Physical-Chemistry Factors Affecting Oral Absorption

Objectives

- Understand the physical-chemical factors that affect oral absorption
- Understand the pH-partition hypothesis as it applies to drug absorption
- Understand Fick's first law as it applies to dissolution

pH - Partition Theory

- Drug will cross membranes better if lipid soluble
- Drugs with acid-base character may be unionized or ionized
- Fraction unionized determined by pH and pKa

pH - Partition Experiments

- Brodie (1957) proposed the pH- partition theory
- Perfused stomach or intestine of rat
- Drug given by IV - varied [drug] until no net transfer
- Measured pH and pKa

pH - Partition Experiment

Brodie D Value

- Determined Ratio, D

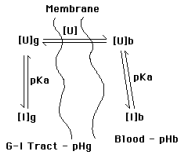
$$D = \frac{\text{Total Concentration in Blood}}{\text{Total Concentration in GI Tract}}$$

- Considering ionized and unionized drug

$$D = \frac{[U]_B + [I]_B}{[U]_G + [I]_G}$$

Schema

- Transfer Across Membrane



At Equilibrium $[U]_G = [U]_B$

Calculation of D

- From theory using Henderson - Hasselbach Equation
  - For weak acids

$$pKa - pH = \log\frac{[U]}{[I]} = \log\frac{[HA]}{[A^-]}$$

  - For weak bases

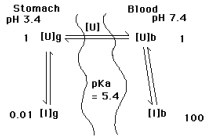
$$pKa - pH = \log\frac{[I]}{[U]} = \log\frac{[HB^+]}{[B]}$$

Conclusion

- Brodie found good correlation between experimental and theoretical results
- Theory gives equilibrium result which may provide concentration gradient which in turn may affect rate of absorption

Example Calculation

- Absorption of a Weak Acid from the Stomach



The Equations

Stomach > $\frac{[U]}{[I]} = 10^{pKa-pH} = 10^{5.4-3.4} = 100$

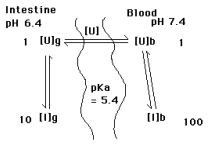
- i.e. [I] = 0.01 x [U]

Blood > $\frac{[U]}{[I]} = 10^{pKa-pH} = 10^{5.4-7.4} = 0.01$

- i.e. [I] = 100 x [U]

$$D = \frac{[I]_B + [U]_B}{[I]_G + [U]_G} = \frac{[U]_B}{[U]_G} \bullet \left(\frac{100+1}{0.01+1}\right) = 100$$

Example Calculation



The Equations

Stomach > $\frac{[U]}{[I]} = 10^{pKa-pH} = 10^{5.4-6.4} = 0.1$

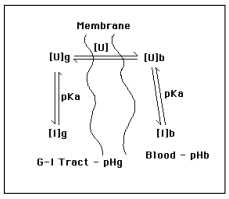
i.e. [I] = 10 x [U]

Blood > $\frac{[U]}{[I]} = 10^{pKa-pH} = 10^{5.4-7.4} = 0.01$

i.e. [I] = 100 x [U]

$$D = \frac{[I]_B + [U]_B}{[I]_G + [U]_G} = \frac{[U]_B}{[U]_G} \cdot \left[\frac{100+1}{10+1}\right] = 9.2$$

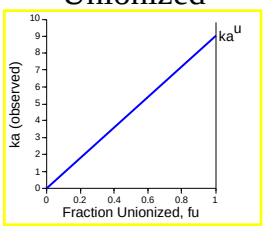
More Examples…



Don't Forget Surface Area

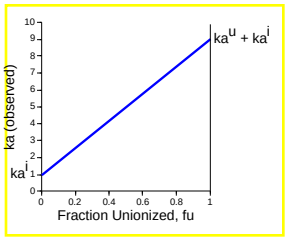
- Previous examples suggests fast absorption of weak acids from the stomach compared with the intestine
- Difference in effective surface area may be more significant
- HH equation will resurface in Chapter on excretion

Absorption versus Fraction Unionized



$ka_{observed} = ka^u \bullet fu$

Absorption versus Fraction Unionized



Ionic absorption - carrier blocking charge

pH - Partition Theory

- Comments
  - Useful for comparing similar compounds under similar conditions (sites)
    - Altered pH (same site)
    - Altered pKa (similar compounds)
  - ka^i from ion-pair absorption or facilitated transport
  - Surface area more important for overall absorption

Drug Dissolution

- Before the drug can transfer through the membrane it must be in solution
- Dissolution: From solid to solution

Dissolution Absorption
Solid ----------> Solution ----------> Blood
GI Tract

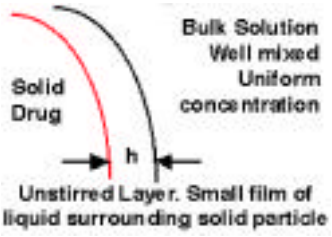
- Which is Rate Determining Step?
  - Dissolution or Absorption!

Drug Dissolution

- High Dose
- Low Solubility
  - Below 1 g per 100 ml
  - e.g. Griseofulvin

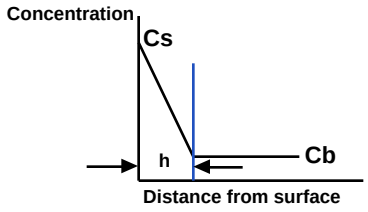
Stagnant Layer Model

- For drug dissolution



Stagnant Layer Model

- After steady state a concentration gradient is established



Fick's First Law again

$$\text{Rate of Solution} = \frac{D \cdot A \cdot (Cs - Cb)}{h}$$

- D: Diffusion Coefficient
- A: Surface Area
- Cs: Solubility
- Cb: Concentration in Bulk Liquid
- h: Stagnant Layer Thickness

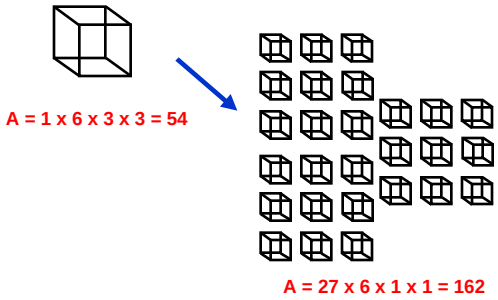
Sink Conditions

- Cb << Cs

$$\text{Rate of Solution} = \frac{D \cdot A \cdot Cs}{h}$$

- Other Models
- Other Conditions

Surface Area



A = 1 x 6 x 3 x 3 = 54

A = 27 x 6 x 1 x 1 = 162

Surface Area

- Break particles into many smaller particles
  - Increases total surface area
  - Irregular shapes even larger surface area
- Examples include griseofulvin and digoxin

Particle Size Reduction

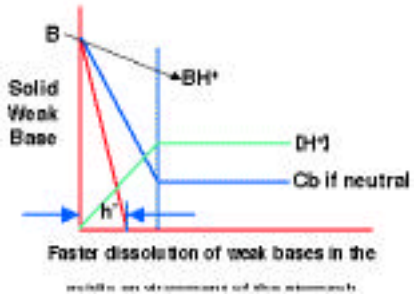
- Mortar and pestle
- Mechanical grinders
- Fluid energy mills
- Solid dispersion in soluble material

Remington's Pharmaceutical Sciences 15th ed., 1975 p 1555 and 1561
Ansel, Allen, Popovich Pharmaceutical Dosage Forms and Delivery Systems, 7th ed., p166

Diffusion Layer Thickness

- Agitation determines thickness
  - Little control *in vivo*
- Important with *in vitro* dissolution testing
  - Agitation must be controlled
- Dissolution into reactive medium can change the 'effective' thickness

Reactive Medium

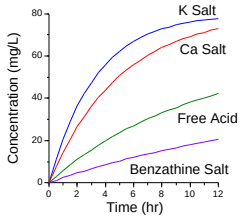


Diffusion Coefficient

- Size of molecule
- Viscosity of medium
  - Increase viscosity to reduce dissolution
  - Possible sustained release

Drug Solubility

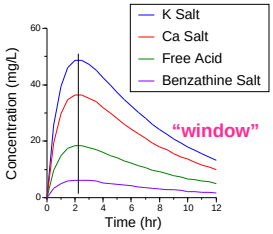
- Salt Form - Dissolution



Penicillin V

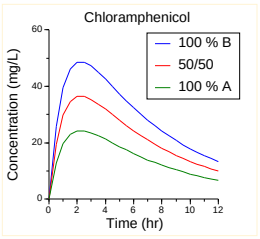
Drug Solubility

- Salt Form - *In vivo* Result



Crystal Form

- or polymorph



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