The Influence of Physicochemical Properties on ADME

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Physchem and ADME

A quick tour of the influence of physicochemical properties on:

Absorption
Distribution
Metabolism
Excretion
Absorption: solubility & permeability

- Aqueous solubility is a prerequisite for absorption
- Aqueous solubility and membrane permeability tend to work in “opposite directions”
- Therefore, a balance of physicochemical properties is required to give optimal absorption
Absorption: solubility & permeability

Absorption: permeability

- Transcellular (Passive diffusion)
  - Concentration gradient (Fick’s law)
  - Lipid solubility
  - Degree of ionisation
  - Hydrogen bonding
  - Size/shape
  - …………..
- Paracellular (passage through cell junctions and aqueous channels)
- Active transport
Permeability: Caco2 assay

\[ y = -0.2183x^2 + 0.8639x + 0.4508 \]

\[ R^2 = 0.5362 \]

Strong relationship between permeability and logD

Riley et al., (2002)
Current Drug Metabolism, 3, p527
Permeability: Caco2 assay

- Issues of Solubility and membrane retention
Absorption - ionisation

- The central principle is that only unionised (neutral) form of drugs will cross a membrane.
Absorption - ionisation

• In man, stomach is ~ pH 2 and small intestine ~ pH 6

(weak) ACIDS
• Unionised form is more prevalent in the stomach.
• Although some absorption of acids takes place in the stomach, absorption also occurs in small intestine due to:
  • Very large surface area (600x cylinder)
  • Removal of cpd by PPB & blood flow
  • Ionisation of cpd in blood shifts equilibrium in favour of absorption

(weak) BASES
• Unionised form is more prevalent in the small intestine.
• Bases are well absorbed from small intestine
  • Very large surface area
  • Removal of cpd by blood flow
  • Ionisation equilibrium is countered by distributional factors
Absorption – H-bonding

• Diffusion through a lipid membrane is facilitated by “shedding” H-bonded water molecules
• The higher the H-bonding capacity, the more energetically-unfavourable this becomes
Absorption: PSA

- The hydrogen-bonding potential of a drug may be expressed as “Polar Surface Area” (PSA)
- Polar surface area is defined as a sum of surfaces of polar atoms (usually oxygens, nitrogens) and their attached hydrogens

Distribution of Polar Surface Area for orally administered CNS (n=775) and non-CNS (n=1556) drugs that have reached at least Phase II efficacy trials. After Kelder et al., (1999) Pharmaceutical Research, 16, 1514
Oral drug properties

- Lipinski’s “Rule of 5”: Poor absorption is more likely when:
  - Log P is greater than 5,
  - Molecular weight is greater than 500,
  - There are more than 5 hydrogen bond donors,
  - There are more than 10 hydrogen bond acceptors.

- Together, these parameters are descriptive of solubility
Oral drug properties

Molecular weight and lipophilicity

- Molecular weight (Mwt) distribution
- ACDlogP distribution
Oral drug properties

Hydrogen bonding

- The number of rotatable bonds (molecular flexibility) may also be important.............
Oral drug properties

<table>
<thead>
<tr>
<th></th>
<th>95th (5th) percentile</th>
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<tbody>
<tr>
<td></td>
<td>Non-CNS</td>
</tr>
<tr>
<td>Mol. Wt.</td>
<td>611</td>
</tr>
<tr>
<td>PSA</td>
<td>127</td>
</tr>
<tr>
<td>HBA</td>
<td>9</td>
</tr>
<tr>
<td>HBD</td>
<td>5</td>
</tr>
<tr>
<td>Rot. Bond</td>
<td>14</td>
</tr>
<tr>
<td>cLogP</td>
<td>6.2 (-1.2)</td>
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</table>

- In general, CNS drugs are smaller, have less rotatable bonds and occupy a narrower range of lipophilicities. They are also characterised by lower H-bonding capacity.
Are Leads different from Drugs?

- Mean increase in properties going from Lead to Drug

<table>
<thead>
<tr>
<th></th>
<th>ΔMW</th>
<th>ΔHAC</th>
<th>ΔRTB</th>
<th>ΔHDO</th>
<th>ΔcLogP</th>
<th>ΔcLogD</th>
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<tbody>
<tr>
<td>Mean</td>
<td>89</td>
<td>1.0</td>
<td>2.0</td>
<td>0.2</td>
<td>1.16</td>
<td>0.97</td>
</tr>
</tbody>
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- If, as a result of Lead “Optimisation”, our compounds become bigger and more lipophilic, we need to make sure that we start from Lead-Like properties rather than Drug-Like properties.
Distribution: Plasma and Tissue binding

- The extent of a drug’s distribution into a particular tissue depends on its affinity for that tissue relative to blood/plasma.
- It can be thought of as “whole body chromatography” with the tissues as the stationary phase and the blood as the mobile phase.
- Drugs which have high tissue affinity relative to plasma will be “retained” in tissue (extensive distribution).
- Drugs which have high affinity for blood components will have limited distribution.
The major plasma protein is albumin (35-50 g/L) which contains lipophilic a.a. residues as well as being rich in lysine.

There is a trend of increasing binding to albumin with increasing lipophilicity. In addition, acidic drugs tend to be more highly bound due to charge-charge interaction with lysine.

Bases also interact with alpha1-acid gp (0.4-1.0 g/L).
Plasma and Tissue binding (pH 7.4)

- Tissue cell membranes contain negatively-charged phospholipid
- Bases tend to have affinity for tissues due to charge-charge interaction with phosphate head-group
- Acids tend not to have any tissue affinity due to charge-charge repulsion with phosphate head-group

\[
\text{R-NH}_3^+ \quad \text{O} \quad \text{R-O}^- \\
\]

\[
\text{Organon} \\
\text{Iain Martin; Physchem Forum 2} \\
19
\]
Distribution - $V_{ss}$

- What effect does plasma and tissue binding have on the values of $V_{ss}$ that we observe?

\[ V_{ss} = V_p + \left( V_T \frac{f_{up}}{f_{uT}} \right) \]

- $V_p$ = physiological volume of plasma
- $V_T$ = physiological volume of tissue(s)
- $f_{up}$ = fraction unbound in plasma
- $f_{uT}$ = fraction unbound in tissue(s)
**Acids** tend to be highly plasma protein bound; hence $fu_P$ is small.

- Acids have low tissue affinity due to charge repulsion; hence $fu_T$ is large.
- Acids therefore tend to have low $V_{SS}$ (< 0.5 L/kg).
**Distribution - \( V_{ss} \)**

- **Neutrals** have affinity for both plasma protein and tissue.
- Affinity for both is governed by lipophilicity.
- Changes in logD tend to result in similar changes (in direction at least) to both \( f_{u_P} \) and \( f_{u_T} \).
- Neutrals tend to have moderate \( V_{ss} \) (0.5 – 5 L/kg).

\[
V_{ss} = V_p + (V_T \cdot \frac{f_{u_P}}{f_{u_T}})
\]
Distribution - $V_{ss}$

- **Bases** have higher affinity for tissue due to charge attraction
- $fu_p$ tends to be (much) larger than $fu_T$
- Bases tend to have high $V_{ss}$ (>3 L/kg)

\[ V_{ss} = V_p + (V_T \cdot \frac{fu_p}{fu_T}) \]
**Distribution - $V_{ss}$**

\[ V_{ss} = V_p + (V_T \cdot \frac{f_{up}}{f_{ut}}) \]

### Clinically-used Drugs

![Graph showing the distribution of clinically-used drugs with LogD on the x-axis and Vss (L/kg) on the y-axis. The graph includes data points for Acid (red squares), Base (blue diamonds), and Neutral (green triangles).](image-url)
Distribution – effect of pH

• Distribution
  – Ion trapping of basic compounds

• Distribution/Excretion
  – Aspirin overdose & salicylate poisoning
**Distribution: Ion trapping**

- Ion trapping can occur when a drug distributes between physiological compartments of differing pH.
- The equilibrium between ionised and unionised drug will be different in each compartment.
- Since only unionised drug can cross biological membranes, a drug may be “trapped” in the compartment in which the ionised form is more predominant.
- Ion trapping is mainly a phenomenon of basic drugs since they tend to distribute more extensively and ..........
- The cytosolic pH of metabolically active organs tends to be lower than that of plasma, typically pH 7.2.
Distribution: Ion trapping

- Ion trapping of a weak base pKa 8.5
Ion trapping: lysosomes

- Lysosomes are membrane-enclosed organelles
- Contain a range of hydrolytic enzymes responsible for autophagic and heterophagic digestion
- Abundant in Lung, Liver, kidney, spleen with smaller quantities in brain, muscle
- pH maintained at ~5 (4.8).
Ion trapping: lysosomes

- Ion trapping of a weak base pH 8.5
Ion trapping: lysosomes

- Effect of lysosomal uptake is more profound for dibasics
- Theoretical lysosome:plasma ratio of ~ 160,000
- Apparent volume of liver may be 1000 X physical volume
- Azithromycin achieves in vivo tissue: plasma ratios of up to 100-fold and is found predominantly in lysosome-rich tissues

Erythromycin $V_{ss} = 0.5 \, \text{L/kg}$

Azithromycin $V_{ss} = 28 \, \text{L/kg}$
Salicylate poisoning

- Aspirin (acetylsalicylic acid) is metabolised to the active component – salicylic acid
- Due to its acidic nature and extensive ionisation, salicylate does not readily distribute into tissues
- But after an overdose, sufficient salicylate enters the CNS to stimulate the respiratory centre, promoting a reduction in blood CO₂
- The loss of blood CO₂ leads a rise in blood pH - respiratory alkalosis
Salicylate poisoning

• The body responds to the alkalosis by excreting bicarbonate to reduce blood pH back to normal
• In mild cases, blood pH returns to normal. However in severe cases (and in children) blood pH can drop too far leading to metabolic acidosis
• This has further implications on the distribution of salicylate, its toxicity and subsequent treatment
Salicylate poisoning

Acidosis leads to increase in unionised salicylate in the blood, promoting distribution into brain resulting in CNS toxicity.

This is treated with bicarbonate which increases blood pH and promotes redistribution out of the CNS.
Salicylate poisoning

- Unbound fraction of both species is filtered; Only neutral species is reabsorbed

- bicarbonate increases urine pH leading to significantly decreased reabsorption and hence increased excretion
As a general rule, liability to metabolism increases with increasing lipophilicity. However, the presence of certain functional groups and SAR of the metabolising enzymes is of high importance.
Metabolism vs. Excretion

- Effect of logD on renal and metabolic clearance for a series of chromone-2-carboxylic acids

Replotted from Smith et al., (1985) Drug Metabolism Reviews, 16, p365

- Balance between renal elimination into an aqueous environment and reabsorption through a lipophilic membrane
Renal Excretion

- Effect of LogD on renal clearance of β-blockers


- Note that only unbound drug is filtered and that PPB increases with logD
Summary

• ADME processes are determined by the interaction of drug molecules with:
  – Lipid membranes
  – Plasma and tissue proteins
  – Drug metabolising enzymes
  – Transporters

• These interactions are governed, to a large extent, by the physicochemical properties of the drug molecules

• Understanding the influence of these properties is therefore pivotal to understanding ADME and can lead to predictive models

• In general, good (oral) ADME properties requires a balance of physicochemical properties

• Lead Optimisation needs “physicochemical room” to optimise
• MacIntyre and Cutler (1988). The potential role of lysosomes in the tissue distribution of weak bases. Biopharmaceutics and Drug Disposition, 9, 513-526


