LADME sistem

Aleš Mrhar

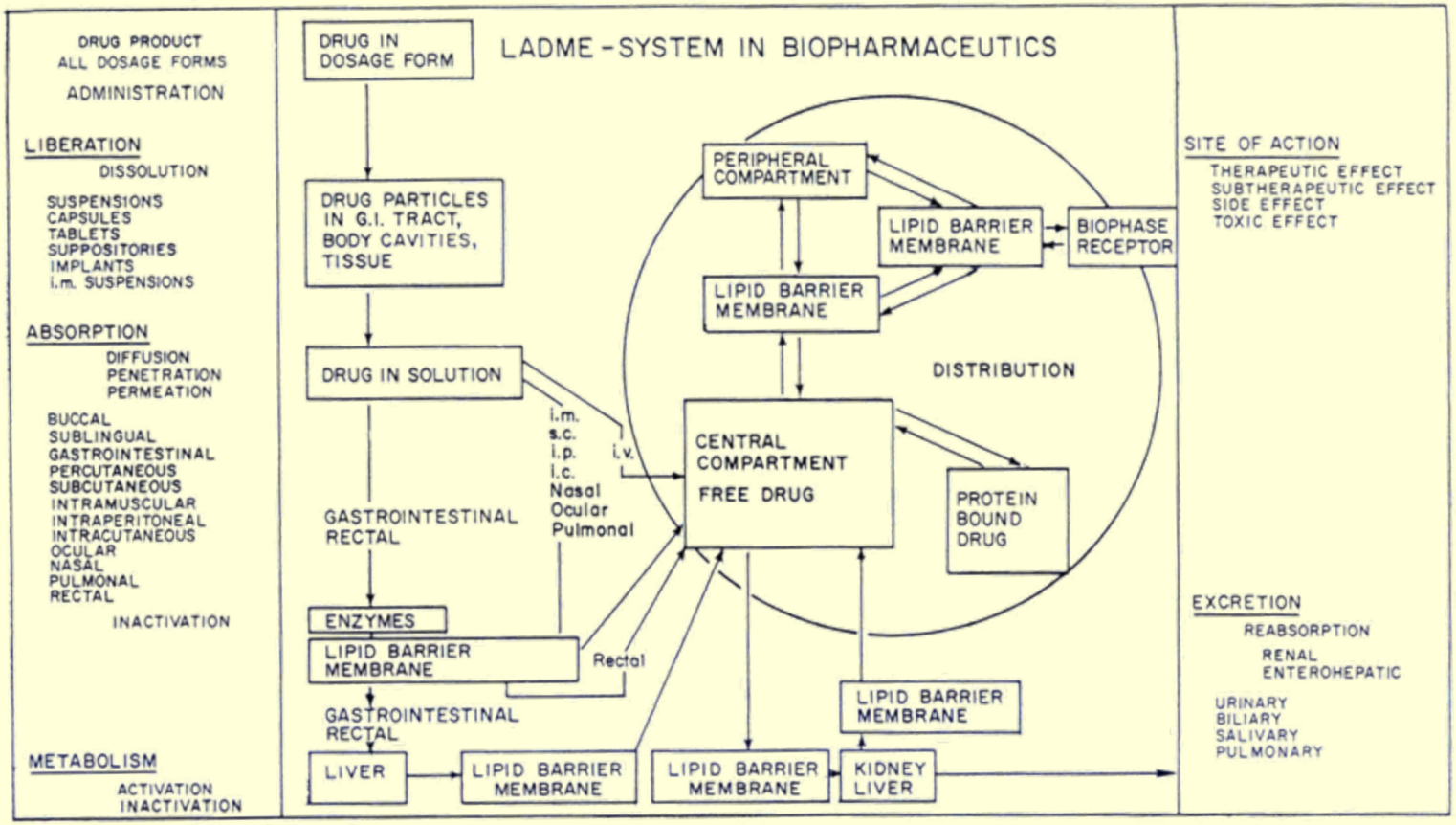
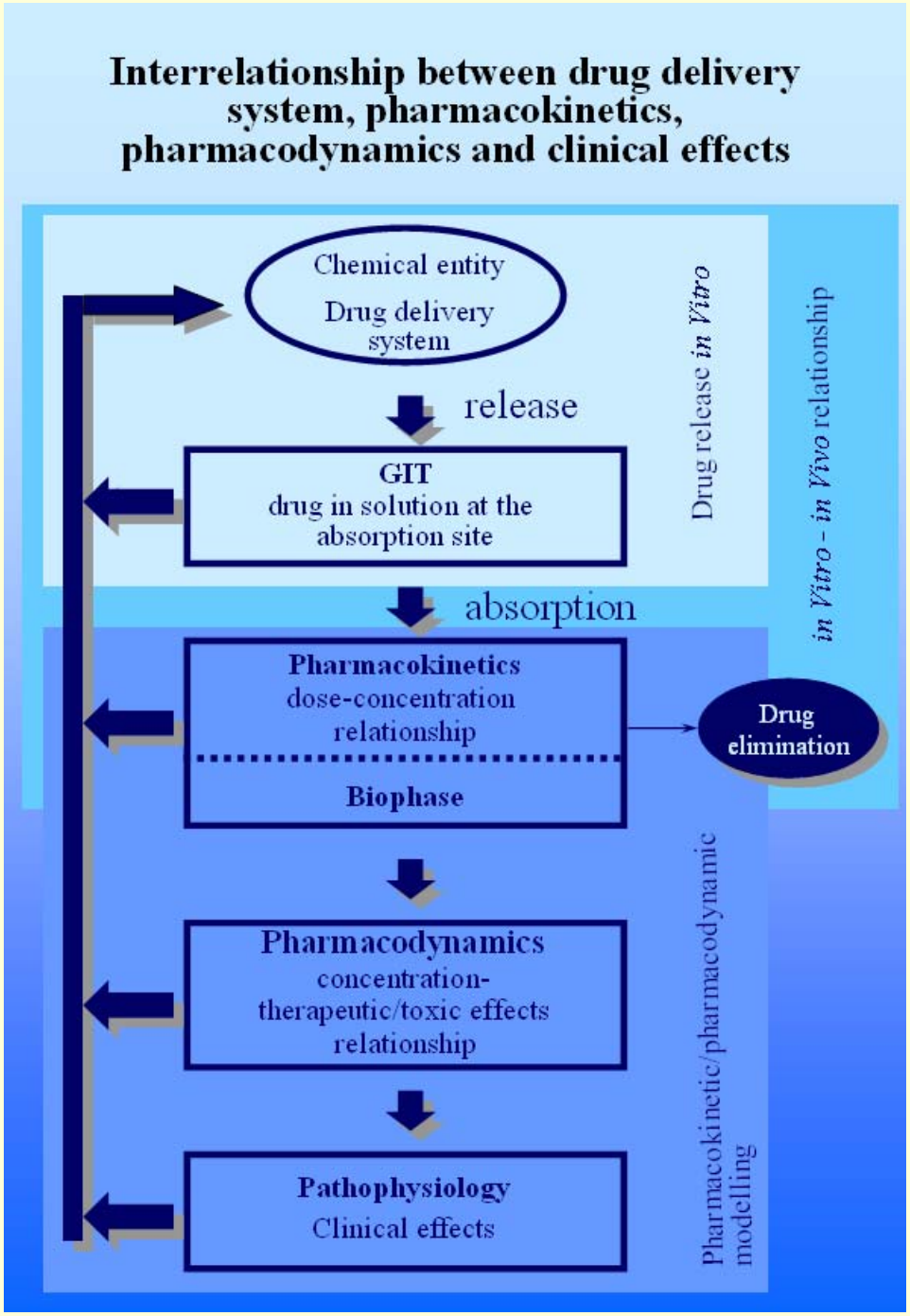
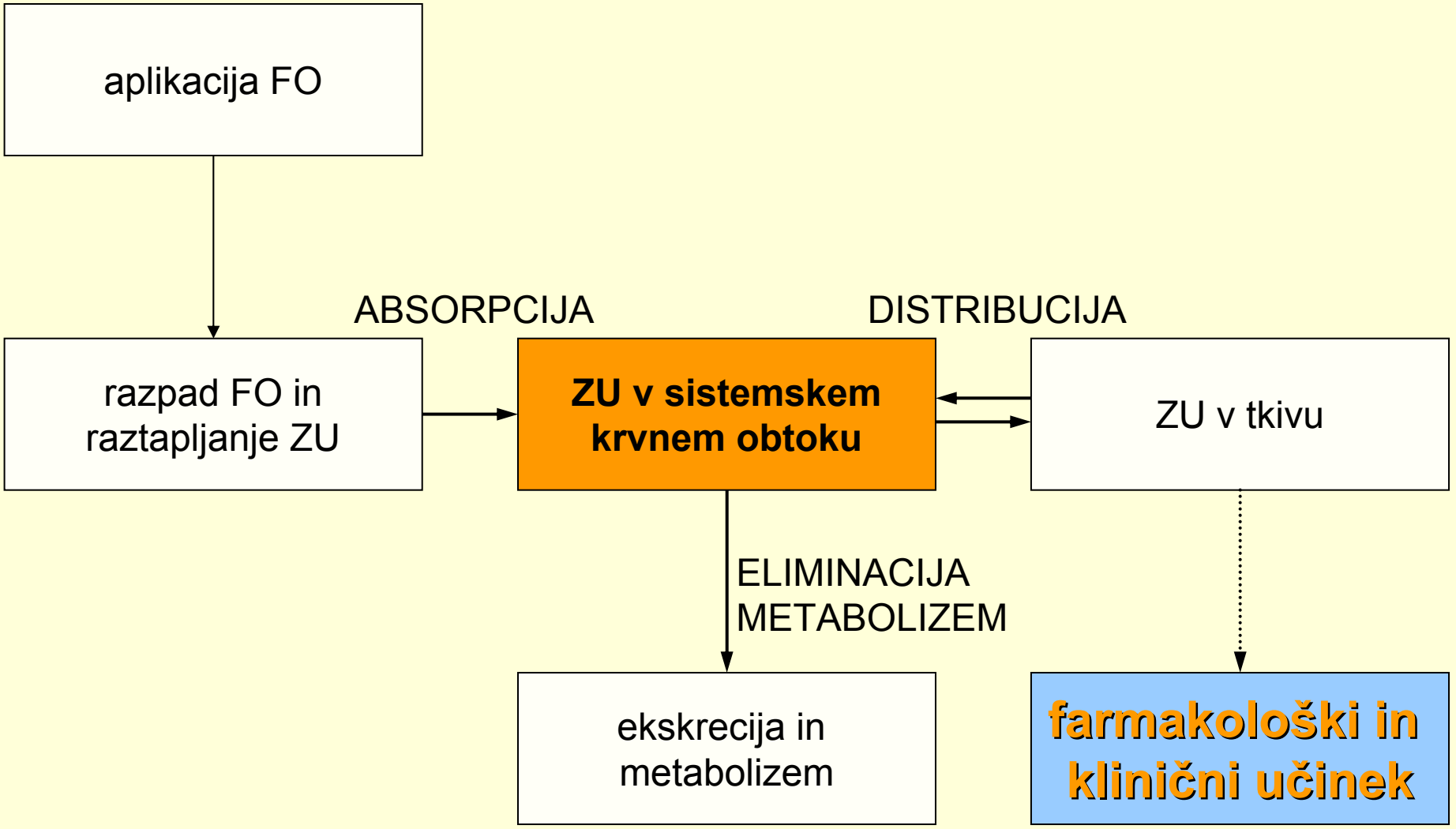


Figure 2-1. Diagram of LADME System in biopharmaceutics showing the complex interrelationship between drug, drug product and body.

Interrelationship between drug delivery system, pharmacokinetics, pharmacodynamics and clinical effects




aplikacija FO
ABSORPCIJA
DISTRIBUCIJA
razpad FO in raztapljanje ZU
ZU v sistemskem krvnem obtoku
ZU v tkivu
ELIMINACIJA METABOLIZEM
ekskrecija in metabolizem
farmakološki in klinični učinek

Načini aplikacije

PARENTERALNA

mimo GIT: koža, sluznice, organ, tkivo, sistemski krvni obtok

- intraarterijska
- intravenska
- intratekalna
- intramuskularna
- oralna
- bukalna
- intranazalna
- pulmonalna
- transdermalna
- vaginalna
- rektalna

ENTERALNA

preko GIT ➔ **ENTEROCITI, JETRA**

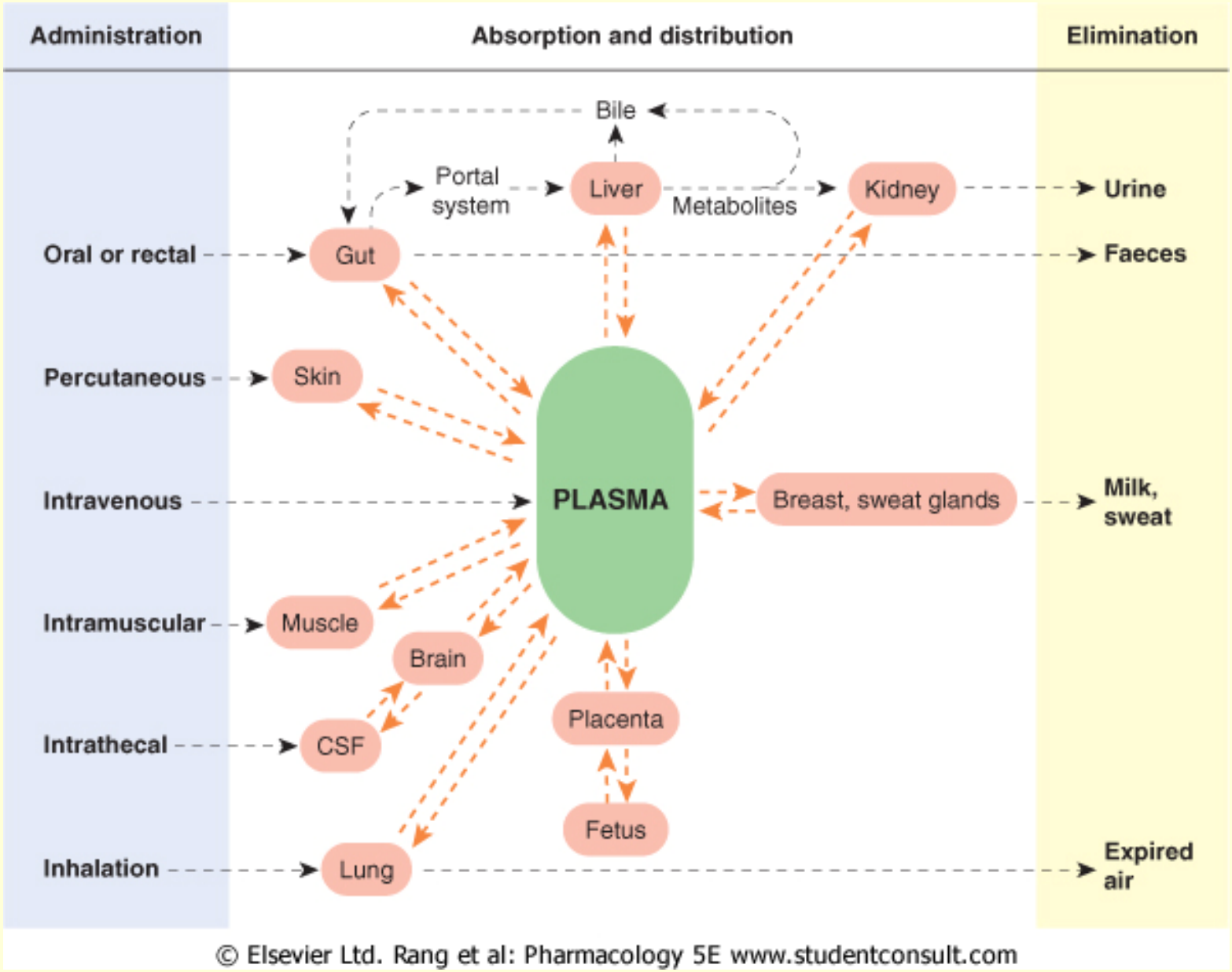
predsistemski metabolizem!

- peroralna

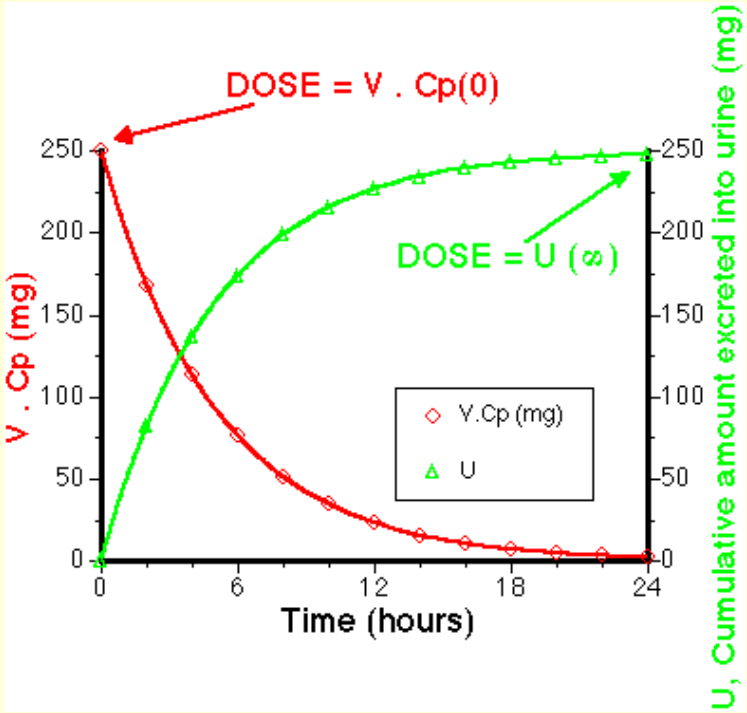
Brez predsistemskega metabolizma

- oralna
- rektalna (2/3)

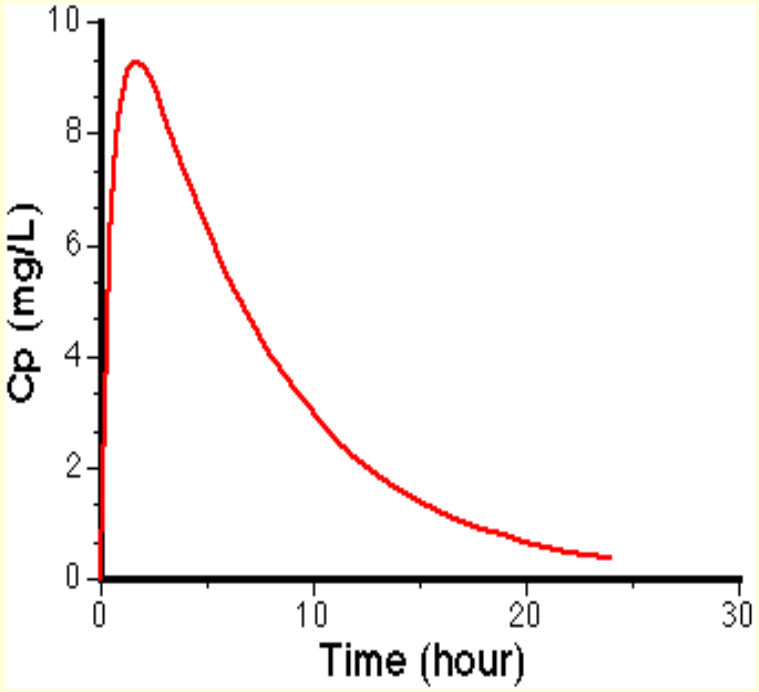
Glavne poti aplikacije in eliminacije učinkovin



Osnovna farmakokinetična informacija
PLAZMA

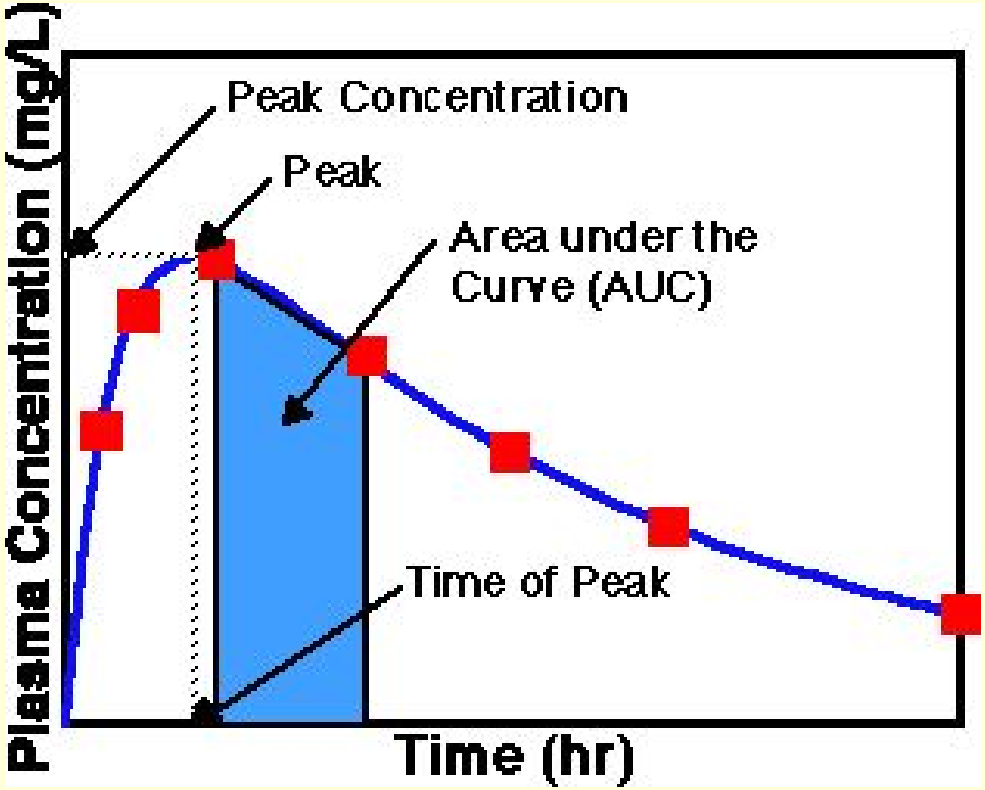


intravenska aplikacija



peroralna aplikacija

- plazemski koncentracijski profil
- urinski količinski kumulativni profil



Biopharmaceutic parameters over a blood time curve. This slide shows some of the biopharmaceutic parameters which can be used to measure drug product performance. Later in the semester we will use the trapezoidal method of calculating AUC.

URIN

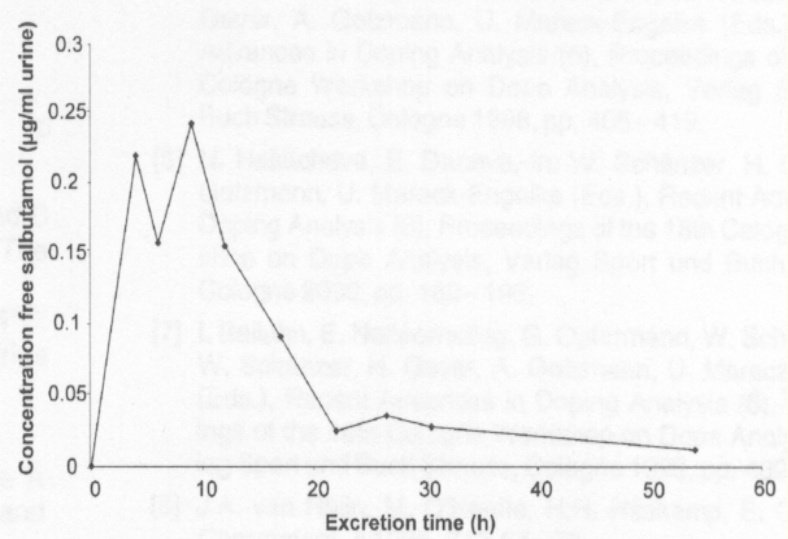
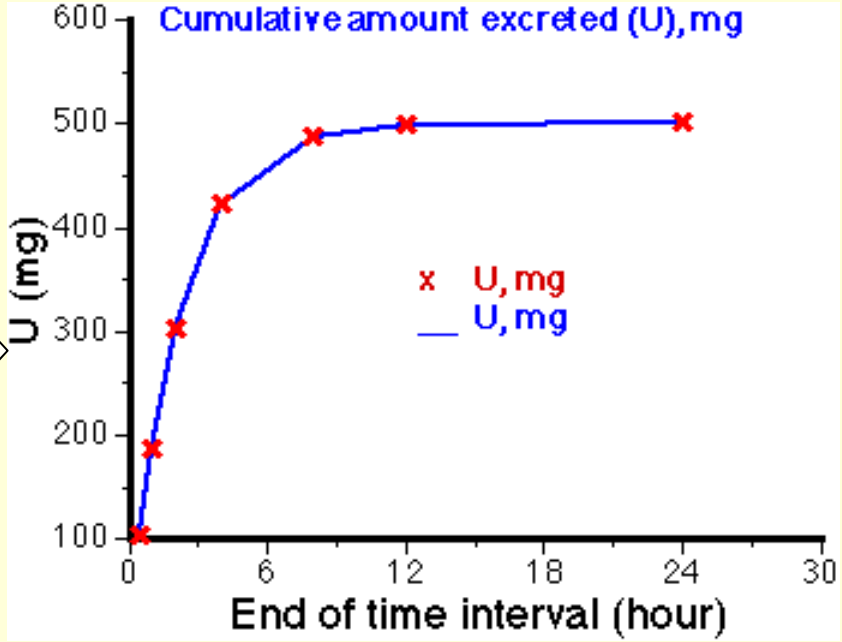


Figure 2. Excretion of free salbutamol in urine after a single dose of 2 mg salbutamol. *J Sep Sci. 2004 Jan;27(1-2):110-4.*

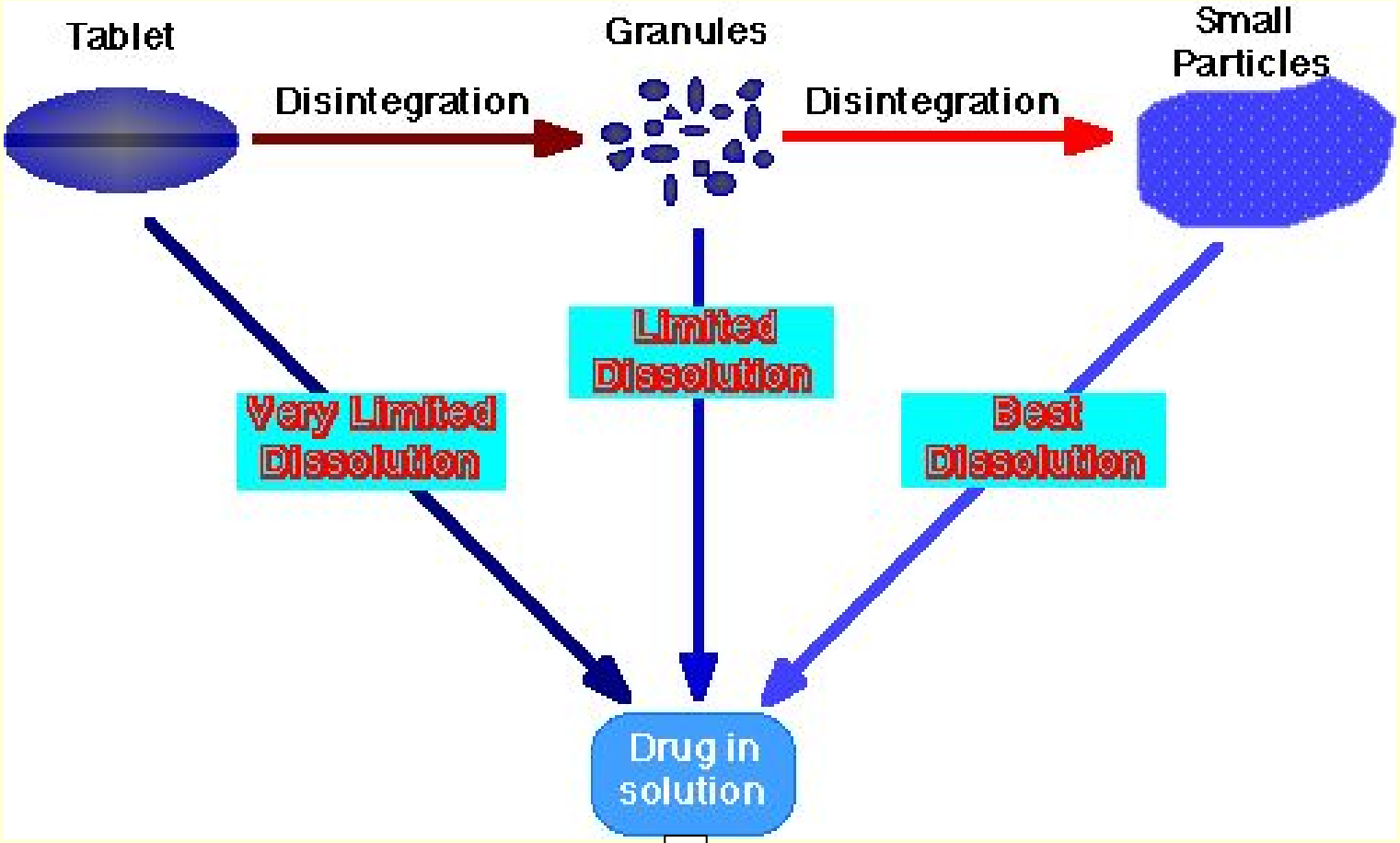
urinski koncentracijski profil



urinski količinski kumulativni profil

L - Sproščanje učinkovin
(Liberation, Dissolution, Release)

- razpad farmacevtske oblike
- raztapljanje učinkovine



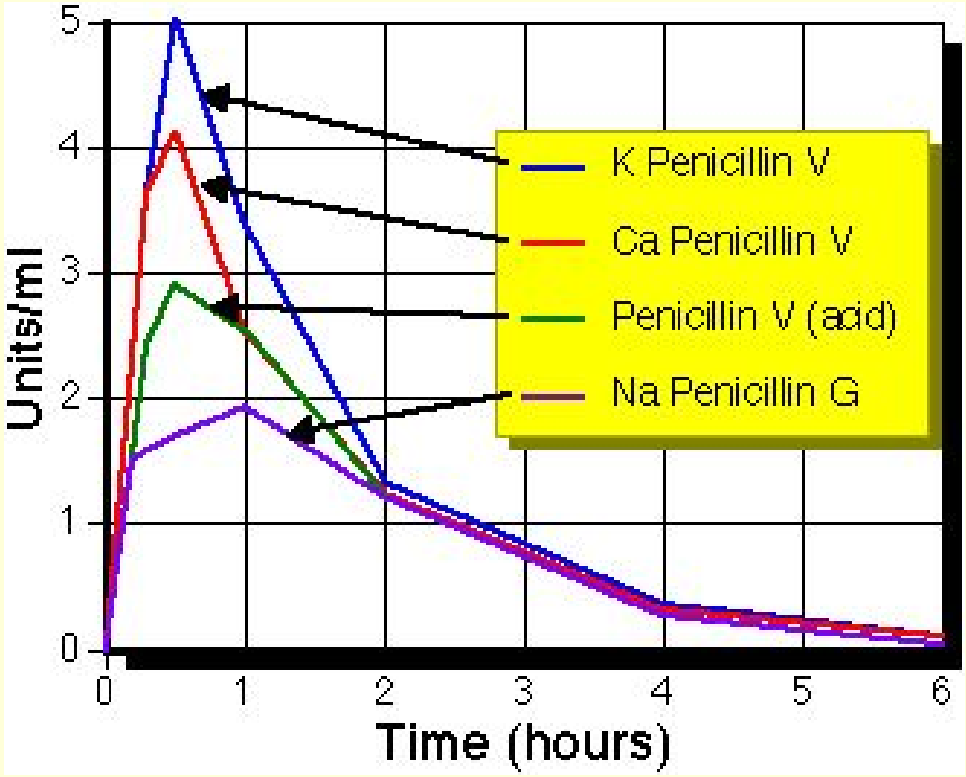
ABSORPCIJA

učinkovina v sistemskem krvnem obtoku

Vplivi na raztapljanje/sproščanje

1. **Lastnosti učinkovin**
   - Kemijske: soli, estri (predzdravila, prodrugs)
   - Fizikalno-kemijske: topnost, hitrost raztapljanja
   - Fizikalne: velikost delcev
2. **Vgrajevanje učinkovin v farmacevtske oblike**
   - Farmacevtske oblike s hitrim sproščanjem
   - Farmacevtske oblike s prirejenim sproščanjem
3. **Fiziološki pogoji**

Plazemski profili različnih soli penicilina V (per os aplikacija)



Plasma penicillin concentration versus time curve after oral administration of various salts (redrawn from Juncher, H. and Raaschou, F. 1957 The solubility of oral preparations of penicillin V, *Antibiot. Med. Clin. Therap.*, **4**, 497). The rate at which a drug dissolves is dependent on the solubility of the drug. A common occurrence is that different salts will have quite different solubility characteristics, and again somewhat different to the free acid (or base) form. In the case of penicillin V it appears that only drug which is dissolved quickly can be absorbed.

Topnost in pH

- učinkovine so šibke kisline/baze
- topnost:
  - slaba
  - odvisna od pH

➔ **tvorba soli** (pospešeno raztapljanje)

- obnašanje šibke kisline/baze in soli v želodcu (pH 1-3)

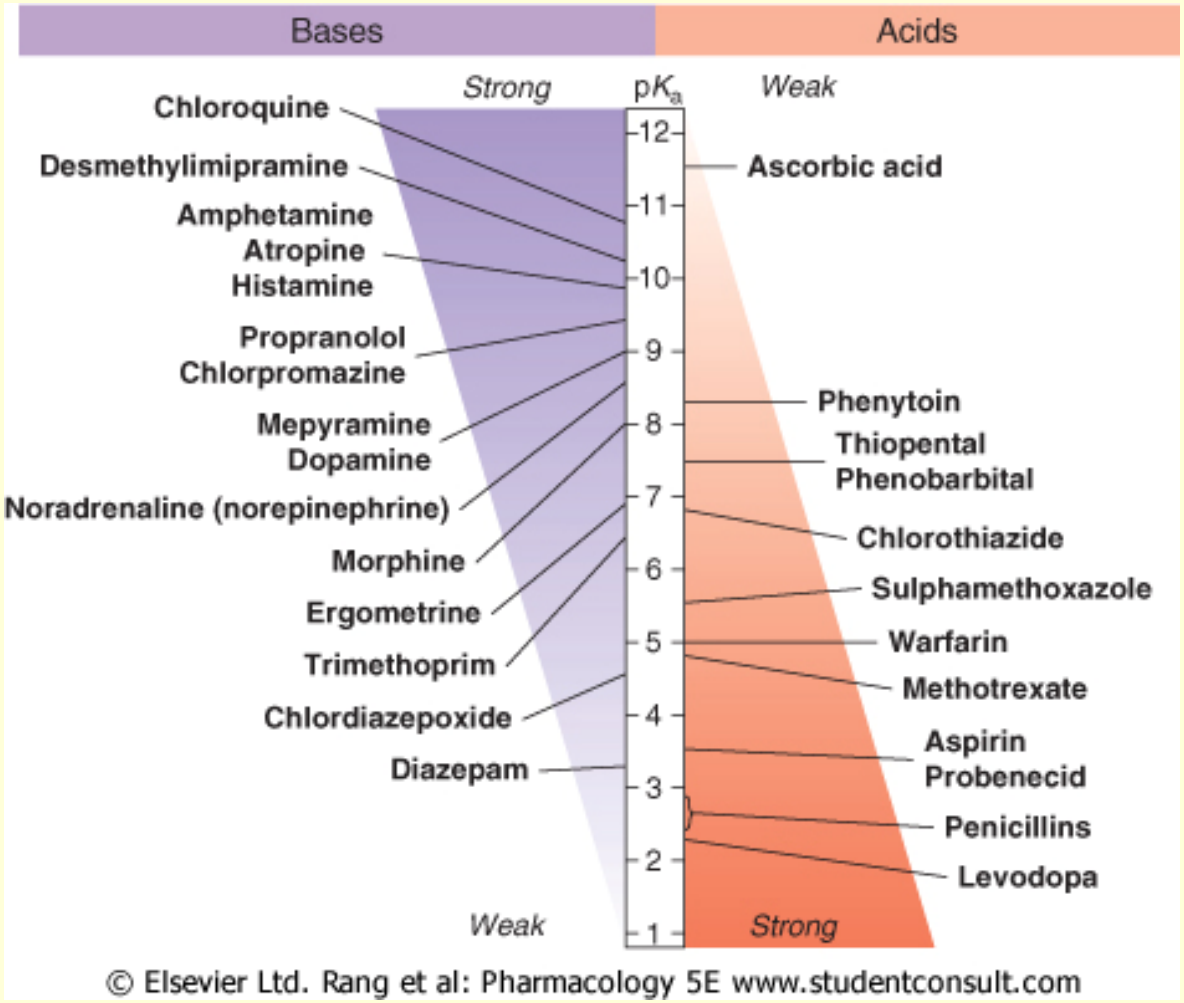
$HA \rightarrow H^+ + A^-$
šibka kislina
v želodcu slabo topna, ker ne tvori soli

$B + H^+ \rightarrow BH^+$
šibka baza
v želodcu dobro topna, ker tvori sol (BH^+)

$A^- + H^+ \rightarrow HA$
sol šibke kisline
v želodcu se tvori slabo topna kislina
IN SITU OBARJANJE
pospešeno raztapljanje

$BH^+ \rightarrow BH^+$
sol šibke baze
v želodcu dobro topna, ker v kislem ostane sol (BH^+)

pK_a nekaterih kislih in bazičnih učinkovin

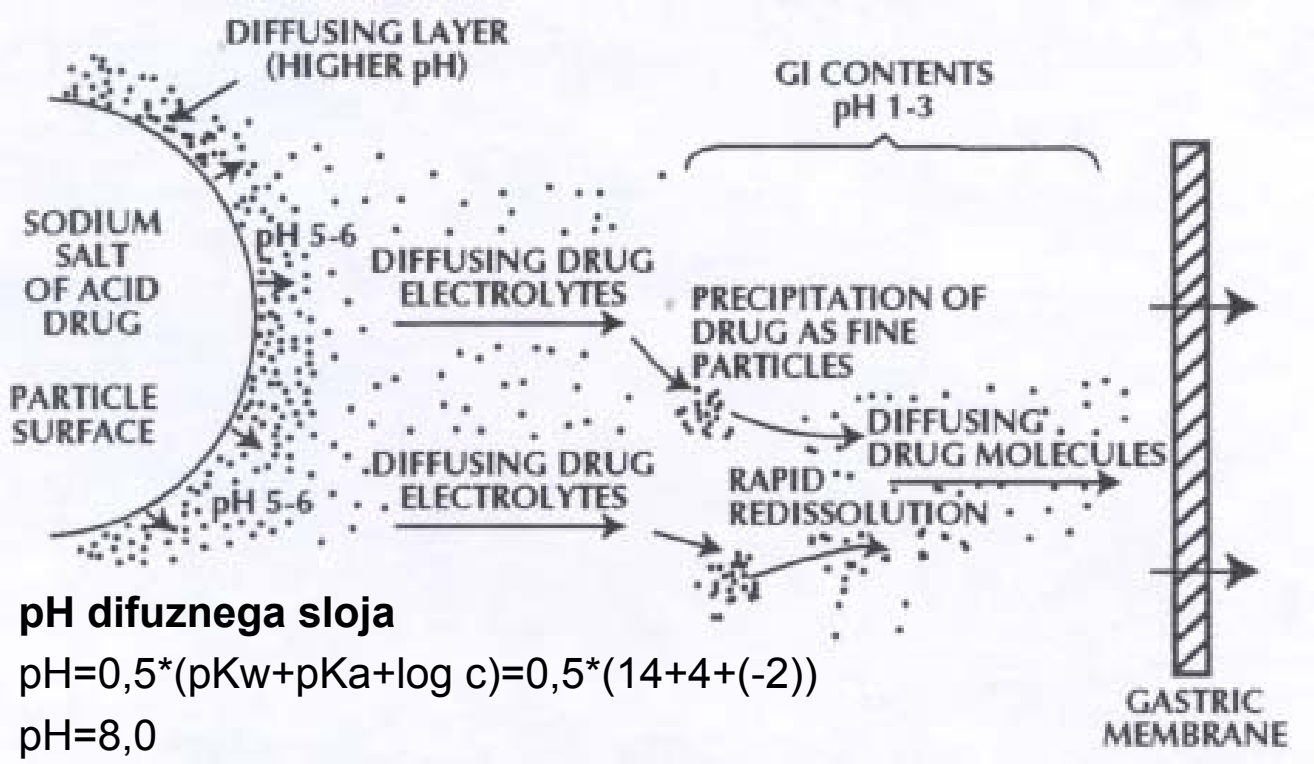


Izračun pH raztopine šibke kisline/baze in soli šibke kisline/baze v difuznem sloju

šibka kislina HA	$pH=0,5*(pK_a-\log[HA])$
sol šibke kisline A^-	$pH=0,5*(pK_w+pK_a+\log[A^-])$
šibka baza B	$pH=pK_w-0,5*(pK_b-\log[B])$
sol šibke baze BH^+	$pH=0,5*(pK_w-pK_b-\log[BH^+])$

In situ obarjanje soli šibke kisline

Primer:
pKa = 4
c = 0,01 M



pH difuznega sloja

pH=0,5*(pKw+pKa+log c)=0,5*(14+4+(-2))

pH=8,0

$A^- + H^+ \rightarrow HA$

sol šibke kisline

Sol šibke kisline se v želodcu raztopi. Medtem se tvori tanek difuzni sloj, ki ima relativno visok pH (za dani primer 8,0) in pospeši raztapljanje šibke kisline. Pri prehodu molekul globlje v želodec se pH zniža (pH 1-3), kar povzroči obarjanje učinkovine → IN SITU OBARJANJE. Kadar se to zgodi, so nastali delci zelo majhni (velika površina), ki se zlahka raztopijo. Cilj: POSPEŠENO RAZTAPLJANJE IN ABSORPCIJA (sol šibke kisline).

Hitrost raztapljanja učinkovin

Noyes-Whitneyeva enačba

VELIKOST DELCEV
manjši delci
↑ A
večja hitrost raztapljanja

$$\frac{dc}{dt} = \frac{A \cdot D}{h} \cdot (C_s - C)$$

kisel medij
↑ [H⁺]
manjša hitrost raztapljanja

šibka kislina :

$$\frac{dc}{dt} = \frac{A \cdot D}{h} \cdot C_o \cdot \left(1 + \frac{K_a}{H^+}\right)$$

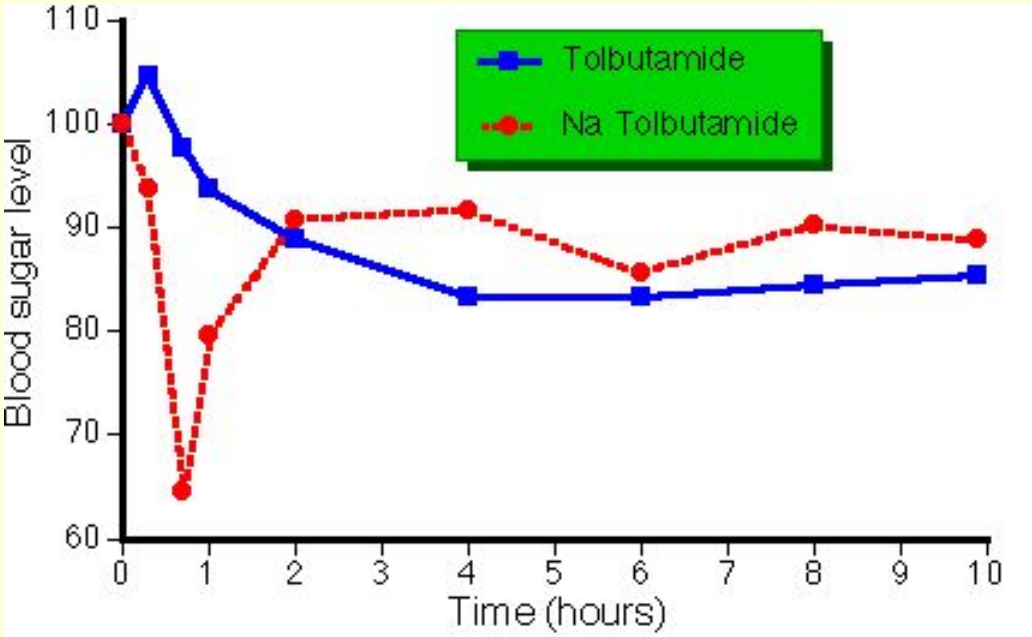
šibka baza :

$$\frac{dc}{dt} = \frac{A \cdot D}{h} \cdot C_o \cdot \left(1 + \frac{H^+}{K_a}\right)$$

kisel medij
↑ [H⁺]
večja hitrost raztapljanja

A…površina
D…difuzijski koeficient
h…debelina difuzijske plasti

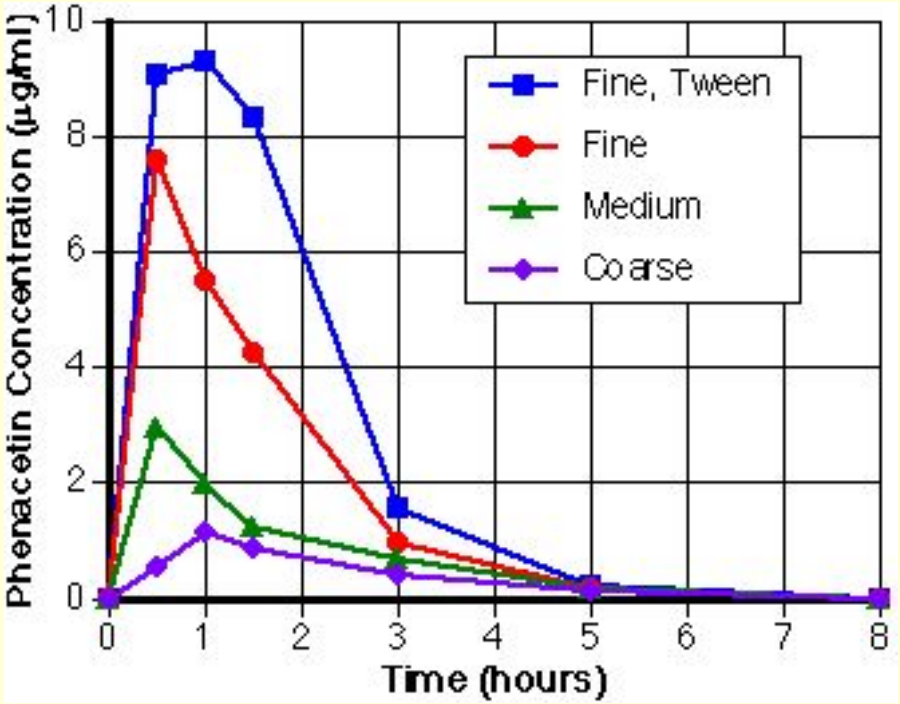
Vpliv hitrosti raztapljanja na absorpcijo tolbutamida in Na soli tolbutamida



The effect of dissolution rate on the absorption and biological response of tolbutamide (1.0 g) and sodium tolbutamide (1.0 g equivalent) when formulated in compressed tablets.

Blood sugar levels after tolbutamide acid and salt (redrawn from Wagner, J.G. 1961 Biopharmaceutics: absorption aspects, *J. Pharm. Sci.*, **50**, 359. Rapid dissolution and absorption is not always the objective. Sometimes a slower release is required. In the case of tolbutamide, used to lower blood sugar concentrations, a more sustained release is better causing a more gradual reduction in blood sugar.

Vpliv velikosti delcev na absorpcijo učinkovine



Plasma phenactin versus time curve after various suspensions (redrawn from Prescott, L.F., Steel, R.F., and Ferrier, W.R. 1970 *Pharmacol. Ther.*, **11**, 496-504). The effect of particle size on drug absorption is shown in this slide. Generally speaking the smaller the particle size the quicker the absorption. By increasing the particle surface area it is possible to increase the dissolution rate. However very small particle can clump together. Therefore a wetting agent such as Tween 80 can have a beneficial effect on the overall absorption. The intestinal fluids usually contain some materials which can act as wetting agents, however drug dissolution testing *in vitro* may neglect this effect.

Farmacevtske oblike

Vgrajevanje učinkovine v farmacevtske oblike za:

1. **hitro sproščanje**

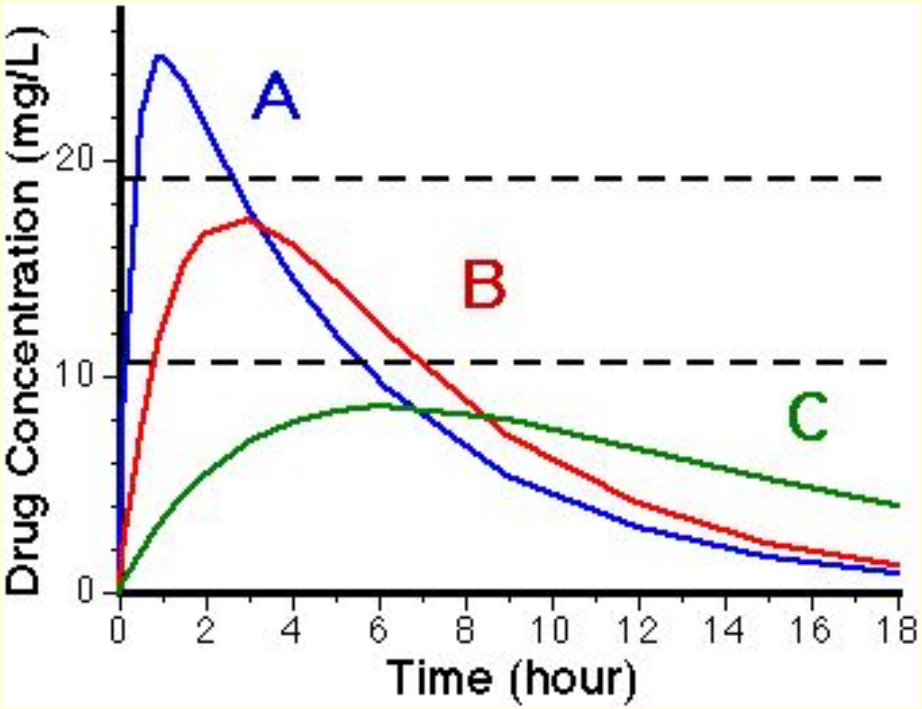
– farmacevtske oblike s takojšnim sproščanjem (*immediate release*)

2. **prirejeno sproščanje** (*modified release*)

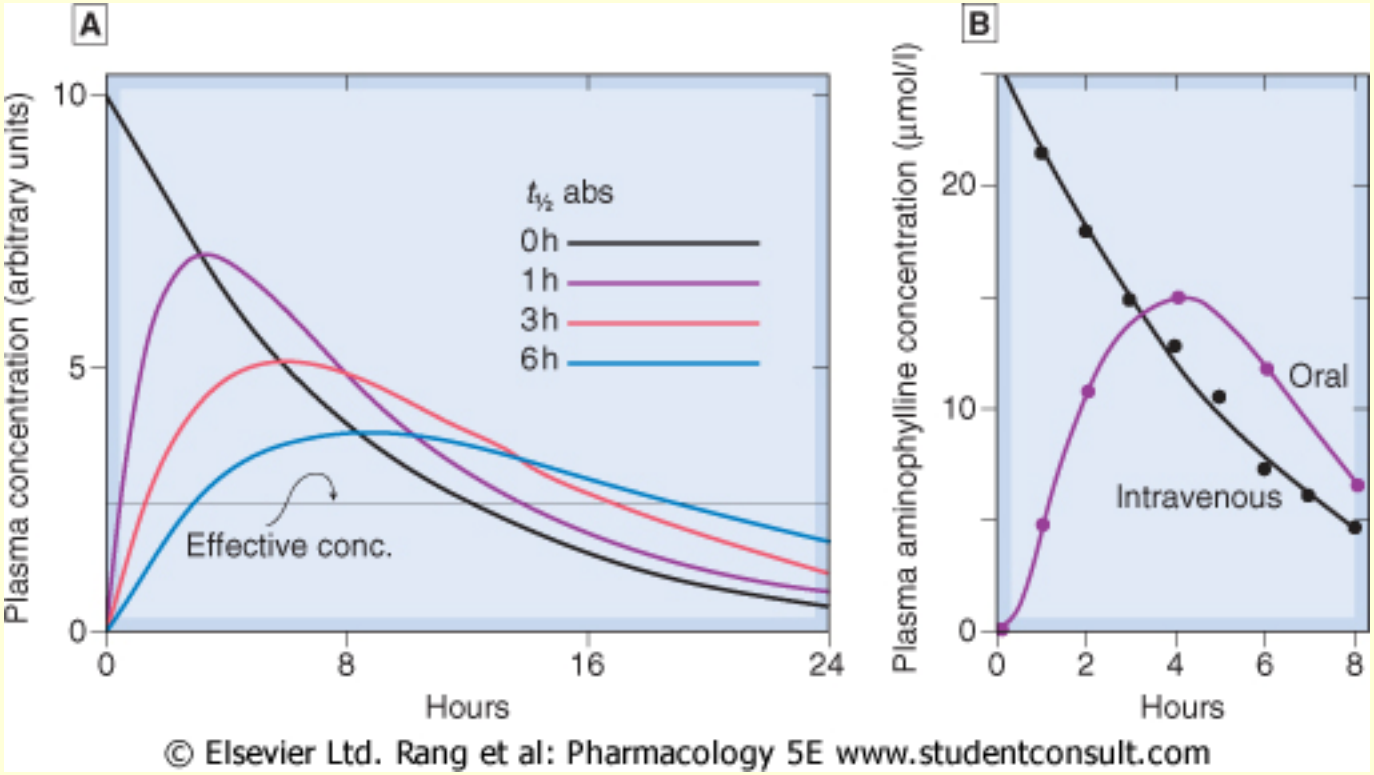
– farmacevtske oblike s podaljšanim sproščanjem (*prolonged/sustained release*)

– farmacevtske oblike z zakasnjenim sproščanjem (*delayed release*)

– farmacevtske oblike s pulzirajočim sproščanjem (*pulsed release*)



Plasma concentration time curves for three theoretical formulations with different ka values. The plasma concentrations achieved can be controlled by the rate of drug absorption. As shown product I would be toxic. A smaller dose, or a slower formulation should be considered. Formulation II appears to be effective in the dose and formulation used. The dosage form III appears to be too slow and thereby ineffective. If it is a drug requiring a sustained effect this formulation may be more useful at a higher dose or after repeated doses.



The effect of slow drug absorption on plasma drug concentration. A Predicted behaviour of single-compartment model with drug absorbed at different rates from the gut or an injection site. The elimination half-time is 6 hours. The absorption half-times (*t*1/2 abs) are marked on the diagram. (Zero indicates instantaneous absorption, corresponding to intravenous administration.) Note that the peak plasma concentration is reduced and delayed by slow absorption, and the duration of action is somewhat increased. **B** Measurements of plasma aminophylline concentration in humans following equal oral and intravenous doses. *(Data from: Swintowsky J V 1956 J Am Pharm Assoc 49: 395.)*

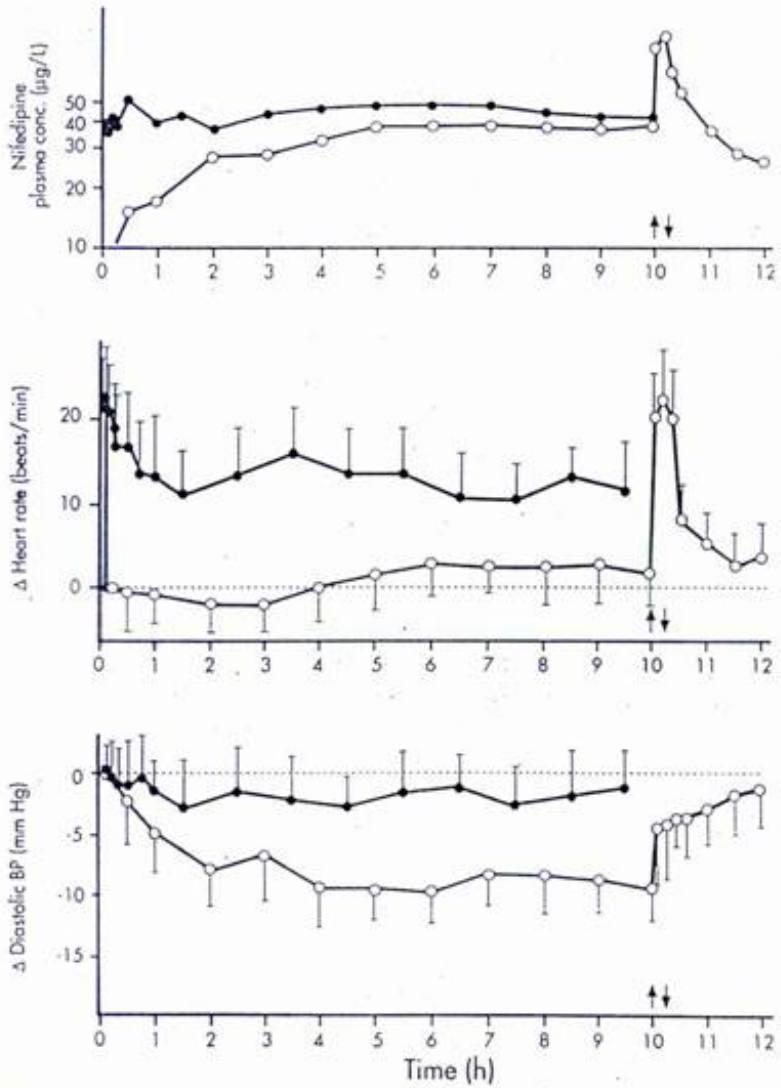


Fig. 5. Plasma concentration–time profile of nifedipine in one subject and effects ($\bar{X} \pm SD$) on heart rate and diastolic blood pressure with an infusion rate of 1.3 mg/hr (○), that was increased 10-fold to 13 mg/hr, (↑), then discontinued after 10 min (↓); and with an exponential infusion (●) intended to achieve an immediate plasma concentration plateau. [Reprinted from Kleinbloesem *et al.* (36) with permission.]

A - Absorpcija učinkovin
(Absorption)

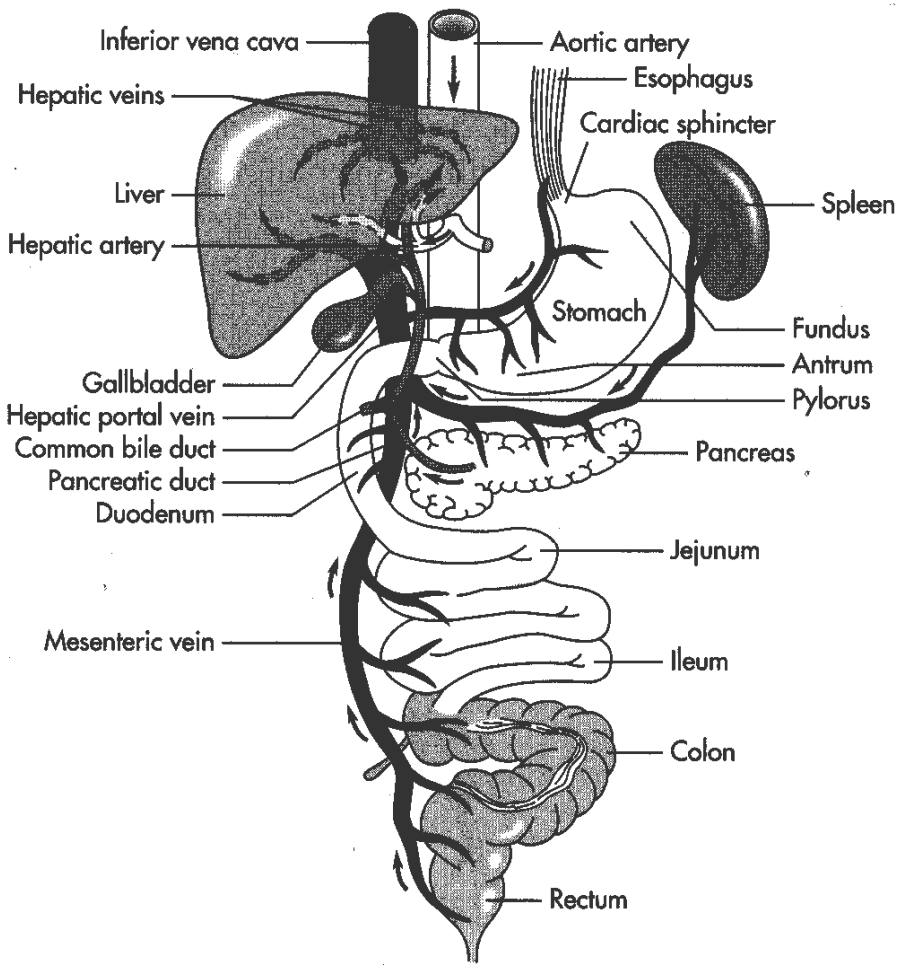


Figure 11-9. The large hepatic portal vein that collects blood from various segments of the GI tract also perfuses the liver.

Absorpcija učinkovin

Učinkovina na mestu absorpcije v raztopljenem stanju

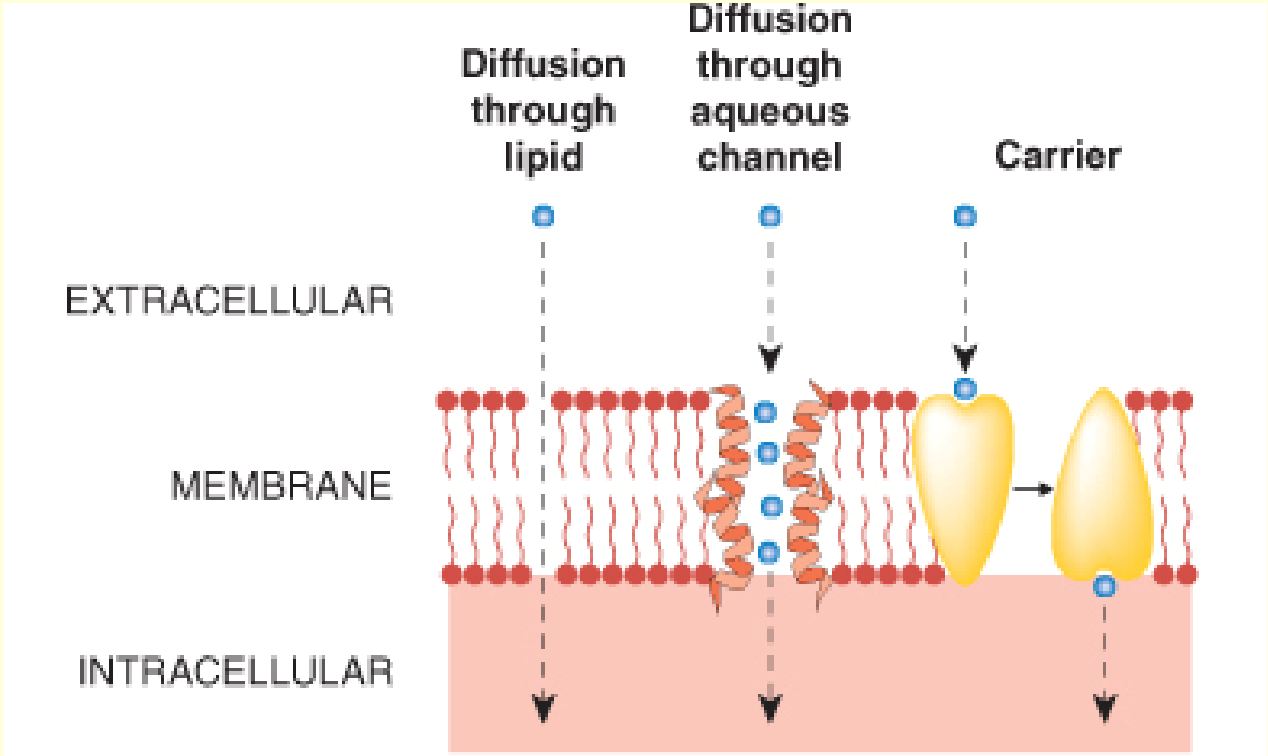
- prehod hidrofilne bariere
- prehod lipofilne bariere

Način prehoda:

- paracelularno
- transcelularno

Mehanizem prehoda skozi membrano:

1. difuzija
2. transport skozi kanalčke za ione, vodo
3. transport s prenašalci: facilitirana difuzija, aktivni transport



Routes by which solutes can traverse cell membranes. (Molecules can also cross cellular barriers by pinocytosis.)

Difuzija

- termično gibanje
- smer koncentracijskega gradienta
- molekulska masa, logP, pKa

- **PASIVNA**
  - facilitirana

- **AKTIVNA**
  - prenašalni proteini
  - nasitljiv proces
  - kompeticija

Fickov zakon difuzije

$$J = -D \cdot \frac{dC}{dr}$$

$$D = \frac{k_b \cdot T}{6 \cdot \pi \cdot \eta \cdot \sigma}$$

Absorpcija učinkovin in pH

šibka kislina

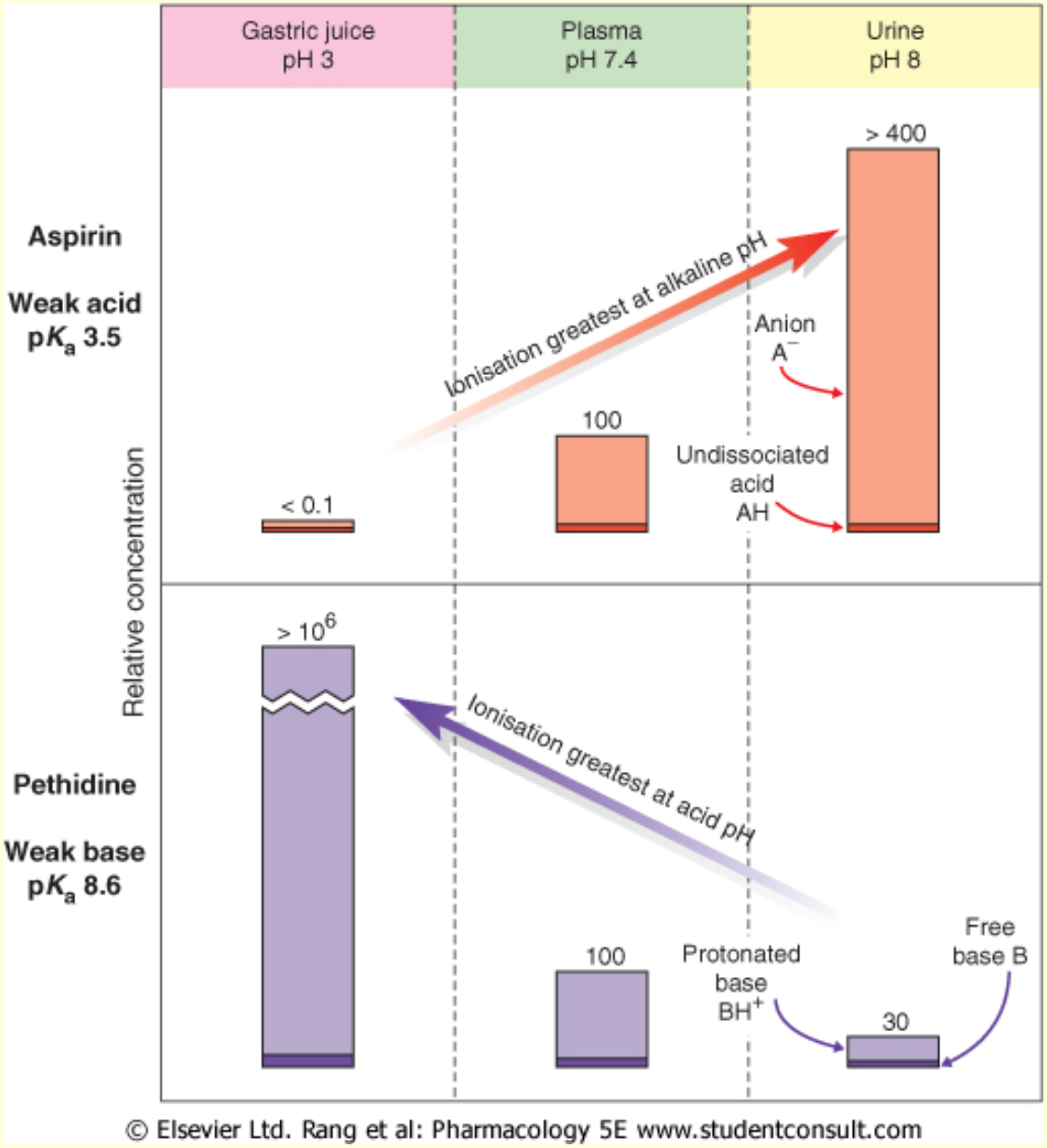
$$\frac{Cgi}{Cp} = \frac{1+10^{pH(gi)-pKa}}{1+10^{pH(pl)-pKa}}$$

šibka baza

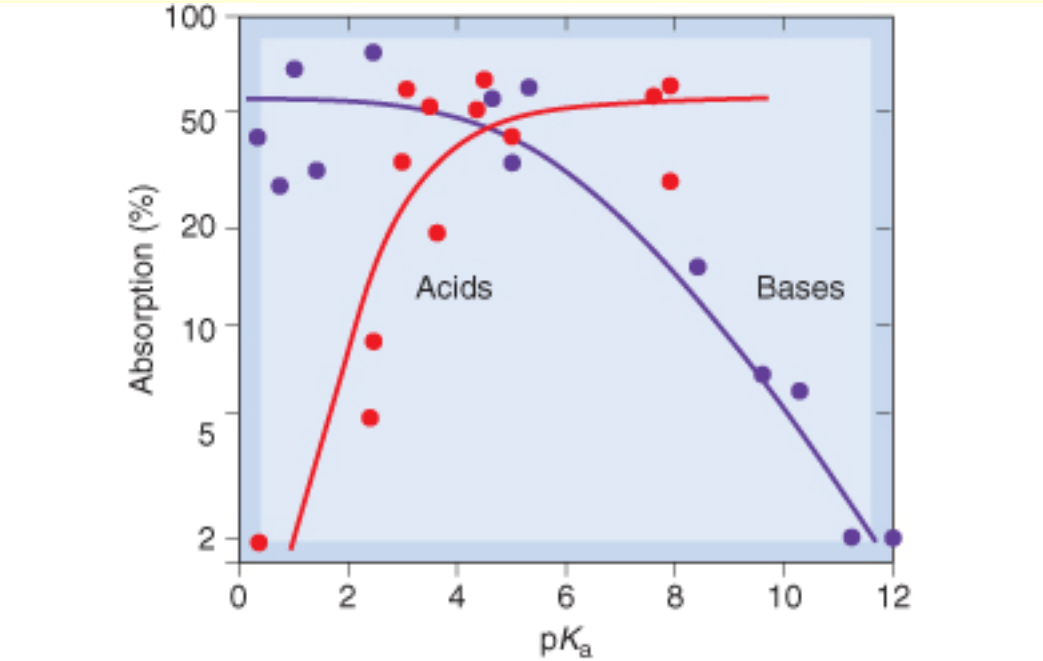
$$\frac{Cgi}{Cp} = \frac{1+10^{pKa-pH(gi)}}{1+10^{pKa-pH(pl)}}$$

ELECTROLYTE	INTESTINAL LUMEN pH 5.5	MEMBRANE	PLASMA pH 7.4
WEAK ACID pK_a 8	[N] = 1 [I] = 0.003 [Total] = 1.003		[N] = 1 [I] = 0.25 [Total] = 1.25
STRONG ACID pK_a 2	[N] = 1 [I] = 3162 [Total] = 3163		[N] = 1 [I] = 251188 [Total] = 251189
WEAK BASE pK_a 2	[N] = 1 [I] = 0.0003 [Total] = 1.0003		[N] = 1 [I] = 0.000004 [Total] = 1.000004
STRONG BASE pK_a 8	[N] = 1 [I] = 316 [Total] = 317		[N] = 1 [I] = 3.98 [Total] = 4.98

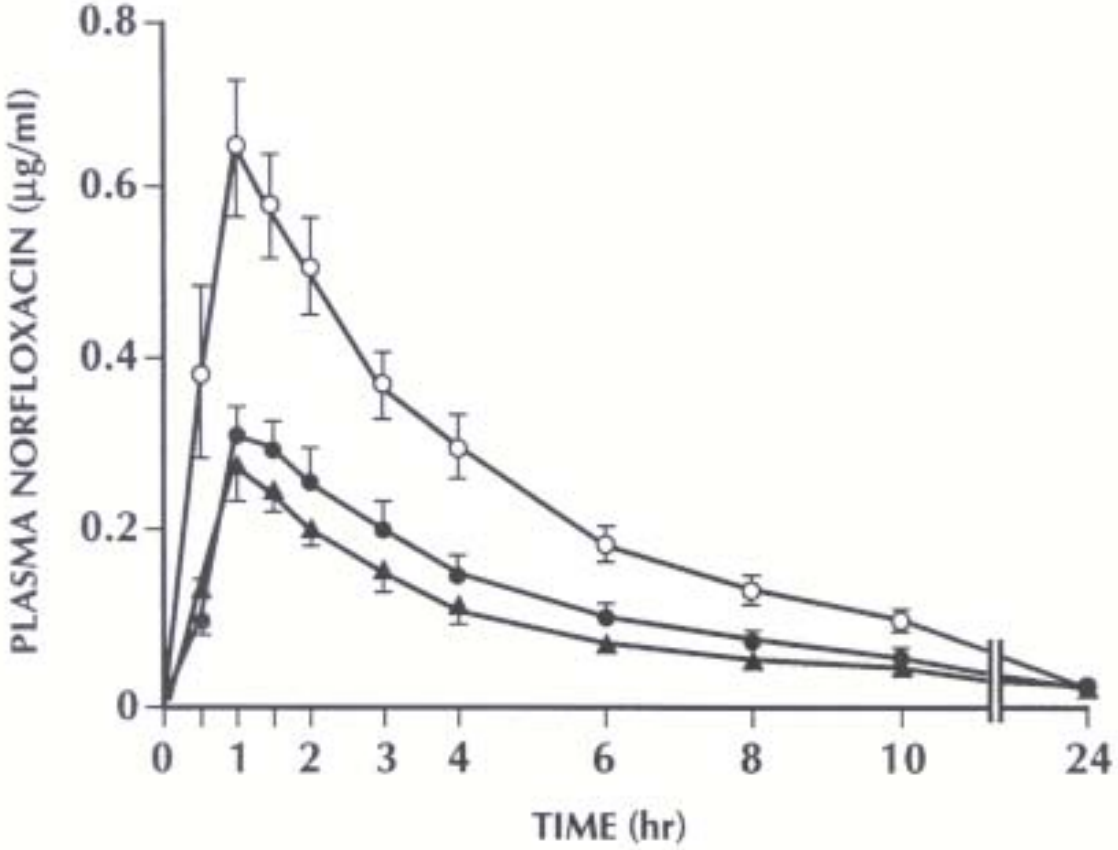
Distribution of organic acids and bases of different pK_a between the intestinal lumen pH 5.5 and plasma pH 7.4 separated by the gastrointestinal membrane under the assumption of passive diffusion. [] = concentrations, N = nonionized moiety, I = ionized moiety.



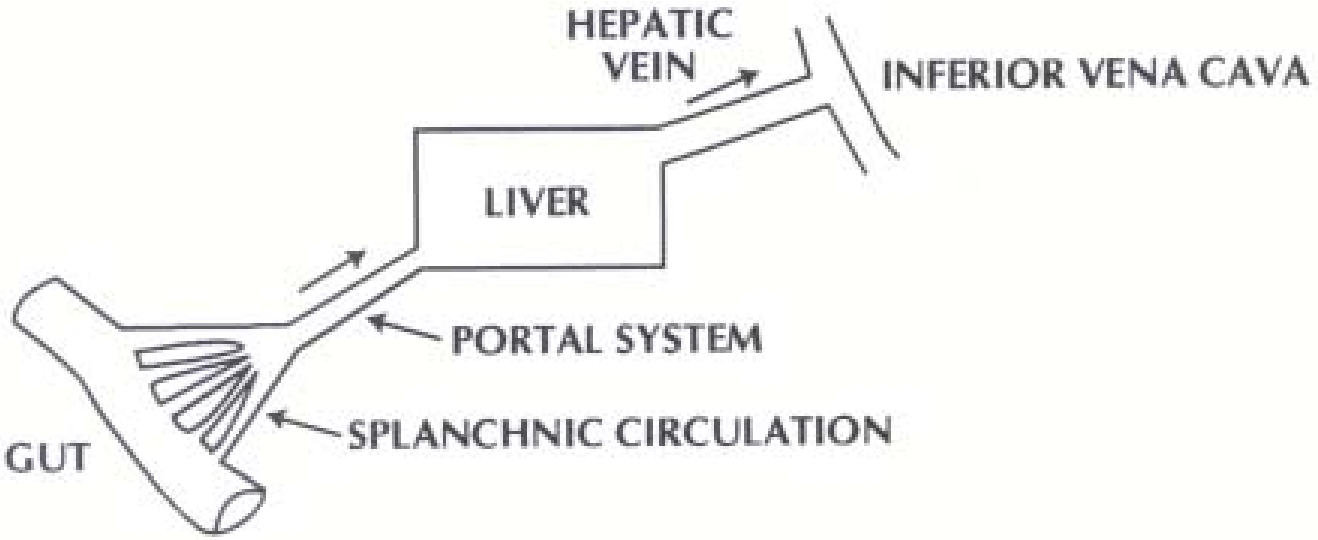
Theoretical partition of a weak acid (acetylsalicylic acid) and a weak base (pethidine) between aqueous compartments (urine, plasma and gastric juice) according to the pH difference between them. Numbers represent relative concentrations (total plasma concentration = 100). It is assumed that the uncharged species in each case can permeate the cellular barrier separating the compartments and, therefore, reaches the same concentration in all three. Variations in the fractional ionisation as a function of pH give rise to the large total concentration differences with respect to plasma.



Absorption of drugs from the intestine as a function of p*K*a, for acids and bases. Weak acids and bases are well absorbed; strong acids and bases are poorly absorbed. (Redrawn from: Schanker L S et al. 1957 J Pharmacol 120: 528.)



Mean plasma concentrations (± standard error) of norfloxacin in seven subjects following a single 500-mg oral dose of norfloxacin with 300 mL of milk (●), yogurt (▲), or water (○). (Reproduced with permission from reference 35.)



Absorption via the splanchnic circulation.

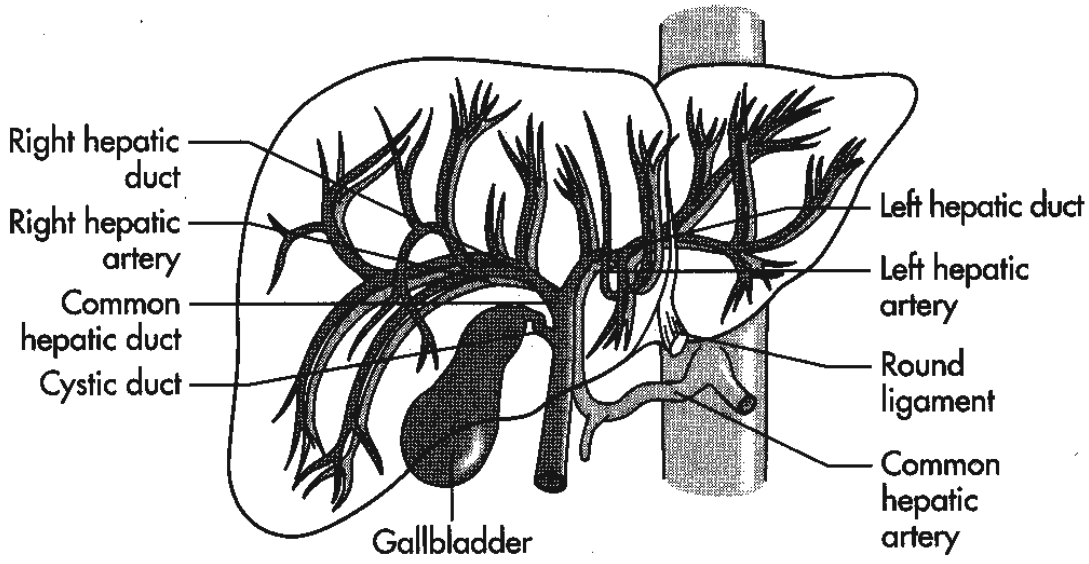


Figure 11-11. Intrahepatic distribution of the hepatic artery, portal vein, and biliary ducts. (From Lindner HH. *Clinical Anatomy*. Norwalk, CT, Appleton & Lange, 1989, with permission.)

V jetra vodijo:
- portalna vena (iz GIT)
- jetrna arterija

Iz jeter:
- jetrna vena *(vena cava inferior)*

Hepatocit

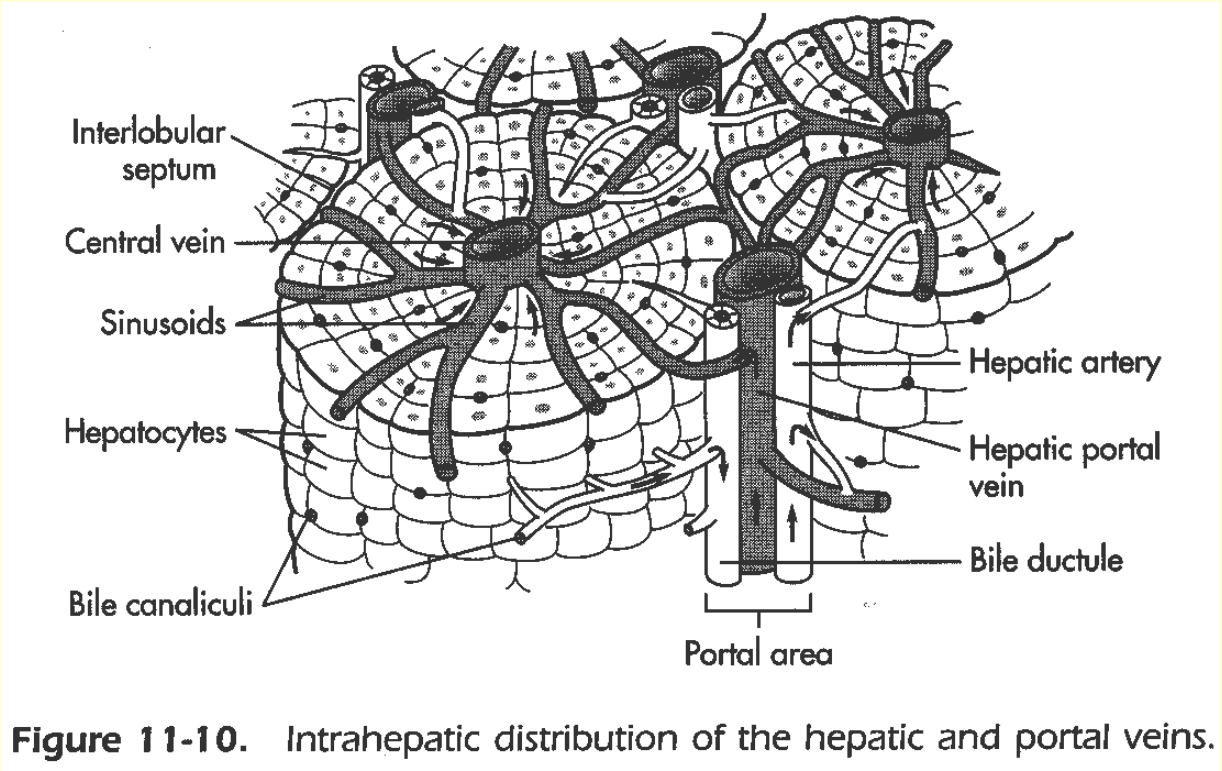


Figure 11-10. Intrahepatic distribution of the hepatic and portal veins.

Enterohepatična cirkulacija

ŽOLČ

- nastaja v jetrih
- proces sinteze žolča je aktivna sekrecija
- žolčni kanalikuli (intrahepatični) se združijo zunaj jeter
- žolč se zbere v žolčnem mehurju
- sestava: voda, žolčne soli, pigmenti, elektroliti, holesterol, maščobne kisline.
- prazni se v duodenum

ENTEROHEPATIČNA CIRKULACIJA

- z žolčem se izločajo endogene in eksogene snovi
- učinkovina/metabolit, ki se izloči v žolč, pride z žolčem v duodenum ➔ učinkovina/metabolit se ponovno reabsorbira ali se izloči s fecesom

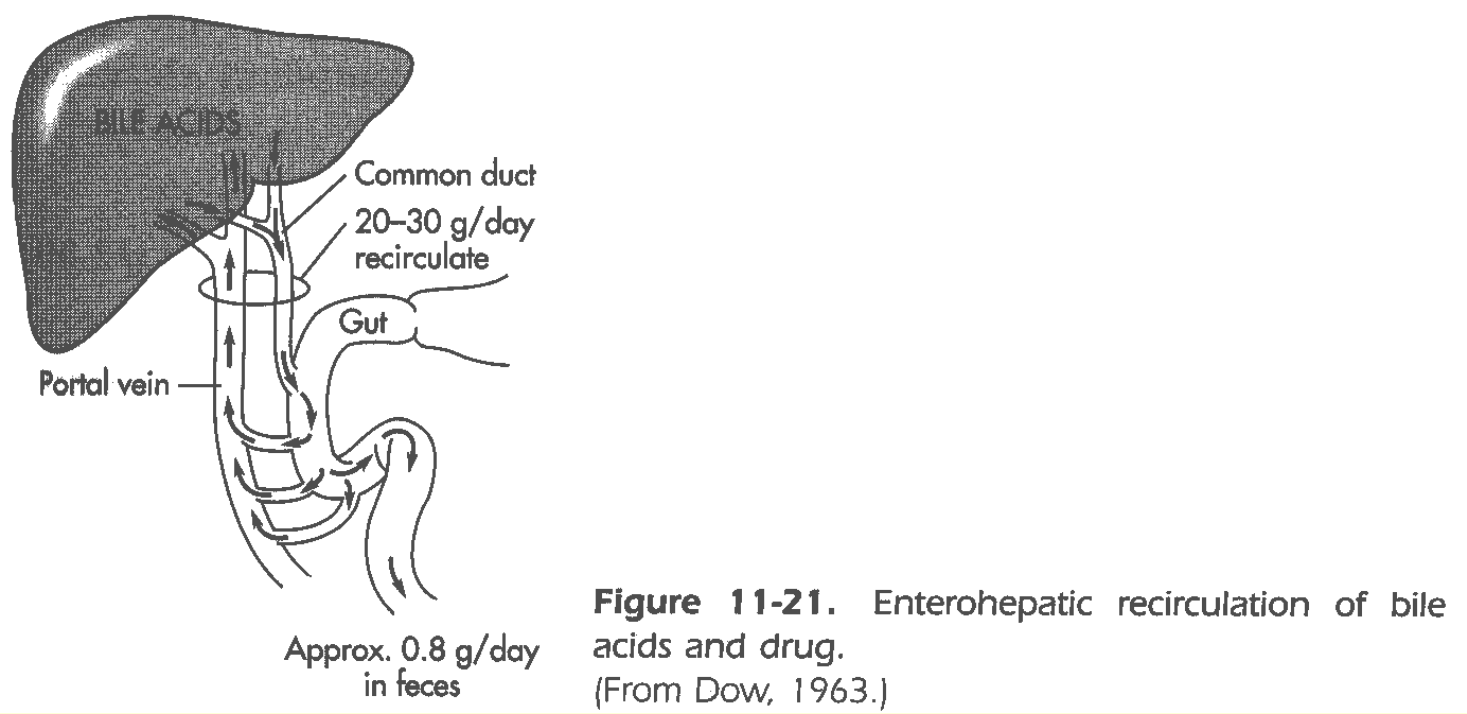
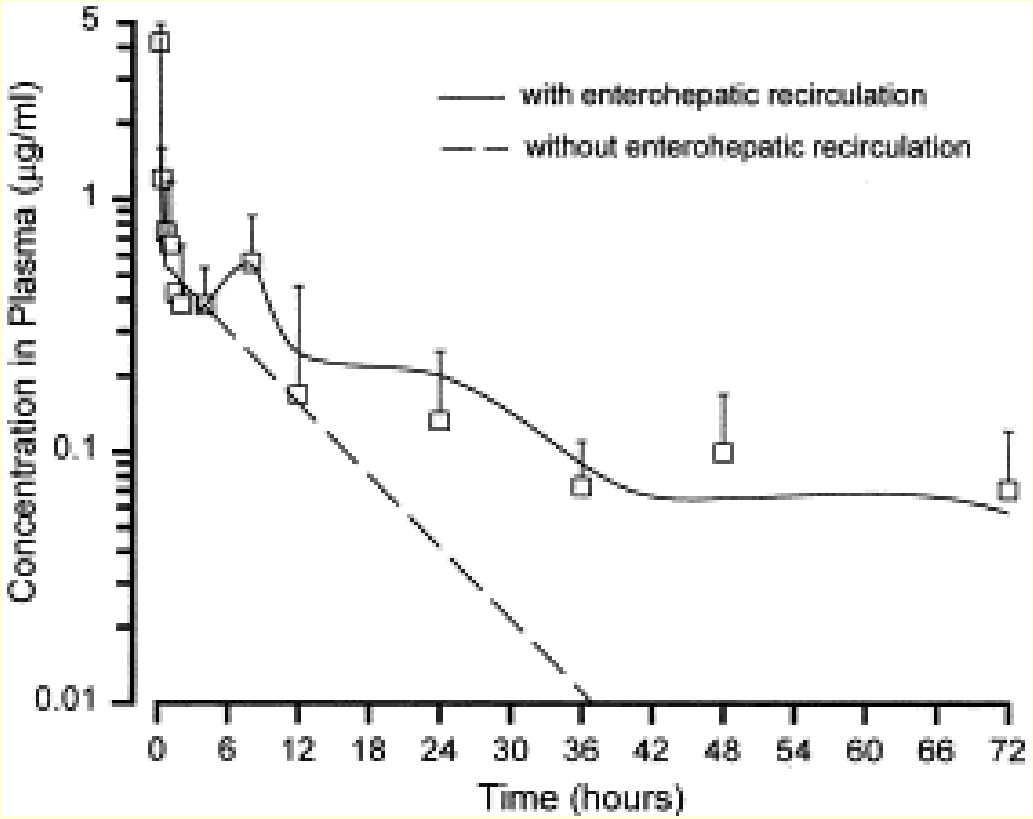


Figure 11-21. Enterohepatic recirculation of bile acids and drug.
(From Dow, 1963.)

Plazemski profil – enterohepatična cirkulacija



Profile of the initial 96 h of the concentration–time profile of 17α-ethynylestradiol after a 1 mg/kg dose. Solid line is the model predicted values using when intact enterohepatic recirculation was included. The dashed line is a computer simulation of the profile when enterohepatic recirculation was turned off. *Aquat Toxicol. 2001 Jan;51(3):305-18.*

D - Porazdeljevanje učinkovin
(Distribution)

Hitrost in obseg porazdelitve ZU v telesu je odvisna od:

1. hitrosti dostave učinkovine ➔ **PERFUZIJA**
2. hitrosti prehoda učinkovine iz krvi v tkivo, prehoda skozi membrane ➔ **DIFUZIJA**
3. afinitete učinkovine do komponent telesa ➔ **VEZAVA NA PLAZEMSKE PROTEINE, KOMPONENTE TKIVA**

Volumni tekočin v organizmu (70 kg moški)

Volumes of Some Body Fluids

Fluid	*Volume (L)*	*Percent of Body Weight*
Plasma	3	4
Blood	5	7
Lymph	10	14
Intracellular water	27	39
Extracellular water	15	21
Total body water	42	60

Note: Volumes are approximate for a 70-kg male person.

Porazdelitev v organizmu je lahko:
homogena
nehomogena

1. Difuzija

- prehod učinkovine preko membrane = lipofilna bariera
- pomembne so hidrolipofilne lastnosti učinkovine, včasih tudi velikost
- membrano prehaja le prosta učinkovine (ki ni vezana na telesne komponente)
- na hitrost difuzije vplivajo: koncentracijski gradient, porazdelitveni in difuzijski koeficient, debelina in površina membrane

2. Perfuzija

- hitrosti dostave učinkovine do tkiva je odvisna od hitrosti pretoka krvi skozi organ
- mehanizmi:
  - razlika v osmotskem tlaku
  - razlika v hidrostatskem tlaku

Blood Perfusion Rates in Certain Tissues

Tissue	*Blood Perfusion Rate (mL/min · g of tissue)*
Lung	10
Kidney	4
Thyroid gland	2.4
Adrenal gland	1.2
Liver	0.8
Heart	0.6
Brain	0.5
Muscle	0.03
Fat	0.03

Source: Adapted with permission from reference 4.

Delitev učinkovin

Distribucija je lahko:

PERFUZIJSKO OMEJENA

- lipofilne učinkovine

DIFUZIJSKO OMEJENA

- hidrofilne učinkovine

3. Vezava na telesne komponente

PLAZEMSKI PROTEINI

- albumin
- α_1-kisli glikoprotein

KOMPONENTE TKIVA

Vezava na plazemske proteine

Percent Binding of Drugs to Plasma Proteins at Therapeutic Drug Concentrations

Drug	*Percent Bound*	*Drug*	*Percent Bound*
Diazoxide	99	Methotrexate	45
Dicoumarol	98	Methadone	40
Diazepam	96	Meperidine	40
Digitoxin	95	Phenacetin	30
Prednisone	90	Acetaminophen	25
Phenytoin	87	Ampicillin	25
Riafampin	85	Digoxin	23
Chlorpropamide	80	Cephalexin	22
Pentothal	75	Barbital	10
Carbamazepine	72	Promethazine	8
p-Aminosalicylate	65	Antipyrine	4
Glutethimide	54	Isoniazid	0
Carbenicillin	47		

Primer izračuna navideznega volumna porazdelitve

- Z intravensko injekcijo apliciramo 100mg učinkovine, ki se v 80% veže na plazemske proteine. V plazmi smo določili koncentracijo 8mg/L

a) Zanemarimo deleže vezave na proteine:

$\mathbf{V_d}$=100mg/8mg/L=**12,5L**

b) Upoštevamo delež vezave na proteine:

C_{vezana}=0,8*8mg/L=6,4mg/L → V=3L (plazemski proteini težko prehajajo membrano)

$\underline{C_{prosta}}$=0,2*8mg/L=<u>1,6mg/L</u>

m_{vezana}=6,4mg/L*3L=19,2mg

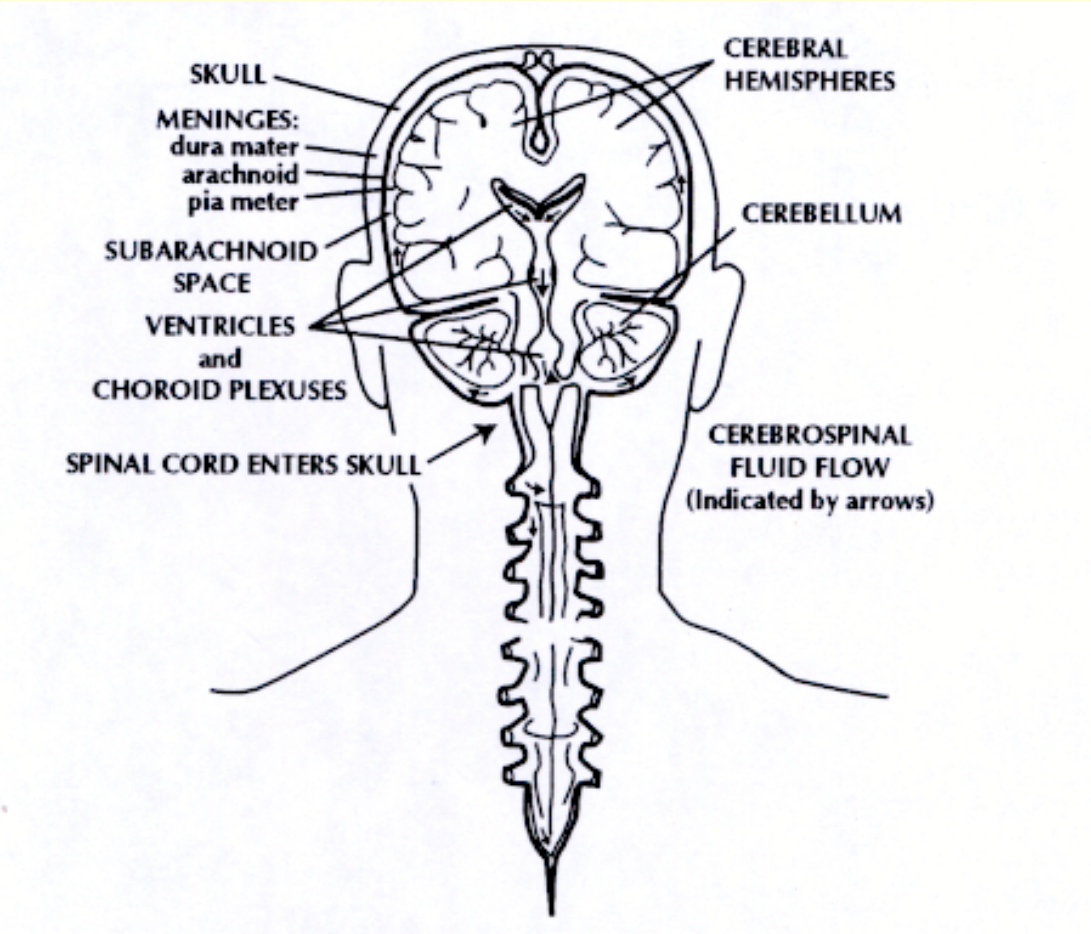
$\underline{m_{prosta}}$=100mg-19,2mg=<u>80,8mg</u>

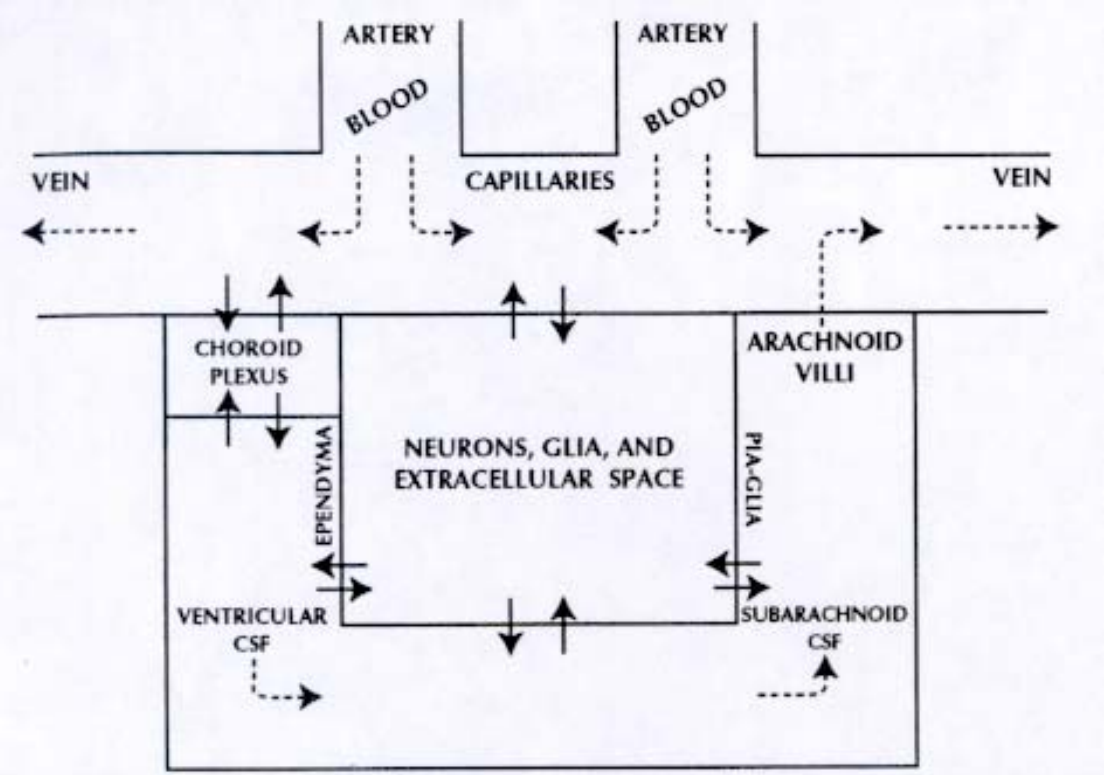
$\mathbf{V_d}$=80,8mg/1,6mg/L=**50,5L**

Komentar:

Izračunani navidezni volumen porazdelitve je 4x višji. Volumen porazdelitve 50,5L nakazuje na porazdeljevanje učinkovine po celem telesu, medtem ko volumen 12,5L nakazuje le omejeno distribucijo, ki vključuje le ekstra- in intra-celularno tekočino.

Distribucija v CŽS





Routes by which compounds can enter and leave the CNS. (Reproduced with permission from reference 8.)

M - Presnova učinkovin
(Metabolism)

Presnova učinkovin

- **Mesta metabolizma:**
  - lumen in stena GIT
  - jetra
  - kri
  - vranica
  - ledvica
  - možgani
  - mišice
  - pljuča

- **Naloga metabolizma:**
  - obrambni mehanizem
  - farmakološka deaktivacija
  - odstraniti snovi iz organizma
  - povečanje hidrofilnosti, da se snovi lažje izločijo (ledvica)

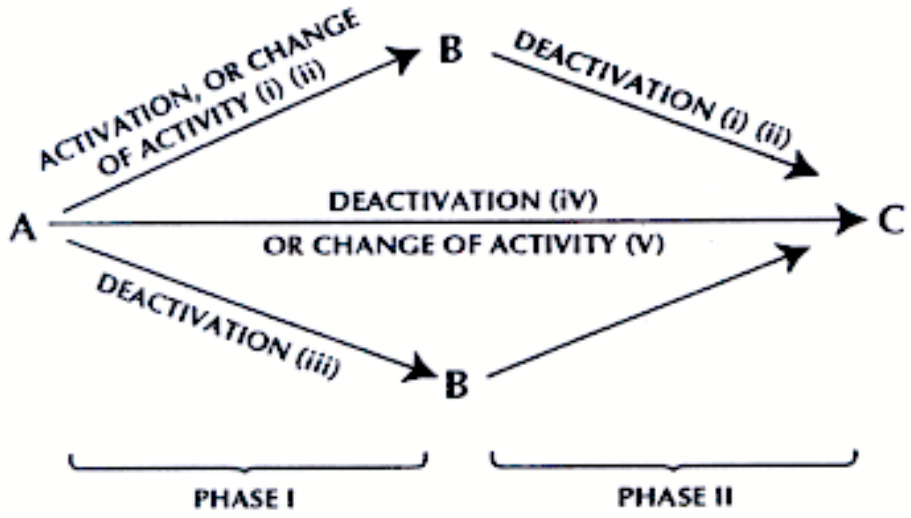
- **Predsistemski metabolizem**
- **Sistemski metabolizem**

Predsistemski metabolizem

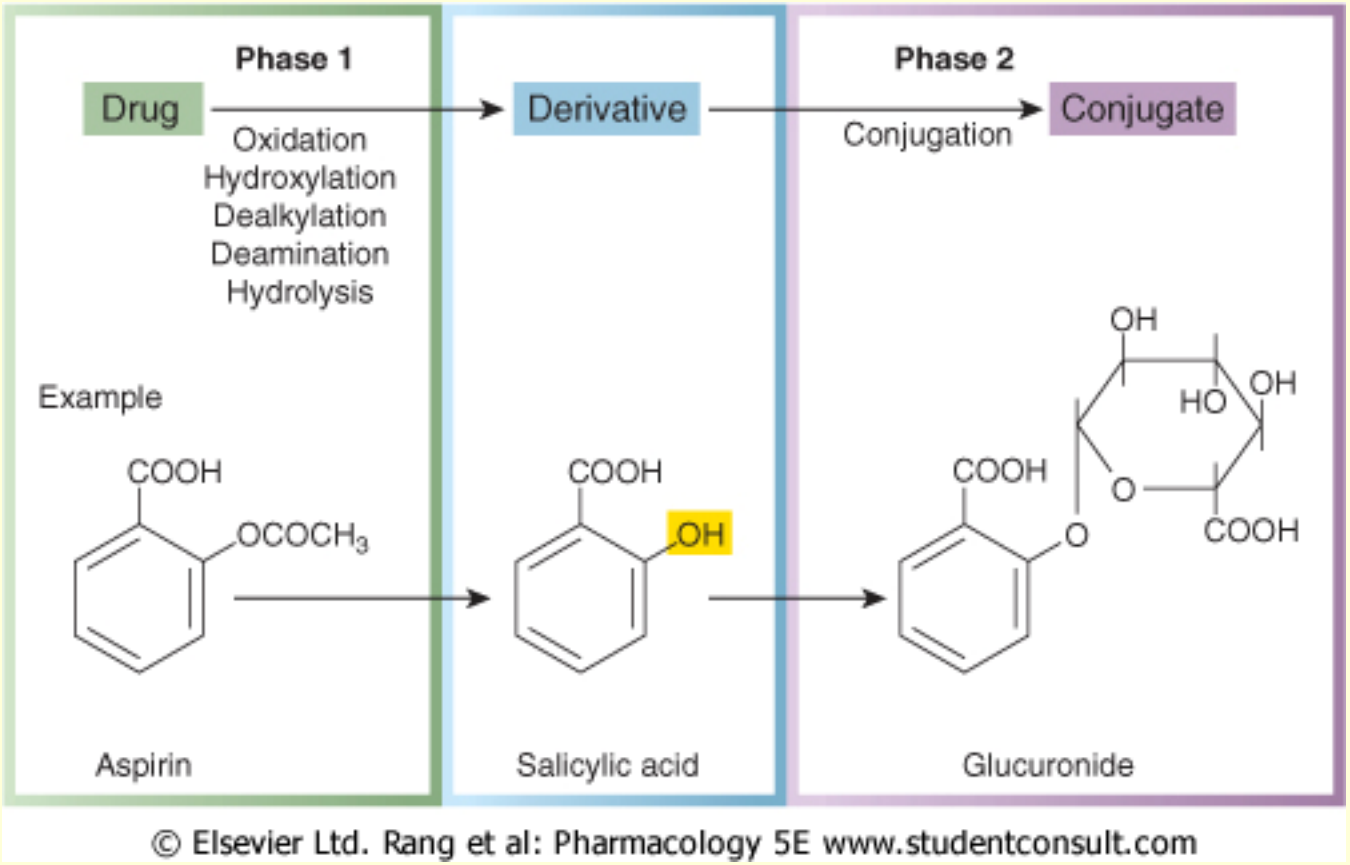
Mesta predsistemskega metabolizma:

- lumen prebavnega trakta: pH, encimi, bakterije
- stena prebavnega trakta: enterociti
- jetra: jetrne parenhimske celice (hepatociti)
- pljuča

Sistemski metabolizem



The two major phases of drug metabolism.



The two phases of drug metabolism.

Sistemski metabolizem
FAZA 1

- **kemijska aktivacija**; tvori se funkcionalna skupina, s katero lahko pride v fazi 2 do konjugacije

1. **OKSIDACIJE**
   - v endoplazmatskem retikulumu (alifatske in aromatske oksidacije, N- in O-dealkilacije, oksidativne deaminacije, sulfoksidacije, N-hidroksilacije)
   - v topni frakciji celic (oksidacije etanola in benzilnega etanola z alkoholno dehidrogenazo)
   - **oksidacije s citokromi P450 (CYP450)**
     - 6 najpomembnejših izoencimov
     - možen polimorfizem genov
     - farmakokinetične interakcije: inhibicija in indukcija izoencimov
2. **REDUKCIJE**
3. **HIDROLIZE**

Najpogostejši izoencimi CYP450 in substrati

Six Major Isozymes of Cytochrome P-450 Responsible for Drug Metabolism in Humans

Isozyme	*Typical Substrates*
CYP1A2	Phenacetin, theophylline
CYP2C8/9/10	Hexobarbital, phenytoin, tolbutamide, warfarin
CYP2C18/19	Diazepam, mephenytoin
CYP2D6	Bufuralol, debrisoquin, encainide, imipramine, metoprolol, propranolol
CYP2E1	Acetaminophen, chlorzoxazone
CYP3A4	Alfentanol, cimetidine, cyclosporine, enoxacin, erythromycin, lidocaine, tacrine

Source: Adapted with permission from reference 4.

Sistemski metabolizem
FAZA 2

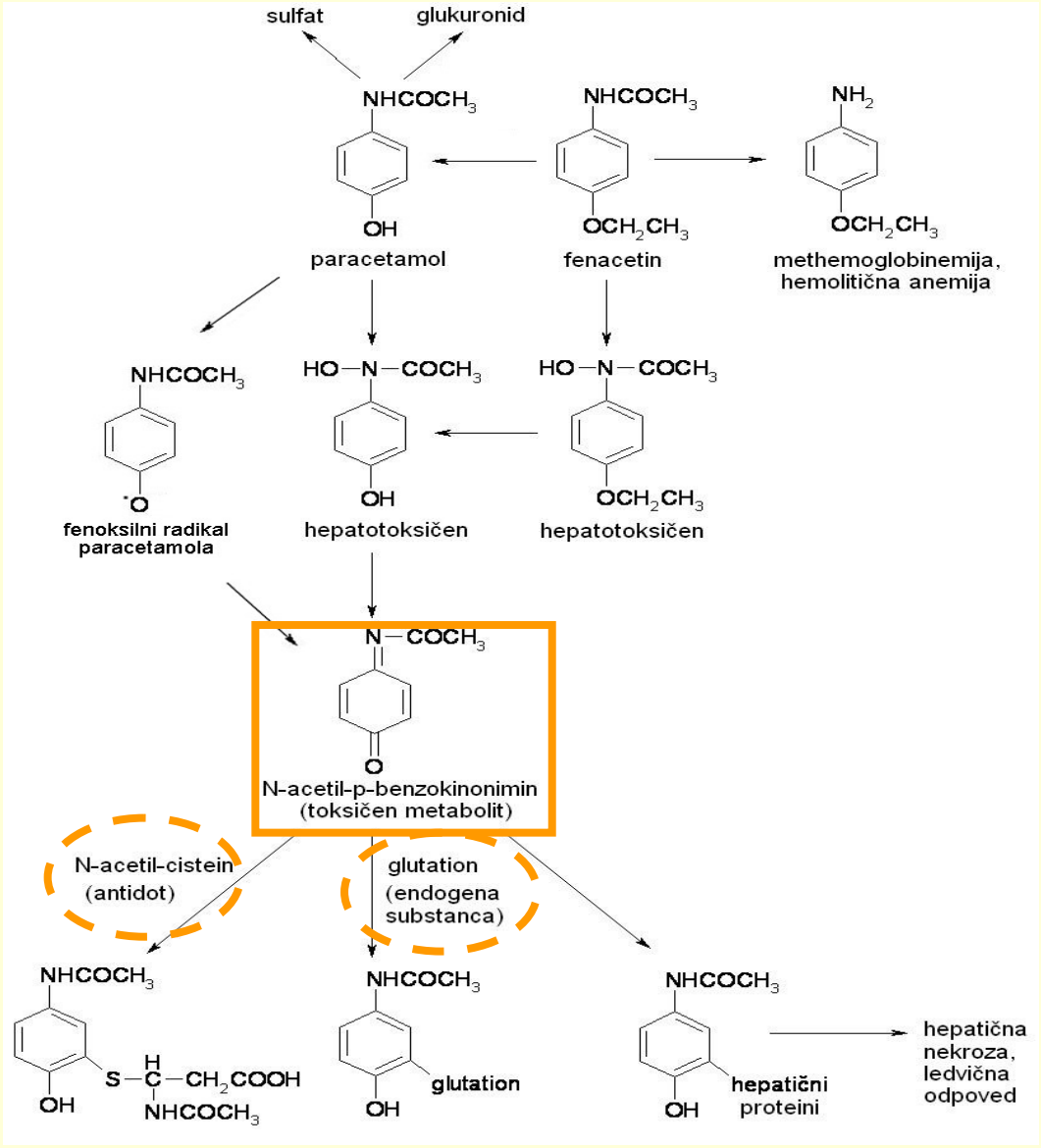
1. **KONJUGACIJA**
   - tvorba glukuronidov,
   - acetatov,
   - sulfatov,
   - konjugatov glicina,
   - konjugatov merkapturne kisline,
   - N-, S- in O-metiliranje.

Table 8.3 Some drugs that produce active or toxic metabolites

Inactive (pro-drugs)	Active drug	Active metabolite		Toxic metabolite	See Ch.
Azathioprine		Mercaptopurine			16
Cortisone		Hydrocortisone			27
Prednisone		Prednisolone			27
Enalapril		Enalaprilat			18
Zidovudine		Zidovudine trisphosphate			46
Cyclophosphamide		Phosphoramide mustard		Acrolein	50
	Diazepam	Nordiazepam	Oxazepam		36
	Morphine	Morphine 6-glucuronide			40
	Halothane			Trifluoroacetic acid	35
	Methoxyflurane			Fluoride	35
	Paracetamol			*N*-Acetyl-*p*-benzoquinone imine	16, 52

Metaboliti so lahko terapevtsko uporabni, neaktivni ali celo toksični.

Metabolizem paracetamola in hepatotoksičnost



PROBLEM:

- veliki odmerki paracetamola
- pomanjkanje glutationa
- indukcija CYP (etanol,…)

Primer – peroralni kontraceptivi (1)

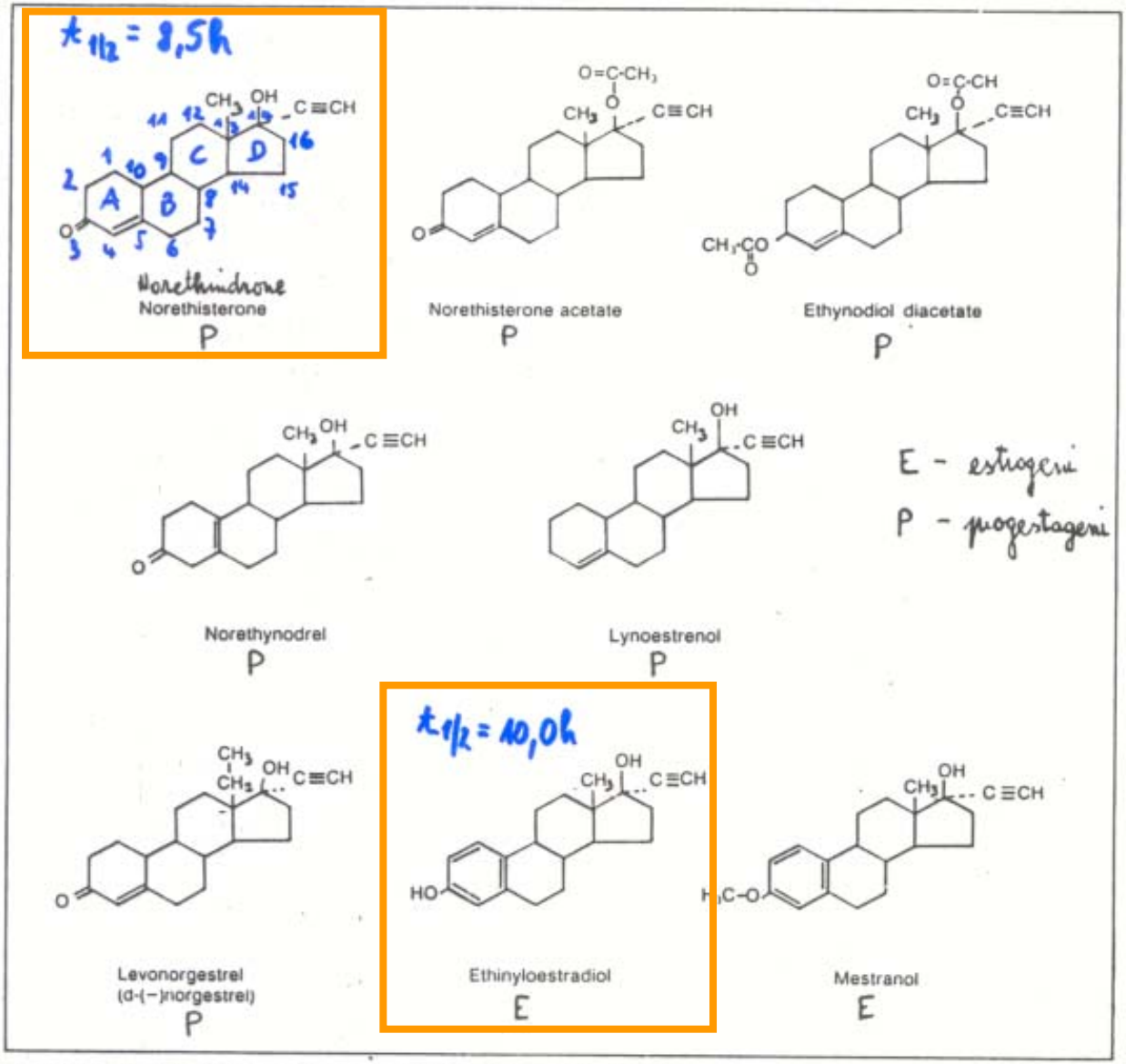


Fig. 1. Chemical structures of the commonly used oral contraceptive steroids.

ETINILESTRADIOL
Na fenolni OH se tvori glukuronid, ki se izloča v žolč in zapade enterohepatičnemu ciklusu. Tako se podaljša čas zadrževanja v telesu ($t_{1/2}$=10h).

NORETISTERON
Izloča se v nespremenjeni oblik ($t_{1/2}$=8,5h).

Primer – peroralni kontraceptivi (2)

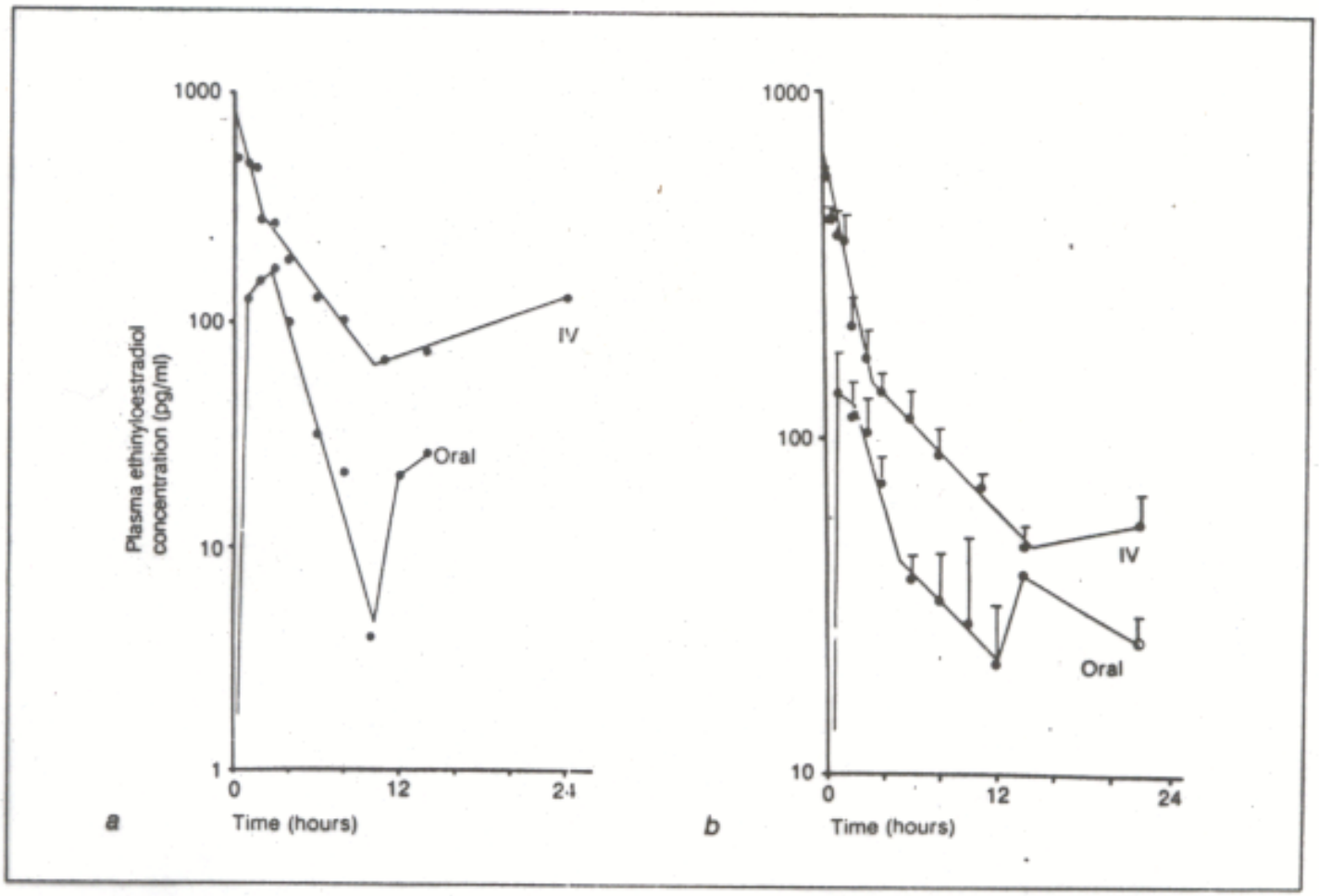


Fig. 2. Plasma concentrations of ethinyloestradiol after the administration of 50μg by mouth and intravenously to one individual (a) and to 6 individuals (b), showing mean data (± SE). [Reproduced with kind permission of the Editor of *Contraception*.]

Plazemske koncentracije etinilestradiola odražajo prisotnost enterohepatične cirkulacije (2 pika).

E - Izločanje učinkovin
(Elimination)

Poti izločanja

- **urin**
- žolč
- feces
- slina
- pljuča
- znoj
- mleko

Table 17-1. Survey of Excretion Patterns

EXCRETION PATTERN		
PATHWAY OF EXCRETION	MECHANISM	EXAMPLES
Urine	Glomerular filtration, active tubular secretion, passive diffusion	Most drugs in free (nonprotein bound) form Salicylic acid Ion, PAH, N-MethylnIcotInamide, PAB, Penicillin, Sulfadimethylpyrimidine, Sulfaethylthiadiazole, Acetylsulfonamides, Organic mercuric diuretics, Chlorothiazide
Bile	Active transport, passive diffusion, pinocytosis	Quaternary ammonium compounds, Strychnine, Quinine, Digitoxin, Penicillin, Streptomycin, Tetracyclines
Intestines	Passive diffusion and unrecycled biliary secretion	Ionized organic acids, Doxycycline
Saliva	Passive diffusion and active transport	Penicillin, Tetracyclines and many other drugs, Thiamine, Desoxycholate, Ethanol, Ether
Lung	Passive diffusion	Camphor, Guaiacol, Ethereal oils, Ammonium chloride, Iodides
Sweat	Passive diffusion	Weak organic acids and bases, Thiamine
Milk	Passive diffusion and active transport	Primarily weak organic bases, Less weak acids, Thyreostatics, Anesthetics, Anticoagulants, Erythromycin and other antibiotics

Anatomija nefrona

Mehanizmi izločanja skozi ledvica:

1. Glomerularna filtracija
2. Tubularna sekrecija
3. Tubularna reabsorpcija

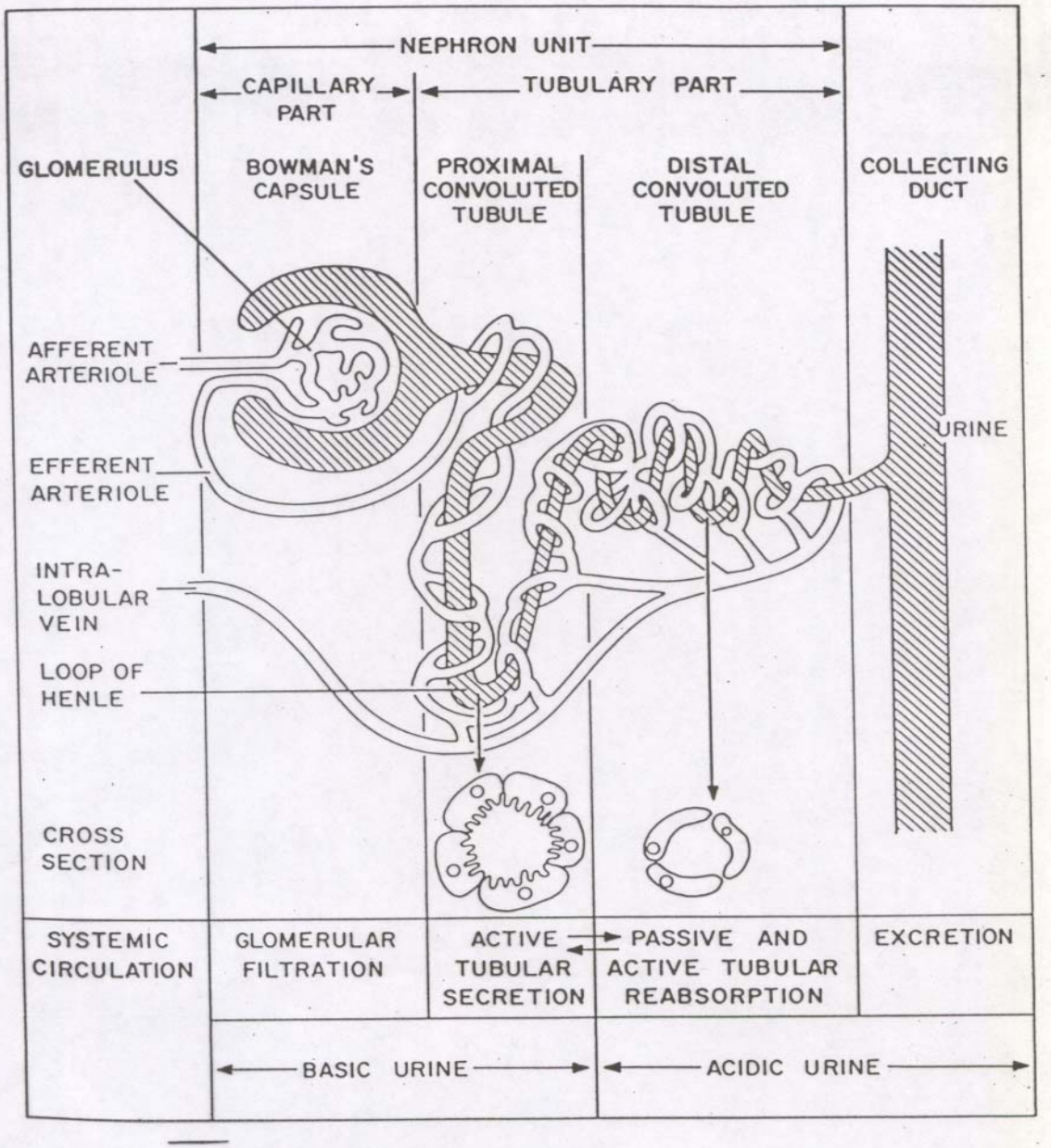


Figure 17-2. Schematic diagram of the structure of a nephron unit and its function.

Table 8.4 Important drugs and related substances actively secreted into the proximal renal tubule

Acids	Bases
p-Aminohippuric acid (PAH)	Amiloride
Furosemide (frusemide)	Dopamine
Glucuronic acid conjugates	Histamine
Glycine conjugates	Mepacrine
Indometacin	Morphine
Methotrexate	Pethidine
Penicillin	Quaternary ammonium compounds
Probenecid	Quinine
Sulphate conjugates	5-Hydroxytryptamine (serotonin)
Thiazide diuretics	Triamterene
Uric acid	

Izločanje učinkovin

Izraženo s

- hitrostjo in maso

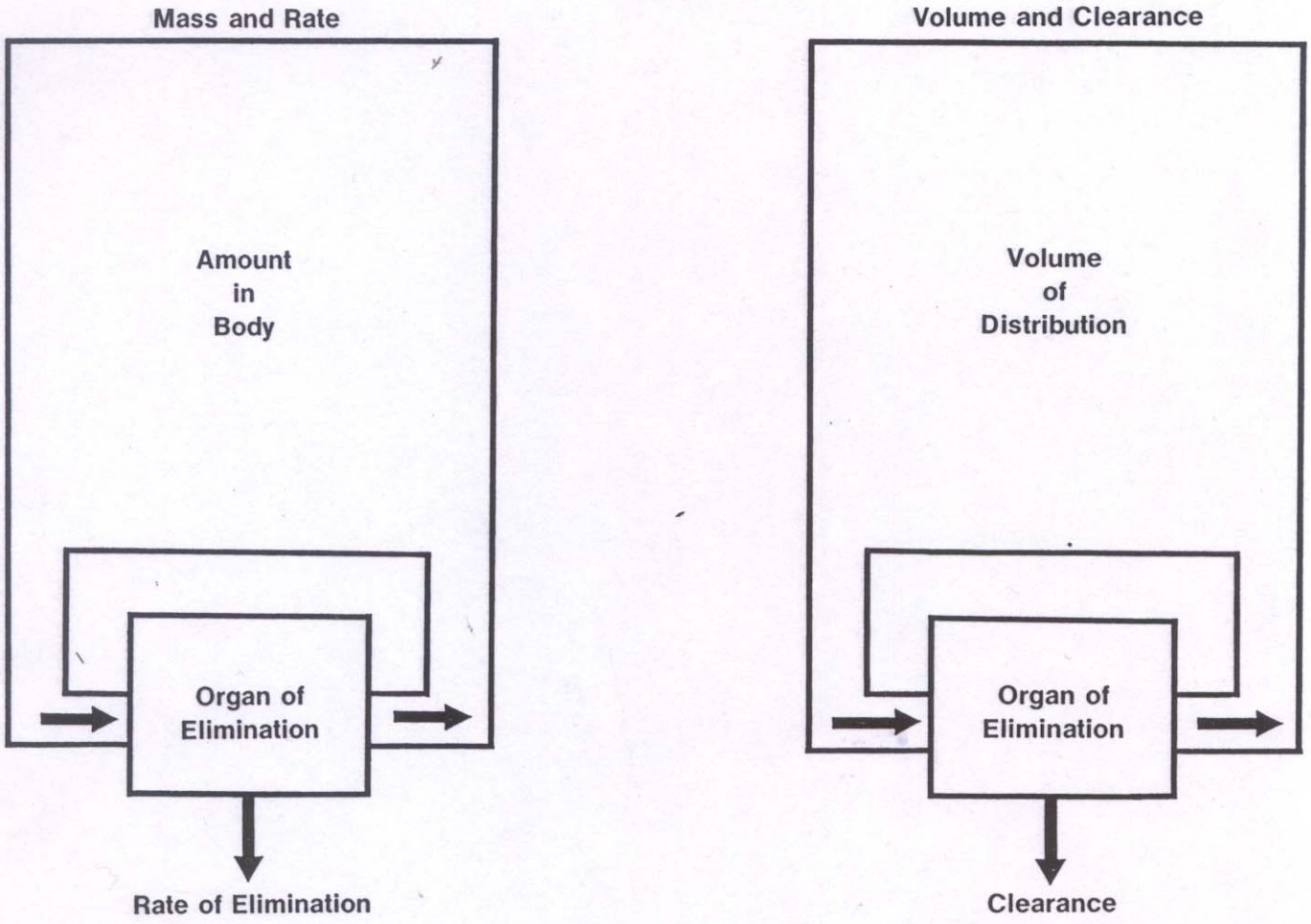
$$\frac{dU_e}{dt} = k_e \cdot U$$

- očistkom in volumnom

$$Cl = k_e \cdot V$$

- **Hitrost eliminacije** je količina učinkovine, ki se eliminira iz telesa na enoto časa preko določenega organa.

- **Očistek** je volumen tekočine, iz katerega se izloči učinkovina na enoto časa preko določenega organa.



$$\text{Fractional Rate of Elimination} = \frac{\text{Rate of Elimination}}{\text{Amount in Body}} = \frac{\text{Clearance}}{\text{Volume of Distribution}}$$

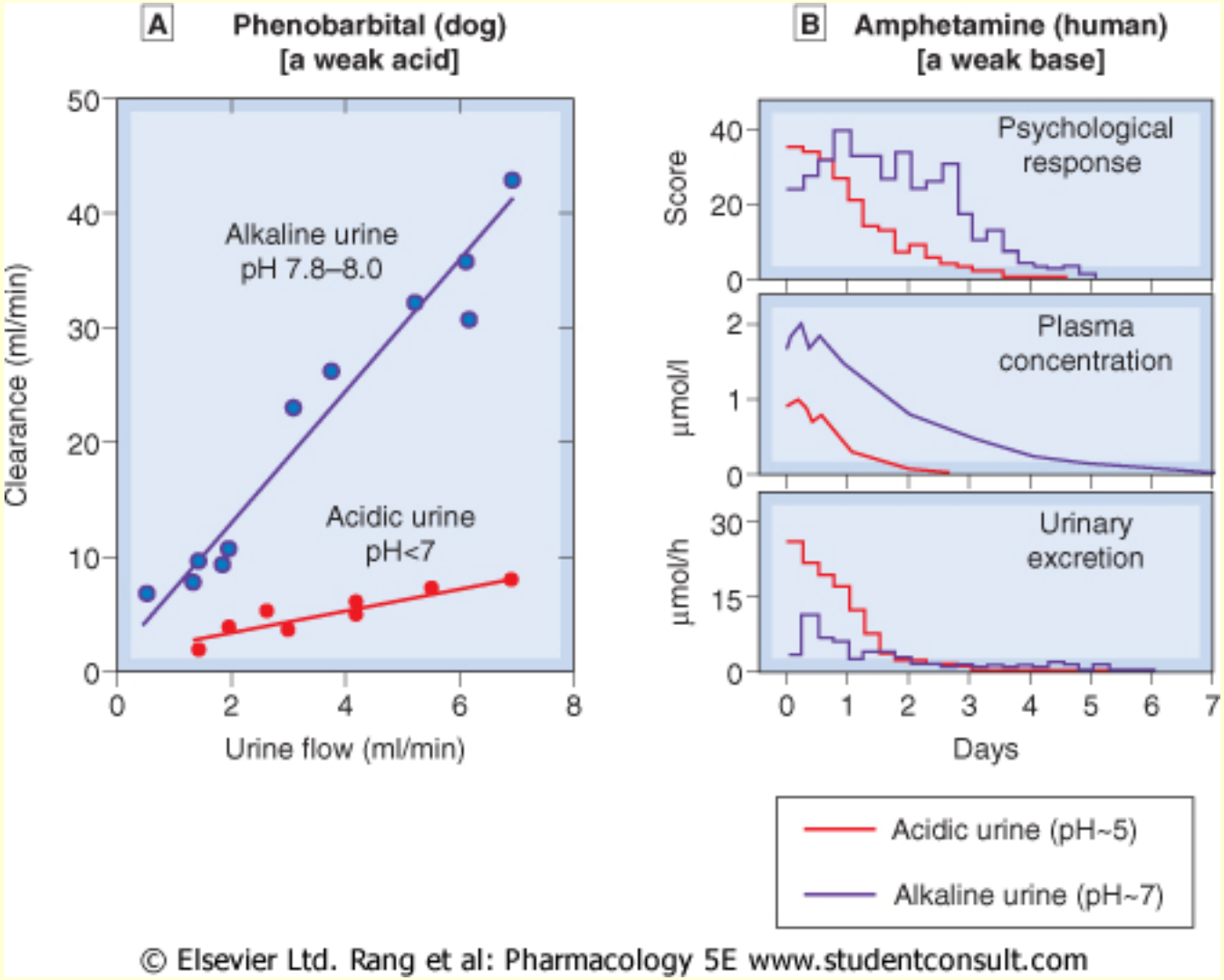
The fractional rate of elimination of a drug can be thought of either as the fraction of the total amount in the body that is eliminated per unit time (left), or as the fraction of the total volume from which the drug is cleared per unit time (right).

Renalni očistek

$$Cl_R = \frac{C_u \cdot \frac{dV}{dt}}{C_P}$$

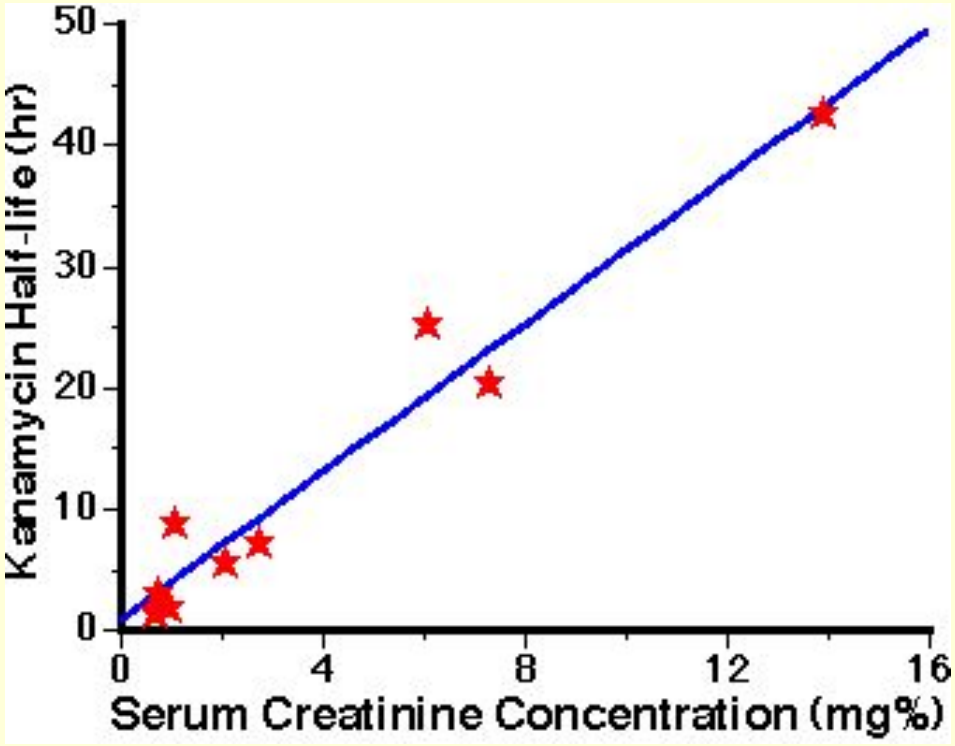
$$Cl_R = k_e \cdot V_D$$

C_U … koncentracija v urinu
dV/dt … hitrost nastajanja urina
C_P … koncentracija v plazmi
k_e … konstanta hitrosti izločanja
V_D … volumen porazdelitve



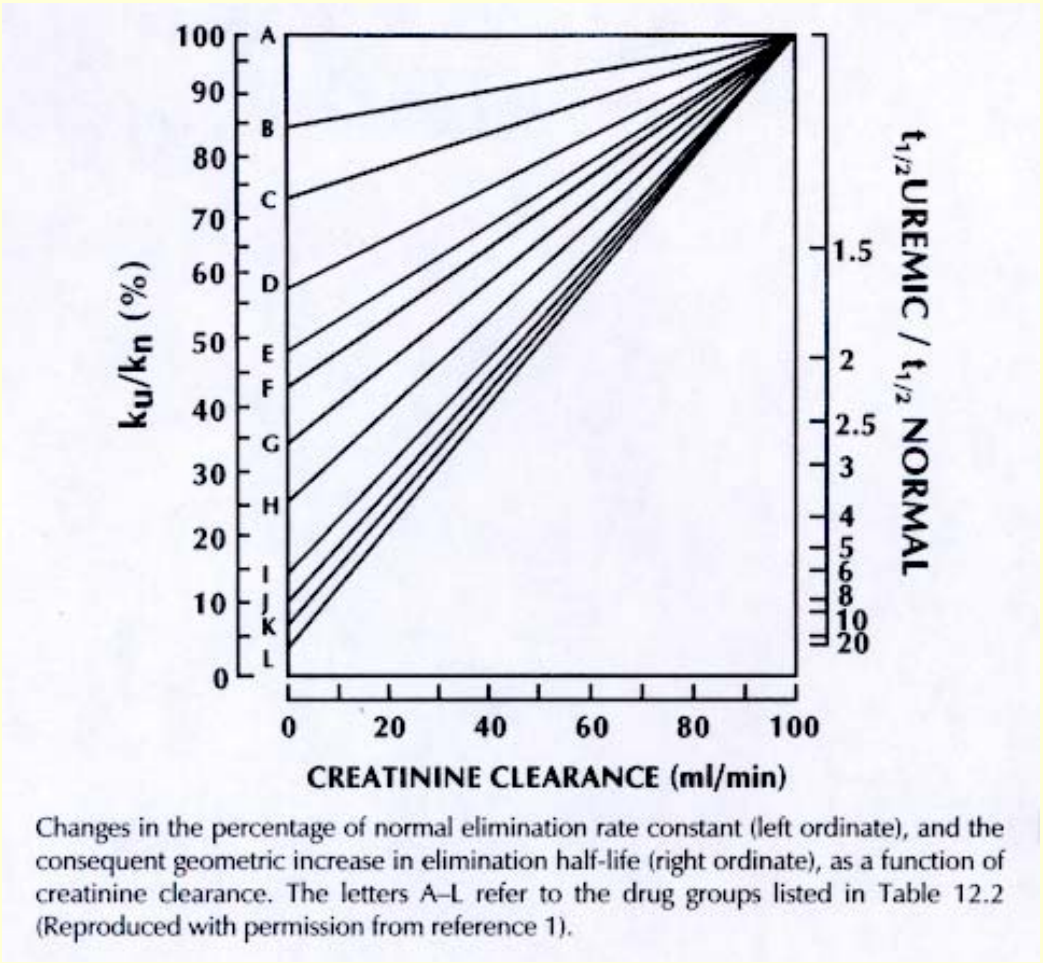
The effect of urinary pH on drug excretion.

A Phenobarbital clearance in the dog as a function of urine flow. Because phenobarbital is acidic, alkalinising the urine increases clearance about five fold. **B** Amphetamine excretion in humans. Acidifying the urine increases the rate of renal elimination of amphetamine, reducing its plasma concentration and its effect on the subject's mental state. *(Data from: Gunne & Anggard 1974 In: Torrell T et al. (eds) Pharmacology and pharmacokinetics. Plenum, New York.)*



Relationship between kanamycin half-life and serum creatinine level. As kidney function is reduced the serum creatinine level increases and the also the kanamycin takes longer to be eliminated from the body.

Eliminacija učinkovin in okvara ledvic

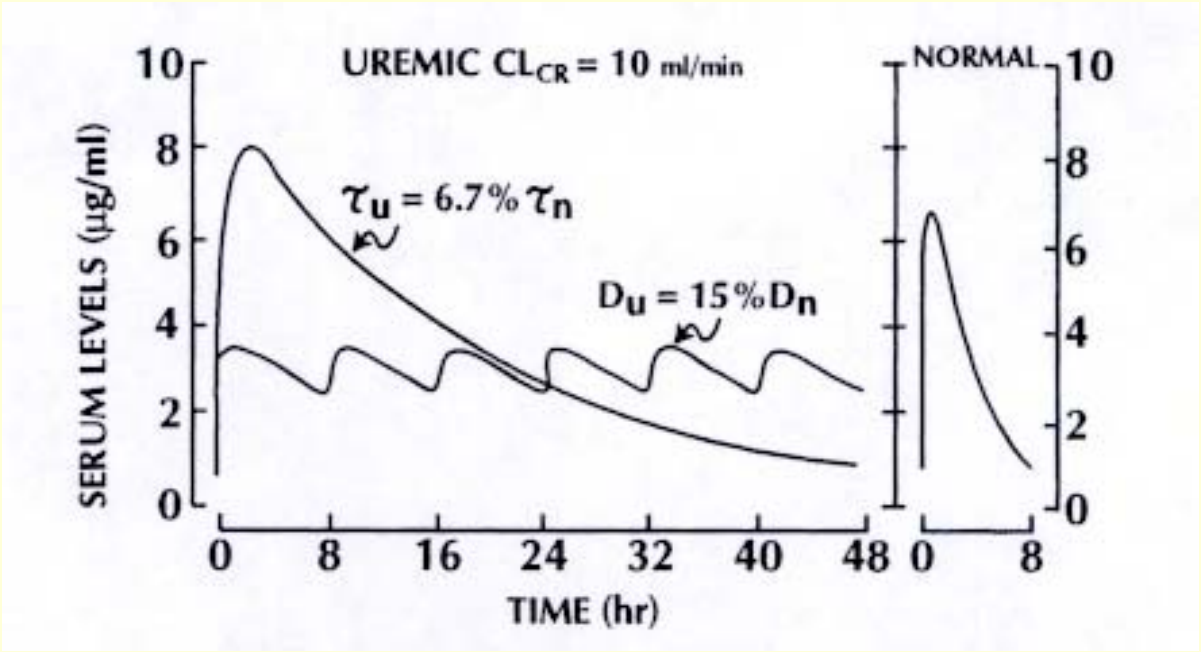


Changes in the percentage of normal elimination rate constant (left ordinate), and the consequent geometric increase in elimination half-life (right ordinate), as a function of creatinine clearance. The letters A–L refer to the drug groups listed in Table 12.2 (Reproduced with permission from reference 1).

Zdravila skupine A se izločijo enako hitro pri zdravih in obolelih ledvicah, ker se v zelo majhnem deležu izločajo skozi ledvica. Zato pri motnjah delovanja ledvic ni potrebno prilagajanje odmerka.
Zdravila skupine L pa se izločajo pretežno skozi ledvica. Izločanje teh zdravil je močno zmanjšano, kadar so ledvica okvarjena. V tem primeru je nujno prilagoditi odmerek.

k_u…konstanta eliminacije pri hudo okvarjenih ledvicah
k_n…konstanta eliminacije pri normalno delujočih ledvicah

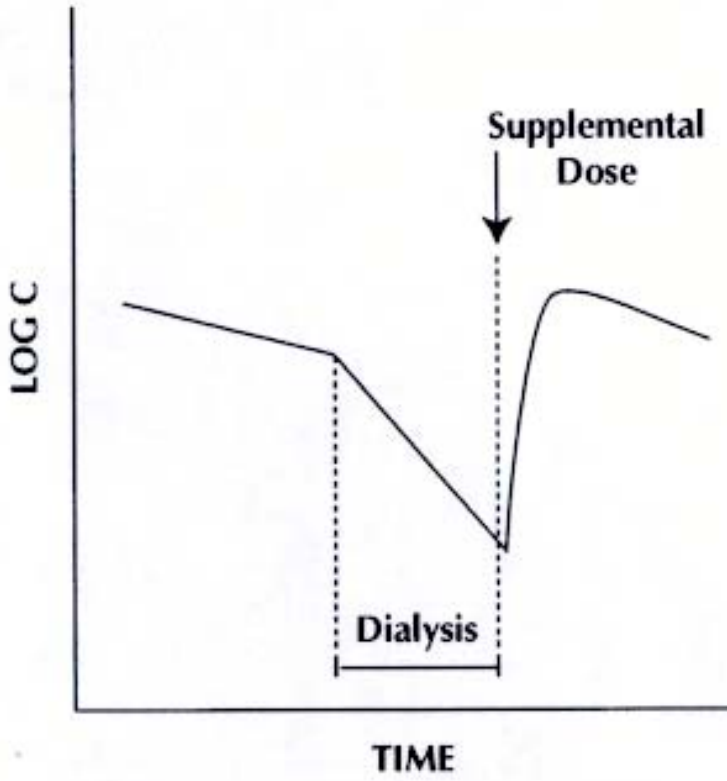
Prilagajanje odmerka pri okvari ledvic



$$D_u = D_n \cdot \frac{k_u}{k_n}$$

$$\tau_u = \tau_n \cdot \frac{t1/2_u}{t1/2_n}$$

Dializa



Interdialysis and intradialysis profiles for a dialyzable drug showing a supplemental dose administered immediately postdialysis.

Farmakokinetični profil učinkovine se med dializo spremeni. Hitrost eliminacije se pri ledvični okvari močno zmanjša. Če se učinkovina odstranjuje z dializo, lahko plazemske koncentracije padejo in je zato takoj po končani dializi potreben nadomestni odmerek.