Drug. pKa · Lipophilicity · GI-pH-pH partition hypothesis. [BDDJF]

↳ The process of drug absorption from the GIT & its distribution across all biological membranes.

↳ mol.wt >100 → passive diffusion → Abs. govn. by

1. pKa of drug (Dissociation constant).
2. lipid sol. of un-ionized drug Ko/w.
3. pH at abs. site.

↳ Drugs (wk. acids / bases) → Ionization depend upon pH of bio fluids

↙ more ionization ↘ un-ionized

↓

↳ for Abs ↑ 'Hypothesis' more permeation & Abs.

& GI is a simple lipoidal barrier

Large fraction of un-ion. form & more lipophilicity of drug Ko/w.

⟹ Drug. pKa · GI. pH:

drug un-ionized form is a f^n of pKa of drug & pH of body fluids.

↳ Lower the pKa of acidic drug → Strong acid & more ionization.

higher the pKa of basic drug → St. base & more ionization.

Henderson. Hasselbach Eq: → Relative amt. of ionized & un-ionized drug.

for wk. acids:

$$pH = pKa + \log \frac{[\text{Ionized drug}]}{[\text{unionized drug}]}.$$

$$\% \text{ Drug ionized} = \frac{10^{(pH-pKa)}}{1+10^{(pH-pKa)}} \times 100.$$

for wk. bases:

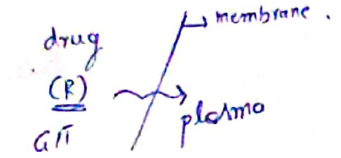
$$pH = pKa + \log \frac{[\text{unionized drug}]}{[\text{ionized drug}]}$$

∴ ionized = unionized.

Log (1) = 0.

pH = pKa

$$\% \text{ Drug ionized} = \frac{10^{(pKa-pH)}}{1+10^{(pKa-pH)}} \times 100.$$



Shore - et al: Theoretical ratio (R)

Wk. acids:

$$P_a = \frac{C_{GIT}}{C_{plasma}} = \frac{1 + 10^{(pH_{GIT} - pK_a)}}{1 + 10^{(pH_{plasma} - pK_a)}}.$$

wk. bases:

$$P_b = \frac{C_{GIT}}{C_{plasma}} = \frac{1 + 10^{(pK_a - pH_{GIT})}}{1 + 10^{(pK_a - pH_{plasma})}}.$$

⇒ pH range Stomach → (1→3). Intestine → (5→8).

↪ Ionisation & Abs. of drugs:

for wk. acids:

1. Very wk. acids ($pK_a > 8.0$) ↪ un-ionised at all pH (pH-independent Abs.) ∴ absorb along GIT.

Ex phenytoin, phenobarbital, Ethosuximide & barbiturates, hexobarbital.

2. mod. wk. acids (pK_a 2.5 - 7.5). ↪ un-ionised in stomach pH → ✓.

Ex: cloxacillin, Aspirin, Ibuprofen, phenylbutazone, NSAIDS. ↳ ionised at Int. pH → ✗. ↳ pH-dependent abs.

3. St. acids ($pK_a < 2.5$) ↪ ionised Entire pH-range of GIT → ✗.

Cromolyn Sodium. → poorly Absorbed.

for basic drugs:

1. very wk. bases ($pK_a < 5.0$): ↪ un-ionised at all pH → ✓.

Ex caffeine, theophylline, diazepam, oxazepam, nitrazepam. pH-independent abs.

2. mod. wk. bases (pK_a 5 - 11.0) ↪ Ionised at Stomach pH → ✗.

morphine, codeine, Heroin, imipramine, amitriptyline, chloroquine un-ionised at Int. pH → ✓.

3. St. bases ($pK_a > 11.0$). ↪ Ionised Entire pH range → ✗.

Guanethidine, mecamylamine.

→ Total aq. solubility (S_T) = Conc^n of ionized drug + Conc^n of un-ionized drug.
(sol). (sol).
↓
Intrinsic solubility.

for acidic drugs

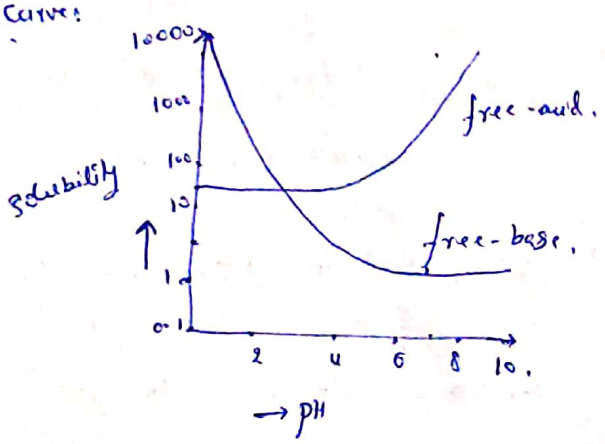
$$S_T = S_a \left[1 + 10^{(pH - pK_a)}\right].$$

S_a → Intrinsic sol^b of wk. Acids.

basic drugs:

$$S_T = S_b \left[1 + 10^{(pK_a - pH)}\right].$$

pH- solubility curve:



for wk. acids:

1- if $pH > pK_a$, $S_T \gg S_a$ → ionisation of drug ↑.

2. $pH = pK_a$, $S_T = 2S_a$ → 50 % of drug ionised.

3. $pH < pK_a$, $S_T \cong S_a$ → un-ionised form of drg → more.

for wk. base:

1. $pH > pK_a$, $S_T \cong S_b$ → un-ionised form.

2. $pH = pK_a$, $S_T \cong 2S_b$ → 50 % of drg ionised.

3. $pH < pK_a$, $S_T \gg S_b$. → ionisation of drg ↑.

Lipophilicity & Drug Absorption:

→ for opt B.A → drug have opt. HLB.
→ Sufficient aq. solubility in fluids at Abs. site
→ penetration of drug through bio-membrane.

drug pka → ionised & unionised
- ionised: ↓ (X) Abs
- unionised: oil sol. ✓ Ko/w ↑ ✓
- ↳ Ko/w ↓, less lipid soluble (X).

→ Lipid solubility measured → log P (P → drug Ko/w).
↳ degree of distribution of drugs bet" lip. solvents (n-octanol) & aq. phase (H_2O / buffer).

Ex. Octanol / pH 7.4 buffer → Ko/w 1→2 → ✓ passive abs.

→ Ionisable drug: ~~not partition into aq. phase.~~

apparent part. coeff (D).

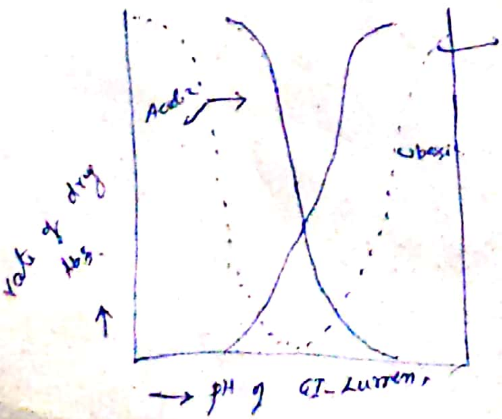
for acidic drugs: $\log D = \log P - \log[1 + 10^{(pH - pKa)}]$

basic drugs $\log D = \log P - \log[1 + 10^{(pKa - pH)}]$.

Limitation of pH-partition hypothesis:

1. presence of virtual membrane pH.
2. Absorption of ionised drug.
3. Influence of GI S.A & residence time of drug.
4. presence of aq. unstirred diffusion layer.

1. presence of v.m. pH:



pH-absorption curve.

for acidic → stomach Abs ↑ Lower pH.

ex. salicylic acid

acidic → shift Right → higher pH.

basic → shift Left → lower pH.

reason: microclimate pH differ from luminal pH.
↳ drug ionisation & Abs.

2) Abs. of ionized drug:

ionized ∠ non-ionized, Abs ↑.

↓ ↳ Abs ↑ ← non-ionic diffusion

Low K/w ⇒ Abs ↓. (3-4)

But: drug ∈ large lipophilic group. → Abs ↑ (passive diffusion)

Ex: morphinan drv.

other mech.
active transport
ion-pair transport.
convective flow.

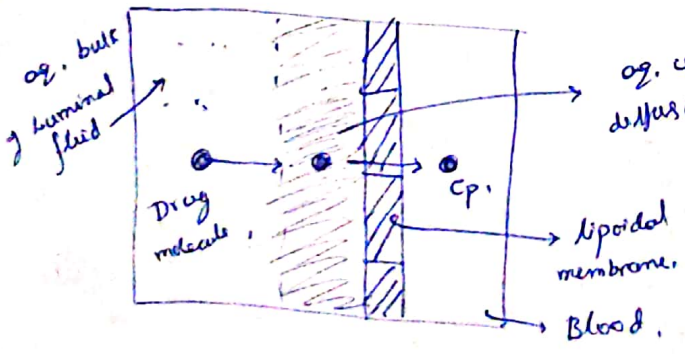
3) Influence of G.I S.A & res. time of drug:

acidic drugs → in stomach abs ↑ ∵ acidic pH
basic drugs → in intestine abs ↑ → alk. pH.
} True if Stomach > Int. S.A is small

→ reach int. → poorly abs
→ reach int → abs ↑.

But practically both H^+/OH^- drugs → Abs ↑ in Intestine.
reason.
Large S.A + Long res. time.

4) presence of aq. unstirred diffusion layer:



aq. unstirred → bulk of luminal fluid not contact ∈ lipoidal membrane.
↳ THICKNESS ∈ barrier → RDS

If drug Ko/w → ↑ penetration to lipid.
RDS → pen. to aq. unstirred.
Ex. fatty acids ∈ bile acids.

opt HLB

Drug permeability & Abs:

↳ drug abs. (M).

$$M = C_{app} \cdot A \cdot P_{eff} \cdot t_{res}$$

M → amt. of drug absorbed · P_{eff} → Effective membrane permeability,

A → S.A. available for Abs, t_{res} → resi. time of drug in GI Lumen.

C → apparent luminal drug conc.

M ↑ → (A) → not changable so, P_{eff} ↑ · C_{app}.

↳ factors: determine drug passive transport.

1) Lipophilicity of drug (Log P).

2) polarity of drug (no. of H-bond acceptors & H-bond donors)

3) mol. size.

↳ Rule of five — Lipinski

↳ mol. wt ≤ 500 ; lipophilicity Log P ≤ 5 — 1/3 → 1-2.

No. of H-bond acceptors ≤ 10 ; no. of H-bond donors ≤ 5.

Drug - stability:

↳ destabilization — during shelf life (or) in GIT.

↳ drug degradation into inactive form,

↳ form complex & GIT components / fluids.

↳ drug. expt. interactions.

Stereochemical nature of drug: Chiral drugs → 60%.

↳ Racemic mixtures.

↳ Optical isomers → differ in potency & physiological response & Effect. A.D.M.E ||.

Enantiomers → diff in spatial configuration.

↳ protein binding ↳ Stereoselectivity.

Carrier - mediated transport.