$f_e = \frac{The\ amount\ excereted\ unchanged}{Dose} = \frac{400}{500} = 0.8$

$k = \frac{0.693}{6} = 0.1155\ h^{-1}$

$k_R = f_e \times k = 0.8 \times 0.1155 = 0.0924\ h^{-1}$

$Cl = k \times V_D = 0.1155 \times 21 = 2.43$ L/h

$Cl_R = k_R \times V_D = 0.0924 \times 21 = 1.94$ L/h

$Cl_{NR} = Cl - Cl_R = 2.43 - 1.94 = 0.49$ L/h

Hepatic elimination

The excretion rate constant (k_e) is easily evaluated for drugs that are primarily renally excreted. Nonrenal drug elimination is usually assumed to be due for the most part to hepatic metabolism. Therefore, the rate constant for metabolism (k_m) is difficult to measure directly and is usually obtained from the difference between k and k_e.

$k_m = k - k_e$

A drug may be biotransformed to several metabolites (metabolite A, metabolite B, metabolite C, etc); thus, the metabolism rate constant (k_m) is the sum of the rate constants for the formation of each metabolite when the drug does not saturate the metabolic enzymes (first-order processes).

$K_m = K_{mA} + K_{mB} + K_{mC}$ .....

$\%\ drug\ metabolised = \frac{k_m}{k} \times 100$

Hepatic clearance

Hepatic clearance may be defined as the volume of blood that perfuses the liver which is cleared of drug per unit of time.

$Cl_T = Cl_{nr} + Cl_r$

$Cl_h = Cl_T - Cl_R$

- **Examples:**
  1. The total body clearance for a drug is 15 mL/ min/kg. Renal clearance accounts for 10 mL/ min/kg. What is the hepatic clearance for the drug?

Solution

Hepatic clearance = 15 – 10 = 5 mL/min/kg

The total body clearance of a drug is 10 mL/ min/kg. The renal clearance is not known. From a urinary drug excretion study, 60% of the drug is recovered intact and 40% is recovered as metabolites. What is the hepatic clearance for the drug, assuming that metabolism occurs in the liver?
Solution
Hepatic clearance = total body clearance × (1 – f_e)
where f_e = fraction of intact drug recovered in the urine.
Hepatic clearance = 10 × (1 – 0.6) = 4 mL/min/kg

Extrahepatic Metabolism

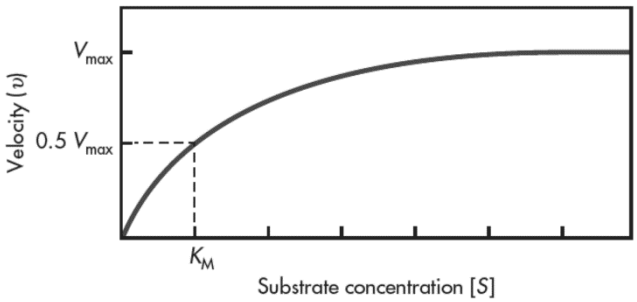
- Few drugs (eg, nitroglycerin) are metabolized extensively outside the liver.
- Extrahepatic metabolism is assessed by calculating hepatic (metabolic) and renal clearance of the drug and compare these clearances to total body clearance.

Example: Morphine clearance, Cl_T, for a 75-kg male patient is 1800 mL/min. After an oral dose, 4% of the drug is excreted unchanged in the urine (f_e = 0.04). The fraction of drug absorbed after an oral dose of morphine sulfate is 24% (F = 0.24). Hepatic blood flow is about 1500 mL/min. Does morphine have any extrahepatic metabolism?

Solution
Since f_e = 0.04,
Renal clearance Cl_r = 0.04 Cl_T
nonrenal clearance Cl_{nr} = (1 – 0.04) Cl_T = 0.96 Cl_T.
Cl_{nr} = 0.96 × 1800 mL/min = 1728 mL/ min.
Since hepatic blood flow is about 1500 mL/ min, the drug appears to be metabolized faster than the rate of hepatic blood flow. Thus, at least some of the drug must be metabolized outside the liver. The low fraction of drug absorbed after an oral dose indicates that much of the drug is metabolized before reaching the systemic circulation.

ENZYME KINETICS—MICHAELIS– MENTEN EQUATION

- *biotransformation* or *metabolism* is the enzymatic conversion of a drug to a metabolite.
- the metabolic enzyme concentration is constant at a given site, and the drug (substrate) concentration may vary.
- When the drug concentration is low relative to the enzyme concentration, the rate of metabolism is a first-order process.
- At high plasma drug concentration the rate process then becomes a zero-order process



- The *maximum reaction rate* is known as V_{max}
- The drug concentration at which the reaction occurs at half the maximum rate corresponds to a composite parameter K_M (*Michaelis constant)*.
- The relationship between V_{max} and K_M is given by *Michaelis–Menten equation*

$$v = \frac{V_{max}\,[D]}{[D]K_M}$$

Competitive and sequential metabolism

- The most common metabolic reactions are oxidation, reduction, hydrolysis and conjugation
- Frequently, a drug simultaneously undergoes metabolism by several competing (**primary**) pathways. The fraction going to each metabolite depends on the relative rates of each of the parallel pathways
- Metabolites may undergo further (**secondary**) metabolism. For example oxidation, reduction and hydrolysis are frequently followed by a conjugation reaction. These reactions occur in series and are said to be **sequential**

Phase I and Phase II reactions

- Because they often occur first, oxidation, reduction, and hydrolysis are commonly referred to as a phase I reactions
- Because they often occur second, conjugations are commonly referred as phase II reactions
- Phase I reactions are commonly considered to be a "preparation" of the drug molecule for phase II reactions
- This is NOT an absolute rule since some drugs undergo primary elimination via phase II reactions. In addition, some drugs undergo only phase I reactions without subsequent phase II step

Phase I metabolism

- Oxidation involving CYP450
- Oxidation – others
- Reduction
- Hydrolysis
- Hydration
- Isomerisation

In most cases, the final product contains a chemically reactive functional groups (-OH, -NH_2, -SH, -COOH): ready for phase II!
Many drugs can undergo a number of phase I reactions, therefore it is difficult to predict exact pathway from the chemical structure.

Phase II metabolism

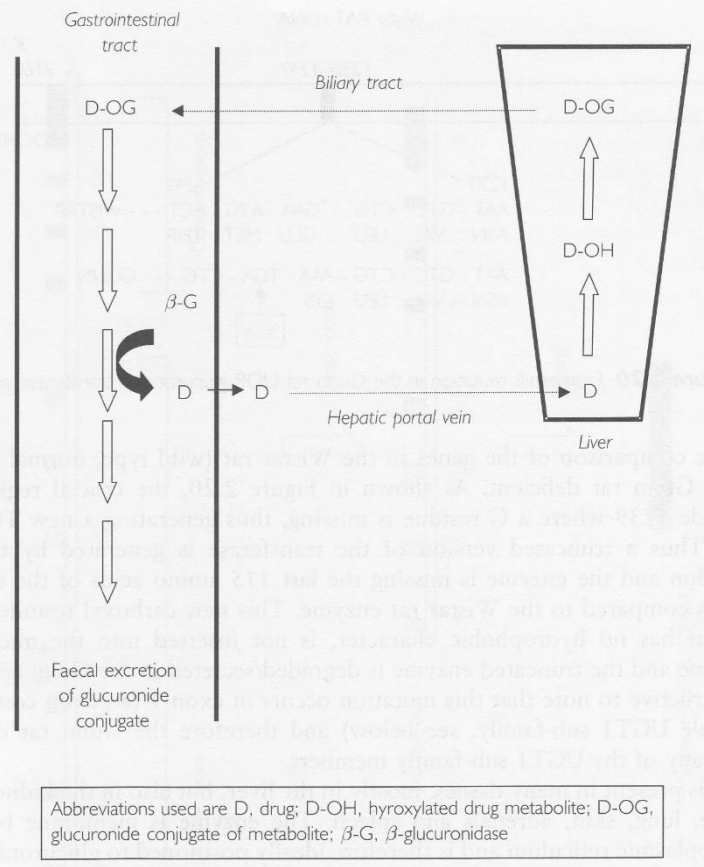
Phase II metabolism generally leads to a water soluble product which can be excreted in bile or urine

Reaction	Enzyme	Functional group
Glucuronidation	UDP–Glucuronosyltransferase	–OH –COOH –NH_2 –SH
Glycosidation	UDP–Glycosyltransferase	–OH –COOH –SH
Sulfation	Sulfotransferase	–NH_2 –SO_2NH_2 –OH
Methylation	Methyltransferase	–OH –NH_2
Acetylation	Acetyltransferase	–NH_2 –SO_2NH_2 –OH
Amino acid conjugation		–COOH
Glutathione conjugation	Glutathione-*S*-transferase	Epoxide Organic halide
Fatty acid conjugation		–OH
Condensation		Various

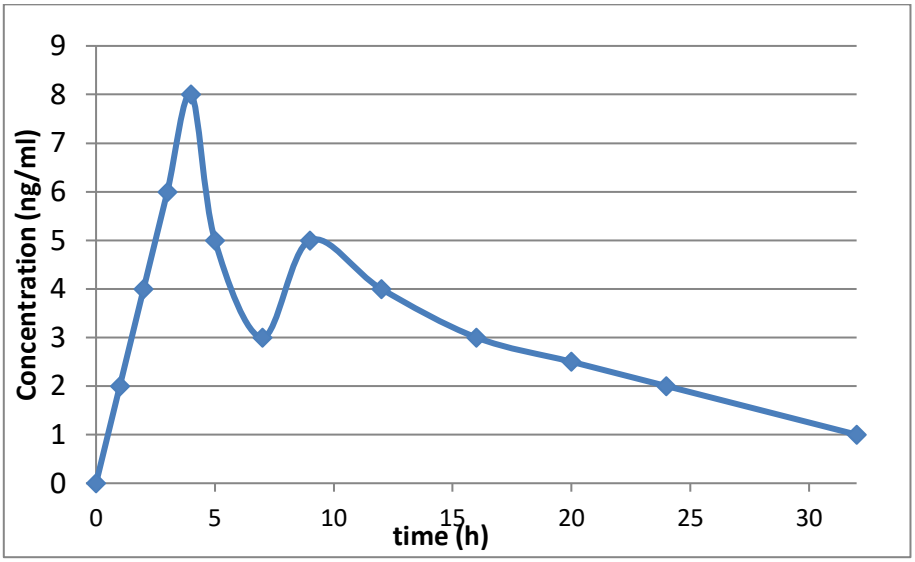
Enterohepatic circulation

Consequences of enterohepatic circulation:

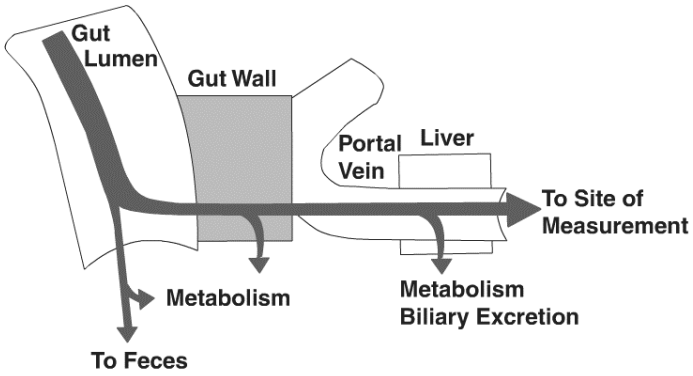
- Prolonged half-life
- Prolonged pharmacological action



- Enterohepatic circulation can be seen sometimes as a "second peak" phenomenon on plasma-concentration time profile after oral administration



FIRST-PASS METABOLISM

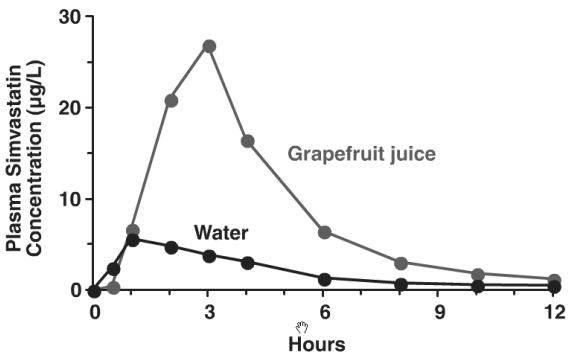


Metabolism during the first passage across the intestinal wall and through the liver reduces the amount reaching the general circulation. The drug is then said to undergo first-pass metabolic loss (or first-pass metabolism).

Example: the oral bioavailability (F) of simvastatin is about 5% when taken with water. The low metabolism is mostly due to first-pass metabolism in the gut and liver.

The oral bioavailability is increased 3.6-fold when simvastatin is given with grapefruit juice

Grapefruit juice components are known inhibitors of CYP3A



Avoiding hepatic first-pass metabolism:

1. Oral cavity

Drugs that are absorbed through the oral mucosa enter the blood stream directly via jugular vein (without passing through liver first) and therefore they avoid metabolism in the liver before they reach the systemic circulation (avoid hepatic first-pass metabolism)

2. Lower rectum and anal canal

Drugs absorbed from the colon and upper rectum are absorbed into portal vein and therefore are subjected for hepatic first-pass metabolism.

Drugs absorbed from the lower rectum and anal canal are not getting into portal vein and therefore avoid hepatic first-pass metabolism.

3. Intestinal lymphatic transport