (pKa > 5) are not absorbed at low pH since BH^+ (ionised form)predominates
- Weak bases better absorb from regions of higher pH – for example the small intestine since .....???
- For better understanding: review pH-partition hypothesis and point out its limitations (see next slide)

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Acid-base equilibria

Mechanisms of drug absorption

1. Passive diffusion
2. Convective transport
3. Active transport
4. Facilitated transport
5. Ion-pair transport
6. Endocytosis (pinocytosis).

- pH-partition hypothesis assumes that ‘’Passive diffusion is responsible for the absorption of most drugs’’

- And, it does not take into consideration all the complex intervening factors shown in **Figure 4.1**

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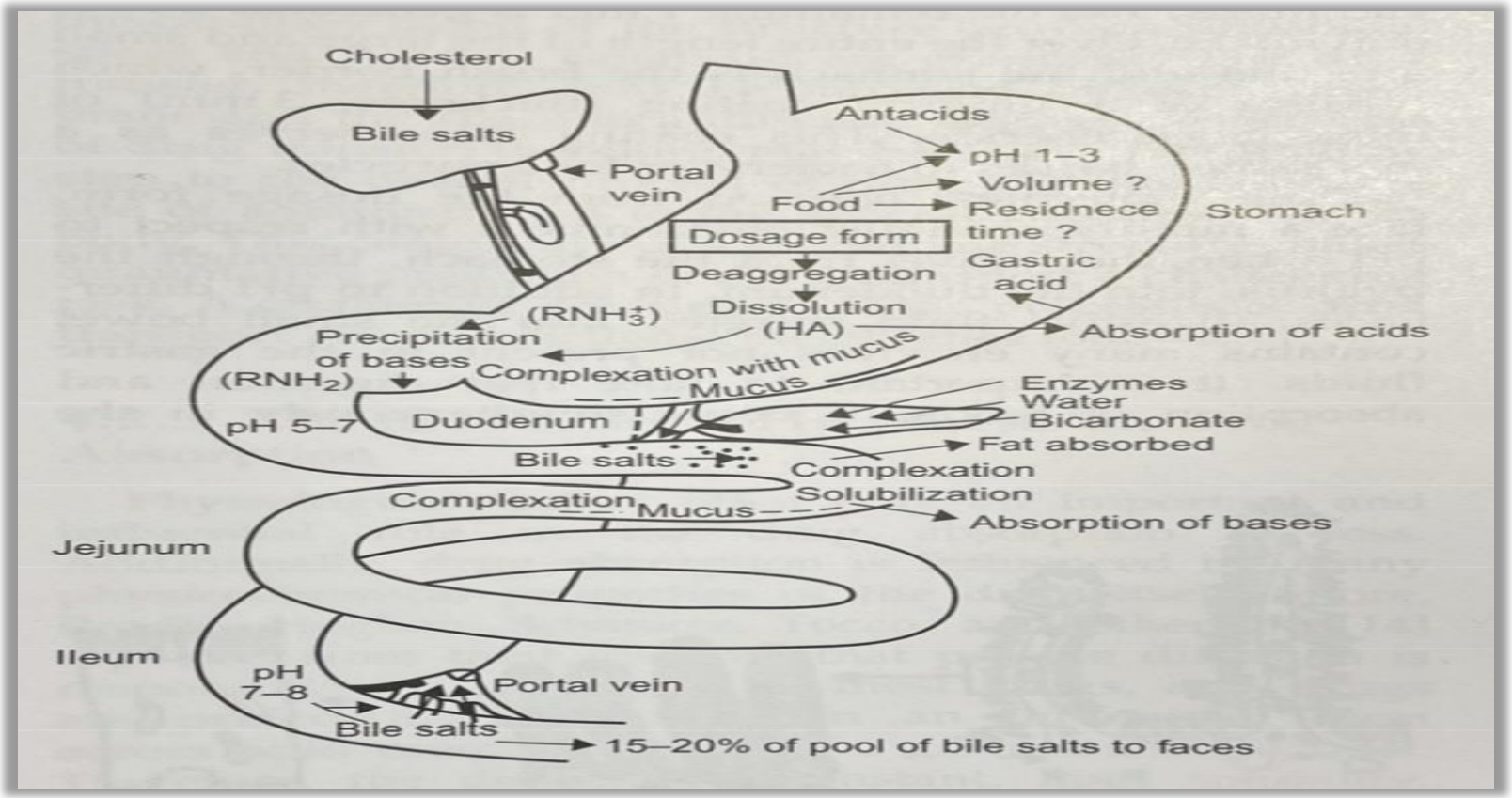
Acid-base equilibria

FIGURE 4.1 Processes occurring along with drug absorption when drug molecules travel down the gastrointestinal tract and the factors that affect to drug absorption (7].



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Acid-base equilibria

TABLE 6.2 Example pH values for different physiological fluids and factors responsible for maintaining the pH

Physiological fluid	Approximate pH	Factors responsible for pH
Blood	7.4	Buffering action of haemoglobin, plasma proteins, carbonic acid, bicarbonate, and phosphate
Urine	5-8	Main constituents are water, urea, chloride, sodium, potassium, creatinine, dissolved organics, and inorganics. pH can be significantly altered by diet and drugs
Cerebrospinal fluid (CSF)	7.4	Physiological buffers maintain pH, The buffering capacity of CSF is lower than that of blood
Sweat	5	Main constituents are water, mineral ions, lactate, and urea. Sebum and sweat combine to form a protective layer on the skin

Acid-base equilibria

TABLE 6.2 Example pH values for different physiological fluids and factors responsible for maintaining the pH

Physiological fluid	Approximate pH	Factors responsible for pH
Lachrymal fluid	7.4	Complex fluid acting to protect and lubricate the eye, contains physiological buffers to maintain pH
Saliva	6.5	Comprises water, electrolytes, mucus, enzymes, and glycoproteins, maintains acid. environment to reduce infection
GIT fluid (stomach)	1-3	Hydrochloric acid secretion gives low pH
GiT fluid (small intestine)	8	Bicarbonate is released into small intestine, neutralizes stomach acid and raises pH , bile salts are released, also released to aid digestion
GIT fluid (colon)	7.0-7.5	Short chain fatty acids formed from fermentation of carbohydrates in gut lowers ph

Acid-base equilibria

Co-solvency (context)

- We've seen that the aqueous solubility of acidic or basic drugs may be improved by using a salt form of the drug.
- However, this means that the drug is present in water as ions (good water solubility), yet are absorbed poorly through lipid biological membranes due to low permeability.
- To be absorbed, a drug must also have a suitable logP and have high enough water solubility at the site of absorption
- We can increase the solubility (especially if the drug does not ionise) by using a co-solvent.

Acid-base equilibria

Requirements for Co-solvents

- If a drug is insoluble in water, it is often possible to make it better dissolve by adding a second solvent (co- solvent) to the water.
- The drug must be more soluble in the co-solvent
- The co-solvent must be completely miscible with water

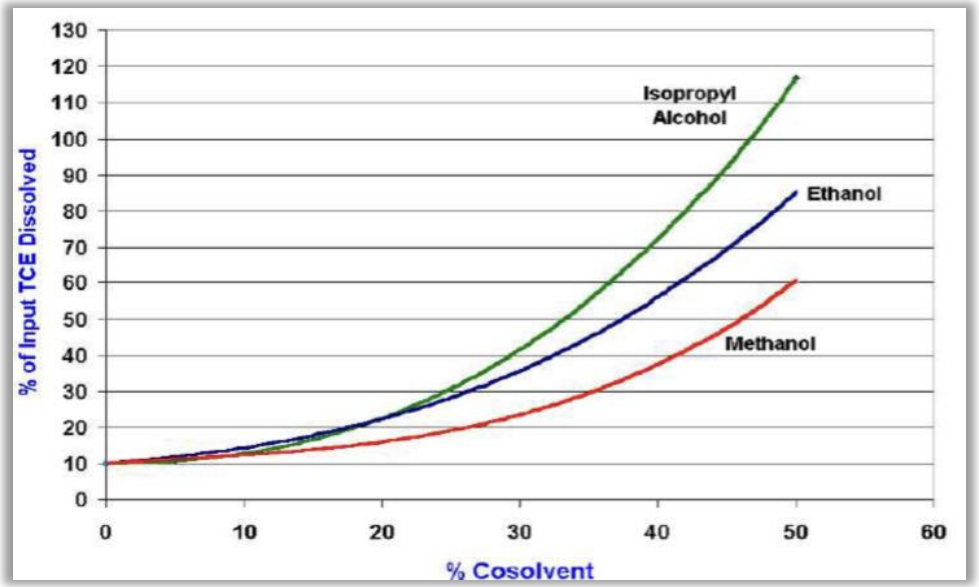

Figure 12. TCE Solubility in Cosolvent-Water Systems for Methanol, Ethanol, and Isopropyl Alcohol.

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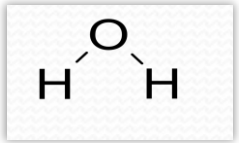
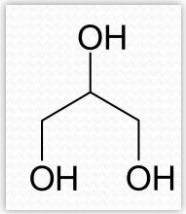
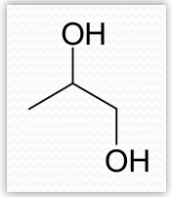
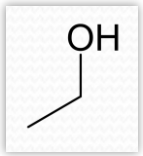
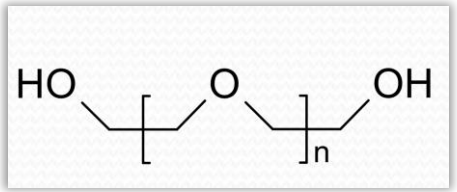
Acid-base equilibria

Common Pharmaceutical Co-solvents

- Water 
- Glycerine (glycerol) 
- Propylene glycol 
- Ethanol 
- Polyethylene glycol (PEG) 

more polar

less polar

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Acid-base equilibria

Common Pharmaceutical Co-solvents

- Non-polar drugs will be dissolved best in PEG, least in water
- PEG > Ethanol > propylene glycol > glycerol > water

Drug	mL solvent to dissolve 1g drug	
	water	ethanol
atropine	455	2
Atropine sulphate	0.5	5
codeine	120	2
Codeine sulfate	30	1280
morphine	5000	210
Morphine sulfate	16	565
phenobarbital	1000	8
Phenobarbital sodium	1	10

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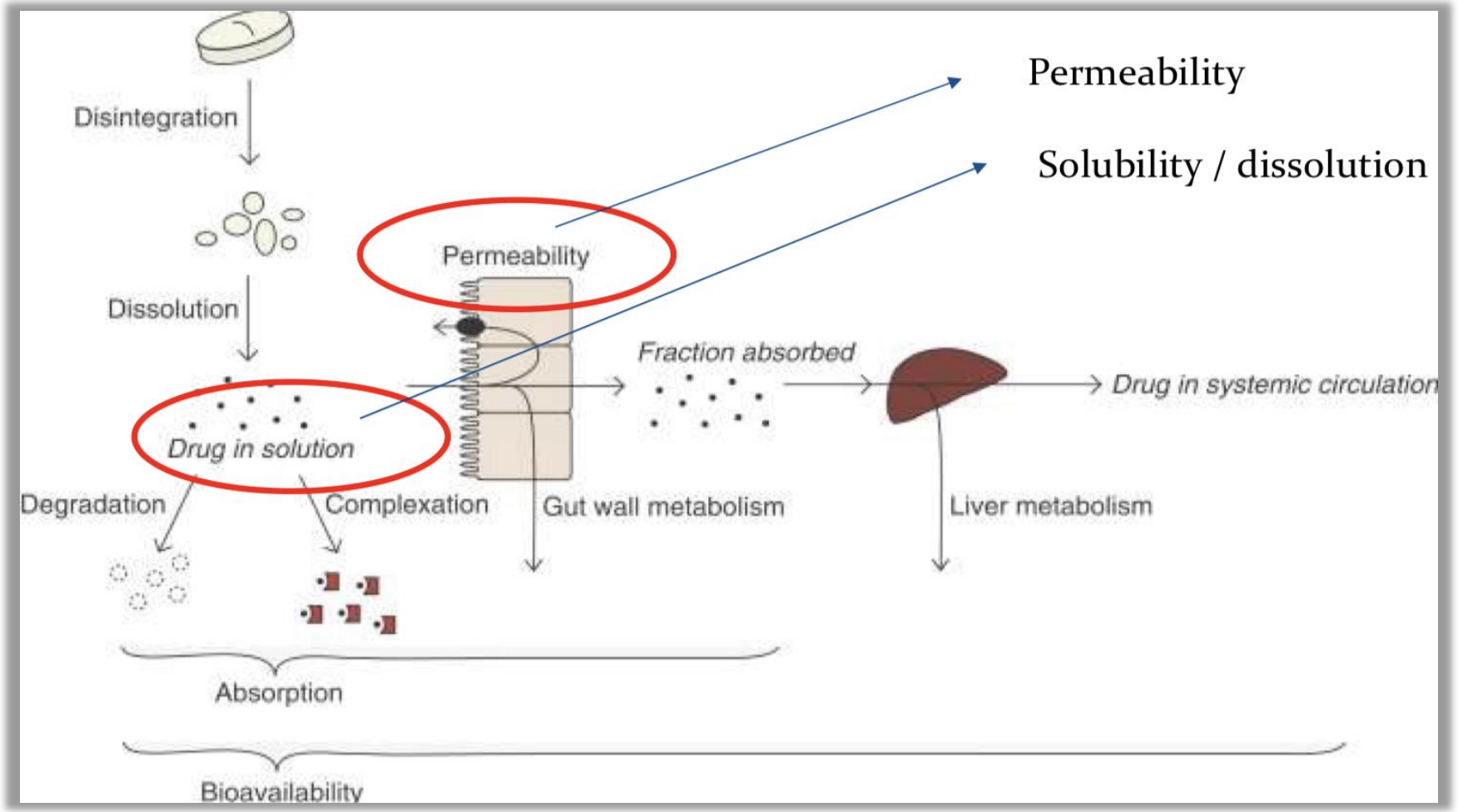
Acid-base equilibria

TABLE 4.9 Substitutent Group Classification [7]

Substituten	Classification
-CH3	Hydrophobic
-CH2-	Hydrophobic
-Cl , -Br , -F	Hydrophobic
-N(CH3)2	Hydrophobi
-SCH3	Hydrophobic
-OCH2CH3	Hydrophobic
-OCH3	Slightly hydrophilic
-NO2	Slightly hydrophilic
-CHO	Hydrophilic
-COOH	Slightly hydrophilic
-COO	Very hydrophilic
-NH2	Hydrophilic
-NH3	Very hydrophilic
-OH	Very hydrophilic

Acid-base equilibria

Two important processes directly impact drug absorption:



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Acid-base equilibria

Biopharmaceutics Classification System (BCS) :

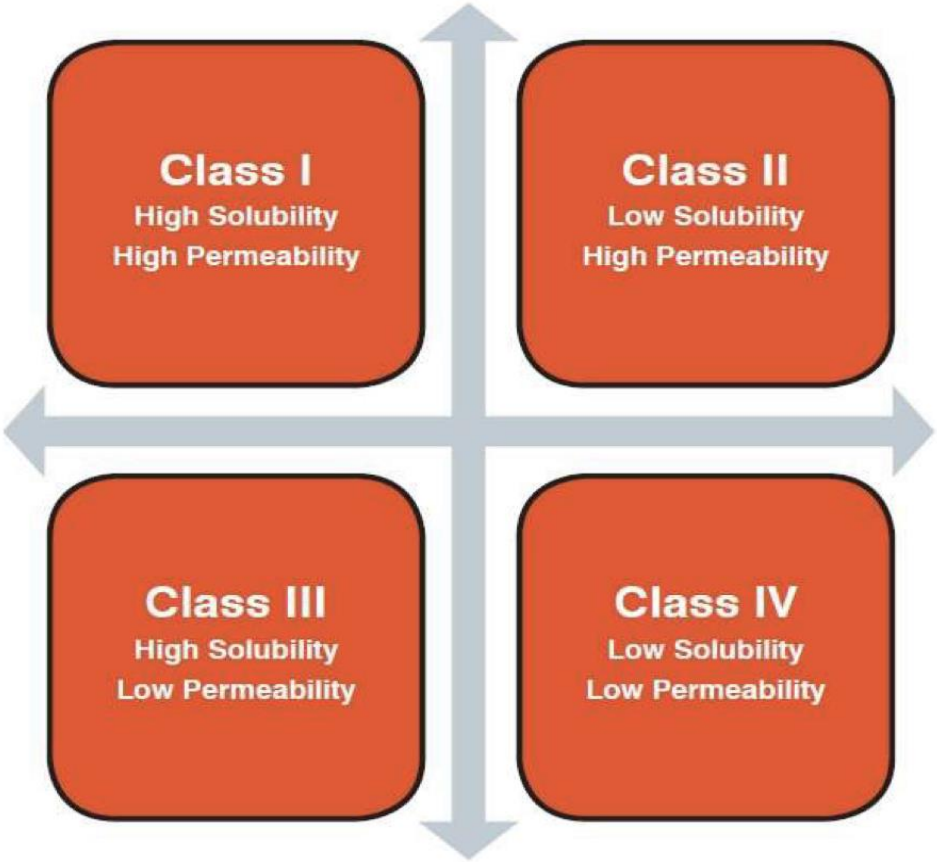

Figure 1: Biopharmaceutics Classification System

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BCS classification in words!

- BCS Divides Compounds into Four Categories:

1. Class I – High Solubility, High Permeability
2. Class II – Low Solubility, High Permeability
3. Class III – High Solubility, Low Permeability
4. Class IV – Low Solubility, Low Permeability

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BCS classification in words!

Class	Features	Examples
1	High permeability. High solubility	Paracetamol, metoprolol, theophylline
2	High permeability. Low solubility	Atovaquone, carbamazepine, danazol, glibenclamide, griseofulvin, ketoconazole, troglitazone
3	Low permeability. High solubility	Acyclovir, atenolol, cimetidine, ranitidine
4	Low permeability. Low solubility	Chlorothiazide, furosemide

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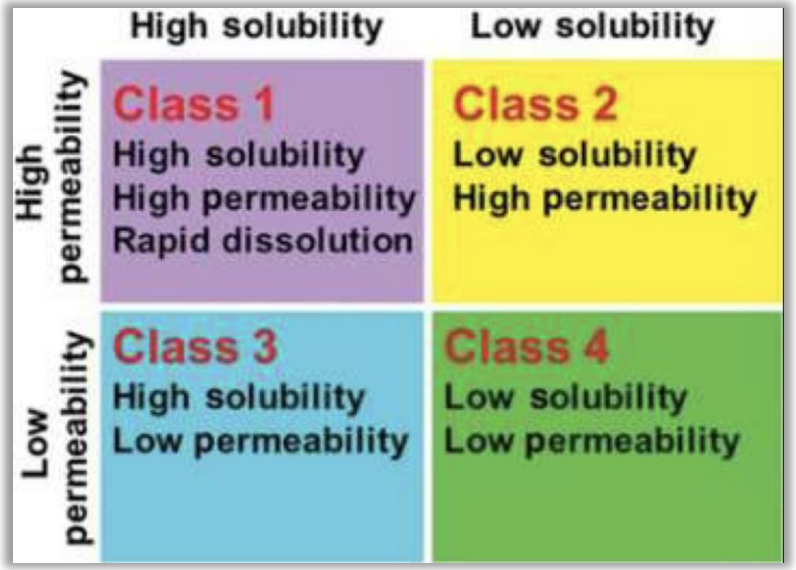
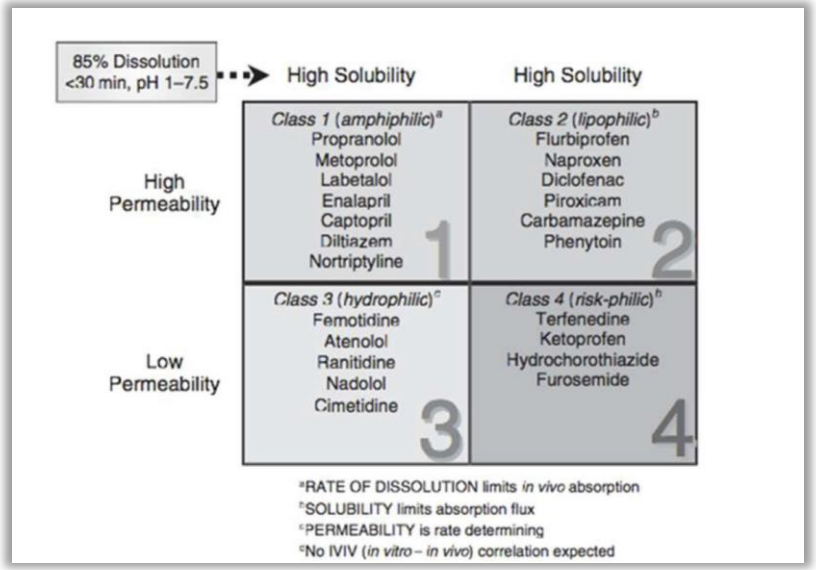
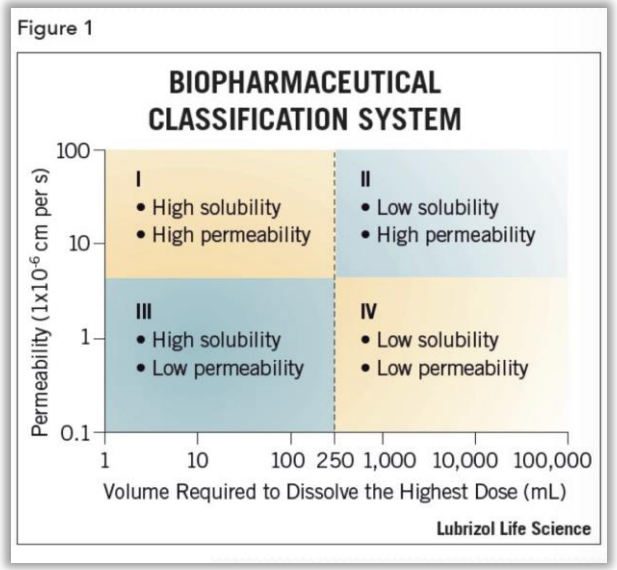
Different presentation of the same information!







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For oral drug delivery, a simplified summary of approaches based on properties might look like Table 1

- **Table 1 :**

BCS Class	Solubility	Permeability	Oral Dosage Form Approach	Chances of Non-oral Dosage Form being Required
1	High	High	Simple solid oral dosage form	
2	Low	High	• Techniques to increase surface area like particle size reduction, solid solution, solid dispersion • Solutions using solvents and/ or surfactants	
3	High	Low	Incorporate permeability enhancers, maximize local lumenal concentration	
4	Low	Low	Combine 2 and 3	

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Fick's Laws of Diffusion , Fick's first law

- The amount, M, of material flowing through a unit area, S, of a barrier in unit time, t, is known as the flux, J:

$$J = \frac{dm}{S.dt}$$

- The flux, in turn, is proportional to the concentration gradient, dC/dx:

$$J = -D\frac{dC}{dX}$$ **Fick's first lawr**

- D is the diffusion coefficient of a penetrant (diffusant) in cm^2/sec,
- C is its concentration in g/cm^3,
- X is the distance in centimeter of movement perpendicular to the surface of the barrier.

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Thank You !

https://t.me/Dr_Cube