

# A SEMINAR ON pH PARTITION THEORY



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# CONTENTS

- INTRODUCTION
- pH-PARTITION THEORY
- DRUG pKa AND GASTROINTESTINAL pH
- LIPOPHILICITY AND DRUG ABSORPTION
- DEVIATIONS FROM THE pH PARTITION THEORY
- A UNIFYING HYPOTHESIS
- CONCLUSION
- REFERENCES

# INTRODUCTION:

## DRUG ABSORPTION:

Drug absorption is defined as the process of movement of unchanged drug from the site of administration to systemic circulation.

## FACTORS INFLUENCING GI ABSORPTION OF A DRUG FROM ITS DOSAGE FORM:

They are classified in to two types:

1. PHARMACEUTIC FACTORS
2. PATIENT RELATED FACTORS

# PHYSICOCHEMICAL PROPERTIES OF DRUG SUBSTANCES:

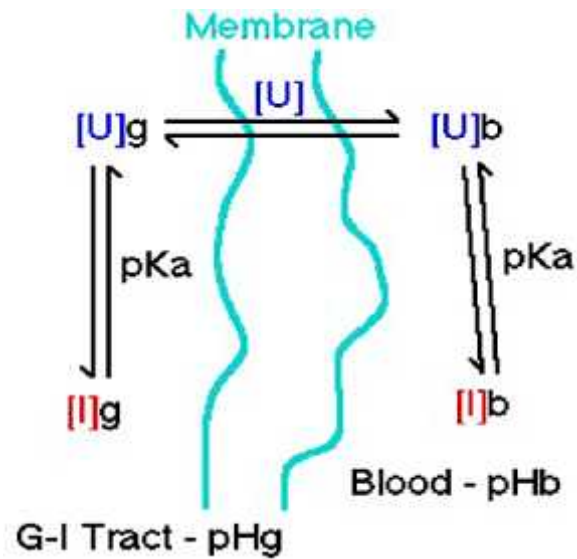
1. Drug solubility and dissolution rate
2. Particle size and effective surface area
3. Polymorphism and amorphism
4. Pseudo polymorphism
5. Salt form of the drug
6. Lipophilicity of the drug
7. pka of the drug and pH
8. Drug stability

## pH PARTITION THEORY:

- The theory states that for drug compounds of molecular weight greater than 100, which are primarily transported across the biomembrane by passive diffusion, the process of absorption is governed by:
  1. The dissociation constant (pka) of the drug.
  2. The lipid solubility of the unionized drug ( a function of drug  $K_{O/W}$ ).
  3. The pH at the absorption site.

- Brodie proposed the pH partition theory to explain the influence of GI pH and drug pka on the extent of drug transfer or drug absorption.
- Ph partition theory of drug absorption is based on the assumption that the GIT is a simple lipid barrier to the transport of drugs and chemicals. Accordingly the unionized form of an acid or basic drug, if sufficiently lipid soluble, is absorbed but the ionized form is not. The larger the fraction of drug is in the unionized form at a specific absorption site, the faster is the absorption.

# DIAGRAM SHOWING THE TRANSFER OF DRUG ACROSS THE MEMBRANE:



## DRUG pka AND GASTROINTESTINAL pH:

- The fraction of drug in solution that exist in the unionized form is a function of both dissociation constant of the drug and the pH of the solution.
- The dissociation constant is often expressed for both acids and bases as pka (the negative logarithm of the acidic dissociation constant.)
- It is customary to express the dissociation constants of both acidic and basic drugs by pka values. The lower the pka of an acidic drug, the stronger the acid i.e., greater the proportion of ionized form at a particular pH. The higher the pka of a basic drug, the stronger the base.



- Thus from the knowledge of pka of the drug and pH at the absorption site (or biological fluid), the relative amount of ionized and unionized drug in solution at a particular pH and the percent of drug in solution at this pH can be determined by Henderson- Hasselbach equation

for an acid:

$$pka-pH = \log ( f_u/ f_i )$$

for a base:

$$pka-pH = \log ( f_i/ f_u )$$

i.e., for weak acids:

$$\text{pH} = \text{pka} + \log [\text{IDC}/\text{UDC}]$$

$$\% \text{ drug ionized} = [10^{\text{pH}-\text{pka}} / 1 + 10^{\text{pH}-\text{pka}}] * 100$$

For weak bases:

$$\text{pH} = \text{pka} + \log [\text{UDC}/\text{IDC}]$$

$$\% \text{ drug ionized} = [10^{\text{pka}-\text{pH}} / 1 + 10^{\text{pka}-\text{pH}}] * 100$$

when the concentration of ionized and unionized drug becomes equal, the second term of the equation becomes zero (since  $\log 1 = 0$ ) and thus  $\text{pH} = \text{pka}$ . The pka is the characteristic of the drug.

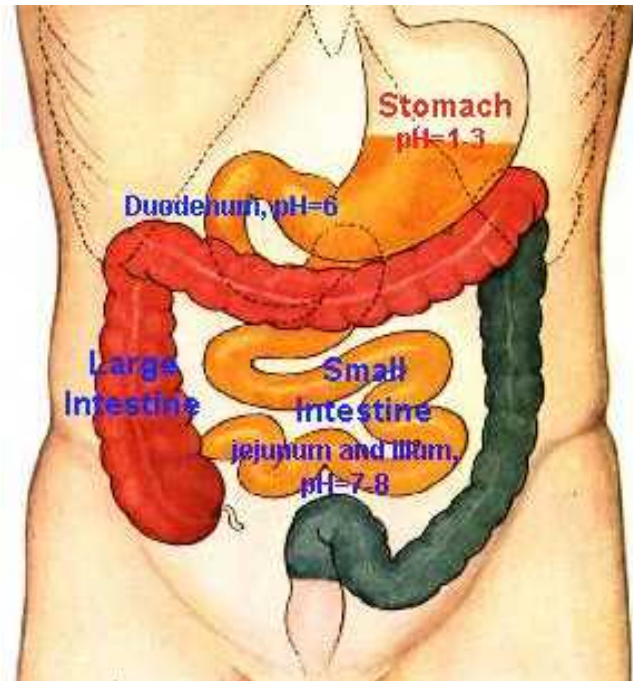
- A barrier that separates the aqueous solutions of different pH such as GIT and plasma then the theoretical ratio R of drug concentration on either side of the membrane can be given by the equation
- For weak acids:

$$R_a = C_{GIT}/C_{Plasma} = \frac{1+10^{pH_{GIT}-pka}}{1+10^{pH_{plasma}-pka}}$$

For weak bases:

$$R = C_{GIT}/C_{Plasma} = \frac{1+10^{pka-pH_{GIT}}}{1+10^{pka-pH_{plasma}}}$$

# THE pH RANGE IN GIT



- The pH range in GIT from 1-8 that of the stomach is from 1-3 and of the intestine ( from duodenum to colon ) 5-8, then certain generalization regarding ionization and absorption of drugs can be made, as predicted from pH partition hypothesis.

- Most acid drugs are predominantly unionized at the low pH of gastric fluids and may be absorbed from the stomach as well as from the intestine.
- Very weak acid ( $pK_a > 8$ ) such as phenytoin, theophylline are essentially unionized throughout the GIT.
- The ionization of weak acids with  $pK_a$  values ranging from about 2.5 - 7.5 is sensitive to changes in pH. More than 99% of the weak acid aspirin ( $pK_a = 3.5$ ) exist as unionized drug in gastric fluids at  $pH = 1$ . on the other hand, only about 0.1% of aspirin is unionized at  $pH 6.5$  in the fluids of small intestine.
- Despite of unfavorable ratio of unionized to ionized drug, aspirin and most weak acids are well absorbed in the small intestine. A large surface area and a relatively long residence time in the small intestine are contributing factors.

- These factors minimize the need for a large fraction of the drug to be in an unionized form in the small intestine.
- Strong acids (di sodium cromoglycate) are ionized throughout the GIT and are poorly absorbed.

## Influence of drug pka and GI pH on drug absorption

Drugs	pka	pH/site of absorption
Very weak acids (pka>8)		
Phenobarbital	8.1	Unionized at all pH values
Phenytoin	8.3	
Moderately weak acids (pka 2.5-7.5)		
Aspirin	3.5	Unionized at gastric pH, ionized at intestinal pH
Ibuprofen	4.4	
Strong acids (pka<2.5)		
Di sodium cromoglycate	2.0	Ionized at all pH values

# Comparison of gastric absorption at pH 1 and pH 8 in the rat

	pka	%absorbed at pH=1	%absorbed at pH=8
Acids			
5-sulfosalicylic	<2.0	0	0
Thiopental	7.6	46	34
Bases			
Aniline	4.6	6	56
Quinine	8.4	0	18



- Most weak bases are poorly absorbed, if at all, in the stomach since they are largely ionized at low pH.
- Codeine, a weak base with a pka of about 8 will have only 1 of every million molecules in the non ionized form in gastric fluid at pH 1.
- The pH range of the intestine from duodenum to the colon is about 5-8. weakly basic drugs (pka<5), such as dapson, diazepam are essentially unionized throughout the intestine. Stronger bases such as mecamylamine and guanethidine are ionized throughout the GIT and tend to be poorly absorbed.

## Influence of drug pka and GI pH on drug absorption

drug	pka	pH /site of absorption
Very weak bases (pka<5.0)		
Theophylline	0.7	Unionized at all pH values
Caffeine	0.8	
Moderately weak bases (pka 5-11)		
Reserpine	6.6	Ionized at gastric pH –unionized at intestinal pH
Heroin	7.8	
Stronger bases (pka>11.0)		
Mecamylamine	11.2	Ionized at all pH values
guanethidine	11.7	

## Comparison of intestinal absorption in rat at several pH values

	pka	pH=4	pH=5	pH=7	pH=8
<b>ACIDS</b>					
Salicylic	3.0	64	35	30	10
Benzoic	4.2	62	36	35	5
<b>BASES</b>					
Aniline	4.6	40	48	58	61
Quinine	4.2	09	11	41	54

# LIPOPHILICITY AND DRUG ABSORPTION:

- The gastro intestinal cell membrane are essentially lipoidal. Highly lipid soluble drugs are generally absorbed while decidedly lipid insoluble drugs are in general poorly absorbed.
- Certain drugs are poorly absorbed after oral administration even though they are largely unionized in the small intestine, low lipid solubility of the uncharged molecule may be the reason.
- A guide to the lipophilic nature of a drug is its partition coefficient between a fat like solvent and water or an aqueous buffer.

- The critical role of lipid solubility in drug absorption is a guiding principle in drug development. Polar molecules such as gentamicin, ceftriaxone, heparin and streptokinase are poorly absorbed after oral administration and must be given by injection.
- Lipid soluble drugs with favorable partition coefficient are usually well absorbed after oral administration. The selection of a more lipid soluble compound from a series of research compounds often result in improved pharmacologic activity.

- Occasionally the structure of an existing drug can be modified to develop a similar compound with improved absorption. Eg: The development of clindamycin, which differs from lincomycin by the single substitution of chloride for a hydroxyl group. Even slight molecular modification, however runs the risk of also changing the efficacy and safety profile of the drug. For this reason, medicinal chemists prefer the development of lipid soluble prodrugs of a drug with poor oral absorption characteristics.

example: cefuroxime (cefuroxime axetil - acetoxy ethyl ester)

- The lipid solubility of a drug is determined from its oil/water partition coefficient ( $k_{o/w}$ ) value.
- This value is a measure of the degree of distribution of drug between one of the several organic, water immiscible, lipophilic solvents and an aqueous phase.
- In general, the octonal /pH 7.4 buffer partition coefficient value in the range of 1 to 2 of a drug is sufficient for passive absorption across lipoidal membranes.

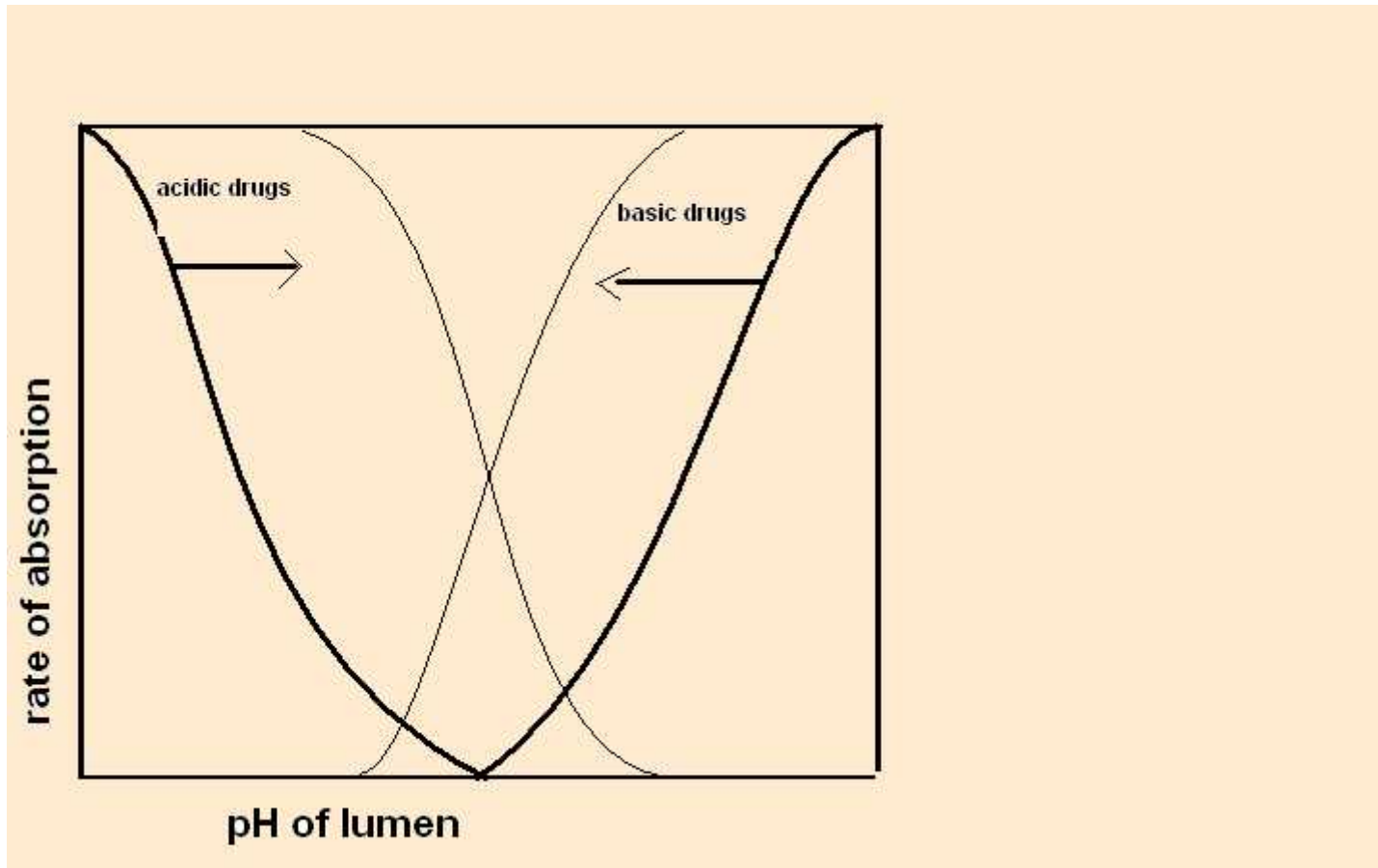
# DEVIATIONS FROM pH-PARTITION THEORY

- The pH-partition theory provides a basic frame work for understanding drug absorption, but it is an over simplification of a more complex process.
- The theory indicates that the relationship between pH and permeation or absorption rate is described by an S- shaped curve corresponding to the dissociation curve of the drug.
- For a simple acid or base, the inflection point of the pH-absorption curve should occur at a pH equal to the pka of the drug. This is rarely observed experimentally.



- In general pH absorption curves are less steep than expected and are shifted to higher pH values for acids and to lower pH values for bases.
- The conditions for deviations of the pH-absorption curve from the course predicted by the simple pH-partition theory are investigated theoretically. The deviations are an elevation of the asymptotic section usually approaching zero and/or a shift of the intermediate section, more exactly of the inflection point, in the direction of the abscissa and/ or the ordinate. In the absence of a special pH at the surface of the barrier (microclimate pH), the elevation of the asymptotic section can be attributed to a permeability of the barrier to the ionized form of the permeating substance.

# pH ABSORPTION CURVE



- A shift of the inflection point to the right for acids and to the left for bases can be explained by a significant unstirred layer at the surface of the barrier or only when the concentration in the well-stirred bulk phase is decreasing with time by a high distribution ratio of the substance between barrier and bulk phase. A variable microclimate pH influenced by bulk phase pH can also produce the described deviations.
- The factors that may contribute to the deviations are
  1. Absorption of the ionized form of the drug.
  2. Presence of an aqueous unstirred diffusion layer adjacent to the cell membrane.
  3. Difference between luminal pH and pH at the surface of the cell membrane.

## ABSORPTION OF THE IONIZED FORM OF A DRUG

- The quaternary ammonium drugs elicit systemic pharmacologic effects after oral administration, suggesting that the restriction to ionized forms of a drug by the GI barriers may not be absolute. Several in situ and in vitro studies support this idea.
- The absorption of organic anions and cations does take place in the small intestine but at a much slower rate than the corresponding unionized form of the drug.
- Crouthamel et al., have estimated that the permeability ratio of unionized to ionized drug across the rat small intestine is about 3 for barbital and about 5.5 for sulfaethidole, but these estimates may be low because

they do not take into account the presence of a stagnant aqueous diffusion layer or a difference between luminal and microclimate pH.

- The absorption of ionized forms of a drug would cause the pH-absorption curve to shift to the right for a weak acid, and to the left for a weak base, the extent of the shift depends on the relative permeability of the ionized form of the drug.

## MUCOSAL UNSTIRRED LAYER

- Adjacent to the gastrointestinal membrane there is usually a stagnant layer that acts as an additional diffusion barrier so that rapidly permeating substances could actually be rate-limited by diffusion. Osmotic volume flow across membranes is also affected by unstirred layers (USL), because the movement of the solvent will carry dissolved solutes along with it.
- That, in turn, may alter the osmotic gradient across the membrane. Concentration gradients of the solute induced within the USL both in the cases of solute permeation and osmosis play an essential role in the transport process across biological membranes. Their size and importance depend on the rate of dissipation through back diffusion of the solute and on the various stirring effects that may be present.

## MICROCLIMATE pH

- Another factor that can contribute to the deviation of pH-absorption curves from those predicted by the unmodified pH-partition theory is a difference between the luminal pH and the microclimate or virtual pH at the cell membrane.
- The microclimate-pH hypothesis is supported by the fact that  $H^+$  ions are secreted into intestinal lumen.
- Hogerle and Winne attempted to characterize the microclimate directly by measuring the pH at the surface of the jejunal mucosa in vivo. The pH of the luminal solutions was varied over a pH range of 4-10.8.
- In all cases, after lowering the pH electrode down the tips of the villi, the pH shifted towards neutral.

- At a luminal pH of 7, the microclimate pH was 6.4. microclimate pH varied relatively little with changes in luminal pH, ranging from about 5.7-7.4 over the entire luminal pH range. The authors proposed the following relationship between microclimate pH and luminal pH:

$$MpH = A + B (LpH - 7) + C(LpH - 7)^3$$

Where MpH = Microclimate pH

LpH = Luminal pH

$$A = 6.36$$

$$B = 12.2 * 10^{-2}$$

$$C = 10.3 * 10^{-3}$$



## A UNIFYING HYPOTHESIS

- Hogerle and Winne have developed a model for intestinal absorption that accounts for the factors discussed above .
- According to this model ,the absorption rate of a drug may be described by the following equation:
- $$\text{absorption rate} = (C * A) / [(T/D) + 1/P_u(f_u + f_i * p_i/p_u)]$$
- Where C is drug concentration in the lumen, A is the absorptive surface area, T is the thickness of the unstirred layer, D is the diffusion coefficient of the drug ,

- $F_u$ , and  $f_i$  are the fractions of the unionized and ionized forms of the drug, and  $p_u$  and  $p_i$  are the permeability coefficients for the unionized and ionized forms of the drug.
- The extent of dissociation is a function of the  $pK_a$  of the drug and microclimate pH;  $f_u$  and  $f_i$  are calculated from the Henderson - Hasselbalch equation.
- For weak acid,
 
$$pK_a - M_{pH} = \log (f_u/f_i)$$
- And for weak base,
 
$$pK_a - M_{pH} = \log (f_i/f_u)$$
- The microclimate pH ( $M_{pH}$ ) is the function of luminal pH ( $L_{pH}$ ).

## CONCLUSION

- The pH-partition principle has been tested in a large number of in vitro and in vivo studies, and it has been found to be only partly applicable in real biologic systems. In many cases, the ionized as well as unionized forms of a drug partitions are appreciably transported across lipophilic membrane. But the extension of pH-partition theory to incorporate the effects of the unstirred layer and microclimate pH provides a far more satisfactory rationalization of the experimental data

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