INTERNATIONAL COLLEGE OF PHARMACEUTICAL INNOVATION

国际创新药学院

Druglikeness and the BCS (I, II)

Course	**BSc (Pharm) or BSc (ATT)**
Year	**2024-2025 I**
Module	**Medicines: Pharmaceutics 1 (MP1)**
Lecturer	**Dr. Shi Du**

LEARNING OUTCOMES

1. Describe the physicochemical properties of a drug that important in solubility and permeability
2. Define the Rule of 5 and apply it to conventional small molecules
3. Define the BCS and the 4 drug categories
4. Predict BCS solubility and permeability
5. Outline the uses of BCS in pharmaceutical science

DRUGS ARE REQUIRE TO HAVE A DELICATE BALANCE BETWEEN HYDROPHILICITY & LIPOHILICITY

- TO DATE, WE HAVE EMPHASISED THE KEY REQUIREMENT THAT A DRUG MUST GO IN TO SOLUTION IN ORDER TO BE ABSORBED AND ACT ON ITS BIOLOGICAL TARGET (e.g. RECEPTOR OR ENZYME).

- WHILE WE EVALUATED SEVERAL STRATEGIES TO IMPROVE SOLUBILITY TO ENSURE SOLUBILISATION, THERE IS A REQUIREMENT FOR A CARFUL BALANCE BETWEEN HYDROPHILICITY AND LIPOPHILICITY.

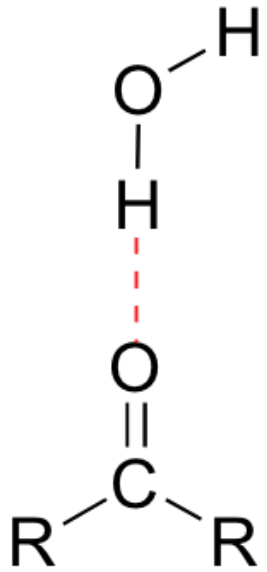
HYDROPHILICITY  LIPOPHILICITY

DRUGLIKENESS: LIPINSKI'S RULE OF FIVE

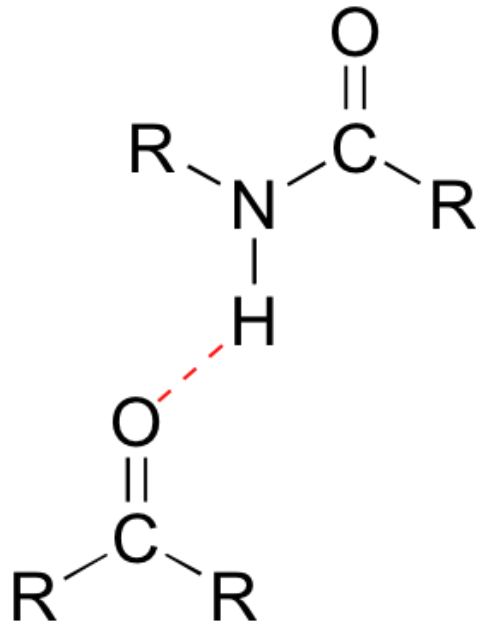
HYDROGEN BOND DONORS	<5
HYDROGEN BOND ACCEPTOR	<10
MOLECULAR WEIGHT	<500 Da
$LOGP_{OCTANOL:WATER}$	<5

As a rule of thumb, a drug must obey two or more of these parameters in order to be orally absorbed

HYDROGEN BOND DONORS & ACCEPTORS



hydrogen bonding between a ketone (acceptor) and water (donor)



hydrogen bonding between a ketone (acceptor) and an amide (donor)

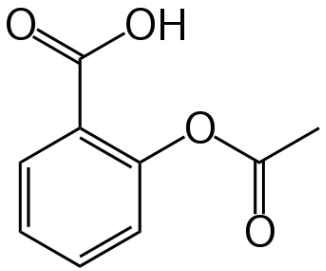
LIMITATIONS TO RULE OF 5

LIMITATIONS
Accounts for solubility but not dissolution
Does not account for drugs absorbed by transporters or substrates of efflux pumps (PGP)
Accounts for drugs with very low aqueous solubility but not very high aqueous solubility

ADDITIONS TO IMPROVE PREDICTIVE POWER
POLAR SURFACE AREA (<14 nm^2)
LOWER LIMIT FOR LogP (I.E. EXCESSIVE SOLUBILITY)
COMBINED H-BOND DONOR AND ACCEPTOR OF <12

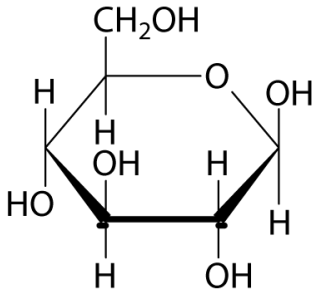
RULE OF 5: CASE DRUGS

ASPIRIN



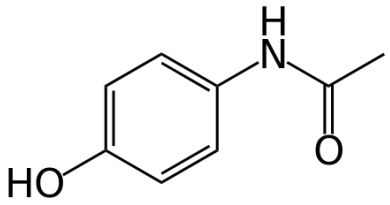
MW: 180.2
H DONOR: 1
H ACCEPTOR: 3
LogP: 1.19
F: 65-71%
Ro5: YES

GLUCOSE



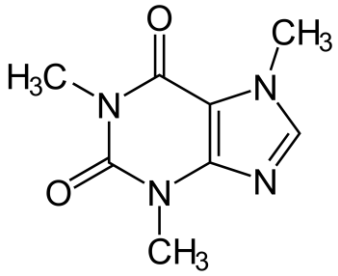
MW: 180.2
H DONOR: 5
H ACCEPTOR: 6
LogP: -3.24
F: 100%
Ro5: YES

PARACETAMOL



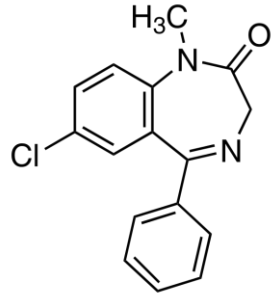
MW: 151.2
H DONOR: 2
H ACCEPTOR: 2
LogP: 0.91
F: 62-89%
Ro5: YES

CAFFEINE



MW: 194.2
H DONOR: 0
H ACCEPTOR: 3
LogP: -0.91
F: 100%
Ro5: YES

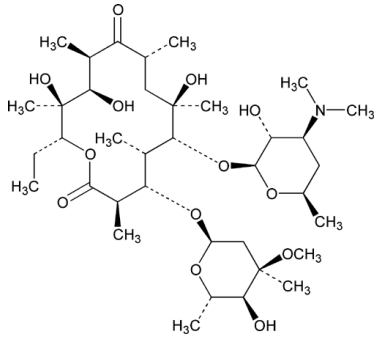
DIAZEPAM



MW: 284.7
H DONOR: 0
H ACCEPTOR: 3
LogP: 2.82
F: 85-100%
Ro5: YES

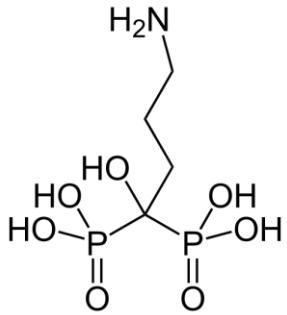
RULE OF 5: OTHER EXAMPLES

ERYTHROMYCIN



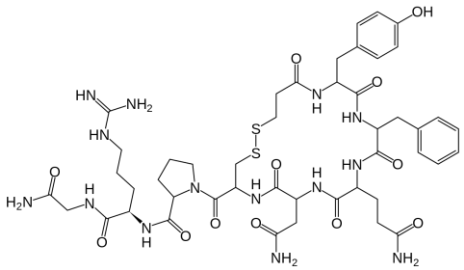
MW: 734
H DONOR: 14
H ACCEPTOR: 5
LogP: 2.6
F: 30-60%
Ro5: No

ALENDRONATE



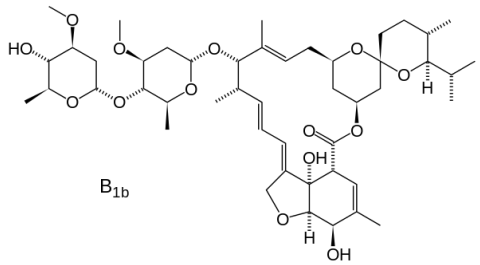
MW: 313.4
H DONOR: 8
H ACCEPTOR: 7
LogP: -2.77
F: 0.7%
Ro5: YES

DESMOPRESSIN



MW: 1041
H DONOR: 17
H ACCEPTOR: 26
LogP: -3.72
F: 0.1%
Ro5: No

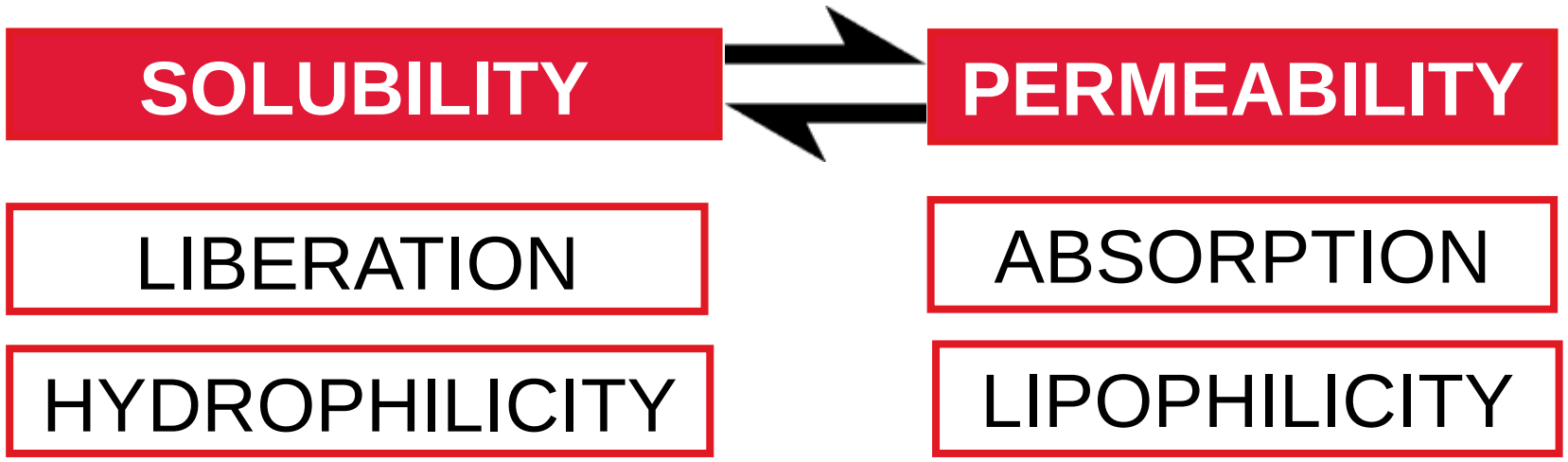
IVERMECTIN



MW: 875
H DONOR:3
H ACCEPTOR: 14
LogP: 6.70
F: Not determined
Ro5: No

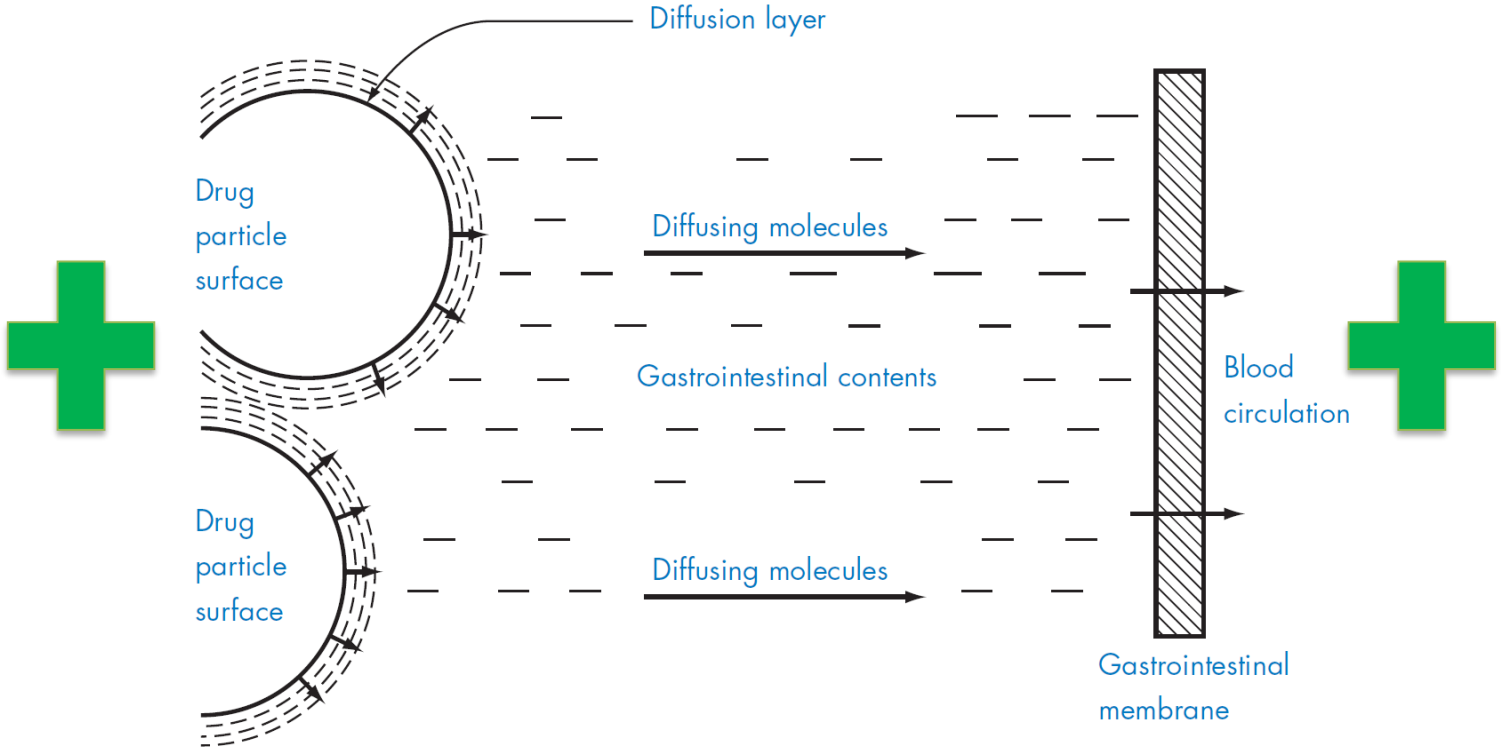
BIOPHARMACEUTICS CLASSIFICATION SYSTEM

- Biopharmaceutics classification system: Is a scientific framework for the classification of orally administered drugs based on two key metrics



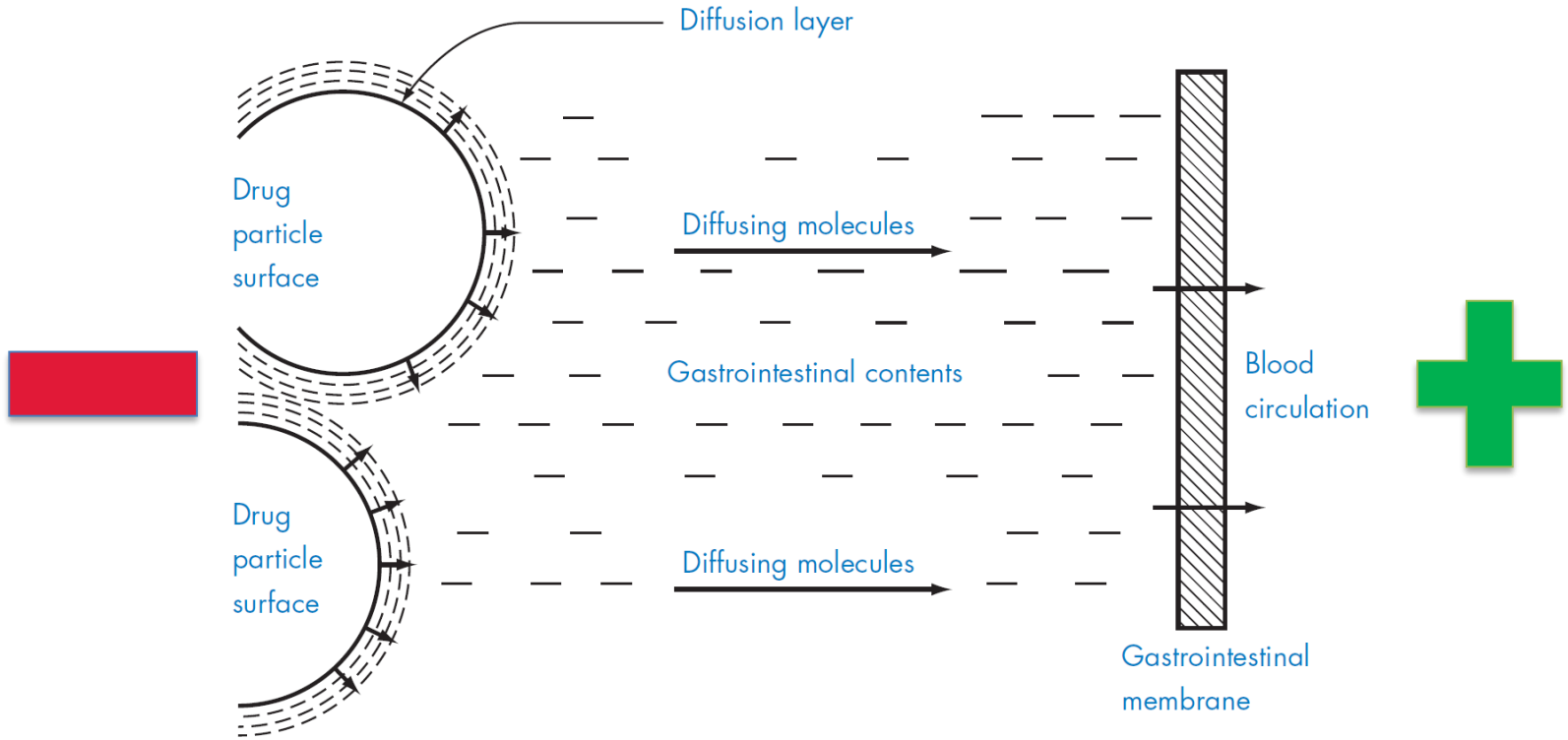
THE BALANCE BETWEEN SOLUBILITY & PERMEABILITY BCS CLASS I

- **BSC CLASS I**: HIGH AQUEOUS SOLUBILITY RESULTS IN GOOD LIBERATION FROM THE DOSAGE FORM (+) AND HIGH PERMEABILITY RESULTS IN HIGH PASSIVE PERMEATION ACROSS LIPID BILAYERS (+)



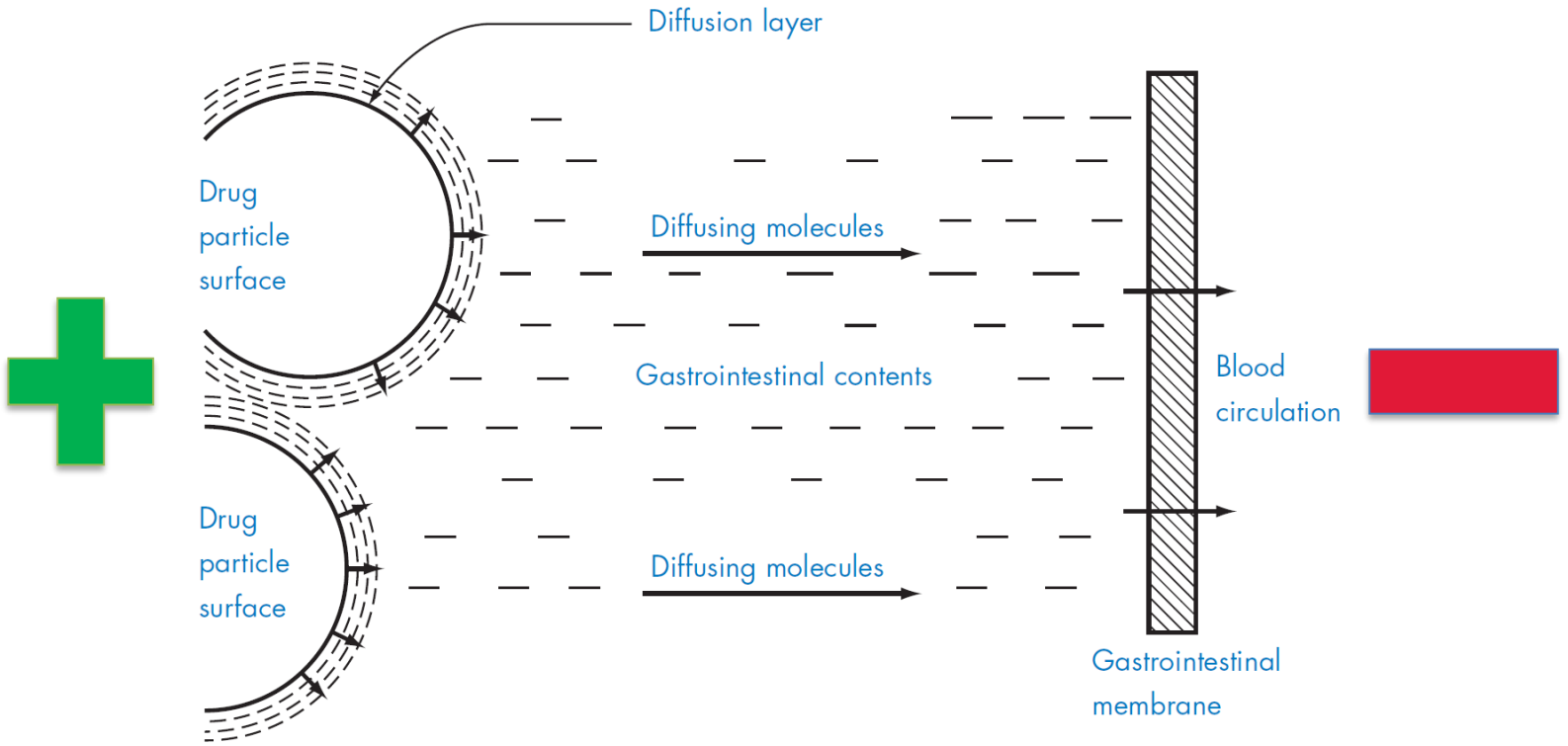
THE BALANCE BETWEEN SOLUBILITY & PERMEABILITY BCS CLASS II

- **BCS CLASS II**: LOW AQUEOUS SOLUBILITY RESULTS IN POOR LIBERATION FROM THE DOSAGE FORM (-) BUT IF THE DRUG CAN BE DISSOLVED IT HAS HIGH PASSIVE PERMEATION ACROSS LIPID BILAYERS (+)



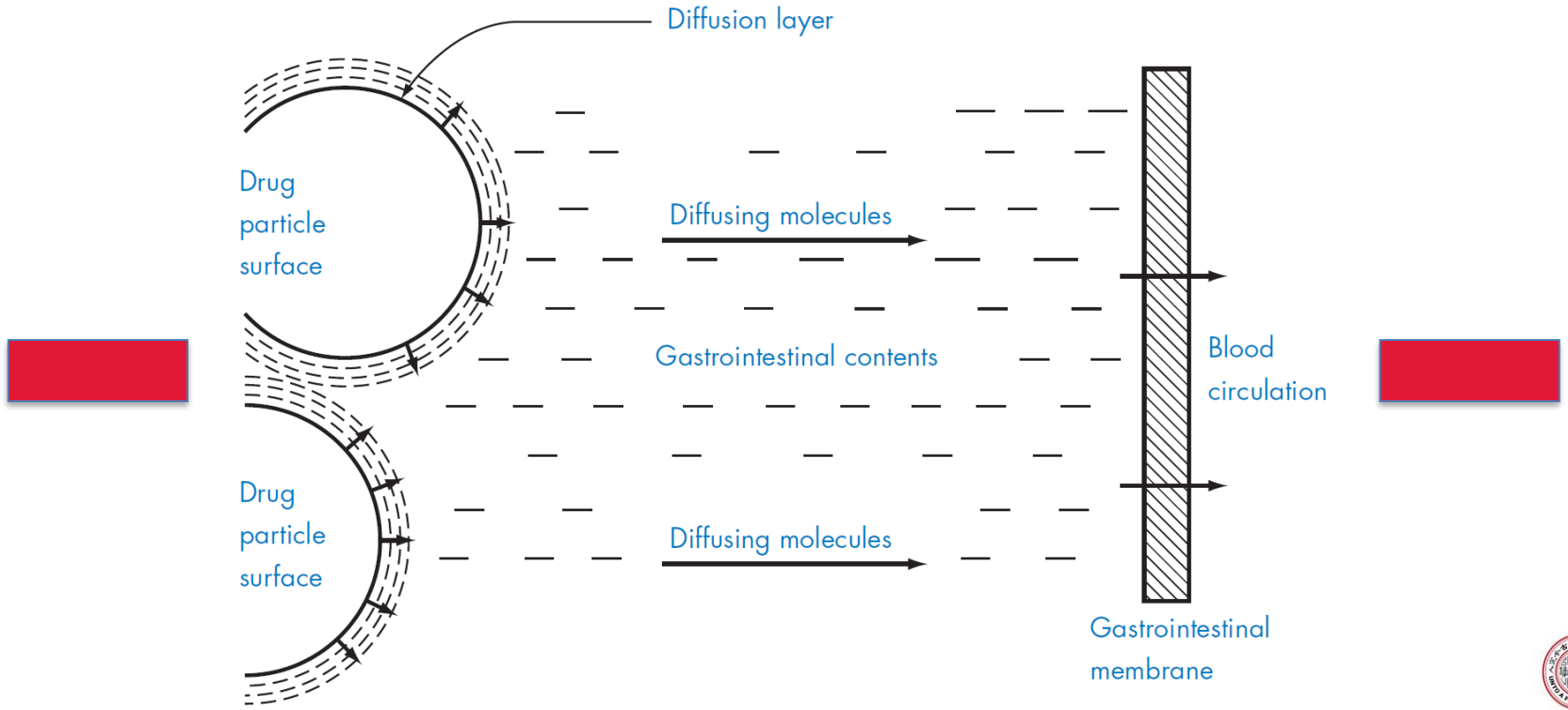
THE BALANCE BETWEEN SOLUBILITY & PERMEABILITY BCS CLASS III

- **BSC CLASS III**: HIGH AQUEOUS SOLUBILITY RESULTS IN GOOD LIBERATION FROM THE DOSAGE FORM (+) BUT LOW PASSIVE PERMEATION ACROSS LIPID BILAYERS (-)



THE BALANCE BETWEEN SOLUBILITY & PERMEABILITY BCS CLASS IV

- **BCS CLASS IV**: LOW AQUEOUS SOLUBILITY RESULTS IN POOR LIBERATION FROM THE DOSAGE FORM (-) AND LOW PASSIVE PERMEATION ACROSS LIPID BILAYERS (-)



SUMMARY OF BCS

CLASS	SOLUBILITY	PERMEABILITY	CONSIDERATION IN DOSAGE FORM DEVELOPMENT
I	HIGH	HIGH	Absorption is not limited by dissolution or permeability (**5% of drugs**)
II	LOW	HIGH	Dissolution is rate limiting; absorption can be enhanced by formulation to maximise dissolution rate (**70% of drugs**)
III	HIGH	LOW	Permeability is rate limiting in drug absorption (**5% of drugs**)
IV	LOW	LOW	Difficult to formulate to provide good absorption (**20% of drugs**)

SOLUBILITY IN BCS

- ***HOW MUCH SOLUBILITY IS ADEQUATE??????***

- A Drug is defined as **HIGH SOLUBILITY** if the highest dose strength will dissolve in < 250 mL of water over a pH range of 1-7.5 at 37ºC

- We therefore take into account dose when considering solubility, rather than using simple solubility metrics alone

COMPENDIAL SOLUBILITY

REQUIRED DOSE

BCS SOLUBILITY

ASPIRIN (HIGH SOLUBILITY) AND IBUPROFEN (LOW SOLUBILITY)

ASPIRIN

- Solubility: 4.6 mg/mL
- USP: "*slightly soluble*"

COMMENT

- A relatively low solubility value in absolute physical terms but the highest dose of this drug is 300mg. Therefore, according to the BCS 300mg/250mL (1.2mg/mL) makes aspirin **high solubility**

IBUPROFEN

- Solubility: 0.021 mg/mL
- USP: "*practically insoluble*"

COMMENT

- A low solubility value in absolute physical terms and highest dose of this drug is 600mg. Therefore, according to the BCS 600mg/250mL (2.4mg/mL) makes ibuprofen **low solubility**

BCS SOLUBILITY
DIGOXIN (HIGH SOLUBILITY)

DIGOXIN

- Solubility: 0.986 mg/mL
- USP: “very slightly soluble”

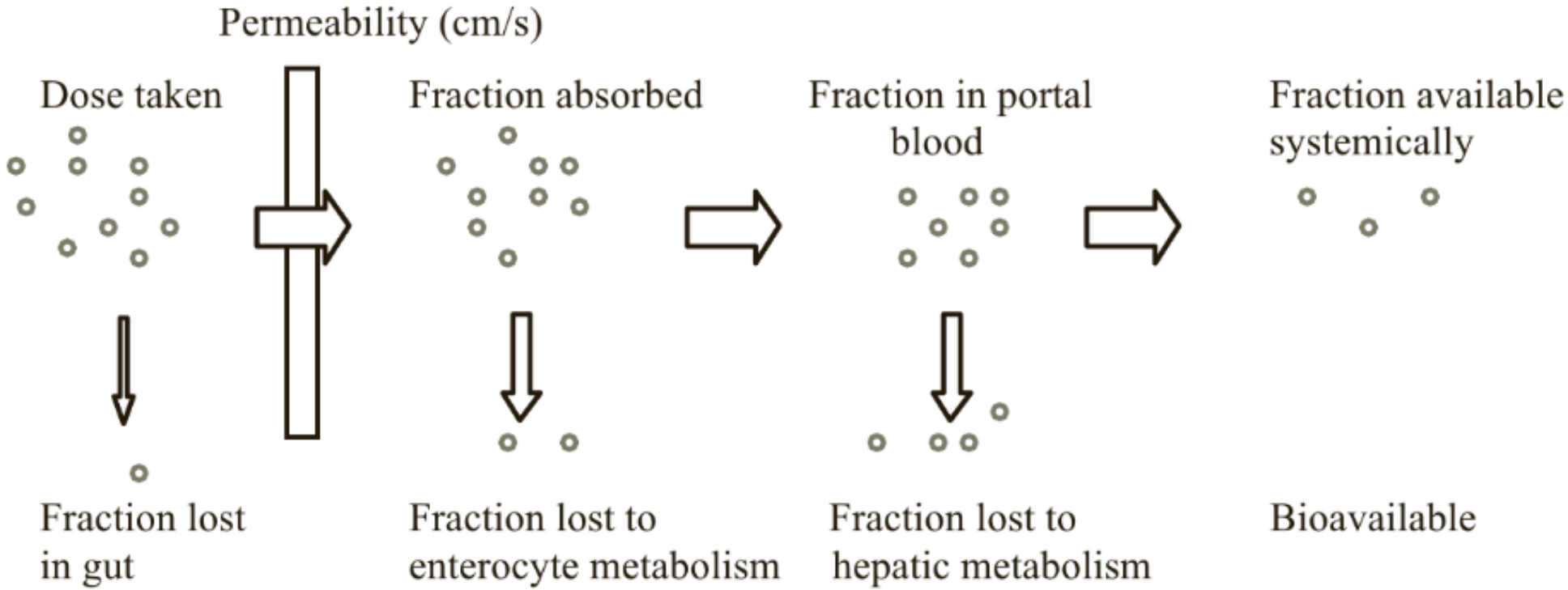
COMMENT

- A intermediate solubility value in absolute physical terms. However this drug is potent and the highest dose strength is 0.25 mg. Therefore, according to the BCS 0.25 mg/250mL (0.001 mg/mL) makes digoxin **high solubility**

BCS: SOLUBILITY

DRUG	SOLUBILITY	CONCENTRATION OF HIGHEST DOSE (mg/mL)	SOLUBILITY
IBUPROFEN	LOW	2.4mg/mL (600mg/250mL)	0.021mg/mL
ASPIRIN	HIGH	1.2mg/mL (300mg/250mL)	4.6mg/mL
Digoxin	HIGH	0.001mg/mL (0.25 mg/250 mL)	0.986 mg/mL

BCS: PERMEABILITY
FRACTION ABSORBED, PERMEABILITY AND BIOAVAILABILITY



BCS PERMEABILITY

- The FDA defines **HIGH PERMEABILITY** as the extent of absorption in humans greater than or equal to 90%

- Permeability can be determined in two ways:
  - (1) Bioavailability testing in man
  - (2) In vitro permeability testing (predictive)

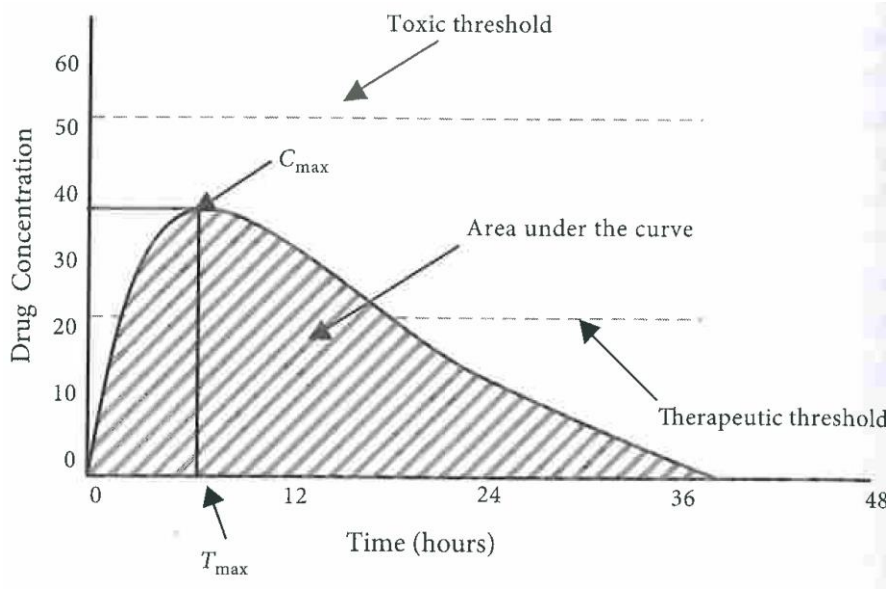
BCS: PERMEABILITY
(1) BIOAVAILABILITY TESTING

- Bioavailability (F) is a measure of the fraction of drug absorbed.

1. Healthy human volunteers receive 1 dose of the drug by IV injection and plasma level of the drug are measured over time. This allows us to understand the drug exposure with no barriers to absorption and no initial metabolism (liver).
2. When the drug is eliminated, the patient takes the drug via the oral route and plasma levels are measured over the same time period
3. Bioavailability is a ratio of the amount of drug absorbed via the tablet to the amount of drug given via bolus injection

BCS: PERMEABILITY
(1) BIOAVAILABILITY TESTING

$$BA = \frac{AUC_{ORAL} \div DOSE_{ORAL}}{AUC_{IV} \div DOSE_{IV}}$$



BA: absolute bioavailability
AUC_{ORAL}: Area Under the Plasma Concentration Curve following oral administration
AUC_{IV}: Area Under the Plasma Concentration Curve following IV administration
$DOSE_{ORAL}$: Dose administered via the oral route
$DOSE_{IV}$: Dose administered via IV bolus

BCS: PERMEABILITY
(1) EXAMPLE MEASUREMENT OF BIOAVAILABILITY

METRIC	ORAL FORMULATION 1	ORAL FORMULATION 2	ORAL FORMULATION 3	IV
AUC_{ORAL} (ng • h/mL)	3456	1728	864	1728
DOSE (mg)	100mg	100mg	100mg	50mg
F_{ABS}	1 (100%)	0.5 (50%)	0.25 (25%)	NA

BCS: PERMEABILITY
(1) BIOAVAILABILITY CALCULATIONS

- F value of 1 indicates that all of the drug is absorbed orally
  - $F_{ABS} = AUC_{ORAL} \div DOSE_{ORAL}] \div [AUC_{IV} \div DOSE_{IV}]$
  - $1 = [3456 \div 100mg] \div [1728 \div 50mg]$

- F value of 0.5 indicates that half the is absorbed orally
  - $F_{ABS} = AUC_{ORAL} \div DOSE_{ORAL}] \div [AUC_{IV} \div DOSE_{IV}]$
  - $1 = [1728 \div 100mg] \div [1728 \div 50mg]$

- F value of 0.25 indicates that only ¼ of the dose is absorbed orally
  - $F_{ABS} = AUC_{ORAL} \div DOSE_{ORAL}] \div [AUC_{IV} \div DOSE_{IV}]$
  - $1 = [864 \div 100mg] \div [1728 \div 50mg]$

BCS: PERMEABILITY
(2) IN VITRO MEASURE OF PERMEABILITY

- In vitro intestinal cell cultures can be used to determine permeability and predict fraction absorbed and bioavailability

$$J = P(C)$$

J: rate of flux (g/cm^2/s)
P: Permeability coefficient (cm/s)
C: concentration at the membrane surface)

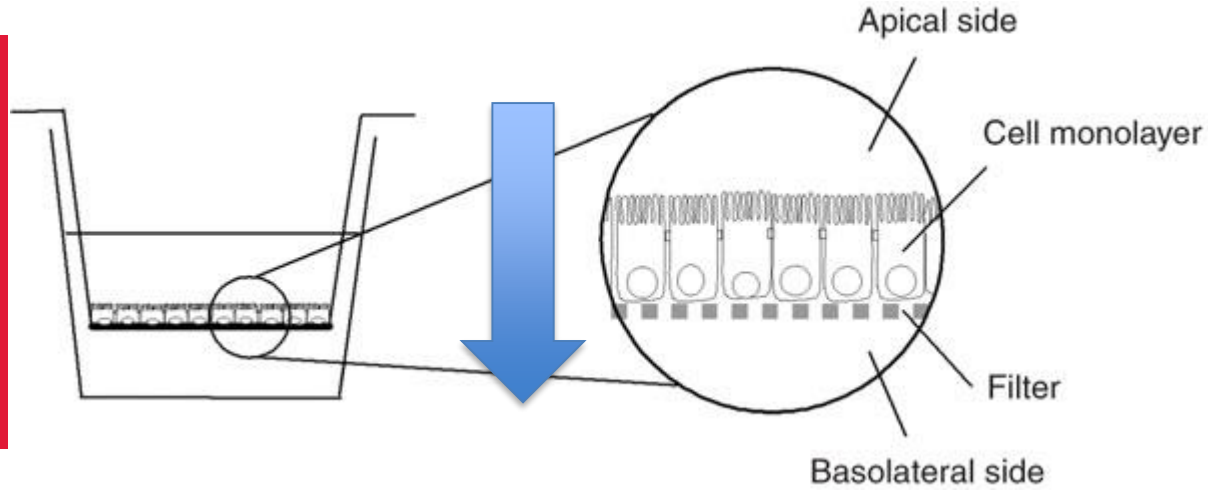
In cell cultures, the **APPARENT PERMEABILITY COEFFICIENT (P_{APP})** gives a numerical estimation of permeability and can be used to determine if a drug is **HIGH PERMEABILITY** or **LOW PERMEABILITY**

BCS: PERMEABILITY

(2) IN VITRO TRANSPORT: MEASUREMENT OF PAPP IN CACO-2 CELLS

- Caco-2 cells are intestinal epithelial cells that form a model of the small intestinal.

P_{APP} VALUE OF > 1 $\times 10^{-5}$ cm/s (OR > LogP_{APP} OF > -5 cm/s IS PREDICTIVE OF HIGH PERMEABILITY BUT MANY EXCEPTIONS EXIST



$$P_{APP} = (dQ/dt) \times 1/A \times C_0$$

P: Permeability coefficient (cm/s)
dQ/dt: Transport rate (mol/s)
A: Surface area (cm^2)
C_0: Initial donor concentration (mol/mL)

BCS: PERMEABILITY

- Permeability data is not widely published for drugs

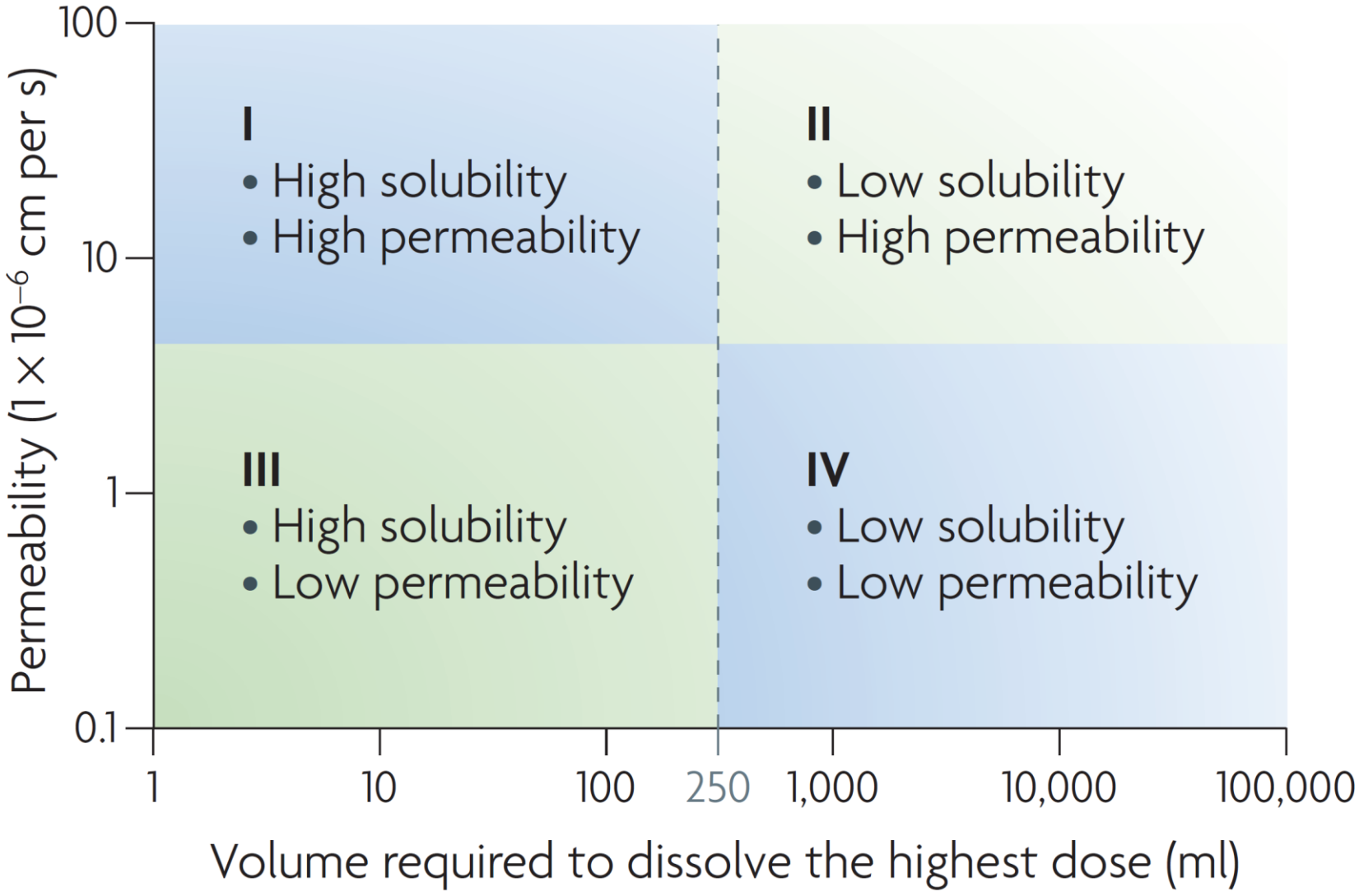
LogP can be used to substitute Papp which is effective approximately two thirds of the time

- As a guide, drugs with LogP >2 and <5 are likely to have good permeability and adequate solubility, nevertheless total number of H-bonds, molecular weight and pKa

SELECTED LOG PAPP VALUES

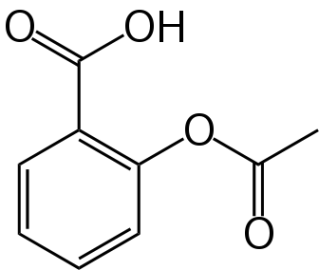
DRUG	Papp (cm/s)	Fa (%)	F	PERMEABILITY
CAFFEINE	0.00004	100%	100%	HIGH
IBUPROFEN	0.00005	95%	80%	HIGH
ASPIRIN	0.000009	84%	65-71%	LOW
CHLOROTHIAZIDE	0.0000002	36-61%	8-20%	LOW
DIAZEPAM	0.00005	100%	85-100%	HIGH

BIOPHARMACEUTICS CLASSIFICATION SYSTEM



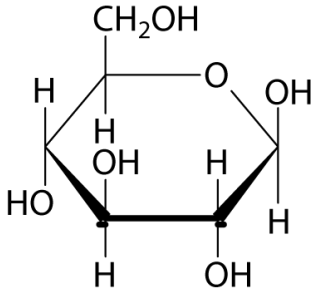
BCS CLASS FOR SELECTED CASE DRUGS

ASPIRIN



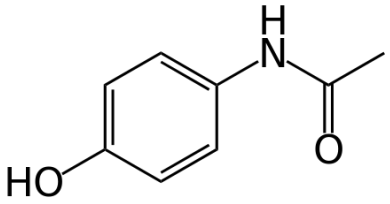
MW: 180.2
H DONOR: 1
H ACCEPTOR: 3
LogP: 1.19
F: 65-71% (Fa 84%)
BCS CLASS III

GLUCOSE



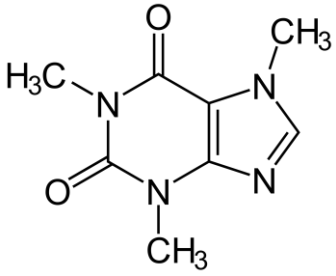
MW: 180.2
H DONOR: 5
H ACCEPTOR: 6
LogP: -3.24
F: 100%
NA

PARACETAMOL



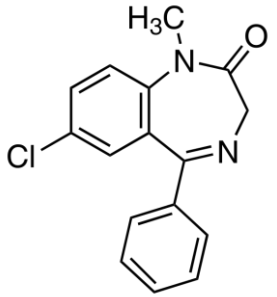
MW: 151.2
H DONOR: 2
H ACCEPTOR: 2
LogP: 0.91
F: 62-89% (Fa 80%)
BCS CLASS III

CAFFEINE



MW: 194.2
H DONOR: 0
H ACCEPTOR: 3
LogP: -0.07
F: 100%
BCLS CLASS I

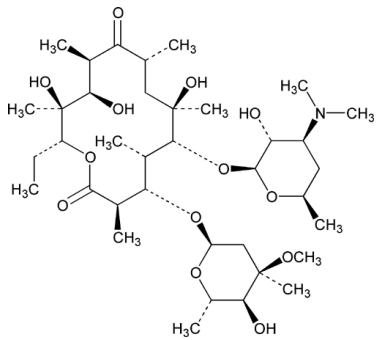
DIAZEPAM



MW: 284.7
H DONOR: 0
H ACCEPTOR: 2
LogP: 2.82
F: 85-100%
BCS CLASS I

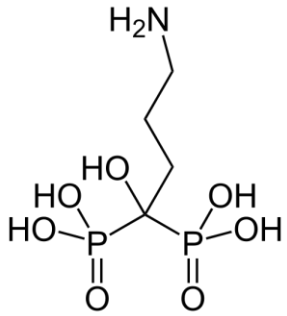
BCS: OTHER EXAMPLES

ERYTHROMYCIN



MW: 734
H DONOR: 13
H ACCEPTOR: 5
LogP: 2.6
F: 30-60% (Fa: ?)
BCS CLASS I or III

ALENDRONATE



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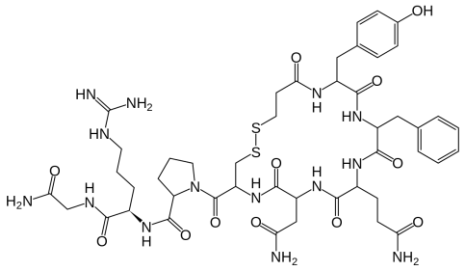
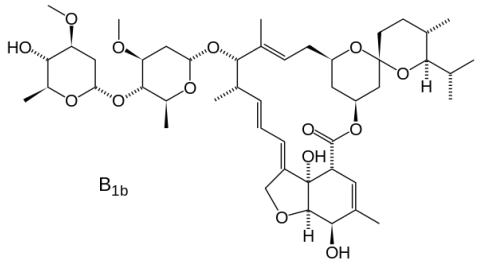
BCS CLASS III

DESMOPRESSIN



MW: 1041
H DONOR: 17
H ACCEPTOR: 26
LogP: -3.72
F: 0.1% (Fa: <90%)
BCS CLASS III

IVERMECTIN



MW: 875
H DONOR:3
H ACCEPTOR: 14
LogP: 6.70
F: 0%
BCS NA

BCS: SOLUBILITY AND PERMEABILITY

DRUG	SOLUBILITY	PERMEABILITY (cm/s)	f_a (%)	F (%)	BCS
CAFFEINE	HIGH	0.00004	100	100	I
DIAZEPAM	HIGH	0.00005	100	85-100	I
IBUPROFEN	LOW	0.00005	95	80	II
ASPIRIN	HIGH	0.000009	84	65-71	III
CHLOROTHIAZIDE	LOW	0.0000002	36-61	8-20	IV

SELF DIRECTED LEARNING

DRUG	SOLUBILITY	LIPINSKI RULE	P_{APP} (cm/s)	f_a (%)	F (%)	PERMEABILITY	BCS
Amoxicillin	HIGH/LOW?	X/4 Y/N?				HIGH/LOW?	I-to-IV
Atenolol	HIGH/LOW?	X/4 Y/N?				HIGH/LOW?	I-to-IV
Cimetidine	HIGH/LOW?	X/4 Y/N?				HIGH/LOW?	I-to-IV
Felodipine	HIGH/LOW?	X/4 Y/N?				HIGH/LOW?	I-to-IV
Metoprolol	HIGH/LOW?	X/4 Y/N?				HIGH/LOW?	I-to-IV
Propranolol	HIGH/LOW?	X/4 Y/N?				HIGH/LOW?	I-to-IV
Theophyline	HIGH/LOW?	X/4 Y/N?				HIGH/LOW?	I-to-IV
Verapamil	HIGH/LOW?	X/4 Y/N?				HIGH/LOW?	I-to-IV

Solubility data: www.drugbank.ca
Permeability data: scientific literature

THE ROLE OF CHARGE (PKA) SHOULD NOT BE FORGOTTEN DESPITE ABSENCE FROM BCS

- To be considered BCS Class I, 85% of the dosage form must dissolve in 30 minutes in 900mL at pH 1.2, 4.5 and 6.8 using USP Apparatus I or II at 37C

THE ROLE OF CHARGE (PKA) SHOULD NOT BE FORGOTTEN DESPITE ABSENCE FROM BCS

Table 9.2 Intestinal absorption of acids and bases in the rat at several pH values[a]

Acid/base	pK_a	Perentage absorption			
		pH 4	pH 5	pH 7	pH 8
Acids					
Acetylsalicylic acid (aspirin)	3.5	41	27	–	–
Bases					
Quinine	8.4	9	11	41	54

[a] Reproduced from B. B. Brodie, in *Absorption and Distribution of Drugs* (ed. T. Binns), Livingstone, Edinburgh, 1964.

APPLICATIONS OF THE BCS
APPROVAL OF GENERIC MEDICINES

GENERICS

- After a period of patent exclusivity an innovator drug can be manufactured by other companies in a formulation referred to as a generic.
- Generic manufacturers must first ensure that their dosage form is equivalent to the innovator formulation. Given the complexity of drug development, regulators (e.g. FDA) have created a pathway to approval of generic medicines termed **bioequivalence** (which typically involves expensive bioavailability equivalence human trials).
- The BCS can be used to waive the requirement for expensive clinical trials if the drug is **BCS CLASS I** (HIGH SOLUBILITY/LOW SOLUBILITY)

APPLICATIONS OF THE BCS
CHARACTERISATION OF DRUG CANDIDATES

INNOVATOR: The innovator drug product or branded product is referred to in FDA databases as the reference listed drug.

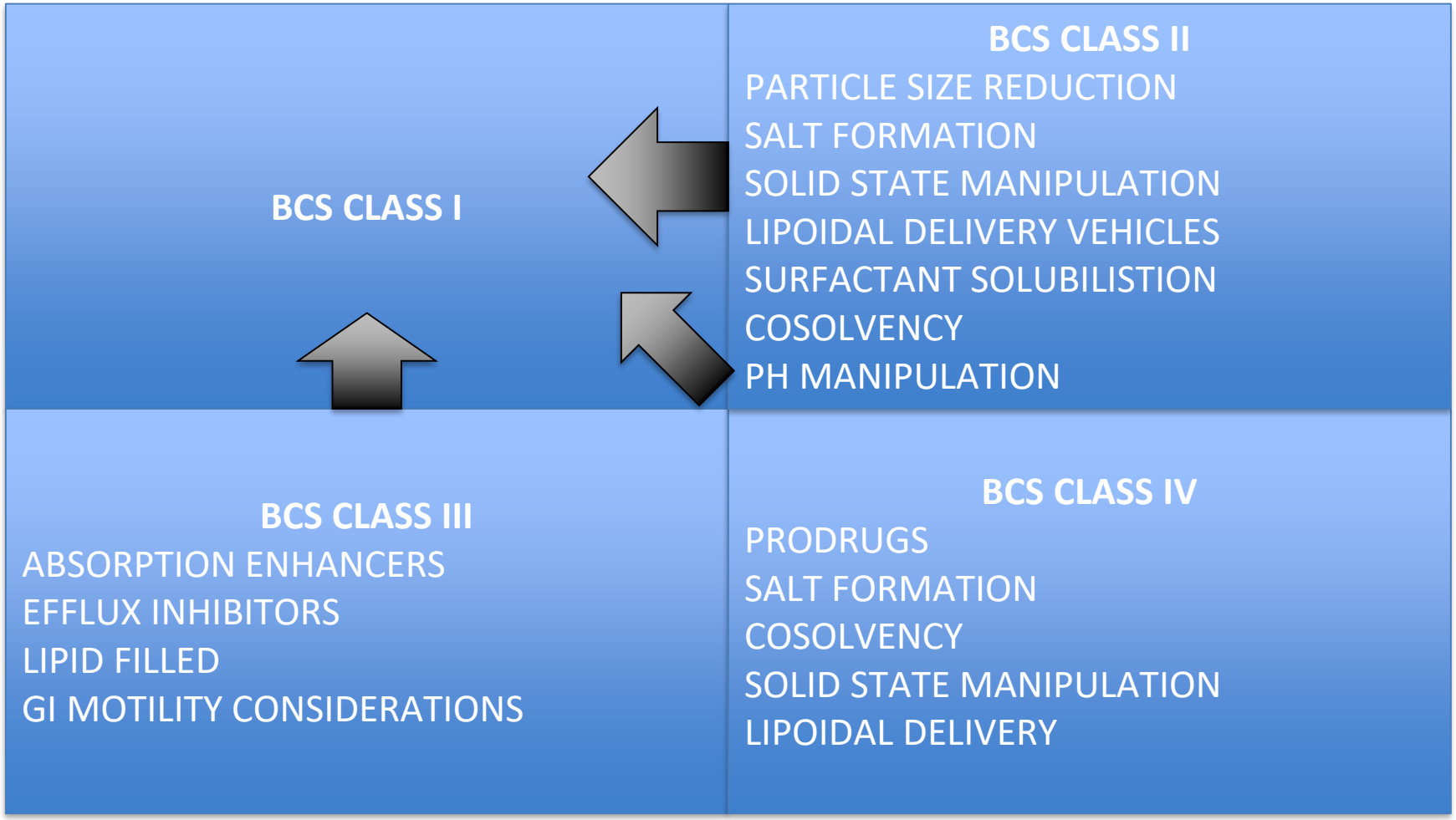
- ***The BCS classification provides useful solubility and permeability data that enables formulation scientists to develop an effective formulation that ensures adequate solubility and permeability and ultimately bioavailability.***

DEVELOPABILITY CLASSIFICATION SYSTEM (DCS)

- DCS has recently been proposed to apply the BCS as an oral product development tool. In this model
  - BCS Class II is divided into dissolution rate limited and solubility rate limited
  - Dissolution is expressed as target particle size (Vs dose/solubility)
  - Dissolution is measured in FSSIF (Vs HCl)
  - Solubility is measured in 500mL volume (Vs 250mL in BCS)

- DCS is a simple system that aids the product design scientist in understanding the absorption limitations for a drug. Once identified, these limitations can be addressed

BCS CLASS I IS THE IDEAL DRUG CLASS



BIOPHARMACEUTICS DRUG DISPOSITION CLASSIFICATION SYSTEM

- BDDCS extends the scientific frame work of BCS to include prediction of in vivo drug behaviour to include their routes of elimination, metabolism, distribution and potential for drug interactions

- Used by industry scientists to predict lead behaviour

- Outlines a framework for understanding the factors that govern drug ADME

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