UNIT

XIII

METHODS FOR ENHANCEMENT OF BIOAVAILABILITY

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INTRODUCTION

One of the most significant pharmacokinetic aspects of drugs is bioavailability, which is used to characterise the percentage of an administered dose of unchanged drug that reaches the systemic circulation. The bioavailability of a drug administered intravenously is 100 percent. However, owing to inadequate absorption or first pass metabolism, the drug's bioavailability diminishes when delivered through other routes (such as oral). The rate and extent to which the active drug moiety is absorbed from the drug product and becomes available at the site of action are indirectly represented by the amount of drug in the plasma measured at specified time intervals. Bioavailability is a crucial component of pharmacokinetics, as it is used to calculate doses for non-intravenous routes of administration. It's measured in terms of absolute or relative bioavailability. The therapeutic efficacy of a drug is determined by the dosage form's capacity to deliver the active drug to the site of action at a rate and amount sufficient to produce the desired pharmacological response. Physiologic availability, biologic availability, or simply bioavailability is terms used to describe this attribute of the dose form. Almost all drugs have a direct relationship between their pharmacologic response and their plasma levels. The term "bioavailability" refers to the rate and extent (quantity) of unchanged drug absorption from its dosage form. It is also the rate and extent to which the components or active moiety are absorbed from the drug product and made available at the site of action. Poor aqueous solubility, sluggish dissolving rate in biological fluids, poor stability of dissolved drug at physiological pH, poor permeation through biological membrane, and extensive presystemic metabolism are all characteristics of a drug with poor bioavailability. The bioavailability of drugs that are poorly water soluble is a crucial problem.

According to the definition of bioavailability, a drug with poor bioavailability has poor aqueous solubility and/or a slow dissolving rate in biological fluids. Protein or peptide drugs like insulin have poor biomembrane permeability due to a low partition coefficient, lipophilicity, or large molecular size.

The Biopharmaceutics Classification System (BCS) was developed by Amidon *et al.*, and it divides drugs into four classes based on intestinal

permeability and solubility, as shown in **Table 13.1**. In addition, the table shows how each drug class has dealt with formulation problems.

Table 13.1: The Biopharmaceutics Classification System for Drugs

Class	Solubility	Permeability	Absorption Pattern	Examples	Challenges in Drug Delivery
I	High	High	Well absorbed	Diltiazem Propranolol Metoprolol	No major challenges for immediate release forms but CR forms need to limit drug release or dissolution since absorption of released drug is rapid.
II	Low	High	Variable	Nifedipine Carbamazepine Naproxen	Formulations are designed to overcome solubility or dissolution problems by various means (see later sections of this chapter).
III	High	Low	Variable	Insulin Metformin Cimetidine	Approaches are employed to enhance permeability (see later sections of this chapter).
IV	Low	Low	Poorly absorbed	Taxol Chlorthiazide Furosemide	Combination of strategies used for Class II and Class III drugs are employed to improve both dissolution and permeability.

Bioavailability Enhancement through Enhancement of Drug Solubility or Dissolution Rate

1. Micronization

To reduce the size of solid pharmaceutical particles to 1 to 10 microns, spray drying or air attrition methods are frequently utilised (fluid energy or jet mill). The method is also known as micro-milling. Micronization has enhanced the bioavailability of drugs like grifofulvin and a variety of steroidal and sulpha medicines.

2. Nanonization

It's a method of converting drug powder into nanocrystals with diameters ranging from 200 to 600 nanometers, such as amphotericin B. Nanoparticles are now prepared using three fundamental technologies:

a. Milling of pearls

b. Water homogenization (wet milling as in a colloid mill)

c. Homogenization in non-aqueous medium or with water-miscible liquids in water.

3. Fluid Supercritical Recrystallization

Another breakthrough nanosizing and solubilization method that has gained prominence in recent years is particle size reduction using supercritical fluid (SCF) techniques. Supercritical fluids (such as carbon dioxide) have temperatures and pressures that are higher than their critical temperatures (Tc) and critical pressures (Tp), allowing them to exhibit both liquid and gas properties.

4. Use of Surfactants

Surfactants are excellent absorption enhancers, increasing both drug dissolution rate and permeability. They improve dissolving rate by enhancing dissolution fluid wetting and penetration into solid drug particles. They are typically utilised at concentrations below their critical micelle concentration (CMC), as the drug entrapped in the micelle structure fails to partition in the dissolving fluid above CMC.

5. Use of Salt Forms

Salts have better solubility and dissolving qualities than the original drug. It's common knowledge that stable salts require a pK_a difference of at least 3 units between the group's pK_a and its counterion's pK_a. There are some limitations to salt formation:

a) It is impossible to make salts of neutral substances.

b) Salts of very weak bases or acids may be difficult to produce.

c) The salt could be hygroscopic, polymorphic, or have poor processing qualities.

d) Preventing or delaying drug release by converting salt to free acid or basic form of the drug on the surface of a solid dosage form.

e) Precipitation of a poorly soluble unionised drug in the GI environment.

6. Use of Amorphs, Anhydrates, Solvates and Metastable Polymorphs

The right form of drug with increased solubility must be chosen based on the internal structure of the solid drug. Amorphs are soluble more than metastable polymorphs, anhydrates are soluble more than hydrates, and solvates are soluble more than non-solvates.

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7. Solvent Deposition

By evaporating the solvent, a poorly water soluble drug like nifedipine is dissolved in an organic solvent like alcohol and deposited on an inert, hydrophilic solid matrix like starch or microcrystalline cellulose.

8. Precipitation

In this approach, a poorly water soluble drug like cyclosporine is dissolved in an organic solvent, then rapidly mixed with a non-solvent to precipitate the drug into nanosize particles. Hydrosol is another name for the finished product.

BIOAVAILABILITY ENHANCEMENT THROUGH ENHANCEMENT OF DRUG PERMEABILITY ACROSS BIO-MEMBRANE

Due to limited permeability, the rate-limiting step in drug absorption is frequently transit via the intestinal epithelium. Aside from using lipophilic prodrugs, there are several more methods for increasing drug penetration rates.

1. Lipid Technologies

With the rise in the number of new hydrophobic drugs, multiple lipid-based formulations have been developed to improve bioavailability through a variety of processes, which are briefly summarised as follows:

Physicochemical: Enhanced dissolution and solubility.

Physiological: potential mechanisms include:

a) Increased effective luminal solubility by increased production of bile salts, endogenous biliary lipids such as phospholipids, and cholesterol, which combine to create mixed micelles that aid drug GI solubilization.

b) Increased time available for breakdown and absorption due to a decrease in stomach emptying rate.

c) Increased permeability of the intestinal membrane.

d) Intestinal blood flow is reduced.

e) A reduction in luminal degradation.

f) Increased lymphatic system absorption from the intestinal lumen (and a reduction in first-pass hepatic and GI metabolism).

Lipid solutions and suspensions, micelle solubilization, coarse emulsions, microemulsions, multiple emulsions, selfemulsifying drug delivery systems (SEDDS), self-microemulsifying drug delivery systems (SMEDDS), nanoparticles, and liposomes are all examples of lipid-based dosage forms.

2. Ion Pairing

The ion pairing method entails combining a hydrophilic or polar drug with an appropriate lipophilic counterion, which increases the partitioning of the resulting ion-pair (which is more lipophilic) through the intestinal membrane. In fact, the method appears to boost the oral bioavailability of ionizable drugs like atenolol by about twofold. A counterion must, however, have a high lipophilicity, enough water solubility, physiological compatibility, and metabolic stability.

3. Penetration Enhancers

Penetration/permeation enhancers or promoters are compounds that make it easier for drugs to cross the biomembrane. This approach is mostly employed when hydrophilic medicines are expected to have trouble entering the biomembrane's lipid structure. Penetration enhancers work by interacting with the polar component of membrane phospholipids through their lipid component. Penetration enhancers are classified into three groups:

a) Fast-acting substances, such as fatty acids like oleic, linoleic, and arachidonic acid, and their monoglycerides, have a powerful effect and produce reversible membrane damage.

b) Fast-acting substances that produce brief harm but have a moderate activity, such as salicylates and some bile salts.

c) SLS, EDTA, and citric acid are examples of substances that have moderate to strong action but produce long-term histological alterations.

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BIOAVAILABILITY ENHANCEMENT THROUGH ENHANCEMENT OF DRUG STABILITY

The different mechanisms in which improved drug stability in the GIT improves bioavailability are explored further down.

1. **Enteric Coating:** Enteric-coated systems make use of polymeric coatings that are insoluble in gastric medium, preventing or delaying drug release in the stomach. Such methods release the drug into the intestine's alkaline environment. Enteric coating can improve the bioavailability of drugs that are unstable in the stomach environment, such as erythromycin, penicillin V, pancreatin, and benzimidazoles like omeprazole.

2. **Complexation:** Complexation, in certain situations, can be utilised to increase the stability of drug in the GI milieu, notably those of ester pharmaceuticals and hence enhance their oral availability. In general, cyclodextrins can be utilised to achieve these goals, although additional complexing agents including caffeine, sodium salicylate, sodium benzoate, and nicotinamide can also be used.

3. **Use of Metabolism Inhibitors:** Co-administration of a low bioavailability drug with a metabolic inhibitor that can selectively block any of the contributing pathways results in greater fractional absorption and thus higher bioavailability. In fact, this method appears to be a viable way to circumvent enzymatic hurdles to oral administration of metabolically labile drugs like peptides and proteins.

BIOAVAILABILITY ENHANCEMENT THROUGH GASTROINTESTINAL RETENTION

Gastro-retentive drug delivery systems (GRDDS) are intended to constrain and localise the drug delivery device in the stomach or upper sections of the small intestine until the full drug is released, based on delayed gastric emptying and CR principles. When added in an oral dosage form, excipients that are bioadhesive or swell on hydration can increase gastro-retention and absorption by increasing contact with epithelial surfaces, prolonging residence time in the stomach, and delaying intestinal transit.