SEMINOR ON

FIRST-PASS METABOLISM,BIOAVAILABILITY

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M.PHARMACY(1ST Semester)

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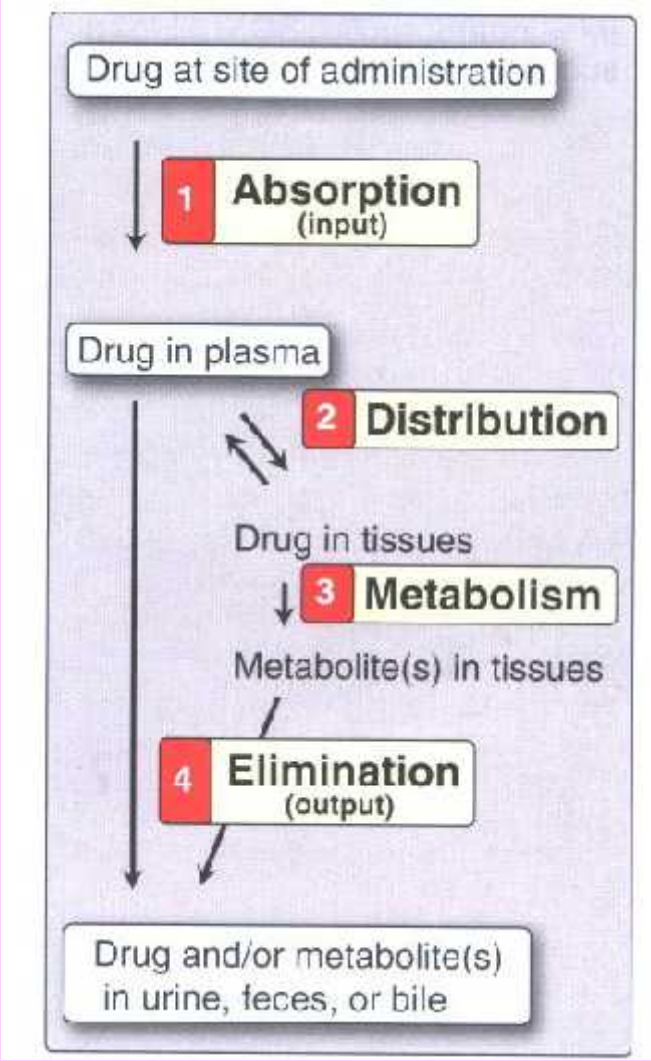
PHARMACOKINETICS

It is concerned with the ADME of drugs as elicited by the plasma drug concentration-time profile and its relationship with the dose, dosage form and frequency and route of administration.



BIOAVAILABILITY

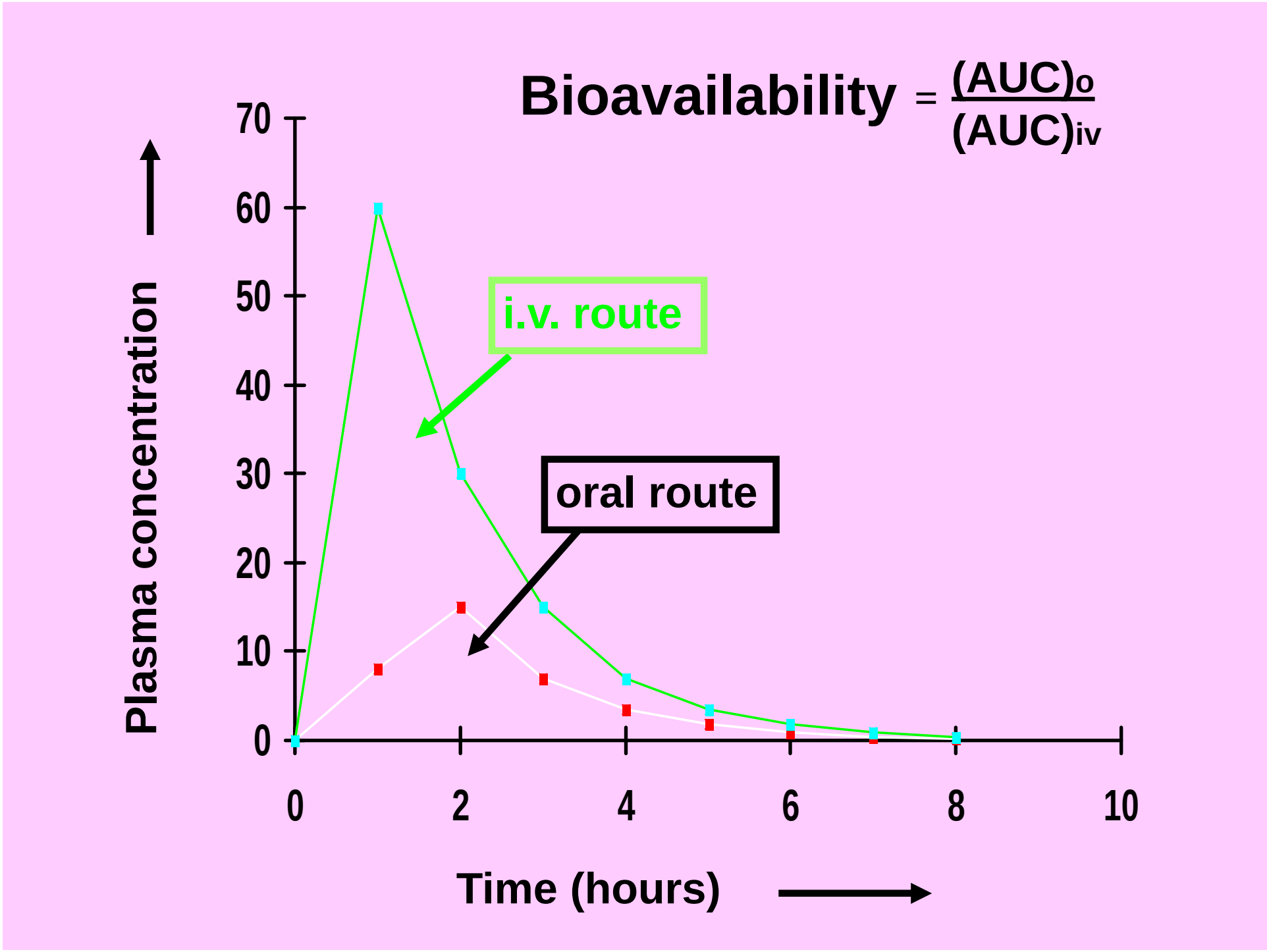
Bioavailability is a measurement of rate and extent of a therapeutically active drug that reaches the systemic circulation and is available at the site of action. It is denoted by letter ‘F’

ABSOLUTE BIOAVAILABILITY

The absolute availability of drug is the systemic availability of a drug after extra vascular administration (e.g., oral, rectal, transdermal, subcutaneous) compared to IV dosing.

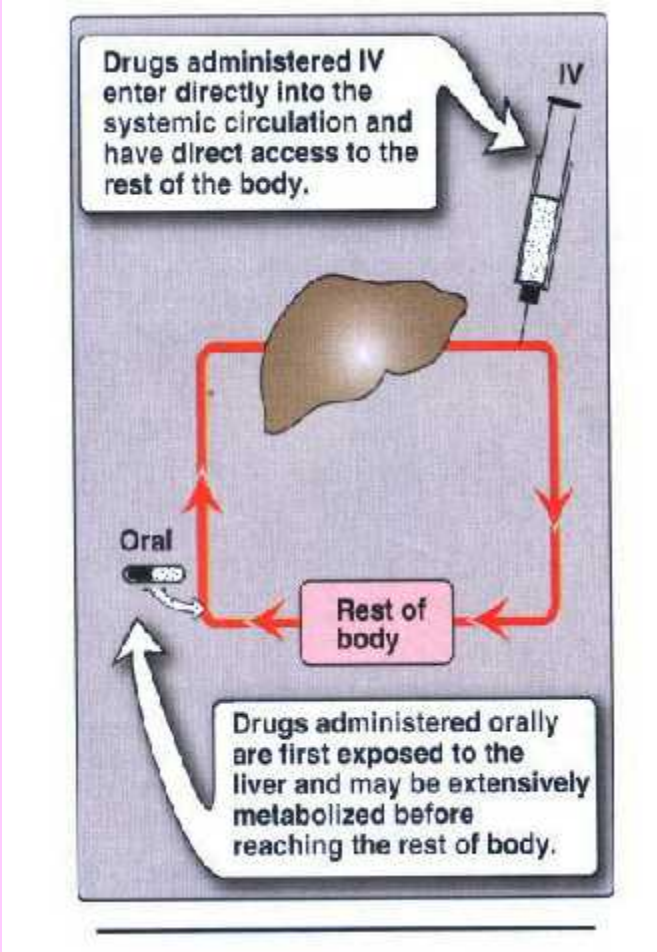
The absolute availability of a drug is generally measured by comparing the respective AUCs after extra vascular and IV administration.

$$F = \frac{[\mathrm{AUC}]_{0,\,\mathrm{oral}}^{\infty} / D_{0,\,\mathrm{oral}}}{[\mathrm{AUC}]_{0,\,\mathrm{IV}}^{\infty} / D_{0,\,\mathrm{IV}}}$$

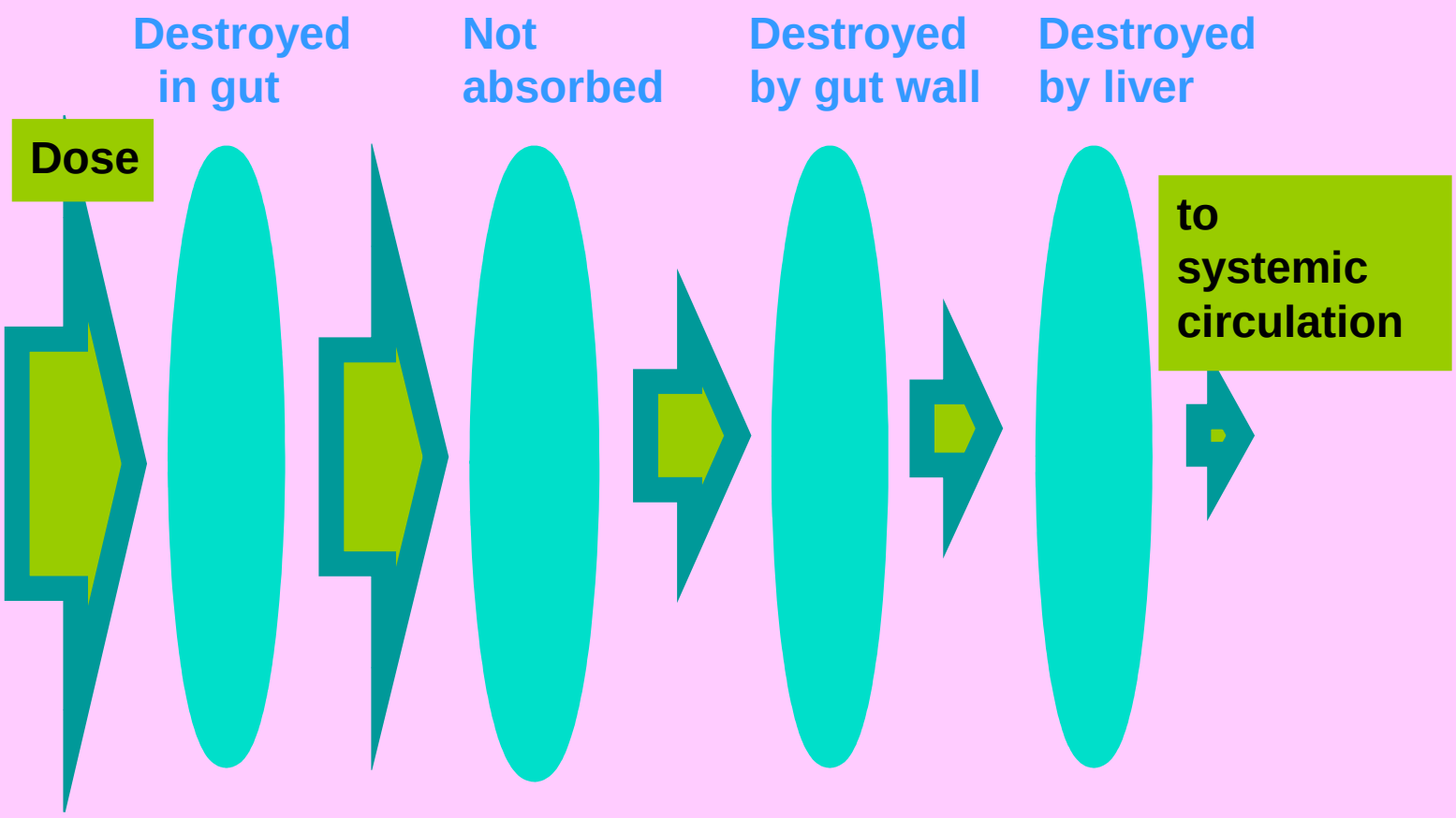

Bioavailability = (AUC)o / (AUC)iv
Plasma concentration
70
60
50
40
30
20
10
0
i.v. route
oral route
0
2
4
6
8
10
Time (hours)

FIRST PASS METABOLISM/ FIRSTPASS EFFECTS/ PRESYSTEMIC METABOLISM

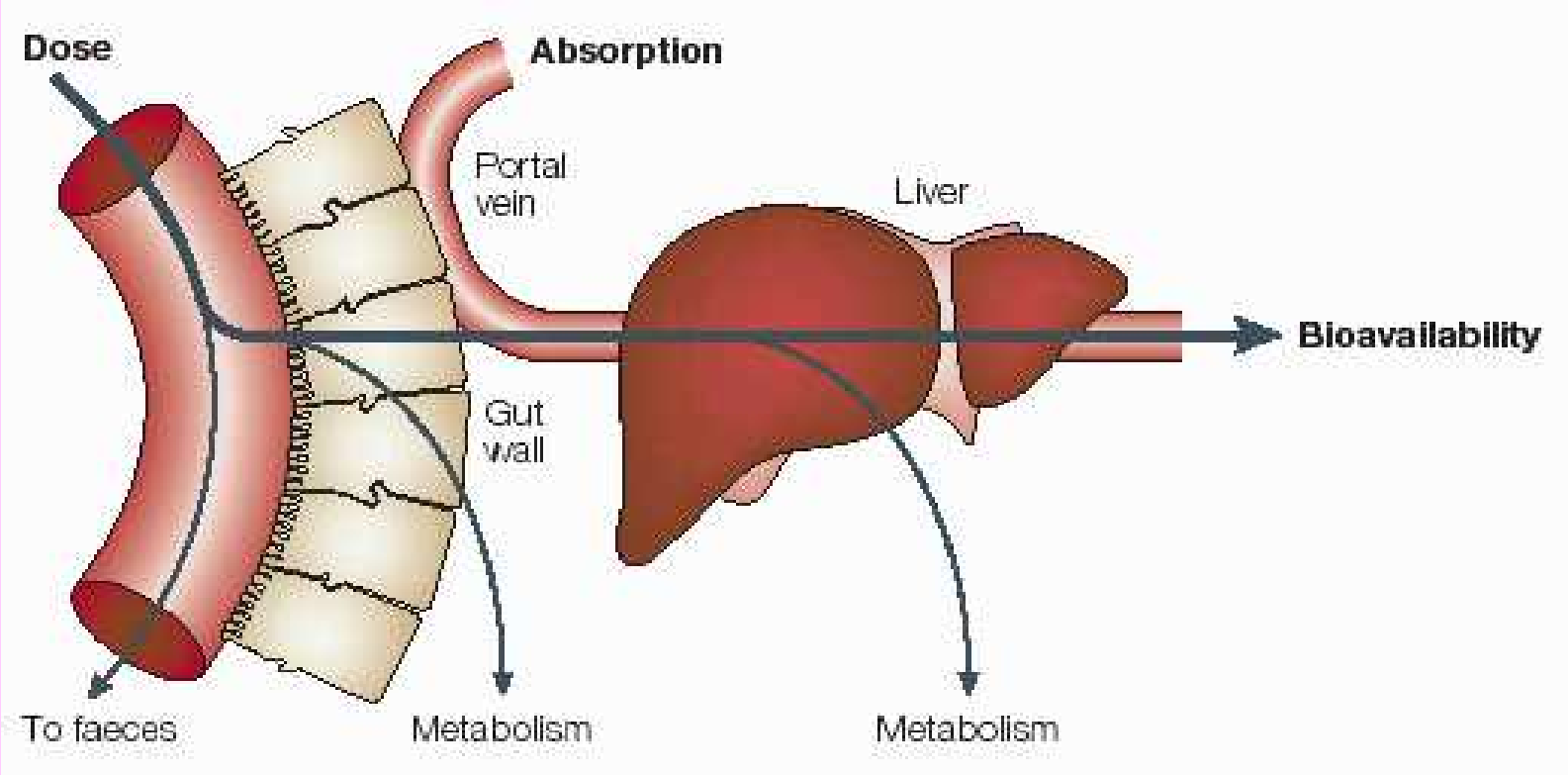
It is the phenomenon of drug metabolism. Where the concentration of a drug is greatly reduced before it reaches the systemic circulation



BIOAVAILABILITY



Uptake of orally administered drug proceeds after the stomach passage via the small intestine.
In the gut and liver, a series of metabolic transformation occurs.



Primary systems which effect presystemic metabolism

1. ***Luminal enzymes***

2. ***Gut wall enzymes/ mucosal enzymes***

3. ***Bacterial enzymes***

4. ***Hepatic enzymes.***

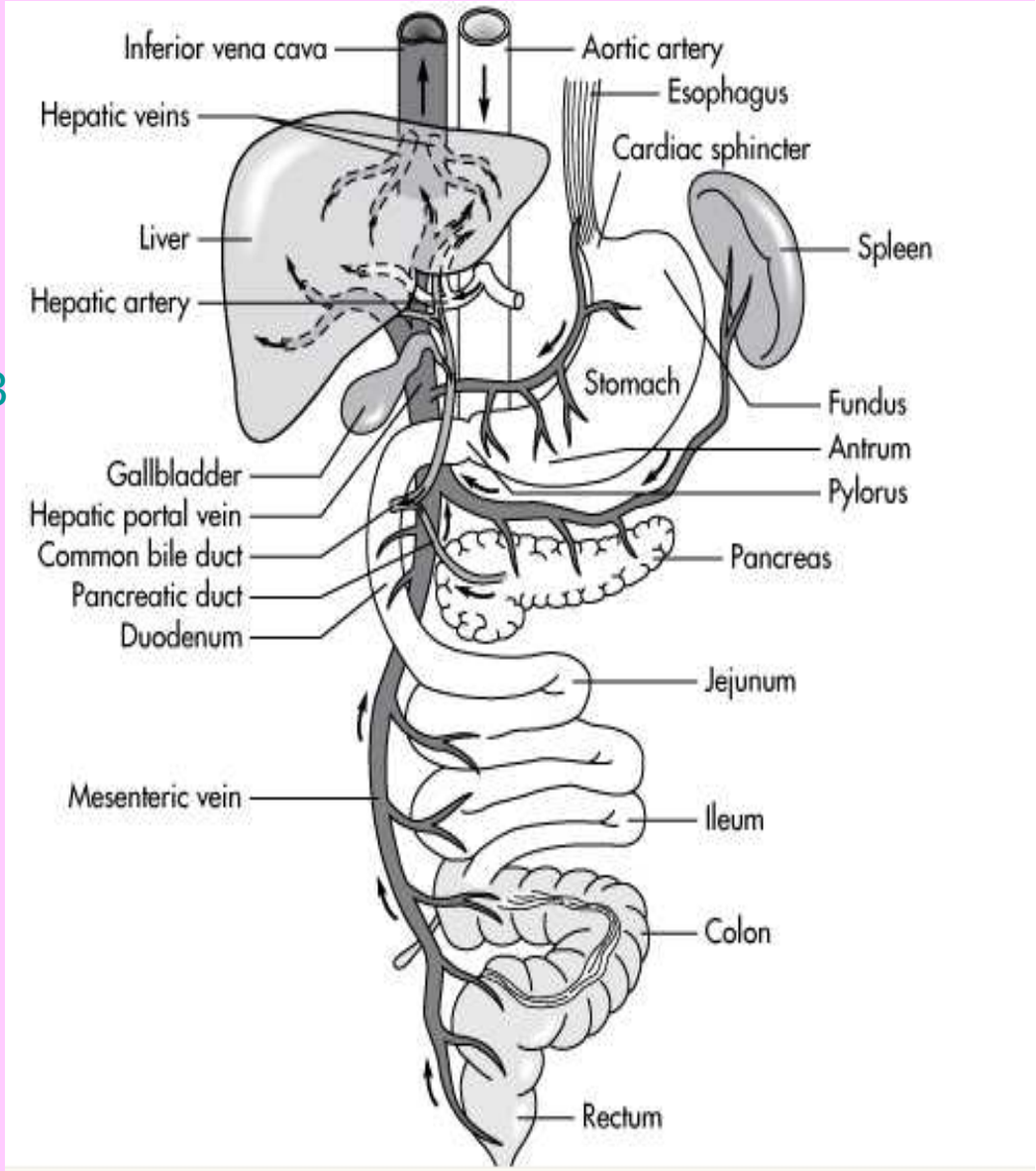
HEPATIC ENZYMES INVOLVED IN DRUG METABOLISM

MIXED FUNCTION OXIDASES (MFO's)/ MONOOXYGENASES

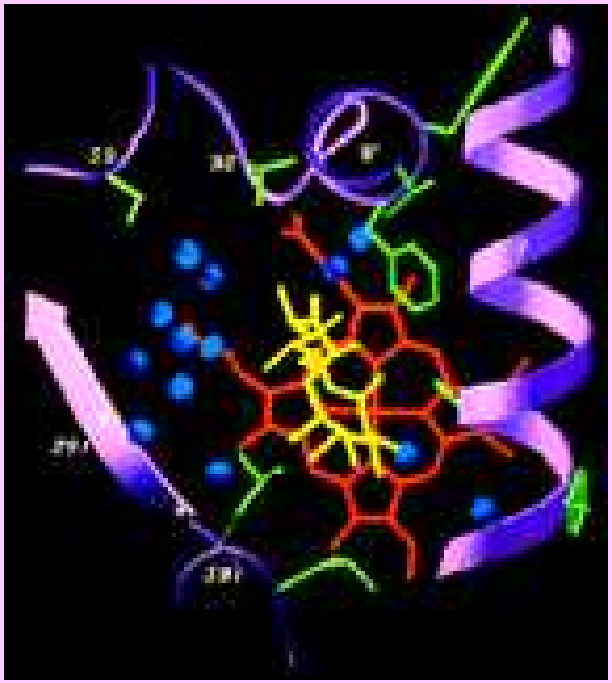
Requires both molecular oxygen and the reducing agent NADPH

Electron transfer chain consisting 3 components

1. Heme protein 'cytochrome p-450'
2. Flavoprotein cytochrome p-450 reductase
3. Heat stable lipid component phosphatidylcholine



Cytochrome P450



CYP1A2	Substrates—amitriptyline, imipramine, theophylline (other enzymes also involved); induced by smoking
	Fluvoxamine, some quinolones and grapefruit juice are inhibitors
CYP2B6	Substrates—cyclophosphamide, methadone
CYP2C9	Metabolism of S-warfarin and tolbutamide by CYP2C9
	Substrates—NSAIDs—ibuprofen, diclofenac
CYP2C19	Omeprazole, S-mephenytoin, and Propranolol
	Diazepam (mixed), and imipramine (mixed)
	Inhibitors: cimetidine, fluoxetine, and ketoconazole.
CYP2D6	Many antidepressants, β-blockers are metabolized by CYP2D6
	SRIIs, cimetidine are inhibitors
	Substrates—amitriptyline, imipramine, fluoxetine, antipsychotics (haloperidol, thioridazine)
	Inhibitors—paroxetine, fluoxetine, sertraline, fluvoxamine, cimetidine, haloperidol
CYP2E1	Substrates—acetaminophen, ethanol, halothane
	Induced by INH and disulfiram
CYP3A4, 5, 6	CYP3A subfamilies are the most abundant cytochrome enzymes in humans and include many key therapeutic and miscellaneous groups:
	Ketoconazole, atorvastatin, lovastatin.
	Azithromycin, clarithromycins, amitriptyline
	Benzodiazepines—alprazolam, triazolam, midazolam
	Calcium blockers—verapamil, diltiazam
	Protease inhibitors—ritonavir, saquinavir, indinavir

DRUG INTERACTIONS INVOLVING DRUG METABOLISM

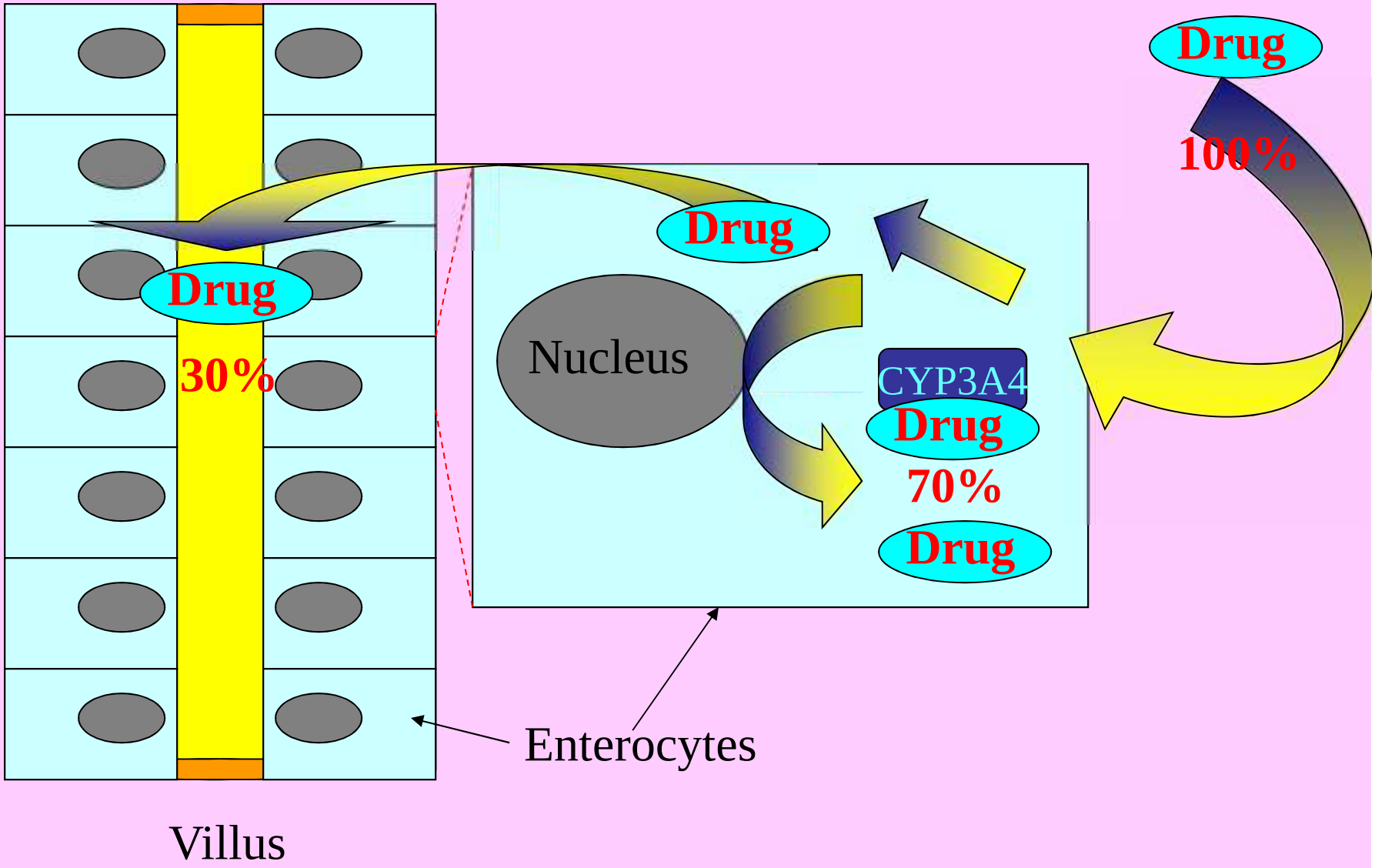
The enzymes involved in the metabolism of drugs may be altered by diet and the co-administration of other drugs and chemicals.

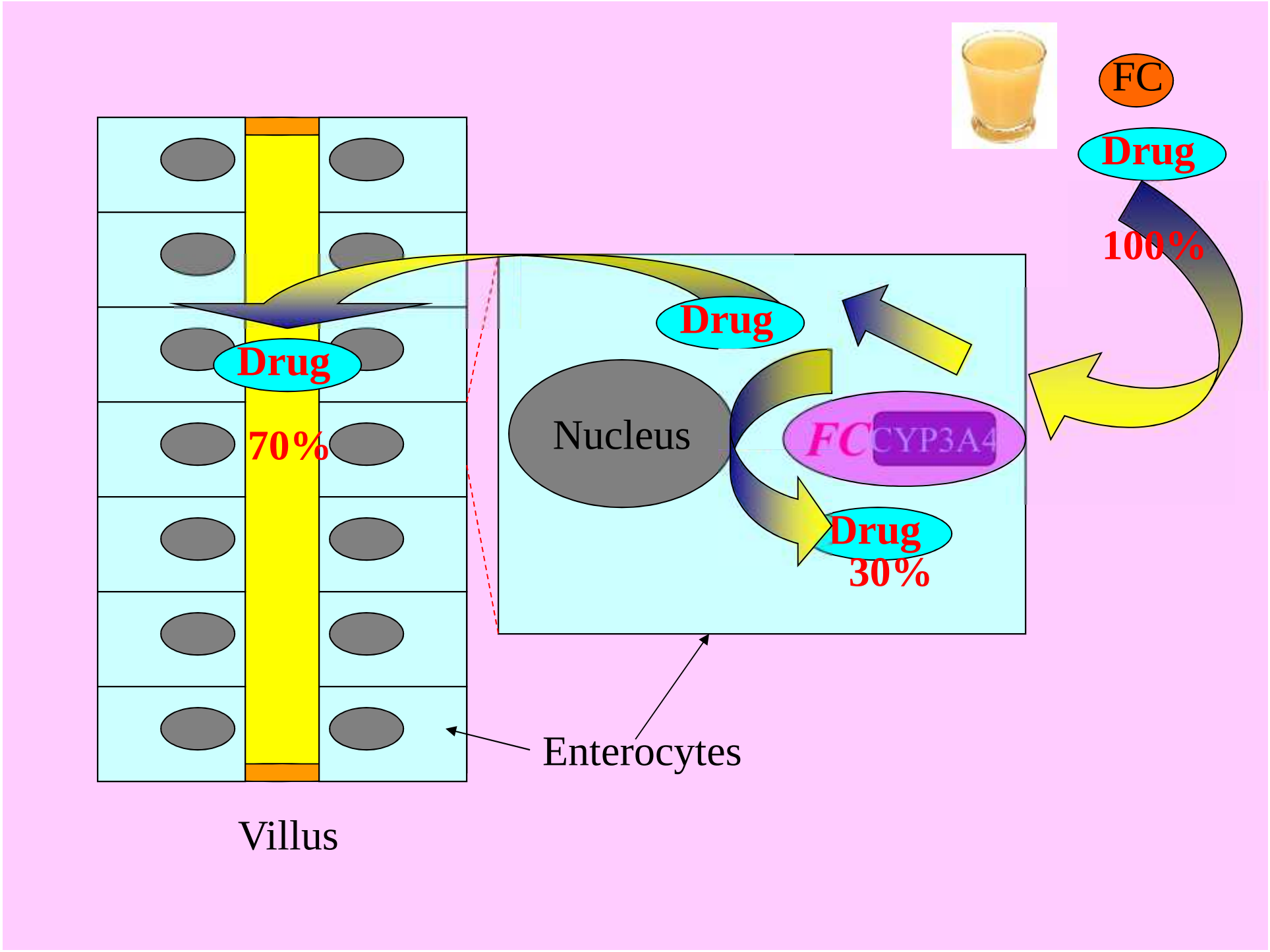
Enzyme induction is a drug- or chemical-stimulated increase in enzyme activity, usually due to an increase in the amount of enzyme present.

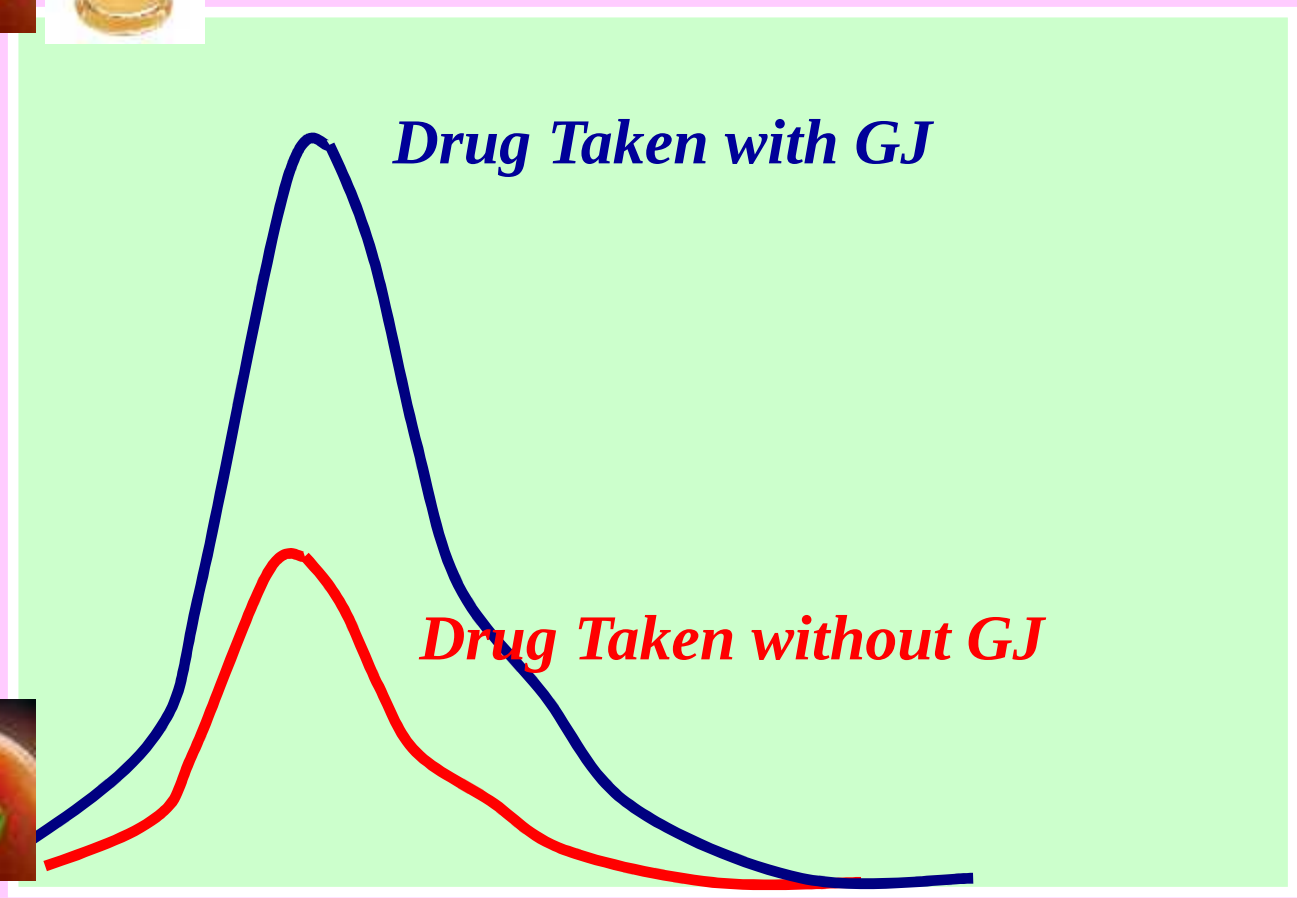
Enzyme inhibition may be due to substrate competition or due to direct inhibition of drug-metabolizing enzymes, particularly one of several of the cytochrome P-450 enzymes.

Diet also affects drug-metabolizing enzymes. For example, plasma theophylline concentrations and theophylline clearance in patients on a high-protein diet are lower than in subjects whose diets are high in carbohydrates.

Drug- Grapefruit Juice Interaction


Drug
100%
Drug
Drug
30%
Nucleus
CYP3A4
Drug
70%
Drug
Enterocytes
Villus

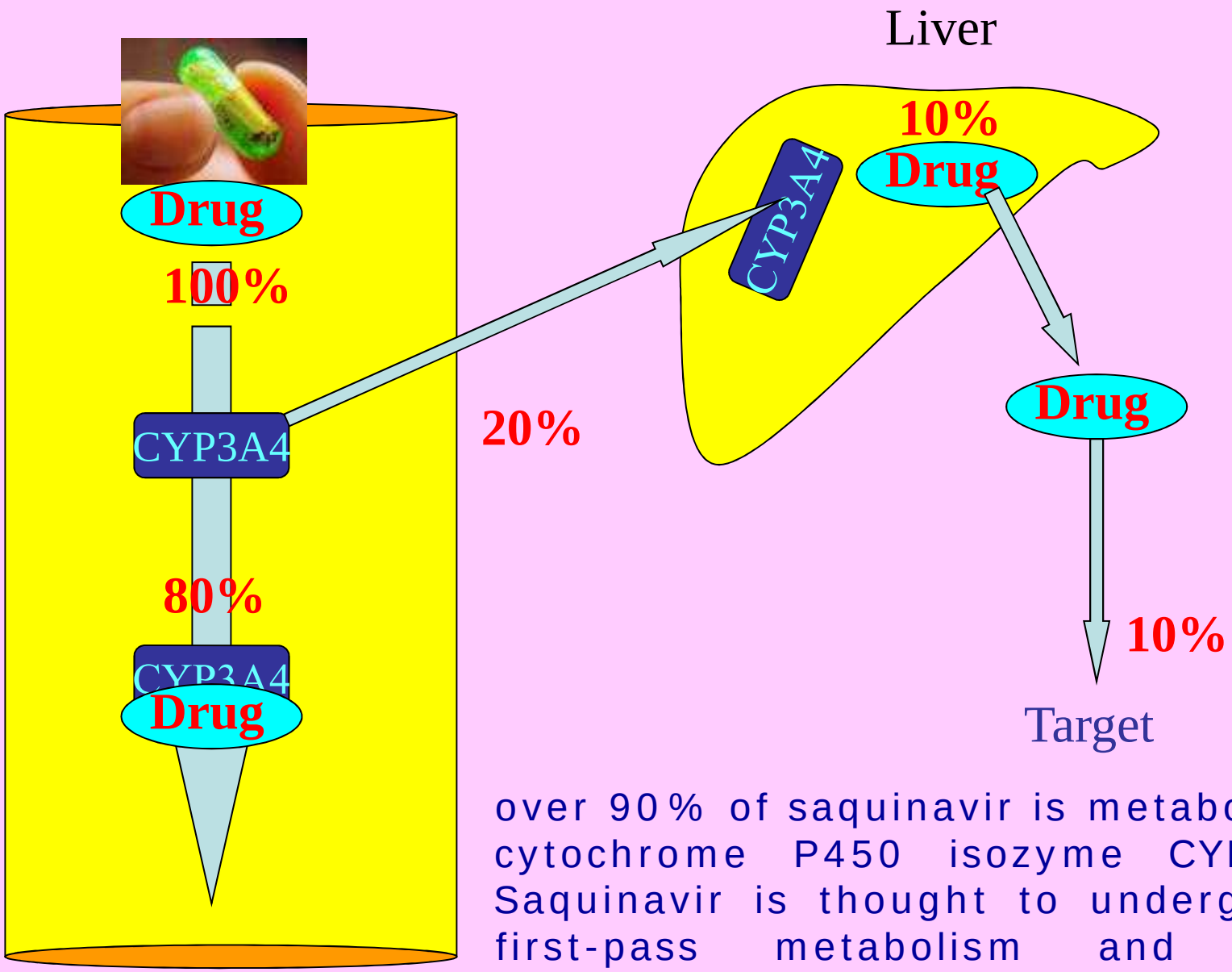

FC
Drug
100%
Drug
Drug
70%
Nucleus
FC
CYP3A4
Drug
30%
Enterocytes
Villus


Drug Blood Concentration (AUC)
Drug Taken with GJ
Drug Taken without GJ
Time

Some drugs influenced by grapefruit juice

Drug	AUC increase
felodipine	~ 3 fold
cisapride	~ 1.4 fold
cyclosporine	~ 1.5 fold
saquinavir	~ 2 fold
terfenadine	~ 2.5 fold
buspirone	~ 9 fold
lovastatin/simvastatin	~ 10 fold

P. B. Watkins 2003



over 90% of saquinavir is metabolized by the cytochrome P450 isozyme CYP3A4 {01}. Saquinavir is thought to undergo extensive first-pass metabolism and is rapidly metabolized to a variety of inactive mono- and di-hydroxylated compounds

HEPATIC ELIMINATION OF DRUGS

HEPATIC CLEARANCE

It is the measure of drug elimination by the liver..

may be defined as volume of blood that perfuses

the liver and is cleared of drug per unit of time

$$Cl_h = Cl_T - Cl_R$$

EVIDENCES OF FIRSTPASS EFFECTS

$$F = \frac{[\mathrm{AUC}]_{0,\,\mathrm{oral}}^{\infty} / D_{0,\,\mathrm{oral}}}{[\mathrm{AUC}]_{0,\,\mathrm{IV}}^{\infty} / D_{0,\,\mathrm{IV}}}$$

Eq. 1

For drugs that undergo first-pass effects AUC∞ 0, oral is smaller than AUC∞ 0, IV and F < 1. Drugs such as propranolol, morphine, and nitroglycerin have F values less than 1 because these drugs undergo significant first-pass effects.

LIVER EXTRACTION RATIO

The liver extraction ratio (ER) provides a direct measurement of drug removal from the liver after oral administration of a drug.

$$ER = \frac{C_a - C_v}{C_a}$$

Eq. 2

where Ca is the drug concentration in the blood entering the liver and Cv is the drug concentration leaving the liver.

Relationship between Absolute Bioavailability and Liver Extraction

$$F = 1 - ER - F''$$

Eq. 3

where F is the fraction of bioavailable drug, ER is the drug fraction extracted by the liver, and F″ is the fraction of drug removed by nonhepatic process.

If F″ is assumed to be negligible

$$F = 1 - ER$$

Eq. 4

After substitution of Equation 1 in 4

$$ER = 1 - \frac{[AUC]_{0,\,oral}^{\infty} / D_{0,\,oral}}{[AUC]_{0,\,IV}^{\infty} / D_{0,\,IV}}$$

Eq. 5

Estimation of Reduced Bioavailability Due to Liver Metabolism and Variable Blood Flow

$$F' = 1 - \frac{Cl_h}{Q} = 1 - ER$$

where Cl h is the hepatic clearance of the drug and
Q is the effective hepatic blood flow.
F' is the bioavailability factor obtained from estimates of liver blood flow and hepatic clearance, ER.

usual effective hepatic blood flow is 1.5 L/min, but it may vary from 1 to 2 L/min depending on diet, food intake, physical activity or drug intake

For the drug propoxyphene hydrochloride, F' has been calculated from hepatic clearance (990 ml/min) and an assumed liver blood flow of 1.53 L/min:

$$F' = 1 - \frac{0.99}{1.53} = 0.35$$

HEPATIC EXTRACTION RATIOS

Extraction Ratios		
Low (<0.3)	**Intermediate (0.3–0.7)**	**High (>0.7)**
Hepatic Extraction		
Amobarbital	Aspirin	Arabinosyl-cytosin
Antipyrine	Quinidine	Encainide
Chloramphenicol	Desipramine	Isoproterenol
Chlordiazepoxide	Nortriptyline	Meperidine
Diazepam		Morphine
Digitoxin		Nitroglycerin
Erythromycin		Pentazocine
Isoniazid		Propoxyphene
Phenobarbital		Propranolol
Phenylbutazone		Salicylamide
Phenytoin		Tocainide
Procainamide		Verapamil
Salicylic acid		
Theophylline		
Tolbutamide		
Warfarin		

Relationship between Blood Flow, Intrinsic Clearance, and Hepatic Clearance

$$\mathbf{ER} = \frac{C_a - C_v}{C_a}$$

Eq. 7

The ER may vary from 0 to 1.0. An ER of 0.25 means that 25% of the drug was removed by the liver.

If both the ER for the liver and the blood flow to the liver are known , then hepatic clearance may be calculated by the following expression:

$$Cl_h = \frac{Q\,(C_a - C_v)}{C_a} = Q \times \mathbf{ER}$$

Eq. 8

For some drugs (such as isoproterenol, lidocaine, and nitroglycerin), the extraction ratio is high (greater than 0.7),

For drugs with very high extraction ratios, the rate of drug metabolism is sensitive to changes in hepatic blood flow. Thus, an increase in blood flow to the liver will increase the rate of drug removal by the organ

INTRIINSIC CLEARANCE

Intrinsic clearance (Cl int) is used to describe the total ability of the liver to metabolize a drug in the absence of flow limitations, reflecting the inherent activities of the mixed-function oxidases and all other enzymes

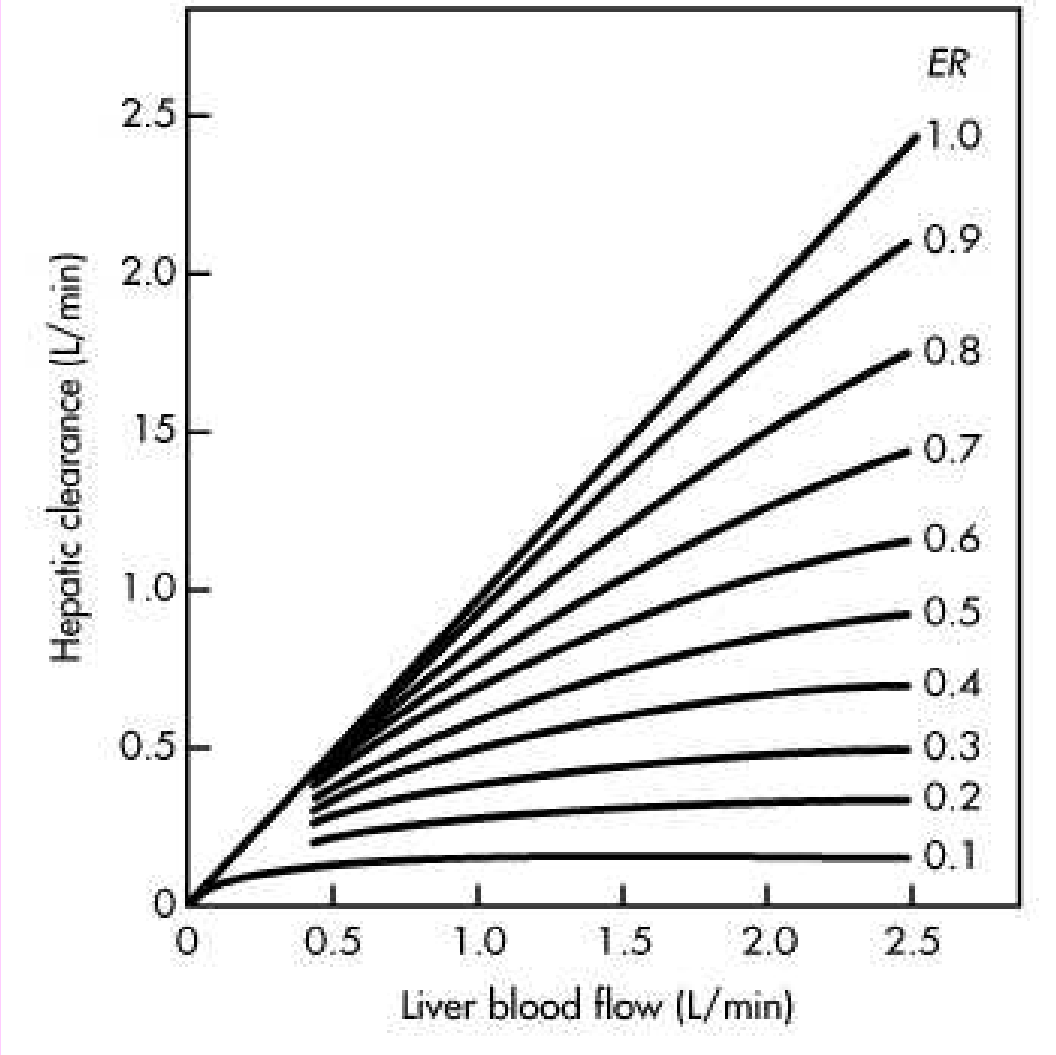
$$Cl_h = Q\frac{Cl_{int}}{Q + Cl_{int}}$$

Eq. 9

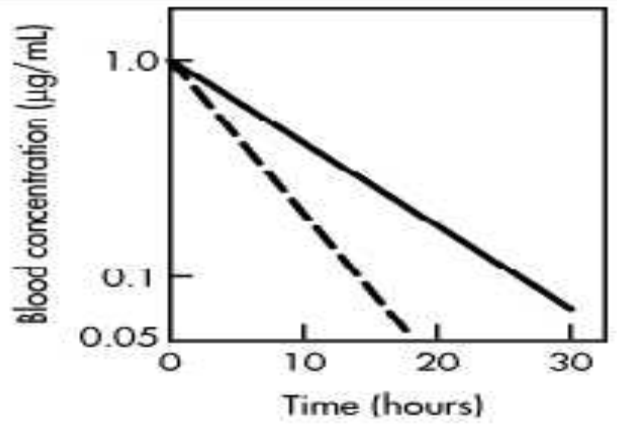
Hepatic clearance changes with blood flow and the intrinsic clearance of the drug, as described in Equation 9

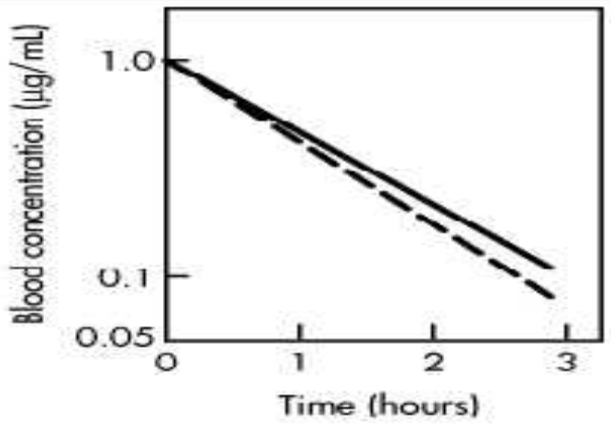
For drugs with low extraction ratios (eg, theophylline, phenylbutazone and procainamide), the hepatic clearance is less affected

The relationship between liver blood flow and total hepatic clearance for drugs with varying extraction rates (ER).



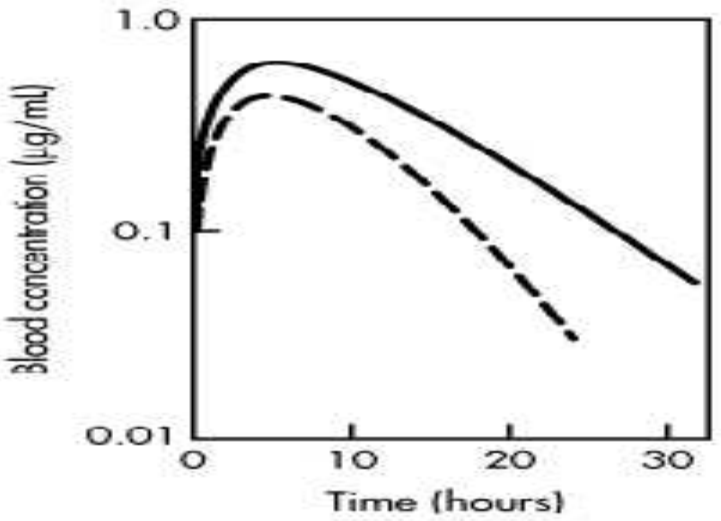
Effect of Changing Intrinsic Clearance after IV and Oral Dosing

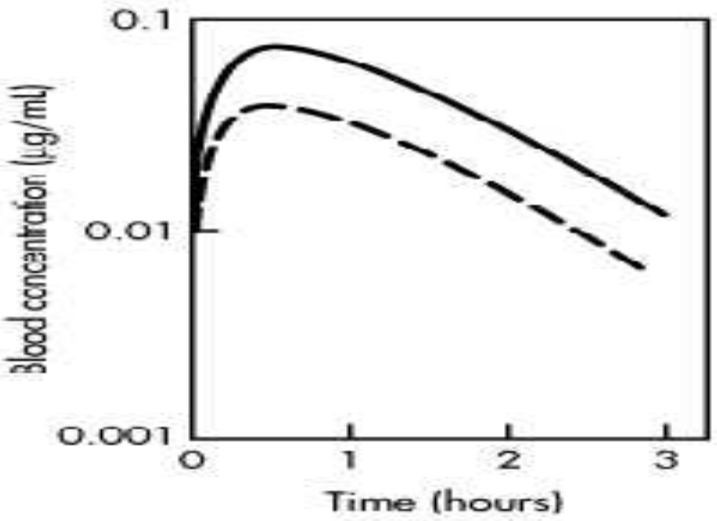




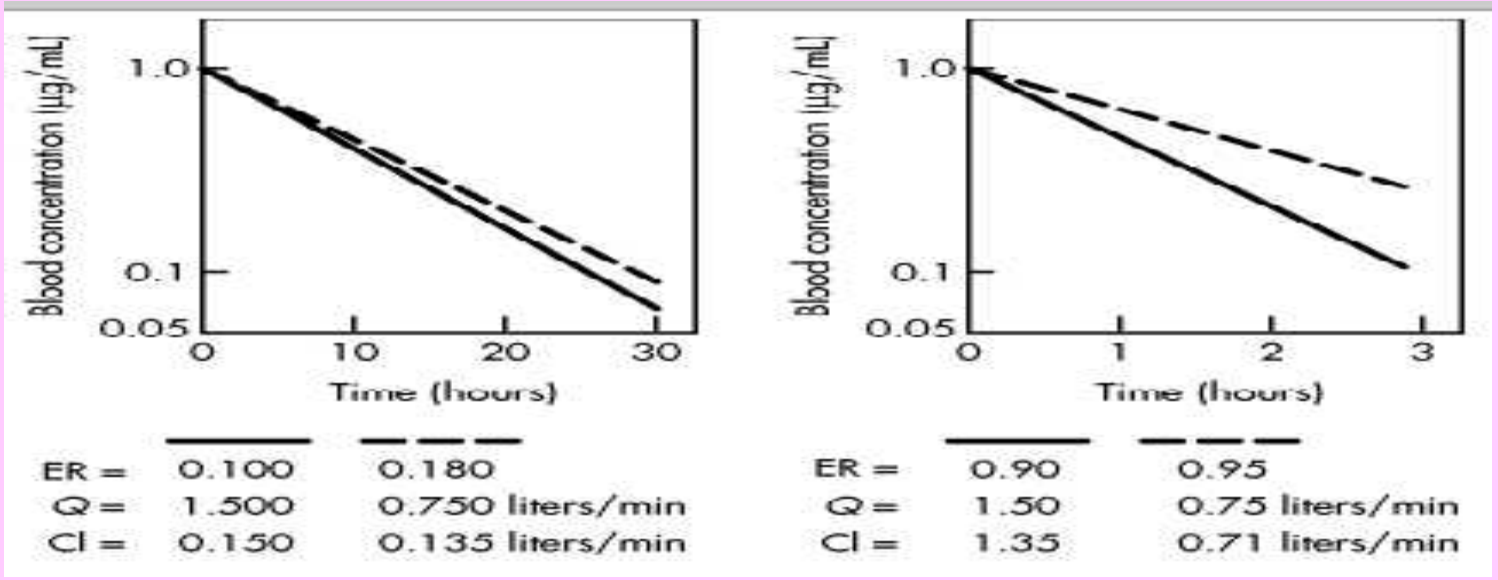
ER =	0.100	0.180
C_{int} =	0.167	0.334 liters/min
Cl =	0.150	0.273 liters/min

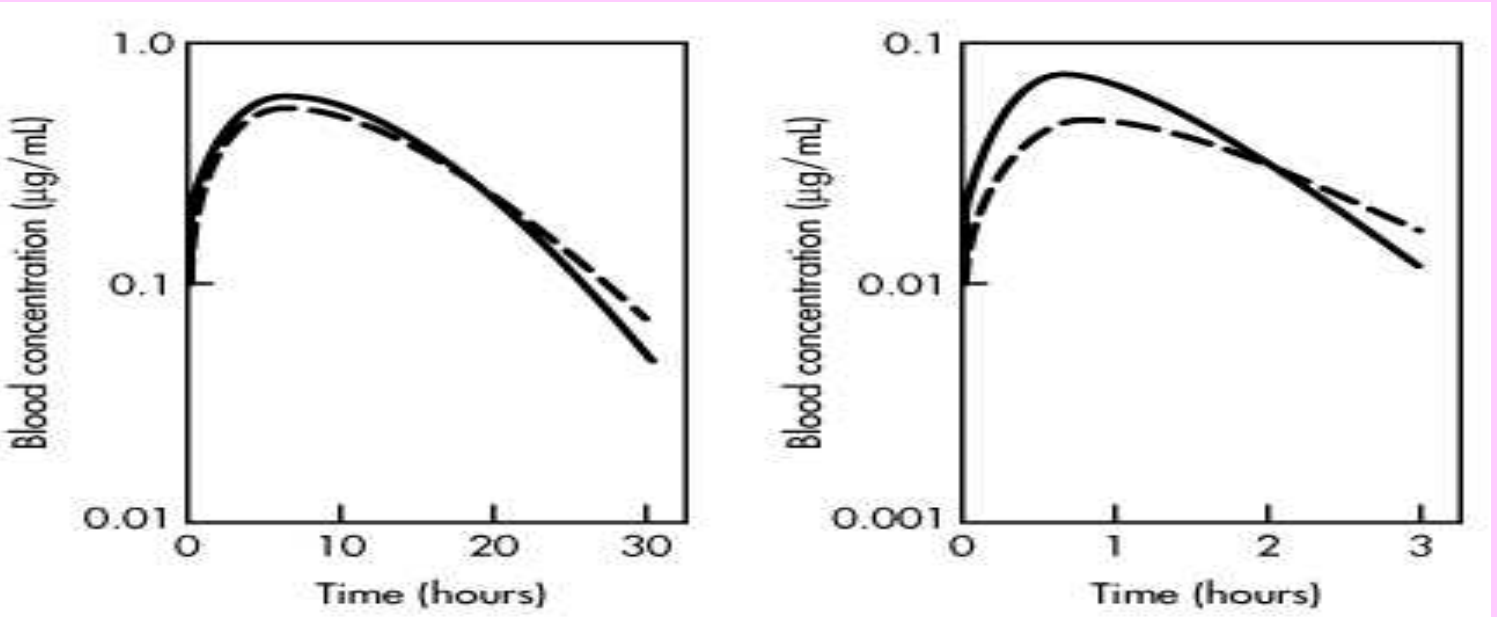
ER =	0.90	0.95
C_{int} =	13.70	27.00 liters/min
Cl =	1.35	1.42 liters/min





Effect of Changing Blood Flow on Drugs with High or Low Extraction Ratio





PREVENTION OF FIRSTPASS METABOLISM

1. Route of drug administered may be changed

Various transmucosal non invasive routes of drug administration to bypass presystemic elimination in

GIT / Liver

Like ocular delivery

- nasal delivery
- pulmonary delivery
- buccal/ sublingual delivery
- rectal delivery
- vaginal delivery

2, alternative routes of administration like suppository, intravenous, intramuscular, inhalation aerosol avoid the first pass effect because they allow drugs to be allowed directly into systemic circulation

3. Another way to overcome the first pass effect is to either enlarge the dose or change the drug product to a more rapidly absorbable dosage form

4. Prodrugs

e.g. sulfasalazine

CONCLUSIONS

Drugs given parenterally, transdermally or by inhalation may distribute within the body prior to metabolism by the liver.

But the drugs that are highly metabolized by the liver or by the intestinal mucosal cells demonstrate poor systemic availability when given orally.

In drug design drug candidates may have good drug likeness but fail on first pass metabolism, because it is biochemically selective.

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