Bioavailability and bio equivalence on oral solid dosage form – A review

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ABSTRACT

The present study aimed towards the essential to ensure uniformity in standards of quality, efficacy & safety of Pharmaceutical products, Reasonable assurance is to be provided that various products containing same active ingredient, marketed by different licensees are clinically equivalent & interchangeable, Release of an active substance should be known & reproducible. Both Bioavailability & Bioequivalence focus on release of drug substance from its dosage form & subsequent absorption in circulation. Similar approaches to measure Bioavailability should be followed in demonstrating Bioequivalence. The knowledge of the BCS characteristics of a drug in a formulation can also be utilized by the formulation scientist to develop a more optimized dosage form based on fundamental mechanistic, rather than empirical, information. This report gives a brief overview of the BCS and its implications.

Keywords: Bioavilability, Bio equivalence, Active substance.

1. INTRODUCTION

Over the last 25 years, Pharmacokinetics has emerged as an integral part of drug development, especially when identifying a drug's biological properties. By pharmacokinetics, one means the application of kinetics to a Pharmakon, the Greek word used to specify drugs and poisons. The term thereby implies the time course and fate of drugs in the body. This general definition broadly embraces *absorption*, *distribution*, *metabolism* (biotransformation) and *excretion* (ADME). The linking of Pharmacodynamics (response) and pharmacokinetics offers a composite understanding both about how the drug affects thebody and how the body affects the drug. Many national and international societies and agencies are organizing workshops and conferences to harmonize the standards and documentation required for drug quality and safety [1].

Biopharmaceutics is based on the chemical and physical properties of a drug, substance, and the formulation and physiology of the route of administration. Today, many molecules are classified through screening processes, and promising candidates enter into drug pipelines for further in vitro and in vivo tests. At the end of the development process stands the approval by the regulatory agencies. The term bioavailability may be translated to mean availability of drug or the active ingredient(s) to the biological system. The extent to which the active ingredient in a dosage form intended for extra-vascular administration becomes available for absorption is dependent on a variety of factors. In this report, recent developments and future trends in bioavailability (BA) and bioequivalence (BE), based on the biopharmaceutics classi®cation system (BCS) are discussed. Some of the factors which are known to affect drug absorption are:

Physicochemical properties of the drug substance[2] e.g..

- ➢ Aqueous solubility
- ➢ Lipid solubility
- ➢ Partition coefficient
- ➢ Extent of ionization etc.
- ➢ Method of manufacture of the dosage form, e.g
- ➢ Wet-granulation
- ➢ Direct compression
- ➢ Dry granulation and
- ➢ Tablet hardness etccand (c) manufacturing aides used in the fabrication of dosage form etc.
- ➢ Bulking agents
- ➢ Binders

- ➢ Lubricants
- ➢ Dyes
- ➢ Disintegrants
- ➢ Coating materials, etc

The most important property of any non-intravenous dosage form, intended to treat a systemic condition, is the ability to deliver the active ingredient to the bloodstream in an amount sufficient to cause the desired response. This property of a dosage form has historically been identified as physiologic availability, biologic availability or bioavailability. Bioavailability captures two essential features, namely how fast the drug enters the systemic circulation (rate of absorption) and how much of the nominal strength enters the body (extent of absorption). Given that the therapeutic effect is a function of the drug concentration in a patient's blood, these two properties of non-intravenous dosage forms are, in principle, important in identifying the response to a drug dose. Onset of response is linked to the rate of drug absorption whereas the time-dependent extent of response is linked to the extent of drug absorption. While the bioavailability of each type of non-intravenous product (e.g. oral, inhalation, topical (e.g. patch), rectal, etc.) could be discussed, this article will of necessity focus only on orally administered products. They certainly represent the major pharmaceutical class in drug development and patient treatment [3].

Bioavailability, as the name implies, refers to availability of the administered drug dose to the biological system. Biavailability, is loosely defined as the rate at which the active drug ingredient is absorbed form a drug product (dosage form) and becomes available at the site of drug action. In actual practice it is difficult, if not impossible, to measure the concentration of drug at the site of action. Therefore, one usually measures concentration of drug in the blood or plasma as an indicator of the extent of availability of drug at the site of action. This is based on the premise that most drugs reach the site of action, or the biophase, through systemic circulation and therefore the concentration of drug in blood or plasma reflects the concentration of drug at the site of action [4].

Bioavailability following oral doses may vary because of either patient-related or dosage-form-related factors. Patient factors can include the nature and timing of meals, age, disease, genetic traits and gastrointestinal physiology. The dosage form factors include

- ➢ The chemical form of the drug (e.g. salt vs. acid)

- ➢ Its physical properties (e.g. crystal structure, particle size)
- ➢ An array of formulation (e.g. non-active ingredients) and manufacturing (e.g. tablet hardness) variables.

Not surprisingly, bioavailability is of clinical, academic, and regulatory interest. The latter includes agencies that approve the sale of products in their nation(s), as well as reimbursement agencies. Applications from manufacturers seeking regulatory approval for a new drug (e.g. New Drug Application (NDA)) must furnish exhaustive information about a drug's pharmacokinetics. Typically, such evidence entails studies wherein the drug has been orally administered. While such trials may broadly be viewed as bioavailability studies, many are ostensibly designed to assess the drug's safety and efficacy via strategies of dose escalation and chronic administration[5].

Since the rate of excretion of drug in the urine is a function of concentration of drug in the blood, it follows that the rate of urinary excretion of drug is a function of concentration of drug in the blood, if follows that the rate of urinary excretion of drug, is representative of the rate of absorption of the drug. Similarly, the extent of urinary excretion of drug is representative of the extent of drug absorption. The data generated during bioavailability studies can be used to obtain a variety of information. This is because bioavailability studies are concerned most with the fraction of dose that is released in vivo and is capable of reaching systemic circulation intact, rather than the label dose" stated on the packaged form of the drug [6]. Some examples where bioavailability data provide useful information concerning efficacy of the drug include the following:

- ➢ Determine the extent of absorption, i.e., the amount or fraction of the administered drug dose absorbed from a dosage form.
- ➢ Determine rate of absorption of the drug
- ➢ Determine the length (duration) of the presence of drug in the biological fluids or tissues
- ➢ Correlate relationship between concentration of drug in the plasma and clinical response.
- ➢ Compare availability of drug from different production batches of dosage form.
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1.1. The potential effect of excipients on bioequivalence studies

Bioequivalence studies usually involve single doses of a medicine.1 It is theoretically possible that excipients used in the generic formulation (preservatives, pH adjusters, thickening agents etc) could affect the absorption and metabolism at steady state without producing these differences from a single dose. However this is extremely unlikely and would normally be apparent from differences observed in the bioequivalence study. Any difference that may exist is negligible compared to the variability of the conditions in the gastrointestinal tract and its effect on absorption [7].

1.2. Non-interchangeable medicines

If approved by Medsafe it can be assumed that a generic medicine is therapeutically equivalent to theinnovator unless the medicine is considered to be noninterchangeable. For a limited number of medicines with a narrow therapeutic range such as carbamazepine, phenytoin and digoxin, a relatively small change in systemic concentration of these medicines can lead to altered therapeutic response or toxicity. Warfarin also has a narrow therapeutic range and bioequivalence has not been established between the two main brands of this medicine. Therefore clinical guidelines state that there should be no switching between different brands of these medicines [8].

1.3. GI considerations

Principally, the rate of release of a drug from a dosage form within the GI tract has to be considered. Drug dissolution, especially for poorly soluble drugs, can be limited due to the volume of intestinal juices available in the gut and to the pH. On the other hand, it is known that bile salts can increase the solubility of lipophilic substances, and the presence of food can have an additional impact on the solubilization and absorption of a drug. Furthermore, gastric emptying and GI transit timeare important parameters for the

onset and the degree of drug absorption.For some controlled or extended-release dosage forms, the intestinal motility pattern may have an impact on the rate and extent of drug dissolution. In addition, the drug amount in the gut lumen can be reduced due to hydrolytic, metabolic, or enzymatic degradation along the GI tract caused by the changing luminal environment or bacteriaand enzymes. Within the GI transit, the permeability of a drug can change due to physiological factors. GI dissolution and membrane permeability of the drug into the mucosa are the key parameters in drug absorption. there are different pathways and mechanisms for membrane transport. There are many factors of obviously complex chemistry and physiology involved. However, the fraction absorbed represents an upper limit to the amount of drug that can reach the systemic circulation [9].

1.4. Parameters of bioavailability

1.4.1. Urinary excretion data

When urinary excretion data are used, the rate of excretion of unchanged drug in the urine is used as an indicator of rate of absorption and the cumulative amount of unchanged drug excreted in the urine indicates the extent of drug absorption [10].

➢ k_{el} can be calculated from urinary excretion data.

➢ The excretion rate of the drug is assumed to be first order.

➢ k_e is the renal excretion rate constant.

➢ D_u is the amount of drug excreted unchanged in the urine.
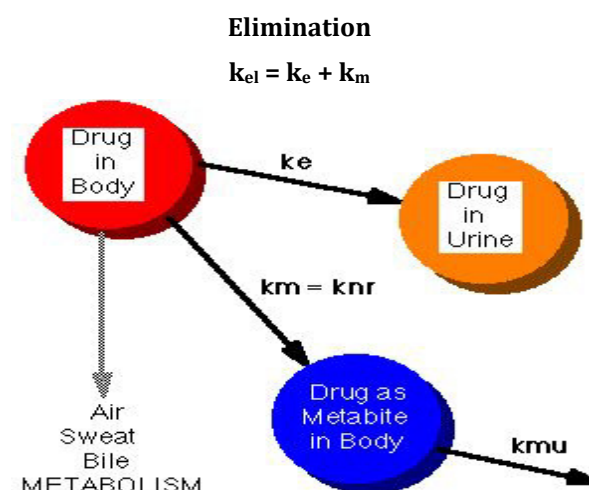
Elimination

$$k_{el} = k_e + k_m$$

Figure - 1: Elimination.

1.5. Plasma concentration data

When plasma concentration data are used to estimate bioavailability, the following three parameters estimate the extent and rate of

absorption of the drug: peak plasma concentration (C_{max}), time of peak plasma concentration (T_{max}), and area under the plasma concentration versus time curve (AUC). The AUC represents extent of drug absorption, and C_{max} and T_{max} and indicative of rate of absorption. Most bioavailability studies, however, use plasma concentration data rather than the urinary excretion data. This is because the appearance of drug in the blood serum occurs immediately after the drug is absorbed and therefore concentration of drug in the plasma is in direct relation to the absorption of drug. Most drugs are not excreted completely unchanged in the urine becomes difficult. It is much easier to determine the concentration of drug in plasma at any time than it is to determine the rate of urinary excretion of the drug. For example, if the plasma concentration is needed at short interval of time (e.g every hour), blood samples can be withdrawn every hour [11].
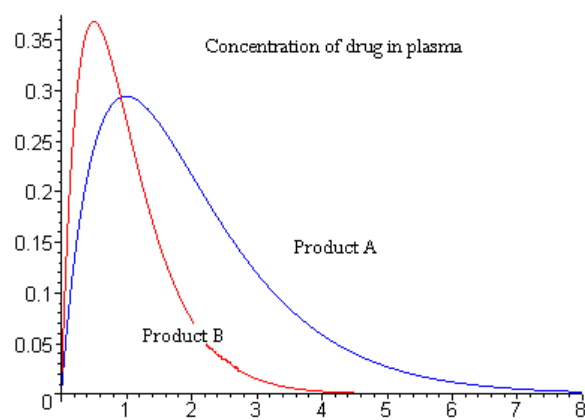

Figure - 2: Plasma concentration curves for two pain relievers.

But, in order to determine the urinary exertion rate every hour, the patient must void the bladder completely every hour. This may not be feasible at all times, since normally individual do not empty bladder every hour except, perhaps, when suffering from a specific physiologic disorder. Thus bioavailability is introduced here and presently it is common practice of formulation studies. Here physicochemical and biological properties especially pertaining to absorption of drugs are emphasized. Certain drugs show differing bioavailability from individual to individual or from one ethnic group to another ethnic group. These aspects may be considered presently for the drugs subjected to N-Acetylaiton and oxidation metabolism in the body. Hence past examples are given in this article to consider the broader aspect of pharmacogenetics. Genes encoding enzymes or proteins that play a role in the drug response differ in some respect form one individual to the next. The difference is referred to as genetic polymorphism. The

differences in response to a drug by different individuals are always modulated by the genetic predisposition of patient. This genetic differences are exhibited by those drugs which show polymorphic acetylation and polymorphic oxidation. Amrinone, p-aminosalicylic acid, caffeine, dapsone, hydralazine, isoniazid, procainamide, sulfadiazine, sulfamethazine and sulfapyridine are examples of drugs which undergo polymorphic acetylation (i.e N-acetylation). Examples of drugs which exhibit polymorphic oxidaiton are alprenolol, debrisoquin, diazepam, encainanide, flecainide, guanoxan, imipramine, metoprolol, phenacetin, Propafenone and timolol. According to rate of acetylation, slow acetylators and rapid acetylators are identified. This is well observed for drug, isoniazid [12].
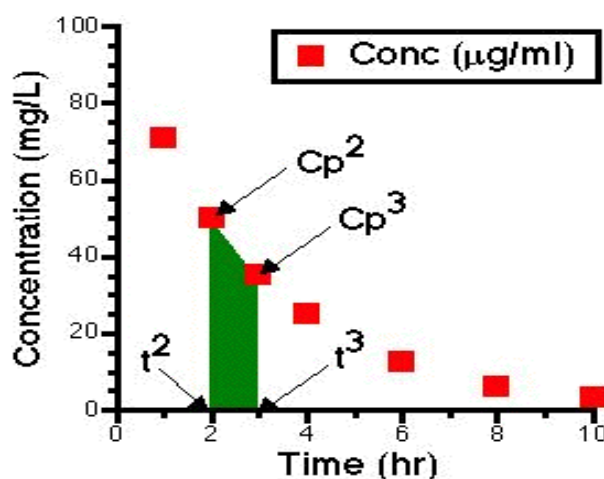

Figure - 3: AUC: Trapezoidal Rule

$$AUC_{2\text{-}3} = \frac{Cp^2 + Cp^3}{2} \times (t_3 - t_2)$$

The acetylation rate seems to have an ethnic component. The slowest acetylators are Chinese, Eskimos, and Japanese, while rapid acetylators are Egyptians, Finns, Israelis and scandinavians. Drugs given in examples are not all prone to ethnic groups but some of them show some percentage higher than a particular ethnic groups. Psychotropic agent nortriptyline showed differences exceeding 100 fold in plasma half life in a large groups of patietns. So this drug may result in undermedicaiton and toxicity affect on the basis of fast metabolizers and slow metabolizers. Examples of genetic variability in pharmacokinetics are found mainly in studies dealing, with drug metabolism. This indicates that renal excretion of drug dose not appear to show genetic polymorphism. So renal clearance of drugs that are predominantly excreted unchanged exhibit much less inter individual variability in metabolism kinetics than those drugs that are extensively metabolized. Thus genetics also

contributes in bioavailability and hence knowledge of pharmacogenetics from individual to ethnic groups may be studied for safe and better efficacy of drugs [13].

1.6. In vitro/in vivo correlations (IVIVC) and dissolution test development

To establish IVIVC, several factors have to be considered. If an IVIVC can be expected, the choice of a suitable medium, i.e. one that can simulate the in vivo dissolution, is critical. National pharmacopoeias describe different test media to cover the physiological pH range between 1.2 and 6.8. However, for many drugs which are poorly soluble within this pH range, these media are not very useful. Aqueous solubility is a function of the lipophilic and hydrophilic properties of a molecule and can be increased by increasing the lipophilicity of the medium, or by increasing the hydrophilicity of the molecule itself, e.g. using its salt. The easiest way to influence the solubility of a pH sensitive drug is to change the pH of the medium, or to introduce organic solvents. If the pH change is within the physiological range of pH 1 ± 8, the obtained solubility and dissolution data may be used to establish an IVIVC. A pH change outside this range makes a comparison between in vitro and the in vivo situation impossible. The same situation occurs if organic solvents are used, which is the less preferred way; because in the case of controlled release dosage forms, the release-controlling component can be influenced by the solvent and a correlation may not be obtained. The composition of modern dissolution media should provide a good predictability of the in vivo performance of a dosage form [14].

The BCS is used to set drug product dissolution standards to reduce the in vivo BE requirements. Knowledge of the BCS can also help the formulation scientist to develop a dosage form based on mechanistic, rather than empirical approaches. This allows one to determine the potential for in vitro and in vivo correlations, and can significantly reduce in vivo studies [15,16].

2. CONCLUSION

The overall conclusions from the different experimental works are that pharmaceutical surfactants can be used to mimic in vivo solubilization of poorly soluble drugs. The in vitro results may be used as surrogates to predict the in vivo performance of a dosage form for establishing IVIVCs. This allows a considerable simplification in dissolution media and methods. The different techniques were ensured that the standards of quality were uniform, efficacy & safety of Pharmaceutical products can be achieved, Reasonable assurance is to be provided

that various products containing same active ingredient, marketed by different licensees were clinically equivalent & interchangeable, Release of an active substance were well known & reproducible.

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