Dosage Form Design

Lecture 8

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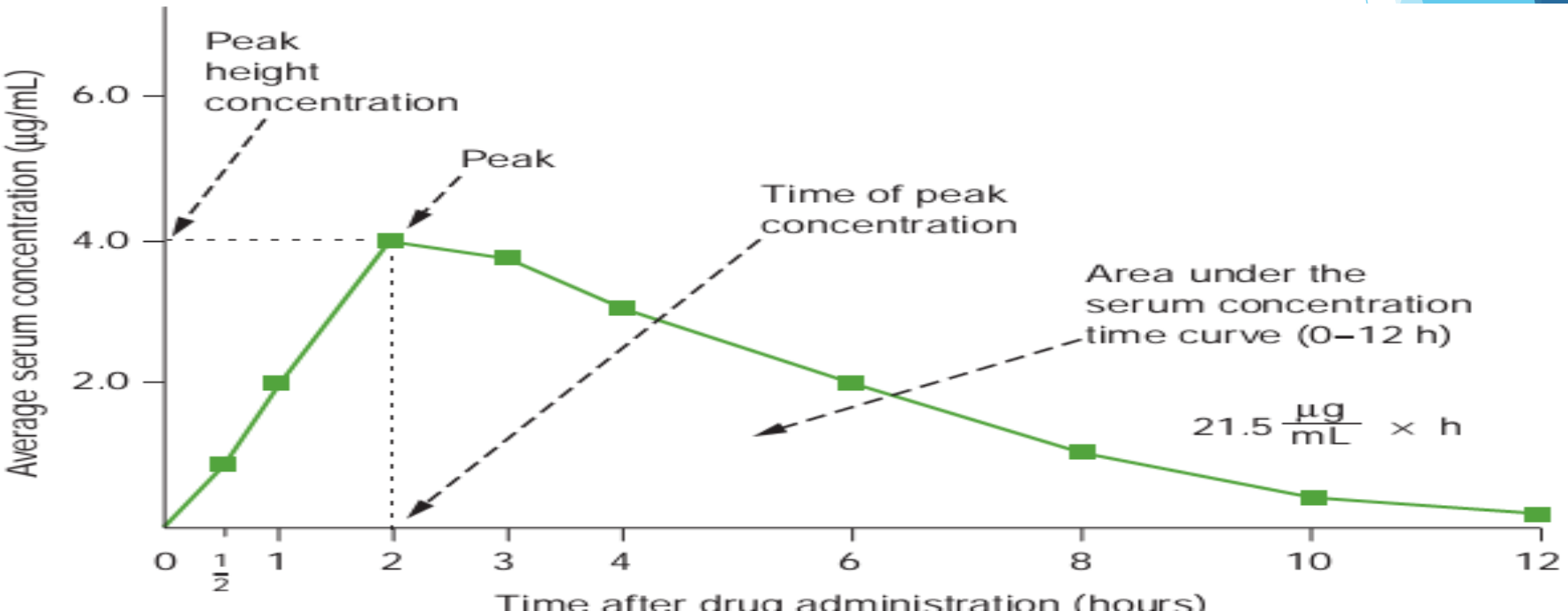
GENERAL CONSIDERATIONS IN DOSAGE FORM DESIGN

1. **Drug Consideration In Dosage Form Design**
    - 1.1 Characteristics of Drug Substances
    - 1.2 Drug Stability
    - 1.3 Determining Drug Formulation Stability
    - 1.4 Prevention Against Microbial Contamination
    - 1.5 Appearance and Palatability
2. **Therapeutic Considerations In Dosage Form Design**
    - 2.1 Nature of the disease or illness
    - 2.2 Age of the Patient
3. **Biopharmaceutics Considerations**
    - 3.1 Biopharmaceutics
    - 3.2 Concept of Bioavailability

Bioavailability and Bioequivalency

- **bioavailability** is the rate and extent of drug absorption from site of administration to the general circulation.
- **bioequivalency** refers to a comparison of bioavailabilities of different formulations, drug products, or batches of the same drug product.



Bioavailability used to determine

1. amount of drug absorbed from a formulation or dosage form,
2. rate at which the drug was absorbed,
3. duration of the drug's presence in biologic fluid or tissue correlated with the patient's response
4. relationship between drug blood levels and clinical efficacy and toxicity.

During product development stages of a new drug the pharmaceutical manufacturer employ bioavailability studies to:

1. compare different formulations of the drug substance to ascertain which one allows the most desirable absorption pattern.
2. Later bioavailability studies may be used to compare the availability of the drug substance in different production batches.
3. They may also be used to compare the availability of the drug substance in different dosage forms (e.g., tablets, capsules, elixirs) or in the same dosage form produced by different (companies) manufacturers.

FDA Bioavailability Submission Requirements

The FDA requires bioavailability data submissions in the following instances (5):

1. *New Drug Applications* (*NDAs*): A section of each NDA is required to describe the human pharmacokinetic data and human bioavailability data, or information supporting a waiver of the bioavailability data requirement (see waiver provisions following).
2. *Abbreviated New Drug Applications* (*ANDAs*): In vivo bioavailability data are required unless information is provided and accepted supporting a waiver of this requirement (see waiver provisions following).
3. *Supplemental Applications*: In vivo bioavailability data are required if there is a change in the following:
   a. Manufacturing process, product formulation, or dosage strength beyond the variations provided for in the approved NDA
   b. Labeling to provide for a new indication for use of the drug product and if clinical studies are required, to support the new indication
   c. Labeling to provide for a new or additional dosage regimen for a special patient population (e.g., infants) if clinical studies are required to support the new or additional dosage regimen

Conditions under which the FDA *may* waive the in vivo bioavailability requirement are as

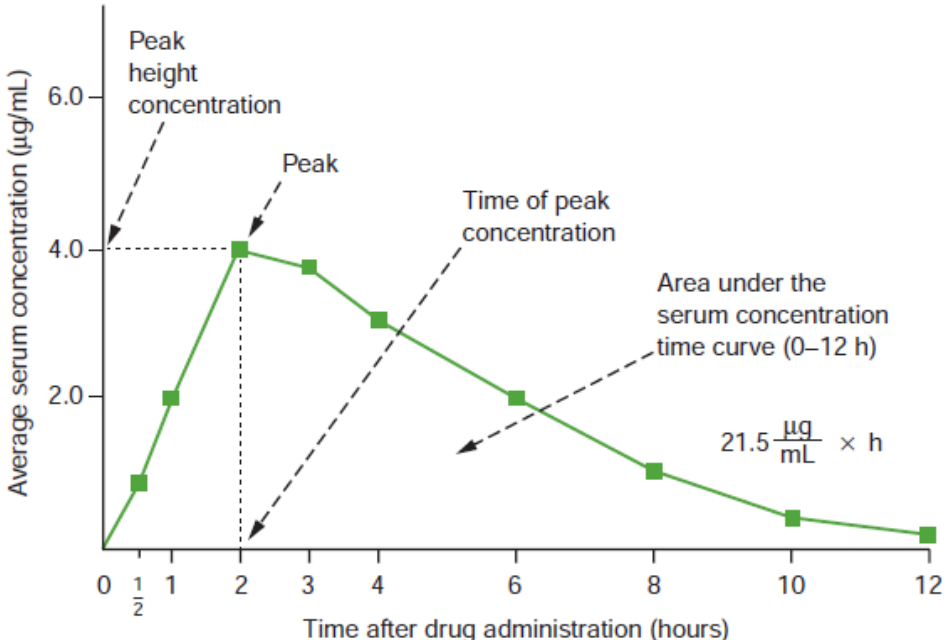
1. The drug product is a parenteral, ophthalmic, or otic solution and contains the same active agent in the same concentration and solvent as a product previously approved through a full NDA.
2. The drug product is administered by inhalation as a gas or vapor and contains the same active agent in the same dosage form as a product previously approved through a full NDA.
3. The drug product is an oral solution, elixir, syrup, tincture, or similar other solubilized form and contains the same active agent in the same concentration as a previously approved drug product through a full NDA and contains no inactive ingredient known to significantly affect absorption of the active drug ingredient.
4. The drug product is a topically applied preparation (e.g., ointment) intended for local therapeutic effect.
5. The drug product is an oral form that is not intended to be absorbed (e.g., antacid or radiopaque medium).
6. The drug product is a solid oral form that has been demonstrated to be identical or sufficiently similar to a drug product that has met the in vivo bioavailability requirement.

Blood, Serum, or Plasma Concentration time curve

oral administration of drug

blood samples are withdrawn at specific time intervals and analyzed for drug content

Results drawn in which the vertical presents the concentration of drug in blood, and horizontal axis presents time the samples were obtained



- **time zero the blood concentration of drug should be zero**.
- As the drug passes into the stomach and/or intestine, dissolves, and absorbed. As the sampling and analysis continue, the blood samples reveal increasing concentrations of drug until maximum (peak) concentration (C_{max}) is reached. Then the blood level of the drug decreases.
- Absorption does not terminate after the peak blood level is reached; it may continue for some time.
- process of drug elimination is continuous. It begins as soon as the drug first appears in the blood stream and continues until all the drug has been eliminated.

Parameters for assessment and comparison of bioavailability following oral administration of single doses of two formulations of the same drug

1. The peak height concentration (C_{max})
2. The time to peak concentration (T_{max})
3. The area under the blood (or serum or plasma) concentration time curve (AUC)

1. The peak height concentration (C_{max})

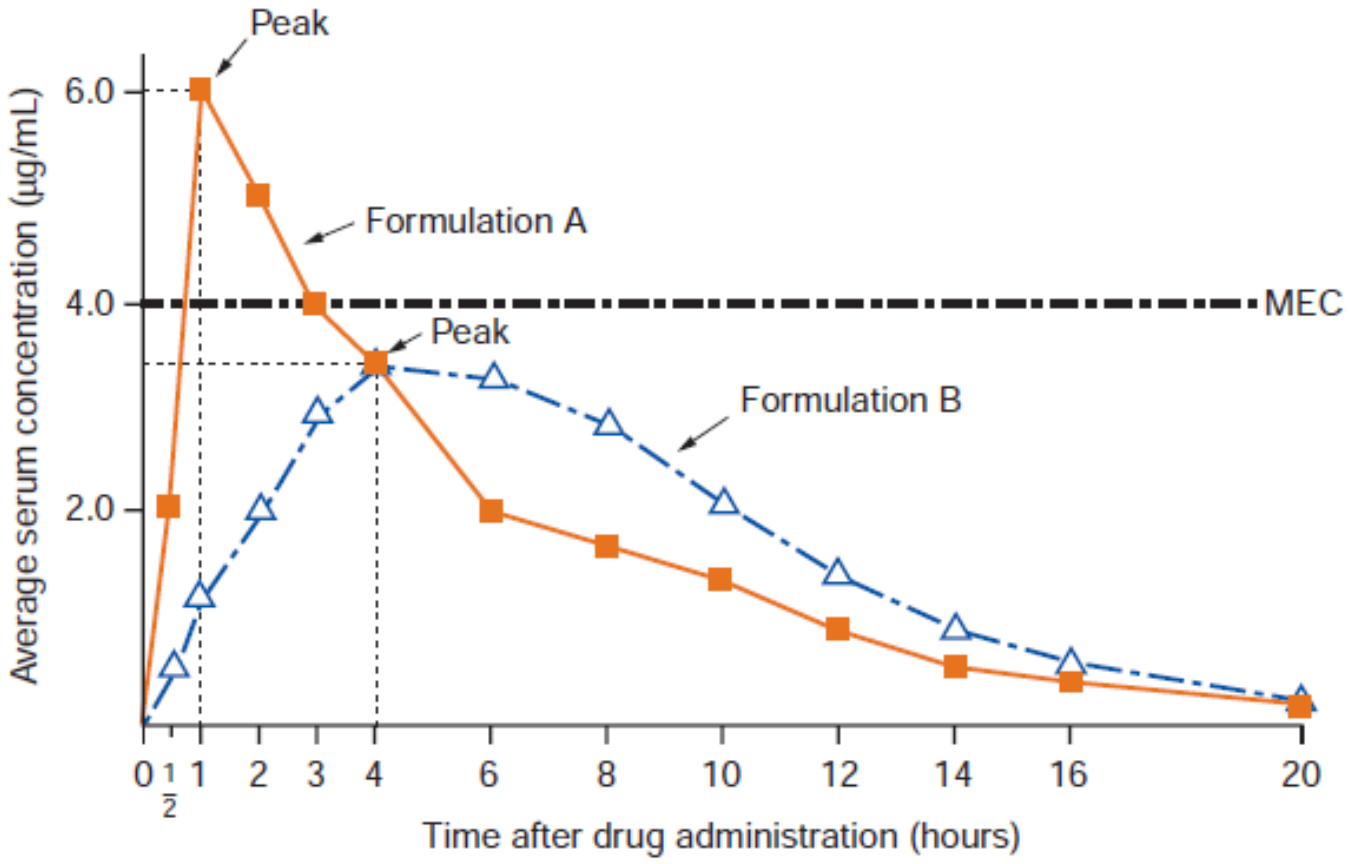


FIGURE 5.6 Serum concentration–time curve showing different peak height concentrations for equal amounts of drug from two different formulations following oral administration. MEC, minimum effective concentration. (Courtesy of D. J. Chodos and A. R. Disanto, Upjohn. With permission from Elsevier.)

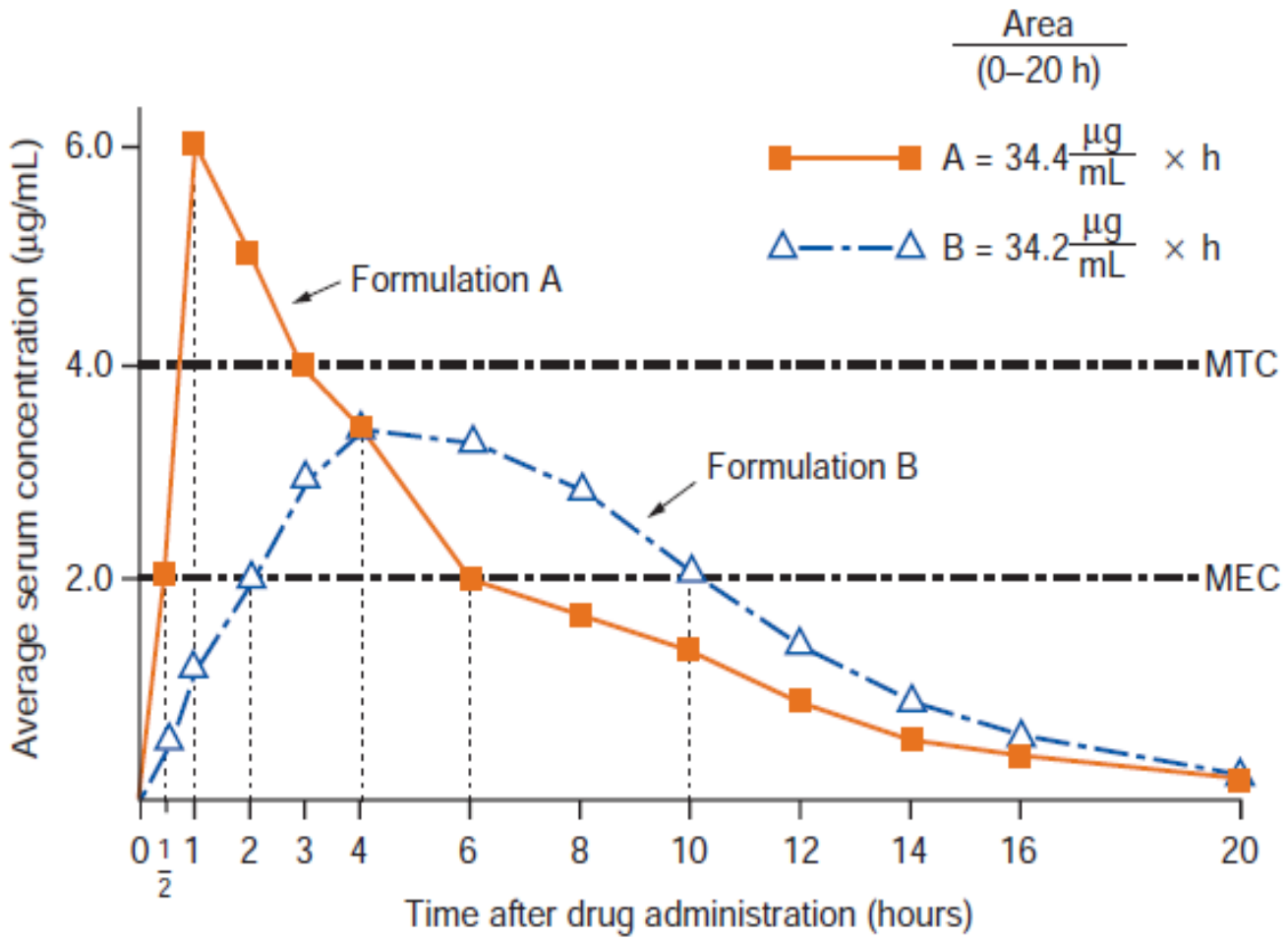


FIGURE 5.7 Serum concentration–time curve showing peak height concentrations, peak height times, times to reach MEC, and areas under the curves for equal amounts of drug from two different formulations following oral administration. MEC, minimum effective concentration; MTC, minimum toxic concentration. (Courtesy of D. I. Chodos and A. R. Disanto, Upjohn.)

- The size of the dose influence C_{max}
- Same rout same dosage form

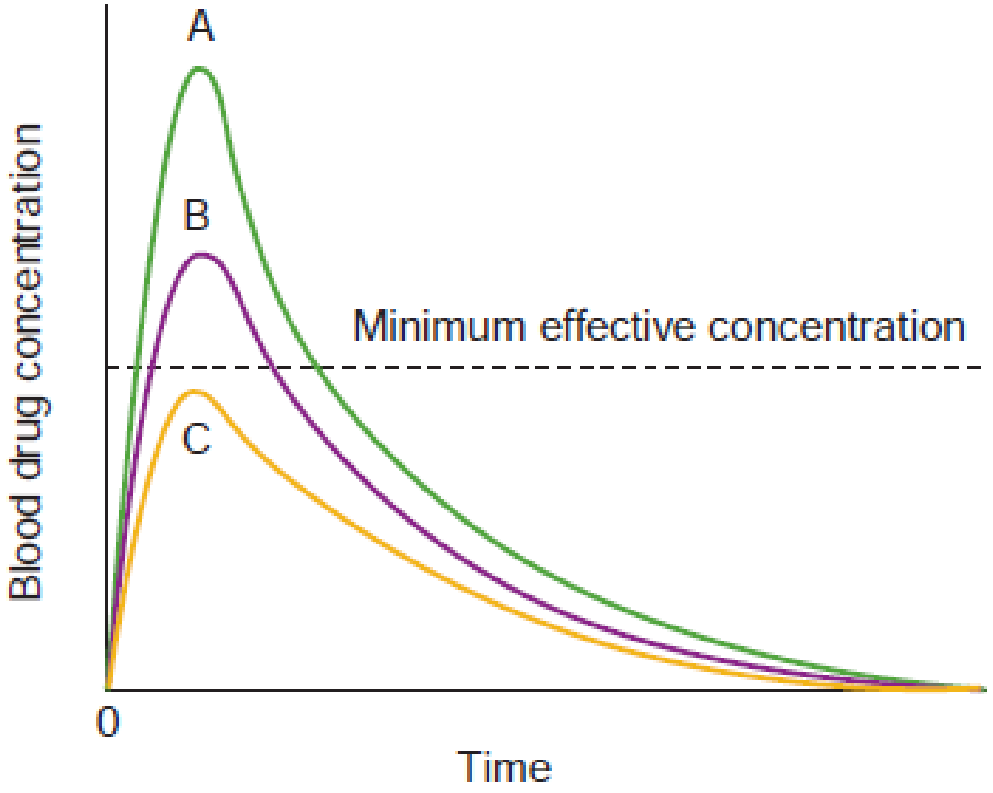
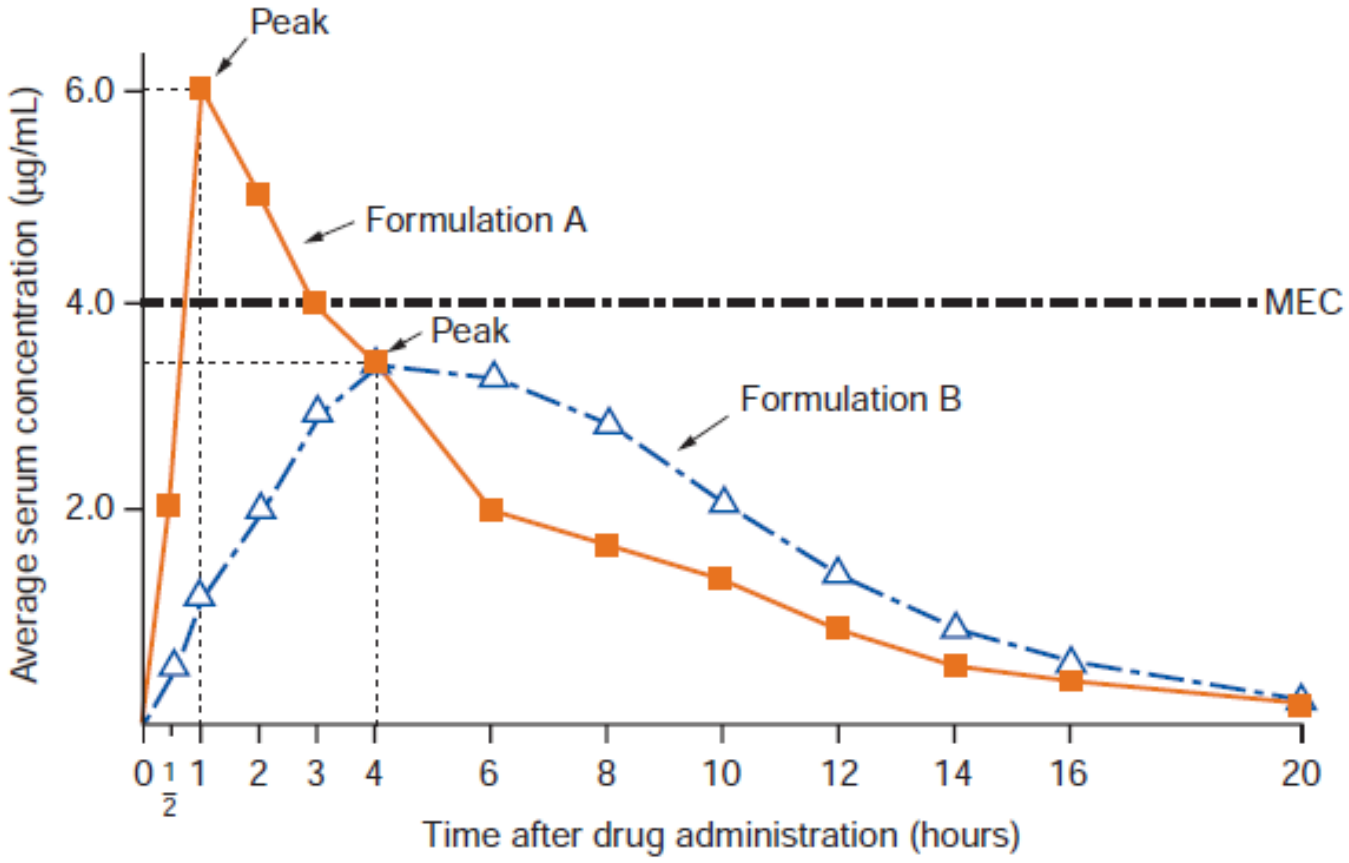


FIGURE 5.8 The influence of dose size on the blood drug concentration–time curves when three different doses of the same drug are administered and the rates of drug absorption and elimination are equal after the three doses. A, 100 mg; B, 80 mg; C, 50 mg.

2.The time to peak concentration (T_{max})

reflects rate of absorption



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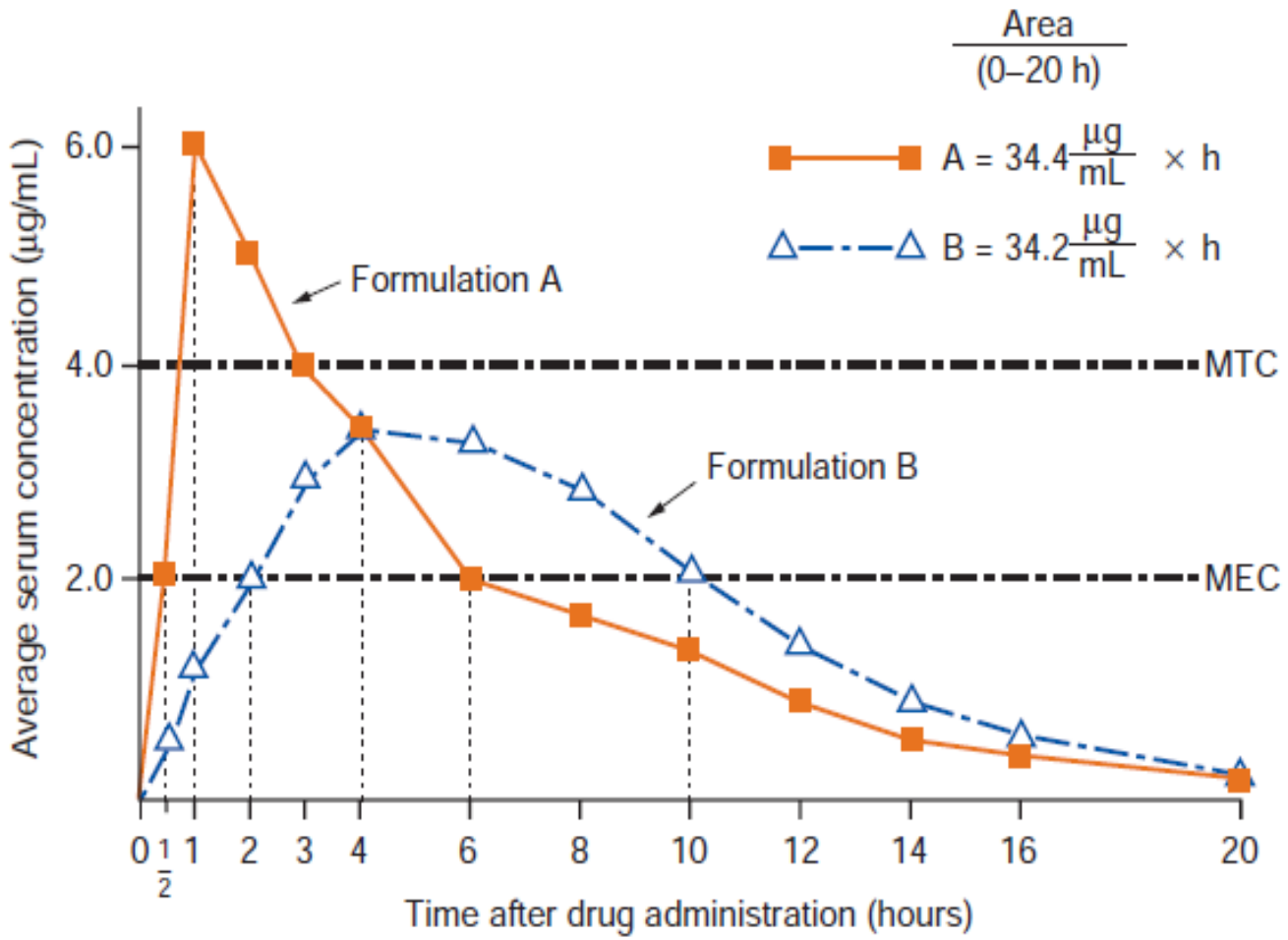

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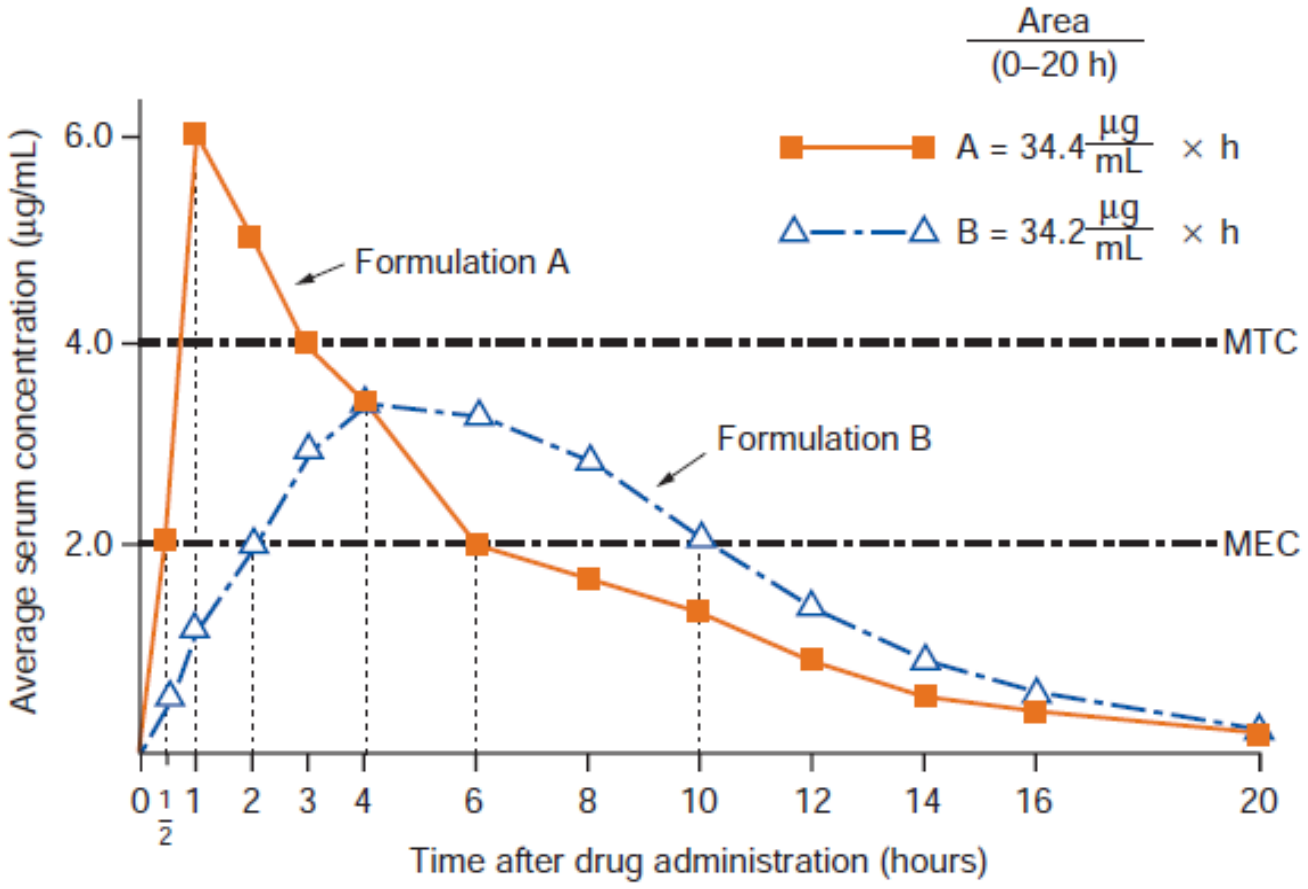
3. The area under the blood concentration time curve (AUC)

The AUC represent total amount of drug absorbed following administration of a single dose of that drug.



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- If similar doses of drug in different formulas produce different AUC values, differences exist in extent of absorption between formulations.
  In general, the smaller AUC, the lesser drug absorbed.

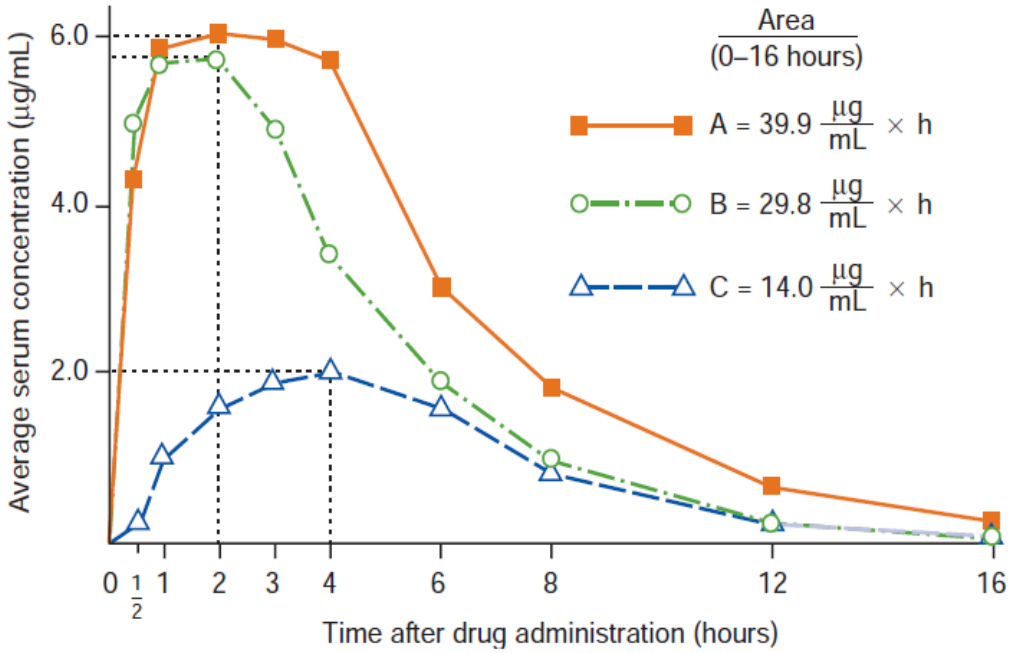


FIGURE 5.9 Serum concentration–time curve showing peak height concentrations, peak height times, and areas under the curves for equal amounts of drugs from three different formulations following oral administration. (Courtesy of D. I. Chodos and A. R. Disanto, Upjohn.)

- F: bioavailability of orally administered drug calculated by comparison of AUC after oral administration with that obtained after intravenous administration:
- $\mathbf{F = (AUC)_{oral}/(AUC)_{IV}}$

Bioequivalence of drug products

- Bioavailability: rate and extent to which a drug in a dosage form becomes available for biologic absorption.
- the **same drug** when formulated in **different dosage forms** have **different bioavailability** and exhibit **different clinical effectiveness**.
- Furthermore, two identical or equivalent products of **same drug** in the **same dosage strength** and in the **same dosage form** but **differing in formulative** materials or **method of manufacture** may vary widely in bioavailability and thus, in clinical effectiveness.
- FDA uses the following terms to define type or level of equivalency between drug products

Pharmaceutical equivalents:

are drug products that contain identical amounts of identical active ingredient, that is, the same salt or ester of the same therapeutic moiety, in identical dosage forms **but not necessarily containing the same inactive ingredients.**

Pharmaceutical alternatives:

are drug products that contain the identical therapeutic moiety or its precursor **but not necessarily in the same amount or dosage form or as the same salt or ester**.

Therapeutic equivalents:

used to indicate pharmaceutical equivalents that provide same therapeutic effect when administered to same individuals in same dosage regimens.

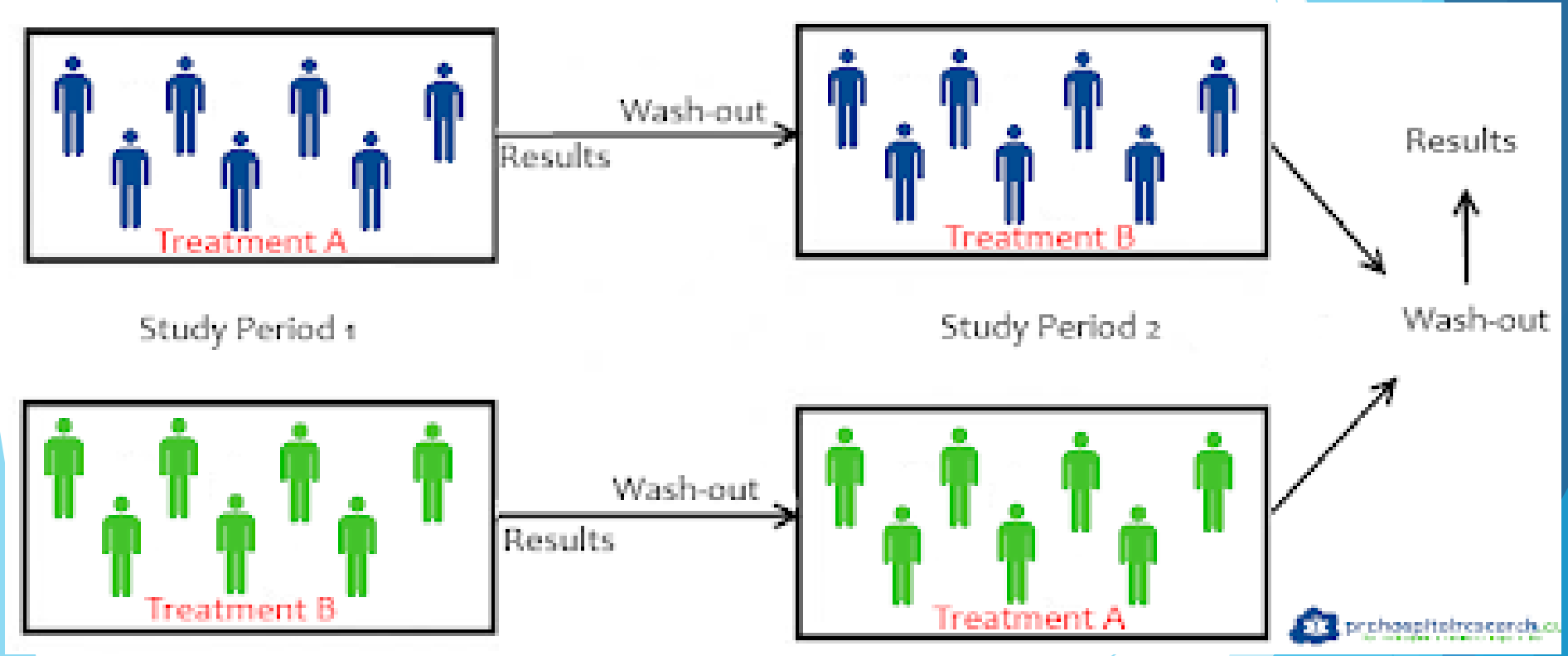
Bioequivalent drug products:

are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption are similar when administered at the same molar dose under the same experimental conditions(single or multiple dose).

- Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent ???

because such differences in rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, or are considered medically insignificant for the drug product studied.

- **The most common experimental plan to compare the bioavailability of two drug products :is simple crossover design study.**



- **12 to 24 individuals carefully matched subjects (usually healthy men aged 18 to 40 years and having similar height and weight) is administered both products under fasting conditions.**
- **each test subject is randomly assigned one of the two products for the first phase of the study.**
- **Once the first assigned product is administered, samples of blood or plasma are drawn from the subjects at predetermined times and analyzed for the active drug moiety and its metabolites as a function of time.**
- **The same procedure is then repeated (crossover) with the second product after an appropriate interval, that is, a washout period to ensure that there is no residual drug from the first administered product that would artificially inflate the test results of the second product.**
- **Afterward, the patient population data are tabulated and the parameters used to assess and compare bioavailability; that is, C_{max}, T_{max}, and AUC are analyzed with statistical procedures.**
- **Statistical differences in bioavailability parameters may not always be clinically significant in therapeutic outcomes.**

The value in the crossover experiment is that each individual serves as his own control by taking each of the products. Thus, inherent differences between individuals are minimized.

- **Absolute bioequivalency** between drug products **rarely occurs**. Such absolute equivalency would yield serum concentration-time curves for the products that would be exactly superimposable.
- This simply is not expected of products that are made at different times, in different batches, or indeed by different manufacturers.
- In most studies of bioavailability, the originally marketed product (**brand name drug product**) is recognized as the established product of the drug and is used as the **standard for the bioavailability** comparative studies.

According to the FDA: generic drug is considered **bioequivalent if the rate and extent of absorption do not show a significant difference from that of standard drug when administered at the same molar dose of the therapeutic ingredient under the same experimental conditions**.

Because in the case of a systemically absorbed drug blood levels even if from identical product may **vary in different subjects**, in bioequivalence studies each subject receives both the standard and the test drug and thus serves as his own control.

Under the **1984** act, to gain FDA **approval a generic drug product** must have these characteristics:

1. The same active ingredients as the standard drug .
2. Identical strength, dosage form, and route of administration
3. The same indications and precautions for use .

If a standard manufacturer reformulates an FDA-approved product, the subsequent formulation must meet the same bioequivalency standards that are required of generic manufacturers of that product .

The bioavailability study is different when single dose multiple-dose is tested

single dose bioavailability studies

- Compare the drug product to be tested against the appropriate reference material
- Crossover design in fasting state unless required a different design
- The sampling time for blood and/or urine is usually at least three times the half-life of the active drug ingredient or therapeutic moiety, its metabolite(s), or at least three times the half-life of the acute pharmacological effect.
- Measured are the peak concentration in the blood and the total area under the curve

Multiple-dose bioavailability studies

Multiple dose bioavailability studies compare **test product** and **reference** after **repeated** administration to determine steady-state levels (Css) of drug in the body.

Studies are conducted in human subjects in fasting or nonfasting state, depending upon the conditions reflected in the proposed labeling of the test product.

A multiple-dose study may be required for a test product if :

(a) there is a difference in **rate of absorption** but not in extent of absorption

(b) there is excessive **variability in bioavailability** from subject to subject

(c) the concentration of drug or its metabolites, in blood resulting from a single dose is too low

(d) the drug product is an extended-release dosage form.

A multiple-dose study is generally **crossover in design** unless scientific reasons dictate otherwise (e.g., if the study is designed to establish pharmacokinetic profile of a **new drug product**, a **new drug delivery** system, or an **extended-release** dosage form). At least **five times the half-life** of active drug ingredient, its therapeutic moiety or its active metabolite(s) is measured in the blood or urine.

Dosage regimen considerations

- There are two basic approaches to the development of dosage regimens.

The **empirical approach**

- which entails administration of a drug in a certain quantity, noting the therapeutic response and modifying the amount and interval of dosage accordingly.
- Besides the desired therapeutic effect, it is necessary to consider the occurrence and severity of side effects.

The **kinetic approach** (use of pharmacokinetics)

* This approach is based on the assumption that the therapeutic and toxic effects of a drug are related to the amount of drug in the body or to the plasma (or serum) concentration of drug at the receptor site.

Dosage regimen considerations

Table 5.10 FACTORS THAT DETERMINE A DOSAGE REGIMEN

ACTIVITY, TOXICITY

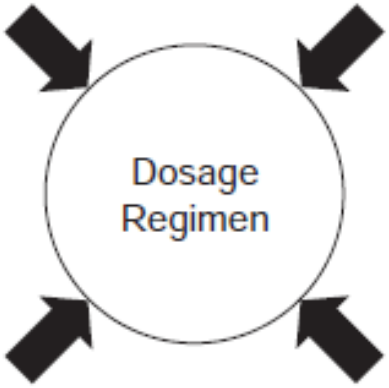
Minimum therapeutic dose

Toxic dose

Therapeutic index

Side effects

Dose–response relationships



PHARMACOKINETICS

Absorption

Distribution

Metabolism

Excretion

CLINICAL FACTORS

Clinical State of Patient

Age, weight, urine pH

Condition being treated

Existence of other disease states

Management of Therapy

Multiple drug therapy

Convenience of regimen

Compliance of patient

OTHER FACTORS

Tolerance–dependence

Pharmacogenetics–idiosyncrasy

Drug interactions

Life style factors, for example, diet, recreational drug use

PHARMACOKINETIC PRINCIPLES

- **one compartment** open-model system.
- **volume of distribution (V_d) **
- **absorption rate constant K_a**
- **elimination rate constant, K_{el}.**
- **plasma protein binding**
- **two-compartment model**
- **Half life**
- **Clearance**

Reference

Ansel's pharmaceutical dosage forms and drug delivery systems , tenth edition