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Factors Effecting Bioavailability Studies

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The goal of most oral dosage forms is to serve as a vehicle for the delivery of drugs to the blood stream for distribution to the site of action. The therapeutic effectiveness of a drug depends up on the ability of the dosage form to deliver the medicament to the site of action at a rate and amount sufficient to elicit the desired pharmacological action. This attribute of the dosage form is referred as physical availability or simply bioavailability. Bioavailability defined as the rate and extent of absorption of unchanged drug from its dosage form. Bioavailability mainly depends on the absorption efficiency of any dosage form. By definition, when a medication is administered intravenously, its bioavailability is 100%.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. Bioavailability of a drug is largely determined by the properties of the dosage form (which depend partly on its design and manufacture), rather than by the drug's physicochemical properties, which determine absorption potential. Bioequivalence means that two or more chemically or pharmaceutically equivalent products produce comparable bioavailability characteristics in any individual when administered in equivalent dosage regimen.

Keyword: Absolute Bioavailability, Therapeutic Bioavailability, Relative bioavailability, Percentage bioavailability and clinical trails

INTRODUCTION: Bioavailability studies are performed for both approved active drug ingredients and therapeutic moieties not yet approved for marketing by the FDA. New formulations of active drug ingredients must be approved by the FDA before marketing. In approving a drug product for marketing, the FDA ensures that the drug product is safe and effective for its labeled indications for use. Moreover, the drug product must meet all applicable standards of identity, strength, quality, and purity. To ensure that these standards are met, the FDA requires bioavailability/pharmacokinetic studies and, where necessary, bioequivalence studies for all drug products. For unmarketed drugs that do not have full NDA approval by the FDA, in-vitro and/or in-vivo bioequivalence studies must be performed on the drug formulation proposed for marketing as a generic drug product. In-vivo bioavailability studies are also performed for new formulations of active drug ingredients or therapeutic moieties that have full NDA approval and are approved for marketing. The purpose of these studies is to determine the bioavailability and to characterize the pharmacokinetics of the new formulation, new dosage form, or new salt or ester relative to a reference formulation. In

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summary, Bioavailability studies are used to define the effect of changes in the physicochemical properties of the drug substance and the effect of the drug product (dosage form) on the pharmacokinetics of the drug. Bioequivalence studies are used to compare the bioavailability of the same drug (same salt or ester) from various drug products.

MATERIALS AND METHODS:

Direct and indirect methods may be used to assess drug bioavailability. The in-vivo bioavailability of a drug product is demonstrated by the rate and extent of drug absorption, as determined by comparison of measured parameters, eg, concentration of the active drug ingredient in the blood, cumulative urinary excretion rates, or pharmacological effects. For drug products that are not intended to be 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. There are several direct and indirect methods of assessing bioavailability in humans. That is

PHARMACOKINETIC METHODS:

It include

1) Plasma drug concentration:

a) Time for peak plasma (blood) concentration (t_{max})

b) Peak plasma drug concentration (C_{max})

c) Area under the plasma drug concentration–time curve (AUC)

2) Urinary drug excretion:

a) Cumulative amount of drug excreted in the urine (D_u)

b) Rate of drug excretion in the urine (dD_u/dt)

c) Time for maximum urinary excretion (t)

PHARMACODYNAMIC METHODS: It include

1) Acute pharmacodynamic effect:

a) Maximum pharmacodynamic effect (E_{max})

b) Time for maximum pharmacodynamic effect

c) Area under the pharmacodynamic effect–time curve

d) Onset time for pharmacodynamic effect

2) Clinical observations:

Well-controlled clinical trials

3) In-vitro studies:

Drug dissolution

1) 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.

The time of peak plasma concentration (t_{max}):

t_{max}, corresponds to the time required to reach maximum drug concentration after drug administration. At t_{max}, peak drug absorption occurs and the rate of drug absorption exactly equals the rate of drug elimination. Drug absorption still continues after t_{max} is reached,

but at a slower rate. Units for t_{max} are units of time (Ex: hours, minutes).

The peak plasma drug concentration(C_{max}):

C_{max} represents the maximum plasma drug concentration obtained after oral administration of drug. For many drugs, a relationship is found between the pharmacodynamic drug effect and the plasma drug concentration. C_{max} provides indications that the drug is sufficiently systemically absorbed to provide a therapeutic response. The units of C_{max} are concentration units (Ex: mg/ml, ng/ml).

The area under the plasma level–time curve (AUC):

AUC is a measurement of the extent of drug bioavailability. The AUC reflects the total amount of active drug that reaches the systemic circulation. The AUC is the area under the drug plasma level–time curve from t = 0 to t = ∞, and is equal to the amount of unchanged drug reaching the general circulation divided by the clearance.

$$[AUC]_0^{\infty} = \int_0^{\infty} Cp\, dt$$

$$[AUC]_0^{\infty} = \frac{FD_0}{\text{Clearance}} = \frac{FD_0}{kVd}$$

Where, F = fraction of dose absorbed, D_0 = dose, k = elimination rate constant, and V_D = volume of distribution. The AUC is independent of the route of administration and processes of drug elimination as long as the elimination processes do not change. The AUC can be determined by a numerical integration procedure, such as the trapezoidal rule method. The units for AUC are concentration time (Ex: g hr/ml). For many drugs, the AUC is directly proportional to dose. In some cases, the AUC is not directly proportional to the administered dose for all dosage levels. For example, as the dosage of drug is increased, one of the pathways for drug elimination may become saturated. For drugs such as salicylate and phenytoin, continued increase of the dose causes saturation of one of the enzyme pathways for drug metabolism and consequent prolongation of the elimination half-life. The AUC thus increases disproportionally to the increase in dose, because a smaller amount of drug is being eliminated (that is, more drugs are retained).

RESULTS AND DISSCUSSION:

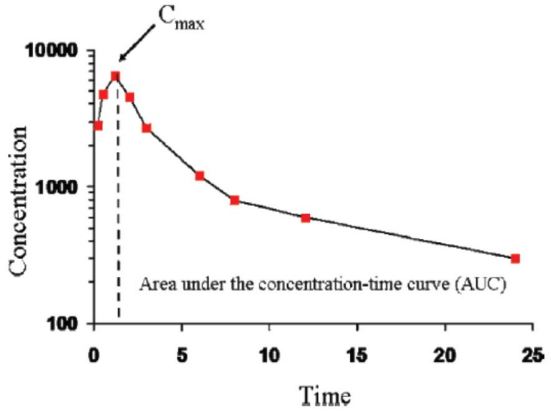

Figure -1 : AUC

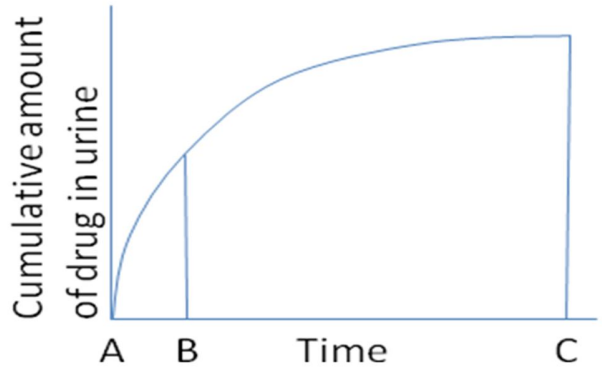

Figure 2: Cumulative amount of drug excreted in the urine

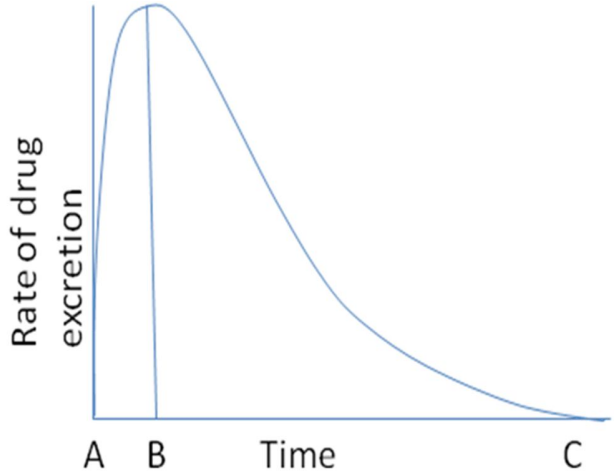

Figure 3: The rate of drug excretion

Two-way cross over		
Group no.	Subjects in Group	Treatment for period no.
		I II
1	1,2,3,4,5,6	A B
2	7,8,9,10,11,12	B A

Table 1: Two-way cross over

Three-way cross over		
Group no	Subjects in Group	Treatment for period no.
		I II III
1	1,2,3,4,5,6	A C B
2	7,8,9,10,11,12	B A C
3	13,14,15,16,17,18	C B A

Table: 2 - Three-way cross over

Four-way cross over		
Group no	Subjects in Group	Treatment for period no.
		I II III IV
1	1,2,3,4,5,6	A B C D
2	7,8,9, 10,11,12	B D A C
3	13,14,15,16,17,18	C A D B
4	19,20,21,22,23,24	D C B A

Table: 3 - Four-way cross over

CONCLUSSION :

Bioavailability is one of the essential tools in Pharmacokinetics, as bioavailability must be considered when calculating dosages for non-intravenous routes of administration. Evaluation of BE for systemically acting drugs using pharmacokinetics is well established. Unusual cases such as endogenous substances and highly variable drugs sometimes require new study designs and new statistical analysis procedures. The knowledge available about formulation development and formulation performance for oral dosage forms has allowed the FDA to determine that in vitro testing in some cases can provide adequate evidence of BE. Drug companies can now request waivers of in vivo BE studies (biowaivers) for some of their products, greatly reducing the cost of such studies. Opportunities for future expansion of biowaivers have been identified and discussed above. Locally acting drugs are more complex in terms of BA/BE. An appropriate BE method often needs to be established based on a scientific analysis of each drug product. The above was a brief overview of bioavailability study protocol with some of its specification and essential features. This provides us with a glimpse of the depth to which the drugs are evaluated for numerous aspects but is designate as a small word

called “Bioavailability or Bioequivalence” which is actually the heart and soul of therapeutic response of a drug moiety in a given drug product.

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