

Bioavailability

In pharmacology, **bioavailability** is used to describe the fraction of an administered dose of unchanged drug that reaches the systemic circulation, one of the principal pharmacokinetic properties of drugs. By definition, when a medication is administered intravenously, its bioavailability is 100%.^[1] However, when a medication is administered via other routes (such as orally), its bioavailability decreases (due to incomplete absorption and first-pass metabolism) or may vary from patient to patient (due to inter-individual variation). Bioavailability is one of the essential tools in Pharmacokinetics, as bioavailability must be considered when calculating dosages for non-intravenous routes of administration.

For dietary supplements, herbs and other nutrients in which the route of administration is nearly always oral, bioavailability generally designates simply the quantity or fraction of the ingested dose that is absorbed.^[2]

Bioavailability is defined slightly differently for drugs as opposed to dietary supplements primarily due to the method of administration and Food and Drug Administration regulations.

Bioaccessibility is a concept related to bioavailability in the context of biodegradation and environmental pollution. A molecule (often a persistent organic pollutant) is said to be bioavailable when "*[it] is available to cross an organism's cellular membrane from the environment, if the organism has access to the chemical.*"^[3]

Definitions

In pharmacology

In pharmacology, bioavailability is a measurement of the extent to which a drug reaches the systemic circulation.^[4] It is denoted by the letter F .

In nutritional sciences

In nutritional sciences, which covers the intake of nutrients and non-drug dietary ingredients, the concept of bioavailability lacks the well-defined standards associated with the pharmaceutical industry. The pharmacological definition cannot apply to these substances because utilization and absorption is a function of the nutritional status and physiological state of the subject,^[5] resulting in even greater differences from individual to individual (inter-individual variation). Therefore, bioavailability for dietary supplements can be defined as the proportion of a the substance capable of being absorbed and available for use or storage.^[6]

In both pharmacology and nutrition sciences, the bioavailability is measured by calculating the area under curve, or AUC, of the drug concentration time profile.

Absolute bioavailability

Absolute bioavailability compares the bioavailability of the active drug in systemic circulation following non-intravenous administration (i.e., after oral, rectal, transdermal, subcutaneous, or sublingual administration), with the bioavailability of the same drug following intravenous administration. It is the fraction of the drug absorbed through non-intravenous administration compared with the corresponding intravenous administration of the same drug. The comparison must be dose normalized (e.g. account for different doses or varying weights of the subjects); consequently, the amount absorbed is corrected by dividing the corresponding dose administered.

In pharmacology, in order to determine absolute bioavailability of a drug, a pharmacokinetic study must be done to obtain a *plasma drug concentration vs time* plot for the drug after both intravenous (IV) and non-intravenous administration. The absolute bioavailability is the dose-corrected area under curve (AUC) non-intravenous divided by AUC intravenous. For example, the formula for calculating F for a drug administered by the oral route (po) is

given below.

$$F = \frac{[AUC]_{po} * dose_{IV}}{[AUC]_{IV} * dose_{po}}$$

Therefore, a drug given by the intravenous route will have an absolute bioavailability of 1 (F=1) while drugs given by other routes usually have an absolute bioavailability of less than one. If we compare the two different dosage forms having same active ingredients and compare the two drug bioavailability is called comparative bioavailability. Although knowing the true extent of systemic absorption (referred to as absolute bioavailability) is clearly useful, in practice it is not determined as frequently as one may think. The reason for this is that its assessment requires an intravenous reference, that is, a route of administration that guarantees that all of the administered drug reaches the systemic circulation. Such studies come at considerable cost, not least of which is the necessity to conduct preclinical toxicity tests to ensure adequate safety, as well as there being potential problems due to solubility limitations.^[7]

There is no regulatory requirement to define the intravenous pharmacokinetics or absolute bioavailability however regulatory authorities do sometimes ask for absolute bioavailability information of the extravascular route in cases in which the bioavailability is apparently low or variable and there is a proven relationship between the pharmacodynamics and the pharmacokinetics at therapeutic doses. In all such cases, to conduct an absolute bioavailability study requires that the drug be given intravenously.^[8]

Intravenous administration of a developmental drug can provide valuable information on the fundamental pharmacokinetic parameters of volume of distribution (V) and clearance (CL).^[8]

Relative bioavailability and bioequivalence

In pharmacology, relative bioavailability measures the bioavailability (estimated as the AUC) of a certain drug when compared with another formulation of the same drug, usually an established standard, or through administration via a different route. When the standard consists of intravenously administered drug, this is known as absolute bioavailability.

$$\text{relative bioavailability} = \frac{[AUC]_A * dose_B}{[AUC]_B * dose_A}$$

0.05 level of significance For FDA approval, a generic manufacturer must show that the 90% confidence interval for the ratio of the mean response (usually AUC and Cmax) of its product to that of the "Brand Name drug" is within the limits of 0.8 to 1.25 at the 0.05 level of significance. Relative bioavailability is extremely sensitive to drug formulation. Relative bioavailability is one of the measures used to assess bioequivalence between two drug products, as it is the Test/Reference ratio of AUC. The maximum concentration of drug in plasma or serum (Cmax) is also usually used to assess bioequivalence. When Tmax is given, it refers to the time it takes for a drug to reach Cmax.

While the mechanisms by which a formulation affects bioavailability and bioequivalence have been extensively studied in drugs, formulation factors that influence bioavailability and bioequivalence in nutritional supplements are largely unknown.^[9] As a result, in nutritional sciences, relative bioavailability or bioequivalence is the most common measure of bioavailability, comparing the bioavailability of one formulation of the same dietary ingredient to another.

Factors influencing bioavailability

The absolute bioavailability of a drug, when administered by an extravascular route, is usually less than one (i.e. $F < 1$). Various physiological factors reduce the availability of drugs prior to their entry into the systemic circulation. Whether a drug is taken with or without food will also affect absorption, other drugs taken concurrently may alter absorption and first-pass metabolism, intestinal motility alters the dissolution of the drug and may affect the degree of chemical degradation of the drug by intestinal microflora. Disease states affecting liver metabolism or

gastrointestinal function will also have an effect.

Other factors may include, but are not limited to:

- Physical properties of the drug (hydrophobicity, pKa, solubility)
- The drug formulation (immediate release, excipients used, manufacturing methods, modified release - delayed release, extended release, sustained release, etc.)
- If the drug is administered in a fed or fasted state
- Gastric emptying rate
- Circadian differences
- Interactions with other drugs/foods:
 - Interactions with other drugs (e.g. antacids, alcohol, nicotine)
 - Interactions with other foods (e.g. grapefruit juice, pomello, cranberry juice)
- Transporters: Substrate of an efflux transporter? (e.g. P-glycoprotein)
- Health of the GI tract
- Enzyme induction/inhibition by other drugs/foods:
 - Enzyme induction (increase rate of metabolism). e.g. Phenytoin (antiepileptic) induces CYP1A2, CYP2C9, CYP2C19 and CYP3A4
 - Enzyme inhibition (decrease rate of metabolism). e.g. grapefruit juice inhibits CYP3A --> higher nifedipine concentrations
- Individual Variation in Metabolic Differences
 - Age: In general, drugs metabolized more slowly in fetal, neonatal, and geriatric populations
 - Phenotypic differences, enterohepatic circulation, diet, gender.
- Disease state
 - e.g. hepatic insufficiency, poor renal function

Each of these factors may vary from patient to patient (inter-individual variation), and indeed in the same patient over time (intra-individual variation). In drug clinical trials, inter-individual variation is a critical measurement used to assess the bioavailability differences from patient to patient in order to ensure predictable dosing.

Bioavailability of drugs versus dietary supplements

In comparison to drugs, there are significant differences in dietary supplements that impact the evaluation of their bioavailability. These differences include the following: the fact that nutritional supplements provide benefits that are variable and often qualitative in nature; the measurement of nutrient absorption lacks the precision; nutritional supplements are consumed for prevention and well-being; nutritional supplements do not exhibit characteristic dose-response curves; and dosing intervals of nutritional supplements, therefore, are not critical in contrast to drug therapy.^[6]

In addition, the lack of defined methodology and regulations surrounding the consumption of dietary supplements hinders the application of bioavailability measures in comparison to drugs. In clinical trials with dietary supplements, bioavailability primarily focuses on statistical descriptions of mean or average AUC differences between treatment groups, while often failing to compare or discuss their standard deviations or inter-individual variation. This failure leaves open the question of whether or not an individual in a group is likely to experience the benefits described by the mean-difference comparisons. Further, even if this issue were discussed, it would be difficult to communicate meaning of these inter-subject variances to consumers and/or their physicians.

Nutritional science: reliable and universal bioavailability

One way to resolve this problem is to define “reliable bioavailability” as positive bioavailability results (an absorption meeting a predefined criteria) that include 84% of the trial subjects and “universal bioavailability” as those that include 98% of the trial subjects. This reliable-universal framework would improve communications with physicians and consumers such that, if it were included on products labels for example, make educated choices as to the benefits of a formulation for them directly. In addition, the reliable-universal framework is similar to the construction of confidence intervals, which statisticians have long offered as one potential solution for dealing with small samples, violations of statistical assumptions or large standard deviations.^[10]

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External links

- <http://www.nottingham.ac.uk/nursing/sonet/rlos/bioproc/metabolism/default.html>
- <http://www.xceleron.com/metadot/index.pl?iid=2724>

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