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Review Article

Bioavailability: A Pharmaceutical Review

Ahmed N.Allam*
Safaa S.El gamal
Viviane F.Naggar

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***Corresponding Author:**
Ahmed N.Allam
Faculty of Pharmacy,
University of Alexandria
El-Azarita,
Alexandria 21521 ,Egypt .
E-mail:
ph.a.allam@gmail.com

allam_basha2002@yahoo.com
Tel. No.: ++2010-5422491

ABSTRACT

In recent years drug bioavailability has become a subject of interest not only in drug development, but also in the early stages of drug discovery. This is a consequence of the finding that most of the candidate drugs that failed in clinical trials did so because of problems with ADME (absorption, distribution, metabolism, excretion) and toxicology, rather than through lack of efficacy. Efforts are being made in the pharmaceutical industry to improve success rates by taking into account the ADME and toxicology aspects in drug discovery from very early one. Therefore, it is not surprising to see that the number of publications on drug bioavailability has been increasing steadily for some time. In this review, attention is focused to briefly discuss some terms of bioavailability, relative bioavailability and bioequivalence, formulation and manufacturing variables that could influence the bioavailability of a drug product, physiologic and other factors affecting bioavailability, characteristics of drugs with the great potential for a bioavailability problem, assessment of bioavailability from pharmacologic as well as therapeutic response, bioavailability of drugs versus dietary supplements, causes of low bioavailability and different approaches to improve it based on biopharmaceutical classification system Thus approaches to improves drug solubility as well as drug permeability are the two main strategies in order to enhance the bioavailability of drugs.

INTRODUCTION

The U.S. Food and Drug Administration (FDA) define bioavailability as "the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action". Because in practice it is rare that drug concentrations can be determined at the site of action [1]

(e.g., at a receptor site), bioavailability is more commonly defined as "the rate and extent that the active drug is absorbed from a dosage form and becomes available in the systemic circulation." Usually bioavailability refers to the absorption of a drug from the gastrointestinal tract following oral administration of a dosage form. The dosage form may be any type of product, including a solution, suspension, tablet, capsule, powder, or elixir. Bioavailability can also refer to other types of dosage form, such as intramuscular injections, ointments and other topical preparations, transdermal patches, and implants, which also require an absorption step prior to reaching the systemic circulation. The only route of drug administration that should always result in a bioavailability of 100 % is an intravenous injection, in which the amount of drug reaching the systemic circulation is equal to the total administered dose [1, 2]

In nutritional sciences, which cover the intake of nutrients and non-drug dietary ingredients, the concept of bioavailability lacks the well-defined standards associated with the pharmaceutical industry. The pharmacological definition cannot apply to these substances because utilization and absorption is a function of the nutritional status and physiological state of the subject, resulting in even greater differences from individual to individual (inter-individual variation). Therefore, bioavailability for dietary supplements can be defined as the proportion of a substance capable of being absorbed and available for use or storage [3, 4].

In both pharmacology and nutrition sciences, the bioavailability is measured by calculating the area under curve, or AUC. It is a method of measurement of the bioavailability of a drug based on a plot of blood concentrations sampled at frequent intervals. It is directly proportional to the total amount of unaltered drug in the patient's blood[5].

Absolute bioavailability

Absolute bioavailability compares the bioavailability of the active drug in systemic circulation following non-intravenous administration (i.e., after oral, rectal, transdermal, subcutaneous, or sublingual administration), with the bioavailability of the same drug following intravenous administration. The comparison must be dose normalized (e.g. account for different doses or varying weights of the subjects); consequently, the amount absorbed is corrected by dividing on the corresponding dose administered [6].

The absolute bioavailability is the dose-corrected area under curve (AUC) non-intravenous divided by AUC intravenous. For example, the formula for calculating F for a drug administered by the oral route (po) is given below.

$$F = \frac{[AUC]_{po} * dose_{IV}}{[AUC]_{IV} * dose_{po}}$$

Therefore, a drug given by the intravenous route will have an absolute bioavailability of 1 (F=1) while drugs given by other routes usually have an absolute bioavailability of less than one. If we compare the bioavailability of two...ingredients, it is called comparative bioavailability. Although knowing the true extent of systemic absorption (referred to as absolute bioavailability) is clearly useful, in practice it is not determined as frequently as one may think. The reason for this is that its assessment requires an intravenous reference, that is, a route of administration which guarantees the entire administered drug reaches the systemic circulation [6].

There is no regulatory requirement to define the intravenous pharmacokinetics or absolute bioavailability; however, regulatory authorities do sometimes ask for absolute bioavailability information of the extravascular route in cases in which the bioavailability is apparently low or

$$relative\ bioavailability = \frac{[AUC]_A * dose_B}{[AUC]_B * dose_A}$$

variable and there is a proven relationship between the pharmacodynamics and the pharmacokinetics at therapeutic doses. In all such cases, to conduct an absolute bioavailability study requires that the drug be given intravenously. Intravenous administration of a developmental drug can provide valuable information on the fundamental pharmacokinetic parameters of volume of distribution (V) and clearance (CL)[7].

Relative bioavailability and bioequivalence

The term ‘‘relative bioavailability’’ refers to a comparison of two or more dosage forms in terms of their relative rate and extent of absorption. If an intravenous injection is employed as the reference dose, one can determine the absolute bioavailability of the test dosage form. Two dosage forms that do not differ significantly in their rate and extent of absorption are termed ‘‘bioequivalent.’’ Bioequivalence determinations may be made for ‘‘pharmaceutical alternatives,’’ defined as ‘‘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. Each drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.’’ In some instance, two pharmaceutical alternatives exhibit markedly different bioavailability, for example, a rapidly absorbed elixir vs. a more slowly absorbed capsule. In other cases, two different dosage forms (e.g., a tablet and a capsule) may or may not exhibit very similar bioavailability[2]. While the mechanisms by which a formulation affects bioavailability and bioequivalence have been extensively studied in drugs, formulation factors that influence bioavailability and bioequivalence in nutritional supplements are largely unknown. As a result, in nutritional sciences, relative bioavailability or bioequivalence is the most common measure of bioavailability, comparing the bioavailability of one formulation of the same dietary ingredient to another[8].

Drug Product Formulation

Most drugs are not taken as pure chemicals, but are formulated into a pharmaceutical dosage form. Such drug products may be a relatively simple solution, compressed tablet-containing binders, fillers, lubricants, a coloring agent, or a controlled-release product. The following are a few of the formulation and manufacturing variables that could influence the bioavailability of a drug product[2]:

- The properties of the drug (salt form, crystalline structure, formation of solvates, and solubility).
- The composition of the finished dosage form (presence or absence of excipients and special coatings).
- Manufacturing variables (tablet compression force, processing variables, particle size of drug or excipients, and environmental conditions).
- Rate and/or site of dissolution in the gastrointestinal tract.

Factors influencing bioavailability

Extravascularly administered drugs must traverse several barriers to reach the systemic circulation and/or their site of action. Many studies illustrate those differences in manufacturing procedures as well as the composition of the dosage form that can affect the bioavailability of a drug product. In addition, the bioavailability of a drug product can also be influenced by the physiology of the patient and other factors, such as the content of the gastrointestinal tract. The steps involved in the disposition of an orally administered solid

dosage form and the experimental approaches that may be used to characterize them are summarized in Table 1. A major factor determining the bioavailability of an orally administered drug product is the dissolution rate of the drug. A drug must be in solution to be absorbed from the gastrointestinal tract taking in consideration the possibilities of drug precipitates as a result of low solubility in the fluids of the gastrointestinal tract.

Table (1): The disposition and evaluation of orally administered solid dosage forms.

Steps involved in disposition	Experimental approaches
Dosage form reaches stomach/intestine	Measurement of pH or scintigraphy
Dosage form disintegrates into small particles*	In vitro disintegration testing
Drug dissolves in gastrointestinal fluids	In vitro dissolution testing
Drug reaches gastrointestinal wall/membrane • Drug is returned to gastrointestinal lumen by P-glycoprotein efflux pump • Drug is metabolized by intestinal enzymes • Drug is absorbed into hepatic circulation	In vitro drug transport studies In vitro drug metabolism studies In situ/In vivo hepatic perfusion studies
Drug reaches systemic circulation • Drug is excreted in urine • Drug is metabolized	Assay of drug in blood, plasma or serum - Measurement of drug excretion in urine - Measurement of metabolite(s) in blood and/or urine
Drug and/or active metabolite reaches its site of action and causes a pharmacologic response • Response is unrelated to desired therapeutic activity • Response is related to desired clinical response	Measurement of onset, duration, and intensity of pharmacologic response Determination of clinical efficacy in patients

*Some dosage forms are designed to remain intact, e.g., certain controlled-release products.

Physiologic and other factors affecting bioavailability:

The rate and extent of drug absorption can also be affected by a wide variety of factors related to the characteristics of the subject/patient receiving the drug product. These factors are important to consider, because they can contribute to intrasubject and intersubject variability in the treatment of patients. Further, if not well controlled during the course of a bioavailability study, these factors can bias the study results and confound interpretation of the data. Examples include the following:

- Contents of the gastrointestinal tract (fluid volume and pH, diet, presence or absence of food, bacterial activity, and presence of other drugs).
- Rate of gastrointestinal tract transit (influenced by disease, physical activity, drugs, emotional status of subject, and composition of the gastrointestinal tract contents).
- Presystemic drug metabolism and/or degradation (influenced by local blood flow; condition of the gastrointestinal tract membranes; and drug transport, metabolism, or degradation in the gastrointestinal tract or during the first pass of the drug through the liver). Age, sex, race, disease, body size, time of day, and physical activity.

Other factors related to the subject or patient, if not recognized or controlled, can also influence the assessment of drug bioavailability and product bioequivalence. For example, bioavailability studies typically involve the collection of blood and/or urine specimens to determine drug appearance in the systemic circulation. Thus, physiologic and pharmacokinetic perturbations that affect the concentration of drug measured in these fluids can potentially influence the results and interpretation of the study. Examples include changes that alter the following [2]:

(i) The rate, extent, and/or route of metabolism (e.g., coadministered drugs that compete for or induce drug-metabolizing enzymes);

(ii) The rate and/ or extent of drug elimination by the kidney (e.g., kidney disease and/or competition and changes in urine pH that affect renal transport mechanisms);

(iii) The degree of binding of the drug to plasma or tissue proteins (e.g., age-related changes in plasma-binding proteins or protein-binding displacements);

(iv) Distribution of drug into the erythrocytes.

Genetic polymorphisms in the drug-metabolizing enzymes of the liver may also contribute to large differences in the pharmacokinetics of a drug and the interpretation of bioavailability studies, a well-designed bioavailability study must either control or account for the influence of such variables[9].

Characteristics of drugs with the great potential for a bioavailability problem:

The total number of marketed drug products known to exhibit a significant bioavailability problem is relatively small. Thus, one point of view is that the bioavailability has been overemphasized and that for most drug products, it is not a matter of concern. Another point of view is that those products that exhibit a bioavailability deficiency in a carefully controlled study provide sample evidence of the potential for many drug products that have not yet been studied to present a bioavailability problem.

With minor exceptions, the FDA have required that bioavailability and bioequivalence of a drug product be demonstrated through in vivo studies, drugs that are poorly permeable, poorly soluble, and/or formulated in slowly dissolving dosage forms would be considered as more likely to demonstrate a bioavailability problem, and would not be candidates for the waiver of in vivo bioavailability studies. To provide some guidance as to which drugs have the greatest potential for a bioavailability problem, the FDA published a summary of the type of evidence that may be employed to assess the importance of establishing the bioavailability of a given drug[2]:

1. Data from clinical trials or bioequivalence studies that indicate a bioequivalence problem.
2. The drug has a narrow therapeutic range, and the concentrations of the drug in the patient must be carefully adjusted.
3. A lack of bioequivalence could have serious medical consequences.
4. Physicochemical evidence that:

- The drug has low solubility in water and/or the dissolution rate of the dosage form is slow.
- The particle size, crystalline structure, and other factors of the drug can affect the dissolution and bioavailability.
- The drug product contains a high ratio of excipients to active ingredients, or the product may require excipients to enhance absorption or contain excipients that inhibit absorption.

5. Pharmacokinetic evidence that:

- The absorption of the active drug is limited to a specific region of the gastrointestinal tract.
- The extent of absorption is low.
- There is rapid metabolism such that rapid dissolution and absorption are required for effectiveness.
- The product requires special formulations to stabilize the drug in the gastrointestinal fluids.
- The drug exhibits dose-dependent pharmacokinetics.

Drugs that meet one or more of the criteria given above and have been shown to exhibit significant differences in the bioavailability of marketed dosage forms include digoxin, quinidine, furosemide, nitrofurantoin, prednisone,chloramphenicol,theophylline,chlorpromazine, phenytoin, amitriptyline, and phenylbutazone.

Assessing bioavailability

Several methods can be used to determine the bioavailability or bioequivalence of a drug product. The vast majority of bioavailability studies involve the administration of the test dosage form to a group of healthy human subjects, followed by collection and assay of drug concentration in blood (plasma or serum) samples. The second most frequent type of study utilizes urinary excretion measurements. Occasionally other types of biologic material such as saliva, cerebrospinal fluid, bile, or feces are also collected. For a few drugs, for which assay methods are not available for the determination of drug concentrations in biologic fluids, a pharmacologic response may be measured. Finally, some bioavailability assessments have been made on the basis of a determination of the therapeutic response of patients to a given dosage form. However, this type of study is usually restricted to drugs that are active at the site of administration (e.g., topical) but are not intended to be available in the systemic circulation. For approval by the FDA, pharmacokinetic, pharmacodynamics, clinical, and in vitro studies are recognized (in descending order of preference) as acceptable approaches to document the bioavailability or bioequivalence of a drug product[2].

Assessment of bioavailability from pharmacologic response

Topical application of a corticosteroid does not generally result in measurable blood concentrations of the drug. Thus, bioavailability and bioequivalence determinations for these drug products may involve measurement of dermatologic vasoconstriction (i.e., skin blanching), a pharmacodynamic response. A few studies have attempted to relate quantitatively a pharmacologic response to the oral bioavailability of a drug. Others have employed pharmacologic end points that were not

necessarily related to the therapeutic activity of the test drug. For example, attempts have been made to relate pharmacologic responses such as changes in pupil diameter, electrocardiogram readings, or electroencephalogram readings to the time course of a given drug in humans and animals. However, pharmacologic data tend to be more variable, and demonstrating a good correlation between the measured response and the amount of drug available from the dosage form may be difficult. Further, the potential exists that the measured response may be owing to a metabolite whose concentration is not proportional to the concentration of the parent drug responsible for therapeutic activity[2, 5].

Assessment of bioavailability from therapeutic response

Because the ultimate goal of drug therapy is to achieve a certain therapeutic response in a patient, ideally the assessment of drug product efficacy should be studied in patients requiring the drug. Unfortunately, the quantitation of patient clinical response is too imprecise to permit a reasonable estimation of the relative bioavailability of two dosage forms of the same drug. Thus, there are good reasons to utilize healthy volunteers rather than patients. Bioequivalence studies are usually conducted using a crossover design in which each subject receives each of the test dosage forms. It is assumed that the physiologic status of the subject does not change significantly over the duration of the study. If patients were utilized, this assumption could be less valid because of changes in their disease state. Further, unless multiple-dose protocols were employed, a patient who might actually require the drug for the disease would receive only a single dose of the drug every few days or perhaps each week. To avoid such problems, one could test each product in different groups of patients, but this would require the use of a large number of subjects and careful matching of the various patient groups. Another problem is that many patients receive more than one drug, and the results obtained from a bioavailability study could be compromised because of a drug–drug interaction. Finally, an ethical question would arise in the case in which a particular product was believed to be defective. Thus, a patient requiring treatment with a given drug would need to consent to receive a product that might not provide sufficient drug to result in adequate treatment. Because of these considerations, the general conclusion is that most bioequivalence studies should be carried out with healthy subjects. However, for drugs not designed to be absorbed into the systemic circulation, and are active at the site of administration, clinical studies in patients are the only means to determine bioequivalence. Such studies are usually conducted using a parallel rather than a crossover design. Examples include studies of topical antifungal agents, drugs used in the treatment of acne, and agents such as sucralfate used in ulcer therapy[2, 5].

Bioavailability of drugs versus dietary supplements

In comparison to drugs, there are significant differences in dietary supplements that impact the evaluation of their bioavailability. These differences include the following: the fact that nutritional supplements provide benefits that are variable and often qualitative in nature; the measurement of nutrient absorption lacks the precision; nutritional supplements are consumed for prevention and well-being; nutritional supplements do not exhibit characteristic dose-response curves; and dosing intervals of nutritional supplements, therefore, are not critical in contrast to drug therapy. In addition, there is lack of defined methodology and regulations in measuring and reporting bioavailability in comparison to drugs [4, 8].

In clinical trials with dietary supplements, bioavailability primarily focuses on statistical descriptions of mean or average AUC differences between treatment groups, while often failing to compare or discuss their standard deviations or inter-individual variation. This failure leaves open the question of whether or not an individual in a group is likely to experience the benefits described by the mean-difference comparisons. Further, even if this issue were discussed, it would be difficult to communicate meaning of these inter-subject variability to consumers and/or their physicians[4, 8].

Causes of low bioavailability

Orally administered drugs must pass through the intestinal wall and then through the portal circulation to the liver; both are common sites of 1st-pass metabolism (metabolism of a drug before it reaches systemic circulation). Thus, many drugs may be metabolized before adequate plasma concentrations are reached. Low bioavailability is most common with oral dosage forms of poorly water-soluble, slowly absorbed drugs. Insufficient time for absorption in the GI tract is usually a cause of low bioavailability. If the drug does not dissolve readily or cannot penetrate the epithelial membrane (eg, if it is highly ionized and polar), time at the absorption site may be insufficient. In such cases, bioavailability tends to be highly variable as well as low [1, 5].

Chemical reactions that reduce absorption can reduce bioavailability. They include formation of a complex (e.g., between tetracycline and polyvalent metal ions), hydrolysis by gastric acid or digestive enzymes (e.g., penicillin and chloramphenicol palmitate hydrolysis), conjugation in the intestinal wall (e.g., sulfoconjugation of isoproterenol), adsorption to other drugs (e.g., digoxin to cholestyramine), and metabolism by luminal microflora [1].

When going first into humans, sufficient and well characterized solubility becomes even more critical. From now on the solubility or dissolution of the dose, ranges in the various biophysiological media to which the drug substance or formulated drug substance will be exposed is expected to be reproducible and remain unchanged for the final development and eventually marketing. It is well accepted today throughout the scientific community that drug substance solubility and especially aqueous drug substance solubility is an issue for the drug discovery as well as the early and late stage pharmaceutical development process and therefore needs to be addressed very early on, during compound design and optimization. The solubility or dissolution of the drug substance can be mainly altered on two levels, through material engineering of the drug substance or through formulation approaches. Whatever route is taken to enhance or modify the solubility and/or dissolution of a lead substance, it needs to be scalable to a commercially viable process later on in the development[1, 5].

Besides the aqueous solubility of a drug substance, its permeability is a second critical aspect for oral bioavailability. The Biopharmaceutical Classification System (BCS) was introduced in the mid-1990s to classify the drug substances with respect to their aqueous solubility and membrane permeability[10, 11].Thus approaches to improves drug solubility as well as drug permeability are the two main strategies in order to enhance the bioavailability of drugs.

The BCS classification takes into account the required dose since low dosed drugs will sufficiently dissolve in the intestinal fluids of the GI tract to be absorbed, while higher doses of drugs with similar aqueous solubility will not. To generally describe “solubility”, the Pharmacopoeia (USP)[12], uses seven different solubility expressions as shown in Table (2). The European Pharmacopoeia[13] uses similar

solubility definitions except the 'practically insoluble' characteristic, which is not specified.

Table 2: Solubility definition in the USP [12, 14]

Description forms (solubility definition)	Parts of solvent required for one part of solute	Solubility range (mg/ml)	Solubility assigned (mg/ml)
Very soluble (VS)	<1	>1000	1000
Freely soluble (FS)	From 1 to 10	100–1000	100
Soluble	From 10 to 30	33–100	33
Sparingly soluble (SPS)	From 30 to 100	10–33	10
Slightly soluble (SS)	From 100 to 1000	1–10	1
Very slightly soluble (VSS)	From 1000 to 10000	0.1–1	0.1
Practically insoluble (PI)	>10.000	<0.1	0.01

SOLUBILIZATION APPROACH

The solubility of poorly water soluble drug candidates for traditional formulation system, can be improved most commonly by cosolvent addition, micellar solubilization, polymer loading, pH adjustment (only for an ionizable drug), modification of drug crystal form, complexation and combinations of techniques[15].

Cosolvent Addition

The solubility of a poorly water soluble drug can be increased frequently by the addition of a water miscible solvent in which the drug has good solubility. Seedher et al[16] investigated that the aqueous solubility of celecoxib, rofecoxib and nimesulide could be enhanced significantly by using ethanol as the second solvent and PEG-400-ethanol had highest solubilization potentiality among the mixed solvent systems. Dimethylsulfoxide (DMSO) and dimethylacetoamide (DMA) have been widely used as cosolvents[17-19] because of their large solubilization capacity for poorly soluble drugs and their relatively low toxicity.

Micellar Solubilization

Surfactants are widely used for improving the solubility of poorly soluble drugs. Micellar solubilization is an area of investigation for improving the pharmaceutical formulations[20]. A search for literature yields many journal references describing the solubilization by surfactant addition[20, 21]. It has been shown that naturally secreted bile salts act as surfactants, enhance the dissolution rate of poorly soluble drugs and thereby increase their bioavailability, however, when there is inadequate biliary secretion or insufficient exposure time, drug dissolution and absorption rates decrease significantly. Hence, the incorporation of another surfactant into the drug formulation may help solubilizing the insoluble drug and increase its dissolution rate[22].

Polymer Loading

The solubility and dissolution related bioavailability of poorly soluble pharmaceuticals could also be improved by loading a drug into a polymeric carrier in a nanocrystalline or amorphous state, both nanocrystals and amorphous drug are not physically stable and they tend to recrystallize into the more thermodynamically stable macrocrystal size[15]. Various stabilizing methods have been reported, including the use of polymer excipients such as

gelatin[23], polyvinylpyrrolidone[24], polyethylene glycol [25] , alginate[26], chitosan and thiolated chitosan[27].

pH Adjustment

The solubility of weak electrolytes (most of the drugs) is strongly influenced by the pH of the solution. Ketoprofen, being a weak acid (pKa 4.6), can be solubilized by adjusting the pH to a higher value. Solubility at pH > 5 (pH in duodenum) may be appropriate because most compounds are mainly absorbed in intestinal region[28].

Solubilization of drugs exhibiting low water solubility is possible by using a combination of pH adjustment and cyclodextrin complexation[29].

Modification of Drug Crystal Form

Drug crystal form may be altered to other distinct crystalline species with different internal lattices. Polymorphism is known to influence not only the technological feature but also the physicochemical stability and the intrinsic dissolution rate that directly affects absorption and bioavailability of drugs[30, 31].

Complexation

The traditional formulation system for poorly soluble drugs involving combination of organic solvents, surfactants and extreme pH conditions are often irritating and may cause adverse reactions. At times, these methods are inadequate for solubilizing enough drugs particularly for a parenteral delivery system. Another recent method for solubilizing poorly soluble drugs involves by cyclodextrin complexation. Drug cyclodextrin complexation can reduce decomposition of drug by protecting the labile region from the potential reactants in the aqueous environment[32, 33].

Solid Dispersion

Solid dispersions (SD) are one of the most promising strategies to improve the oral bioavailability of poorly water soluble drugs. By reducing drug particle size to the absolute minimum, and hence improving drug wettability, bioavailability may be significantly improved. They are usually presented as amorphous products, mainly obtained by two major different methods, for example, melting and solvent evaporation. Recently, surfactants have been included to stabilize the formulations, thus avoiding drug recrystallization and potentiating their solubility. New manufacturing processes to obtain solid dispersions have also been developed to reduce the drawbacks of the initial process[34].

Solid dispersions could be classified as first, second and third generation solid dispersions.

Different carriers used in preparation of SD are summarized in Table (3).

Liquisolid Tablets Technology

Liquisolid system is a novel concept of drug delivery via oral route. This technique is applied to water insoluble drugs and lipophilic drugs to sustain their release. Formulation and manufacture of the Liquisolid tablets is a quite simple method according to new mathematical model described by Spireas et al[35]. It involves dissolving the drug in a suitable non-volatile solvent and then adding this liquid medication to the mixture of carrier and coating materials. Mixing of this will lead to Liquisolid system which is subjected to tabletting by direct compression. Increase in dissolution rate and in turn improvement in bioavailability is observed in case of poorly water soluble drugs[36].

Table (3): Classification of different classes of solid dispersions

Class	Carrier
First generation SD	Crystalline carriers including urea[37] and sugars[38]
Second generation SD	Amorphous and polymeric carriers including: (i) Fully synthetic polymers such as povidone (PVP)[39, 40], polyethylene glycols (PEG)[41] and polymethacrylates[42] (ii) Natural and semi synthetic polymers such as hydroxypropylmethylcellulose (HPMC)[43], ethylcellulose[44], hydroxypropylcellulose[45] and starch derivates, like cyclodextrins[46]
Third generation SD	surfactant carrier, or a mixture of polymers and surfactants as inulin[40] ,Compritol 888 ATO[47], gelucire 44/14[48] and Poloxamer 407[49]

PERMEATION APPROACH

Permeability along with solubility forms the backbone of BCS that helps in assessing oral absorption and bioavailability of drug molecules. The various methods used for permeability screening are mentioned below[1]

- Determination of o/w pH partition profile of the drug.
- Studies of the extent of absorption in humans, pharmacokinetic mass balance and absolute bioavailability studies.
- Intestinal permeability studies-The following tissues can be used:
    - In vivo intestinal perfusion studies in human.
    - In vivo or in situ perfusion studies in animals.
- In vitro permeation studies using excised human or animal intestinal tissues.
- In vitro permeation experiments across a monolayer of cultured human intestinal cells.
- Coca-2 cell lines are derived from human colon carcinoma and used widely for permeability determination. The technique is expensive and requires specialized skills.
- Initial screening can also be carried out using parallel artificial membrane permeability analysis (PAMPA), which is carried out on microplates. It measures the permeation of compounds through a phospholipids coated filter medium that mimics intestinal cell structures.

Micro and Nanoemulsions

These novel drug delivery systems have been reported to improve the rate and extent of absorption of lipophilic drugs[50-52]. Microemulsions are homogeneous, transparent, thermodynamically stable dispersions of water and oil, stabilized by a surfactant, usually in combination with a cosurfactant (typically a short-chain alcohol).

Nanoemulsions are the thermodynamically stable isotropic system in which two immiscible liquids (water and oil) are mixed to form a single phase by means of an appropriate surfactant or its mixture with a droplet diameter approximately in the range of 0.5-100 um[53].

As pharmaceutical drug delivery systems, they have many advantages, including clarity, high stability, and ease of preparation. It was reported that microemulsion technique could improve permeation of Acyclovir because of the

presence of surfactant, which reduces the interfacial tension to nearly zero [54].

Dry Emulsion system

One possible way to make emulsion-based formulations stable is to formulate them into dry emulsions[55]. Dry emulsion formulations are typically prepared from O/W emulsions containing a soluble or an insoluble solid carrier in the aqueous phase, by spray drying, lyophilization or evaporation. Dry emulsions are regarded as lipid-based powder formations from which an O/W emulsion can be reconstituted. From a pharmaceutical point of view, they are attractive due to their physical strength and ease of administration as capsules and tablets[56].

Self emulsifying drug delivery systems (SEDDS)

Among the lipid-based systems, self micro and nanoemulsifying drug delivery system is a promising technology to improve the rate and extent of the absorption of poorly water-soluble drugs[57]. The clinical usefulness of the SMEDDS is evident from the commercially available formulation containing cyclosporine A, ritonavir and saquinavir. SMEDDS is pre-concentrate mixture of surfactants, cosurfactants, and lipophilic phase, which creates fine droplets of emulsion (5–100 nm), when diluted with water or the body fluids in the aqueous lumen of the gut[58].

Many mechanisms were suggested for the reported enhanced bioavailability and improved oral absorption of several drugs from these systems including the increase in membrane fluidity that facilitate transcellular absorption, opening tight junction to allow paracellular transport, inhibiting P-glycoprotein to increase intracellular concentration and residence time by surfactants, stimulating lipoprotein/chylomicron production by lipid and large interfacial surface area provided by fine droplet size of the formulation promote rapid release of the drug substance and/or the formation of mixed micelles containing the drug[59] .

Solid Lipid Nanoparticles (SLN)

SLN were derived from o/w emulsions by replacing the liquid lipid (oil) by a solid lipid, i.e. a lipid being solid at room and simultaneously at body temperature. SLN proved to be a suitable oral delivery system to enhance the oral bioavailability of drugs[60, 61].

A second generation of lipid nanoparticles was developed. This so-called nanostructured lipid carriers (NLC) are prepared not from a solid lipid but from a blend of a solid lipid with an oil[62]

Liposomes and Niosomes

Drug delivery system using colloidal particulate carrier, such as liposomes or niosomes, has distinct advantages over conventional dosage form and micelles because the particles can act as drug containing reservoirs[63].The niosomal system is supposed to enhance bioavailability of poorly bioavailable drugs by crossing the anatomical barrier of gastrointestinal tract via transcytosis of M-cells of Peyer's patches at the intestinal lymphatic tissues[64].

Proliposomes and Proniosomes

Proliposomes and proniosomes are dry, free-flowing granular products, which, upon the addition of water, disperse to form liposomal and niosomal suspension respectively[65, 66]. Several studies have been reported which prove the utility of oral

proliposomes and proniosomes in providing enhanced solubility and bioavailability for insoluble/poorly soluble drugs[67-69].

Gastroretentive delivery systems

Gastroretentive systems can remain in the gastric region for several hours, and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestine. Gastroretention helps provide better availability of new products with new therapeutic possibilities and substantial benefits for patients[70, 71]

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