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 $[U]_c = [U]_b$

Calculation of D

- From theory using Henderson - Hasselbach Equation
  - For weak acids
    \[ pK_a - pH = \log \frac{[U]}{[I]} = \log \frac{[HA]}{[A^-]} \]
  - For weak bases
    \[ pK_a - pH = \log \frac{[I]}{[U]} = \log \frac{[HB^+]}{[B]} \]

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

• i.e. \([I] = 0.01 \times [U] \)

Blood > \[ \frac{[U]}{[I]} = 10^{pK_a-pH} = 10^{7.4-3.4} = 0.01 \]

• i.e. \([I] = 100 \times [U] \)

\[
\begin{align*}
D &= \frac{[I_b] + [U_b] - [I_b] \left[ 0.01 + 1 \right] - [U_b]}{[I_b] + [U_b] - [I_b] \left[ 0.01 + 1 \right] - [U_b]} \\
&= \frac{100}{100} = 1
\end{align*}
\]
The Equations

\[
\frac{[U]}{[I]} = 10^{pK_a - pH} = 10^{5.4 - 6.4} = 0.1
\]

i.e. \([I] = 10 \times [U]\)

\[
\frac{[U]}{[I]} = 10^{pK_a - pH} = 10^{5.4 - 7.4} = 0.01
\]

i.e. \([I] = 100 \times [U]\)

\[D = \frac{[I]_{[U]} + [U]_{[I]}}{[I]_{[U]} + [U]_{[I]}} \cdot \frac{[100 + 1]}{[100 + 1]} = 9.2\]


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

\[ ka_{\text{observed}} = ka^u \cdot fu \]

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)
  - \( ka' \) 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
  - Solid $\xrightarrow{\text{Dissolution}}$ Solution $\xrightarrow{\text{Absorption}}$ Blood
  - 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.

\[ C_b \]  
\[ C_s \]  
\[ h \]  
Distance from surface

Fick’s First Law (again)
- Rate of Solution: \( D \cdot A \cdot \frac{(C_s - C_b)}{h} \)
- D: Diffusion Coefficient
- A: Surface Area
- C_s: Solubility
- C_b: Concentration in Bulk Liquid
- h: Stagnant Layer Thickness

Sink Conditions
- \( C_b << C_s \)
  - Rate of Solution: \( D \cdot A \cdot \frac{C_s}{h} \)

- Other Models
- Other Conditions
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

![Graph showing concentration vs. time for different forms of Penicillin V](image1)

- K Salt
- Ca Salt
- Free Acid
- Benzathine Salt

Penicillin V

Drug Solubility

• Salt Form - *In vivo* Result

![Graph showing concentration vs. time for different forms of Penicillin V](image2)

- K Salt
- Ca Salt
- Free Acid
- Benzathine Salt

Crystal Form

• or polymorph

![Graph showing concentration vs. time for Chloramphenicol](image3)

- 100% B
- 50/50
- 100% A
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