ISSN: 2707-1146
e-ISSN: 2709-4189

https://doi.org/10.36719/2707-1146/54/30-34

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What Should We Know About Bioavailability and Bioequivalence?

Abstract

Bioequivalence studies a crucial role in the development and approval of generic drugs, requiring input from multiple disciplines, including regulatory affairs, pharmacokinetics, and statistics. These studies assess whether the test (T) and reference (R) formulations exhibit similar bioavailability, ensuring therapeutic equivalence. Typically, they involve well-established study designs, such as parallel or crossover approaches, which help compare the pharmacokinetic parameters of both formulations. The bioanalytical methods used in these studies must be highly accurate, precise, selective, sensitive, and reproducible to generate reliable data. Peripheral blood, including plasma, serum, or whole blood, is the most commonly used biological matrix for evaluating a drug's systemic availability. The collection and analysis of biological fluid samples allow for the quantification of the active drug ingredient, its active moiety, and, when necessary, its active metabolites. These measurements are essential for determining the pharmacokinetic properties of the drug and ensuring compliance with regulatory bioequivalence criteria, ultimately supporting safe and effective drug substitution.

Keywords: *bioequivalence, bioavailability, biological fluid, dosage form*

Introduction

Pharmaceuticals have become an indispensable consumption item today. In order to increase their market share, pharmaceutical companies produce, licence and offer for sale over-sold drug products under different names. Thus, the number of similar preparations containing the same active substance in the same amounts is increasing rapidly. One of the most important factors affecting the success of medication applications is the bioavailability of the drug, that is, the amount that can reach the target area from the application site. The fact that the effectiveness of drugs containing the same active substance at the same rate in treatment is close to each other indicates that their bioavailability is equal. Whether the expected therapeutic response can be obtained from systemically effective drugs is determined by bioavailability studies. Bioavailability, which is important in the development of both new and generic drugs, can be investigated in two different ways, absolute and relative bioavailability, and these two concepts give us different information about the active substance and the preparation containing it. Similar preparations containing the same active substances in the same ratio must be pharmaceutically bioequivalent in order to be equivalent (Canbolat, 2002).

Research

The efficacy, safety, quality, control and supervision of drugs are primarily performed by bioequivalence and bioavailability studies. Bioavailability and/or bioequivalence studies are among the documents required for the licensing of pharmaceutical products.

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In particular, proving the therapeutic equivalence between the drug of the company that first discovered the drug and a drug produced as a pharmaceutical equivalent that is not under patent protection is considered as the most important factor showing that this drug can be used clinically instead of the other. Therefore, in the licensing of drugs, it is as important for the health and safety of the patient whether they can be used interchangeably (equivalence) as quality, efficacy and safety. Bioequivalence tests play an important role in the evaluation of drug formulations with similar clinical and pharmacological effects and similar plasma drug concentration-time curves (Mehta, 2023). Bioequivalence tests are the most important tests in demonstrating therapeutic equivalence, especially for active substances and/or pharmaceutical dosage forms that are used orally and show bioavailability problems. Drugs with proven therapeutic equivalence are interchangeable drugs. In other words, they can be used interchangeably. In a broad sense, bioavailability is the rate and degree to which the active substance is absorbed from its pharmaceutical form (except iv) and passes into the systemic circulation and is thus present at the site of action in the body or in biological fluids (usually serum and plasma) that reflect it. These two parameters determine the 'bioavailability' of a drug (Feng, 2008).

Compared to the solid pharmaceutical form of a drug with a liquid, it is absorbed from the gastrointestinal tract faster and sometimes more. The drug effect starts earlier. Drugs in solid form such as tablets undergo disintegration and dissolution in gastrointestinal fluids after oral administration and are absorbed. An undispersed or slowly disintegrating tablet may result in inadequate absorption or, in the best case, a further delay in the clinical response. Depending on the pharmaceutical form of the drug, bioavailability is in the order of solution > capsule > tablet > coated tablet.

Source of Raw Material; Purity and quality differences that may arise due to the supply of both the active substance and the excipients in the composition of the preparation from different sources may lead to significant bioavailability and bioequivalence problems (Lee, 2008).

Particle Size of Active Substance; The smaller the drug molecule, the faster it is absorbed. As the particles become smaller, the dissolution rate increases as the surface area increases. In studies, it has been observed that the dissolution rate and absorption of griseofulvin increases as the particle size decreases (Dortunç, 2007).

Crystal Shape of the Active Substance; The solubility of a drug with polymorphous structure in water and therefore in the gastrointestinal system varies according to its crystal shape. Amorphous shapes are better soluble than crystallised shapes. Differences in bioavailability may occur as a result of the use of a different crystal form of the active substance, the transformation of an unstable crystal form into another form in the preparation or the use of an amorphous form of the active substance. The amorphous form of novobiocin has at least 10 times more solubility than the crystalline form. In studies in dogs, the amorphous form was rapidly absorbed by oral administration, whereas the crystalline form could not be absorbed.

Formation of Complex with Active Substance; The formation of a drug complex in the gastrointestinal reduces the rate and amount of absorption. For example, the polysaccharide called mucin in the intestine can bind streptomycin and dihydrostreptomycin to a high degree. This binding may cause poor absorption of antibiotics. Similarly, bile salts in the small intestine can form insoluble complexes with some drugs including neomycin and kanamycin. Sometimes bioavailability of drugs that cause bioavailability problems due to their slow and low solubility in water can be increased by complexing them with other drugs or substances (Traş, 2005).

Ionisation Degree of the Active Substance: The degree of ionisation affects the solubility of drugs in oil or water. Since it is determined by the pH of the environment in which the drug is administered and absorbed, even small changes in the pH of the digestive system affect the bioavailability of some drugs. As the environment becomes more acidic, the proportion of non-ionised parts of weakly acidic substances increases and their absorption becomes easier. The ionisation of weak basic substances increases and their absorption rate decreases. When the environment becomes alkaline, ionisation of weak acidic substances is encouraged and absorption

ISSN: 2707-1146
e-ISSN: 2709-4189

rates decrease, while the ratio of non-ionised parts of weak basic substances increases and absorption becomes easier (Güç, 2008).

Interaction; Drugs are mixed with excipients (fillers, dyes, binders, binders, lubricants, surfactants) during their production while forming solid pharmaceutical forms. These substances may change the disintegration and dissolution rate of the active substance.

Patient Related Factors Stomach Emptying Rate; Rapid emptying of the stomach increases the absorption rate and rate of drugs absorbed from the small intestine. Absorption rate of many drugs decreases in the presence of food. Digoxin, cephalexin and various sulphonamides can be given as examples. Drugs that are broken down as a result of acid hydrolysis in the stomach are absorbed at a higher rate. In general, absorption is better when the stomach is empty. However, absorption of some drugs increases when they are taken after a meal. For example, absorption of riboflavin is higher than normal after a standard breakfast. In general, weakly acidic drugs are better absorbed from the stomach than from the intestine.

In the small intestine; absorption increases due to the length of the transit time and the fact that the surface area suitable for absorption in the small intestine is much larger than in the stomach. Intestinal Motility; Slowing of intestinal motility prolongs the transit time through the intestine. Some drugs, which are absorbed difficultly because they are hardly soluble in the intestine, remain in the intestine for a long time, increasing their solubility and allowing them to be absorbed at a high rate.

Perfusion of the gastrointestinal tract; Blood flow in the digestive tract is generally important for lipophilic drugs absorbed by simple diffusion. Acceleration of blood flow here is important for absorption rate and clearance, especially for drugs with high presystemic elimination (FDA, 2002).

Individual Differences; A small genetic variation in each enzymatic step involved in the CT of drugs may cause intra-individual or inter-individual differences in the effect of the drug. Bioavailability is the genetic polymorphism shown by liver enzymes. In vitro and in vivo (clinical) trials in the determination of bioavailability In Vitro Trials In vitro tests, which require less expense, are performed in a short time and with simple techniques, have practical and economic importance. In vitro tests can actually provide an indication of bioavailability. These tests are applied to solid pharmaceutical forms.

Disintegration Test; It is a test applied to tablets other than chewable and slow-release tablets. It is performed with the help of hanging basket system and discs. The purpose of the test is to compare the level of disintegration of the tablets in the appropriate liquid with the limits of disintegration determined in the monographs. Usually at least 16 out of 18 tablets should be completely disintegrated.

Dissolution Test; The dissolution rate of the drug in solid pharmaceutical form in a certain environment, such as artificial gastric or intestinal juice, under certain test conditions (370C) is determined. At the end of this test, the dissolution of 50% of the amount of the drug in the pharmaceutical form is evaluated.

Determination of Plasma Concentration Profile; The drug is administered to patients or volunteers and the drug concentration in blood samples is measured at certain intervals and the drug concentration-time curve is drawn. As a rule, the total sampling time should be the half-life of the drug. If the Cmax and tmax of the two preparations analysed are equal, they are considered equivalent in terms of absorption rates.

Measurement of Cumulative Drug Amount in Urine; After the drug is given to the patient, the urine of the subject is collected at certain intervals for a certain period of time (5-10 times the half-life) and the curve of the cumulative amount of the drug excreted in the urine is drawn according to time. These curves are evaluated in terms of the maximum amount reached and their slope, i.e. the rate at which they reach the maximum (FDA, 2003).

Bioequivalence can be defined as the bioavailability (the rate and extent to which the active ingredient in the pharmaceutical alternatives reaches the site of action) of two pharmaceutically equivalent preparations (one test and one reference) after administration of the same molar dose,

ISSN: 2707-1146
e-ISSN: 2709-4189

within accepted limits (±20%), so that their therapeutic effects are similar enough to be identical in terms of both efficacy and safety (Armando, Serra, Porta, Koono, Kano, 2009).

Therapeutic Equivalence: A preparation is therapeutically equivalent if it contains the same active substance or therapeutically effective molecule part with another preparation whose efficacy and safety have been previously determined and if it shows the same efficacy and safety clinically with that (Gozzo, 2022).

Pharmacological equivalence is the situation where molecules that are chemically different but produce the same active molecules in the body and cause the same pharmacological effect are added into two different pharmaceutical forms.

Pharmaceutical Alternatives; Pharmaceutical products are pharmaceutical alternatives if they contain the same active molecule part, but differ in chemical form, dosage form or quantity (Novakovic, 2019).

Pharmacokinetic Properties of the Active Substance; Non-linear (dose-dependent) kinetics of the drug within the therapeutic dose range, presystemic elimination of more than 70%, absorption of less than 70%, absorption and elimination rate of the preparation showing high variability between individuals (Kaya, 2006).

Conclusions

In ***in vivo*** bioequivalence studies, bioavailability is typically evaluated based on the rate and extent of drug absorption into the bloodstream of human subjects. However, for certain locally acting drug products, such as nasal aerosols and nasal, which are not meant to enter the bloodstream, bioavailability is instead assessed using measurements that indicate how efficiently the active ingredient or moiety reaches the site of action.

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Received: 14.12.2024
Accepted: 26.02.2025