BIOPHARMACEUTICS: AN INTRODUCTION

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Introduction

This chapter aims to introduce biopharmaceutics and to define some key terms used within biopharmaceutics and introduces its involvement in the drug development process. Drugs are chemical substances, used as a medication which induces change(s) in an organism's physiology and psychology *(Wichrowski et al,2020)*. However, the changes induced may either be therapeutic or toxic effect(s). The origin of drug is versatile such as plants, animals, minerals, microorganisms, chemical synthesis, biotechnological, genetical, computer-aided, etc. *(Susa et al,2023)*.

Drugs are the substances that are intended to diagnose, prevent or treat a disease. Drugs in the form of different dosage forms such as solids (tablets, capsules), semisolids (pastes, ointments), liquids (mixtures, solutions), suspensions and emulsions etc. are administered to provide systemic or local therapeutic effect. These drug products are considered to be drug delivery systems that releases and delivers the drug to the site of action so that it may provide the desired therapeutic effect and are designed to meet the patient's acceptability, convenience, palatability and safety.

Pharmaceutics is the branch of science that focuses on the design and development of pharmaceutical dosage forms that helps in treatment, prevention and diagnosis of a particular disease. It is concerned with novel drug product measures. It deals with the fabrication of a drug product. Drug products that contain same therapeutically active drug uses different inactive ingredients. The selection of inactive ingredients depends upon the physicochemical properties of the drug, the type of formulation and the route from where it gets administered. The usage of drugs serves several stable, fruitful and preventive purposes *(Marino et al,2023)*.

The use of drugs to treat disease is a multifaceted process that involves:

- A pharmacologically active compound either synthesized, isolated or extracted and being rationalized for toxicity and potential key features by clinical and preclinical studies. *(Rasul,2018)*.
- Formulation of a dosage form that delivers a dose through appropriate route to the site of action or target tissue.
- Physiological, pathological and clinical response is produced (*Chu,2023*).

Even though differences in therapeutic efficacy are also observed if the same drug is administered as different dosage forms or similar dosage forms formulated by different manufacturers. So, in this regard, a novel and distinct discipline known as biopharmaceutics has been developed to consider such factors that may decide the therapeutic efficacy of a drug *(Selker et al,2018)*.

Biopharmaceutics is the study of basic and applied research that focuses on the interactions between drugs and their physicochemical properties and dosage form, as well as their pharmacokinetics and clinical responses in response to its administration *(Shargel et al,2012)*. The term "**Biopharmaceutics**" was coined by Dr. Gerhard Levy in 1960. It is the major branch of pharmaceutical sciences. Biopharmaceutical drugs have transformed the medical care of a broad spectrum of ailments and are being used more frequently in almost all areas of medicine.

Biopharmaceutics influenced by circumstances which contributes towards:

- the rate of drug dissolution at the absorption site (*in vivo*)
- the release of the drug from the dosage form
- the systemic drug absorption

To administer drugs optimally, knowledge is needed not only on the mechanisms of drug absorption, distribution, metabolism and excretion but also on the rate at which they occur i.e., pharmacokinetics *(Aiache,2005)*. The process of drug movement from the site of administration to the systemic circulation is known as **absorption**. The drug concentration in plasma and its onset and duration of action depends upon the bioavailability of drug from its specific dosage form. The other processes that play a key role in the therapeutic activity of a drug are distribution and elimination i.e., drug disposition. The movement of drug from the blood to the extravascular tissues (usually between one compartment and other) is termed as **drug distribution**. The intensity and the duration of drug response depends upon the effective concentration of a drug for a particular period of time at the site of action which largely depends upon elimination process. It occurs by two mechanisms- metabolism (transformation of drug from one form to

another) and excretion (mechanism of exit of drug/ metabolites from the body) (*Price & Patel, 2023*).

The goal of biopharmaceutical studies is to formulate a dosage form that provides a consistent bioavailability to the systemic circulation, if the drug has a narrow therapeutic index. The study of various factors associated with biopharmaceutics allows to design the drug product in a rationale manner so as to deliver the drug to optimize therapeutic potential and to reduce the adverse effects.

Apart from biopharmaceutics, "**Pharmacokinetics"** of drug determines the onset, duration, and potency of a drug's impact. The Greek words pharmakon (drug) and kinesis (motion or rate of change) are the origin of the word "pharmacokinetics" *(Rimmington)*. Pharmacokinetics of a drug is divided into different steps i.e., digestion, delivery to a target site, and elimination via biotransformation of drug and its excretion. The method of administration and how the body organs work have an impact on each of these processes. Various pharmacokinetic parameters are clearance (CL), volume of distribution (V_d), half-life ($t_{1/2}$), bioavailability, protein binding *(Adepu & Ramakrishna,2021).*

The term "**Pharmacodynamics**" describes the connection between drug concentration at the site of action and the impact that follows, including the progression and efficacy of both therapeutic and negative effects. A drug's relationship with a receptor at the site of action affects how drug *(Wankhade et al.,2022)*.

KEY TERMS

1. **Biopharmaceutics:** It is defined as the study of factors affecting the dose and extent of drug that provides systemic or local effect after reaching systemic circulation to measure the therapeutic potential of drug.
2. **Pharmacokinetics:** It is a branch of biopharmaceutics that deals with the study of body's effect on the drug i.e., the drug ADME properties with its therapeutic and toxic effects.

There are several applications of these pharmacokinetic studies such as:

- Measurement of bioavailability
- Clinical pharmacokinetics
- Predict the designing of optimal dosage regimen
- Design and development of sophisticated pharmacokinetic models

- Analytical techniques (HPLC, gas chromatography, mass spectrometry) for the assay of drugs and its metabolites *jam*.

Pharmacokinetics

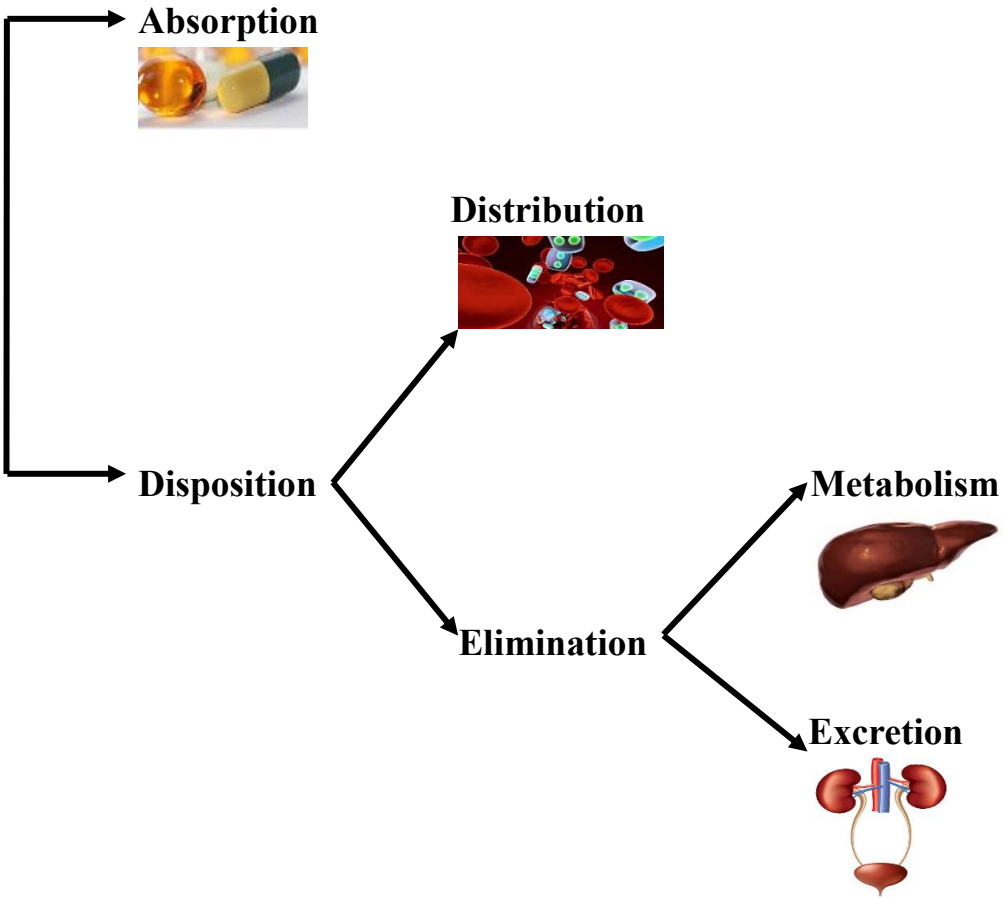

Figure 1: Schematic illustration of Pharmacokinetic processes

3. **Pharmacodynamics:** It deals with the study of drug's effect on the body i.e., deals with the drug's mechanism of action and is related to the response of drug concentration in the body. It is defined as the relationship between the drug concentration at the receptor site and the corresponding pharmacological response i.e., the various biochemical and physiological effects that influences the interaction of a drug molecule with the receptor. This interaction either produces a pharmacological response or a toxic response.

   It involves the study of:

   - mechanism of action
   - biochemical reaction
   - physiological effect

4. **Absorption:** Drug absorption is the process in which the drug from the dosage form reaches the systemic circulation from the site of administration. There are various mechanisms of drug absorption such as transcellular/ intracellular transport (Passive transport, active transport, facilitated diffusion), paracellular/ intercellular transport and vesicular transport (pinocytosis and phagocytosis).
5. **Distribution:** Once drug molecules enter the systemic circulation, these molecules mix with the body fluids and reaches the site of action. Drug distribution refers to the transfer of drug from one compartment to other compartment i.e., from blood to extravascular tissues through passive diffusion. Drug distribution can occur through blood and other fluids, cells, central nervous system and placenta.
6. **Metabolism:** It is defined as the chemical conversion of drug from one form to another form by enzymatic action. The term metabolism is used synonymously with biotransformation. The drug can be metabolized either by phase I (oxidation, reduction and hydrolysis) or phase II (conjugation) reactions.
7. **Excretion:** It is a process in which drugs or their metabolites are removed from the body irreversibly either through kidney (renal excretion) or by other organ (non-renal excretion).
8. **Bioavailability:** It is defined as the rate and amount to which drug gets absorbed from site of administration to the site of action after reaching systemic circulation. The drug concentration in plasma and the onset of action, the intensity and duration of drug response depends upon drug bioavailability from a dosage form.
9. **Clinical Pharmacokinetics:** It is defined as a multidisciplinary approach in which the dose of a drug is optimised for a particular patient depending on its disease conditions, age and gender using various pharmacokinetic principles to achieve maximum therapeutic potential. It basically involves the designing of dosage regimen by determination of drug interactions and medication errors, if any.

   The main objectives of clinical pharmacokinetics are to improve a patient's pharmacological therapeutic efficacy and reduction in its toxicity.
10. **Toxicology:** It deals with the study of harmful poisons (either natural or man-made) and its related adverse effects in the human body *(Jambhekar & Breen,2013)*.
11. **Therapeutic Drug Monitoring:** Therapeutic drug monitoring (TDM) is a process in which a detailed monitoring is carried out to find the therapeutic potential of given medicaments to a particular patient in a disease *(Zhao & Jacqz-Aigrain,2011)*.

12. **Pharmacokinetic Models:** These are the mathematical models used to predict the drug absorption, distribution, metabolism and excretion of drugs in human and animals. It includes compartment models and non-compartment models.

    Since, the study of drugs handling by a human body is a complicated process due to the complexity of human anatomy and physiology. So, in this situation, the pharmacokinetic models serve as a useful source of information. It is assumed that the body is composed of a number of compartments and these compartments are imaginary or virtual. They help to predict the drug concentration in body fluids and calculates dosage regimens *(Daryaee & Tonge,2018)*.

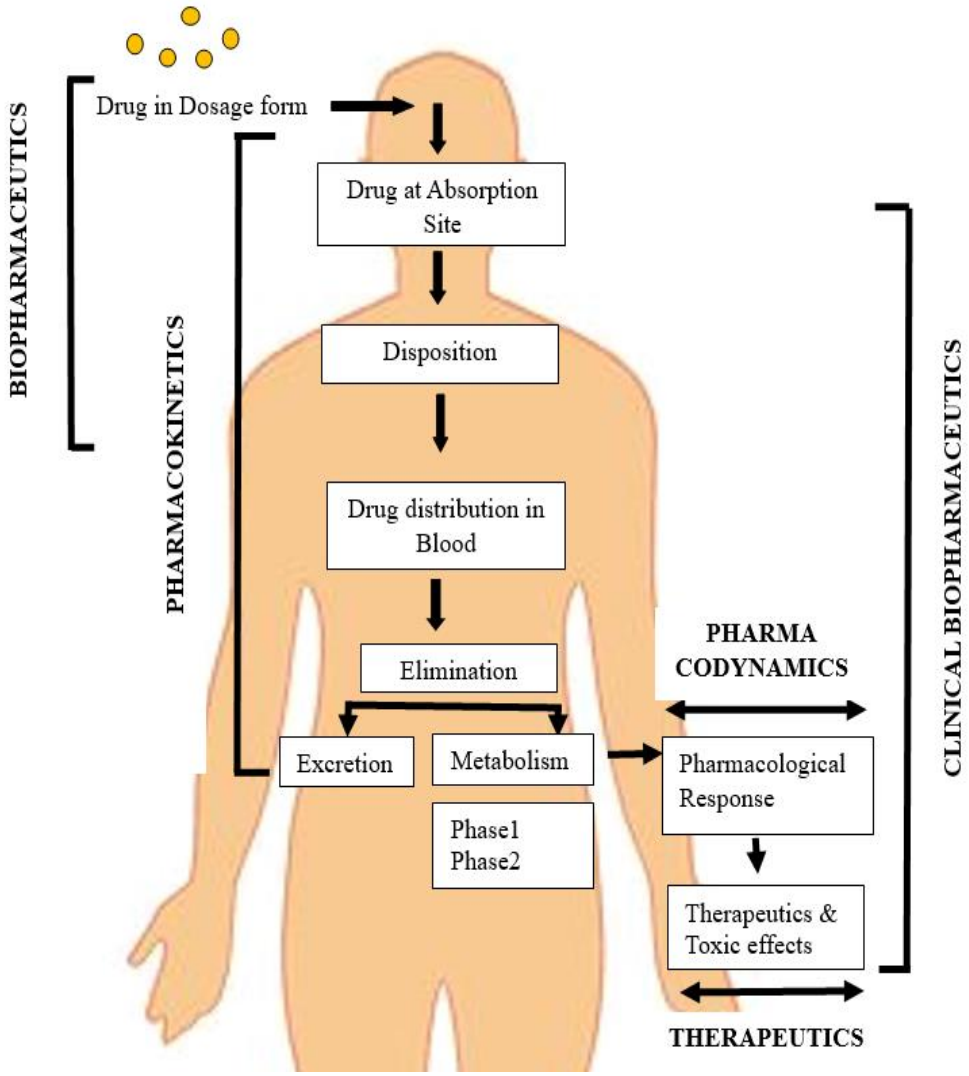

Figure 2: Diagrammatic representation of the dynamic relationship between drug, dosage form, pharmacological and pharmacokinetic response

The knowledge and concepts of biopharmaceutics and pharmacokinetics have an integral role in the design and development of new drugs and improvement of therapeutic efficacy of existing drugs.

Drug administration and therapy is conveniently divided into four phases.

1. **The Pharmaceutical Phase**: It involves physico-chemical properties of drug by which design and manufacturing of suitable dosage form occurs.
2. **The Pharmacokinetic Phase**: It involves the ADME of drug elicited by plasma drug concentration-time profile and its relationship with the dose, dosage form and dosing frequency and route of administration. It is the sum of all the processes inflicted by the body on the drug.
3. **The Pharmacodynamic Phase**: It is related with the drug's mechanism with its biochemical and physiological effects and is characterized by drug concentration at site of action.
4. **The Therapeutic Phase**: This phase is related to the pharmacological effect of drug in relation with its clinical benefit. *(Kang & Lee,2009)*

Management of drug therapy in individual patient often requires evaluation of response of the patient to the recommended dosage regimen. This is monitoring of drug therapy. It is necessary to ensure that the therapeutic objective is being attained and failure to do so requires readjustment of dosage regimen.

Depending upon the drug and the type of disease to be treated, management of drug therapy is divided into:

- **Therapeutic Monitoring**: to monitor therapeutic effects i.e., the incidence and intensity of desired therapeutic effects and undesired side effects
- **Pharmacodynamic Monitoring**: to monitor pharmacological actions that can be used as a guide for therapeutic process
- **Pharmacokinetic Monitoring**: to monitor drug plasma concentration so that free drug at site of action must be in equilibrium with the drug in plasma *(Reichel & Lienau,2016)*.

The most important stage in case of drug discovery and development is to evaluate pharmacokinetic and physicochemical properties of the drugs. The chief parameters that control the rate and extent of oral drug absorption are the drug solubility and gastrointestinal

permeability and their importance has been emphasized in the BCS that categorizes drug into four categories based on their solubility and permeability *(Benet,2013).*

BCS Classification: BCS stands for Biopharmaceutics Classification System. It was developed by Amidon and his colleagues in 1995 as "a scientific approach for selecting the drug molecule" in order to establish the correlation between *in vitro* drug dissolution studies and *in vivo* bioavailability studies. *(Varma et al,2004)*.

The two parameters of biopharmaceutics, solubility and permeability plays a vital role in new drug discovery and lead optimization because of its dependence on drug absorption and pharmacokinetics.

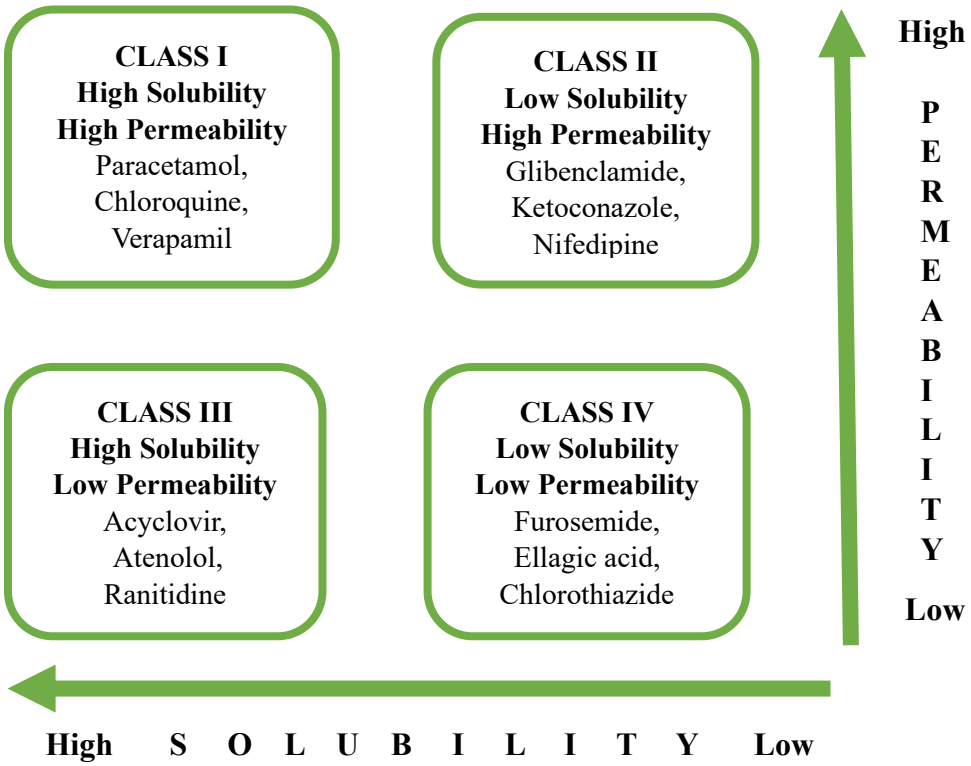

Figure 3: Biopharmaceutics Classification System (BCS)

Class 1: High Solubility and High Permeability: Drug is rapidly absorbed and dissolved but dissolution is rate limiting step, but if dissolution becomes rapid, then gastric emptying rate becomes rate limiting step *(Dutta et al,2021).*

Rate of Absorption > Rate of Excretion

Class 2: Low Solubility and High Permeability: Drug is rapidly absorbed due to its high permeability across membranes but dissolves slowly. Since, absorption is slower than BCS class I drugs so, it occurs over a long period of time.

Class 3: High Solubility and Low Permeability: Drug Permeability is rate limiting step for absorption of drug *(Shekhawat & Pokharkar, 2017)*.

Class 4: Low Solubility and Low Permeability: Drugs have low dissolution rate and produces low therapeutic effect. These drugs exhibit a lot of issues for an effective oral administration due to its limited absorption and permeability *(Dev,2018)*.

Biopharmaceutics Drug Disposition Classification System (BDDCS): The BCS was developed to predict the *in vivo* pharmacokinetics of a drug product using the solubility and permeability measurements. A modification in such a classification system known as Biopharmaceutics Drug Disposition Classification System (BDDCS) has been developed which predicts the drug overall drug disposition such as elimination route of drugs, drug-drug interactions in the intestine and liver *(Manzari et al,2021).*

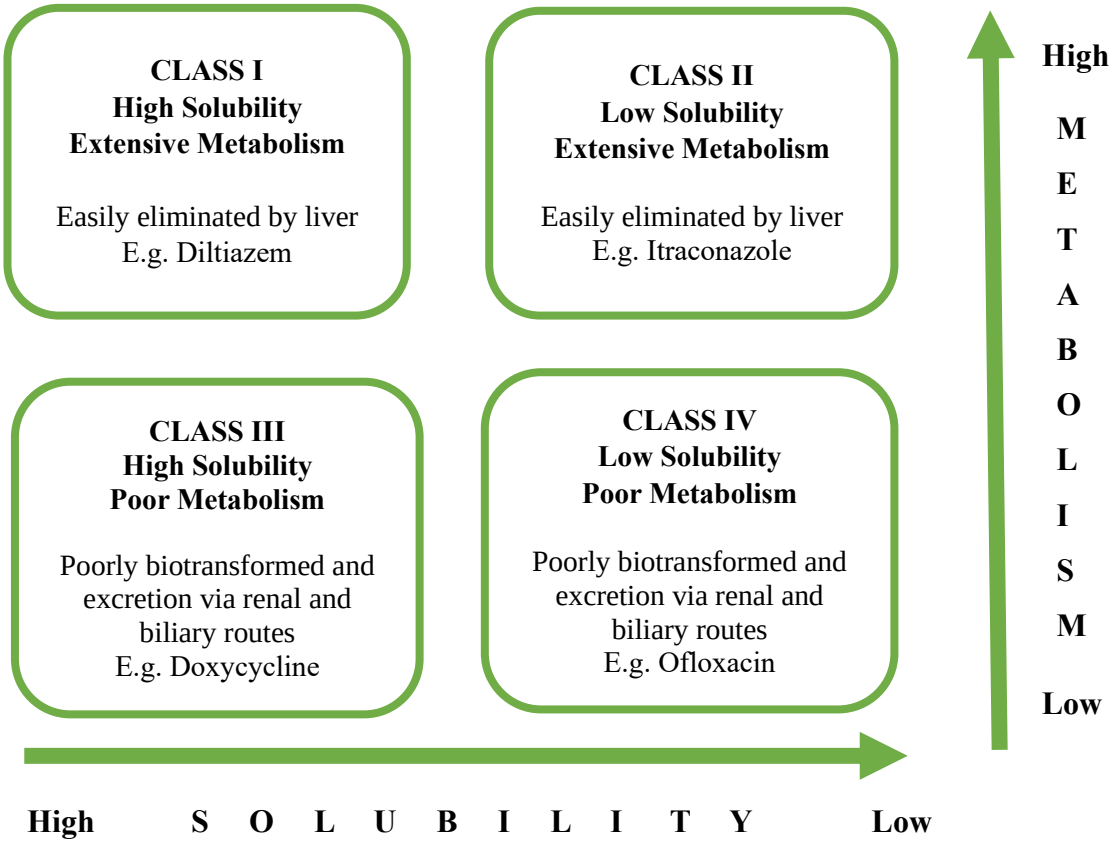

Figure 4: Biopharmaceutics Drug Disposition Classification System (BDDCS)

Applications of Biopharmaceutics

To achieve optimal drug therapy, the drug is designed in such a way so that it may deliver an ideal rate and amount of drug. Rational use of drug can only be achieved by the determination of drug pharmacokinetics and pharmacodynamics parameters that helps in designing a proper dosage regimen *(Gupta et al,2013)*.

The goal of biopharmaceutical studies is to formulate a dosage form that provides consistent bioavailability after reaching systemic circulation, providing maximum therapeutic potential with minimal side effects *(Zane et al,2019)*.

- Biopharmaceutics deals with the study of *in-vivo* (estimation of systemic drug availability after administering a drug) and *in-vitro* (estimation of drug availability using laboratory animals or human volunteers, e.g., Disintegration tests, Dissolution tests) methods.
- It deals with the visualization of *in vivo* drug performance from *in vitro* drug permeability and solubility.
- It helps in improvement of the safety and efficacy of drug.
- It helps in the formulation of a dosage form by changing various formulation factors so as to provide optimum onset of action.
- These studies evaluate the performance of API i.e., its pure form or salt form.
- These studies help in predicting the bioavailability of new dosage forms in comparison with existing dosage forms to determine whether they are equivalent or not.
- Biopharmaceutics focuses on the consistency, robustness and predictability of the formulation *(Chow,2014)*.

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