The Influence of Physicochemical Properties on ADME

Iain Martin

Physchem and ADME

A quick tour of the influence of physicochemical properties on:

Absorption

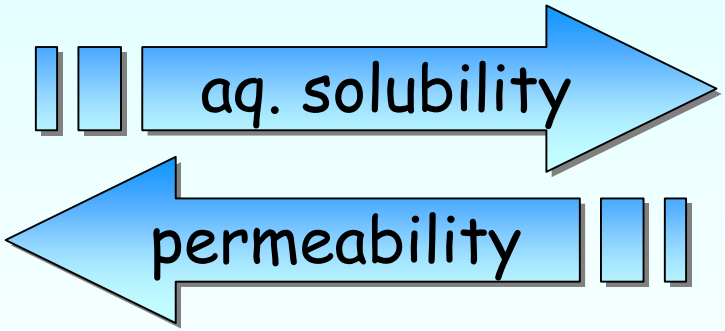
Distribution

Metabolism

Excretion

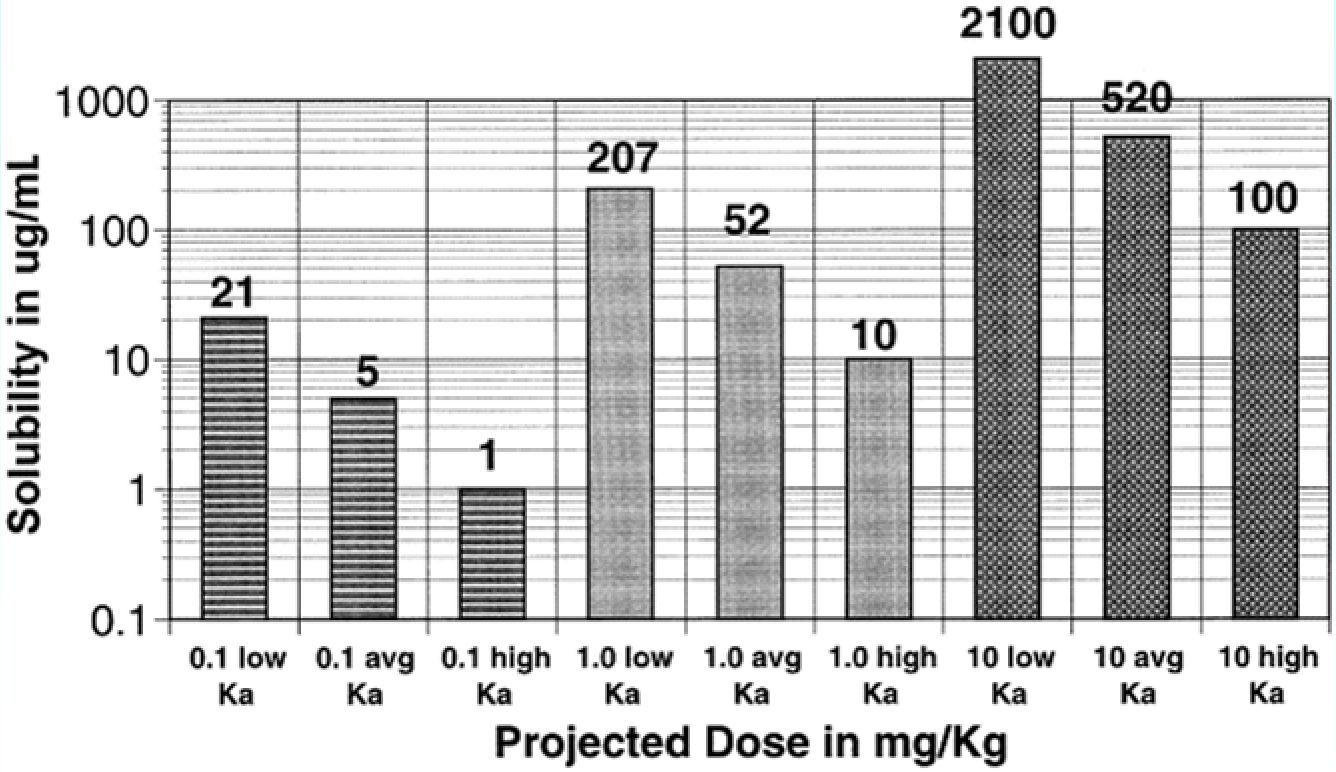
Absorption: solubility & permeability

- 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

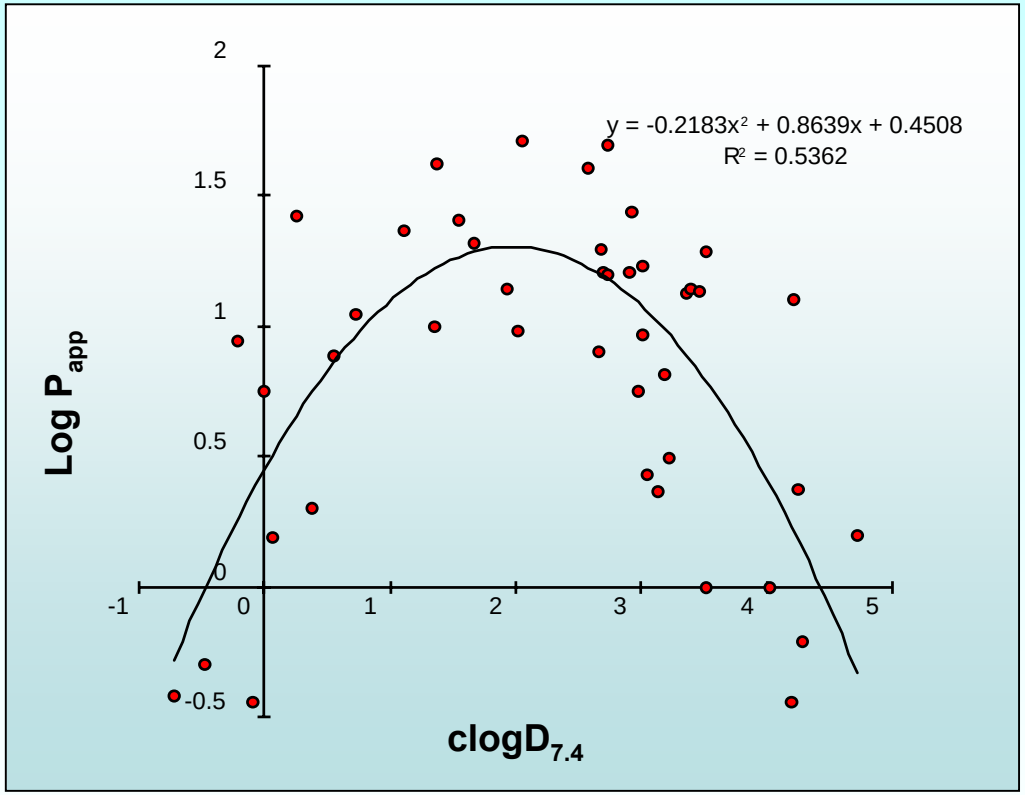


Lipinski (2000) *J. Pharmacol. Toxicol. Meth.*, **44**, p235

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

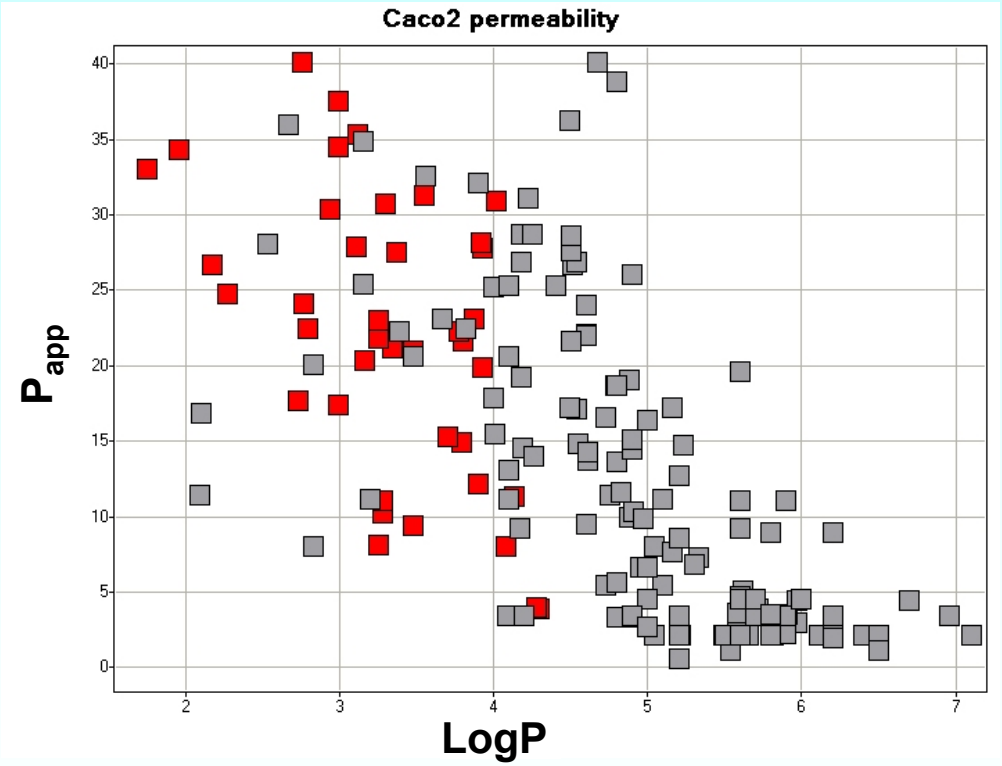
Permeability: Caco2 assay



Riley *et al.*, (2002) *Current Drug Metabolism*, **3**, p527

Strong relationship between permeability and logD

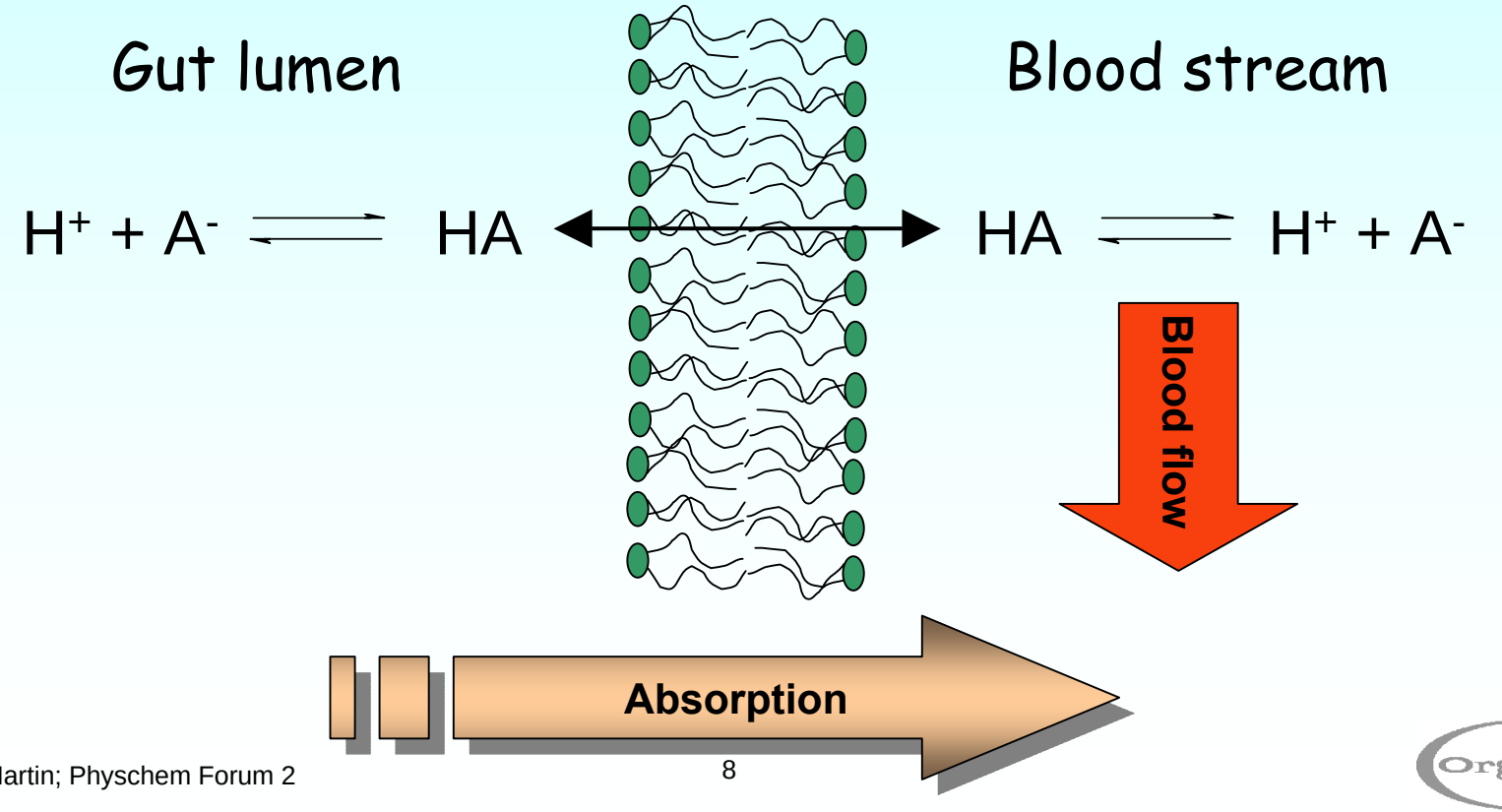
Permeability: Caco2 assay



- 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

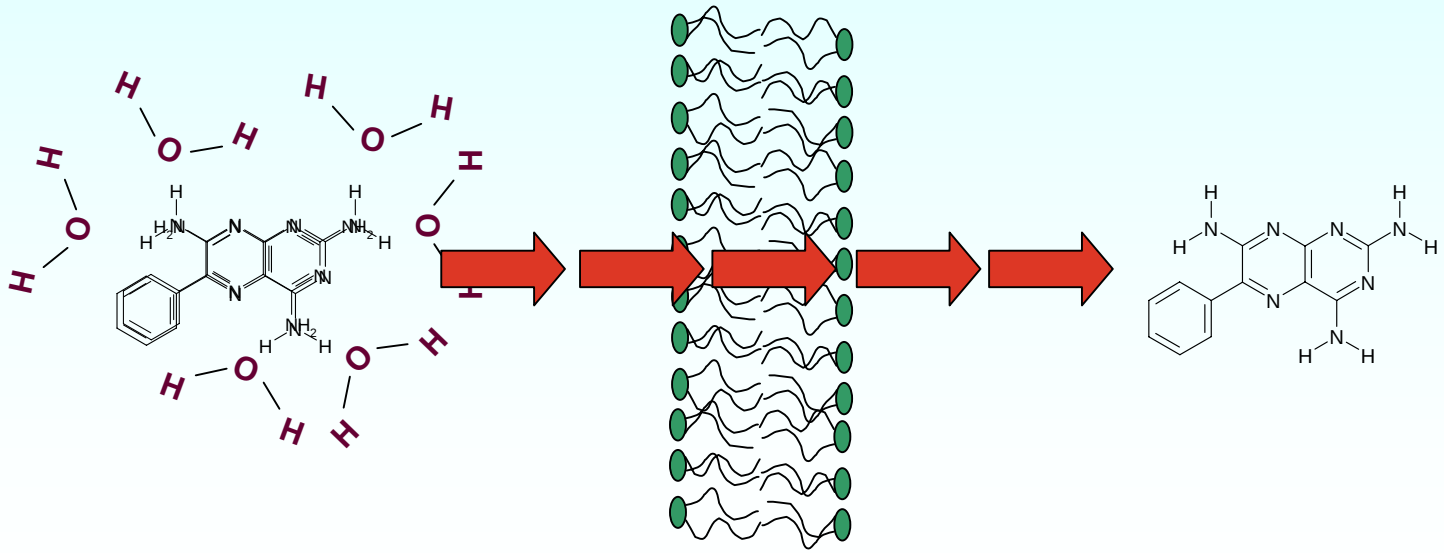
- Unionised form is more prevalent in the stomach.
- Although some absorption of acids takes place in the stomach, absorption also occurs in small intestine due to:
  - Very large surface area (600x cylinder)
  - Removal of cpd by PPB & blood flow
  - Ionisation of cpd in blood shifts equilibrium in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

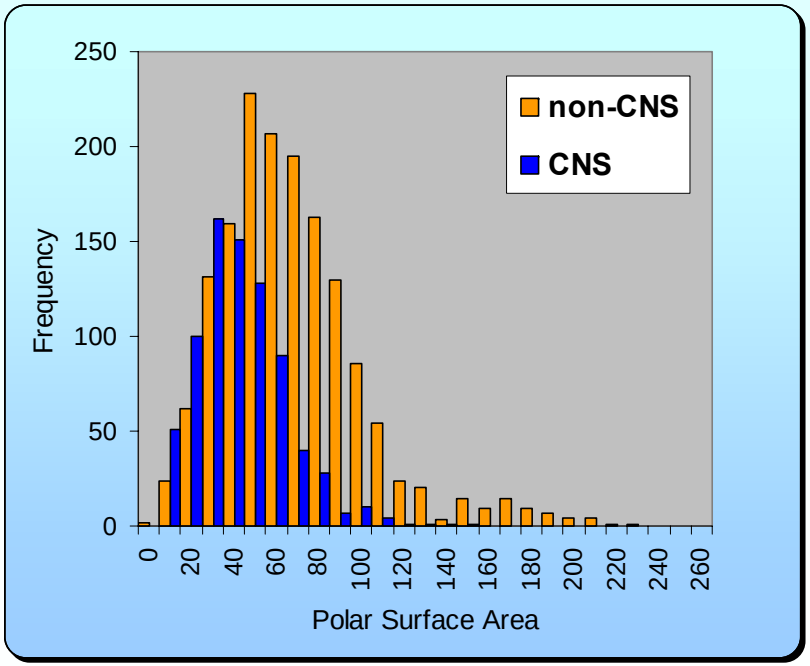
Absorption – H-bonding

- 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

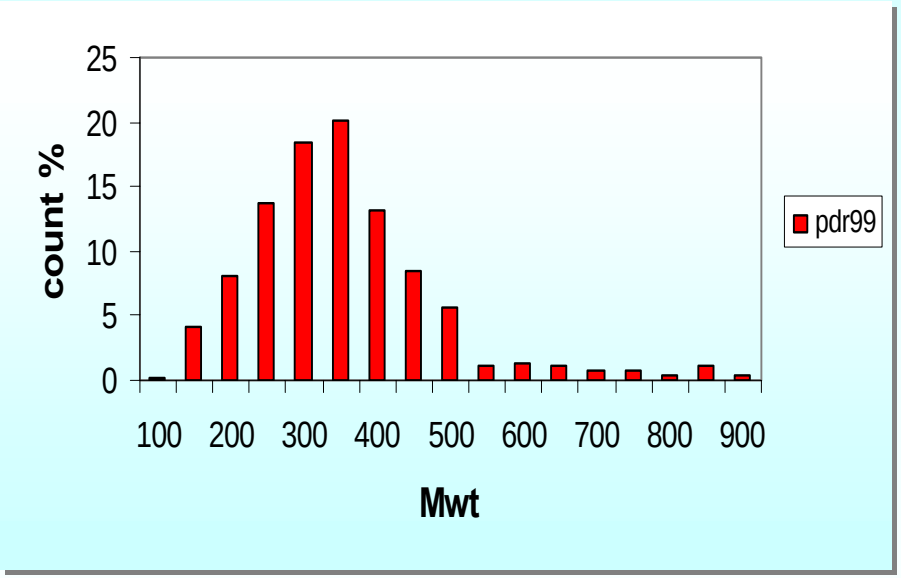
Oral drug properties

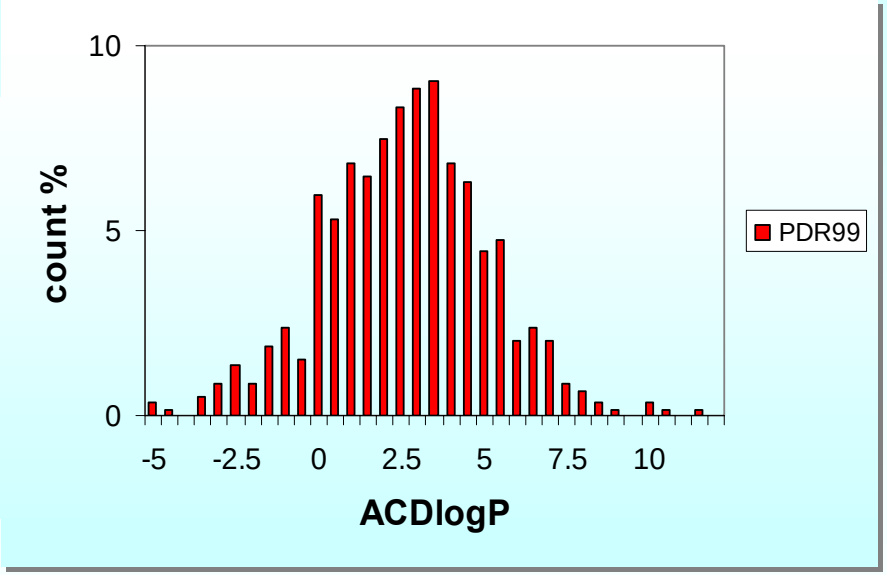
- Lipinski's "Rule of 5": Poor absorption is more likely when:
  - Log P is greater than 5,
  - Molecular weight is greater than 500,
  - There are more than 5 hydrogen bond donors,
  - There are more than 10 hydrogen bond acceptors.

- Together, these parameters are descriptive of solubility

Oral drug properties

Molecular weight and lipophilicity

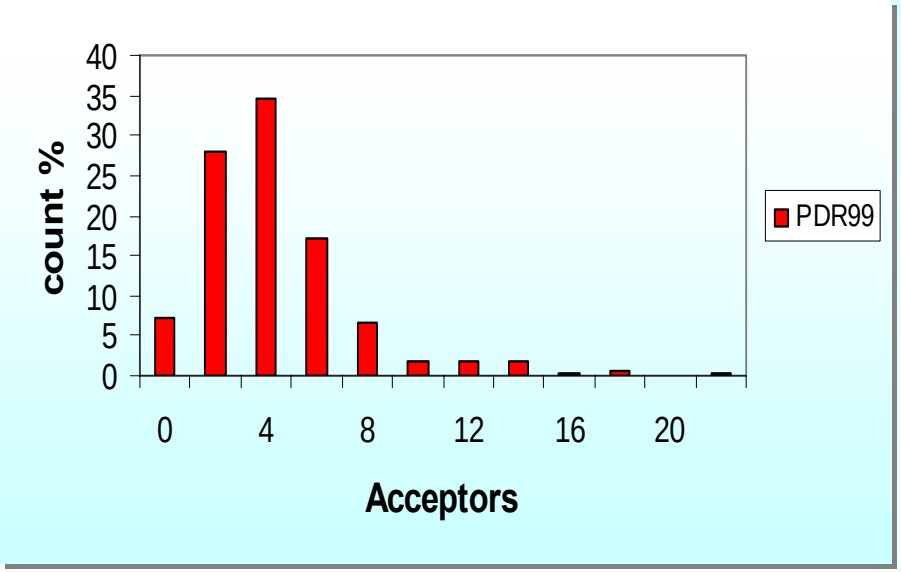


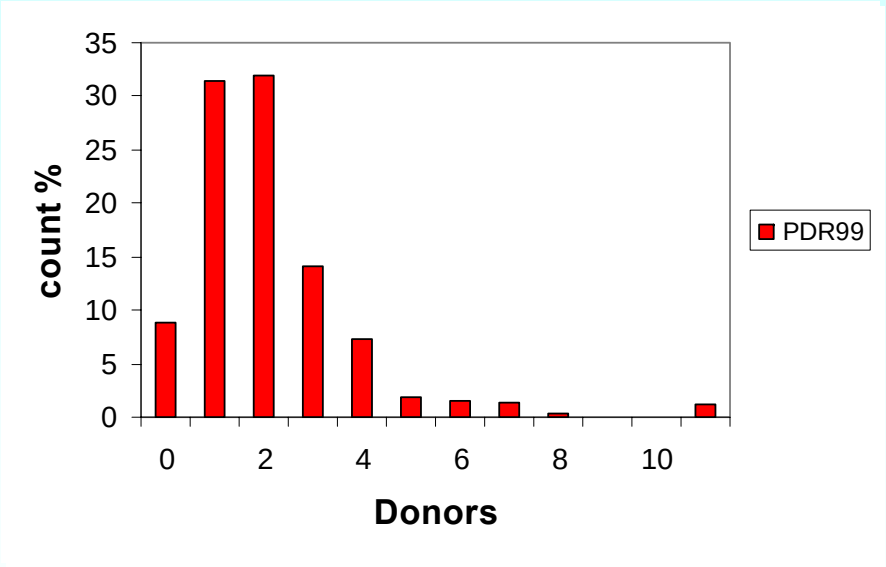


Organon

Oral drug properties

Hydrogen bonding





- The number of rotatable bonds (molecular flexibility) may also be important……..

Oral drug properties

	95th (5th) percentile	
	Non-CNS	CNS
Mol. Wt.	611	449
PSA	127	73
HBA	9	5
HBD	5	3
Rot. Bond	14	9
cLogP	6.2 (-1.2)	5.7 (0.4)

- 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?

- Oprea et al., (2001). Property distribution analysis of leads and drugs.
- Mean increase in properties going from Lead to Drug

	ΔMW	ΔHAC	ΔRTB	ΔHDO	ΔcLogP	ΔcLogD
Mean	89	1.0	2.0	0.2	1.16	0.97

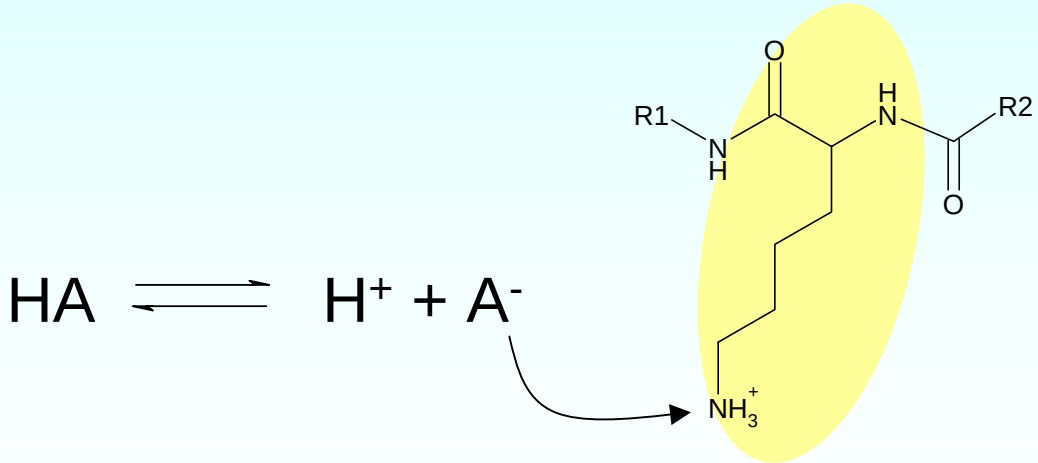
- If, as a result of Lead "Optimisation", our compounds become bigger and more lipophilic, we need to make sure that we start from Lead-Like properties rather than Drug-Like properties

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

Distribution: Plasma and Tissue binding

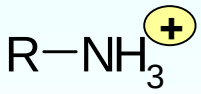
- The major plasma protein is albumin (35-50 g/L) which contains lipophilic a.a. residues as well as being rich in lysine
- There is a trend of increasing binding to albumin with increasing lipophilicity. In addition, acidic drugs tend to be more highly bound due to charge-charge interaction with lysine

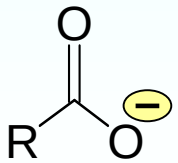


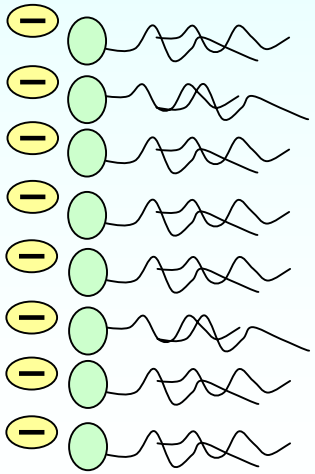
- Bases also interact with alpha1-acid gp (0.4-1.0 g/L)

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







Distribution - V_{ss}

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

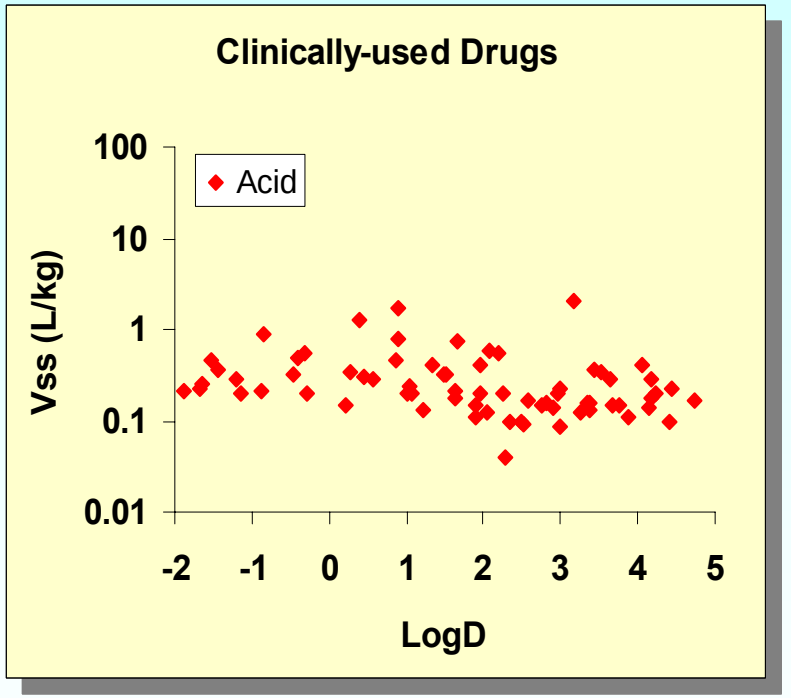
$$V_{SS} = V_p + (V_T . \frac{fu_P}{fu_T})$$

V_p = physiological volume of plasma
V_T = physiological volume of tissue(s)
fu_p = fraction unbound in plasma
fu_T = fraction unbound in tissue(s)

Distribution - V_{ss}

$$V_{SS} = V_p + (V_T . \frac{fu_P}{fu_T})$$

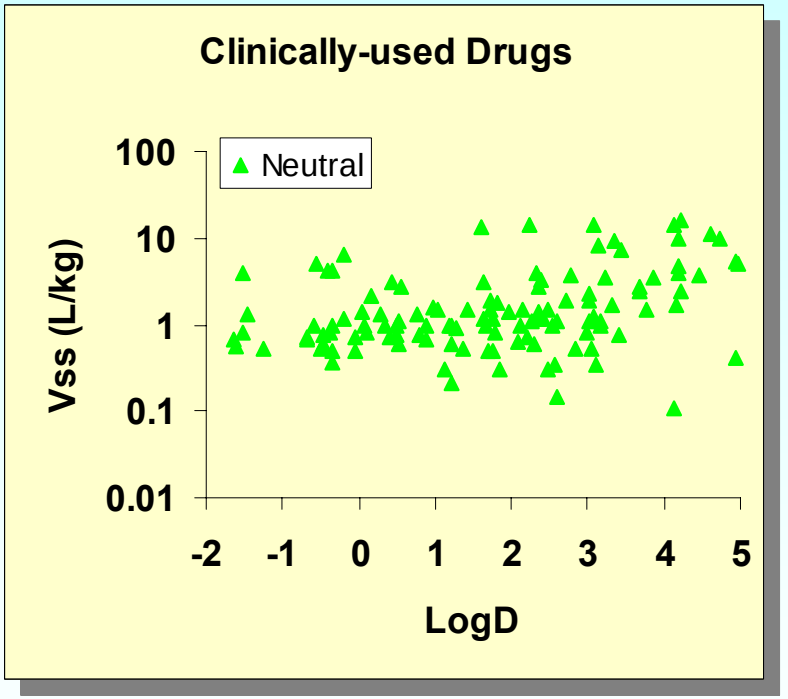
- Acids tend to be highly plasma protein bound; hence fu_P is small
- Acids have low tissue affinity due to charge repulsion; hence fu_T is large
- Acids therefore tend to have low V_{SS} (< 0.5 L/kg)



Distribution - V_{ss}

$$V_{SS} = V_p + (V_T . \frac{fu_P}{fu_T})$$

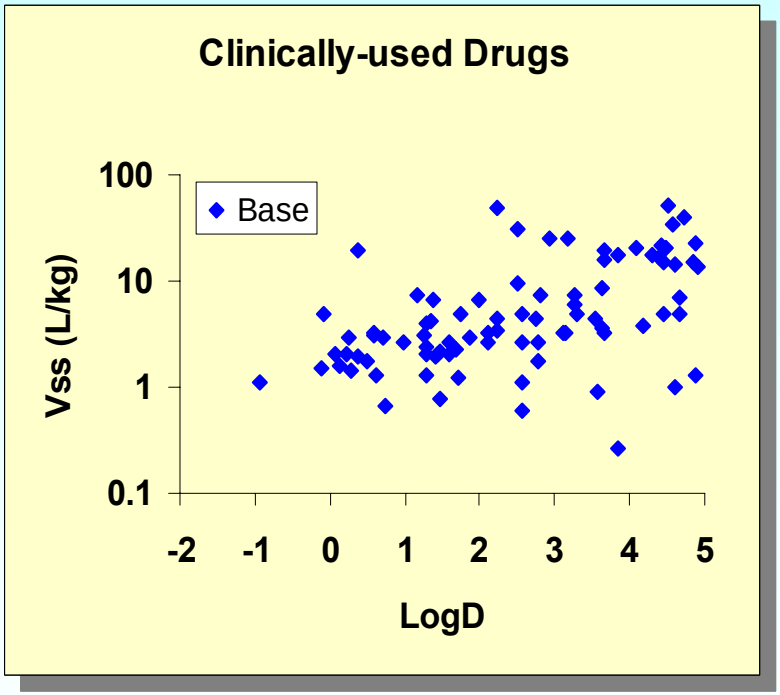
- Neutrals have affinity for both plasma protein and tissue
- Affinity for both is governed by lipophilicity
- Changes in logD tend to result in similar changes (in direction at least) to both fu_P and fu_T
- Neutrals tend to have moderate V_{SS} (0.5 – 5 L/kg)



Distribution - V_{ss}

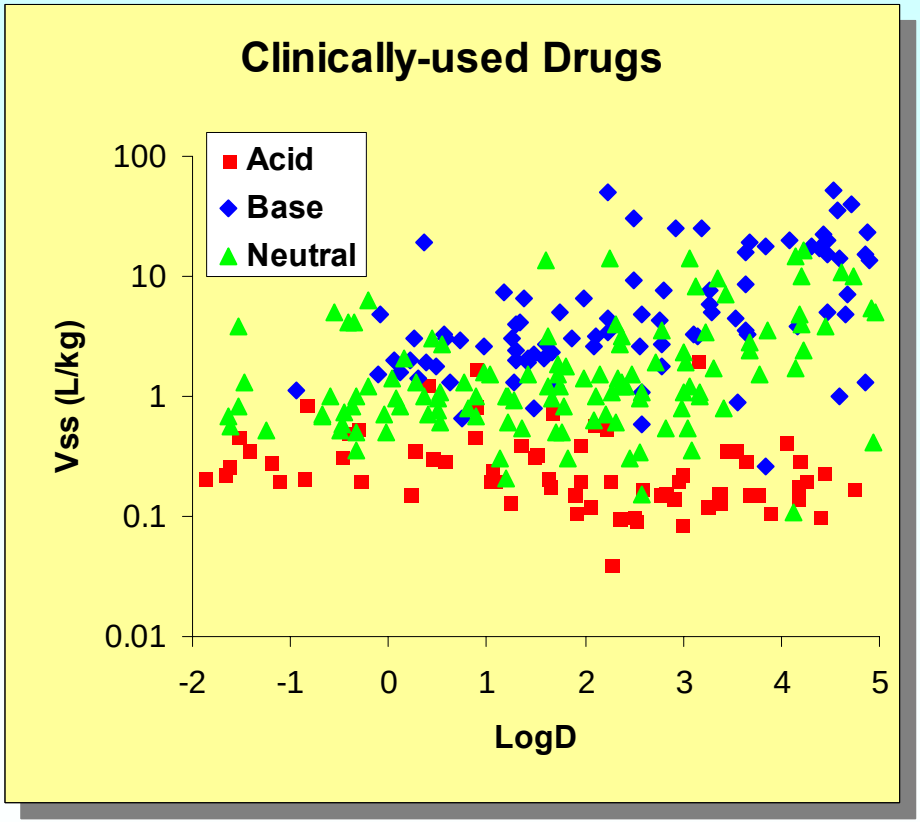
$$V_{SS} = V_p + (V_T . \frac{fu_P}{fu_T})$$

- 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)



Distribution - V_{ss}

$$V_{SS} = V_p + (V_T . \frac{fu_P}{fu_T})$$



Organon

Distribution – effect of pH

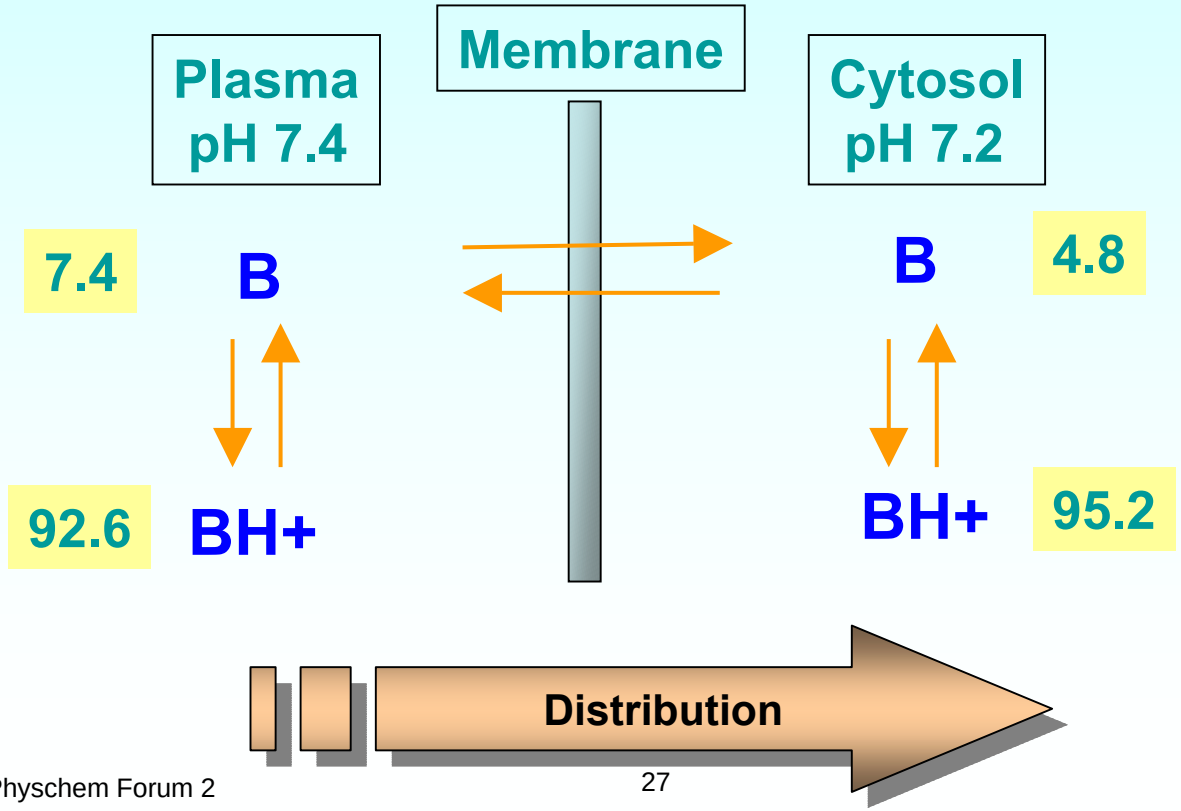
- Distribution
  - Ion trapping of basic compounds
- Distribution/Excretion
  - Aspirin overdose & salicylate poisoning

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

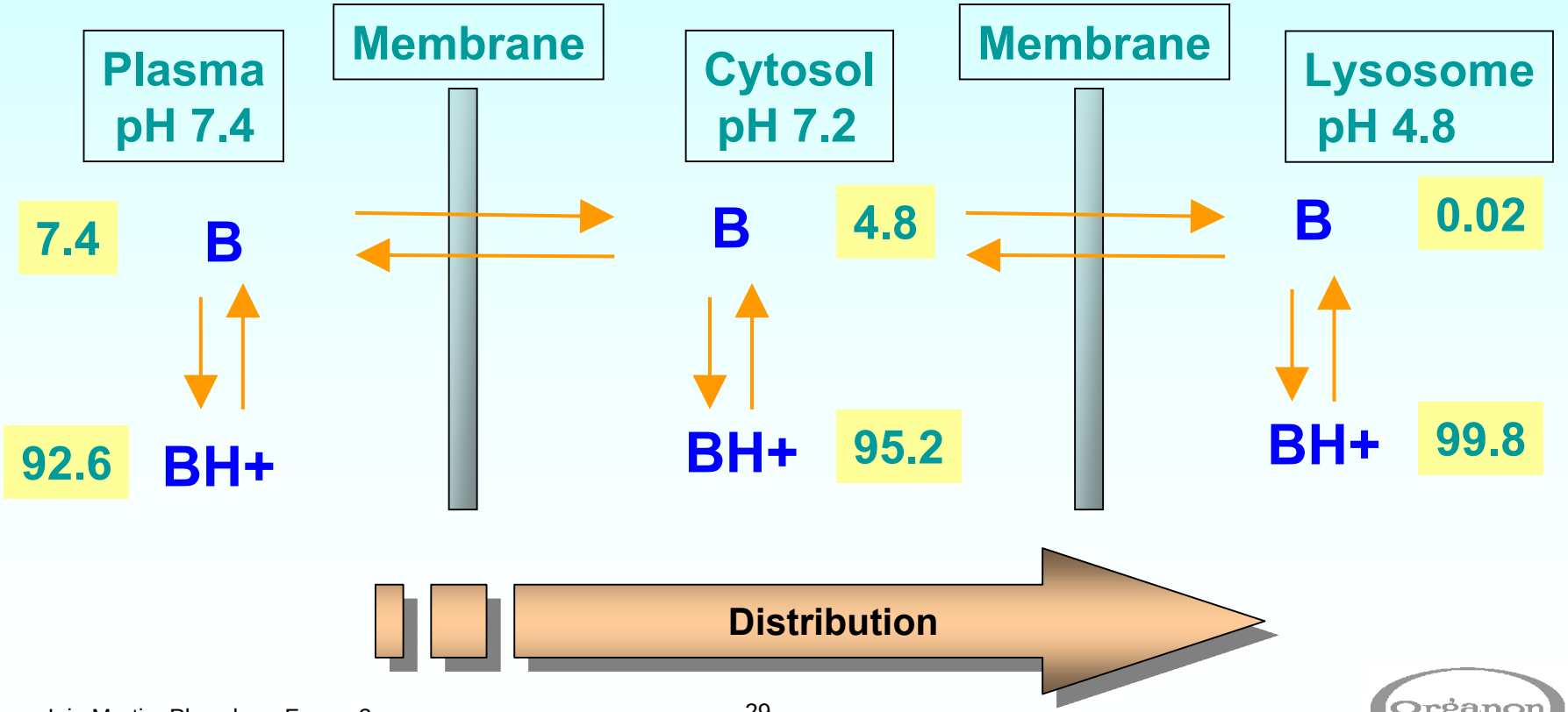


Ion trapping: lysosomes

- 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).

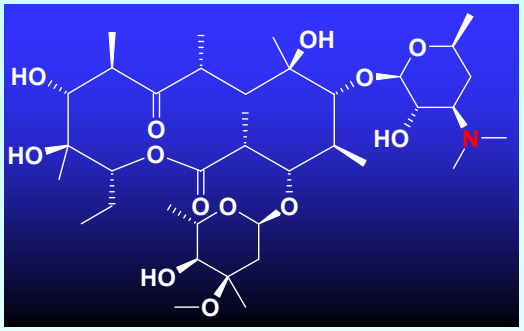
Ion trapping: lysosomes

- Ion trapping of a weak base pH 8.5

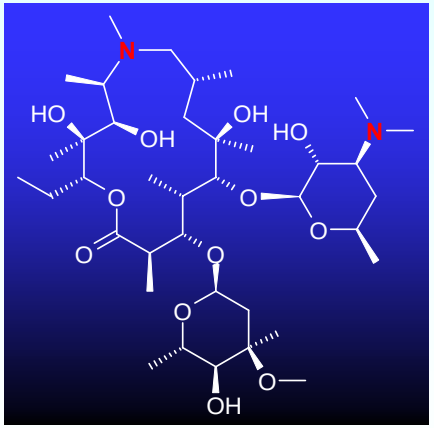


Ion trapping: lysosomes

- 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

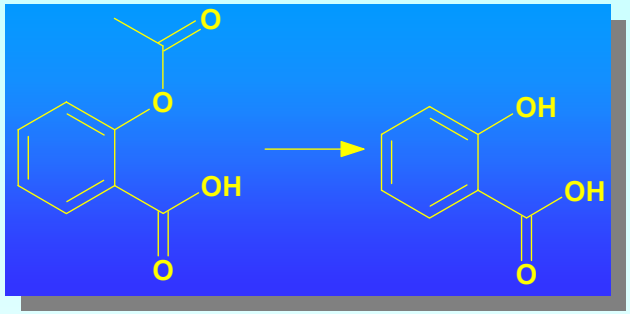


Erythromycin V_{SS} = 0.5 L/kg



Azithromycin V_{SS} = 28 L/kg

Salicylate poisoning

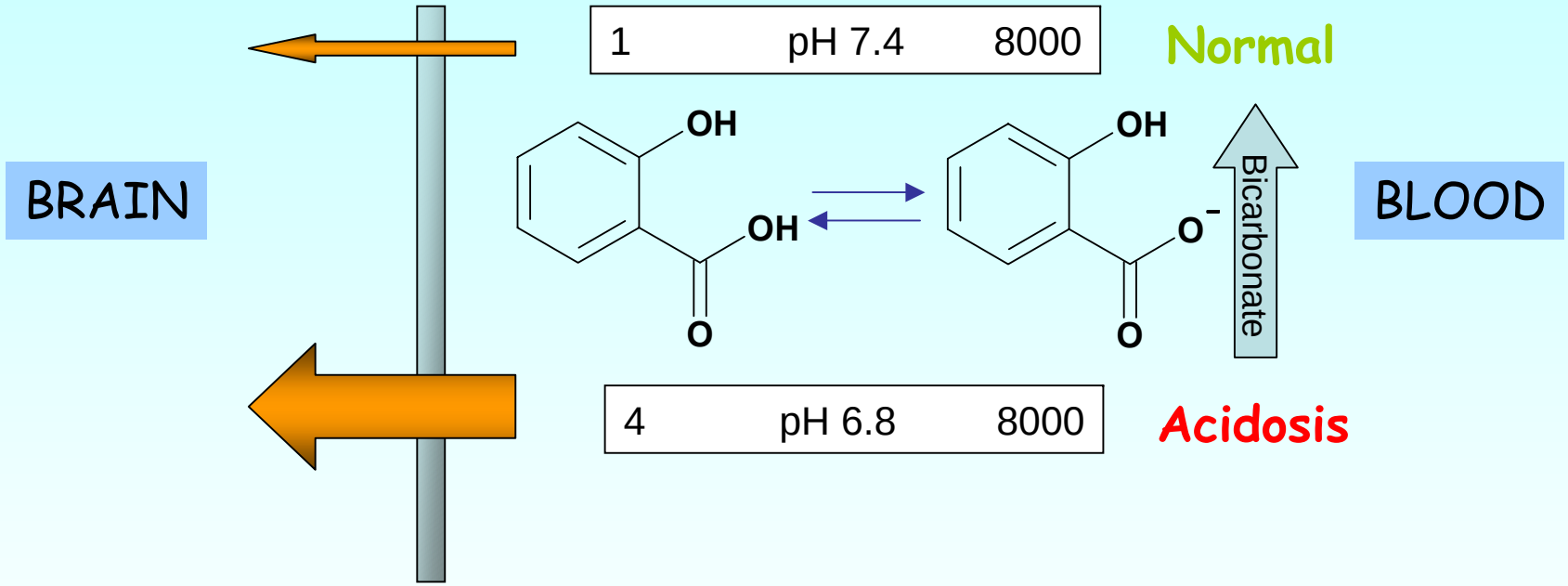


- Aspirin (acetylsalicylic acid) is metabolised to the active component – salicylic acid
- Due to its acidic nature and extensive ionisation, salicylate does not readily distribute into tissues
- But after an overdose, sufficient salicylate enters the CNS to stimulate the respiratory centre, promoting a reduction in blood CO_2
- The loss of blood CO_2 leads a rise in blood pH - **respiratory alkalosis**

Salicylate poisoning

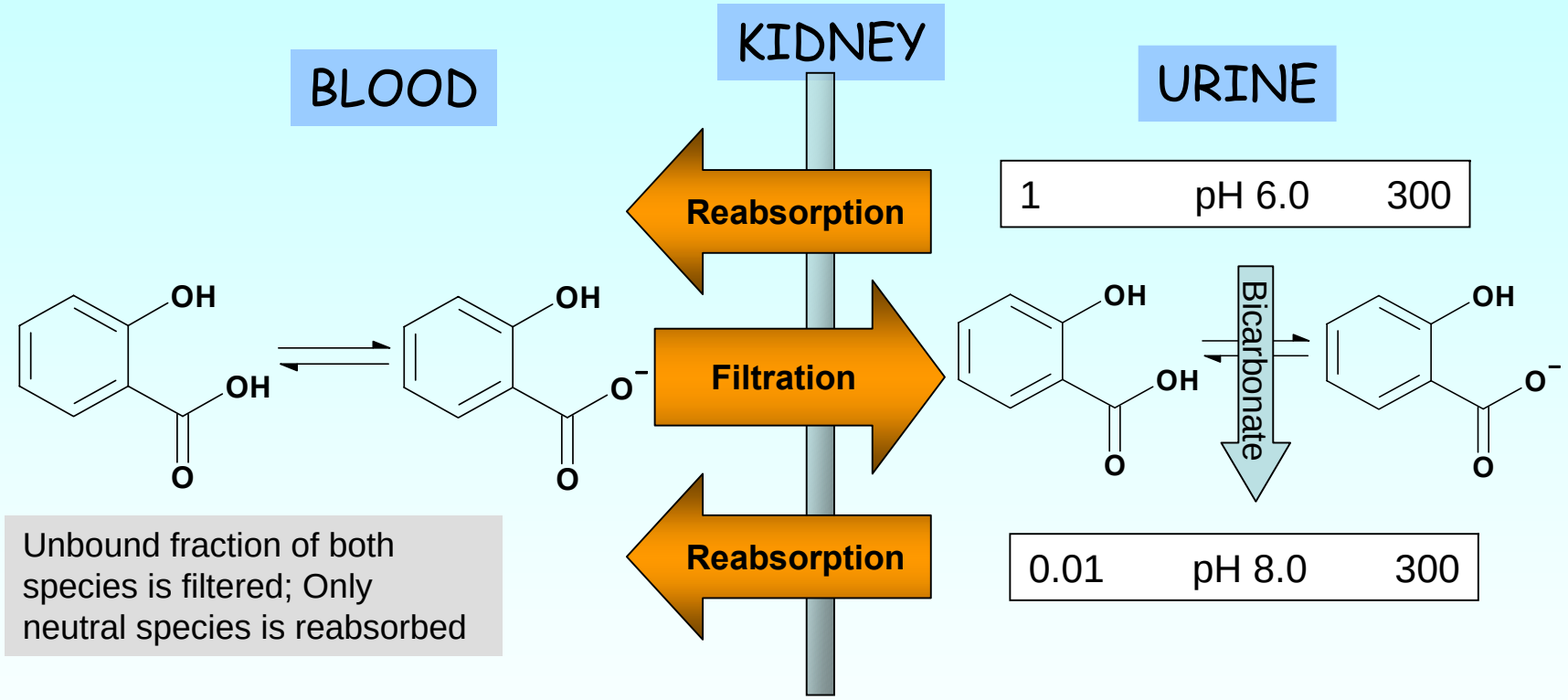
- The body responds to the alkalosis by excreting bicarbonate to reduce blood pH back to normal
- In mild cases, blood pH returns to normal. However in severe cases (and in children) blood pH can drop too far leading to **metabolic acidosis**
- This has further implications on the distribution of salicylate,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

Salicylate poisoning



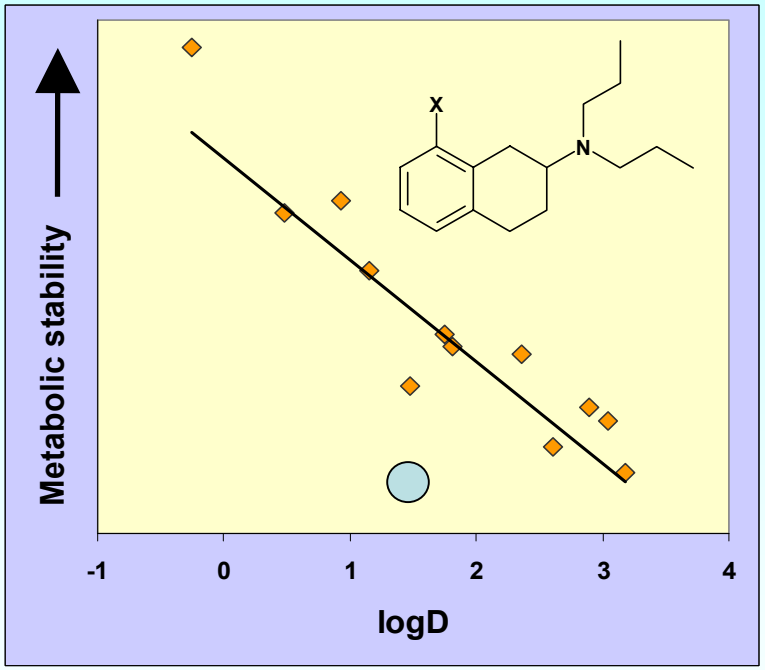
- Acidosis leads to increase in unionised salicylate in the blood, promoting distribution into brain resulting in CNS toxicity.
- This is treated with bicarbonate which increases blood pH and promotes redistribution out of the CNS.

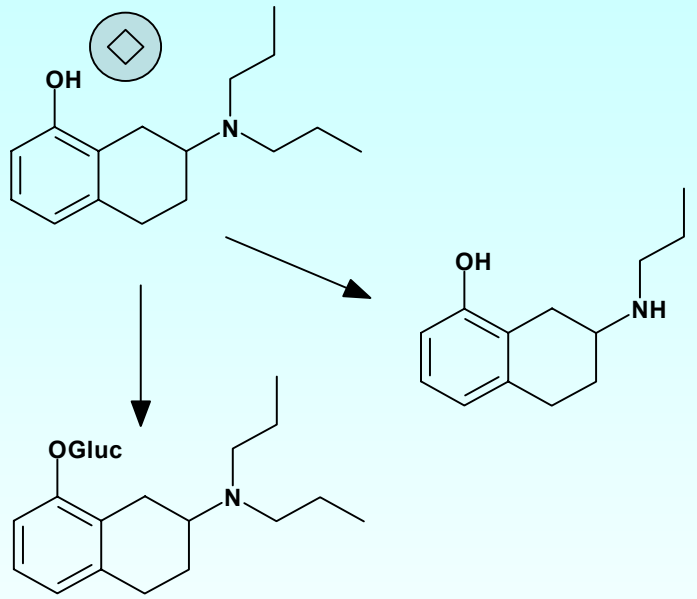
Salicylate poisoning



- Bicarbonate incrseases urine pH leading to significantly decreased reabsorption and hence increased excretion

Metabolism: lipophilicity

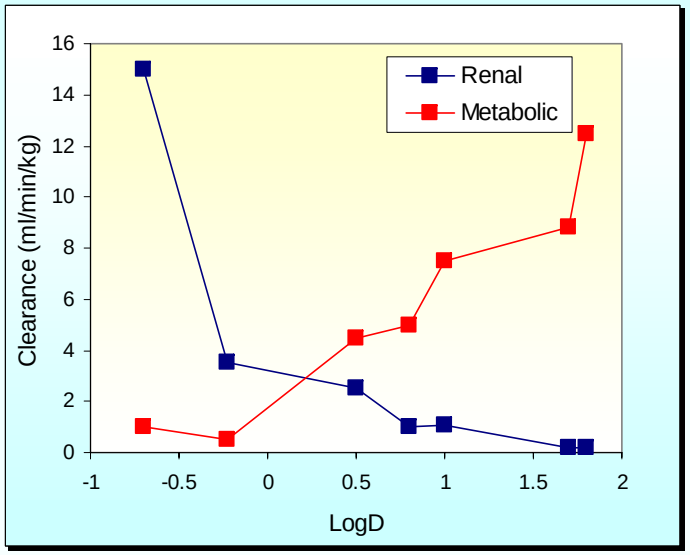




As a general rule, liability to metabolism increases with increasing lipophilicity. However, the presence of certain functional groups and SAR of the metabolising enzymes is of high importance

Metabolism vs. Excretion

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

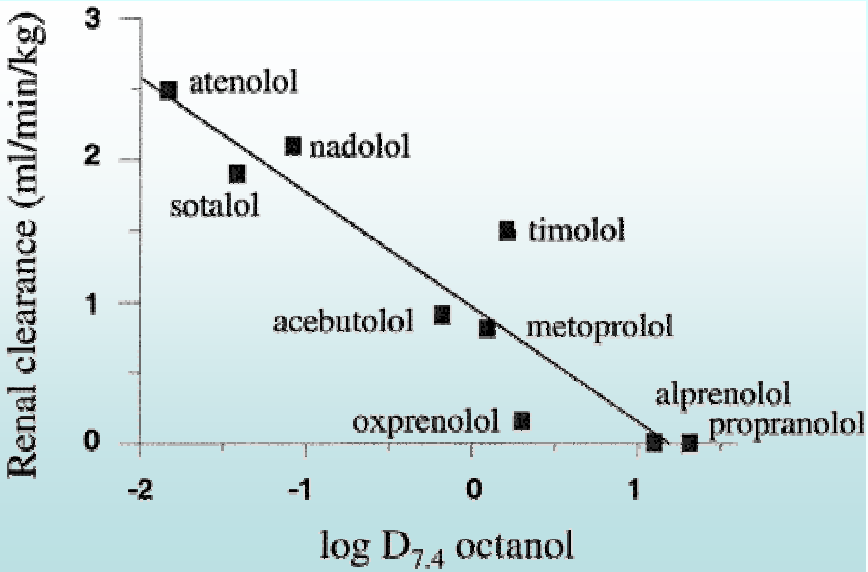


Replotted from Smith *et al.*, (1985) *Drug Metabolism Reviews*, **16**, p365

- 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



Van de Waterbeemd *et al.*, (2001) *J. Med. Chem*, **44**, p1313

- 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

References & Further Reading

- MacIntyre and Cutler (1988). The potential role of lysosomes in the tissue distribution of weak bases. Biopharmaceutics and Drug Disposition, 9, 513-526
- Proudfoot (2005). The evolution of synthetic oral drug properties. Bioorganic and Medicinal Chemistry Letters 15, 1087-1090
- Oprea et al., (2001) J. Chem. Inf. Comput. Sci. 41, 1308-1315
- van de Waterbeemd et al., (2001). Lipophilicity in PK design: methyl, ethyl, futile. Journal of Computer-Aided Molecular Design. 15, 273-86
- Wenlock et al., (2003). A comparison of physiochemical property profiles of development and marketed oral drugs. J. Med. Chem. 2003