DOSAGE FORM DESIGN

LEC. 10 DR. HAYDER KADHIM DRAIS

Bioequivalence of drug product:

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**.

 Bioequivalent drug products are **pharmaceutical equivalents or pharmaceutical alternatives** whose **rate and extent of absorption are similar.**

 Some pharmaceutical equivalents or pharmaceutical alternatives **equivalent in extent absorption** but **not in 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**.

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

 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**) are 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**.

Bioequivalency:
 The same batch-to-batch requirements for **identity**, **strength**, **purity**, and **quality.**
 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 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 study:

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.**

With multiple dose study, the method involves drug administration for at least **5 biological half-lives** with a dosing interval **equal to** or **greater than the biological half-life (i.e. administration of at least 5 doses) to reach the steady-state.** A blood sample should be taken at the end of previous dosing interval and **8 to 10 samples after the administration of next dose**. The extent of bioavailability is given as:

$$F_r = \frac{[AUC]_{test}\ D_{std}\ \tau_{test}}{[AUC]_{std}\ D_{test}\ \tau_{std}}$$

Where:

[AUC] values are **area under the plasma level-time curve** of one dosing interval in a multiple dosage regimen, after reaching the steady-state (Fig.1) and

τ (Greek letter tau) is the **dosing interval.**

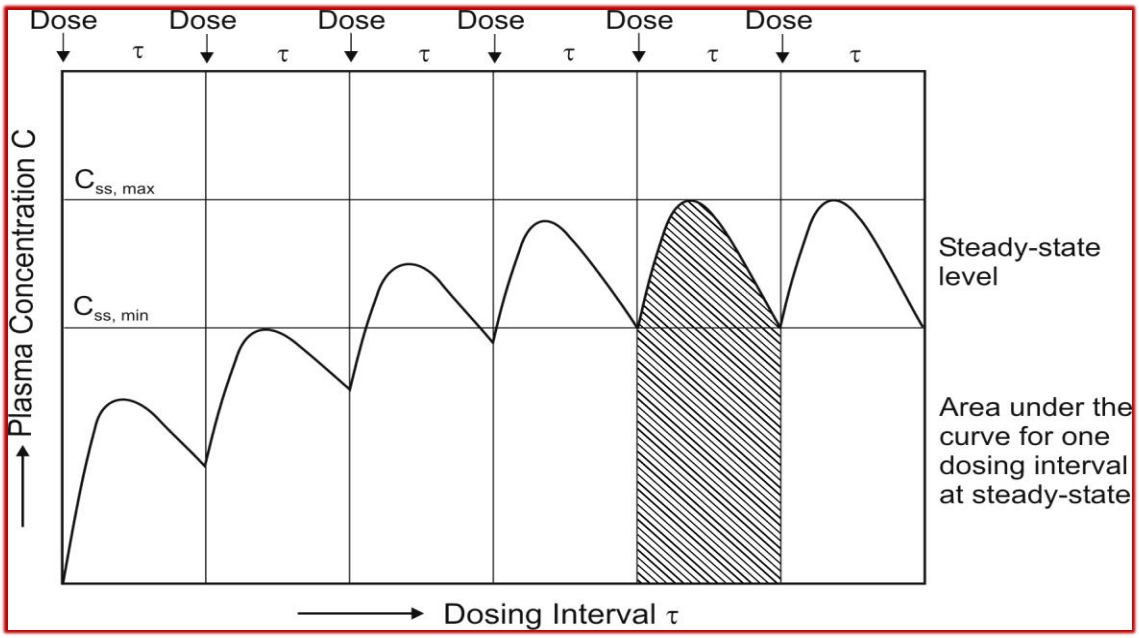

Fig. Determination of AUC and $C_{ss,max}$ on multiple dosing upto steady-state