Journal of Pharmaceutical Biology

www.jpbjournal.com

e-ISSN - 2249-7560
Print ISSN - 2249-7579

EVALUATION OF EXCREATION OF DRUGS-A REVIEW

Ankith Kumar Reddy B*, Subhashis Debnath, M. Niranjan Babu

Department of Pharmaceutics, Seven Hills College of Pharmacy, Tirupati, Andhra Pradesh- 517 561, India.

ABSTRACT

Recent studies have revealed the import role played by transporters in the renal and hepatobiliary excretion of many drugs. These transporters exhibit a broad substrate specificity with a degree of overlap, suggesting the possibility of transporter-mediated drug-drug interactions with other substrates. This review is an overview of the roles of transporters and the possibility of transporter-mediated drug-drug interactions. Among the large number of transporters, we compare the K_i values of inhibitors for organic anion transporting polypeptides (OATPs) and organic anion transporters (OATs) and their therapeutic unbound concentrations. Among them, cephalosporins and probenecid have the potential to produce clinically relevant OAT-mediated drug-drug interactions, whereas cyclosporin A and rifampicin may trigger OATP-mediated ones. These drugs have been reported to cause drug-drug interactions in vivo with OATs or OATP substrates, suggesting the possibility of transporter-mediated drug-drug interactions. To avoid adverse consequences of such transporter-mediated drug-drug interactions, we need to be more aware of the role played by drug transporters as well as those caused by drug metabolizing enzymes.

Keywords: Renal excretion, Bilary excretion, Tubular reabsorction.

INTRODUCTION

Drugs and/or their metabolites are removed from the body by excretion. Excretion is defined as the process whereby drugs and/or their metabolites are irreversibly transferred from internal to external environment. Excretion of unchanged or intact drug is important in the termination of its pharmacologic action. The principal organs of excretion are kidneys. Excretion by organs other than kidneys such as lungs, biliary system, intestine, salivary glands and sweat glands is known as non-renal excretion [1].

RENAL EXCRETION OF DRUGS

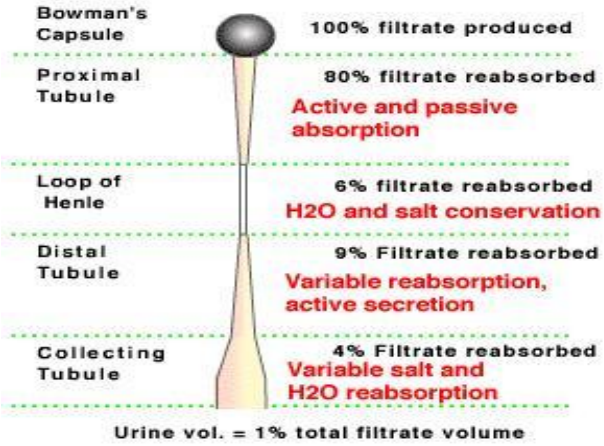
Almost all drugs and their metabolites are excreted by the kidneys to some extent or the other. Some drugs such as gentamicin are exclusively eliminated by renal route only. Agents that are water-soluble, non-volatile, small in molecular size (less than 500 daltons) and which are metabolized slowly, are excreted in the urine.

The basic functional unit of the kidney involved in excretion is the nephron. Each kidney comprises of one million nephrons. Each nephron is made up of the glomerulus, the proximal tubule, the loop of Henle, the distal tubule and the collecting tubule.

The principal processes that determine the urinary excretion of a drug are:-

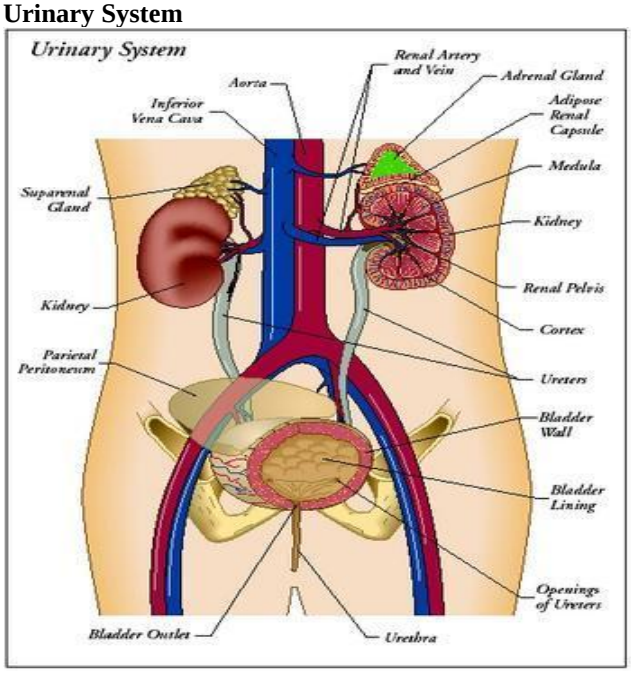
1. Glomerular filtration,
2. Active tubular secretion, and
3. Active or passive tubular reabsorption.

These processes are depicted in Fig.

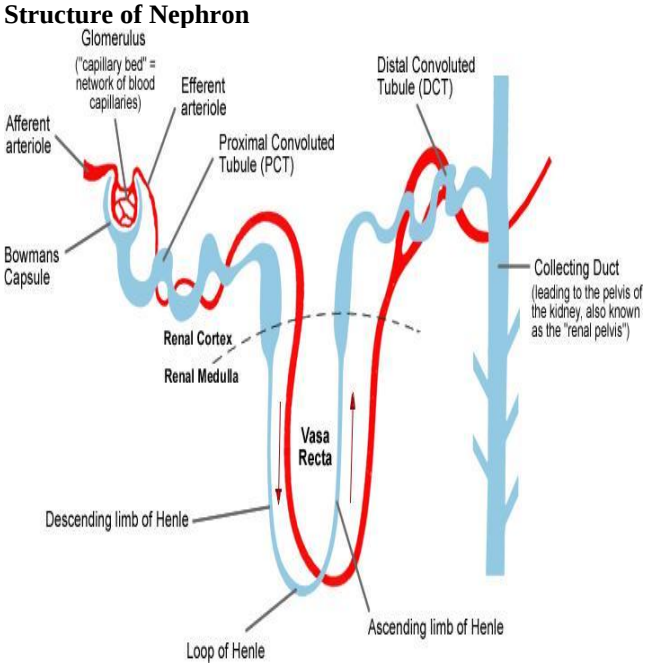


Corresponding Author:- **Ankith Kumar Reddy B** Email:- ankithpharmaline0002@gmail.com

Urinary System



Structure of Nephron



- The driving force for filtration through the glomerulus is hydrostatic pressure of the blood flowing in the capillaries.
- Out of 25% of cardiac output or 1.2 lit of blood/min that goes to the kidneys via renal artery only 10% or 120 to 130 ml/min is filtered through the glomeruli. The rate being called GFR.
- The GFR can be determined by an agent i.e. excreted exclusively by filtration and is neither secreted nor reabsorbed in the tubules.
- The excretion rate value of such an agent is 120 to 130 ml/min.
- Creatinine, insulin, mannitol and sodium thiosulphate are used to estimate GFR of which the former two are widely used to estimate renal function.

Active Tubular Secretion

Carrier-mediated process, which requires energy for transportation of compounds against concentration gradients. The system is capacity limited and saturable. To achieve tubular secretion mechanism: -

- System for secretion of organic acids/ anions like penicillins, salicylates, glucuronides, sulfates, etc. It is the same system by which endogenous acids such as uric acid are secreted.
- System for secretion of organic bases/ cations like morphine, mecamylamine, hexamethonium and endogenous amines such as choline, histamine etc.

- Both the systems, non-selective, independent of each other but both can be bidirectional i.e. agents may both be secreted as well as reabsorbed actively e.g. Uric acid.
- Active secretion is unaffected by changes in pH and protein binding since the bound drug rapidly dissociates the moment the unbound drug get excreted.
- Active secretion have excretion rate values greater than the normal GFR value of 130ml/min.

Tubular Reabsorption

- **Occurs after glomerular filtration of drug.**
- Reabsorption of drug is indicated when the excretion rate values are less than the GFR of 130ml/min.

Tubular reabsorption can either be

1) Active process, or
2) Passive process

Active tubular reabsorption is commonly seen in which high threshold endogenous substances or nutrients that the body needs to conserve such as electrolytes, glucose, vitamins, amino acids.

- Uric acid also actively reabsorbed.
- Very few drugs are known to undergo reabsorption actively e.g. oxopurinol.
- Passive tubular reabsorption is common for a large number of exogenous substances including drugs.
- The primary determinant in the passive reabsorption of drugs is their lipophilicity.
- Lipophilic substances are extensively reabsorbed.

While polar molecules are not since majority of drugs are weak electrolytes (weak acids or bases).

Diffusion of such agents through the lipoidal tubular membrane depends upon the degree of ionization which in turn depends upon two important factors - pH of urine and pKa of urine.

- pH of urine varies between 4.5 to 7.5.

- pH of urine is dependent upon diet, drug intake and pathophysiology of the patient.
- Food rich in carbohydrates results in higher urinary pH whereas proteins lower it.
- Drugs such as acetazolamide and antacids produce alkaline urine while ascorbic acids make it acidic.
- Alteration in urine pH is brought about by i.v. infusion of solutions of Na_2CO_3 and NH_4Cl which are used in acid-base imbalance.
- Respiratory and metabolic acidosis and alkalosis results in acidification and alkalinization of urine resp.

The relative amount of ionized and unionized drug in the urine at a particular pH and % of drug ionized at this pH can be computed from Henderson-Hesselbach equations:

For Weak acids

$$pH = pka + \log \frac{[ionized]}{[unionized]}$$

$$\% \text{ drug ionized} = \frac{10^{pH - pka}}{1 + 10^{pH - pka}} \times 100$$

For Weak bases

$$pH = pka + \log \frac{[Unionized]}{[ionized]}$$

$$\% \text{ drug ionized} = \frac{10^{pH - pka}}{1 + 10^{pH - pka}} \times 100$$

The concentration ratio R of the drug in urine to that in plasma (U:P) can be given by equation;

For Weak bases:-

$$Rb = \frac{U}{P} = \frac{1 + 10^{pKa - pH\ urine}}{1 + 10^{pKa - pH\ plasma}}$$

For weak acids:-

$$Ra = \frac{U}{P} = \frac{1 + 10^{pH\ urine - pKa}}{1 + 10^{pH\ plasma - pKa}}$$

Drug pKa:

- The significance of pH dependent excretion for any particular compound is greatly dependent upon its pKa, and lipid solubility.
- A characteristics of drugs pKa values govern the degree of ionization at a particular pH.
- A polar and ionized drug will be poorly reabsorbed passively and excreted rapidly.
- Reabsorption is also affected by the lipid solubility of drug, an ionized but lipophillic drug will be reabsorbed while an unionized but polar one will be excreted.

CONCEPT OF CLEARANCE

- **Was first introduced to describe renal excretion of endogenous compounds in order to measure the kidney function.**
- The term applied to all organ involved in drug elimination such as liver, lungs, the biliary system etc and referred to as hepatic clearance, pulmonary clearance and biliary clearance and so on.
- The sum of individual clearances by all eliminating organs is called as total body clearance or total systemic clearance.
- It sometime expressed as a sum of renal clearance and non-renal clearance.
- Clearance is defined as the hypothetical volume of body fluids containing drugs from which the drug is removed or cleared completely in a specific period of time.
- It is expressed in ml/min and const for any given plasma drug concentration.

$$\text{Clearance (Cl)} = \frac{\text{Elimination rate}}{\text{Plasma drug conc.}}$$

Renal clearance: The volume of blood or plasma which is completely cleared of the unchanged drug by kidney per unit time.

$$Cl_R = \frac{\text{Rate of urinary excretion}}{\text{Plasma drug concentration}}$$

Physiologically speaking renal clearances is the ratio of:-

$$Cl_R = \frac{\text{Rate of filtration + Rate of secretion – Rate of reabsorption}}{C}$$

Where 'C' = Plasma drug concentration.

Hepatic clearance

$$Cl_H = Q_H \cdot ER_H$$

Two types

Q_H =Drugs with hepatic blood flow rate limited clearance

ER_H = Drugs with intrinsic capacity limited clearance

Drugs with hepatic blood flow rate limited clearance

When ER_H is one, Cl_H approaches its maximum value i.e. hepatic blood flow in such clearance is said to hepatic perfusion rate limited clearance

Alteration blood flow affects the elimination of drugs with high ER_H

e.g. propranolol, lidocaine

Indocyanonine green is rapidly eliminated by liver, clearance is often is used as indicator.

Intrinsic capacity clearance

It is defined as the inherent ability of an organ to irreversibly remove a drug in the absence of any flow limitation.

It depends hepatic enzymatic activity.

Drugs with low ER_H and with elimination primarily by metabolism are greatly affected by changes in enzyme activity

FACTORS AFFECTING RENAL EXCRETION

1. Physicochemical properties of drug
2. Plasma concentration of drug
3. Distribution and binding characteristics of drug
4. Urine pH
5. Blood flow to the kidneys
6. Biological factors
7. Drug interaction
8. Disease state

1) Physicochemical Properties of Drug

- Important factors affecting renal excretion of a drug are mole size, pka and lipid solubility. Molecular size : Small, easily filtered through glomerulus.
- Molecular weight 300 daltons good candidate.
- Excreted in both i.e. bile and urine.
- More than 500 dalton excreted in urine to a lesser extent.
- Lipid solubility: Urinary excretion of an unchanged drug is inversely proportional to its lipophilicity [2].

Plasma concentration of drug

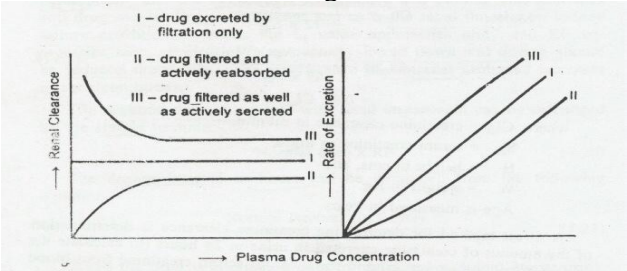


Fig. 7.3 Renal clearance and rate of excretion of a drug in relation to its plasma concentration as affected by the physiologic processes —filtration, active reabsorption and active secretion

I : Drug excreted by filtration only shows a linear graph.

II : Here renal clearance and rate of excretion is increases with increase in plasma concentration but up to a saturation level.

III : Here rate of excretion is negligible at low plasma concentration.

Distribution and binding characteristics of drug:

Distribution :-

$$\text{Clearance} = \frac{1}{\text{App. Vol. of distribution (Vd)}}$$

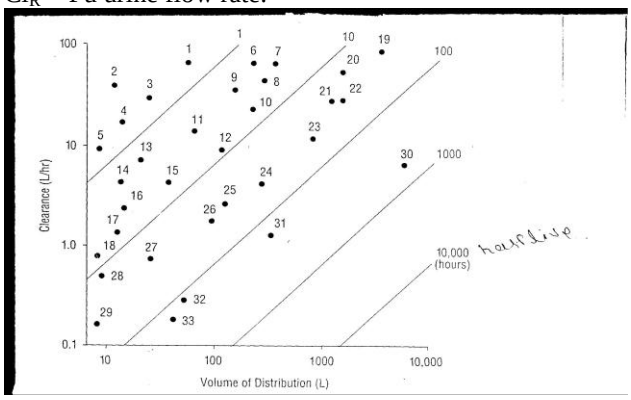
Large Vd – poorly excreted in urine.

Binding characteristics:

- Drug – bound to plasma protein → not filtered by glomerulus.
- Only unbound / free drug → filtered by glomerulus

$$Fu = \frac{Cu}{C}$$

Cl_R = Fu urine flow rate.



Blood flow to the kidneys

Renal blood flow is important in cases of drug excreted by glomerular filtration only and those that are actively secreted.

Increase perfusion increase contact of drug with secretory sites which enhances their elimination.

Renal clearance is said to be perfusion rate limited.

Biological factors

S/A – Age, sex, species and strain differences and differences in genetic make up.

Sex – Cl_R is 10% lower in females than in males.

Age – Cl_R in newborn is 30 to 40% less in comparison to adults.

Old age – slow excretion.

Species: Excretion is altered by different species.

Drug interaction

Any drug interaction that results in alteration of binding characteristics, renal blood flow, active secretion, urine pH, can alter the renal clearance of drug.

e.g. Urinary excretion of digoxin is decreased by diazepam.

Disease state

Renal dysfunction

Greatly impairs the elimination of drugs specially those that are primarily excreted by kidney. E.g. Aminoglycosides, Phenacetin.

Uremia

Characterized by impaired glomerular filtration and accumulation of fluids and protein metabolites also impairs renal clearance of drug i.e. slow excretion may leads to drug accumulation.

Renal function:

Rf can be determined by GFR.

$$RF = \frac{\text{Clcr of patient}}{\text{Clcr of a normal person}}$$

Clcr: creatinine clearance

$$Clcr = \frac{\text{Rate of creatinine excretion}}{\text{Serum creatinine in mg\%}}$$

DOSE ADJUSTMENT IN RENAL FAILURE:

- Drug in patients with renal impairment have altered pharmacokinetic profile.
- Their renal clearance and elimination rate are reduced; the elimination half-life is increased and apparent volume of distribution altered.
- Since dose must be altered depending upon renal function in such patient.
- Except for drug having low therapeutic indices, the therapeutic range of others is sufficiently large and dose adjustment is not essential.
- The required dose in patient with renal impairment can be calculated by simple formula:-

Normal dose x RF
The dosing interval in hrs

$$\frac{\text{Normal interval in hrs}}{\text{RF}}$$

When the drug is eliminated both by renal and non-renal mechanisms, the dose to be administered in patients with renal failure is obtained from Normal dose (RF x Fraction excreted in urine + Fraction eliminated non-renally).

Methods of adjustments

There are two additional methods for dose adjustments in renal insufficiency. These methods are based on maintaining the same average steady state concentration multiple dosage regimen and normal renal function [3].

Dose adjustment based on the total body clearance

According to the average concentration and body content on multiple dosing to steady state

$$Css.av = \frac{F\,X_O}{Cl_T\,\Gamma}$$

There fore,
Css.av= the average drug concentration at steady state
X_o = maintenance dose
F = Fraction of dose absorbed
Γ =Dosing interval
Cl_T = total clearance

Re writing the equation

$$Css.av = F \times \frac{1}{Cl_T} \times \frac{XO}{\Gamma}$$

To be kept adjustment Constant — **assumed constant** — **Decreased due to diseased** — **needs**

The parameter to be adjusted in renal insufficiency is above see equation
If Cl_T, X_O, Γ represents the values for the renal failure patient then dose adjustment equation is

$$CSS.AV = \frac{X_O}{Cl_{T\Gamma}} = \frac{X^1_O}{Cl_T{}^1\Gamma^1}$$

Rearranging in terms of dose and dose interval to adjusted the equ is

$$\frac{X^1_O}{\Gamma^1} = \frac{Cl^1_T\,X_O}{Cl_T\,\Gamma}$$

The Above equation the regimen may be adjusted by reduction in dosage or increase in dosing interval or combination of the both.

Dose adjustment based on elimination rate constant of half life

The parameters to be adjusted in renal insufficiency are

$$Css.av = \frac{1.44\,F\,X\,t_{1/2}}{Vd} \times \frac{X_O}{\Gamma}$$

If $t_{1/2}$, X_O ,Γ represent the values for the renal failure patient then

$$Css.av = \frac{t_{1/2}X_O}{\Gamma} = \frac{t^1_{1/2}X^1_O}{\Gamma^1}$$

Rearranging the above equation in terms of dose and dose interval to be adjusted
We get

$$\frac{X^1_O}{\Gamma^1} = \frac{t_{1/2}\,X_O}{t^1_{1/2}\,\Gamma}$$

Because of prolongation of half-life of a drug due to reduction in renal function. Hence patient needs loading dose

NON-RENAL ROUTES OF DRUG EXCRETION

Drugs and their metabolites may also be excreted by routes other than renal route.

The various excretion processes are:-
1) Biliary excretion
2) Pulmonary excretion
3) Salivary excretion
4) Mammary excretion
5) Skin/dermal excretion
6) Gastro-intestinal excretion
7) Genital excretion

Biliary Excretion

- **Hepatic cells produce bile and are a active process.**
- Bile secreted in liver and stored in gall bladder.
- Bile flow rate 0.5 to 1ml/min.
- Bile is important in digestion and absorption of fat.
- Hence bile secretion is capacity limited process so it is analogous to active renal secretion.
- Different transport mechanisms exist for the secretion of organic anions, cations and neutral polar compounds.
- A drug whose biliary concentration is less than that in plasma has a small biliary clearance and vice versa.
- Compounds that are excreted in bile have been classified into 3 categories on the basis of their bile/ plasma concentration ratio.

Group A : Whose ratio 1 e.g. sodium, potassium and chloride ions and glucose.
Group B : Whose ratio >1 usually from 10 to 1000 e.g. bile salt, bilirubin glucuronide, creatinine, sulfobromophthalein conjugates etc.

Group C : Whose ratio <1 e.g. sucrose, insulin, phosphates, phospholipids and mucoproteins.

Pulmonary Excretion

- **Gaseous and volatile substances undergo pulmonary excretion. It takes place by lungs by simple diffusion.**
- Factors influencing are : Pulmonary blood flow rate of respiration, solubility of volatile substances. E.g. Gaseous anesthetics, nitrous oxide not very soluble in blood are excreted rapidly. Compounds like alcohol which have high solubility in blood and tissue are excreted slowly by the lungs [4].

Mammary Excretion

- **Excretion of drug in milk.**
- Passive process
- Factors affecting are : pH partition molecular weight, lipid solubility, degree of ionization.
- The extent of drug excretion in milk can be determined from milk/ plasma drug concentration ratio (M/P).
- Since milk acidic in nature, as comparison to plasma.
- Therefore basic drug concentrate more in milk and have M/P ratio greater than 1.
- Drug bound to plasma protein and are less secreted by milk. Amount of drug excreted is less than 1%.

Salivary Excretion

- **Passive diffusion process and predicted on the basis of pH-partition hypothesis.**
- PH of saliva varies from 5.8 to 8.4 (mean pH 6.4). Hence at this pH unionized lipid soluble drugs are excreted through saliva passively.
- Saliva/ plasma drug concentration ratio S/P can be given by,

For Weak Acids:-

$$Ra = \frac{S}{P} = \frac{1 + 10\,(pH\ saliva - pKa)}{1 + 10\,(pH\ plasma - pKa)} \times \frac{F\ Plasma}{F\ Saliva}$$

For Weak Bases:-

$$Ra = \frac{S}{P} = \frac{1 + 10\,(pKa - pH\ saliva)}{1 + 10\,(pKa - pH\ plasma)} \times \frac{F\ Plasma}{F\ Saliva}$$

Where,

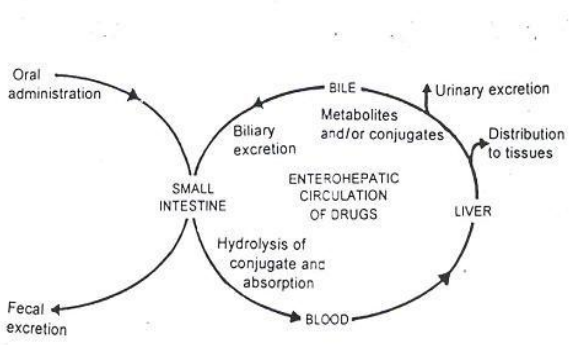
F Plasma : Free drug fraction in plasma.
F Saliva : Free drug fraction in saliva.
S/p ratio is <1 for weak acids
S/p ratio is >1 for weak bases

- It means that basic drugs are excreted more in saliva as compared to acidic drug.
- E.g. of drugs whose blood concentration can be determined by detecting the amount of drug excreted in saliva. E.g. caffeine, theophylline, phenytoin.

An indication of a drug excretion in saliva is the bitter after taste in the mouth of a patient on medication.

Drugs excreted in saliva can undergo cycling in a similar fashion to enterohepatic cycling.

e.g. Sulfonamides, clonidine.



Gastrointestinal Excretion

Excretion of drugs into the GIT usually occurs after parenteral administration when the concentration gradient for passive diffusion is favourable.

- The process is reverse of G.I. absorption of drugs.
- Water soluble and ionized form of weakly acidic and basic drugs is excreted in the G.I.T. E.g. Nicotine and quinine are excreted in stomach.
- Orally administered drugs can also be absorbed and excreted in GIT.
- Drugs excreted in GIT are reabsorbed into the systemic circulation and undergo recycling.

Skin Excretion

- **Drugs excreted through skin via sweat also follow pH partition hypothesis.**
- Passive excretion of drugs and their metabolites through skin is responsible to some extent for urticaria and dermatitis and other hypersensitivity reactions.
- Compounds such as benzoic acid, salicylic acid, alcohol and antipyrine and heavy metals like lead, mercury and arsenic are excreted in sweat.

Genital Excretion:

Reproductive tract and genital secretions may contain the excreted drugs.

- Some drugs have been detected in Semen.
- Drugs can also get excreted via the lachrymal fluid [5].

DOSAGE REGIMMEN

Definition:-it is defined as the manner in which a drug is taken.

- Dose (D):- is the amount of drug administered as a part of the dosage regimen.
- Dose interval:-is the time period between administration of doses
- When an oral multiple dosing regimen is initiated – plasma concentration will increase reach a maximum and begin to decline.
- A second dose should be administered before the entire first dose is eliminated.
- Loading dose:-a dose that gives the desired steady state immediately after administration such an initial dose intended to be therapeutic is referred to as priming or loading dose.
- Subsequent doses administered to maintain the response by replacing the drug lost during the dosing interval is known as maintenance dose.

REFERENCES

1. Biopharmaceutics and Pharmacokinetics - A Treatise by Brahmankar DM and Jaiswal SB, 1st ed, Vallabh Prakashan, 178-201.
2. Text Book of Biopharmaceutics and Pharmacokinetics by Shoba Rani.
3. Applied Biopharmaceutics and Pharmacokinetics, IV edition, by Leon Shargel's, 337.
4. Biopharmaceutics and Chemical Kinetics, IX edition, Lea & Febiger.
5. Biopharamaceutics and clinical pharmacokinetics. Fourth edition Lea and febiger Philadelphia London, 1991.