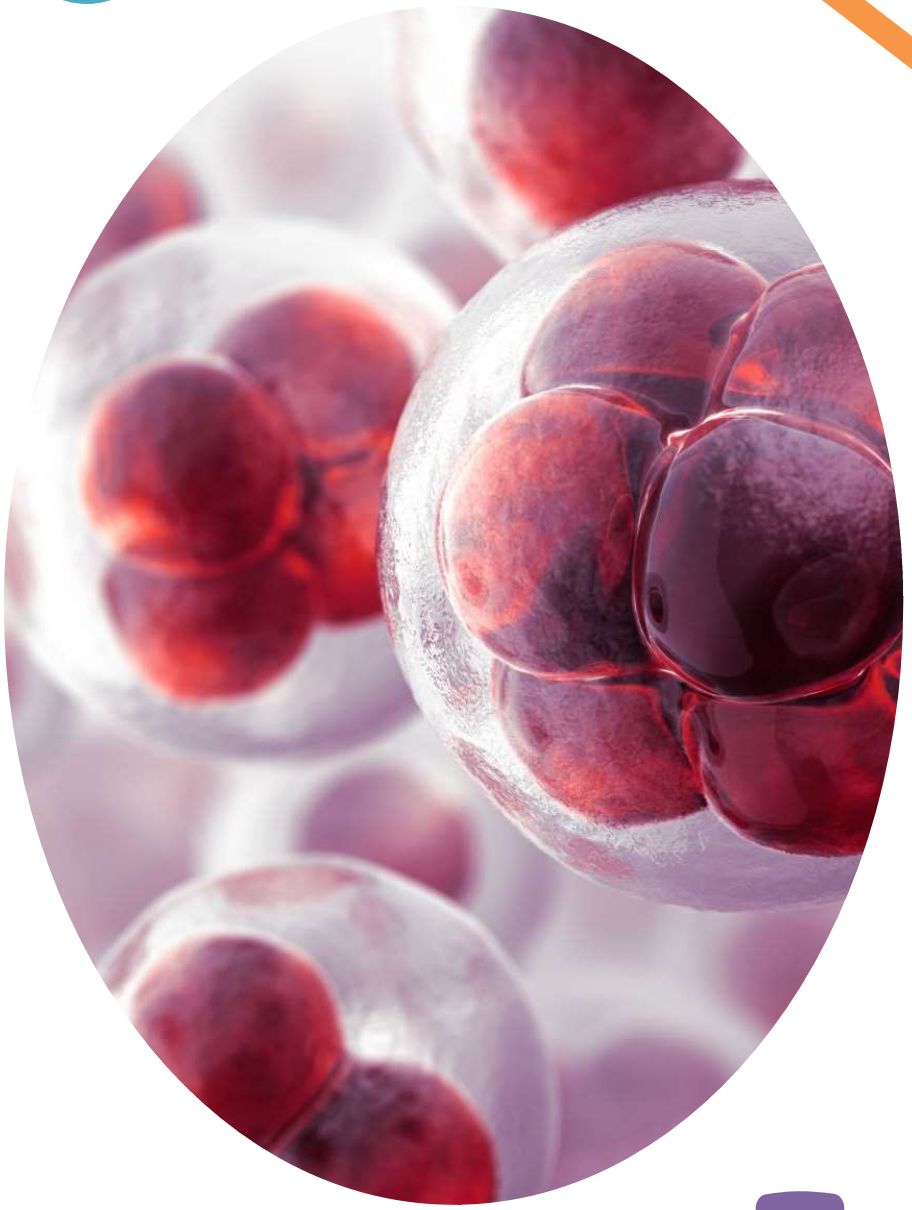


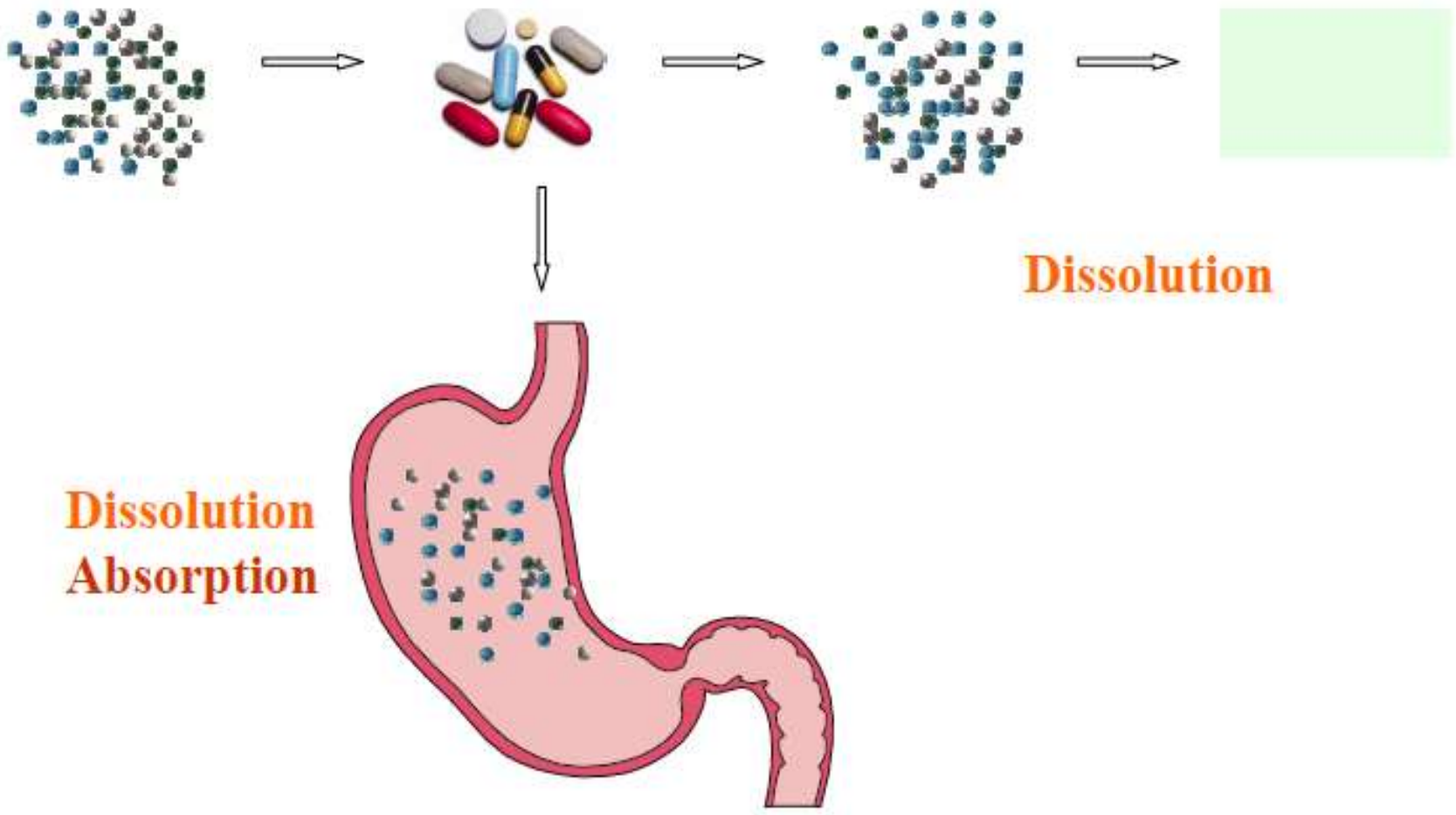
Biopharmaceutics Classification System

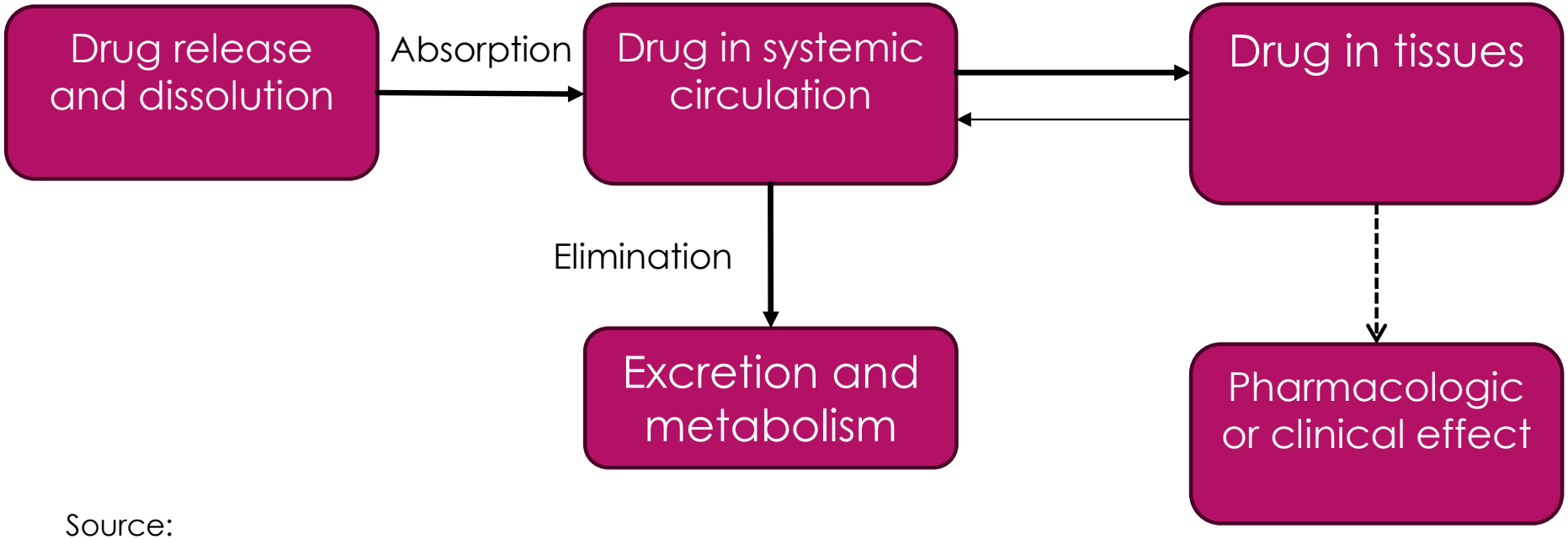
Program Studi Farmasi
Fakultas Kedokteran dan Ilmu Kesehatan
Universitas Muhammadiyah Yogyakarta

BIOPHARMACEUTIC STUDIES ALLOW FOR THE RATIONAL DESIGN OF DRUG PRODUCTS BASED ON:

- THE PHYSICOCHEMICAL PROPERTIES OF THE DRUG.
- ROUTE OF DRUG ADMINISTRATION INCLUDING THE ANATOMIC AND PHYSIOLOGIC NATURE OF THE APPLICATION SITE.
- DESIRED PHARMACODYNAMIC EFFECT (EG, IMMEDIATE OR PROLONG ACTIVITY).
- TOXICOLOGIC PROPERTIES OF THE DRUG.
- SAFETY OF EXCIPIENTS.
- EFFECT OF EXCIPIENTS AND DOSAGE FORM ON DRUG DELIVERY.

Dissolution of Solid Oral Dosage Forms





Source:
Shargel, Leon, Andrew B.C YU. **Applied Biopharmaceutics And Pharmacokinetics** Seventh Edition. 7 New York: Mc Graw-Hill Educaton, 2016.

Scheme demonstrating the dynamic relationship between the drug, the drug product, and the pharmacologic effect

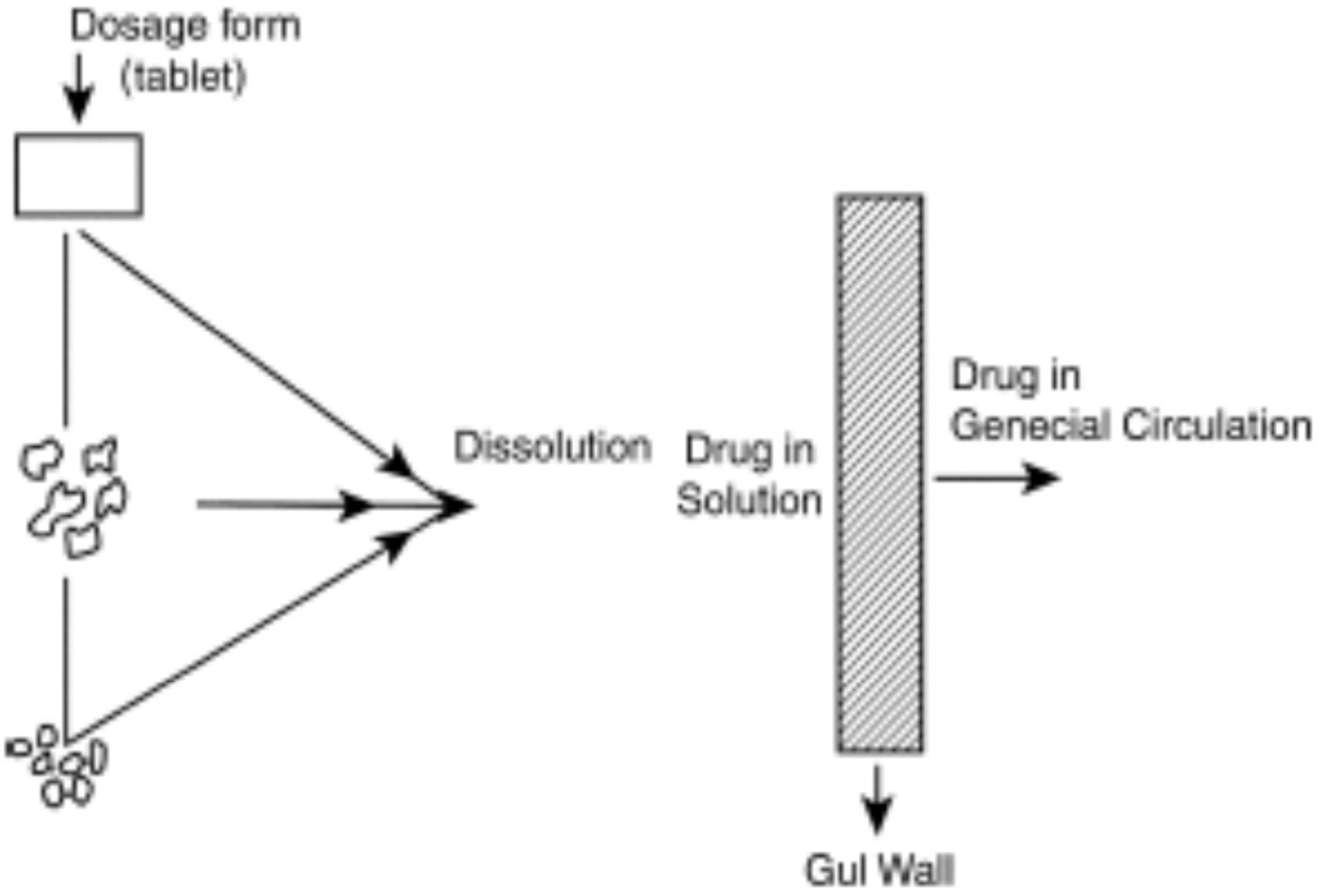
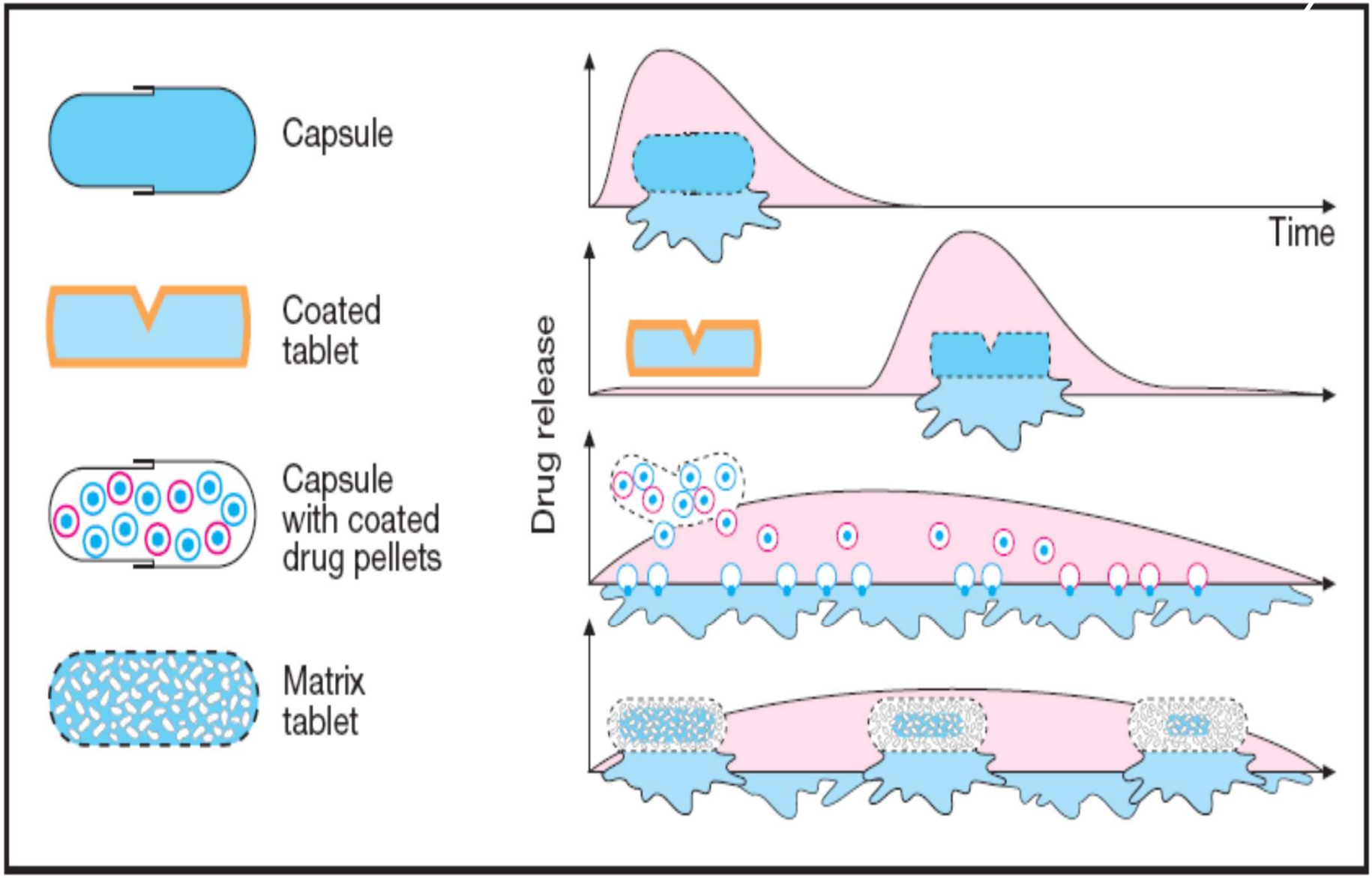


Figure 2 Schematic representation of the process of the drug dissolution and its entry into the general circulation.



C. Dosage forms controlling rate of drug dissolution

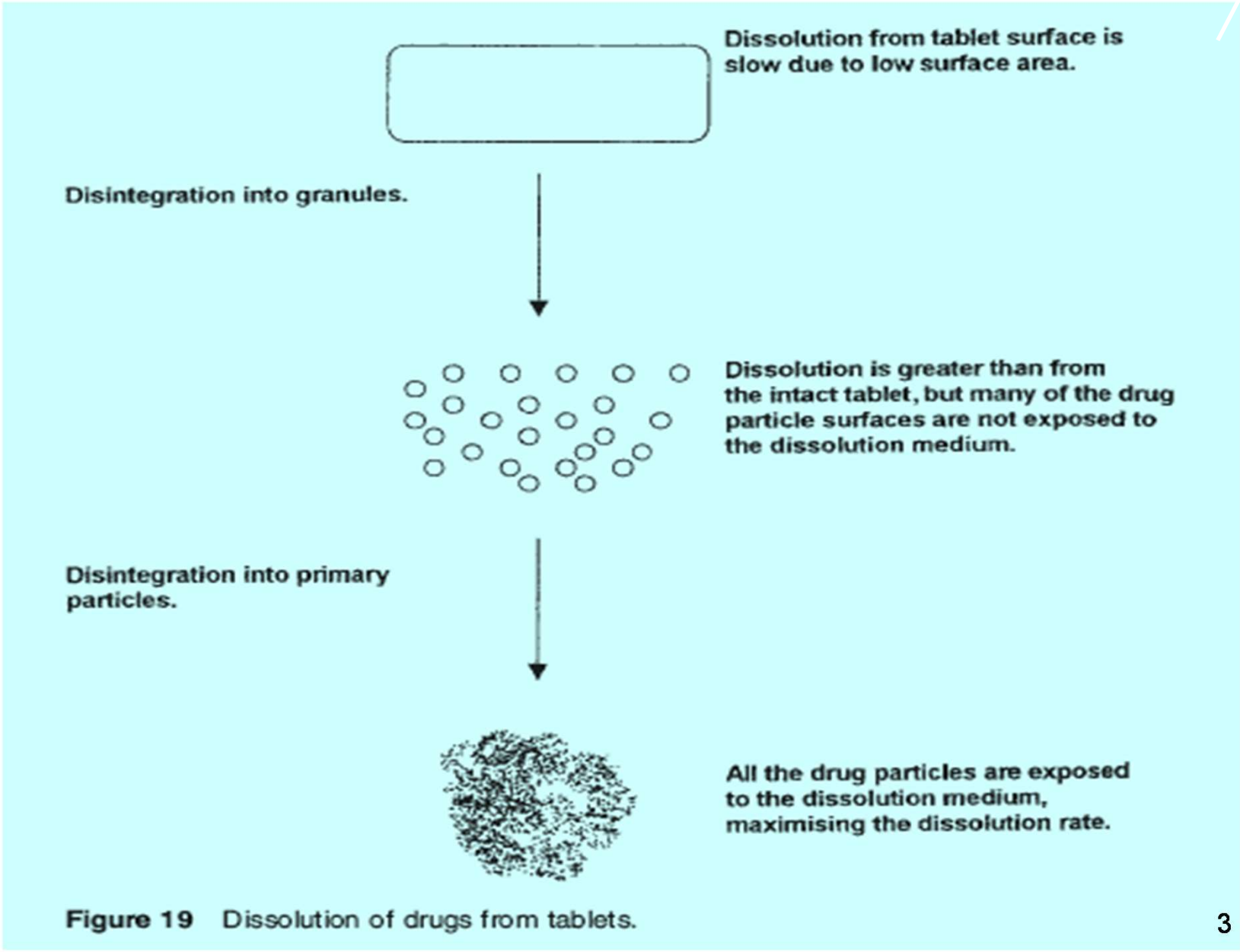


Figure 19 Dissolution of drugs from tablets.

The Noyes-Whitney equation

- $dM / dt = (DS / h) (C_s – C)$

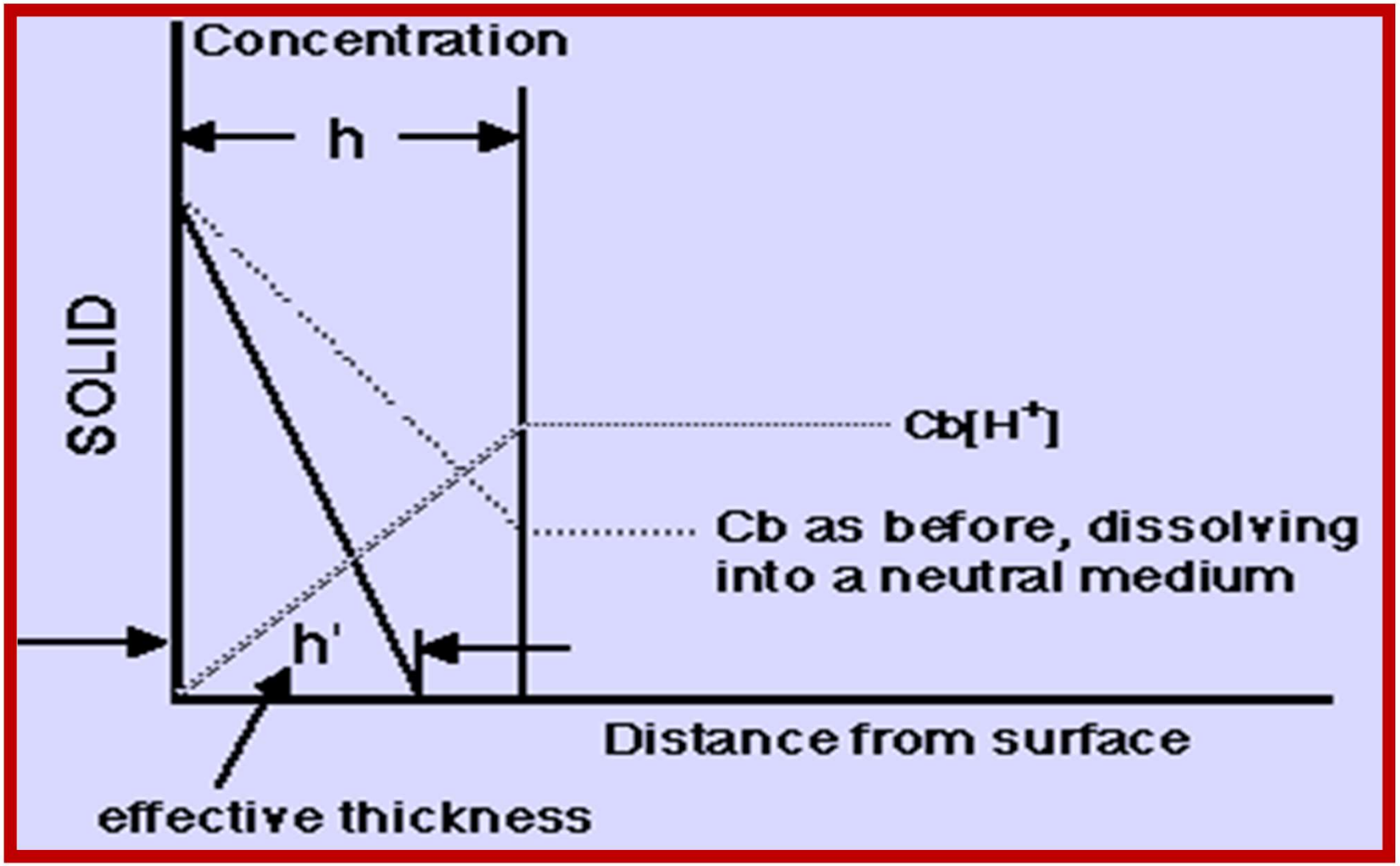
or

- $dC / dt = (DS / V h) (C_s – C)$

- **M**: the mass of solute dissolved in time t
- **dM/dt**: the mass rate of dissolution (mass/time)
- **D**: the diffusion coefficient of the solute in solution
- **S**: the surface area of exposed solid
- **h**: the thickness of the diffusion layer
- **C_s**: the solubility of the solid
- **C**: the concentration of solute in the bulk solution and at time t

The *Noyes-Whitney equation* which is a modified Fick's equation as the following

$$dc/dt = D*A*(Cs - Cb) / h$$



Driving Force for Dissolution and Sink Conditions

- The driving force for dissolution is the concentration gradient across the boundary layer.
- The driving force depends on the thickness of the boundary layer and the concentration of drug that is already dissolved.
- When C is less than 20% of the C_s, the system is to operate under "sink conditions."

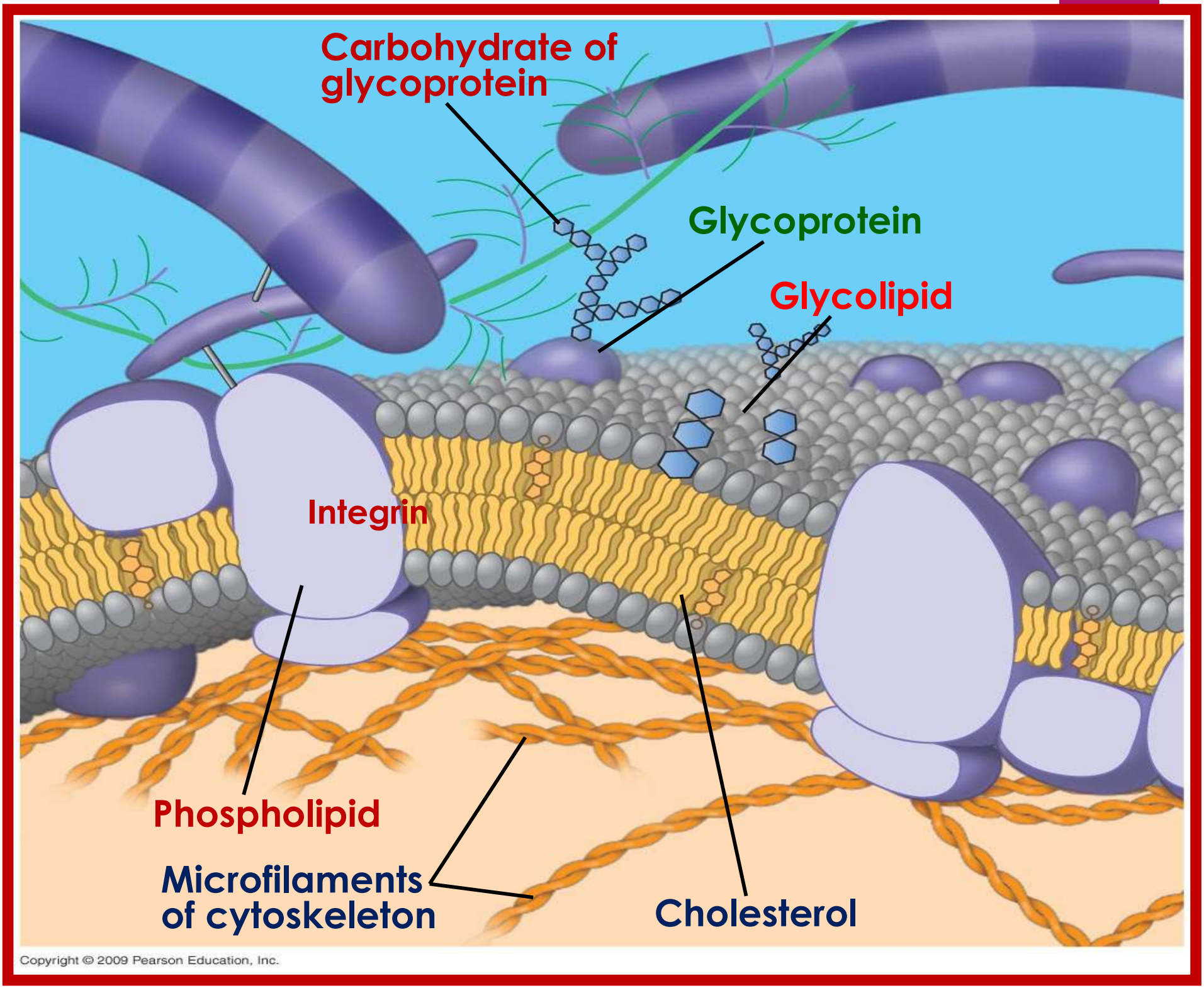
$$\rightarrow dM / dt = (DS / h)(C_s)$$

THE ROLE OF DISSOLUTION TESTS

Dissolution tests are used for many purposes in the pharmaceutical industry:

1. **The development of new products**
2. **For quality control, and**
3. **To assist with the determination of bioequivalence.**

Recent regulatory developments such as the Biopharmaceutics Classification Scheme (BCS) have highlighted the importance of dissolution in the regulation of post approval changes and introduced the possibility of substituting dissolution tests for clinical studies in some cases.



Passive Transport

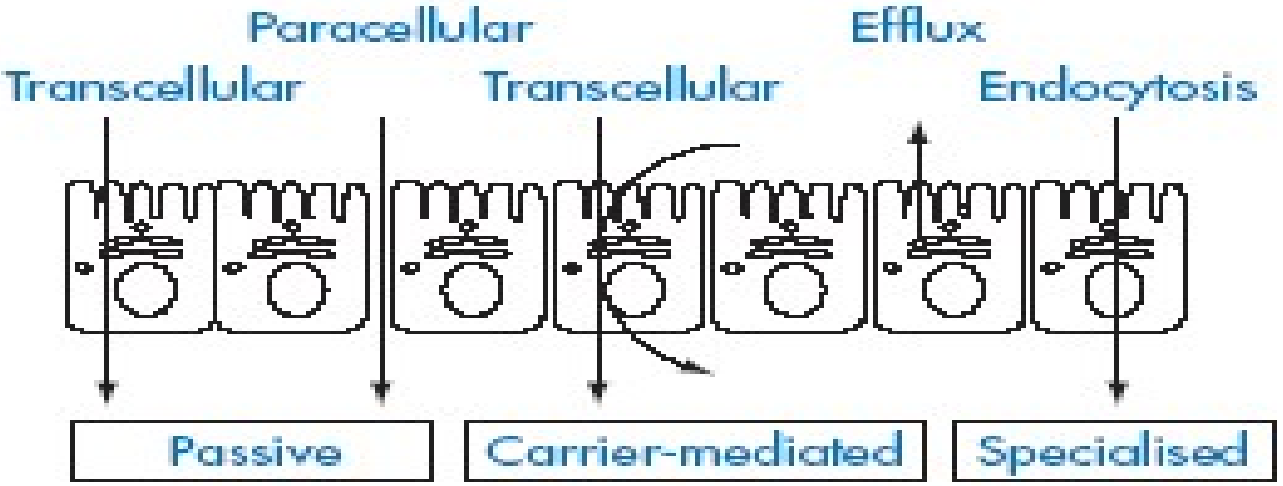


Figure 9.11 GI membrane transport. Transport through the enterocyte barrier can be divided into active, passive and specialized transport; and into the paracellular and transcellular routes. Efflux mechanisms can reduce absorption by these routes.

- In **passive transport** substances cross the membrane by **diffusion**
  - **Diffusion - net movement of substances from an area of high concentration to low concentration**
    - **no energy required**

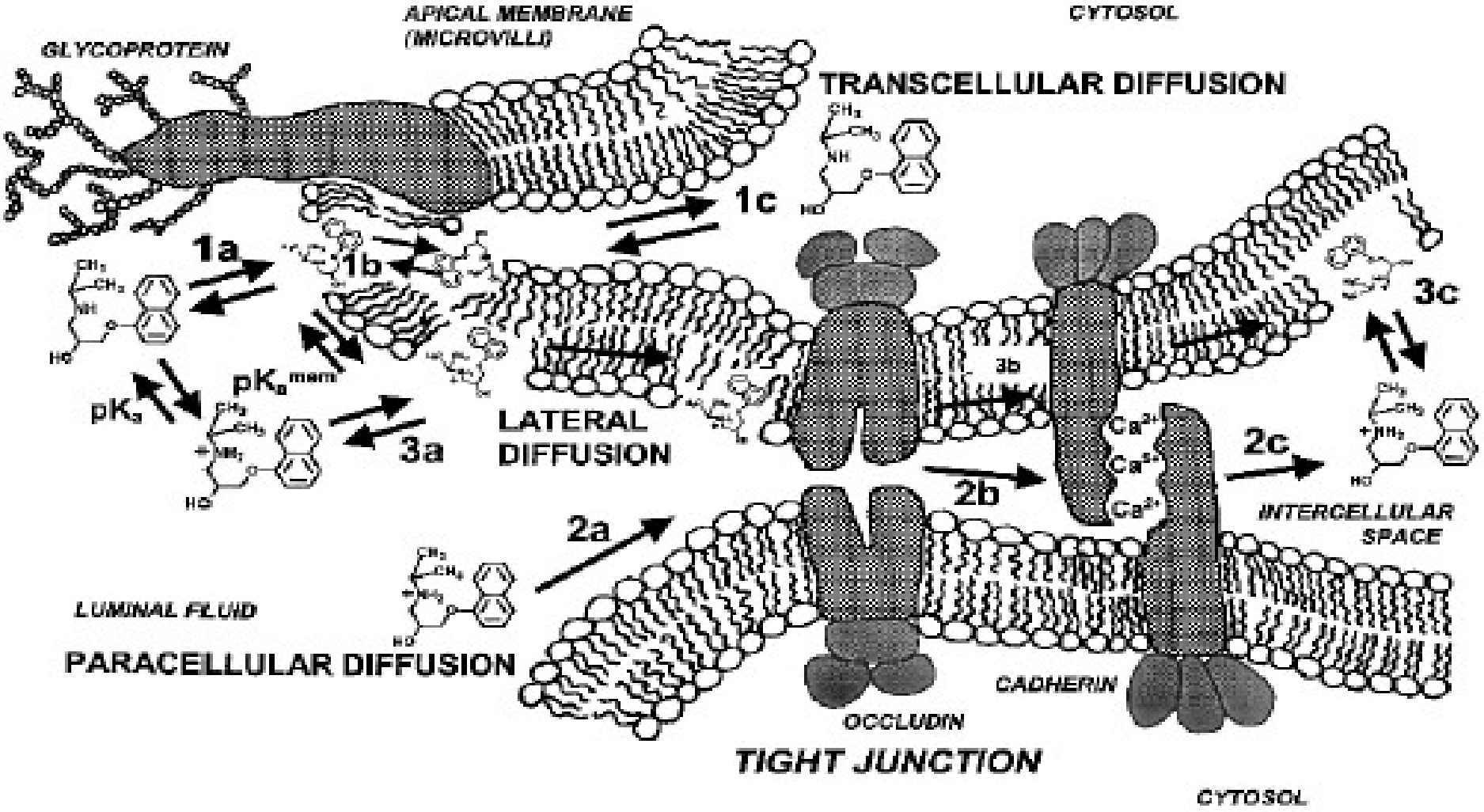


Figure 2.7 Schematic of the apical phospholipid bilayer surface of the epithelial cells, indicating three types of passive diffusion: transcellular (1a→1b→1c), paracellular (2a→2b→2c), and the hypothesized lateral, "under the skin of the tight junction" (3a→3b→3c) modes. Tight-junction matrix of proteins highly stylized, based on Ref. 75. [Avdeef, A., *Curr. Topics Med. Chem.*, 1, 277–351 (2001). Reproduced with permission from Bentham Science Publishers, Ltd.]

PASIVE DIFFUSION

Fick's Law: $dM / dt = (DKS / h) (C_s - C)$

dM / dt = J = Flux

DK / h = Permeability (coefficient) (P)

$C_s - C$ = ΔC = Concentration gradient

S = Surface area

h = membrane thickness

K = Partition coefficient

Simple Diffusion

- **Nonpolar, hydrophobic molecules** diffuse directly through the lipid bilayer
  - Simple diffusion does not require the use of transport proteins.
  - Examples: O_2, CO_2, steroids

- **Polar, hydrophilic substances** cannot pass directly through the lipid bilayer
  - Examples: water, ions, carbohydrates

Simple Diffusion

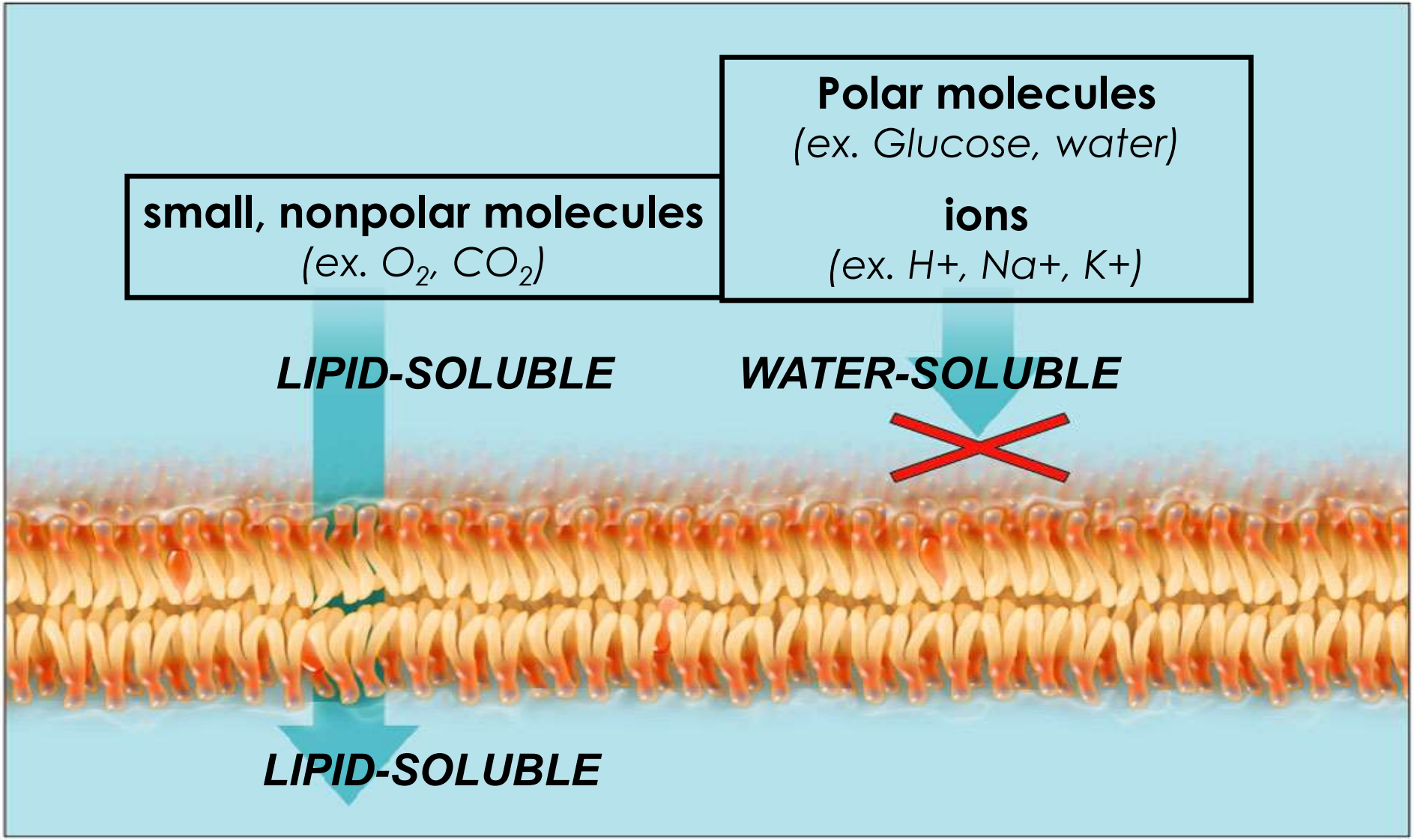
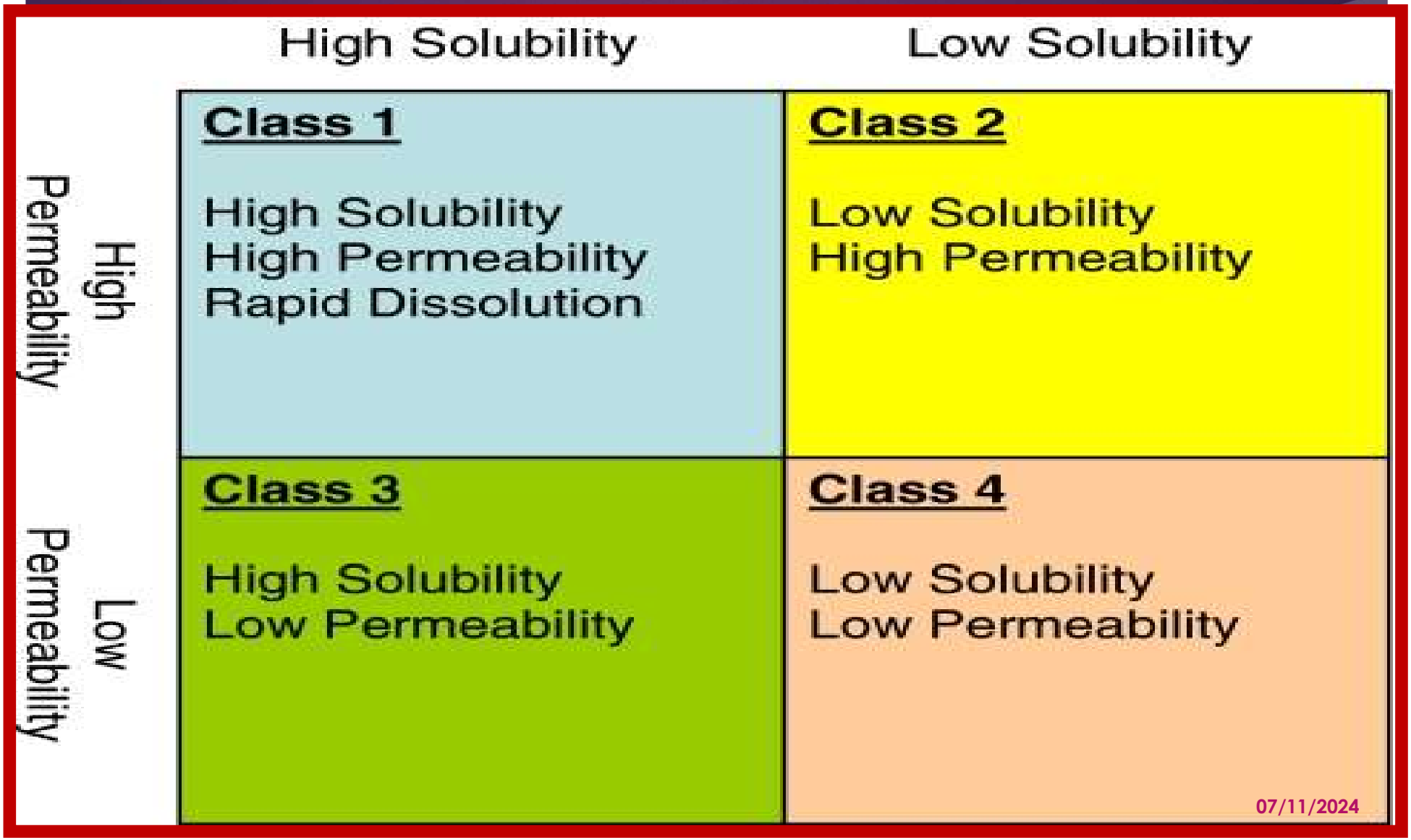


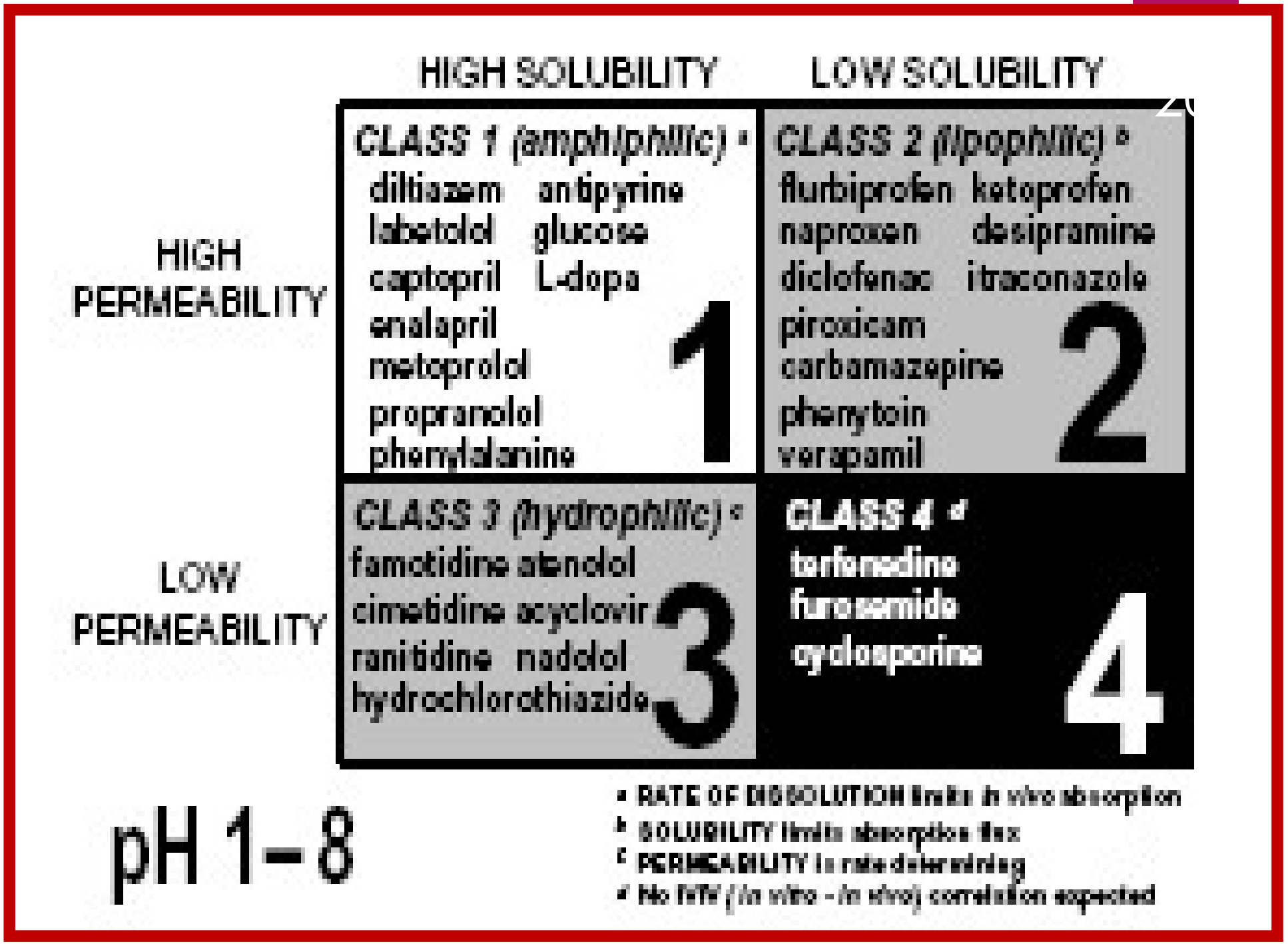
Table 2.1 Factors influencing gastrointestinal absorption of drugs.

Physiochemical factors of drug substances	Physiological factors of GIT	Dosage form and formulation factors
Solubility	Stomach emptying rate	Dissolution rate
log *P*	Intestinal motility/flow rate	Disintegration rate
pK_a	Membrane surface area	Drug release mechanisms
H-bonding potential	Intestinal metabolism	Excipient effects
Molecular weight/size	Transport mechanisms	
PSA	Native surfactants	
	Intestinal secretions, e.g. mucous, enzymes	
	Intestinal blood/lymph flow	

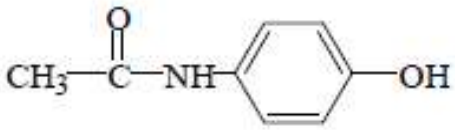
GIT: gastrointestinal tract; PSA: polar surface area; log *P*: octanol/water partition coefficient.

THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

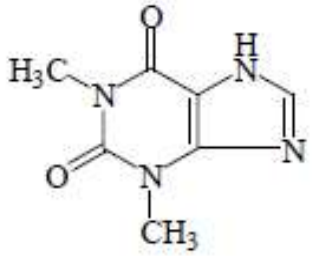



HIGH SOLUBILITY
LOW SOLUBILITY
HIGH PERMEABILITY
LOW PERMEABILITY
CLASS 1 (amphiphilic) a
diltiazem antipyrine
labetolol glucose
captopril L-dopa
enalapril
metoprolol
propranolol
phenylalanine
1
CLASS 2 (lipophilic) b
flurbiprofen ketoprofen
naproxen desipramine
diclofenac itraconazole
piroxicam
carbamazepine
phenytoin
verapamil
2
CLASS 3 (hydrophilic) c
famotidine atenolol
cimetidine acyclovir
ranitidine nadolol
hydrochlorothiazide
3
CLASS 4 d
terfenadine
furosemide
cyclosporine
4
pH 1–8
a RATE OF DISSOLUTION limits in vivo absorption
b SOLUBILITY limits absorption flux
c PERMEABILITY is rate determining
d No IVIV (in vitro - in vivo) correlation expected

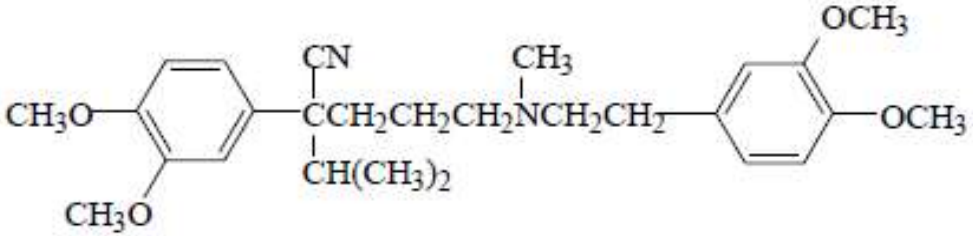
Examples of Class I Drugs



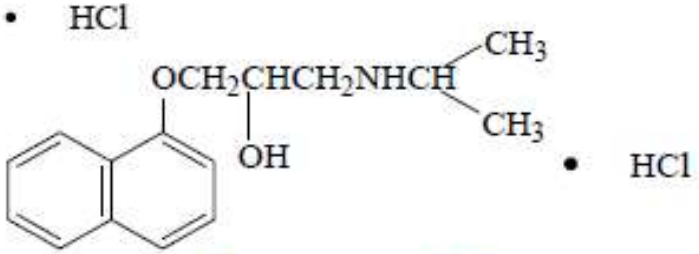
Acetaminophen, Paracetamol



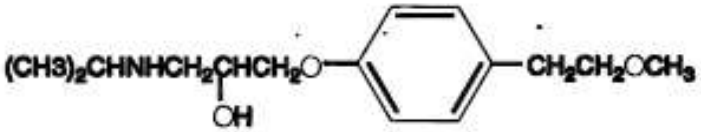
Theophylline (NTI)



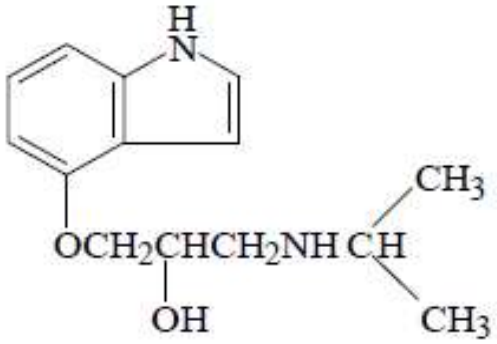
Verapamil



Propranolol

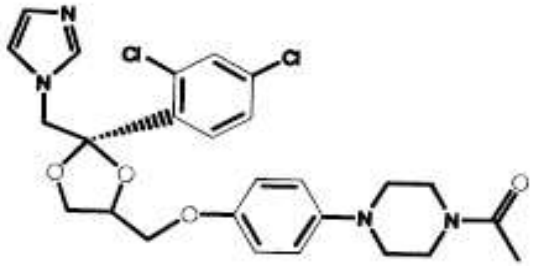


Metoprolol

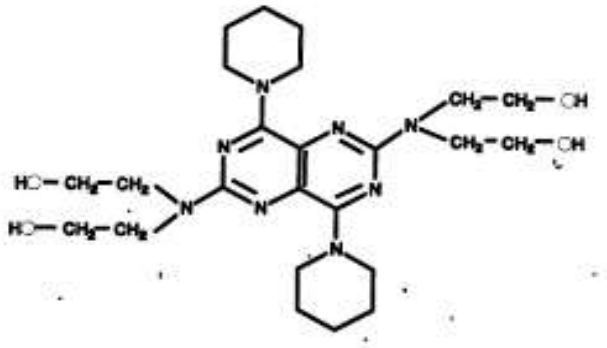


Pindolol

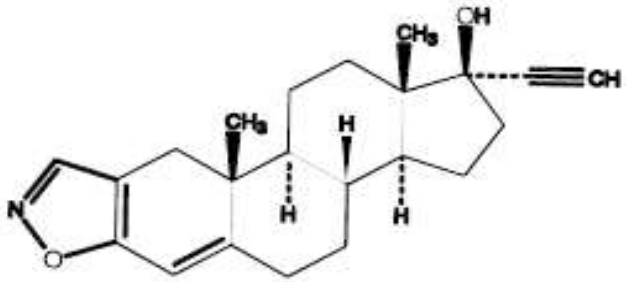
Examples of Class II Drugs



Ketoconazole (pKa = 6.5, 2.9)



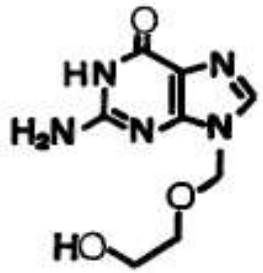
Dipyridamole (pKa = 6.4)



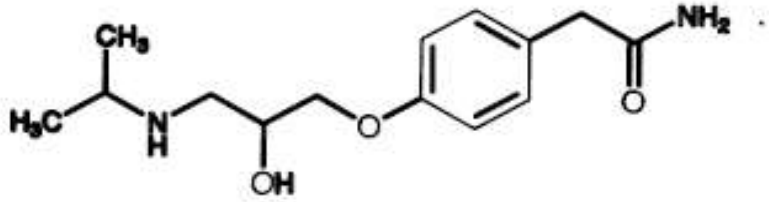
Danazol

Atovaquone
Carbamazepine
Glibenclamide
Griseofulvin
Troglitazone
Ibuprofen

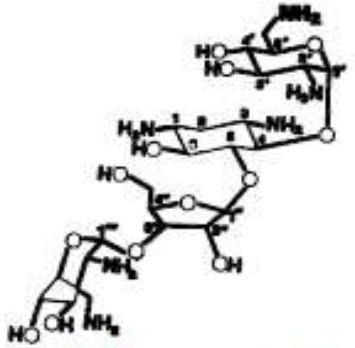
Examples of Class III Drugs



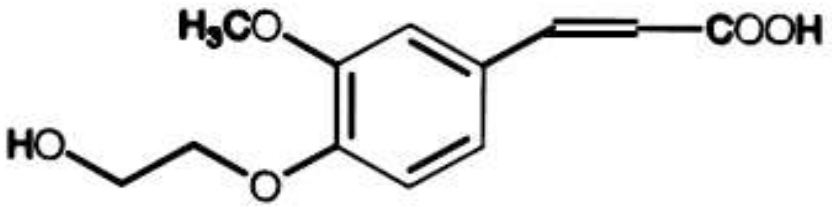
Acyclovir



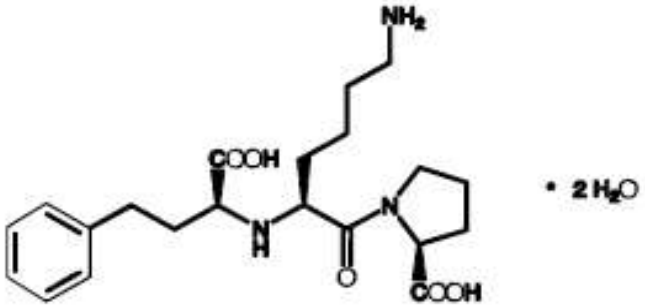
Atenolol (F = 0.5)



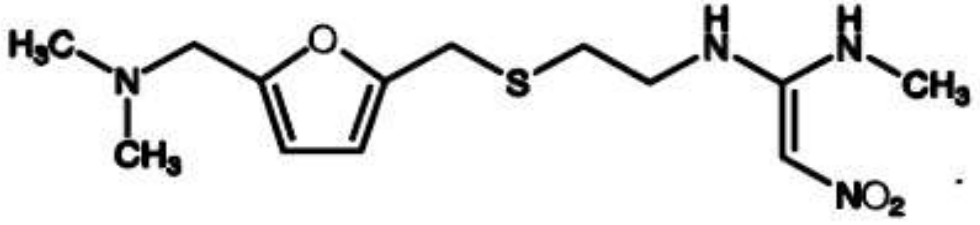
Neomycin



Cimetidine (F = 0.84)

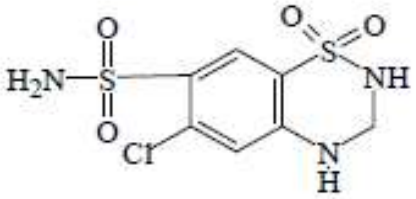


Lisinopril

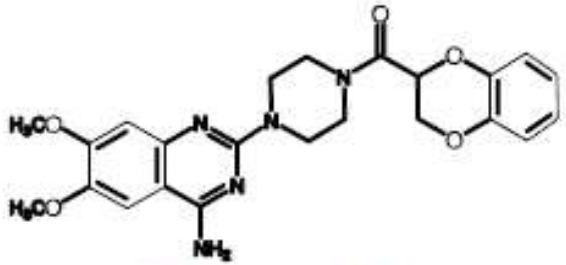


Ranitidine (F = 0.52)

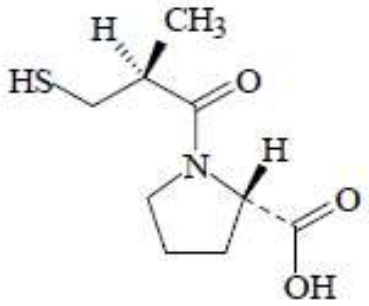
Examples of Class III Drugs *(continued)*



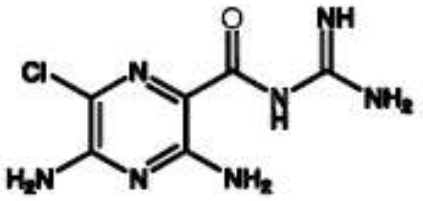
Hydrochlorothiazide (0.71)



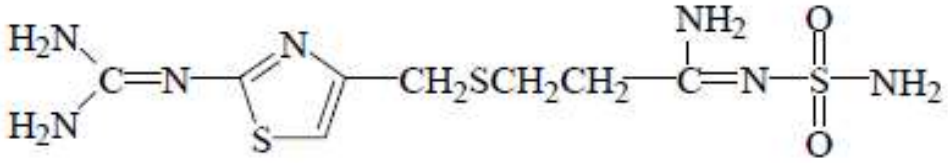
Doxazosin



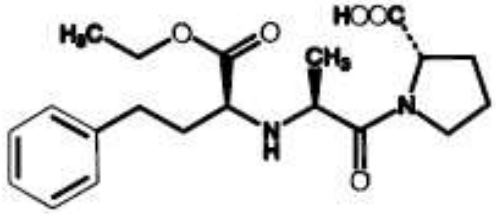
Captopril (0.37)



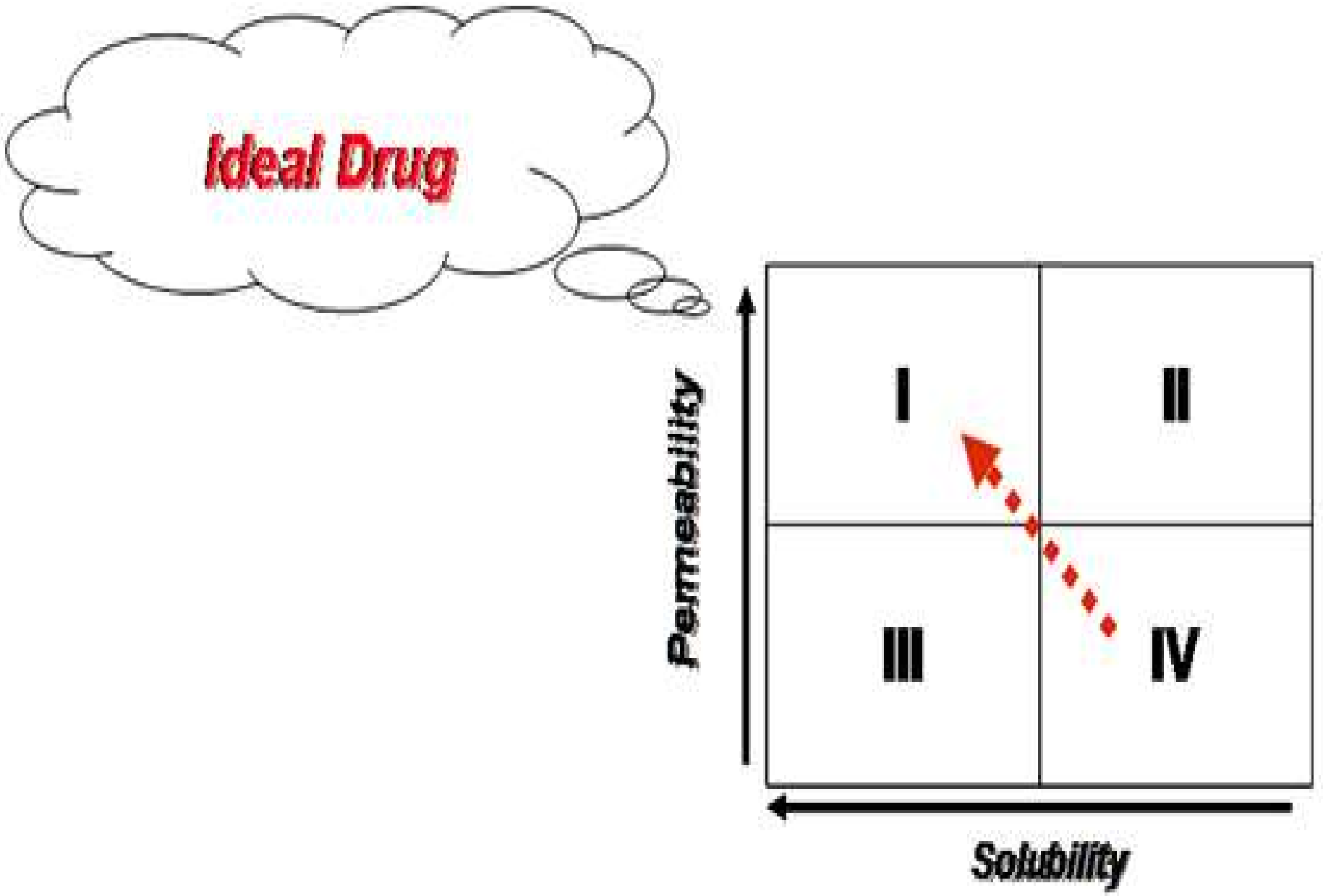
Amiloride



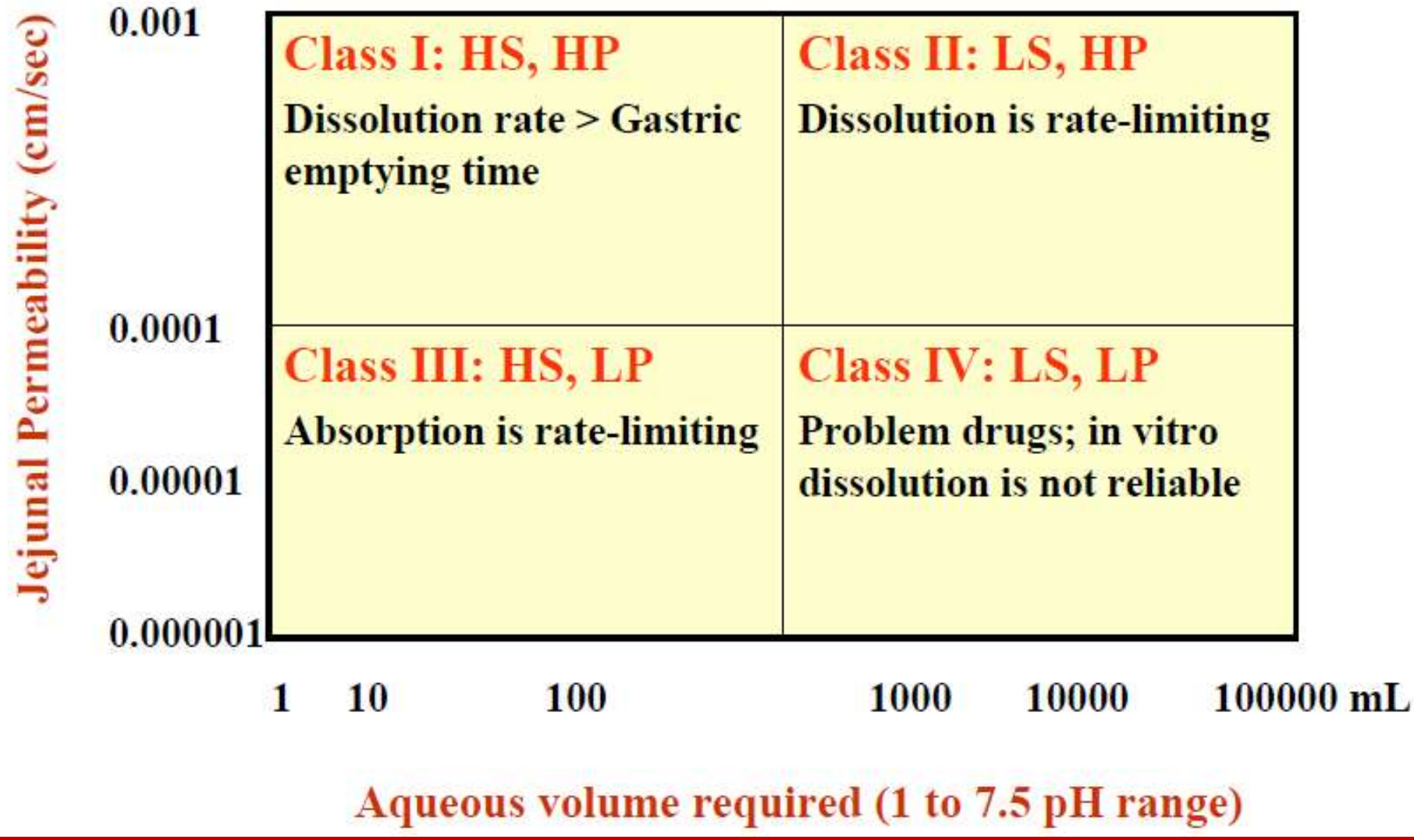
Famotidine (0.45)



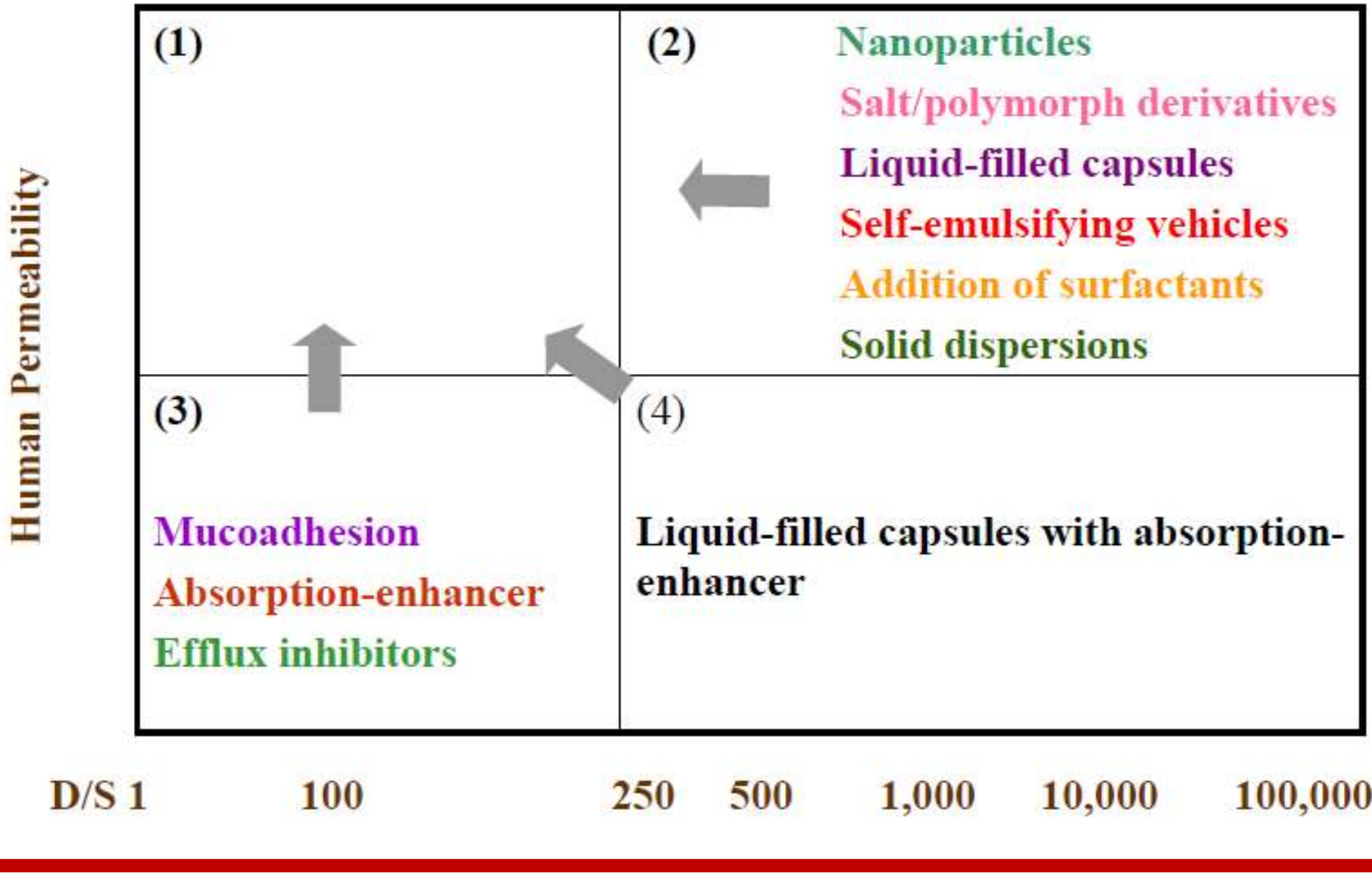
Enalapril

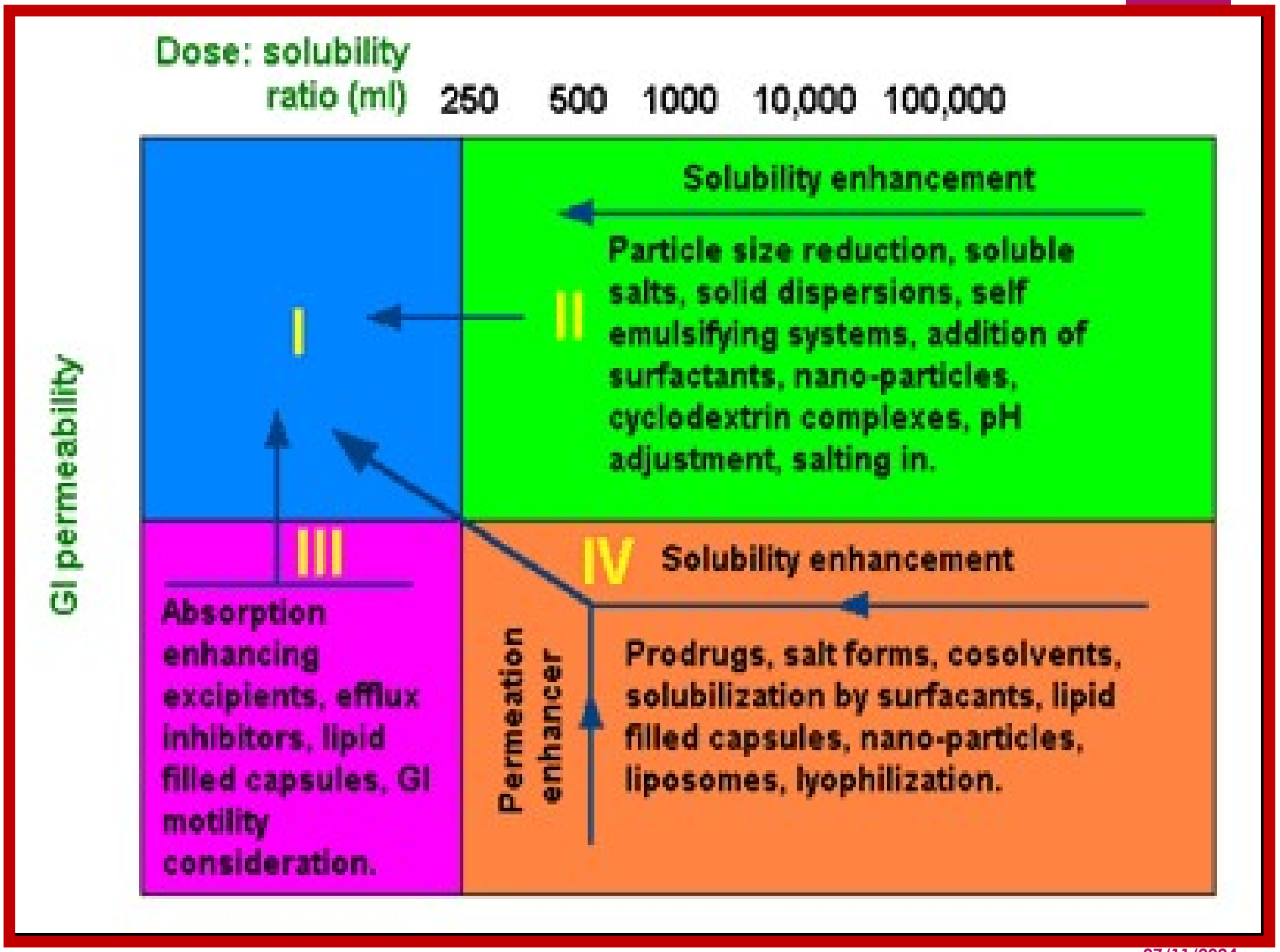

Ideal Drug
I
II
III
IV
Permeability
Solubility

Biopharmaceutics Classification System



Formulation Approaches




Dose: solubility ratio (ml)
250
500
1000
10,000
100,000
GI permeability
Solubility enhancement
I
II
Particle size reduction, soluble salts, solid dispersions, self emulsifying systems, addition of surfactants, nano-particles, cyclodextrin complexes, pH adjustment, salting in.
III
Absorption enhancing excipients, efflux inhibitors, lipid filled capsules, GI motility consideration.
IV
Solubility enhancement
Permeation enhancer
Prodrugs, salt forms, cosolvents, solubilization by surfacants, lipid filled capsules, nano-particles, liposomes, lyophilization.

Proposed Limits of Drug Dissolution on Solubility to Avoid Absorption Problems

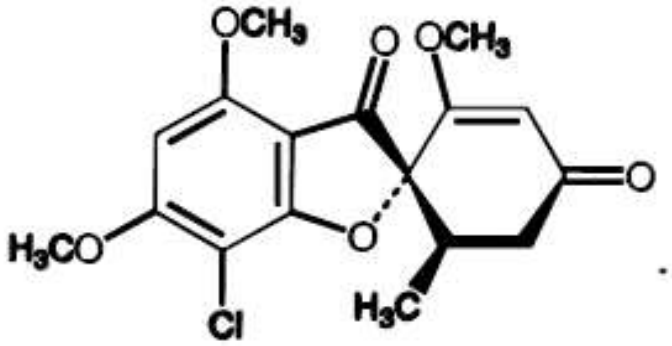
Factor	Limit	References
Solubility in pH 1–7	>10 mg/mL at all pH	Kaplan (1972)
Solubility in pH 1–8 and dose	Complete dose dissolved in 250 mL at all pH	Amidon et al. (1995)
Water solubility	>0.1 mg/mL	Hörter and Dressman (1997)
Dissolution rate in pH 1–7	>1 mg/min/cm^2 (0.1–1 mg/nm/cm^2 borderline) at all pH	Kaplan (1972)

Solubility Criterion: D/S Ratio

$$\frac{\text{Dose}}{\text{Solubility}} = \frac{\text{Dose (mg)}}{\text{Aqueous Solubility (mg/mL)}} = 250\ \text{mL}$$

(a) When D/S is < 250 mL over a pH range of 1 to 7.5;

(b) When D/S is > 250 mL;



D/S = 33 liters
Log P = 2.18

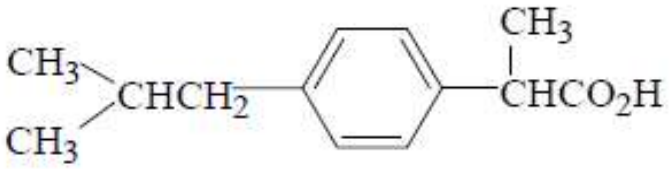
Class 2 Drug Candidate?

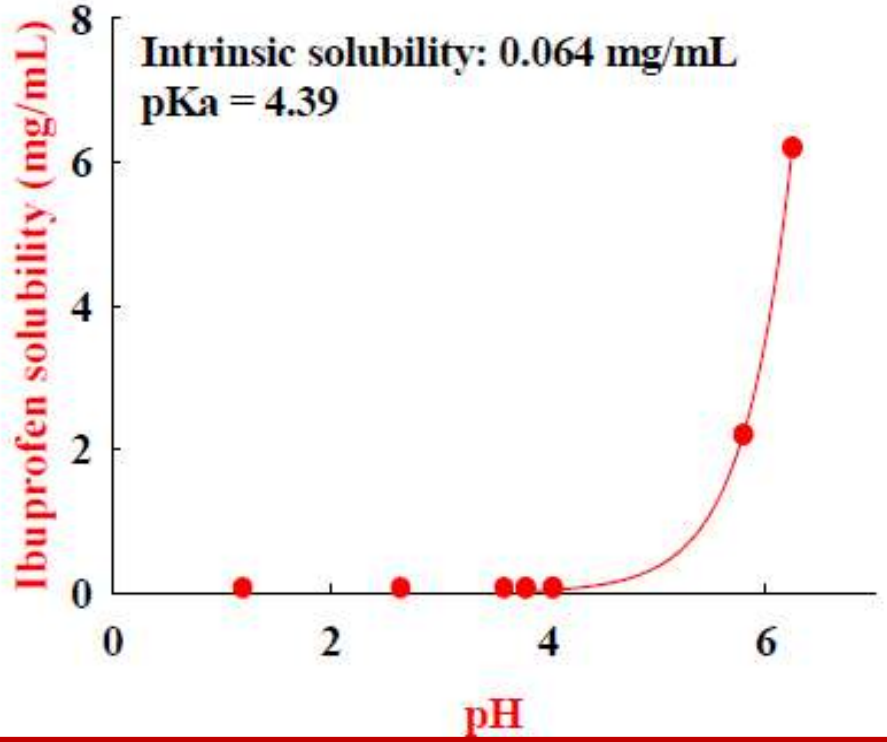
Griseofulvin: S = 15 μg/mL; Dose = 500 mg

Extension Opportunities for Class II Drugs: Solubility Issue (pH)

- **Some class 2 drugs with pKa <4.5 and instrinsic solubility of > 0.01 mg/mL are consistently and completely absorbed after oral administration**

- **These drugs will have solubility of >1 mg/mL in the jejunum (pH 6.5), resulting in fast and reliable dissolution of the drug. However, they can't fulfill the BCS solubility criteria (poorly soluble at gastirc pH)!**





Other Class II Drugs: Solubility (pH)

Compound	pKa	Human BA (%)	Sol, pH 1.2 (mg/mL)	Sol, pH 7.4 (mg/mL)	Dose (mg)
Fenoprofen	4.5	85	0.1	> 3.1	200
Flurbiprofen	4.3	92	0.007	2.6	100
Ibuprofen	4.4	> 80	0.06	2.3	200
Ketoprofen	4.6	100	0.13	> 1.4	75
Naproxen	4.2	99	0.005	> 2.5	200
Oxaprozin	4.3	95 – 100	0.004	1.7	600

Proposed permeability

A general guide would be:

= 1 × 10^{-6} cm per sec (10 nm per sec) or lower is classed as low permeability

- According to WHO guidance an API is considered highly permeable when the extent of absorption in humans is 85% or more based on a mass balance determination or in comparison with an intravenous comparator dose.

- An acceptable alternative test method for permeability determination of the API could be *in vivo* intestinal perfusion in humans. When this method is used for permeation studies, suitability of the methodology should be demonstrated, including determination of permeability relative to that of a reference compound whose fraction of dose absorbed has been documented to be at least 85%, as well as use of a negative control.

- According to EMEA BCS guidance if a drug substance has linear and complete absorption then it is considered highly permeable.

Permeability Determination for BCS

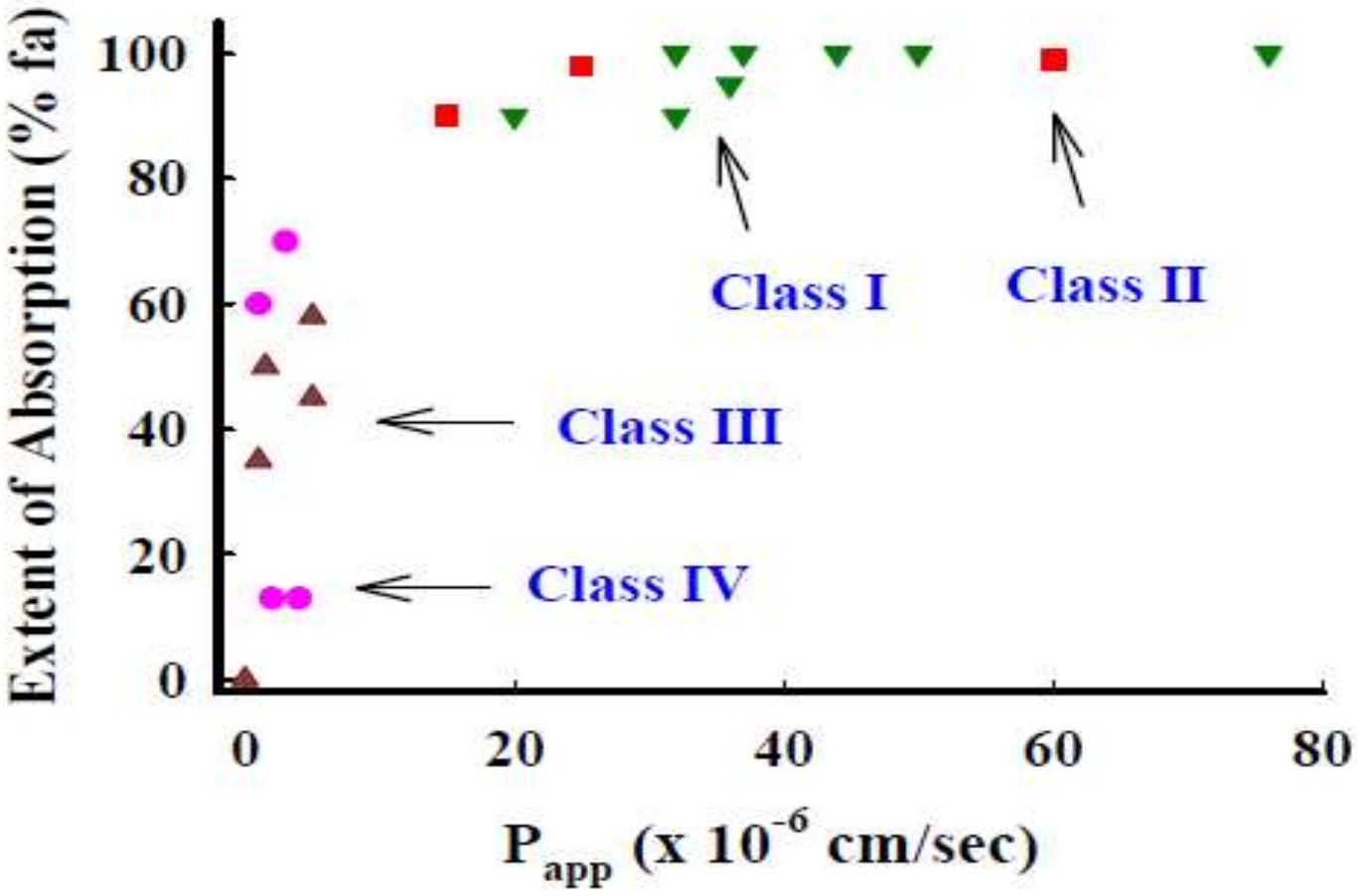
Pharmacokinetic Studies

- Absolute bioavailability studies
- Mass balance studies with use of radiolabeled drug

Intestinal Permeabililty Studies

- Jejunal perfusion method
- In vitro Caco-2 permeability study

Permeability Assay: Method Suitability



USFDA BCS guidance

- According to USFDA BCS guidance a drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1-7.5.

- According to USFDA BCS guidance, in the absence of evidence suggesting instability in the GI tract, a drug substance is considered to be highly permeable when the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.

THE RULE OF 5 or LIPINSKI'S RULE

This rule of 5 states that poor absorptions or permeations are more likely when:

1. There are more than 5 H-bond donors
   (expressed as the sum of OHs and NHs)
2. There are more than 10 H-bond acceptors
   (expressed as the sum of Ns and Os)
3. The MW (Molecular Weight) is over 500
4. The log partition coefficient is over 5
5. Compound classes that are substrates for biological transporters are exceptions to the rule.

- The rule also states that if two or more parameters are not within the limits the compound is expected to show poor absorption properties.

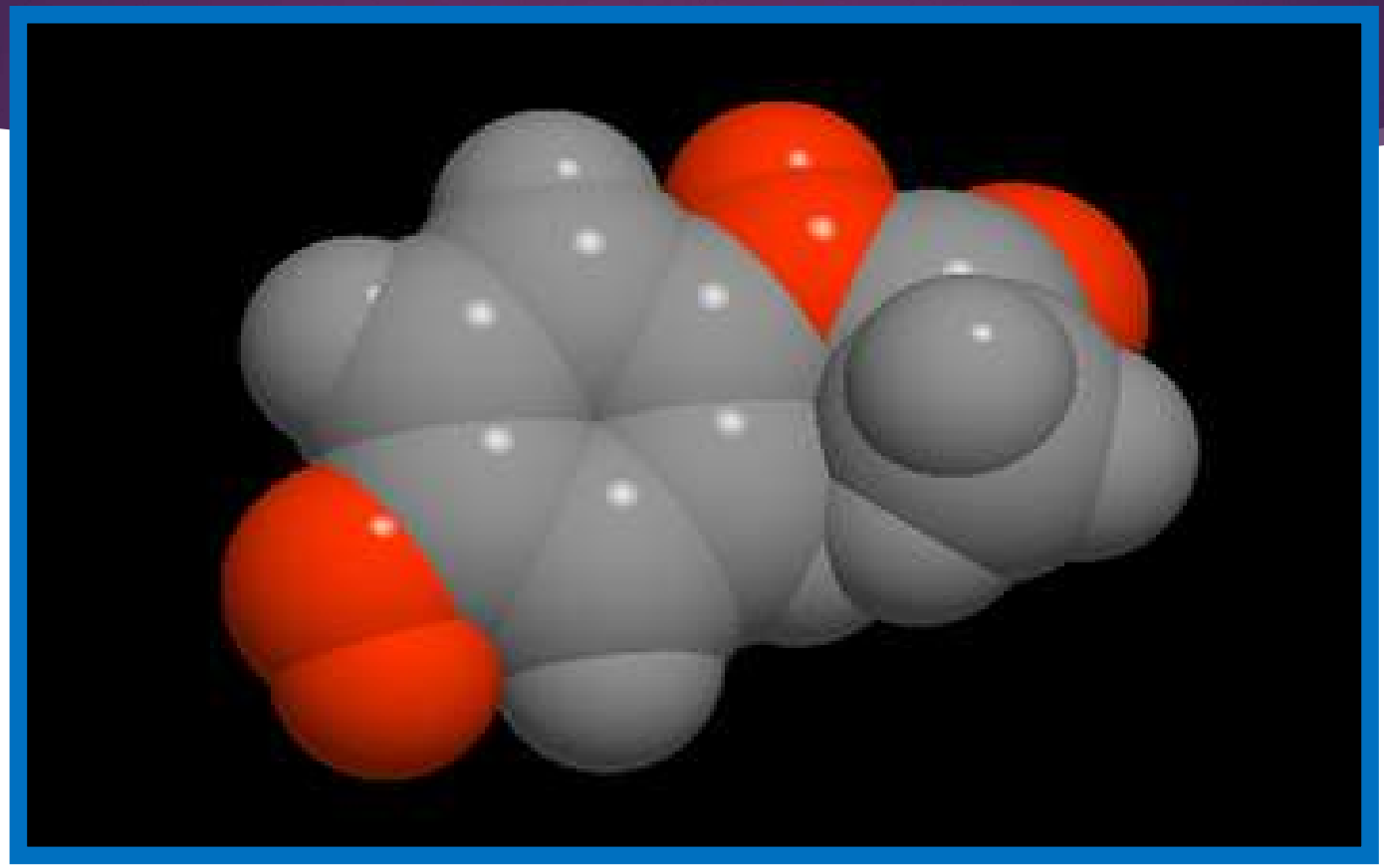
- To improve the predictability using the rule of five, Veber et al. have suggested additional parameters to be included, in order a drug may be absorbed of 90% or better, such as:

1. polar surface area (PSA) (<140A^2),

2. the sum of H-bond donors and acceptors (<12), and

3. the number of rotatable bonds (<10)

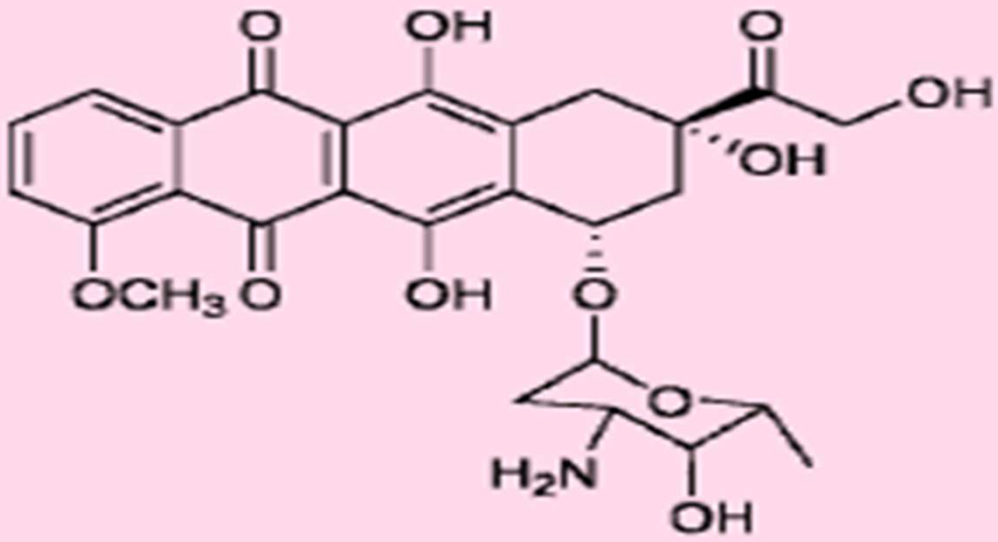
Polar Surface Area (PSA)



Polar surface area (in red) of Paracetamol

Functional group	H-bond donor	H-bond acceptors
Hydroxyl	1 (OH)	1 (O)
Carboxylic acid	1 (OH)	2 (2 Os)
–C(O)-N-R_2	0	2 (N, O)
Primary amine	2 (NH_2)	1 (N)
Secondary amine	1 (NH)	1 (N)
Aldehyde	0	1 (O)
Ester	0	2 (O)
Ether	0	1 (O)
Nitrile	0	1 (N)
Pyridine	0	1 (N)

- The polar surface area (PSA) is defined as the surface sum over all polar atoms, (usually oxygen and nitrogen), including also attached hydrogens.
- PSA is a commonly used medicinal chemistry metric for the optimization of cell permeability.
- Molecules with a polar surface area of greater than 1.4 square nanometres (140 A) are usually believed to be poor at permeating cell membranes.
- For molecules to penetrate the blood-brain barrier (and thus acting on receptors in the central nervous system), PSA should be less than 0.6 square nanometres.



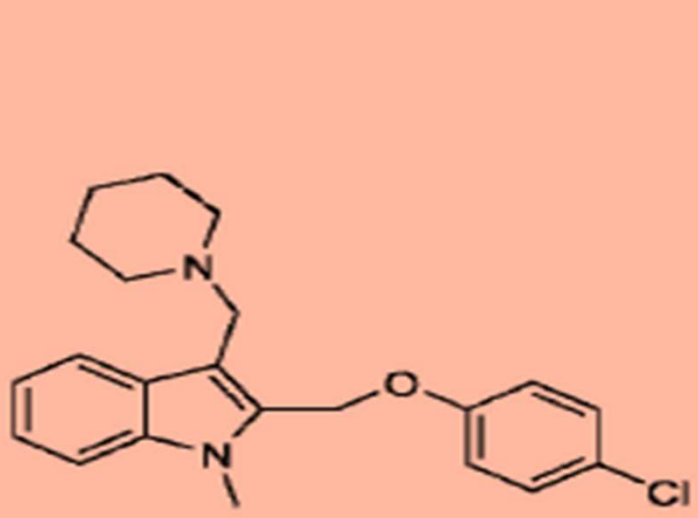
Lipinski Rules

- H-bond donors = 7
- MW = 543
- ClogP = −1.7
- H-bond acceptors = 12

Veber Rules

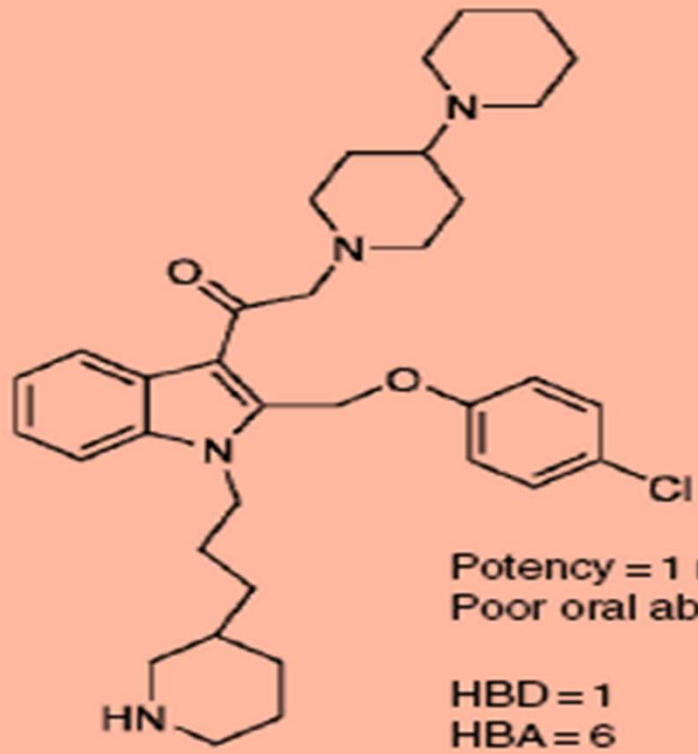
- Rotatable bonds = 11
- PSA = 206
- Total H-bonds = 19

Example of counting and calculations for the Lipinski and Veber rules for doxorubicin, which has an oral bioavailability of approximately 5%. Guidelines are exceeded for all rules except Clog P.



Potency = 2 μM

HBD = 0
HBA = 3
MW = 369
Log P = 5.7
PSA = 17
Rotatable bonds = 6



Potency = 1 nM
Poor oral absorption

HBD = 1
HBA = 6
MW = 591
Log P = 7.3
PSA = 50
Rotatable bonds = 14
Total HB = 6

Structural optimization for activity in this neuropeptide Y Y1 antagonist discovery project modified the lead on the left to the compound on the right.

Although a 2,000-fold increase in potency was achieved, the resulting compound had poor absorption properties after oral dosing, as anticipated from the structural rules.

Table 9 Most Commonly Used Classes of Enhancers to Drug Absorption from the Gastrointestinal Tract

Nonsteroidal anti-inflammatory drugs and derivatives
- Sodium salicylate
- Sodium 5-methoxysalicylate
- Indomethacin
- Diclofenac

Surfactants
- Nonionic: polyoxyethylene ethers
- Anionic: sodium laurylsulfate
- Cationic: quaternary ammonium compounds

Bile salts

Dihydroxy bile salts: sodium deoxycholate

Trihydroxy bile slats: sodium cholate

Derivative: sodium tauro-24,25-dihydrofusidate

Medium-chain fatty acids
- Octanoic acid

Medium-chain glycerides
- Glyceryl-1-monooctanoate
- Glyceryl-1-monooctanoate

Enamines
- DL-Phenylalanine ethylacetoacetate enamine

Mixed micelles
- Glyceryl monooleate + sodium taurocholate
- Linoleic acid + HCO60

Calcium-binding agents
- Ethylenediaminetetraacetic acid (EDTA)

Phenothiazines
- Chlorpromazine

Liposomes

Azone

Fatty acid derivatives of carnitine and peptides
- Palmitoyl-DL-carnitine
- *N*-myristoyl-L-propyl-L-propyl-glycinate

Saponins

Concanavalin A

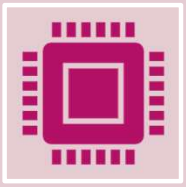
Phosphate and phosphonate derivatives
- DL-α-Glycerophosphate
- β-Amino-1-hydroxypropylidene-1,1-diphosphonate

Polyacrylic acid
- Diethyl maleate and diethylethoxy-
- Methylene malonate

Source: From van Hoogdalem et al. (1989).

Dissolution

According to USFDA BCS guidance an IR drug product is considered rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes,



→ using USP apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 ml or less in each medium: 0.1 N HCl or simulated gastric fluid USP without enzymes; buffer (pH 4.5); and buffer (pH 6.8) or simulated intestinal fluid USP without enzymes.

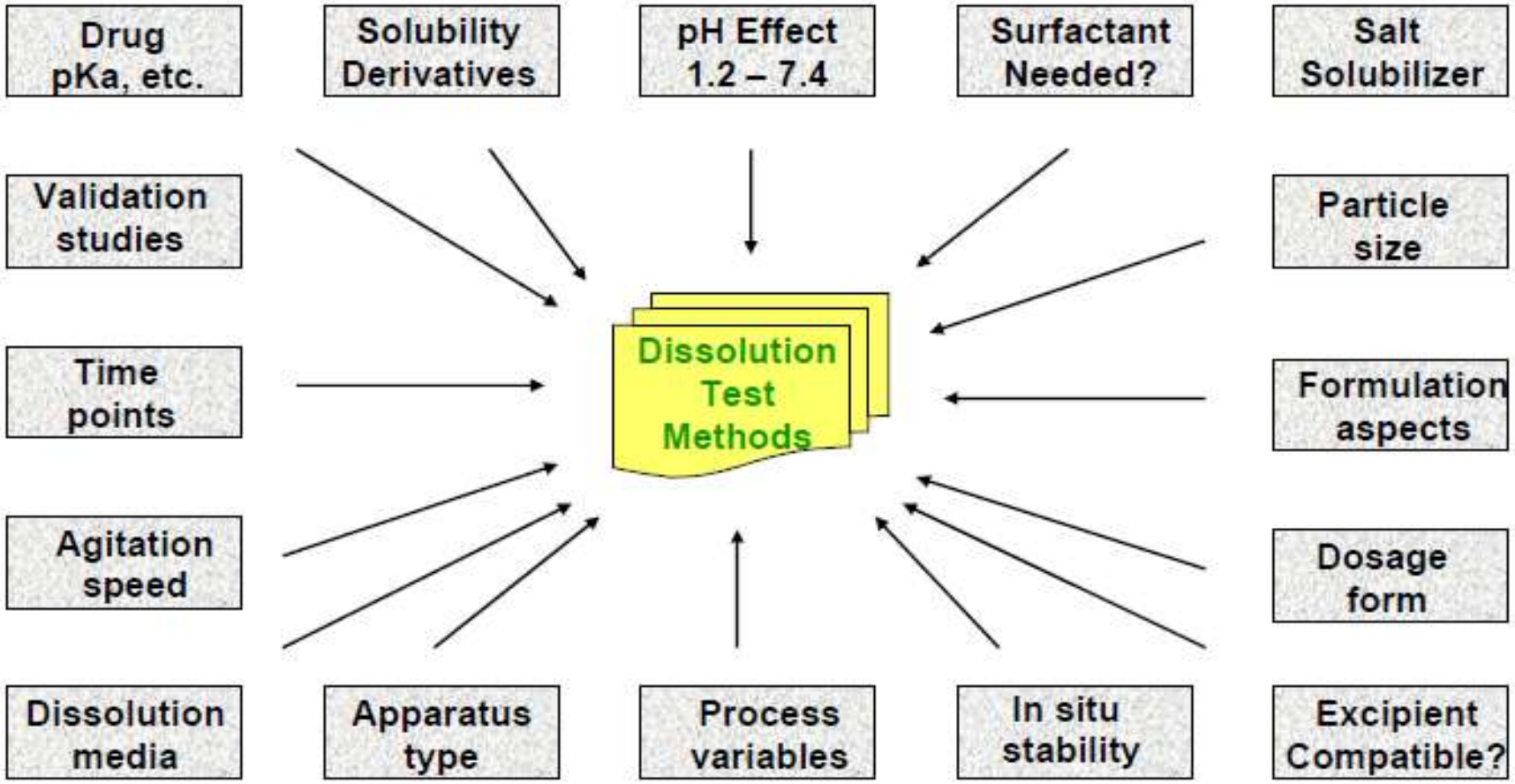
According to WHO BCS guidance a multisource product (pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent) is considered to be very rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves in 15 minutes using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 ml or less in each medium: HCl solution (pH 1.2); acetate buffer (pH 4.5); and phosphate buffer (pH 6.8).

Dissolution

- A multisource product is considered to be rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves in 30 minutes using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 ml or less in each of the media: HCl solution (pH 1.2); acetate buffer (pH 4.5); and phosphate buffer (pH 6.8).

- According to EMEA BCS guidance drug products are considered very rapidly dissolving when more than 85% of the labeled amount is dissolved in 15 minutes, using USP Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 500 ml in each of the media: 0.1 N HCl or simulated gastric fluid without enzymes; buffer (pH 4.5); and buffer (pH 6.8) or simulated intestinal fluid without enzymes and similarity of dissolution profiles should be demonstrated.

Development of Dissolution Test Methods




Thank
you

ADDITIONAL…

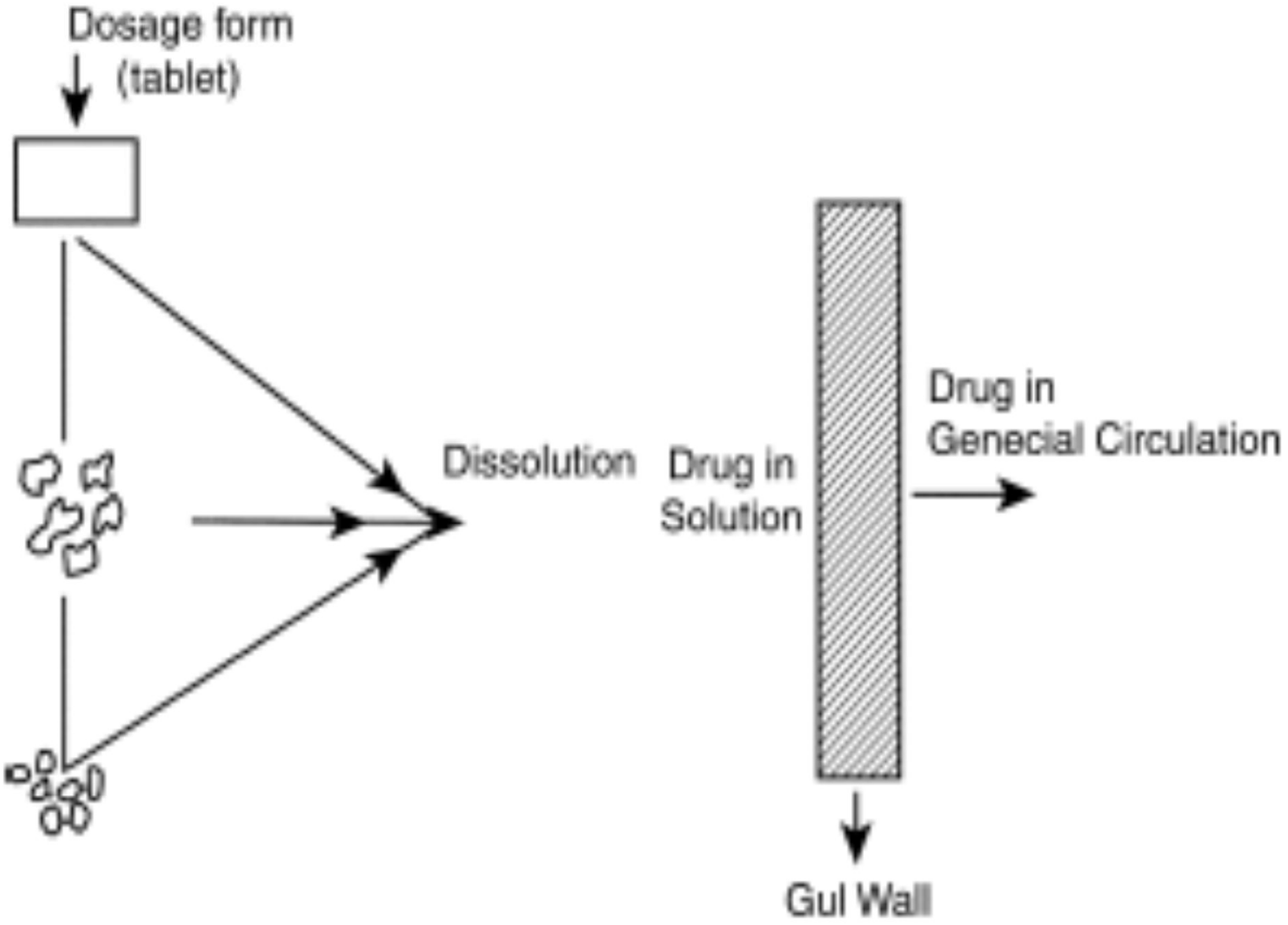


Figure 2 Schematic representation of the process of the drug dissolution and its entry into the general circulation.

Table 2.1 Factors influencing gastrointestinal absorption of drugs.

Physiochemical factors of drug substances	Physiological factors of GIT	Dosage form and formulation factors
Solubility	Stomach emptying rate	Dissolution rate
log *P*	Intestinal motility/flow rate	Disintegration rate
pK_a	Membrane surface area	Drug release mechanisms
H-bonding potential	Intestinal metabolism	Excipient effects
Molecular weight/size	Transport mechanisms	
PSA	Native surfactants	
	Intestinal secretions, e.g. mucous, enzymes	
	Intestinal blood/lymph flow	

GIT: gastrointestinal tract; PSA: polar surface area; log *P*: octanol/water partition coefficient.

Table 14.1 Physicochemical Properties for Consideration in Drug Product Design

pKa and pH profile	Necessary for optimum stability and solubility of the final product.
Particle size	May affect the solubility of the drug and therefore the dissolution rate of the product.
Polymorphism	The ability of a drug to exist in various crystal forms may change the solubility of the drug. Also, the stability of each form is important, because polymorphs may convert from one form to another.
Hygroscopicity	Moisture absorption may affect the physical structure as well as stability of the product.
Partition coefficient	May give some indication of the relative affinity of the drug for oil and water. A drug that has high affinity for oil may have poor release and dissolution from the drug product.
Excipient interaction	The compatibility of the excipients with the drug and sometimes trace elements in excipients may affect the stability of the product. It is important to have specifications of all raw materials.
pH stability profile	The stability of solutions is often affected by the pH of the vehicle; furthermore, because the pH in the stomach and gut is different, knowledge of the stability profile would help to avoid or prevent degradation of the product during storage or after administration.

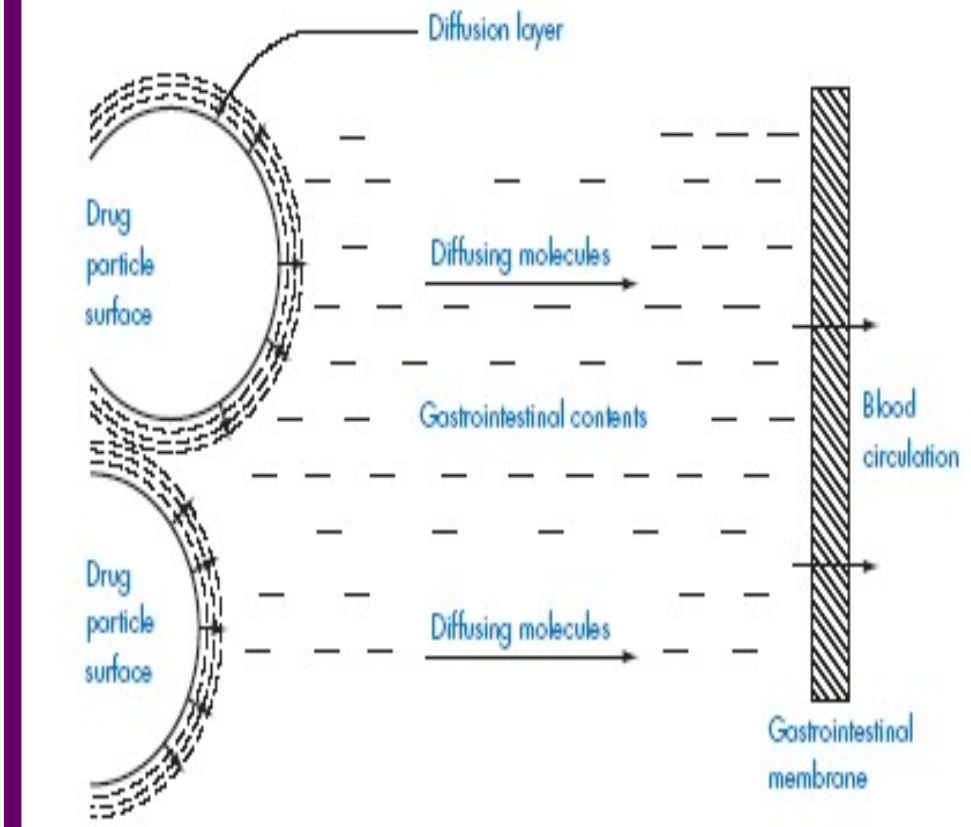
What is drug dissolution?

Drug dissolution:

- **The process by which drug molecules are liberated from a solid phase and enter into solution phase.**

- **The rate at which a solid dissolves in a solvent was proposed in quantitative terms by Noyes and Whitney (1897).**

The Noyes-Whitney equation:



Schematic diagram of dissolution from a solid surface.

$$dM / dt = (DS / h) (C_s - C)$$

or

$$dC / dt = (DS / V h) (C_s - C)$$

- **M**: the mass of solute dissolved in time t
- **dM/dt**: the mass rate of dissolution (mass/time)
- **D**: the diffusion coefficient of the solute in solution
- **S**: the surface area of exposed solid
- **h**: the thickness of the diffusion layer
- **C_s**: the solubility of the solid
- **C**: the concentration of solute in the bulk solution and at time t

Table 1.6 How the parameters of the dissolution equation can be changed to increase (+) or decrease (–) the rate of solution

Equation parameter	Comments	Effect on rate of solution
D (diffusion coefficient of drug)	May be decreased in presence of substances which increase viscosity of the medium	(–)
A (area exposed to solvent)	Increased by micronisation and in 'amorphous' drugs	(+)
δ (thickness of diffusion layer)	Decreased by increased agitation in gut or flask	(+)
c_s (solubility in diffusion layer)	That of weak electrolytes altered by change in pH, by use of appropriate drug salt or buffer ingredient	(–)/(+)
c (concentration in bulk)	Decreased by intake of fluid in stomach, by removal of drug by partition or absorption	(+)

- **The driving force for dissolution is the concentration gradient across the boundary layer.**
- **The driving force depends on the thickness of the boundary layer and the concentration of drug that is already dissolved.**
- **When C is less than 20% of the C_s, the system is to operate under "sink conditions."**
- $$\rightarrow dM / dt = (DS / h)(C_s)$$
- **Dissolution tests are used for many purposes in the pharmaceutical industry:**
  1. **The development of new products**
  2. **For quality control, and**
  3. **To assist with the determination of bioequivalence.**

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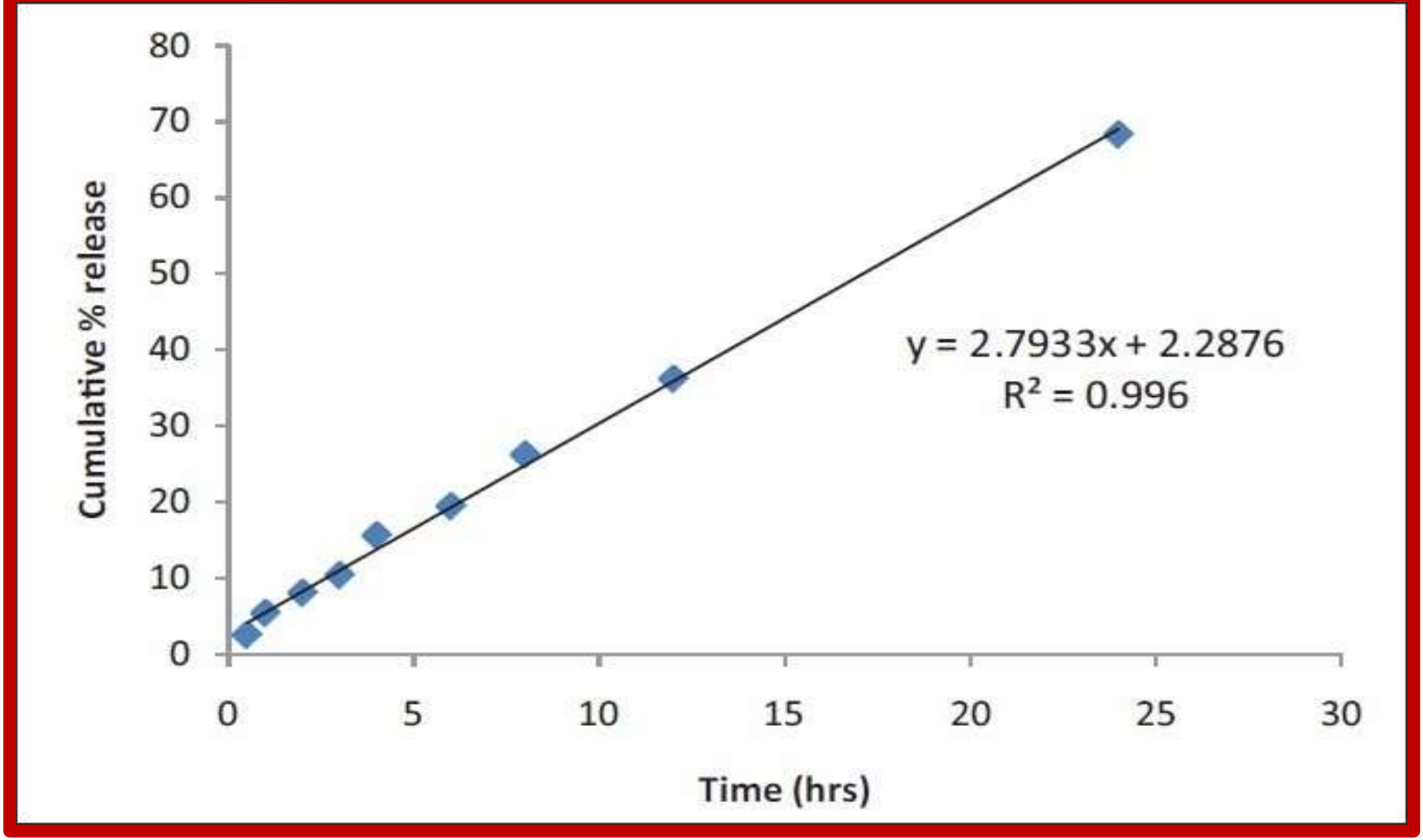
  3. To assist with the determination of bioequivalence.

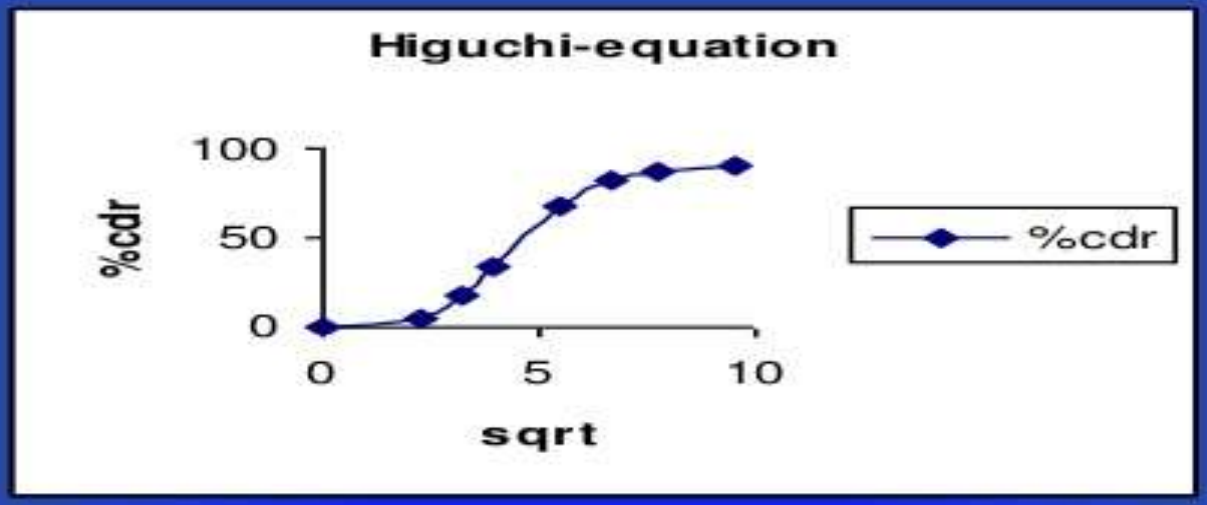
DRUG RELEASE KINETICS

- The mathematical models are used to evaluate the kinetics and mechanism of drug release from the tablets.
- The model that best fits the release data is selected based on the correlation coefficient (r) value in various models.
- The model that gives high 'r' value is considered as the best fit of the release data.

Noyes-Whitney equation



Higuchi Model Kinetics Cont....



APPLICATION

Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependant. This relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal and matrix tablets with water a soluble drugs

$$Q = A\sqrt{D(2C - C_s)C_s t}$$

HIXSON - CROWELL RELEASE EQUATION

- The Hixson - Crowell release equation is

$$\sqrt[3]{Qo} - \sqrt[3]{Qt} = K_{HC}.t$$

Where

Q_0 = Initial amount of drug

Q_t = Cumulative amount of drug release at time "t"

K_{HC} = Hixson crowell release constant

t = Time in hours.

- It describes the drug releases by dissolution and with the changes in surface area and diameter of the particles or tablets

ZERO ORDER RELEASE

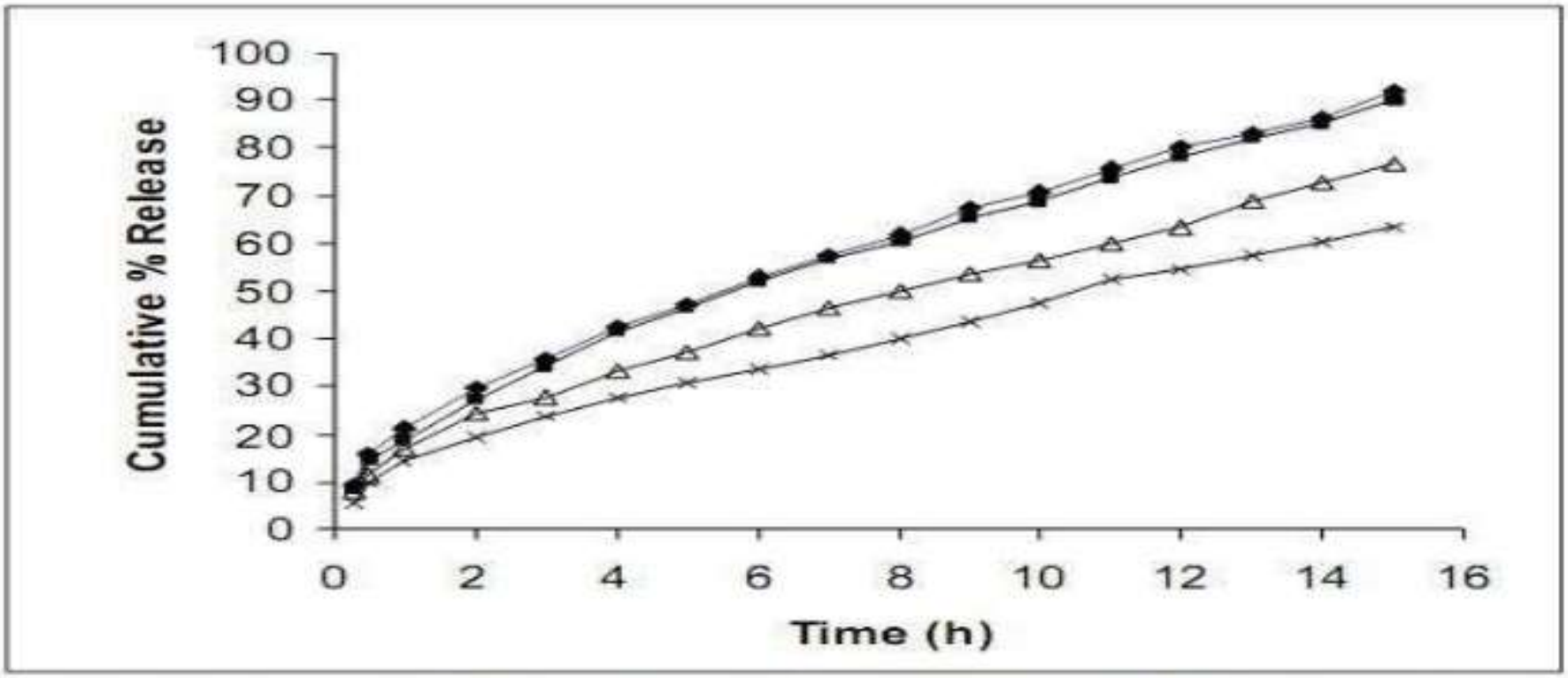
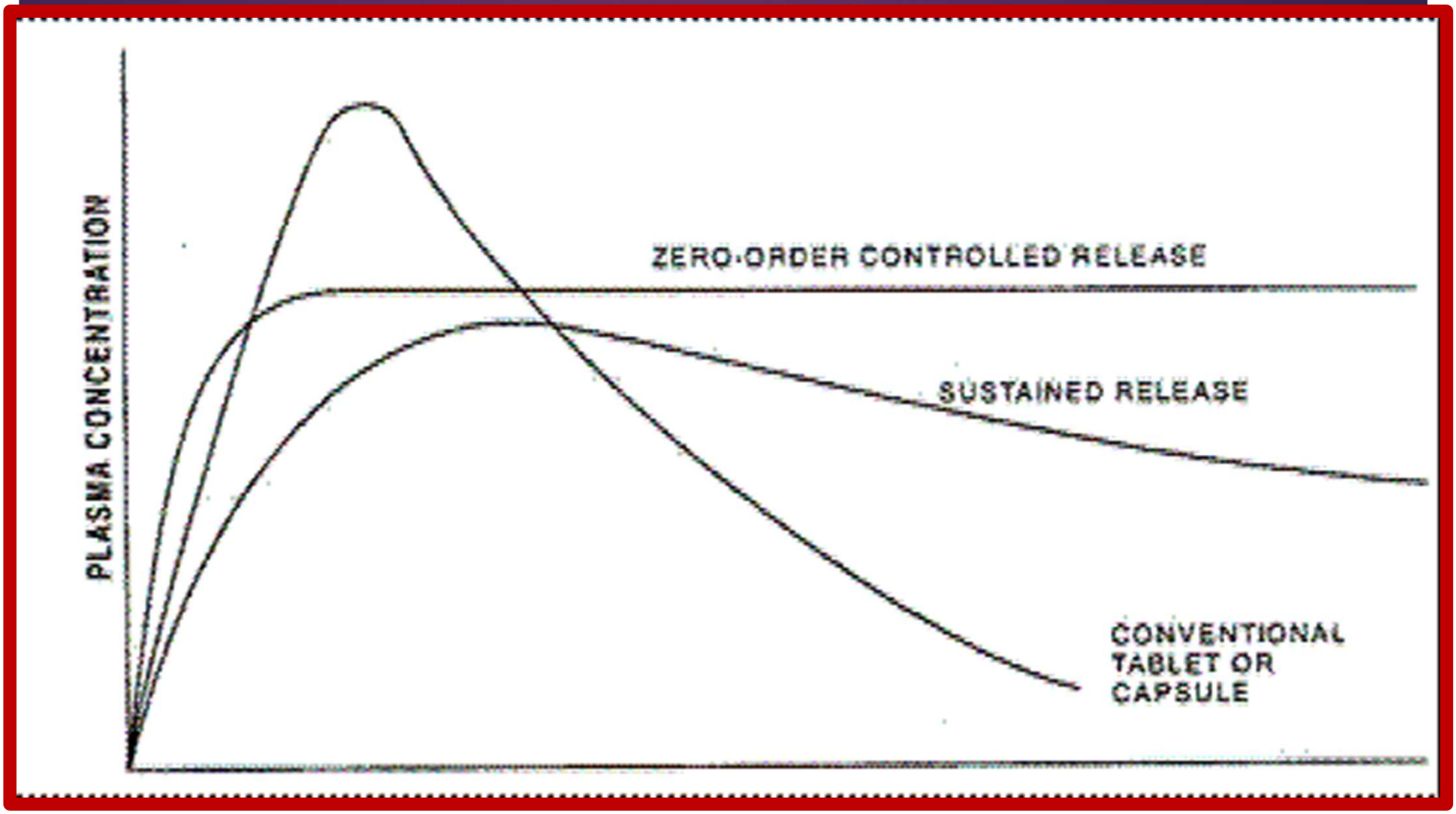


Fig. 3: *In vitro* drug release of pentoxifylline from poly(ε-caprolactone) microspheres
In vitro dissolution profiles of pentoxifylline from poly(ε-caprolactone) microspheres formulation F1 (-◆-), F2(-■-), F3(-△-) and F4(-×-) were studied in pH 7.4 phosphate buffer over a period of 15 h.

Factors affecting the dissolution rate of a drug from a dosage form:

- Factors related to the physicochemical properties of the drug
- Factors related to drug product formulation
- Factors related to dosage form
- Factors related to dissolution testing device
- Factors related to dissolution test parameters
- Miscellaneous factors

Drug profile as a function of release from dosage forms



Factors affecting drug release

Parameters	Possible effect
Basic properties of drug	
Drug hydrophobicity/hydrophilicity	Affects aqueous solubility, protein binding, tissue retention characteristics and local drug concentrations
Diffusion/dissolution characteristics	Affects release kinetics
Solubility in polymer	Affects release kinetics
Solubility in release media	With higher solubility, higher drug release rate
Properties of rate controlling polymer	
Thermal properties (Tg, Tm)	Affects degradation, hydrophobicity, drug release and drug solubility in the case of biodegradable polymers,
Degree of crystallinity	Affects water penetration and drug solubility in the case of non-erodible polymers Influences degradation and drug release for biodegradable polymers
For biodegradable polymers – initial molecular weight, co-polymer ratio, absorption rate and time period, pH of dissolution medium	Affects degradation behavior and time

Factors affecting drug release

Processing Parameters	
Selection of coating process (ultrasonic atomization, air brush, dip coating)	Coating film property and drug elution
Properties of solvent (BP, thermal history) Solvent evaporation rate Phase diagram of ternary system (drug-polymer-solvent)	Residual solvent effects, merging of coating layers, thus influencing release kinetics
Coating Design	
Drug to polymer ratio	Effect on drug carrying capacity of polymer and drug elution rate
Coating layer composition and thickness	Affects diffusion of drug through film
Drug (initial solid phase) concentration and distribution inside the matrix	Describes initial burst effect and dissolution mechanism
Microstructure of coating (spatial variation in physical and chemical composition)	Exhibits process conditions and eventual effect on drug delivery kinetics
Top layer (drug free) thickness and hydrophobicity of polymer	Regulates drug kinetics by lowering diffusion phenomena.
Mechanical properties of coated film	Affects coating integrity during processes like stent crimping and expansion. Improper coating may induce adverse and interrelated effects such as local inflammation and thrombosis and hinder homogeneous drug uptake
Stent design (system geometry)	Affects extent of drug dose differentiation within arterial wall