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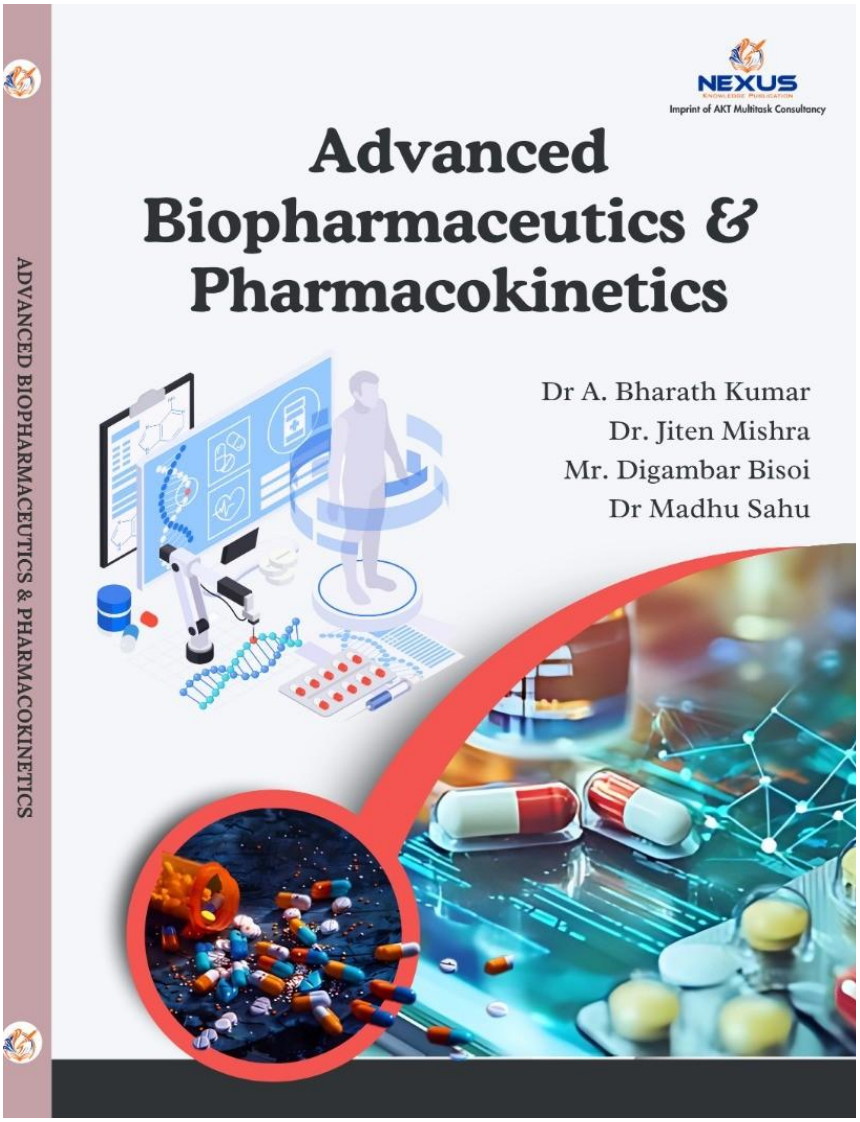

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Chapter- 6

PHARMACOKINETICS: BASIC CONSIDERATIONS

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The study of drug ADME (absorption, distribution, metabolism and excretion) constitutes pharmacokinetics in pharmacology. The knowledge of pharmacokinetics enables healthcare professionals to maximize drug treatment efficiency and enhance medication delivery together with reducing drug-induced side effects. This section tackles basic pharmacokinetic concepts by examining drug body-related models especially compartment models alongside drug absorption models. The chapter explains non-linear pharmacokinetics which happens when particular medications produce inconsistent relationships between dosing and drug levels compared to linear pharmacokinetics [1]. This chapter explains drug body movements through mathematical frameworks that integrate Michaelis-Menten equations to gain complete understanding of crucial movement mechanisms for therapeutic agent development. These concepts serve a vital role in drug interaction forecasting and developing correct dosing schedules and advancing treatment results for patients.

6.1 PHARMACOKINETIC MODELS

Mathematical models named pharmacokinetic models provide descriptions of drug behavior while following the steps of drug absorption and distribution along with metabolism and excretion (ADME) throughout the human body [2]. The drug development process and medical therapy heavily rely on these mathematical tools to conduct time-based drug behavior models. The models help doctors forecast drug levels at different stages following administration because this information guides suitable dose planning. Among pharmacokinetic models two main types exist as compartment models including the one-compartment model together with the multi-compartment model.

6.1.1 One-Compartment Model

The one-compartment model stands as an elemental pharmacokinetic model which describes drug behavior in the body. The one-compartment model streamlines drug distribution along with elimination because it views the body as a uniform entire container. When a drug enters blood circulation it distributes homogeneously throughout the body until equilibrium occurs quickly. Numerous drugs which follow uncomplicated pharmacokinetics demonstrate such assumptive characteristics.

- **Drug Absorption and Distribution**

The one-compartment model presents drug absorption processes in a simple manner. A drug reaches bloodstream through oral or parenteral pathways including intravenous, intramuscular and subcutaneous injections. All tissues in the body receive the drug at an equal rate according

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to the standard model. Within the one-compartment framework scientists eliminate the need for tissues and organs distinction since they adopt the premise of drug distribution uniformity throughout all body tissues.

Under this scenario the drug becomes equally available to all body parts without delay after entering bloodstream. The model has value for drugs which show low tissue binding properties or experience limited metabolic processes within organs including the liver and kidneys. Drugs provided through intravenous routes adopt this model since they bypass gastrointestinal tract absorption and immediately access the bloodstream.

- **Drug Elimination and First-Order Kinetics**

The movement of drugs out of bloodstream remains the core principle in one-compartment model analysis. The drug elimination method in this model activates first-order kinetics because drug concentration levels in the bloodstream directly influence the elimination speed. The declining amount of drug concentration in the bloodstream results in an equivalent reduction of elimination rate. The drug concentration rate decreases predictably in an exponential fashion until reaching a mathematical value that represents the half-life.

The pharmacokinetic pattern of first-order kinetics applies to most drugs that remove themselves by passive elimination mechanisms (such as glomerular filtration in kidneys or liver metabolic pathways) [3]. Medical professionals determine drug half-life values for straightforward calculation of drug duration and body concentration stabilization times. The one-compartment model enables direct estimation of drug clearance which represents plasma volume removal capability and volume of distribution which indicates drug body placement volume.

- **Application of the One-Compartment Model**

The one-compartment model provides excellent predictions for medications that quickly spread throughout the system and have basic elimination processes. The approach works effectively for modeling pharmacokinetics in intravenous (IV) medications since these drugs enter directly into blood circulation. These drugs enter the bloodstream directly without absorption complexities so they are assumed to spread evenly through the whole body space and their elimination depends on blood concentration levels.

The model effectively describes drugs that experience minimal plasma protein or tissue binding since these factors hinder drug distribution and elimination processes. Drugs with fast absorption and elimination profiles such as analgesics together with certain antibiotics can

achieve appropriate description through the one-compartment model. The one-compartment model enables fast calculation of pharmacokinetic parameters including half-life measurement as well as clearance determination and estimation of volume of distribution for drugs that fit this model's characteristics.

- **Limitations of the One-Compartment Model**

The one-compartment model although commonly used aids many drug investigations lacks accuracy given its reduction of complex drug distribution and metabolism pathways. This model fails to interpret drugs which display complex distribution behavior since they first focus in one body region until they achieve full systemic diffusion. McIntrlipid drugs tend to settle into fat tissue while hydropod drugs stay predominantly in plasma and water-based body components [4].

The model fails to examine thorough chemical transformations of drugs occurring in tissue and organ cells particularly those found in the liver and kidneys. The pharmacokinetic predictions for drugs with extended distribution characteristics and multiple organ excretion mechanisms need sophisticated multiple-compartment models for accurate simulation results.

6.1.2 Multi-Compartment Model

Drug kinetics receive enhanced understanding by utilizing the multi-compartment model because it represents drug non-uniform body distribution dynamics. The multi-compartment model surpasses the one-compartment model because it segments the human body into separate areas according to drug movement between regions. Drugs distribute through the body into various compartments which get split into central parts and peripheral areas.

- **Central Compartment**

The bloodstream with its well-perfused organs makes up the central part of the model. Among these organs include heart, liver, lungs and kidneys. The drug absorbs and distributes initially throughout this area following the administration process. The drug quickly reaches these organs because they obtain a major share of blood flow in the body. IV drug administration produces rapid distribution in the central compartment as a step toward reaching other body regions.

- **Peripheral Compartments**

Less perfused tissues along with organs that absorb drugs at a slower pace form the peripheral compartments. The drug distribution pathway consists primarily of muscles together with fat tissues and additional tissues with low blood supply. The peripheral distribution rate of

medications depends on drug physical attributes like their binding with proteins together with their lipophilicity status and molecular dimensions. Drugs with lipophilic properties collect mainly in fat tissues yet drugs with hydrophilic properties stay predominantly within blood and highly water-rich tissues [5]. The different ways drugs spread throughout the body results in the multi-compartment model serving drugs with complicated kinetic characteristics.

➢ **Drug Movement Between Compartments**

The multi-compartment model depends on rate constants for drug movement between compartments to determine how quickly a drug moves from one compartment to another. Absorption happens through the central compartment but additional drug reservoirs are present as peripheral compartments where distribution and binding processes occur. Drug rate constants evolve from the drug's temporal conduct which indicates its transport mechanisms and its metabolic procedures alongside distribution outcomes.

- **Distribution Phase:** The drug follows specific rate constants to move from the central compartment to peripheral compartments after medication administration. During drug distribution the body first reaches well-perfused organs rapidly then distributes more slowly to less perfused areas.
- **Elimination Phase:** The clearance process of the drug begins by following rate constants which control the departure from each separate compartment. Most elimination occurs within the central compartment before other parts of the body because the drugs within this zone are closest to tissue structures that perform the elimination processes.

➢ **Types of Multi-Compartment Models**

The complexity of multi-compartment models depends on the number of body compartments used for representation. The standard format of these models divides into two- or three-compartment systems while additional complexity increases through additional compartments under specific conditions.

- **Two-Compartment Model:** The two-compartment model distinguishes between the central body section and a sole peripheral section. The model demonstrates that drugs spread rapidly through the central compartment before entering independently to one tissue or organ group. Many lipophilic drugs which healthcare professionals use to treat cardiovascular diseases require analysis through a two-compartment model structure.

- **Three-Compartment Model:** Drugs that feature intricate distribution patterns require a three-compartment system. This distribution model divides drugs between three compartments representing tissues whose blood flow levels differ. Highly complex drugs such as anticancer agents require this model to study their distribution and metabolism changes during the time period.

➢ **Applications of Multi-Compartment Models**

The multi-compartment model serves as an important tool for analyzing drug pharmacokinetics when the pharmacological effects do not meet one-compartment model assumptions. When lipophilic drugs accumulate within fatty tissues after administration their distribution along with elimination duration becomes longer therefore requiring multi-compartment modeling to achieve proper prediction results [6].

In multi-compartment modeling protein binding strongly influences drug behavior because drugs which strongly adhere to plasma proteins spend more time in the central compartment which affects both volume of distribution (Vd) and half-life (t1/2).

Anti-cancer medications need multi-compartment distribution models for precise predictions because they distribute quickly into major blood-supplied tissues and slowly reach tumors and stores in fat. The models assist medical professionals to predict drug behavior patterns over time while they create individualized treatment plans using specific pharmacokinetic characteristics of patients.

➢ **Advantages of Multi-Compartment Models**

Drug ADME processes receive better understanding through multi-compartment models which go beyond initial compartment systems. The prediction of drug behavior in various tissues and organs remains accurate through these models for improved drug dosing plans and monitoring. Multi-compartment models function as tools for both simulating different dosing protocols such as single dose versus repetitive administrations as well as analyzing route specific drug effects .

The multi-compartment model helps therapeutic management by enhancing pharmacokinetic understanding of complex drugs which achieves optimal tissue drug concentrations coupled with minimal side effect exposure. Pharmaceutical manufacturers consider these models essential operational instruments for creating medication formats and deciding correct treatment intervals.

- **Limitations of Multi-Compartment Models**

The multiple-compartment system presents unresolved constraints which affect their utilization. The modeling approach needs detailed parameters and lengthy data collection activities for determining pharmacokinetic parameter definitions including rate constants. The models operate under the assumption that drug distribution and elimination activities maintain constant rates while several evidence suggests these conditions may not hold true especially when patient's exhibit altered physiological characteristics (e.g., liver or kidney disease).

6.1.3 Application of Compartment Models in Drug Development

Pharmacokinetic field depends on compartment models which serve as scientific systems to calculate drug ADME patterns including absorption distribution metabolism and elimination. Drug development making use of compartment models occurs throughout all stages from preclinical screening to clinical trial phases and continues into post-release medication control [7]. The models developed by pharmaceutical scientists assist in predicting drug performance within human bodies while helping to optimize treatment schedules to ensure efficient drug outcome across different circumstances.

- **Predicting Plasma Concentration Profiles**

Compartment models achieve their most vital function when they estimate the evolution of plasma drug concentrations during time intervals. Through modeling drug distribution and elimination paths compartment models generate predictions of drug bloodstream concentrations following drug administration. Plasma concentration profiles serve as essential data for determining the most suitable drug dosage and moment of drug delivery. Maintaining plasma drug levels within therapeutic boundaries remains essential because it enables proper drug effectiveness without exposing patients to toxic side effects [8]. Compartment models provide simulation capabilities for generating drug concentration profiles which aid researchers to determine appropriate drug administration schedules.

- **Simulating Dosing Regimens**

Compartment models efficiently simulate various drug dosing plans because their application is essential for optimizing drug effectiveness. The efficacy of drugs solely depends on keeping their plasma concentrations within a particular therapeutic range. The modeling process works to determine optimal medication strategies by letting researchers modify medicine amounts together with treatment frequency and distribution ways for reaching target drug levels.

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Releasing models determine sustained-release formulation drug concentration behavior to prevent peak-related adverse effects during sustained drug maintenance.

The evaluation of drug accumulation alongside multiple doses within the system becomes possible through compartment models. Researchers conduct simulations to find drug-related issues through which accumulation might occur or sub-therapeutic drug levels might develop. Failure to achieve this capacity would result in inferior clinical trials which produce both less safe and less effective treatments.

- **Drug Interactions and Physiological Variations**

Pharmacokinetic research depends largely on compartment models to determine how drugs influence one another inside human bodies. Multiple drugs that interact with each other modify absorption and distribution and metabolism and elimination of treatments thus affecting their therapeutic effects and safe outcomes [9]. Research models based on compartment principle allow scientists to model the combined pharmacokinetic behaviors of drugs provided together. Prediction of possible adverse drug combinations and clinical trial design improvement for multi-drug administration become possible through these systems.

The evaluation of drug pharmacokinetics benefits from compartment models when researchers want to measure physiological factors including age and disease states along with genetic variations. Patients with liver or kidney dysfunction will show slower drug elimination because their metabolism and excretion processes are impaired. The drug distribution among elderly patients changes due to body composition and blood flow modifications thus requiring health professionals to adjust their dosage amounts. Compartment models enable scientist to predict drug behavior across patient populations with different physiological characteristics while developing treatment strategies for both security and effectiveness levels.

- **Refining Drug Development through Simulation**

Primary drug development stage failure risks decrease significantly through silico simulation operations that test different clinical scenarios before actual clinical trials. During early preclinical phases compartment models enable researchers to evaluate drug candidate pharmacokinetics for deciding clinical development continuation. Researchers determine whether to continue investment into clinical trials or transition to drug formulation modifications and alternative compound validation based on suboptimal bioavailability alongside unfavourable drug elimination profiles in the model.

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Compartment models support researchers as they adjust dosage levels and make respective dose modifications based on observed clinical data throughout trials. The model allows adjustments when clinical data indicates plasma drug values differ from predictions thus enabling simulation of optimal drug formulation or scheduling variations.

- **Long-Term Post-Market Applications**

Compartment models continue to serve an essential role throughout drug market availability by facilitating long-term medication use understanding. Compartment models serve as predictive instruments to evaluate expansions of new patient populations using a medication and emerging drug interaction and adverse effect knowledge. These models help healthcare providers evaluate how long-term drug usage interacts with patient condition changes along with disease progression and potential new medication introductions to affect drug pharmacokinetics. The models help establish if drug formulations plus dosing recommendations need adjustments to preserve patient safety and drug performance throughout time.

6.2 DRUG ABSORPTION MODELS

Through pharmacokinetic processes drug absorption establishes the movement of drugs from their administration site until they reach the systemic circulation [10]. The creation of effective drug formulations depends on drug absorption knowledge and simulation tools since these elements determine therapeutic outcomes and drug availability levels. Physicochemical properties of drugs combined with gastrointestinal conditions and absorption location factors determine how models predict drug absorption rates and amounts.

6.2.1 Intravenous Bolus and Infusion Models

Medicinal drugs administered through intravenous (IV) injection or infusion represent a straightforward direct delivery method to the bloodstream. This delivery approach provides drug substances directly to bloodstream circulation instead of using absorption mechanisms available for oral administration or other extravascular routes. A single rapid drug injection triggers the IV bolus model which describes drug distribution as well as drug elimination processes from the bloodstream.

- **Intravenous Bolus**:

A drug given through an IV bolus immediately reaches the blood circulation before spreading throughout the entire body system. Such drugs follow one-compartment kinetic modeling to represent their body-wide instant distribution. Drug removal rate follows first-order kinetics

which produces an exponential decrease of drug concentration throughout time. A drug given as an IV bolus shows single-exponential decay in its concentration-time profile and the elimination rate constant serves as the key element for understanding drug behavior.

- **Intravenous Infusion**:

Infusion through a vein requires a drug to be gradually delivered for an established time. The bloodstream reaches a constant drug concentration level as the drug concentration builds up steadily until reaching it. The model consists of two distinct periods: when drug concentration expands during the uptake phase along with the maintenance phase in which drug administration matches elimination rates. The therapeutic drug concentration during steady-state can be mathematically determined by the infusion speed alongside the clearance rate and volume distribution of the drug. The model works best for drugs such as chemotherapy agents and anesthetics which require constant therapeutic drug levels.

The drug behavior analysis begins with IV bolus and infusion models since they remove additional complexities that appear when drugs absorb through other routes. The models find limited use in drugs which are administered extravascularly because they do not include an absorption calculation model which depends on factors including formulation along with the injection site.

6.2.2 Extra-Vascular Absorption Models

Most drug treatments find their administration path as extravascular approaches that include oral, transdermal, and subcutaneous administration [11]. The drug needs to pass biological membranes and tissues before reaching systemic circulation during these cases. Drug absorption processes depend on various controlling factors that consist of the pharmaceutical compound's physical and chemical structure together with the preparation structure and state of the gastrointestinal area and physiological effects like pH and blood circulation levels.

- **Oral Absorption**:

The most frequently used method to deliver drugs systemically is through oral routes. The drug needs gastrointestinal fluid dissolving before it can pass through intestinal membranes to reach bloodstream circulation. Drug absorption follows membrane transport which occurs after dissolution while also requiring passage through the blood-brain barrier when needed. The drug absorption process through the gastrointestinal tract is analyzed with first-order models or Michaelis-Menten models based on the drug concentration levels and saturation at the absorption site. During first-order absorption the body readily absorbs a fixed portion of

medication during specific time intervals yet Michaelis-Menten kinetics show the absorption rate decreases at drug concentrations that reach saturation.

- **Gastric Emptying and Intestinal Transit**:

The most frequently used method to deliver drugs systemically is through oral routes. The drug needs gastrointestinal fluid dissolving before it can pass through intestinal membranes to reach bloodstream circulation. Drug absorption follows membrane transport which occurs after dissolution while also requiring passage through the blood-brain barrier when needed. The drug absorption process through the gastrointestinal tract is analyzed with first-order models or Michaelis-Menten models based on the drug concentration levels and saturation at the absorption site. During first-order absorption the body readily absorbs a fixed portion of medication during specific time intervals yet Michaelis-Menten kinetics show the absorption rate decreases at drug concentrations that reach saturation.

- **Bioavailability**:

One essential variable in oral absorption models is bioavailability that defines the amount of administered dose which becomes biologically active within systemic circulation. Systemic circulation bioavailability depends on drug metabolism through the liver during first-pass effect together with drug solubility and membrane permeability leading to gastrointestinal transit. A drug's bioavailability stands influenced by its solubility and dissolution rate together with permeability (which fits the Biopharmaceutics Classification System standards).

6 Non-Oral Extravascular Absorption

Drugs injected into subcutaneous or intramuscular tissues avoid first-pass metabolism while they absorb into the bloodstream from these external locations. The absorption models represent the time-dependent drug release that happens from the injection site leading to drug entry within the bloodstream.

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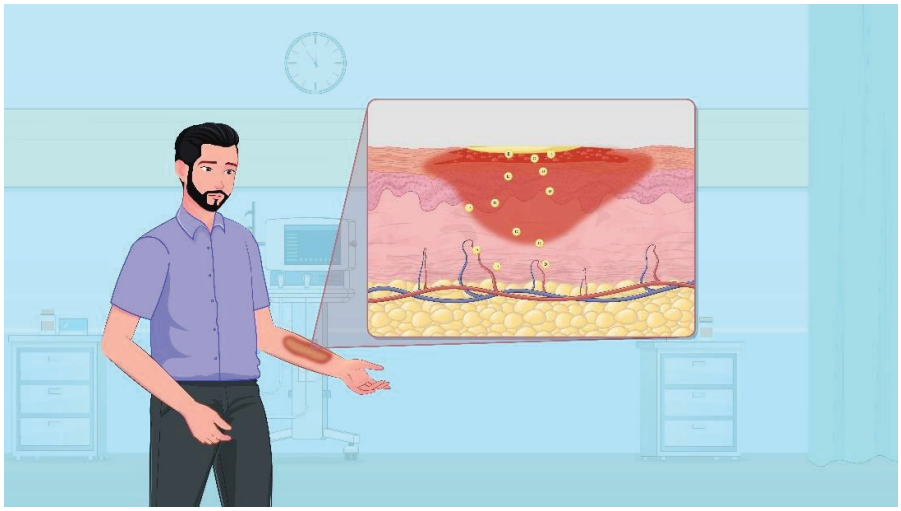

Figure 1: Non-Oral Extravascular Drug Absorption Routes

These models include factors that evaluate tissue permeability together with drug diffusion and blood flow rate to the absorption site.

6.2.3 Factors Affecting Absorption

Several physiological and formulation-related factors can influence drug absorption. These include:

- **Physicochemical Properties**: The drug must be both water-soluble and permeable to enable proper absorption [12]. The absorption of drugs is hindered by insoluble drugs that dissolve at a slow rate and by drugs with high lipid distribution properties that have trouble crossing watery membranes such as the stomach lining.
- **Formulation Characteristics**: The absorption speed of a drug depends heavily on its substance form among tablets capsules solutions or sustained-release formulations. Drugs using specific excipients which improve drug dissolution or permeation like surfactants might enhance their absorption speed.
- **Gastric and Intestinal pH**: A drug's solubility along with absorption depends significantly on the stomach and intestinal pH. The drug dissolution and absorption profiles undergo modifications due to changing conditions between stomach acidity and small intestinal neutrality or slight basicity.
- **Food and Other Drugs**: Food in the stomach changes both stomach emptying efficiency and acid base levels which affects how drugs dissolve and absorb into the body. Certain foods and drug interactions modify both medication absorption rates as well as drug-drug interactions influence these rates.

6.2.4 Application of Absorption Models in Drug Development

The early drug development process counts on absorption models for formulation optimization together with human pharmacokinetic predictions. The human body behavior of different drug formulations can be predicted through the use of in vitro-in vivo correlation (IVIVC) and absorption models thus helping scientists make better formulation decisions. Research models assist scientists in developing optimal drug delivery methods that minimize variability through the identification of effective pathways for drug concentration delivery within desired time parameters. The design of clinical trials depends crucially on absorption models for their development. Researchers utilize absorption simulation to predict optimal dosing regimens as well as specific drug adjustments needed for distinct population groups including patients with gastrointestinal disorders and children and elderly patients. The predictive mathematical systems used in drug development help reduce clinical trial failures by generating new therapeutic approaches that target individual needs.

6.3 NON-LINEAR PHARMACOKINETICS

The pharmacokinetic parameters which include drug absorption distribution metabolism and excretion do not show proportional changes in response to variations of drug dose or concentration in non-linear pharmacokinetic scenarios [13]. The pharmacokinetic behavior of a drug deviates from linear conditions when non-linear pharmacokinetics emerges because doubling the dose fails to double drug concentration in plasma. Drug absorption as well as distribution and metabolization processes tend to demonstrate non-linearity which produces unexpected therapeutic outcomes and makes drug development more complex.

Higher drug concentrations create saturation conditions that affect pharmacokinetics through activities of metabolic pathways and transport mechanisms and receptor binding sites. Raising drug doses after saturation points in the pathways causes the plasma concentration and effects to stop increasing proportionally. Accurate drug predictions at different dosages depend on understanding non-linear pharmacokinetics because it ensures safe therapeutic effects and minimizes toxicity levels. Non-linear pharmacokinetics in drugs appears as a result of three phenomena: saturation of enzymes, barriers to active transport and changes in protein binding at different dosages.

6.3.1 Michaelis-Menten Kinetics and Its Application

The Michaelis-Menten model functions as a non-linear pharmacokinetic example to describe drug metabolism processes handled by enzymes [14]. When elimination processes become

saturated the drug concentration relationship with elimination rate becomes characterized through this model.

The Michaelis-Menten equation is given as:

$$v = \frac{V_{max} \cdot C}{K_m + C}$$

Where:

- v is the rate of elimination,
- Vmax is the maximum elimination rate,
- KmK is the Michaelis constant (which reflects the drug concentration at which the elimination rate is half of Vmax,
- C is the concentration of the drug.

The drug elimination rate exhibits direct correlation with drug concentration at lower drug amounts (C≪Km) [15]. When drug concentrations rise towards the limiting value of KmK the elimination rate becomes limited to Vmax but shows no additional changes in speed with higher concentrations. At high dose levels the risk of drug toxicity increases because drug concentrations rise disproportionately.

The Michaelis-Menten model serves as a standard approach for modeling drug non-linear metabolism because it assesses substrates metabolized by enzymes with restricted capacity mainly cytochrome P450 enzymes. The elimination rates of drugs like phenytoin theophylline and warfarin become saturated at therapeutic drug levels so healthcare providers must closely monitor these medications for proper dosing adjustments.

6.3.2 Estimation of k_{max} and V_{max}

The calculation of both k_{max} (maximum rate constant) and Vmax allows optimal analysis of drug non-linear pharmacokinetic processes[16]. Experimental data processing through Michaelis-Menten equation fitting enables researchers to obtain these parameters.

- **k_{max}**: The maximum elimination rate constant functions as an essential parameter because it demonstrates the peak operating capacity of metabolic or transport systems. Standard drug elimination tests at different concentrations help researchers determine when the elimination rate has reached its highest capacity.
- **V_{max}**: The maximum metabolic rate defines the fastest elimination speed of a drug which remains unresponsive to higher concentrations. Drugs' high concentration

prediction relies on V_{max} estimates which supports dosage decisions to prevent metabolic pathway saturation.

Thanks to these parameters the development of proper dosing schedules becomes achievable while maintaining drug safety which production requires linear pharmacokinetic behavior. Drugs with restricted metabolic capabilities experience vast changes in plasma concentrations when dose amounts change slightly which heightens the chance of negative side effects.

6.3.3 Factors Contributing to Non-Linear Pharmacokinetics

Several factors contribute to the non-linearity in the pharmacokinetics of a drug[17]:

1. **Saturation of Metabolic Enzymes**: Enzymes located in the liver together with additional tissues metabolize numerous pharmaceutical substances. The drug concentration rises beyond a proportional relationship after dose increases because enzyme saturation reduces the drug's elimination rate.
2. **Saturation of Transporters**: Drugs that use active transporters to absorb or eliminate themselves might experience saturation at high drug concentration levels similarly to metabolic enzymes. At such drug concentrations the absorption rate and elimination rate reach a plateau level which results in non-linear pharmacokinetics.
3. **Protein Binding**: A higher concentration of drug within plasma creates maximum protein binding to plasma proteins that reduces the amount of free drug available for tissue distribution. An increase in drug dosage results in limited free drug concentration elevation since plasma protein binding capacity reaches its maximum at higher concentrations.
4. **Dose-Dependent Pharmacodynamics**: Drug pharmacodynamic consequences at elevated doses cause non-linear drug behaviors by activating feedback systems that modify drug absorption and distribution as well as elimination rates[18].
5. **Genetic and Physiological Variability**: Some patient factors such as drug-metabolizing enzyme and transporter genetic differences control drug interactions at very high concentrations. The physiological process of drug metabolism becomes non-linear when patients possess gene variants that slow down drug clearing from their bodies.

6.3.4 Implications for Drug Therapy

Effective drug therapy optimization requires a full comprehension of non-linear pharmacokinetics for medications that use saturation kinetics[19]. A linear relationship between drug dosage and blood concentration does not exist because small dose variations produce large changes in therapeutic levels. Special attention requires dose changes and frequent plasma drug tests particularly when using drugs with narrow therapeutic indexes such as phenytoin and lithium. Drug interactions become unpredictable when drug substances exhibit non-linear pharmacokinetic behavior. When drug enzymes or transporters encounter medications which either promote or prevent their metabolism and elimination processes it causes the pharmacokinetics of the affected drug to change in a nonlinear fashion[20]. The inhibition of cytochrome P450 enzymes by a certain medication results in unreasonable concentration elevations of other metabolized drugs leading to toxic outcomes.

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