Bioavailability and Bioequivalence

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Multisource drug product

- contains the same active drug substance in the same dosage form
- marketed by more than one pharmaceutical manufacturer

Single-source drug products

- The patent has not yet expired
- or has certain exclusivities so that only one manufacturer can make it.
- Are usually brand-name (innovator) drug products

Single-source drug products

- After the patent and other exclusivities for the brand-name drug expires, the generic drug manufacturer must demonstrate that the generic drug product is bioequivalent and therapeutically equivalent to the brand-name drug product.

U.S. Food and Drug Administration (FDA) publishes annually, in print and on the Internet:

Approved Drug Products with Therapeutic Equivalence Evaluations

also known as the *Orange Book*

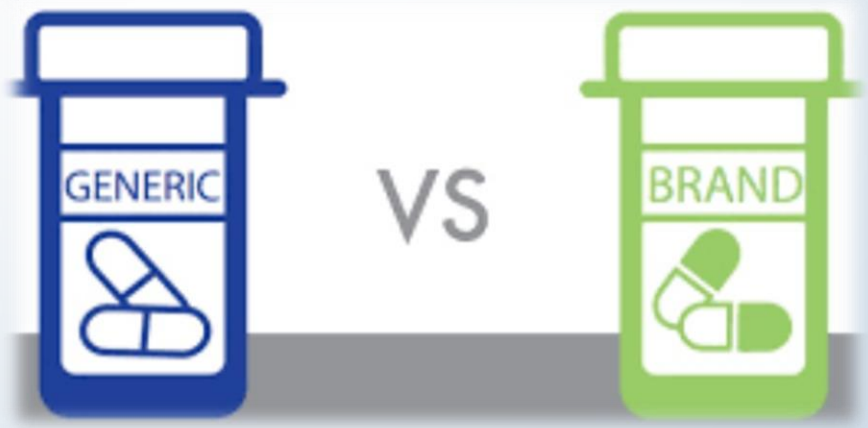
Definitions

- ***Bioavailability***. Bioavailability means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.

- ***Bioequivalence requirement***. A requirement imposed by the FDA for *in-vitro* and/or *in-vivo* testing of specified drug products, which must be satisfied as a condition for marketing.

- ***Bioequivalent drug products***. This term describes pharmaceutical equivalent or pharmaceutical alternative products that display comparable bioavailability when studied under similar experimental conditions.

- ***Brand name***. The trade name of the drug. This name is privately owned by the manufacturer or distributor and is used to distinguish the specific drug product from competitor's products



- ***Chemical name***. The name used by organic chemists to indicate the chemical structure of the drug

  (eg N-acetyl-*p*-aminophenol).

- ***Equivalence***. Relationship in terms of bioavailability, therapeutic response, or a set of established standards of one drug product to another.

- ***Generic name***. The established, nonproprietary, or common name of the active drug in a drug product (eg, acetaminophen).

- **Generic substitution.** The process of dispensing a different brand or an unbranded drug product in place of the prescribed drug product.

- ***Pharmaceutical alternatives***. Drug products that contain the same therapeutic moiety but as different salts, esters, or complexes.

  For example,

  tetracycline phosphate or tetracycline hydrochloride equivalent to 250 mg tetracycline base

- ***Pharmaceutical equivalents***. Drug products in identical dosage forms that contain the same active ingredient(s)
  - i.e., the same salt or ester, are of the same dosage form, use the same route of administration, and are identical in strength or concentration
  - (eg, chlordiazepoxide hydrochloride, 5-mg capsules).

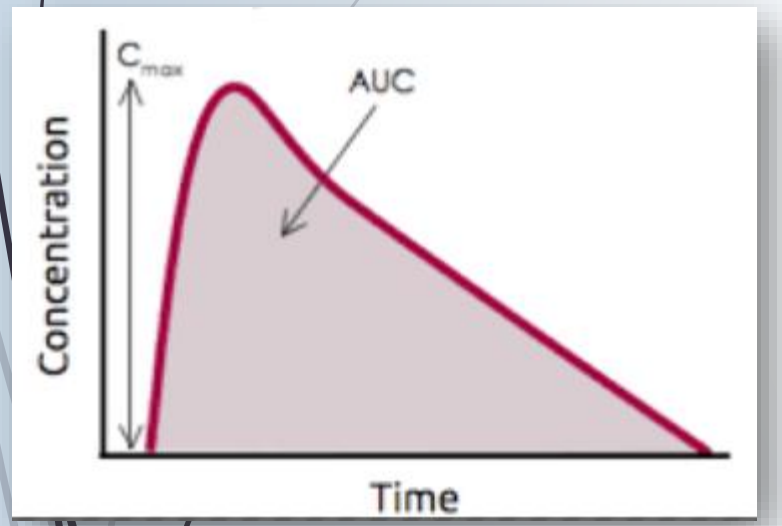
Purpose of Bioavailability Studies

for both:

- ✓ approved active drug ingredients
- ✓ therapeutic moieties not yet approved for marketing by the FDA.

- New formulations of active drug ingredients must be approved by the FDA before marketing.
- The FDA ensures that the drug product is safe and effective.
- must meet all applicable standards of identity, strength, quality, and purity.

Relative and Absolute Availability



- The area under the drug concentration–time curve (AUC):

is a measure of the total amount of unaltered drug that reaches the systemic circulation.

Relative Availability

- The availability of the drug from a drug product as compared to a recognized standard.
- The relative availability of two drug products given at the same dosage level and by the same route of administration can be obtained using the following equation:

$$\text{Relative availability} = \frac{[\text{AUC}]_{\text{A}}}{[\text{AUC}]_{\text{B}}}$$

B is the recognized reference standard

- When different doses are administered:

$$\text{Relative availability} = \frac{[\text{AUC}]_{\text{A}}/\text{ dose A}}{[\text{AUC}]_{\text{B}}/\text{ dose B}}$$

Absolute Availability

- The absolute availability of drug is the systemic availability of a drug after extravascular administration

(eg, oral, rectal, transdermal, subcutaneous) compared to IV dosing.

- Absolute availability is sometimes expressed as a percent

ie, $F = 1$, or 100%.

Practice Problem:

The bioavailability of a new investigational drug was studied in 12 volunteers

Drug Product	Dose (mg)	AUC (μg hr/mL)	Standard Deviation
Oral tablet	200	89.5	19.7
Oral solution	200	86.1	18.1
IV bolus injection	50	37.8	5.7

Solution

The relative bioavailability of the drug from the tablet is estimated:

$$\text{Relative bioavailability} = \frac{89.5}{86.1} = 1.04 \quad \text{or} \quad 104\%$$

The relative bioavailability of the drug from the tablet is 1.04, or 104%, compared to the solution.

The absolute drug bioavailability from the tablet is calculated using The following Equation and adjusting for the dose.

$$F = \text{absolute bioavailability} = \frac{89.5/200}{37.8/50} = 0.592 \quad \text{or} \quad 59.2\%$$

Because *F*, the fraction of dose absorbed from the tablet, is less than 1, the drug is not completely absorbed systemically

Methods for Assessing Bioavailability

- Direct and indirect methods
- the rate and extent of drug absorption:

as determined by comparison of measured parameters, e.g.,

- concentration of the active drug ingredient in the blood
- cumulative urinary excretion rates
- or pharmacological effects

Methods for Assessing Bioavailability

- Drug products that are not absorbed into the bloodstream:

bioavailability may be assessed by measurements intended to reflect the **rate** and **extent** to which the active ingredient or active moiety becomes available at the site of action.

Methods for Assessing Bioavailability and Bioequivalence

Plasma drug concentration
Time for peak plasma (blood) concentration (t_{max})
Peak plasma drug concentration (C_{max})
Area under the plasma drug concentration–time curve (AUC)

Urinary drug excretion
Cumulative amount of drug excreted in the urine (D_u)
Rate of drug excretion in the urine (dD_u/dt)
Time for maximum urinary excretion (t)

Acute pharmacodynamic effect
Maximum pharmacodynamic effect (E_{max})
Time for maximum pharmacodynamic effect
Area under the pharmacodynamic effect–time curve
Onset time for pharmacodynamic effect

Clinical observations
Well-controlled clinical trials

***In-vitro* studies**
Drug dissolution

Plasma Drug Concentration

- Measurement of drug concentrations in blood, plasma, or serum after drug administration is the most direct and objective way to determine systemic drug bioavailability

Plasma Drug Concentration

- ***t*** $_{max}$. The *time of peak plasma concentration*
- *t* $_{max}$, corresponds to the time required to reach maximum drug concentration after drug administration.
- absorption rate for the drug becomes more rapid.
- Units for *t* $_{max}$ are units of time (eg, hours, minutes).

Plasma Drug Concentration

- C max. The peak plasma drug concentration
- C max, represents the maximum plasma drug concentration
- For many drugs, a relationship is found between the pharmacodynamic drug effect and the plasma drug concentration.
- The units of C max are concentration units (eg, mg/mL, ng/mL).
- C max is used in bioequivalence studies as a measure for the rate of drug bioavailability.

Plasma Drug Concentration

- ***AUC.*** The *area under the plasma level–time curve*
- is a measurement of the *extent* of drug bioavailability
- reflects the total amount of active drug that reaches the systemic circulation
- is equal to the amount of unchanged drug reaching the general circulation divided by the clearance.

Plasma Drug Concentration

- is the area under the drug plasma level–time curve from $t = 0$ to $t = \infty$

$$[\mathrm{AUC}]_0^\infty = \int_0^\infty C_\mathrm{p}\, dt$$

Plasma Drug Concentration

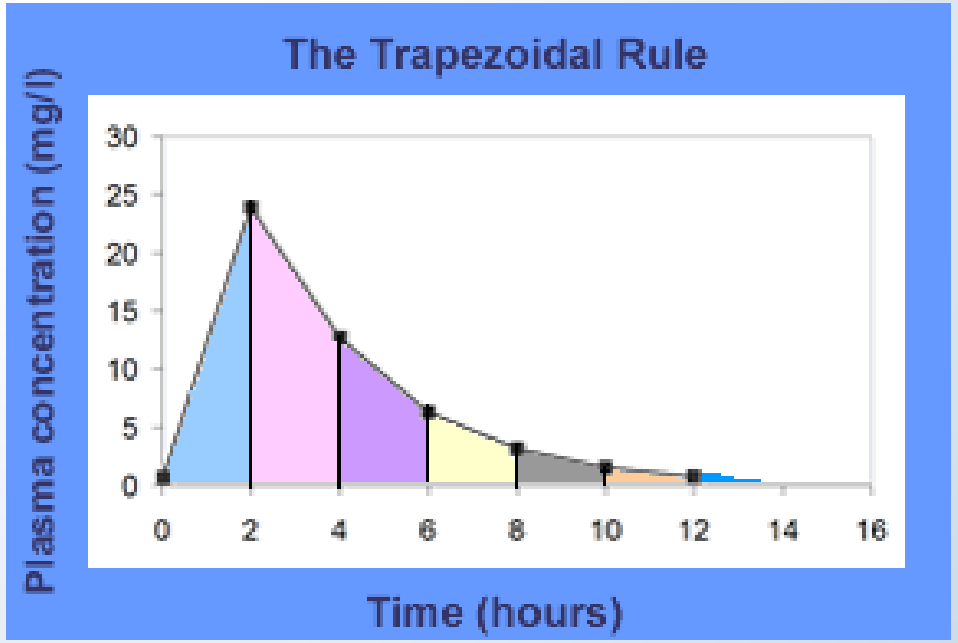
$$[\mathrm{AUC}]_0^\infty = \frac{FD_0}{\text{clearance}} = \frac{FD_0}{kV_\mathrm{D}}$$

Where:

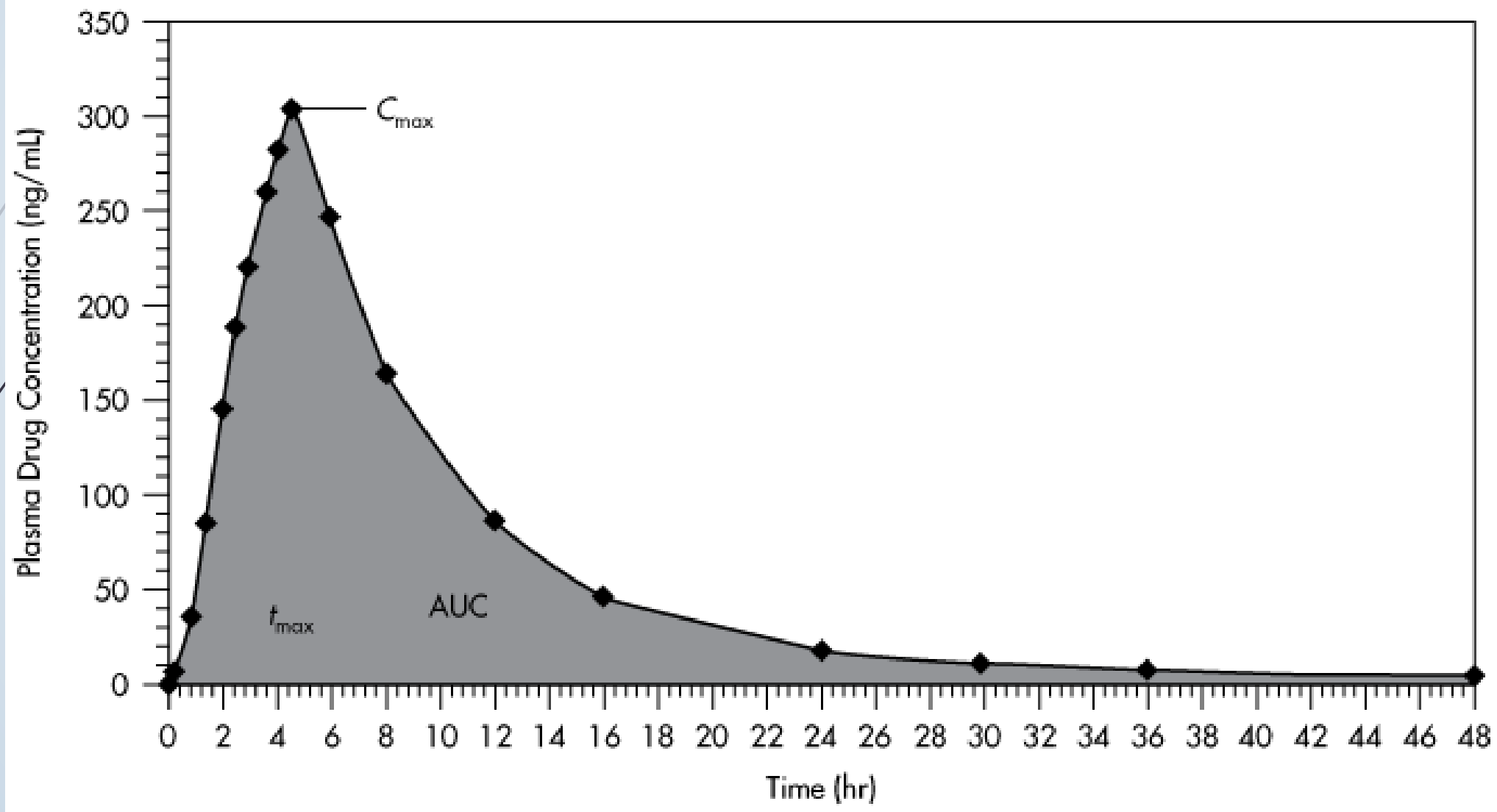
- F = fraction of dose absorbed
- D_0 = dose
- k = elimination rate constant
- V_D = volume of distribution.

- The AUC is independent of the route of administration
- AUC can be determined by a numerical integration procedure, such as the trapezoidal rule method.
- The units for AUC are concentration time

  (eg, µg hr/mL).



Plasma Concentrations-Time Curve

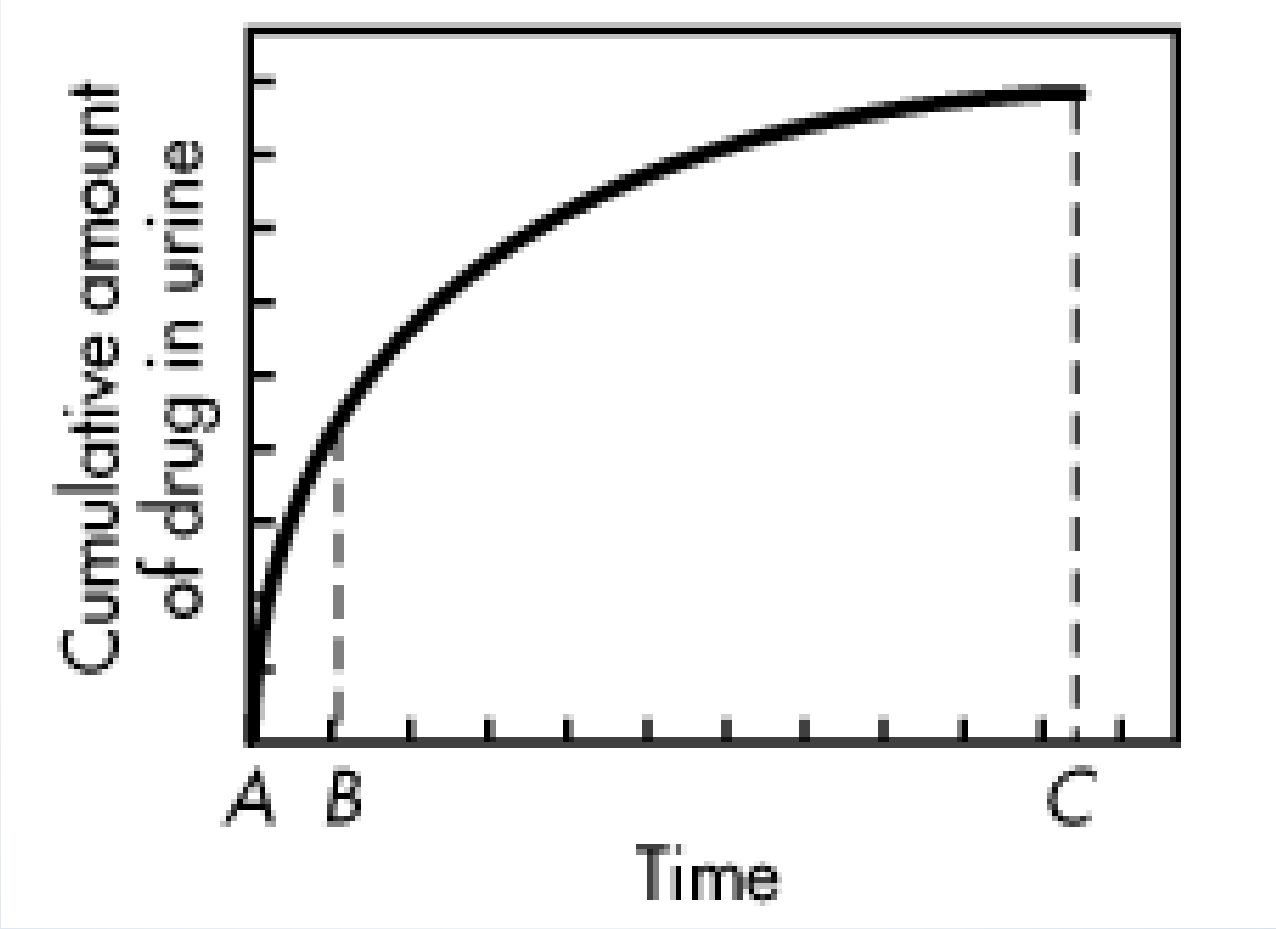


Urinary Drug Excretion Data

- is an indirect method for estimating bioavailability
- ***D*** $^{\infty}{}_{u}$. The *cumulative amount of drug excreted in the urine*
- $D^{\infty}{}_{u}$, is related directly to the total amount of drug absorbed.

- ***dD*** $_{U}$***/dt.*** The *rate of drug excretion*. Because most drugs are eliminated by a first-order rate process, the rate of drug excretion is dependent on the first-order elimination rate constant *k*

- ***t*** **∞.** The *total time for the drug to be excreted*



In-Vitro Studies

Drug dissolution studies may under certain conditions give an indication of drug bioavailability

- Ideally, the *in-vitro* drug dissolution rate should correlate with *in-vivo* drug bioavailability
- *in-vivo–in-vitro* correlation, IVIVC

Bioequivalence Studies

- Differences in clinical response is due to differences in the pharmacokinetic and/or pharmacodynamic behavior of the drug among individuals
- or to differences in the bioavailability of the drug from the drug product

Bases for Determining Bioequivalence

- *in vitro evaluation:*
  (eg, drug dissolution/release test)
- *in vivo evaluation:*
  (eg, bioequivalence study)

Design and Evaluation of Bioequivalence Studies

- to compare the bioavailability of the generic drug product to the brand-name product.
- Statistical techniques should be of sufficient sensitivity to detect differences in rate and extent of absorption
- Once bioequivalence is established, the generic and brand-name dosage forms will produce the same therapeutic effect.

Design

well-controlled bioequivalence studies :

require cooperative input from pharmacokineticists, statisticians, clinicians, bioanalytical chemists, and others.

The Biopharmaceutics Classification System (BCS)

Class	Solubility	Permeability
Class 1	High	High
Class 2	Low	High
Class 3	High	Low
Class 4	Low	Low

Solubility

- pH–solubility profiles over a pH range of 1–8 is suggested.
- volume estimate of 250 mL

Permeability

For a drug To be classified as highly permeable, a test drug should have an extent of absorption > 90% in humans

Dissolution

not less than 85% of the label amount of drug substance dissolves within 30 minutes

Statistical Evaluation of the Data

To prove bioequivalence:

- no statistical difference between the bioavailability of the Test product and the Reference product
- T-test (Student's test)
- Analysis of variance (ANOVA)

- Dissolution Profile Comparison

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_1 - T_1)^2\right]^{-5} \times 100\right\}$$

where n is the number of time points, R_1 is the dissolution value of the Reference product at time t, and T_1 is the dissolution value of the Test product batch at time t.

Clinical Significance of Bioequivalence Studies

- comparison of AUC, C_{max}, and t_{max}
- Generally, two formulations whose rate and extent of absorption differ by 20% or less are considered bioequivalent.