Chapter 18
Bioavailability and Bioequivalence Testing

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INTRODUCTION

Understanding the concepts of bioavailability and bioequivalence testing is essential in the drug development process because they create the foundation for regulatory decision making when evaluating formulation changes and lot-to-lot consistency in innovator products. They also serve as the primary components to demonstrate therapeutic equivalence between generic products and the reference innovator product.

Changes in bioavailability can be thought of in terms of changes in exposure to the drug. If these changes are substantial, then they can alter the safety and efficacy profile of the compound in question. The bioavailability of orally administered drugs can be affected by numerous factors. These include food or fed state, differences in drug metabolism, drug–drug interactions, gastrointestinal transit time, and changes in dosage form release characteristics (especially for modified release products).

Bioequivalence is an important consideration in ensuring lot-to-lot consistency, including whenever evaluating changes in a marketed product's formulation, manufacturing process, and dosage strength. Bioequivalence is also critical in regulatory authority decision making when determining whether a generic product is therapeutically equivalent to the original innovator product.

In addition, chemical equivalence, lot-to-lot uniformity of physicochemical characteristics, and stability equivalence are other factors that are important, as they too can affect product quality. In this chapter, bioavailability and bioequivalence topics are emphasized for solid oral dosage forms. However, many of the general concepts can also be applied to other dosage forms, including biologics.

GENERAL CONCEPTS

The terms used in this chapter require careful definition, since, as in any area, some terms have been used in different contexts by different authors.

Bioavailability is a term that indicates measurement of both the rate of drug absorption and the total amount (extent) of drug that reaches the systemic circulation from an administered dosage form. It is specific to the parent or active drug substance as contrasted to metabolites.

Equivalence is more a general and relative term that indicates a comparison of one drug product with another. Equivalence may be defined in several ways:

- *Bioequivalence* indicates that a drug in two or more similar dosage forms reaches the systemic circulation at the same relative rate and extent (i.e., the plasma level profiles of the drug obtained using the two dosage forms are the same).
- *Chemical equivalence* considers that two or more dosage forms contain the same labeled quantities (within specified limits) of the drug.
- *Clinical equivalence* occurs when the same drug from two or more dosage forms gives identical *in vivo* effects as measured by a pharmacological response or by control of a symptom or disease.
- *Pharmaceutical equivalence* refers to two drug products with the same dosage form and same strength.
- *Therapeutic equivalence* implies that two brands of a drug product are expected to yield the same clinical result. The FDA specifically uses the term "therapeutic equivalence" in the evaluation of multi-source prescription drug products (generic drugs).

Area under the Concentration–Time Curve (AUC) is the integral of the concentration–time curve after administration of a single dose of drug or after achieving a steady state. The calculated area under the serum, blood, or plasma concentration–time curve is reported in amount/volume multiplied by time (e.g., μg/mL × h or g/100 mL × h) and can be considered representative of the amount of drug absorbed. Several variants of AUC exist, including $AUC_{0\text{-}t}$; $AUC_{0\text{-}\infty}$; and $AUC_{\tau,\ SS}$, corresponding to the calculated area from time zero to a truncated time point (e.g., $AUC_{0\text{-}48}$), the total area under the curve, and the area when steady state has been achieved.

Peak-height Concentration (C_{max}) is the peak of the blood level–time curve and represents the highest drug concentration achieved after drug administration.

Time of Peak Concentration (T_{max}) is the measured length of time necessary to achieve the maximum concentration (C_{max}) after drug administration.

DISSOLUTION

For a drug to be absorbed, it must first go into solution. In Figure 18-1 the steps in the dissolution and subsequent absorption process of a tablet or capsule dosage form are outlined. Similar profiles could be obtained for any solid or semisolid dosage form, including oral suspensions, parenteral suspensions, and suppositories. The theory and mechanics of drug dissolution rate are described in detail in Chapter 22. The physical characteristics of the drug and the composition of the tablet (dosage form) can have an effect on the rates of disintegration, deaggregation, and dissolution of the drug. As such, these can affect the rate of absorption and resultant blood levels of the drug.

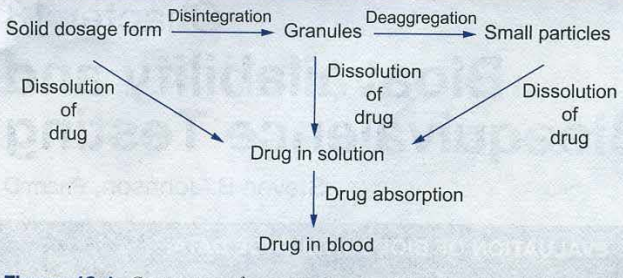

Figure 18-1. Sequence of events involved in the dissolution and absorption of a drug from a solid oral dosage form.

An important aspect of product quality for marketed oral solid dosage forms relates to dissolution testing. The dosage forms actually used by patients will be from lots that have not directly undergone human bioavailability testing. Once adequate product quality has been established by bioavailability testing, subsequent batches manufactured using the same formulation, equipment, and process are likely to be bioequivalent to the original batch tested in humans. This is an important concept in the regulatory control of product quality and is where *in vitro* testing such as assay, content uniformity, tablet hardness, and dissolution are important. Among these several *in vitro* tests, dissolution testing is probably the most important, related to bioavailability. As part of the drug approval process, a dissolution test procedure is established for all oral solid dosage forms. These dissolution tests are incorporated into the United States Pharmacopeia (USP) and apply both to innovator and generic drug products. All marketed batches of these drug products must meet the Abbreviated New Drug Application (ANDA)/New Drug Application (NDA)/USP dissolution tests throughout the shelf-life of the product. Products failing their approved dissolution test and/or a USP dissolution test must be removed from the market.

PROPERTIES OF THE DRUG

The physical characteristics of the drug that can alter bioavailability are discussed in Chapters 9 and 54 and consist of the polymorphic crystal form, choice of the salt form, particle size, hydrated or anhydrous form, wettability, and solubility of the drug. Chapter 9 also discusses several other properties that can adversely affect drug product quality. These factors should be investigated during product development and should not, therefore, affect the bioavailability of the drug product.

PROPERTIES OF THE DOSAGE FORM

The various components of the solid or semisolid dosage form, other than the active ingredient, are discussed in Chapter 45. Only an overview, for tablet dosage forms, is given here. In addition to the active ingredient, a tablet product usually will contain the following types of inactive ingredients:

- *Glidants* are used to provide a free-flowing powder from the mix of tablet ingredients so that the material will flow when used on a tablet machine.
- *Binders* provide cohesiveness to the tablet. Too little binder will produce tablets that do not maintain their integrity; too much may affect adversely the release (dissolution rate) of the drug from the tablet.
- *Fillers* are used to give the powder bulk so that an acceptably sized tablet is produced. Most commercial tablets weigh from 100 mg to 500 mg, so it is obvious that for many potent drugs the filler constitutes a large portion of the tablet. Binding of drug to the fillers may occur and affect bioavailability.
- *Disintegrants* are used to cause the tablets to disintegrate when exposed to an aqueous environment. Too much will produce tablets that may disintegrate in the bottle because of atmospheric moisture, and too little may be insufficient for disintegration to occur and may therefore alter the rate and extent of release of the drug from the dosage form.
- *Lubricants* are used to enhance the flow of the powder through the tablet machine and to prevent sticking of the tablet in the die of the tablet machine after the tablet is compressed. Lubricants are usually hydrophobic materials such as stearic acid, magnesium, or calcium stearate. Too little lubricant will not permit satisfactory tablets to be made; too much may produce a tablet with a water-impervious hydrophobic coat, which can inhibit the disintegration of the tablet and dissolution of the drug.

ABSORPTION FACTORS

A significant factor related to drug bioavailability is the fact that many drugs are administered, not as a solution, but as a solid dosage form. Optimal bioavailability might be expected from a solution, since a solid drug must first dissolve to be absorbed, but considerations such as drug stability, unpalatable taste, and the desired duration of action (for controlled-release drug products) may prevent the development of solution-based dosage form.

In the dose titration of any patient the objective is, in conceptual terms, to attain and maintain a blood level that exceeds the minimum effective level required for response but does not exceed the minimum toxic (side-effect) level. This is shown graphically in Figure 18-2. There are several absorption factors that can affect the general shape of this blood-level curve and thus drug response.

DOSE ADMINISTERED

The blood levels will rise and fall in proportion to the dose administered.

AMOUNT OF DRUG ABSORBED

Blood levels achieved are also dependent on the amount of drug absorbed. For example, the effect of having only one-half of the drug absorbed from a dosage form is equivalent to lowering the dose (Figure 18-3).

RATE OF ABSORPTION

If absorption from the dosage form is more rapid than the rate of absorption that gave profile C in Figure 18-4, minimum toxic (side-effect) levels may be exceeded. If absorption from the dosage form is sufficiently slow, minimum effective levels may never be attained, as in profile B in Figure 18-4.

In either instance, the time course and extent of clinical response to the drug may be altered because of changes in dose or rate and extent of absorption.

Both factors, rate and extent of drug absorption, can be affected by the dosage form in which the drug is contained. The

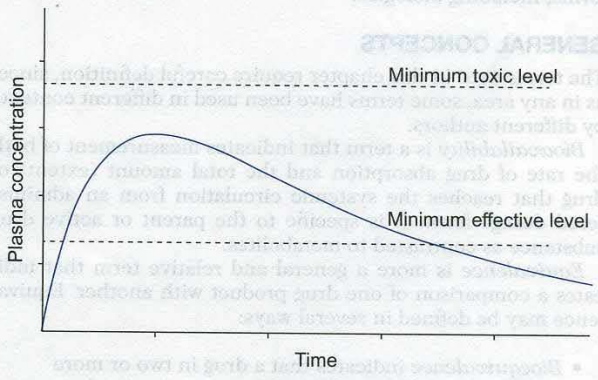

Figure 18-2. Typical plasma-level curve of a drug with effective and toxic (side-effect) profile levels defined.

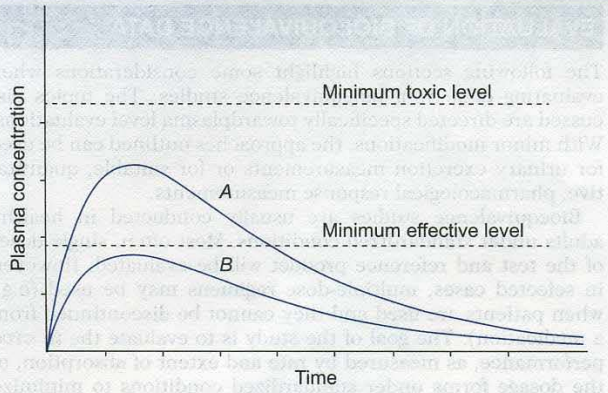

Figure 18-3. Effect of the extent of drug absorption from a dosage form on drug-plasma levels and efficacy. The extent of absorption from dosage form B is 50% of that from dosage form A.

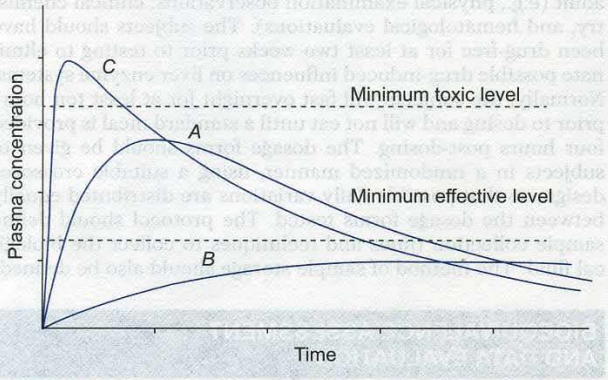

Figure 18-4. Effect of the rate of drug absorption from a dosage form on the plasma-level profile and efficacy. The rates of absorption from dosage forms B and C are 1/10 and 10 times those from dosage form A.

effect of rate of absorption may be intentional, as in controlled-release products, or unintentional, for example, as brought about by a change in the composition and/or method of manufacture of the dosage form.

The choice of the inactive ingredients (excipients) used to prepare a dosage form is up to the individual manufacturer. It is through these changes in composition and manufacturing technique that unintended changes in bioavailability and bioequivalence may occur. Revalidation of bioequivalence may be needed for major changes in the manufacturing process, whereas small changes may not raise significant bioavailability concerns. In situations involving minor changes in the manufacturing process, comparative dissolution testing of the original and reformulated product provides adequate documentation of continued product quality, if the resulting dissolution profiles are similar. These considerations apply to all drug manufacturers, both innovator and generic companies. A description of the formulation of dosage forms and the factors that must be considered is given in Chapter 9.

BIOEQUIVALENCE TESTING

The awareness of the potential for clinical differences between otherwise chemically equivalent drug products has been brought about by a multiplicity of factors that include, among others:

- better methods for clinical efficacy evaluation
- development of techniques to measure microgram or nanogram quantities of drugs in biological fluids
- improvements in the technology of dosage form formulation and physical testing
- awareness of reported clinical differences from the literature in otherwise similar products
- increased cost of classical clinical evaluation
- objective and quantitative nature of bioavailability tests
- an increase in the number of chemically equivalent products on the market because of patent expirations and the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act), which established the generic drug approval procedures that are in place today.

The increase in the number of drugs that are available from multiple sources frequently has placed people involved in the delivery of healthcare in the position of having to select one from among several marketed products. As with any decision, the more data available, the more comfortable one is in arriving at the final decision. The need to make these choices, in light of the potential failure to demonstrate *in vivo* equivalence between products or different batches of the same product, has increased the demand for quantitative data. Bioequivalence testing represents a bridging alternative to clinical testing for efficacy and safety in such cases and is the means by which generic drugs are approved for marketing. In addition, this is also the means by which the quality of all drug products is maintained in situations involving major changes in formulation or manufacturing process.

Requirements for bioequivalence data on drug products should be applied reasonably. The reason for bioequivalence testing should not be overlooked (i.e., it is used as a surrogate, in certain situations, for the clinical evaluation of drug products). In some instances, bioequivalence data cannot reliably be obtained if the bioanalytical methodology is not available. However, in such cases pharmacodynamic data may provide a more sensitive, objective evaluation of a product's therapeutic equivalence and may be explored as an alternative evaluation method in the absence of relevant bioanalytical methodology.

Basic pharmacokinetic evaluation of bioavailability data is not necessary to show bioequivalence of two drug products. Pharmacokinetics has its major utility in the prediction or projection of dosage regimens and/or in providing a better understanding of observed drug reactions or interactions that result from the accumulation of drug in some specific site, tissue, or compartment of the body. The basis for the conclusion that two drug products are bioequivalent must be that the drug concentrations measured in a biological matrix, or alternatively the pharmacological response, for one drug product are essentially the same for the second drug product. The more straightforward decisions in the evaluation of bioequivalence between two drug products are those in which the two products are exactly superimposable (definitely bioequivalent). Those in which the two products differ in their bioequivalence parameters by a large amount, such as 50% or more, are most definitely not bioequivalent. Statistical evaluation of the data is necessary for all situations, particularly for data that exist between these two extremes.

METHODS FOR DETERMINING BIOEQUIVALENCE

Bioequivalence usually involves human testing but sometimes may be demonstrated using an *in vitro* bioequivalence standard, especially when such an *in vitro* test has been correlated with human *in vivo* bioavailability data. In other situations, bioequivalence may be demonstrated through comparative clinical trials or pharmacodynamic studies.

The FDA has categorized (21CFR320.24) various *in vivo* and *in vitro* approaches that may be utilized to establish bioequivalence. These are, in descending order of accuracy, sensitivity and reproducibility,

1. An *in vivo* test in humans in which the active drug substance, as well as active metabolites when appropriate, is measured in plasma.
2. An *in vitro* test that has been correlated with human *in vivo* bioavailability data. This approach is most likely for oral modified release products and is described in detail in FDA Guidance.
3. An *in vivo* test in animals that has been correlated with human bioavailability data.
4. An *in vivo* test in humans, where urinary excretion of the active drug substance, as well as active metabolites when appropriate, is measured.
5. An *in vivo* test in humans in which an appropriate acute pharmacological effect is measured.
6. Well-controlled clinical trials in humans that establish the safety and efficacy of the drug product, for establishing bioavailability. For bioequivalence, comparative clinical trials may be considered. This approach is the least accurate, sensitive, and reproducible approach and should be considered only if other approaches are not feasible.
7. A currently available *in vitro* test, acceptable to FDA, that ensures bioavailability. This approach is intended only when *in vitro* testing is deemed adequate, but no *in vitro–in vivo* correlation (IVIVC) has been established. It also can relate to considerations involving the Biopharmaceutics Classification System (BCS).

Most bioequivalence studies involve the direct measurement of the parent drug, as described in item 1 above. Bioequivalence testing in animals is not a recommended approach due to possible differences in metabolism, gastrointestinal physiology, weight, and diet.

MINIMIZING THE NEED FOR BIOEQUIVALENCE STUDIES

If a drug product has been adequately tested and approved for marketing, and if no changes in the manufacturing of the product are made, it is reasonable to assume that all subsequent batches of the product would be expected to be bioequivalent to the original product. If subsequently manufactured batches meet all tests of quality, including the dissolution test, no further human bioequivalence testing is needed.

Depending on the degree of change, bioequivalence may sometimes need to be reconfirmed. Although it is somewhat difficult to categorize such major changes, this issue has been described in a series of FDA guidance documents related to Scale-Up and Post-Approval Changes (SUPAC).

Drug characteristics related to solubility and permeability may allow a reasonable expectation that the drug is unlikely to be subject to significant bioavailability problems. For such drugs, *in vitro* dissolution testing may be adequate, in lieu of *in vivo* testing. These concepts are described in the Biopharmaceutics Classification System (BCS). This classification system provides a scientific framework for classifying drugs based on aqueous solubility and intestinal permeability. In addition, criteria for rapid dissolution are described (not less than 85% dissolved in 30 minutes, using mild agitation and physiological media). The BCS permits waivers of *in vivo* bioequivalence testing for high solubility, high permeability drugs (Class I), which are formulated into immediate release dosage forms having rapid dissolution. The basic tenet behind the BCS is that solutions of drugs are thought to have few bioavailability or bioequivalence issues. Dosage forms containing drugs that are of high solubility and exhibit rapid dissolution behave similarly to a solution. Particularly for such drugs that are, in addition, highly permeable (well absorbed), the likelihood of bioavailability problems is quite small, and consequently, bioequivalence testing for such drugs is thought to be unnecessary. Similarly for oral solutions, bioequivalence testing is not necessary.

EVALUATION OF BIOEQUIVALENCE DATA

The following sections highlight some considerations when evaluating data from bioequivalence studies. The topics discussed are directed specifically towardplasma level evaluations. With minor modifications, the approaches outlined can be used for urinary excretion measurements or for suitable, quantitative, pharmacological response measurements.

Bioequivalence studies are usually conducted in healthy adults under standardized conditions. Most often, single doses of the test and reference product will be evaluated. However, in selected cases, multiple-dose regimens may be used (e.g., when patients are used and they cannot be discontinued from a medication). The goal of the study is to evaluate the *in vivo* performance, as measured by rate and extent of absorption, of the dosage forms under standardized conditions to minimize patient-related and other variability.

The protocol should define the acceptable age and weight range for the subjects to be included in the study, as well as the clinical parameters that will be used to characterize a healthy adult (e.g., physical examination observations, clinical chemistry, and hematological evaluations). The subjects should have been drug-free for at least two weeks prior to testing to eliminate possible drug-induced influences on liver enzyme systems. Normally, the subjects will fast overnight for at least ten hours prior to dosing and will not eat until a standard meal is provided four hours post-dosing. The dosage forms should be given to subjects in a randomized manner, using a suitable crossover design, so that possible daily variations are distributed equally between the dosage forms tested. The protocol should define sample collection times and techniques to collect the biological fluid. The method of sample storage should also be defined.

BIOEQUIVALENCE ASSESSMENT AND DATA EVALUATION

Several parameters are used to provide a general evaluation of the overall rate and extent of absorption of a drug. An analysis of all characteristics is required before one can determine bioequivalence or lack of bioequivalence. It is implicit that the analytical methodology used for analysis of drug in the samples is specific, sensitive, and precise.

In assessing the bioequivalence of drug products, one must quantitate the rate and extent of absorption, which can be determined by evaluating parameters derived from the blood-level concentration–time profile. Three parameters describing a blood-level curve are considered important in evaluating the bioequivalence of two or more formulations of the same drug. These are the peak-height concentration (C_{max}), the time of the peak concentration (T_{max}), and the area under the blood (serum or plasma) concentration–time curve (AUC).

PEAK-HEIGHT CONCENTRATION (C_{max})

The peak of the blood-level–time curve represents the highest drug concentration achieved after oral administration. It is reported as an amount per volume measurement (e.g., microgram/milliliter (μg/mL), unit/mL, or gram/100 mL). The importance of this parameter is illustrated in Figure 18-5, where the blood concentration–time curves of two different formulations of a drug are represented. A line has been drawn across the curve at 4 μg/mL. Suppose that the drug is an analgesic, and 4 μg/mL is the minimum effective concentration (MEC) of the drug in blood. If the blood concentration curves in Figure 18-5 represent the blood levels obtained after administration of equal doses of two formulations of the drug and it is known that analgesia would not be produced unless the MEC was achieved or exceeded, it becomes clear that formulation A would be expected to provide pain relief, while formulation B, even though it is well absorbed regarding extent of absorption, might be ineffective in producing analgesia.

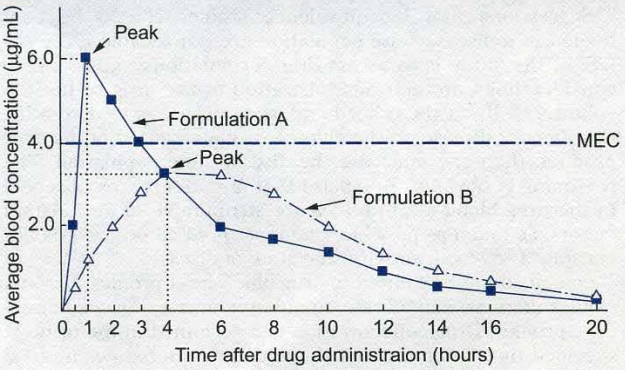

Figure 18-5. Blood concentration–time curves obtained for two different formulations of the same drug, demonstrating relationship of the profiles to the minimum effective concentration (MEC).

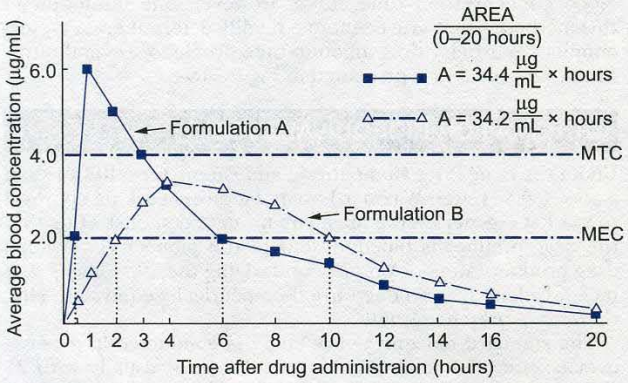

Figure 18-6. Blood concentration–time curves obtained for two different formulations of the same drug, demonstrating relationship of the profiles to the minimum toxic concentration (MTC) and the minimum effective concentration (MEC).

On the other hand, if the two curves represent blood concentrations following equal doses of two different formulations of the same cardiac glycoside, and 4 µg/mL now represents the minimum toxic concentration (MTC) and 2 µg/mL represents the MEC (Figure 18-6), formulation A, although effective, may also present safety concerns, while formulation B produces concentrations well above the MEC but never reaches toxic levels.

Time of Peak Concentration (T_{max})

The second parameter of importance is the measurement of the length of time necessary to achieve the maximum concentration after drug administration. This parameter is called the time of peak blood concentration (T_{max}). In Figure 18-5, for formulation A the time necessary to achieve peak blood concentration is 1 h. For formulation B, T_{max} is 4 h. This parameter is related closely to the rate of absorption of the drug from a formulation and may be used as a simple measure of rate of absorption but is normally not evaluated statistically.

To illustrate the importance of T_{max}, suppose that the two curves in Figure 18-6 now represent two formulations of an analgesic and that in this case the MEC is 2.0 g/mL. Formulation A will achieve the MEC in 30 minutes; formulation B does not achieve that concentration until 2 h. Formulation A would produce analgesia much more rapidly than formulation B and would probably be preferable as an analgesic agent. On the other hand, if one were more interested in the duration of the analgesic effect than on the time of onset, formulation B would present more prolonged activity, maintaining serum concentrations above the MEC for a longer time (8 h) than formulation A (5.5 h).

AREA UNDER THE CONCENTRATION–TIME CURVE (AUC)

The third, and sometimes the most important parameter for evaluation, is the area under the serum, blood, or plasma concentration–time curve (AUC). This area is reported in amount/volume multiplied by time (e.g., µg/mL × h or g/100 mL × h) and can be considered representative of the amount of drug absorbed following administration of a single dose of the drug.

Although several methods exist for calculating the AUC, the trapezoidal rule method is most often used. This method assumes a linear function, $y = bt + a$, and its accuracy increases as the number of appropriate sampling intervals are increased. Table 18-1 and Figure 18-7 describe the process for calculating the AUC using the trapezoidal rule.

Returning to Figure 18-6, the curves, although much different in shape, have approximately the same areas (A = 34.4 µg/mL × h; B = 34.2 µg/mL × h), and both formulations can be considered to deliver the same amount of drug to the systemic circulation. Thus, one can see that AUC should not represent the only criterion on which bioequivalence is judged. All the results, as a composite, must be considered in reaching a decision about bioequivalence since no single parameter is adequate to serve this purpose.

The plasma concentration–time curve is the focal point of bioequivalence assessment and is obtained when serial blood samples are analyzed for drug concentration. The concentrations are plotted on the ordinate (*y*-axis), and the times after drug administration that the samples were obtained are plotted on the abscissa (*x*-axis).

A drug product is administered orally at time zero, and the plasma drug concentration at this time clearly should be zero. As a product passes through the gastrointestinal (GI) tract, it must undergo a sequence of events depicted in Figure 18-1. As

Table 18-1. Using the Trapezoidal Rule to Calculate Area Under the Concentration-Time Curve.

$AUC_{(0\text{-}E_i)}$ is used for bioequivalence analyses when the $AUC_{(0\text{-}t)}$ makes up ≥ 80% of the $AUC_{(0\text{-}E_i)}$. $AUC_{(0\text{-}t)}$ is used when the $AUC_{(0\text{-}t)}$ makes up < 80% of the $AUC_{(0\text{-}E_i)}$. When drugs with long half-lives are evaluated, $AUC_{(0\text{-}t)}$ may sometimes be used with a truncated time point.

Area under the concentration-time curve from time zero to time *t* ($AUC_{0\text{-}t}$)

1. Plot the concentration-time data for each subject
2. Divide the curve into trapezoids by drawing vertical lines from each datum point to the *x*-axis. Calculate the area of the trapezoids using the following formula:
3. $AUC_{(t2\text{-}t1)} = [(C_2 + C_1)(t_2 - t_1)] / 2$
   $AUC_{(0\text{-}t)}$ is then calculated by summing the individual areas to the time of the last concentration:
4. $AUC_{(0\text{-}t)} = AUC_{(t2\text{-}t1)} + AUC_{(t3\text{-}t2)} + \ldots + AUC_{(tn\text{-}(tn\text{-}1))}$

Area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}E_i}$)

5. To calculate $AUC_{(0\text{-}E_i)}$, the tail region of the curve must be added to $AUC_{(0\text{-}t)}$: $AUC_{(0\text{-}E_i)} = AUC_{(0\text{-}t)}$ + AUC "tail"
6. AUC "tail" = C_t/λ_z, where: C_t is the last detectable concentration, and λ_z is the terminal elimination rate constant (see Figure 18-9).

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