

Drug elimination and Hepatic clearance Chapter 6

DRUG ELIMINATION

Drugs are removed from the body by various elimination processes. **Drug elimination refers to the irreversible removal of drug from the body by all routes of elimination. Drug elimination is usually divided into two major components: excretion and biotransformation.**

Drug excretion is the removal of the intact drug. **Nonvolatile drugs are excreted mainly by renal excretion, a process in which the drug passes through the kidney to the bladder and ultimately into the urine.** Other pathways for drug excretion may include the excretion of drug into bile, sweat, saliva, milk (via lactation), or other body fluids. **Volatile drugs, such as gaseous anesthetics or drugs with high volatility, are excreted via the lungs into expired air.**

Biotransformation or drug metabolism is the process by which the drug is chemically converted in the body to a metabolite. Biotransformation is usually an enzymatic process. A few drugs may also be changed chemically by a nonenzymatic process (eg, ester hydrolysis). The enzymes involved in the biotransformation of drugs are located mainly in the liver. Other tissues such as kidney, lung, small intestine, and skin also contain biotransformation enzymes.

Drug elimination in the body involves many complex rate processes. Although organ systems have specific functions, the tissues within the organs are not structurally homogeneous, and elimination processes may vary in each organ. In elimination was modeled by an overall first-order elimination rate process.

In this chapter, drug elimination is described in terms of clearance from a well-stirred compartment containing uniform drug distribution. The term *clearance* describes the process of drug elimination from the body or from a single organ without identifying the individual processes involved. Clearance may be defined as the volume of fluid cleared of drug from the body per unit of time. The units for clearance are milliliters per minute (mL/min) or liters per hour (L/hr). The volume concept is simple and convenient, because all drugs are dissolved and distributed in the fluids of the body.

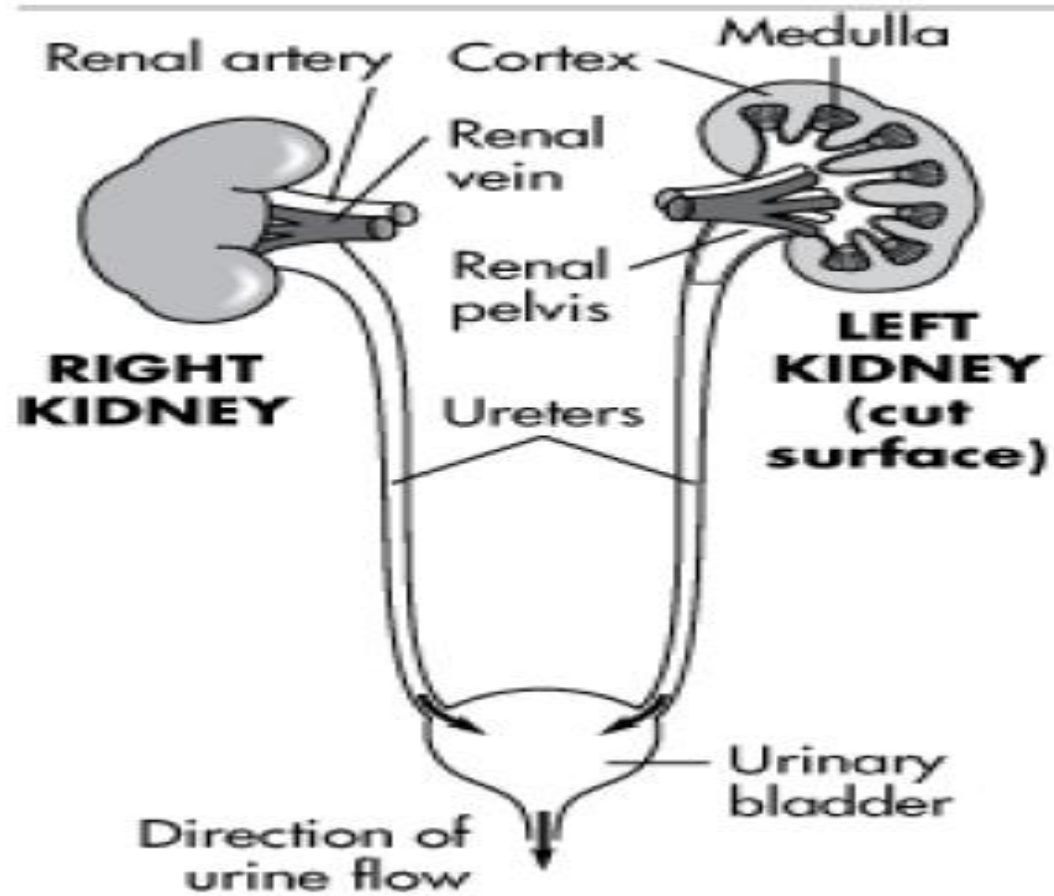
THE KIDNEY

The liver and kidney are the two major drug elimination organs in the body, though drug elimination can also occur almost anywhere in the body. **The kidney is the main excretory organ for the removal of metabolic waste products and plays a major role in maintaining the normal fluid volume and electrolyte composition in the body.** To maintain salt and water balance, the kidney excretes excess electrolytes, water, and waste products while conserving solutes necessary for proper body function. **In addition, the kidney has two endocrine functions:**

(1) secretion of renin, which regulates blood pressure; and (2) secretion of erythropoietin, which stimulates red blood cell production.

Anatomic Considerations

The kidneys are located in the peritoneal cavity. The outer zone of the kidney is called the *cortex*, and the inner region is called the *medulla*. The *nephrons* are the basic functional units, collectively responsible for the removal of metabolic waste and the maintenance of water and electrolyte balance. Each kidney contains 1 to 1.5 million nephrons. The *glomerulus* of each nephron starts in the cortex. *Cortical nephrons* have short *loops of Henle* that remain exclusively in the cortex; *juxtamedullary nephrons* have long loops of Henle that extend into the medulla. The longer loops of Henle allow for a greater ability of the nephron to reabsorb water, thereby producing a more concentrated urine.



Blood Supply

The kidneys represent about **0.5% of the total body weight** and receive approximately **20 - 25% of the cardiac output**. The kidney is supplied by blood via the renal artery, which subdivides into the interlobar arteries penetrating within the kidney and branching farther into the afferent arterioles. Each afferent arteriole carries blood toward a single nephron into the glomerular portion of the nephron (*Bowman's capsule*). **The filtration of blood occurs in the glomeruli in Bowman's capsule.** From the capillaries (*glomerulus*) within Bowman's capsule, the blood flows out via the efferent arterioles and then into a second capillary network that surrounds the tubules (*peritubule capillaries* and *vasa recti*), **including the loop of Henle, where some water is reabsorbed.**

The *renal blood flow* (RBF) is the volume of blood flowing through the renal vasculature per unit time. Renal blood flow exceeds 1.2 L/min or 1700 L/day. *Renal plasma flow* (RPF) is the renal blood flow minus the volume of red blood cells present. Renal plasma flow is an important factor in the rate of drug filtration at the glomerulus.

$$\text{RPF} = \text{RBF} - (\text{RBF} \times \text{Hct}) \quad (6.1)$$

where Hct is hematocrit.

Hct is the fraction of blood cells in the blood, about 45% of the total blood volume, or 0.45. The relationship of renal blood flow to renal plasma flow is given by a rearrangement of Equation 6.1:

$$\text{RPF} = \text{RBF}(1 - \text{Hct})$$

Assuming a hematocrit of 0.45 and a RBF of 1.2 L/min, using the above equation, $RPF = 1.2 - (1.2 \times 0.45) = 0.66$ L/min or 660 mL/min, approximately 950 L/day. The *glomerular filtration rate* (GFR) is about 125 mL/min in an average adult, or about 20% of the RPF. The ratio GFR/RPF is the *filtration fraction*.

Glomerular Filtration and Urine Formation

A normal adult male subject has a GFR of **approximately 125 mL/min**. About 180 L of fluid per day are filtered through the kidneys. In spite of this large filtration volume, the average **urine volume is 1- 1.5 L**. Up to 99% of the fluid volume filtered at the glomerulus is reabsorbed. **Besides fluid regulation, the kidney also regulates the retention or excretion of various solutes and electrolytes. With the exception of proteins and protein-bound substances, most small molecules are filtered through the glomerulus from the plasma. The filtrate contains some ions, glucose, and essential nutrients as well as waste products, such as urea, phosphate, sulfate, and other substances.** The essential nutrients and water are reabsorbed at various sites, including the proximal tubule, loops of Henle, and distal tubules.

RENAL DRUG EXCRETION

Renal excretion is a major route of elimination for many drugs. Drugs that are 1-nonvolatile, 2-water soluble, 3-have a low molecular weight (MW), or are 4-slowly biotransformed by the liver are eliminated by renal excretion. The processes by which a drug is excreted via the kidneys may include any combination of the following:

Glomerular filtration

Active tubular secretion

Tubular reabsorption

Glomerular filtration is a unidirectional process that occurs for most small molecules (**MW < 500**), including undissociated (nonionized) and dissociated (ionized) drugs. Protein-bound drugs behave as large molecules and do not get filtered at the glomerulus. The major driving force for glomerular filtration is the hydrostatic pressure within the glomerular capillaries. The kidneys receive a large blood supply (approximately 25% of the cardiac output) via the renal artery, with very little decrease in the hydrostatic pressure.

Glomerular filtration rate (GFR) is measured by using a drug that is eliminated by filtration only (ie, the drug is neither reabsorbed nor secreted). **Examples of such drugs are inulin and creatinine.** Therefore, the clearance of inulin is equal to the GFR, which is equal to 125-130 mL/min. **The value for the GFR correlates fairly well with body surface area.** **Glomerular filtration of drugs is directly related to the free or nonprotein-bound drug concentration in the plasma.**

As the free drug concentration in the plasma increases, the glomerular filtration for the drug increases proportionately, thus increasing renal drug clearance for some drugs.

Active tubular secretion is an active transport process. As such, active renal secretion is a carrier-mediated system that requires energy input, because the drug is transported against a concentration gradient. The carrier system is capacity limited and may be saturated. Drugs with similar structures may compete for the same carrier system. **1-Two active renal secretion systems have been identified, systems for (1) weak acids and (2) weak bases.**

For example, **probenecid competes with penicillin for the same carrier system (*weak acids*).**

2-Active tubular secretion rate is dependent on renal plasma flow. **3-Drugs commonly used to measure active tubular secretion include *p*-amino-hippuric acid (PAH) and iodopyracet (Diodrast).**

4-These substances are both filtered by the glomeruli and secreted by the tubular cells. **5-Active secretion is extremely rapid for these drugs, and practically all the drug carried to the kidney is eliminated in a single pass.** The clearance for these drugs therefore reflects the *effective renal plasma flow* (ERPF), which varies from 425 to 650 mL/min.

6-For a drug that is excreted solely by glomerular filtration, the elimination half-life may change markedly in accordance with the **binding affinity of the drug for plasma proteins.** **In contrast,** drug protein binding has very little effect on the elimination half-life of the drug excreted mostly by active secretion. Because drug protein binding is reversible, drug bound to plasma protein rapidly dissociates as free drug is secreted by the kidneys. For example, some of the penicillins are extensively protein bound, but their elimination half-lives are short due to rapid elimination by active secretion.

Tubular reabsorption occurs after the drug is filtered through the glomerulus and can be an active or a passive process. If a drug is completely reabsorbed (eg, glucose), then the value for the clearance of the drug is approximately zero. For drugs that are partially reabsorbed, clearance values are less than the GFR of 125-130 mL/min.

The reabsorption of drugs that are acids or weak bases is influenced by the pH of the fluid in the renal tubule (ie, urine pH) and the pKa of the drug. Both of these factors together determine the **percentage of dissociated (ionized) and undissociated (nonionized) drug.** Generally, the undissociated species is more lipid soluble (less water soluble) and has greater membrane permeability. 1-The undissociated drug is easily reabsorbed from the renal tubule back into the body. 2-This process of drug reabsorption can significantly reduce the amount of drug excreted, depending on the pH of the urinary fluid and the pKa of the drug. The pKa of the drug is a constant, 3-but the normal urinary pH may vary from 4.5 to 8.0, depending on diet, pathophysiology, and drug intake. 4-Vegetable and fruit diets or diets rich in carbohydrates result in higher urinary pH, 5-whereas diets rich in protein result in lower urinary pH. Drugs such as ascorbic acid and antacids such as sodium carbonate may decrease (acidify) or increase (alkalinize) the urinary pH, respectively, when administered in large quantities. 6-By far the most important changes in urinary pH are caused by fluids administered intravenously. Intravenous fluids, such as solutions of bicarbonate or ammonium chloride, are used in acid-base therapy. Excretion of these solutions may drastically change urinary pH and alter drug reabsorption and drug excretion by the kidney.

The percentage of ionized weak acid drug corresponding to a given pH can be obtained from the *Henderson-Hasselbalch equation*

$$\text{pH} = \text{pK}_a + \log \frac{[\text{ionized}]}{[\text{nonionized}]} \quad (6.3)$$

Rearrangement of this equation yields

$$\frac{[\text{ionized}]}{[\text{nonionized}]} = 10^{\text{pH} - \text{pK}_a} \quad (6.4)$$

$$\begin{aligned} \text{Fraction of drug ionized} &= \frac{[\text{ionized}]}{[\text{ionized}] + [\text{nonionized}]} \\ &= \frac{10^{\text{pH} - \text{pK}_a} [\text{nonionized}]}{[\text{ionized}] + [\text{nonionized}]} \\ &= \frac{10^{\text{pH} - \text{pK}_a}}{1 + 10^{\text{pH} - \text{pK}_a}} \end{aligned} \quad (6.5)$$

The fraction or percent of weak acid drug ionized in any pH environment may be calculated with Equation 6.5. For acidic drugs with pK_a values from 3 to 8, a change in urinary pH affects the extent of dissociation. The extent of dissociation is more greatly affected by changes in urinary pH for drugs with a pK_a of 5 than with a pK_a of 3. Weak acids with pK_a values of less than 2 are highly ionized at all urinary pH values and are only slightly affected by pH variations.

TABLE 6.2 Effect of Urinary pH and pK_a on the Ionization of Drugs

pH OF URINE	PERCENT OF DRUG IONIZED: $pK_a=3$	PERCENT OF DRUG IONIZED: $pK_a=5$
7.4	100	99.6
5	99	50.0
4	91	9.1
3	50	0.99

For a weak base drug, the Henderson-Hasselbalch equation is given as

$$\text{pH} = \text{pK}_a + \log \frac{[\text{nonionized}]}{[\text{ionized}]} \quad (6.6)$$

and

$$\text{Percent of drug ionized} = \frac{1 + 10^{\text{pH} - \text{pK}_a}}{10^{\text{pH} - \text{pK}_a}} \quad (6.7)$$

The greatest effect of urinary pH on reabsorption occurs with weak base drugs with pKa values of 7.5-10.5.

From the Henderson-Hasselbalch relationship, a concentration ratio for the distribution of a weak acid or basic drug between urine and plasma may be derived. **The urine-plasma (U/P) ratios for these drugs are as follows.**

For weak acids,

$$\frac{U}{P} = \frac{1 + 10^{\text{pH}_{\text{urine}} - \text{pK}_a}}{1 + 10^{\text{pH}_{\text{plasma}} - \text{pK}_a}} \quad (6.8)$$

For weak bases,

$$\frac{U}{P} = \frac{1 + 10^{\text{pK}_a - \text{pH}_{\text{urine}}}}{1 + 10^{\text{pK}_a - \text{pH}_{\text{plasma}}}} \quad (6.9)$$

For example, amphetamine, a weak base, will be reabsorbed if the urine pH is made alkaline and more lipid soluble nonionized species are formed. In contrast, acidification of the urine will cause the amphetamine to become more ionized (form a salt). The salt form is more water soluble and less likely to be reabsorbed and has a tendency to be excreted into the urine more quickly. In the case of weak acids (such as salicylic acid), acidification of the urine causes greater reabsorption of the drug and alkalinization of the urine causes more rapid excretion of the drug.

DRUG CLEARANCE

***Drug clearance* is a pharmacokinetic term for describing drug elimination from the body without identifying the mechanism of the process.** Drug clearance (*body clearance, total body clearance* , or Cl_T) considers the entire body as a single drug-eliminating system from which many unidentified elimination processes may occur. **Instead of describing the drug elimination rate in terms of amount of drug removed per time unit (eg, mg/min), drug clearance is described in terms of volume of fluid clear of drug per time unit (eg, mL/min).**

There are several definitions of clearance, which are similarly based on volume of drug removed per unit time.

The simplest concept of clearance regards the body as a space that contains a definite volume of body fluid (apparent volume of distribution, VD) in which the drug is dissolved.

1-Drug clearance is defined as the fixed volume of fluid (containing the drug) cleared of drug per unit of time. The units for clearance are volume/time (eg, mL/min, L/hr). For example, if the Cl_T of penicillin is 15 mL/min in a patient and penicillin has a VD of 12 L, then from the clearance definition, 15 mL of the 12 L will be cleared of drug per minute.

2-Alternatively, Cl_T may be defined as the rate of drug elimination divided by the plasma drug concentration. **This definition expresses drug elimination in terms of the volume of plasma eliminated of drug per unit time.** This definition is a practical way to calculate clearance based on plasma drug concentration data.

$$Cl_T = \frac{\text{elimination rate}}{\text{plasma concentration}(C_p)} \quad (6.10)$$

$$Cl_T = \frac{dD_E/dt}{C_p} = \frac{\mu\text{g}/\text{min}}{\mu\text{g}/\text{mL}} = \text{mL}/\text{min} \quad (6.11)$$

where D_E is the amount of drug eliminated and dD_E/dt is the rate of elimination. Rearrangement of Equation 6.11 gives Equation 6.12.

$$\text{Elimination rate} = \frac{dD_E}{dt} = C_p Cl_T \quad (6.12)$$

The two definitions for clearance are similar because dividing the elimination rate by the C_p yields the volume of plasma cleared of drug per minute, as shown in Equation 6.10.

As discussed in previous chapters, a first-order elimination rate, dD_E/dt , is equal to $k D_B$ or $k C_p V_D$. Based on Equation 6.10, substituting elimination rate for $k C_p V_p$,

$$Cl_T = \frac{k C_p V_D}{C_p} = k V_D \quad (6.13)$$

Equation 6.13 shows that clearance is the product of V_D and k , both of which are constant. As the plasma drug concentration decreases during elimination, the rate of drug elimination, dD_E/dt , decreases accordingly, but clearance remains constant. **Clearance is constant as long as the rate of drug elimination is a first-order process.**

Just as the elimination rate constant (k) represents the sum total of all the rate constants for drug elimination, including excretion and biotransformation, Cl_T is the sum total of all the clearance processes in the body, including clearance through the kidney (renal clearance), lung, and liver (hepatic clearance).

$$\text{Renal clearance} = k_e V_D$$

$$\text{Lung clearance} = k_l V_D$$

$$\text{Hepatic clearance} = k_m V_D$$

$$\begin{aligned}\text{Body clearance} &= k_e V_D + k_l V_D + k_m V_D \\ &= (k_e + k_l + k_m) V_D = k V_D\end{aligned}$$

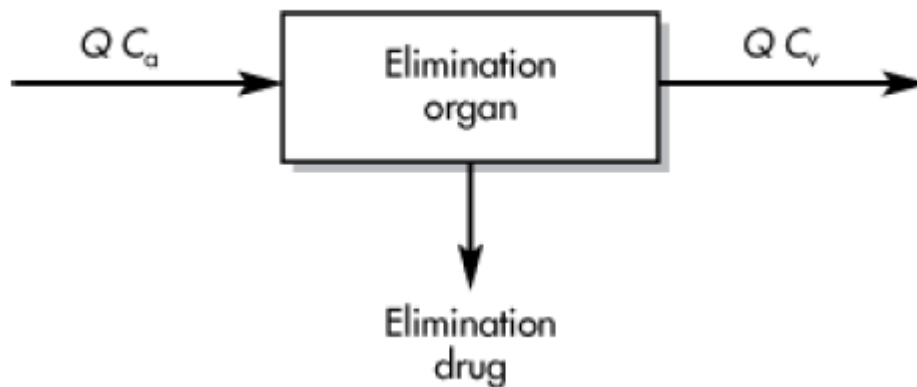
From Equation 6.14, body clearance Cl/T of a drug is the product of two constants, k and V_D , which reflect all the distribution and elimination processes of the drug in the body. The volume of distribution and elimination rate constant are affected by blood flow, which will be considered below using a physiologic model.

CLEARANCE MODELS

The calculation of clearance from k and VD assumes (sometimes incorrectly) a defined model, whereas clearance estimated directly from the plasma drug concentration time curve does not assume any model. Although clearance may be regarded as the product of k and VD , Equation 6.10 is far more general because the reaction order for the rate of drug elimination, dD_E/dt , is not specified, and the elimination rate may or may not follow first-order kinetics.

Physiologic/Organ Clearance

Clearance may be calculated for any organ involved in the irreversible removal of drug from the body. **Many organs in the body have the capacity for drug elimination, including drug excretion and biotransformation. The kidneys and liver are the most common organs involved in excretion and metabolism, respectively.** Physiologic pharmacokinetic models are based on drug clearance through individual organs or tissue groups.



For any organ, clearance may be defined as the fraction of blood volume containing drug that flows through the organ and is eliminated of drug per unit time. From this definition, clearance is the product of the blood flow (Q) to the organ, and the extraction ratio (ER). The ER is the fraction of drug extracted by the organ as drug passes through.

$$\text{Clearance} = Q(\text{ER}) \quad (6.15)$$

If the drug concentration in the blood (C_a) entering the organ is greater than the drug concentration of blood (C_v) leaving the organ, then some of the drug has been extracted by the organ. The ER is $C_a - C_v$ divided by the entering drug concentration (C_a), as shown in Equation 6.16.

$$\text{ER} = \frac{C_a - C_v}{C_a} \quad (6.16)$$

ER is a ratio with no units. The value of ER may range from 0 (no drug removed by the organ) to 1 (100% of the drug is removed by the organ). An ER of 0.25 indicates that 25% of the incoming drug concentration is removed by the organ as the drug passes through. Substituting for ER into Equation 6.15 yields

$$Cl = Q \left(\frac{C_a - C_v}{C_a} \right) \quad (6.17)$$

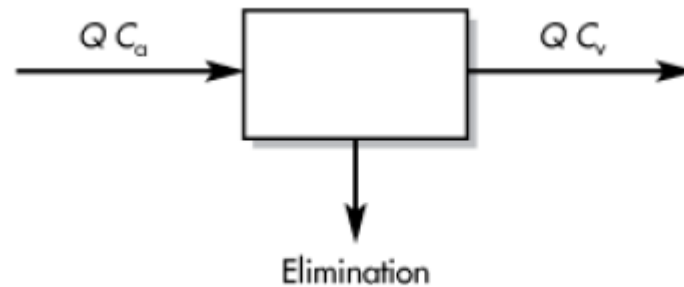
The physiologic approach to clearance shows that clearance depends on the blood flow rate and the ability of the organ to eliminate drug, whereas the classical definitions of clearance is that a constant or static fraction of the volume in which the drug is contained is removed per unit time by the organ. However, clearance measurements using the physiologic approach require **invasive techniques to obtain measurements of blood flow and extraction ratio.** The physiologic approach has been used to describe hepatic clearance, which is discussed under hepatic elimination. More classical definitions of clearance have been applied to renal clearance because direct measurements of plasma drug concentration and urinary drug excretion may be obtained.

Compartment model



Static volume and first-order elimination is assumed.
Plasma flow is not considered. $Cl_T = k V_D$.

Physiologic model



Clearance is the product of the plasma flow (Q) and the extraction ratio (ER).
Thus $Cl_T = Q ER$

RENAL CLEARANCE

Renal clearance , Cl_R , is defined as the volume of plasma that is cleared of drug per unit of time through the kidney. Similarly, renal clearance may be defined as a constant fraction of the VD in which the drug is contained that is excreted by the kidney per unit of time. More simply, renal clearance is defined as the urinary drug excretion rate (dD_u / dt) divided by the plasma drug concentration (C_p).

$$Cl_R = \frac{\text{excretion rate}}{\text{plasma concentration}} = \frac{dD_u / dt}{C_p} \quad (6.20)$$

An alternative approach to obtaining Equation 6.20 is to consider the mass balance of drug cleared by the kidney and ultimately excreted in the urine. For any drug cleared through the kidney, the rate of the drug passing through kidney (via filtration, reabsorption, and/or active secretion) must equal the rate of drug excreted in the urine.

Rate of drug passing through kidney = rate of drug excreted

$$Cl_R \times C_p = Q_u \times C_u \quad (6.21)$$
$$\text{mL/min} \times \text{mg/mL} = \text{mL/min} \times \text{mg/mL}$$

where Cl_R is renal clearance, C_p is plasma drug concentration, Q_u is the rate of urine flow, and C_u is the urine drug concentration. Rearrangement of Equation 6.21 gives

$$Cl_R = \frac{Q_u C_u}{C_P} = \frac{\text{excretion rate}}{C_P} \quad (6.22)$$

because the excretion rate = $Q_u C_u = dD_u / dt$, Equation 6.22 is the equivalent of Equation 6.20.

Comparison of Drug Excretion Methods

Renal clearance may be measured without regard to the physiologic mechanisms involved in this process. From a physiologic viewpoint, however, **renal clearance may be considered as the ratio of the sum of the glomerular filtration and active secretion rates less the reabsorption rate divided by the plasma drug concentration:**

$$Cl_R = \frac{\text{filtration rate} + \text{secretion rate} - \text{reabsorption rate}}{C_P} \quad (6.23)$$

The actual renal clearance of a drug is not generally obtained by direct measurement. The clearance value for the drug is often compared to that of a standard reference, such as inulin, which is cleared completely through the kidney by glomerular filtration only. The clearance ratio, which is the ratio of drug clearance to inulin clearance, may give an indication for the mechanism of renal excretion of the drug. However, further renal drug excretion studies are necessary to confirm unambiguously the mechanism of excretion.

TABLE 6.3 Comparison of Clearance of a Sample Drug to Clearance of a Reference Drug, Inulin

CLEARANCE RATIO	PROBABLE MECHANISM OF RENAL EXCRETION
$\frac{Cl_{\text{drug}}}{Cl_{\text{inulin}}} < 1$	Drug is partially reabsorbed
$\frac{Cl_{\text{drug}}}{Cl_{\text{inulin}}} = 1$	Drug is filtered only
$\frac{Cl_{\text{drug}}}{Cl_{\text{inulin}}} > 1$	Drug is actively secreted

Hepatic elimination of drugs

Chapter 11

First-Order Elimination

The rate constant of elimination (k) is the sum of the first-order rate constant for **metabolism** (k_m) and the first-order rate constant for excretion (k_e):

$$k = k_e + k_m \quad (11.1)$$

In practice, 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, though metabolism or degradation can occur in any organ or tissue that contains metabolic enzymes or is in a degradative condition. Therefore, the rate constant for metabolism (k_m) is difficult to measure directly and is usually found 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:

$$k_m = k_{mA} + k_{mB} + k_{mC} + \cdots + k_{mI} \quad (11.2)$$

The relationship in this equation assumes that the process of **metabolism is first order and that the substrate (drug) concentration is very low**. Drug concentrations at therapeutic plasma levels for most drugs are much lower than the Michaelis-Menten constant, K_M , and do not saturate the enzymes involved in metabolism.

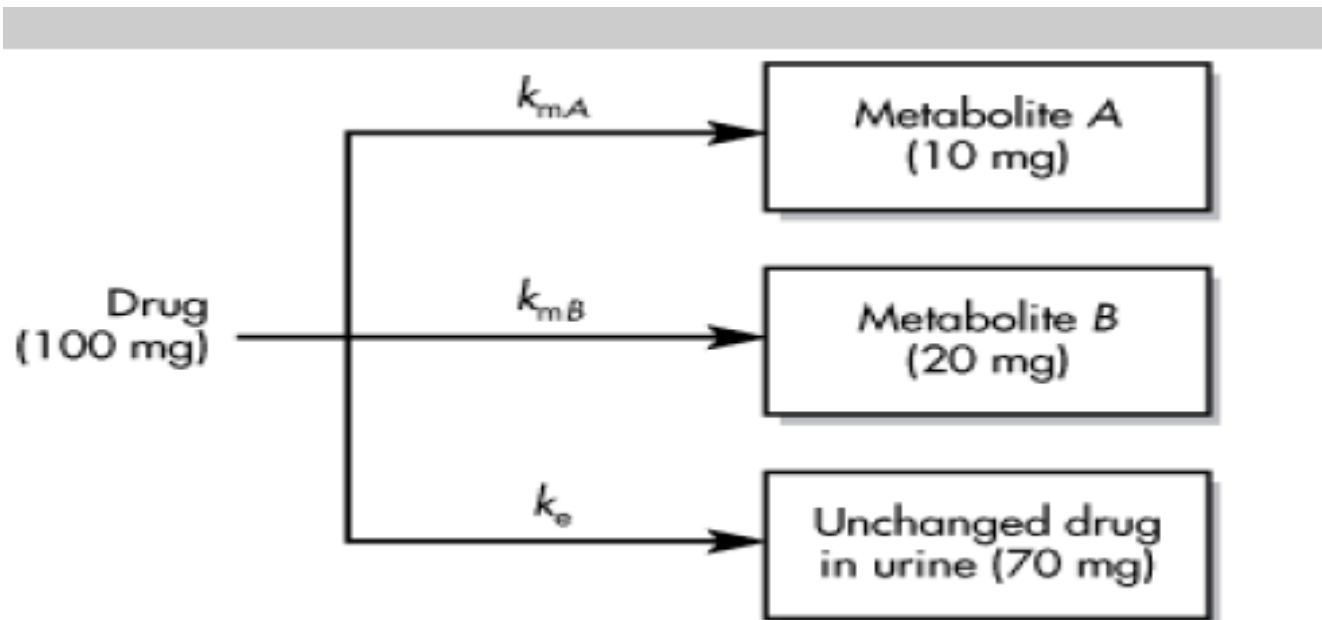
Nonlinear Michaelis-Menten kinetics must be used when drug concentrations saturate metabolic enzymes.

Because these rates of elimination at low drug concentration are considered first-order processes, the percentage of total drug metabolized may be found by the following expression:

$$\% \text{ drug metabolized} = \frac{k_m}{k} \times 100 \quad (11.3)$$

Fraction of Drug Excreted Unchanged (f_e) and Fraction of Drug Metabolized ($1-f_e$)

For most drugs, **the *fraction of dose eliminated unchanged* (f_e) and the *fraction of dose eliminated as metabolites* can be determined**. For example, consider a drug that has two major metabolites and is also eliminated by renal excretion. Assume that 100 M of the drug were given to a patient and the drug was completely absorbed (bioavailability factor $F = 1$). A complete (cumulative) urine collection was obtained, and the quantities in parentheses indicate the amounts of each metabolite and unchanged drug that were recovered. The overall elimination half-life ($t_{1/2}$) for this drug was 2.0 hours ($k = 0.347 \text{ hr}^{-1}$).



To determine the renal excretion rate constant, the following relationship is used:

$$\frac{k_e}{k} = \frac{\text{total dose excreted in urine}}{\text{total dose absorbed}} = \frac{D_u^\infty}{FD_0} \quad (11.4)$$

where D_u^∞ is the total amount of unchanged drug recovered in the urine. In this example, k_e is found by proper substitution into Equation 11.4:

$$k_e = (0.347) \frac{70}{100} = 0.243 \text{ hr}^{-1}$$

To find the percent of drug eliminated by renal excretion, the following approach may be used:

$$\% \text{ drug excretion} = \frac{k_e}{k} \times 100 = \frac{0.243}{0.347} \times 100 = 70\%$$

For many drugs, the literature has approximate values for the fraction of drug (f_e) excreted unchanged in the urine. In this example, the value of k_e may be estimated from the literature values for the elimination half-life of the drug and f_e . Assuming that the elimination half-life of the drug is 2 hours and f_e is 0.7, then k_e is estimated by Equation 11.5.

$$k_e = f_e k \quad (11.5)$$

Because $t_{1/2}$ is 2 hours, k is $0.693/2 \text{ hr} = 0.347 \text{ hr}^{-1}$, and k_e is

$$k_e = (0.7) (0.347) = 0.243 \text{ hr}^{-1}$$

HEPATIC CLEARANCE

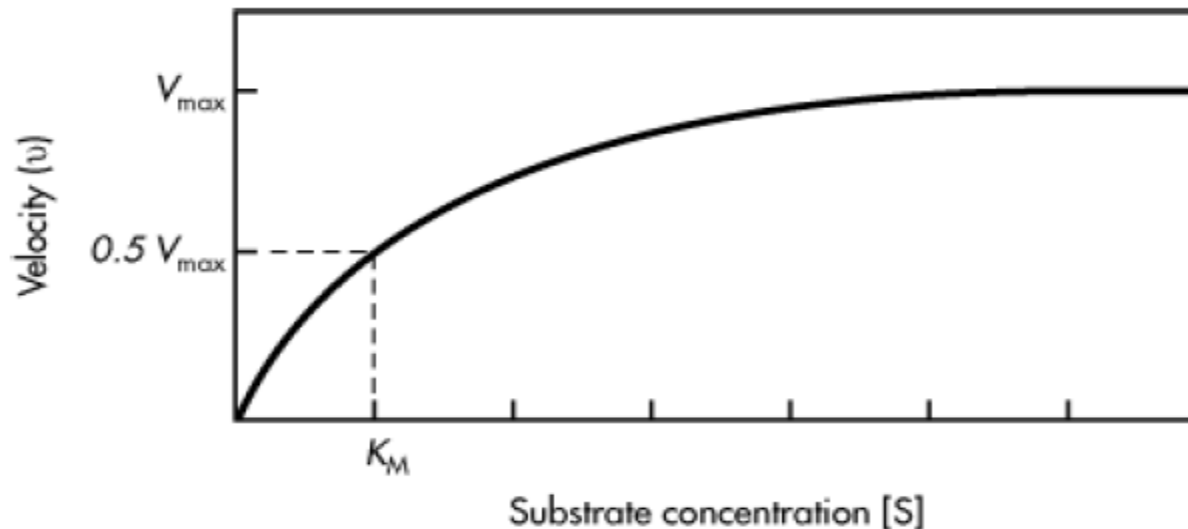
The clearance concept may be applied to any organ and is used as a measure of drug elimination drug by the organ. ***Hepatic clearance may be defined as the volume of blood that perfuses the liver and is cleared of drug per unit of time.*** As discussed in , total body clearance is composed of all the clearances in the body:

$$Cl_T = Cl_{nr} + Cl_r \quad (11.6)$$

where Cl_T is total body clearance, Cl_{nr} is nonrenal clearance (often equated with hepatic clearance, Cl_h), and Cl_r is renal clearance. Hepatic clearance (Cl_h) is also equal to total body clearance (Cl_T) minus renal clearance (Cl_r) assuming no other organ metabolism, as shown by rearranging Equation 11.6 to

ENZYME KINETICS

The process of **biotransformation or metabolism** is the **enzymatic conversion of a drug** to a metabolite. In the body, **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, there are **abundant** enzymes to **catalyze the reaction**, and the rate of metabolism is a **first-order process**. **Saturation** of the enzyme occurs when the drug concentration is **high**, all the enzyme molecules become complexed with drug, and the reaction rate is at a maximum rate; the rate process then becomes a **zero-order process**. The **maximum reaction rate** is known as **V_{\max}** , and the **substrate or drug concentration at which the reaction occurs at half the maximum rate corresponds to a composite parameter K_M** . These two parameters determine the profile of a simple enzyme reaction rate at various drug concentrations. The relationship of these parameters is described by the *Michaelis-Menten* equation.



Enzyme kinetics generally considers that **1 mole of drug interacts with 1 mole of enzyme** to form an **enzyme-drug (ie, enzyme-substrate) intermediate**. The enzyme-drug intermediate further reacts to yield a reaction product or a drug metabolite. The rate process for drug metabolism is described by the Michaelis-Menten equation , which assumes that the rate of an enzymatic reaction is dependent on the concentrations of both the enzyme and the drug and that an energetically favored drug-enzyme intermediate is initially formed, followed by the formation of the product and regeneration of the enzyme.

$$v = \frac{V_{\max}[D]}{[D] + K_M} \quad (11.20)$$

Equation 11.20 describes the **rate of metabolite formation**, or the Michaelis-Menten equation. The maximum velocity (**V_{\max}**) corresponds to the rate when **all of the available enzyme is in the form of the drug-enzyme (ED) intermediate**. At V_{\max} , the drug (substrate) concentration is in excess, and the forward reaction, $k_3[ED]$, is dependent on the availability of more free enzyme molecules. The *Michaelis constant*, K_M , is defined as the substrate concentration when the velocity (v) of the reaction is equal to one-half the maximum velocity, or $0.5V_{\max}$. The K_M is a useful parameter that reveals the concentration of the substrate at which the reaction occurs at half V_{\max} . **In general, for a drug with a large K_M , a higher concentration will be necessary before saturation is reached.**

The Michaelis-Menten equation assumes that **one drug molecule is catalyzed sequentially by one enzyme at a time**. However, **enzymes may catalyze more than one drug molecule (multiple sites) at a time**, which may be demonstrated *in vitro*. In the body, drug may be eliminated by enzymatic reactions (metabolism) to one or more metabolites and by the excretion of the unchanged drug via the kidney. In , the Michaelis-Menton equation is used for modeling drug conversion in the body.

