CHAPER 3

Review of Literature

3.1 Sustained drug delivery system and physiology of drug absorption

The design of oral sustained drug delivery system should be primarily aimed to achieve the more predictability and reproducibility to control the drug release, drug concentration in the target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose. These preparations may provide an immediate dose required for the normal therapeutic response, followed by the gradual release of drug in amounts sufficient to maintain the therapeutic response for a specific extended period of time usually 8-12 hrs and this can be better understood in the figures 3.1, 3.2 and figure 3.3. In the traditional drug delivery systems, the drug level in the blood rises after each administration of the drug and then decreases until the next administration. The goal of traditional drug administration is the blood level of the agent should remain between a maximum value, which may represent a toxic level, and a minimum value, below which the drug is no longer effective that is the therapeutic concentration level.

The oral absorption of any chemical entity reflects a complex spectrum of events. Factors influencing product bioavailability include drug solubility, permeability, and the rate of in vivo dissolution. In this regard, the Biopharmaceutics Classification System (BCS) has proven to be an important tool for predicting compounds likely to be associated with bioavailability problems. It also helps in identifying those factors that may alter the rate and extent of drug absorption.

Product bioavailability can also be markedly influenced by patient attributes such as the integrity of the gastrointestinal tract, physiological status, site of drug absorption, membrane transporters, presystemic drug metabolism (intrinsic variables), and extrinsic variables such as the effect of food or concomitant medication.
Figure 3.1: Plasma drug concentration-profiles for conventional tablet or capsule formulation, a sustained release formulation, and a zero order sustained release formulation.

Figure 3.2: Comparison of Conventional and Controlled Release Profiles

Figure 3.3: Dosage Regime for Conventional and Controlled Release Systems

Most of the orally administered drugs, targeting is not a primary concern and it is usually intended for drugs to penetrate to the general circulation and perfuse to other body tissues. For this reason, most systems employed are of the sustained release variety. It is assumed that
increasing concentration at the absorption site will increase circulating blood levels, which in
turn, promotes greater concentration of drug at the site of action. If toxicity is not an issue, therapeutic levels can thus be extended. In essence, drug delivery by these systems usually depends on release from some type of dosage form, permeation through biological milieu and absorption through an epithelial membrane to the blood. There are a variety of both physicochemical and biological factors that come into play in the design of such system.  

3.2 Principle of sustained release drug delivery
The conventional dosage forms release their active ingredients into an absorption pool immediately.

![Figure 3.4: Illustration of simple kinetic scheme.](image)

The absorption pool represents a solution of the drug at the site of absorption, and the term Kr, Ka and Ke are first order rate-constant for drug release, absorption and overall elimination respectively. Immediate drug release from a conventional dosage form implies that Kr>>Ka. Alternatively speaking the absorption of drug across a biological membrane is the rate-limiting step. For non immediate release dosage forms, Kr<<Ka i.e. the release of drug from the dosage form is the rate limiting step. This causes the above Kinetic scheme to reduce to the following (Figure 2.5).

![Figure 3.5: Kinetic Scheme](image)

Essentially, the absorptive phase of the kinetic scheme become insignificant compared to the drug release phase. Thus, the effort to develop a non immediate release delivery system must be directed primarily at altering the release rate. The main objective in designing a sustained release
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delivery system is to deliver drug at a rate necessary to achieve and maintain a constant drug blood level. This rate should be analogous to that achieved by continuous intravenous infusion where a drug is provided to the patient at a constant rate. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time. It means that the drug release from the dosage form should follow zero-order kinetics, as shown by the following equation

\[ \text{Kr}^\circ = \text{Rate in} = \text{Rate out} = \text{Ke Cd Vd} \]

Where,

\( \text{Kr}^\circ \) = Zero-order rate constant for drug release - Amount/time

\( \text{Ke} \) = First-order rate constant for overall drug elimination - time\(^{-1}\)

\( \text{Cd} \) = Desired drug level in the body - Amount/volume, and

\( \text{Vd} \) = Volume space in which the drug is distributed - Liters

The value of Ke, Cd and Vd are obtained from appropriately designed single dose pharmacokinetic study. The equation can be used to calculate the zero order release rate constant. For many drugs, however, more complex elimination kinetics and other factors affecting their disposition are involved. This in turn affects the nature of the release kinetics necessary to maintain a constant drug blood level. It is important to recognize that while zero-order release may be desirable theoretically, non zero-order release may be equivalent clinically to constant release in many cases.\(^{97, 98, 99}\)

The basic rationale for sustained release drug delivery is to alter the pharmacokinetics and pharmacodynamics of drugs by using novel drug delivery systems or by modifying the molecular structure or physiological parameters inherent in a selected route of administration. It is desirable that the duration of drug action becomes more a design property of a rate controlled dosage form and less or not at all a property of the drug molecule’s inherent kinetic properties. Thus, optimal design of a sustained release system necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drug. When the drug is administered in a conventional dosage form, it results in a fluctuation of drug concentration at the site of action (peak and valley pattern) and therefore in systemic circulation and tissue compartment (Figure 3.1)\(^4\)
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The pharmaceutical applications of polymers range from their use as binders in tablets to viscosity and flow controlling agents in liquids, suspensions and emulsions. Polymers can be used as film coatings to disguise the unpleasant taste of a drug, to enhance drug stability and to modify drug release characteristics. The release of the active agent may be constant over a long period, it may be cyclic over a long period, or it may be triggered by the environment or other external events. In any case, the purpose behind controlling the drug delivery to achieve more effective therapies while eliminating the potential for both under and overdosing.

Nonionic cellulose ethers and hydroxypropyl methyl cellulose (Hypromellose, HPMC) have been widely studied for their application in oral sustained release formulations. Such hydrophilic polymers are most popular because of their flexibility to get a desirable drug release profile, cost effectiveness and broad regulatory acceptance. $^{100}$

HPMC has always been a first choice for formulation of hydrophilic matrix systems, because of providing robust mechanism, choice of viscosity grades, nonionic nature, consistent reproducible release profiles, cost effectiveness and utilization of existing conventional equipment and methods. $^7$ HPMC most widely used as the gel forming agent in the formulations of solid, liquid, semisolid and controlled release dosage forms. The adjustment of the polymer concentration, the viscosity grades and the addition of different types and levels of excipients to the HPMC matrix can modify the drug release rates $^{101}$

Drug release from dosage form like tablets capsules, and granules shows complex interaction between mechanisms like wetting, capillary penetration, swelling, disintegration diffusion, dissolution, erosion etc. These processes are mainly depends on type, quantity and properties of the drug and excipients as well as manufacturing processes. Polymer dissolution, erosion in solvent is an important area in drug delivery system, which allows for optimization of design and processing of drug dosage form as well as selection of suitable excipients. The ideal drug delivery system is one which provides the drug only when and where required and in minimum dose is required to give the desired therapeutic.
When the dosage form introduced into the solvent, swelling occur allowing increased mobility of drug and it diffuses out of polymer in the surrounding fluid. Various mathematical models can be applied to the dissolution profile to describe the mechanism and kinetics of dissolution process. Whereas it is quite difficult to create mathematical equations due to different dissolution curves shows very different shapes.

### 3.3 Advantages of sustained release drug delivery

1. Decreased local and systemic side effects; reduced gastrointestinal irritation.
2. Better drug utilization and reduction in total amount of drug used.
3. Improved efficiency in treatment, optimized therapy, more uniform blood concentration.
4. Reduction in fluctuation in drug level and hence more uniform pharmacological response, cure of control of condition more promptly, less reduction in drug activity with chronic use.
5. Method by which sustained release is achieved can improve the bioavailability of some drugs e.g. drugs susceptible to enzymatic inactivation can be protected by encapsulation in polymer systems suitable for sustained release.
6. Improved patient compliance, less frequent dosing, reduced night-time dosing, reduced patient care time. The importance of patient compliance in successful drug therapy is well recognized. It has been found that there is an inverse relationship between the number of dosages per day and the compliance rate.
7. Although the initial unit cost of sustained release products is usually greater than that of conventional dosage forms because of the special nature of these products, the average cost of treatment over an extended time period may be less. Economy may also result from a decrease in nursing time and hospitalization time.

### 3.4 Disadvantages of sustained release drug delivery

1. Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time complete release, site specific absorption, pH dependent stability, etc.
2. Poor in vitro - in vivo correlation.
3. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
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4. Reduced potential for dose adjustment of drugs normally administered in varying strengths.

The majority of oral sustained release systems depend on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal milieu. Theoretically and desirably a sustained release delivery device, should release the drug by a zero-order process which would result in a blood level time profile similar to that after intravenous constant rate infusion (figure 3.1, 3.2, 3.3).

3.5 Classes of sustained drug delivery system.\(^3\)

1. Diffusion sustain system:
   a. reservoir type
   b. matrix type
2. Dissolution sustained system.
   a. reservoir type
   b. matrix type
3. Methods using Ion-exchange
5. pH independent formulations.
6. Altered density formulations.

3.5.1 Diffusion sustain system

In this type of systems, the diffusion of dissolved drug through a polymeric barrier is a rate limiting step. The drug release rate is never zero-order, since the diffusional path length increases with time as the insoluble matrix is gradually depleted of drug. Diffusion of a drug molecule through a polymeric membrane forms the basis of these controlled drug delivery systems. Similar to the dissolution controlled systems, the diffusion-controlled devices are manufactured either by encapsulating the drug particle in a polymeric membrane or by dispersing the drug in a polymeric matrix. Unlike the dissolution-controlled systems, the drug is made available as a result of partitioning through the polymer.

In order to achieve a constant release rate, all of the terms on the right side of equation must be held constant. It is very common for diffusion controlled devices to exhibit a non-zero-order release rate due to an increase in diffusional resistance and a decrease in effective diffusion area as the release proceeds. Another configuration of diffusion-controlled systems includes matrix
devices, which are very common because of ease of fabrication. Diffusion control involves
dispersion of drug in either a water-insoluble or a hydrophilic polymer. The release rate is
dependent on the rate of drug diffusion through the matrix but not on the rate of solid dissolution.  
The drug is released much more slowly than would be expected from the simplest
consideration of aqueous diffusion.  

**Reservoir type**
Reservoir types are those in which a core of drug is surrounded by polymeric membrane. The
nature of membrane determines the rate of release of drug from system. The
process of diffusion is generally described by a series of equations governed by Fick’s first
law of diffusion: 

\[ J = -D \frac{DC}{DX} \]  

**Equation 24**

Where,

- \( J \) = flux of drug across the membrane given in units of amount / area time.
- \( D \) = diffusion coefficient of drug in membrane in units of area / time. This is reflecting to drug
  molecule’s ability to diffuse through the solvent and is dependent on the factors as molecular
  size and charge.
- \( \frac{dc}{dt} \) = represents rate of change in concentration \( C \) relative to a distance \( X \) in the membrane.

The law states that amount of drug passing across a unit area, is proportional to the concentration
difference across that plane.

Schematic representation of reservoir diffusion device \( C_m (o) \), and \( C_m (d) \) represent
concentration of drug inside surfaces of membrane and \( C (o) \) & \( C(d) \) represents concentration in
adjacent regions.

![Schematic representation of reservoir diffusion device](image)

**Figure 3.6**: Schematic representation of reservoir diffusion device
adapted from Bramhankar et.al
If it is assumed that the drug on the both side of membrane is in equilibrium with its respective membrane surface which in equilibrium between the membrane surfaces and their bathing solutions as shown in figure 3.6.

A constant effective area of diffusion, diffusional path length, concentration difference, and diffusion coefficient are required to obtain a release rate that is constant. Reservoir diffusional systems have several advantages over conventional dosage forms. They can after zero order release of drug, kinetics of which can be controlled by changing the characteristics of the polymer to meet the particular drug and therapy conditions.

Pot showing approach to steady state for reservoir device that has been stored for an extended period (the burst effect curve) and for device that has been freshly made (the time lag curve)

![Figure 3.7: Time lag and burst effect](image)

Common methods used to develop reservoir type of devices include micro encapsulation of drug particles and press coating of tablets containing drug cores. In most cases particles coated by microencapsulation form a system where the drug is contained in the coating film as well as in the core of micro capsule. The drug release generally involves combination of dissolution and diffusion with dissolution being process that controls the release rate. If encapsulating material is selected properly will be the controlling process. Some materials such as membrane barrier coat alone or in combination, are hardened gelatin, methyl or methylcellulose, polyhydroxymethacrylate hydroxypropylmethylcellulose, polyhydroxymethacrylate, polyvinyl acetate & various waxes.¹⁰⁷
Matrix type \textsuperscript{26, 27}

Matrix device, as the name implies, consists of drug dispersed homogenously throughout a polymer.

Matrix diffusion system before release (time =0) & after partial drug release (time = t)

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{matrix_diffusion_system.png}
\caption{Matrix diffusion system}
\end{figure}

In this model drug in outside layer exposed to the bathing solution is dissolved first and diffused out of the matrix. This process continues with the interface between bathing solution and the solid drug moving controlled, the rate of dissolution of drug particles within the matrix must be faster that the diffusion rate of dissolved drug leaving matrix.

Following assumptions are made in retrieving the mathematical models are:

i. A pseudo steady state is maintained during drug release.

ii. The diameter of drug particles is less than the average distance of drug Diffusion through the matrix.

iii. The bathing solution provides sink conditions.

iv. The diffusion coefficient of drug in the matrix remains constant.

The next equation that describes the rate of release drugs dispersed in an inert matrix system has been derived by Higuchi.
**Figure 3.9:** Schematic representation of the physical model used for a planer slab matrix diffusion device.

The change in amount of drug released per unit area \( dM \) and change in the thickness of the zone of the matrix that has been depleted of the drug,

\[
dM/dh = C_0 dh - Cs/2 \quad \text{Equation 25}
\]

by Fick’s first law,

\[
dm = (DmCs/h) \, dt \quad \text{Equation 26}
\]

where,

\( Dm \) is diffusion coefficient in matrix if equation (25) & (26) are equated & solved for \( D \) that value of \( h \) is substituted back into the integrated form of equation (26) An equation for \( M \) is obtained.

\[
M = [Cs \, Dm \, (2C_0 - Cs) \, t]^{1/2} \quad \text{Equation 27}
\]

Similarly, a drug released from porous or granular matrix is described.

\[
M = [Ds \, Ca \, (\epsilon/\tau)(2C_0 - \epsilon Ca) \, t]^{1/2} \quad \text{Equation 28}
\]

Where,

\( \epsilon = \) Porosity of matrix

\( \tau = \) tortuosity.

\( Ca = \) Solubility of drug in release medium

\( Ds = \) diffusion coefficient of drug in release medium.
In this system drug is leached from matrix through channels or pores.
For purpose of data treatment equation (8) & (9) are reduced to
\[ M = Kt^{\frac{1}{2}} \]  
Equation 29

Where K is constant so, that plot amount of drug released verses square root of time should be linear if the release of drug from the matrix is diffusion controlled. The release rate of drug from such a device is not zero order, since if decreases with time but as previously mentioned, this may be clinically equivalent to constant drugs.

### 3.5.2 Dissolution sustained system

The drug present in such system may be the one:

i. Having high aqueous solubility and dissolution rate

ii. With inherently slow dissolution rate e.g. Griseofulvin and Digoxin

iii. That produces slow dissolving forms, when it comes in contact with GI fluids

Dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness. The rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant fluid diffusional boundary layer. The rate of dissolution (dm/dt) can be approximated by following equation:

\[ \frac{dm}{dt} = \frac{ADS}{h} \]  
Equation 30

Where,

A = Surface area of the dissolving particle or tablet
D = Diffusivity of the drug
S = Aqueous solubility of the drug
h = Thickness of the boundary layer

### 3.5.3 Methods using ion-exchange

It is based on formulation of drug resin complex formed when ionic solution is kept in contact with ionic resins. The drug from this complex gets exchanged in gastrointestinal tract and released with excess of Na⁺ and Cl⁻ present in gastrointestinal tract. This system generally
utilize resin compound of insoluble cross linked polymer. They contain salt forming function group in repeating position on a polymer chain.\textsuperscript{108}

### 3.5.4 Methods using osmotic pressure

A semipermeable membrane is placed around the tablet, particle or drug solution that allows transport of water into tablet with eventual pumping of drug solution out of the tablet through the small delivery aperture in tablet core. Two type of osmotic pressure controlled systems are:

- Type 1 contains an osmotic core with drug.
- Type 2 contains the drug in flexible bag with osmotic core surrounding

By optimizing formulation and processing factor, it is possible to develop osmotic system to deliver the drug of diverse nature at preprogrammed rate.\textsuperscript{83}

### 3.5.5 pH independent formulations

Most of the drug are either weak acid or weak base, the release from sustain release formulation is pH dependent. However, buffer such as salt of citric acid, amino acid, tartaric acid can be added to the formulation, to help to maintain to constant pH their by retarding pH independent drug release. A buffer sustain release formulation is prepared by mixing a basic or acidic drug one or more buffering agent, granulating with appropriate excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agent adjusts the fluid inside to suitable constant pH there by rendering a constant rate of drug release.\textsuperscript{109}

### 3.5.6 Altered density formulations

It is reasonable to expect that unless a delivery system remains in the vicinity of the absorption site until most, if not all of its drug contents is released, it would have limited utility. To this end, several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract.\textsuperscript{110}

**High density approach**

In this approach the density of the pellets must exceed that of normal stomach content and should therefore be at least 1-4gm/cm\textsuperscript{3}

**Low density approach**

Globular shells which have an apparent density lower than that of gastric fluid can be used as a carrier of drug for sustained release purpose.\textsuperscript{26}
3.6 Pharmacokinetics

3.6.1 Pharmacokinetic model

Drug movement within the body is a complex process. The major objective is, therefore, to develop a generalized and simple approach to describe, analyze and interpret data obtained during in vitro drug dissolution studies. This involves development of pharmacokinetic models which provide concise means of expressing mathematically or quantitatively the time course of drugs throughout the body and computation of pharmacokinetic parameters. Pharmacokinetic models are hypothetical structures that are used to describe the fate of a drug in a biological system following its administration. Drug movement within the body is a complex process. The major objective is therefore to develop a generalized and simple approach to describe, analyze and interpret the data obtained during in vivo drug disposition studies. This involves development of pharmacokinetic model which provide concise means of expressing mathematically or quantitatively, the time course of drug(s) throughout the body and compute meaningful pharmacokinetic model.

Pharmacokinetic models are useful in:

1. Characterizing the behaviour of drugs in patients
2. Predicting the concentration of drug in various body fluids with any dosage regimen.
3. Predicting the multiple dose concentration curves from single dose experiment.
4. Calculating the optimum dosage regimen for individual patients.
5. Evaluating the risk of toxicity with certain dosage regimen.
6. Correlating plasma drug concentration with pharmacologic response.
7. Evaluating the bioequivalence/ bioinequivalence between different formulations of the same drug.
8. Estimating the possible drug and/or metabolites(s) accumulation in the body.
9. Determining the influence of altered physiology / disease state on drug ADME.
10. Explaining drug interaction.

Mathematical explanation of a drug’s movement inside the body is a complicated process; hence pharmacokinetic models are devised for better understanding. The three different approaches to pharmacokinetic analysis of experimental data are as follows-

1. Compartmental modelling
2. Non-compartmental modelling
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3. Physiologic modelling

3.6.2 Compartment model:
Compartmental analysis is the traditional and most commonly used approach to pharmacokinetic characterization of a drug. Here, the body is considered as composed of several compartments that communicate reversibly with each other. If one considers every organ, tissue or body fluid that can get equilibrated with the drug as a compartment, infinite number of compartments can exist in the body and mathematical description of such a model will be too complex. Hence, tissues which are approximately similar in their drug distribution characteristics are pooled to form a kinetically homogeneous hypothetical compartment. Such a compartment, thus, is not a real physiologic or anatomic region but a fictive or virtual one, considered as a reflection of the biosystem and assumed to comprise of tissues having similar blood flow and drug affinity. The kinetics of most drugs can be described by a hypothetical model consisting of one, two or at the most, three functional compartments arranged either in series or parallel to each other. It is also assumed that the rate of drug movement between compartments (i.e. entry or exit) follow first order kinetics.\textsuperscript{24, 26}

One-compartment model
Following drug administration, the body is depicted as a kinetically homogeneous unit (see Figure 3.10). This assumes that the drug achieves instantaneous distribution throughout the body and that the drug equilibrates instantaneously between tissues. Thus the drug concentration–time profile shows a monophasic response (i.e. it is mono exponential). It is important to note that this does not imply that the drug concentration in plasma (Cp) is equal to the drug concentration in the tissues. However, changes in the plasma concentration quantitatively reflect changes in the tissues.

![Figure 3.10: One-compartment model. ka absorption rate constant, k elimination rate constant.](image)

\[ \text{Single component} \]

\[ k_a \quad \text{ka absorption rate constant, k elimination rate constant.} \]
Two-compartment model

The two-compartment model resolves the body into a central compartment and a peripheral compartment (see Figure 3.12). Although these compartments have no physiological or anatomical meaning, it is assumed that the central compartment comprises tissues that are highly perfused such as heart, lungs, kidneys, liver and brain. The peripheral compartment comprises less well-perfused tissues such as muscle, fat and skin. A two-compartment model assumes that, following drug administration into the central compartment, the drug distributes between that compartment and the peripheral compartment. However, the drug does not achieve instantaneous distribution, i.e. equilibration, between the two compartments. The
drug concentration–time profile shows a curve (Figure 3.13a), but the log drug concentration–time plot shows a biphasic response (Figure 3.13b) and can be used to distinguish whether a drug shows a one- or two-compartment model.

**Figure 3.12:** Two-compartment model.

Where,

- $k_{12}$, $k_{21}$ and $k$ are first-order rate constants:
- $k_{12}$ - rate of transfer from central to peripheral compartment;
- $k_{21}$ - rate of transfer from peripheral to central compartment;
- $k$ - rate of elimination from central compartment.
Figure 3.13: (a) Plasma concentration versus time profile of a drug showing a two compartment model. (b) Time profile of a two-compartment model showing log \( C_p \) versus time.

Figure 3.13 (b) shows a profile in which initially there is a rapid decline in the drug concentration owing to elimination from the central compartment and distribution to the peripheral compartment. Hence during this rapid initial phase the drug concentration will decline rapidly from the central compartment, rise to a maximum in the peripheral compartment, and then decline. After a time interval \( t \), distribution equilibrium is achieved between the central and peripheral compartments, and elimination of the drug is assumed to occur from the central compartment. As with the one compartment model, all the rate processes are described by first-order reactions. \(^{24, 26}\)

**Multicompartment model**

In this model the drug distributes into more than one compartment and the time profile shows more than one exponential. Each exponential on the concentration–time profile describes a compartment. For example, gentamicin can be described by a three-compartment model following a single IV dose (see Figure 3.14 b).
Figure 3.14: (a) Plasma concentration versus time profile of a drug showing multi-compartment model. (b) Time profile of a multi-compartment model showing log Cp versus time.

**Advantages of compartment modeling**

1. It gives a visual representation of various rate processes involved in drug disposition.
2. It shows how many rate constants are necessary to describe these processes.
3. It enables the pharmacokineticist to write different equations for each of the rate processes in order to describe drug-concentration changes in each compartment.
4. It is useful in predicting drug concentration-time profile in both normal pathologic conditions.
5. It is important in the development of dosage regimen.
Disadvantages of compartment modeling: 24, 26

1. The compartment and parameters bear no relationship with the physiologic functions or the anatomic structure of the species; several assumptions have to be facilitating data interpretation.
2. Extensive efforts are requires in the development of an exact model that predicts and describes correctly the ADME of a certain drug.
3. The model is based on curve fitting of plasma concentration with complex multi-exponential mathematical equations.
4. The model may vary within a study population.
5. The approach can be applied only to a specific drug under study.
6. The drug behavior within the body may fit different compartmental models depending upon the routes of administration.
7. Difficulties generally arise when using models to interpret the differences between results from human and animal experiments.

3.7 Hypertension

Hypertension is an important public health challenge in both economically developing and developed countries. It is becoming an increasingly common health problem because of increasing longevity and prevalence of contributing factors such as obesity, physical inactivity and an unhealthy diet. The current prevalence of hypertension in many developing countries, particularly in urban societies, is reported to be already as high as is seen in developed countries. The prevalence of hypertension is expected to increase even further in the absence of broad and effective preventive measures. 111 Despite the availability of a wide range of antihypertensive drugs, hypertension and its complications are still important causes of adult morbidity and mortality. More than 50% of treated hypertensive patients have a blood pressure level greater than 140/90 mm Hg (uncontrolled hypertension). 112

In India, hypertension is the leading NCD risk and estimated to be attributable for nearly 10 per cent of all deaths. Adult hypertension prevalence has risen dramatically over the past three decades from 5 per cent to between 20-40 per cent in urban areas and 12-17 per cent in rural areas. The number of hypertensive individuals is anticipated to nearly double from 118 million in 2000 to 213 million by 2025. 113
Blood pressure is the force of the blood against the walls of the arteries. Blood pressure rises and falls throughout the day. When the blood pressure stays elevated over time, hypertension develops. A systolic pressure less than 120 mm Hg and a diastolic blood pressure of less than 80 mm Hg (120/80) are considered optimal. Hypertension is usually defined as a systolic pressure above 140 mm Hg and a diastolic pressure above 90 mm Hg (figure 3.15). Most cases of hypertension have no known cause. When there is no known cause of hypertension, the term essential hypertension is used. Essential hypertension has been linked to certain risk factors, such as diet and lifestyle.  

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>SYSTOLIC* (in mm Hg)</th>
<th>DIASTOLIC* (in mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>less than 120</td>
<td>less than 80</td>
</tr>
<tr>
<td>Normal</td>
<td>less than 130</td>
<td>and</td>
</tr>
<tr>
<td>High-normal</td>
<td>130–139</td>
<td>and 85–89</td>
</tr>
</tbody>
</table>

- **HYPERTENSION**
  - Stage 1: 140–159 or 90–99
  - Stage 2: 160–179 or 100–109
  - Stage 3: 180 or higher or 110 or higher

**Figure 3.15:** Blood pressure levels for adults

Once essential hypertension develops, management of this disorder becomes a lifetime task. When a direct cause of the hypertension can be identified, the condition is described as secondary hypertension. Among the known causes of secondary hypertension, kidney disease ranks first, with tumors or other abnormalities of the adrenal glands following. In malignant hypertension the diastolic pressure usually exceeds 130 mm Hg taking care of the medical condition causing the hypertension results in the patient regaining a normal blood pressure.

Office blood pressure (BP) is typically used as the primary tool for diagnosis of hypertension, for assessment of severity of hypertension in clinical practice, and in current guidelines. However, the circadian rhythm of BP, in particular the rapid surge to peak values shortly after waking, may contribute to cardiovascular events independently of the office BP. Circumstantial evidence for this is provided by a simultaneous peak in such cardiovascular events as myocardial infarction and stroke. Because BP may vary dramatically among individuals, office and even self-measurement of BP may miss patients with dangerously elevated BPs on arising, a phenomenon now recognized as “masked morning hypertension”. In current clinical practice, no adequate control of hypertension has been achieved; morning BP levels before dosing are increased in
more than half of hypertensive patients on antihypertensive therapy, even if they are under relatively good BP control at clinics (figure 3.16).\textsuperscript{116} Thus, morning hypertension is a challenge to the current clinical practice of hypertension.

![Figure 3.16: Abnormal diurnal variation in blood pressure in two types of morning (predominant) hypertension.]

### 3.7.1 Treatment of hypertension

Many antihypertensive drugs lower the blood pressure by dilating or increasing the size of the arterial blood vessels (vasodilatation). Vasodilatation creates an increase in the lumen (the space or opening within an artery) of the arterial blood vessels, which in turn increases the amount of space available for the blood to circulate. Because blood volume (the amount of blood) remains relatively constant, an increase in the space in which the blood circulates (ie, the blood vessels) lowers the pressure of the fluid (measured as blood pressure) in the blood vessels. Although the method by which antihypertensive drugs dilate blood vessels varies, the result remains basically the same. Antihypertensive drugs that have vasodilating activity include:

- Adrenergic blocking drugs
- Antiadrenergic blocking drugs
- Calcium channel blocking drugs
- Vasodilating drugs

Another type of antihypertensive drug is the **diuretic**. The mechanism by which the diuretics reduce elevated blood pressure is unknown, but it is thought to be based, in part, on their ability to increase the excretion of sodium from the body.

### 3.7.2 ACE inhibitors

The Joint National Committee (JNC) VII guidelines have placed ACE inhibitors as one of the first line drugs for hypertension. Patients belonging to stage-I hypertension (systolic BP 140-159
or diastolic BP 90-99 mm of Hg) may be offered ACE inhibitors.\textsuperscript{117} The Antihypertensive and Lipid Lowering Therapy in Heart Attack Trial (ALLHAT) trial also supports the use of ACE inhibitors as initial therapy alone or in combination with thiazide diuretics with overall response of 50\% to 70\% in mild to moderate disease.\textsuperscript{118} Cilazapril, enalapril, fosinopril, lisinopril, perindopril, trandolapril were all confirmed by 24-hour blood pressure monitoring as effective once daily dosage regimens. The mechanism of action of the \textbf{ACE inhibitors} is believed that to prevent (or inhibit) the activity of angiotensin-converting enzyme, which converts angiotensin I to angiotensin II, a powerful vasoconstrictor. Both angiotensin I and ACE normally are manufactured by the body and are called endogenous substances. The vasoconstricting activity of angiotensin II stimulates the secretion of the endogenous hormone aldosterone by the adrenal cortex. Aldosterone promotes the retention of sodium and water, which may contribute to a rise in blood pressure. By preventing the conversion of angiotensin I to angiotensin II, this chain of events is interrupted, sodium and water are not retained, and the blood pressure decreases. \textbf{The angiotensin II receptor antagonists} act to block the vasoconstrictor and aldosterone effects of angiotensin II at various receptor sites, resulting in a lowering of the blood pressure.\textsuperscript{118}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{angiotensin_diagram.png}
\caption{Activity of angiotensinogen in relation to increased blood pressure. (Adopted from Chobanian AV)}
\end{figure}
3.7.3 Treatment of morning hypertension

Since not only blood pressure but also various other cardiovascular risk factors are aggravated in the early morning, antihypertensive treatment for morning hypertension is likely to offer greater benefit in preventing cardiovascular events. Hypertensive patients on standard antihypertensive treatment often have morning hypertension of the nocturnal hypertension type because the effect of most antihypertensive drugs does not last for 24 hours. Antihypertensive treatment targeting morning hypertension combined with standard treatment may enable more effective prevention of cardiovascular events. Step in the treatment of morning hypertension in clinical practice include:

1. Self-monitor early morning BP at home
2. Patients with prominent morning hypertension in whom the difference between morning and evening systolic BP is more than 15–20 mmHg, it is important to determine by ambulatory blood pressure monitoring whether the hypertension is of the nocturnal-hypertension type or the morning-surge type.
3. Specifically, it is recommended to combine non-specific and specific antihypertensive treatments to control morning BP levels to achieve an average of morning (before dosing) and evening (at bedtime) BP of under 135/85 mmHg and a morning-evening pressure difference of less than 15–20 mmHg.
4. A long-acting antihypertensive drug whose effect lasts for 24 hours initially is used as non-specific treatment. (long-acting antihypertensive drugs twice-daily, morning and evening, doses should also be considered), diuretics.
5. Specific treatment includes inhibitors of the sympathetic nervous system and rennin angiotensin system, which show aggravation in the early morning. (α-blockers used at bedtime Renin-angiotensin-aldosterone system inhibitors (dosing at bedtime should also be considered) Heart rate-controlling calcium antagonists (cilnidipine, azelnidipine, diltiazem).

Since the renin-angiotensin system is augmented in the early morning, treatment with angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists can be considered specific treatment. In a study, controlled-onset extended release (COER) verapamil-inhibitor led to greater reductions in morning heart rate, the rate-pressure product, and the rate-of-rise of BP compared with a losartan. Reductions in mean 24-hour BP were greater in patients treated with
COER-verapamil compared with placebo and ARB, and similar to reductions in patients treated with an enalapril.\textsuperscript{121}

Enalapril maleate is a medicine which blocks the action of a chemical in the body. It is used to lower blood pressure. It can also help to reduce the amount of work the heart needs to do so it can also be used to help relieve the symptoms of heart failure.

Further Enalapril Maleate was selected for the study based on the market research. Given below are the specific points considered for selecting the Enalapril Maleate.

1. Market need
2. BCS Class II (high permeability, Low Solubility)
3. Patient compliance
4. Improved efficacy (sustained therapeutic levels for longer period)
5. Pharmaco economics (higher cost benefits)

### 3.7.4 Clinical pharmacology – enalapril maleate

Enalapril Maleate is the maleate salt of enalapril, the ethyl ester of a long-acting angiotensin converting enzyme inhibitor, enalaprilat. Enalapril maleate is chemically described as (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (Z)-2-butenedioate salt (1:1). Its empirical formula is $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$, and its structural formula is:

![Structure of Enalapril Maleate](image)

**Figure 3.18:** Structure of Enalapril Maleate

Enalapril maleate is a white to off-white, crystalline powder with a molecular weight of 492.53. It is sparingly soluble in water, soluble in ethanol, and freely soluble in methanol. Enalapril is a pro-drug; following oral administration, it is bioactivated by hydrolysis of the ethyl ester to enalaprilat, which is the active angiotensin converting enzyme inhibitor.
3.7.5 Mechanism of action

Enalapril, after hydrolysis to enalaprilat, inhibits angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl-dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. The beneficial effects of enalapril in hypertension and heart failure appear to result primarily from suppression of the rennin angiotensin-aldosterone system. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. Although the latter decrease is small, it results in small increases of serum potassium. In hypertensive patients treated with enalapril alone for up to 48 weeks, mean increases in serum potassium of approximately 0.2 mEq/L were observed. In patients treated with enalapril plus a thiazide diuretic, there was essentially no change in serum potassium. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of enalapril remains to be elucidated. While the mechanism through which enalapril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, enalapril is antihypertensive even in patients with low-renin hypertension. Although enalapril was antihypertensive in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to enalapril monotherapy than non-black patients.

3.7.6 Pharmacokinetics and metabolism

Following oral administration of enalapril maleate, peak serum concentrations of enalapril occur within about one hour. Based on urinary recovery, the extent of absorption of enalapril is approximately 60 percent. Enalapril absorption is not influenced by the presence of food in the gastrointestinal tract. Following absorption, enalapril is hydrolyzed to enalaprilat, which is a more potent angiotensin converting enzyme inhibitor than enalapril; enalaprilat is poorly absorbed when administered orally. Peak serum concentrations of enalaprilat occur three to four hours after an oral dose of enalapril maleate. Excretion of enalapril is primarily renal. Approximately 94 percent of the dose is recovered in the urine and feces as enalaprilat or enalapril. The principal components in urine are enalaprilat, accounting for about 40 percent of
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The serum concentration profile of enalaprilat exhibits a prolonged terminal phase, apparently representing a small fraction of the administered dose that has been bound to ACE. The amount bound does not increase with dose, indicating a saturable site of binding. The effective half-life for accumulation of enalaprilat following multiple doses of enalapril maleate is 11 hours.¹²⁵

The disposition of enalapril and enalaprilat in patients with renal insufficiency is similar to that in patients with normal renal function until the glomerular filtration rate is 30 mL/min or less. With glomerular filtration rate ≤30 mL/min, peak and trough enalaprilat levels increase, time to peak concentration increases and time to steady state may be delayed. The effective half-life of enalaprilat following multiple doses of enalapril maleate is prolonged at this level of renal insufficiency. Enalaprilat is dialyzable at the rate of 62 mL/min.

Studies in dogs indicate that enalapril crosses the blood-brain barrier poorly, if at all; enalaprilat does not enter the brain. Multiple doses of enalapril maleate in rats do not result in accumulation in any tissues. Milk of lactating rats contains radioactivity following administration of 14C-enalapril maleate. Radioactivity was found to cross the placenta following administration of labeled drug to pregnant hamsters.¹²⁶

3.7.7 Indication

1. Hypertension

Enalapril maleate is indicated for the treatment of hypertension. Enalapril maleate is effective alone or in combination with other antihypertensive agents, especially thiazide-type diuretics. The blood pressure lowering effects of enalapril maleate and thiazides are approximately additive.¹²⁷

2. Heart Failure

Enalapril maleate is indicated for the treatment of symptomatic congestive heart failure, usually in combination with diuretics and digitalis. In these patients enalapril maleate improves symptoms, increases survival, and decreases the frequency of hospitalization symptomatic.¹²⁸
3. **Left Ventricular Dysfunction**

In clinically stable asymptomatic patients with left ventricular dysfunction (ejection fraction < 35 percent), enalapril maleate decreases the rate of development of overt heart failure and decreases the incidence of hospitalization for heart failure.\textsuperscript{129}

**Absorption, Distribution, Metabolism and Excretion**

Following oral administration of Enalapril, peak serum concentrations of Enalapril occur within about one hour. Based on urinary recovery, the extent of absorption of Enalapril is approximately 60 percent. Enalapril absorption is not influenced by the presence of food in the gastrointestinal tract. Following absorption, Enalapril is hydrolyzed to Enalaprilat, which is a more potent angiotensin converting enzyme inhibitor than Enalapril; Enalaprilat is poorly absorbed when administered orally. Peak serum concentrations of Enalaprilat occur three to four hours after an oral dose of Enalapril maleate. Excretion of Enalapril is primarily renal. Approximately 94 percent of the dose is recovered in the urine and feces as Enalaprilat or Enalapril. The principal components in urine are Enalaprilat, accounting for about 40 percent of the dose, and intact Enalapril. There is no evidence of metabolites of Enalapril, other than Enalaprilat.

The serum concentration profile of Enalaprilat exhibits a prolonged terminal phase, apparently representing a small fraction of the administered dose that has been bound to ACE. The amount bound does not increase with dose, indicating a saturable site of binding. The effective half-life for accumulation of Enalaprilat following multiple doses of Enalapril maleate is 11 hours.

**3.7.8 Adverse effects**

**Body as a Whole**: Anaphylactoid reactions.

**Cardiovascular**: Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients; pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; palpitation.

**Digestive**: Ileus, pancreatitis, hepatitis (hepatocellular (proven on rechallenge) or cholestatic jaundice), melena, anorexia, dyspepsia, constipation, glossitis, stomatitis, dry mouth.

**Musculoskeletal**: Muscle cramps.
Nervous/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, peripheral neuropathy (e.g., paresthesia, dysesthesia).

Respiratory: Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection, pulmonary infiltrates.

Skin: Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, Pruritus, alopecia, flushing, diaphoresis, photosensitivity.

Special Senses: Blurred vision, taste alteration, anosmia, tinnitus, conjunctivitis, dry eyes, tearing.

Urogenital: Renal failure, oliguria, renal dysfunction, flank pain, gynecomastia, impotence.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.