CHAPTER 1

Introduction

LEARNING OBJECTIVES

- Introduction to biopharmaceutics
- Aim and scope of Biopharmaceutics
- Understanding the concept of pharmacokinetics
- Applications and applied fields of pharmacokinetics

Biopharmaceutics

"Pharmaceutics" is a field of science that involves the preparation, use, or dispensing of medicines. Addition of the prefix "bio-" coming from the Greek "bios," relating to living organisms or tissues, expands this field into the science of preparing, using, and administering drugs to living organisms or tissues. Inherently biopharmaceutics is the interdependence of biological aspects of the living organism (the patient) and the physicochemical principles that govern the preparation and behavior of the medicinal agent or drug product. This philosophy was introduced in the mid-twentieth century by the biopharmaceutical scientists who recognized the importance of absorption, distribution, metabolism, and elimination (ADME) on the clinical performance of medicinal agents as well as the impact of the physicochemical properties of the materials on their *in vivo* performance. As a result, biopharmaceutics has evolved into a discipline that encompasses fundamental principles from basic scientific and related disciplines, including chemistry, physiology, physics, statistics, engineering, mathematics, microbiology, enzymology, and cell biology. The biopharmaceutical scientist, therefore, must have sufficient understanding of all of these scientific fields in order to be most effective in a drug development role. One should also be well versed with interrelated specialty disciplines including formulation, pharmacokinetics, cell-based

transport, drug delivery, or physical pharmacy as these are significant for the drug development (design) process.

A drug is designed as dosage form with the aim to deliver the drug to produce desired therapeutic effect. Additionally, the dosage form is expected to meet the patient's needs including elegance, safety, convenience and favourable organoleptic properties. The focus primarily is to achieve desired clinical effect that entirely relies on how the dosage form (drug product) performs in the body. Hence, the onus lies on the release of the drug substance from the drug product either for local drug action or for absorption of drug into the blood for systemic action. The release of drug from the dosage form is dependent on the physicochemical properties of the drug, its formulation strategy and route of administration.

Biopharmaceutics evaluates the interrelationship of the various factors namely, the physicochemical properties of the drug, its dosage form characteristics and the route of administration of the dosage form on the rate and extent of systemic drug absorption. The dosage form when administered is subjected to various processes that play a key role in drug absorption, in addition to the physicochemical properties of drug. Absorption followed by *in vivo drug* distribution to the site of action, elicits the therapeutic response. A general scheme describing the events is illustrated in Fig. 1.1.

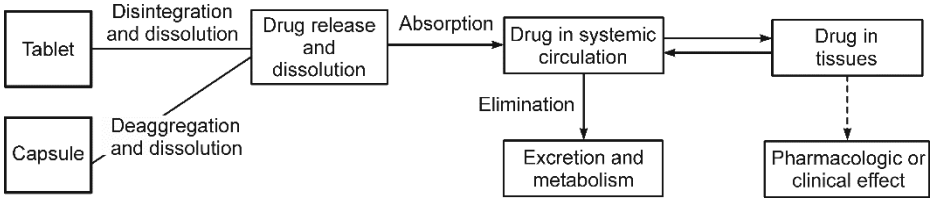

Fig 1.1 Scheme depicting the fate of oral dosage form of a drug and its therapeutic effect.

The drug in its dosage form is administered to the patient by a specific route (oral/ parenteral) depending on the dosage form. This is followed by drug release from the dosage form in a predictable manner. Thereafter, a fraction of the drug is absorbed either into the blood or the adjacent tissue /organ, or both. Next, the drug reaches the site of action and the pharmacological/ clinical effect is observed when the drug approaches a concentration equal to or more than *minimum effective concentration* (MEC). It is important to predetermine the

dosing regimen, including the initial dose, maintenance dose, and the dosing interval, through clinical trials to achieve drug concentration(s) that are clinically effective in large number of patients. The efficacy and safety of drug are primarily dependent on the dosing regimen. Different drugs have different optimal dosage and dosing intervals. Furthermore, for a given drug, the optimal dosage and dosing intervals can vary widely between the patients.

Historically, the pharmaceutical researchers have assessed the relative drug availability *in vivo* after administering a drug product via different routes to either animals or humans, followed by comparing a specific pharmacological, clinical, or potential toxic responses. For example, isoproterenol administration results in an increase in heart rate when given by intravenous route, however, no such effect on the heart is observed when the drug is given orally. Thus development of biopharmaceutical principles allow for rational design of drug products, which would enhance the delivery of active drug, and optimize the therapeutic efficacy of the drug in the patient. Box 1 highlights the biopharmaceutical principles.

Box 1

Biopharmaceutics is

- Study of the effect of formulation factors on therapeutic activity of a drug product.
- Study evaluates the relationship between the physical, chemical and biological sciences as applied to drug, its dosage form(s), and to the drug action.
- Modern biopharmaceutics studies the interrelationship of the physicochemical properties and *in vitro* behavior of the drug and its product on administration of the drug to the body under normal or pathological conditions.

Biopharmaceutical studies involve both *in vitro* and *in vivo* methods. The *in vitro* methods use laboratory test apparatus without involving test animals and humans. For e.g. disintegration test, dissolution test, etc. The in *vivo* test involves measurement of systemic drug availability (bioavailability) after administering a drug product to test animals or human volunteers. The ultimate

aim is to achieve effective therapeutics. Box 2 summarizes the aims of biopharmaceutical studies.

Box 2

Aims:

- The aim of biopharmaceutics is to adjust the delivery of drug to the general circulation in such a manner as to provide optimal therapeutic activity for the patient.
- Some drugs are intended for topical or local therapeutic action at the site of administration. For these drugs, systemic absorption is undesirable.
- Drugs intended for local activity generally have a direct pharmacodynamic action without affecting other body organs. These drugs may be applied topically to the skin, nose, eyes, mucous membranes, buccal cavity, throat and rectum.

Each product is a formulation unique unto itself. Biopharmaceutical considerations often determine the ultimate dose and dosage form of a drug product. For example, the dosage for a drug intended for local activity, such as a topical dosage form, is often expressed in concentration or as percent of the active drug in the formulation. The amount of drug is not specified because it is the concentration of the drug at the active site that relates to the pharmacodynamic action. Biopharmaceutical studies must be performed to ensure that the dosage form does not irritate, cause an allergic response or allow systemic drug absorption. The dosage of a drug intended for systemic absorption is given on the basis of absolute amount, such as mg or g.

Secondly, each route of drug application presents special biopharmaceutical considerations in drug product design. By carefully choosing the route of drug administration and properly designing the drug product, the bioavailability of the active drug can vary from rapid and complete absorption to a slow, sustained rate of absorption or even virtually no absorption, depending on the therapeutic objective. For e.g.: The design of a vaginal tablet formulation for the treatment of a fungal infection must consider ingredients compatible with vaginal anatomy and physiology. An eye medication may require specific biopharmaceutical considerations including appropriate pH, isotonicity, local irritation to the cornea, draining by tears, and concern for systemic drug absorption.

A primary concern in biopharmaceutics is the bioavailability of drugs. Bioavailability refers to the measurement of the rate and extent of active drug that reaches the systemic circulation. It means access of drug to the bloodstream (Figure 1.2). The pharmaceutical factors affecting drug bioavailability are (i) type of the drug product, (ii) nature of excipients in the drug product, (iii) physicochemical properties of the drug, and (iv) measurable characteristics by which a drug interacts with other systems.

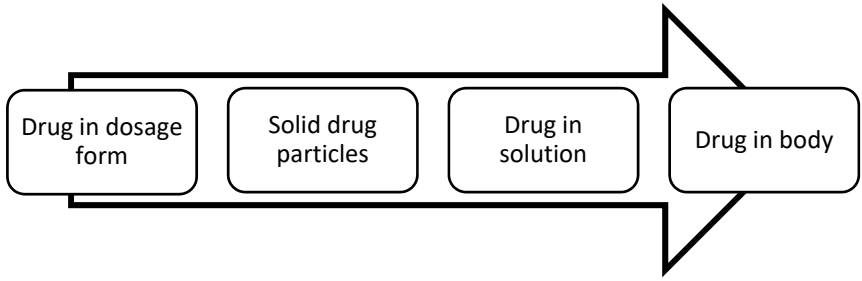

Fig. 1.2 Schematic representation of drug bioavailability process.

Scope of Biopharmaceutics

1. Encompasses all possible effects observed following the administration of the drug in various dosage forms.
2. Encompasses all possible effects of various dosage forms on biological response.
3. Encompasses all possible physiological factors which may affect the drug in various dosage forms.

Applications of Biopharmaceutics

1. A company is going to market a new dosage form of a certain drug (the dose is known). When this dosage is administered to a healthy human, there are two possibilities: (i) the drug may not be release quickly and hence the action of drug will be delayed, (ii) the drug may be released quickly and hence the duration of action will be very short. With the knowledge of biopharmaceutics we can change various formulation factors to obtain optimum onset of action and duration of action.

2. A company is marketing tablets of certain drug. Now it wants to change a few ingredients or some formulation factors. Whether or not the new tablets will behave in a manner similar to the previous one; bioavailability studies are done. So the bioavailability of the newer tablets is compared with the old tablets. If it is found that the bioavailability of the newer tablets is equivalent (i.e. bioequivalent) to that of older tablets then the new tablets will be permitted to be marketed.
3. A company is marketing the tablets of a certain drug. Now they have planned to make transdermal dosage form of the same drug. To establish its efficacy the bioavailability of the transdermal dosage form is compared to that of the established tablet dosage form. If both are found to be close then the transdermal dosage form will be accepted by the FDA.

Pharmacokinetics

Knowing what the drug does to the body is just not sufficient; it is also extremely important to know what the body does to the drug. Thus knowledge of both the pharmacodynamic and pharmacokinetic aspects of the drug and its metabolites in animals and humans is significantly important for adjusting drug dosing. The final aim of a drug is to achieve optimal therapy and to attain this aim:

1. The drug is first developed into a suitable dosage form which is administered in to the body through a suitable route of administration.
2. The drug is released at the site of absorption at a certain rate.
3. The drug is then absorbed from the site of absorption into the systemic circulation.
4. The drug is carried to various tissues through blood for distribution to the extravascular tissues. Distribution is a reversible process and hence the drug returns back to systemic circulation.
5. The drug produces its action at the site of action: extravascular/ intravascular.
6. The drug is metabolized in liver/tissues.
7. Finally the drug is eliminated from the body.

The events have been illustrated in Fig 1.3 for quick understanding. All the processes occur at a certain rate. In pharmacokinetics we study those rates and pharmacokinetic equations are used to predict these rates. Pharmacokinetics is the study of the time course of a drug in the body (extent and duration of systemic exposure) and it also encompasses the study of the rate processes involved in *absorption*, *distribution, metabolism* and *excretion* (ADME).

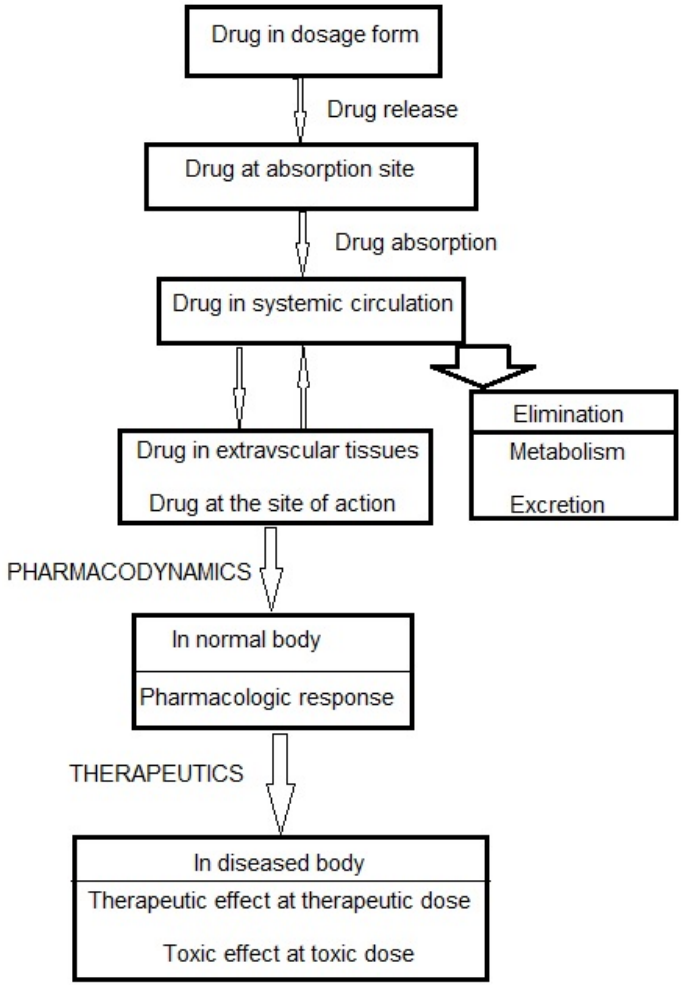

Fig. 1.3 Schematic representation of the processes involved in drug therapeutics.

The plasma drug concentration is the primary fundamental of pharmacokinetics. Furthermore, the plasma drug concentration is in equilibrium with certain tissues in the body. In case the drug binds to plasma proteins, the concentration of free drug available in the systemic circulation influences the dose calculations. In general, the pharmacokinetic parameters of a drug are derived from the measurement of the drug concentration(s) in either blood or plasma. The goal is to quantitatively account for the amount which has entered the body (bioavailable dose) from the time of administration until it has been completely cleared. The mathematical descriptions that have emerged have proven valuable for both drug research and drug therapy.

The study of pharmacokinetics involves both experimental and theoretical approaches. The experimental approach involves development of biological sampling techniques, analytical method development for measurement of drug(s) and metabolites, and procedures for data collection and interpretation. The theoretical aspect of pharmacokinetics involves the development of pharmacokinetic models that predict drug disposition after drug administration. The application of statistics is an integral part of pharmacokinetic models to determine data errors, deviation in models and correlation.

Application of Pharmacokinetics

1. The bioavailability of a dosage form is calculated by pharmacokinetic equations.
2. The frequency of dosing is calculated from pharmacokinetic equations.
3. The equations also assist in calculation of dose for controlled release formulations.
4. In case of patients with kidney/ liver failure the dose of a drug should be calculated very cautiously. If the rate of absorption of drug is greater than the elimination rate of the drug, then the drug will be accumulated in the body in such patients and may show toxic effects. The rate of elimination of a drug from the body is calculated with the help of pharmacokinetic equations.
5. When a potent anticancer drug is administered to a patient the plasma concentration of the drug must be very close to minimum effective concentration. Since the therapeutic index of the drug is very narrow in

case of potent drugs, so rate of administration must also be very slow. This rate of administration is calculated by pharmacokinetic principles.

6. Antagonism or potentiation of the effects of one drug by another has a pharmacokinetic basis and not pharmacological basis. ADME may be affected by concomitant administration of second drug leading to clinical differences.
7. Selecting or modifying dosage regimen requires an understanding of clinical pharmacokinetics. For e.g. higher dose of theophylline is required for children and smokers, and lower dose for patients with congestive heart failure.

Fields in Pharmacokinetics

Based on the variety of applications of pharmacokinetics, various specialized fields have emerged.

1. **Clinical pharmacokinetics** is the application of the pharmacokinetic methods in drug therapy. It is a multidisciplinary approach where the dose of a drug is optimized for a specific patient depending on the disease state, age and sex of the patient. This subject requires information from medical and pharmaceutical research.
2. **Population pharmacokinetics** is the study of pharmacokinetic differences of drug in various population groups.
3. **Pharmacodynamics** deals with the relationship between the drug concentration at the site of action (receptor) and pharmacological response, including biochemical and physiological effects that influence the interaction of drug with the receptor.
4. **Toxicokinetics** refers to the application of pharmacokinetic principles to the design, conduct and interpret the drug safety and is also used in validating dose related toxicity in animals. Toxicokinetic studies are conducted in animals and the result obtained is used to interpret possible toxic reactions in humans.

Therapeutic Drug monitoring: When drug with narrow therapeutic indices are used in patients, it is necessary to monitor plasma drug concentration closely by taking periodic blood samples. Some drugs that are frequently monitored are

aminoglycoside antibiotics, anticonvulsants and anticancer drugs in order to minimize adverse effects.

Pharmacokinetic studies date back to 1924 when Widmark and Tandberg published two theoretical papers on the one-compartment open model followed by additional two papers by Teorell in 1937. The work was largely disregarded owing to complexity of the equations and lack of analytical tools. However, with the advent of computers and proliferation sophisticated analytical tools pharmacokinetics has emerged as a significant branch with numerous applications.

Questions

Multiple Choice Questions

1. The release of drug from the dosage form is not dependent on
   (a) The physicochemical properties of the drug
   (b) Route of administration
   (c) Its formulation strategy
   (d) Pharmacodynamic property
2. Systemic absorption is desirable for
   (a) Nasal preparation (c) Opthalmic preparation
   (b) Otic formulation (d) SR formulation
3. The strength of topical dosage form is expressed as
   (a) Amount of drug (c) Volume of drug
   (b) Percent of drug (d) Moles of drug
4. Pick the odd one. Biopharmaceutical studies on topical dosage form must be performed to ensure that the dosage form does not
   (a) Irritate (c) Cause an allergic response
   (b) Allow systemic drug absorption (d) Have foul odor
5. Select the wrong one. The pharmacokinetic parameters are derived from the measurement of drug concentration(s) in
   (a) Blood (b) Urine (c) Plasma (d) Lymph

6. Pharmacokinetic models are used to predict
   (a) Drug disposition after drug administration
   (b) Physicochemical properties of drug
   (c) Bioavailability
   (d) Presystemic metabolism
7. Statistics, an integral part of pharmacokinetic models is not used to determine
   (a) Data errors
   (b) Correlation
   (c) Deviation in models
   (d) Frequency

Descriptive Questions

1. Define biopharmaceutics. What are its aims and scope?
2. Explain the applications of biopharmaceutics.
3. Define pharmacokinetics. Highlight various fields of pharmacokinetics.
4. With the help of diagram explain the events of drug release and ADME.
5. Enlist the applications of pharmacokinetics.