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NOVEL STRATEGIES OF ENHANCING THE BIOAVAILABILITY: A REVIEW

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ABSTRACT
Poor solubility remains a major challenge for pharmaceutical industry last decade, which is now considered to be an area of prime importance in the field of biomedical research for the development of new drug formulation. Approximately 40% new molecular entities synthesized in pharmaceutical Reaction with advanced combinatorial chemistry and computer aided drug designing (CADD) approaches suffer from poor solubility and bioavailability related issues. Apart from these presence of intestinal tight junctional epithelial cells, transporters and enzymatic barriers further reduces the oral absorption of drugs. Implication of the novel lipid based nanocarriers and nanomaterials like dendrimers and carbon nanotubes, liposome, nanosuspention, noisome, phytosomes as a delivery system can effectively enhance the oral bioavailability of drugs by breaching the barriers, and resolve all critics related to solubility and bioavailability. Thus prime goal of this review are to give in-depth knowledge and critical appraisal on the barriers for poor oral bioavailability of drugs, along with various novel formulation approaches used for bioavailability enhancement such as lipid based formulations, nanosizing techniques, complexation with polymers and nanomaterials like dendrimers, carbon nanotubes, and penetration enhancers.

KEYWORDS: Solubility, Permeability, Bioavailability, Stability.

1. INTRODUCTION

1.1 Bioavailability

The term **Bioavailability,** one of the principal pharmacokinetic properties of drugs, is used to describe the fraction of an administered dose of unchanged drug that reaches the systemic circulation. By definition, when a medication is administered intravenously, its bioavailability is 100%. However, when a medication is administered via other routes (such as oral), its bioavailability decreases (due to incomplete absorption or first-pass metabolism) depicts different pathways of drug absorption from gastrointestinal tract to systemic circulation.[1] The measurement of the amount of the drug in the plasma at periodic time intervals indirectly indicates the rate and extent at which the active pharmaceutical ingredient is absorbed from the drug product and becomes available at the site of action. Bioavailability is one of the essential tools in pharmacokinetics, as it must be considered when calculating dosages for non-intravenous routes of administration. It is expressed as either absolute or relative bioavailability .the major scope of bioavailability help manufacturers develop the formulations for a drug by studying the effect of ingredient and method of manufacture.[2] Finally the best formulation is selected based on desired absorption pattern. By bioavailability study the manufacturer can be ensure batch to batch uniformity of drug. The manufacturer can develop their own product using bioavailability studies by comparing it with the competitor's products.[3] The results of bioavailability study of original product (first developed product) are referred as bench mark for subsequent batches. This bioavailability study is helpful in bioequivalence studies, which is a compliance requirement of the regulatory authorities.

1.1.1 Absolute bioavailability: Absolute bioavailability compares the bioavailability of the active drug in systemic circulation following non-intravenous administration (i.e., after oral, ocular, rectal, transdermal, subcutaneous, or sublingual administration), with the bioavailability of the same drug following intravenous administration.[4] It is the fraction of the drug absorbed through non-intravenous administration compared with the corresponding intravenous administration of the same drug. 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 the corresponding dose administered.[5] In Biopharmaceutics, in order to determine absolute bioavailability of a drug, a pharmacokinetic study must be done to obtain a plasma drug concentration vs. time plot for the drug after both intravenous (IV) and extravascular (non-intravenous, i.e., oral) administration. The absolute bioavailability is the dose-corrected area

under curve (AUC) non-intravenous divided by AUC intravenous. The formula for calculating the absolute bioavailability, F, of a drug administered orally (p^o) is given below (where D is dose administered).Therefore, a drug given by the intravenous route will have an absolute bioavailability of 100% (f = 1), whereas drugs given by other routes usually have an absolute bioavailability of less than one. If we compare the two different dosage forms having same active ingredients and compare the two drug bioavailability 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.[6] The reason for this is that its assessment requires an intravenous reference; that is, a route of administration that guarantees the entire administered drug reaches systemic circulation. Such studies come at considerable cost, not least of which is the necessity to conduct preclinical toxicity tests to ensure adequate safety, as well as potential problems due to solubility limitations. These limitations may be overcome, however, by administering a very low dose (typically a few micrograms) of an isotopically labelled drug concomitantly with a therapeutic non-isotopically labelled oral dose (the isotopically-labelled intravenous dose is sufficiently low so as not to perturb the systemic drug concentrations achieved from the non-labelled oral dose). The intravenous and oral concentrations can then be deconvoluted by virtue of their different isotopic constitution, and can thus be used to determine the oral and intravenous pharmacokinetics from the same dose administration. This technique eliminates pharmacokinetic issues with non-equivalent clearance as well as enabling the intravenous dose to be administered with a minimum of toxicology and formulation. The technique was first applied using stable-isotopes such as ^{13}C and mass-spectrometry to distinguish the isotopes by mass difference. More recently, ^{14}C labelled drugs are administered intravenously and accelerator mass spectrometry (AMS) used to measure the isotopically labelled drug along with mass spectrometry for the unlabelled drug.[7] 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 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.[8]

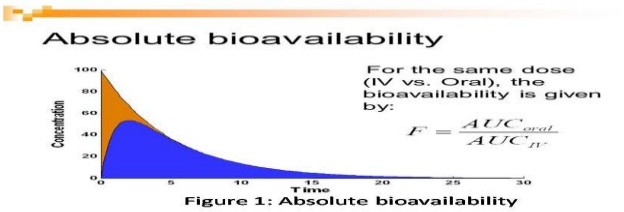

Figure 1: Absolute bioavailability

1.1.2 Relative bioavailability: In Biopharmaceutics, relative bioavailability measures the bioavailability (estimated as the AUC) of a formulation (A) of a certain drug when compared with another formulation (B) of the same drug, usually an established standard, or through administration via a different route. When the standard consists of intravenously administered drug, this is known as absolute bioavailability, Relative bioavailability is one of the measures used to assess bioequivalence (BE) between two drug products.[9] For FDA approval, a generic manufacturer must demonstrate that the 90% confidence interval for the ratio of the mean responses (usually of AUC and the maximum concentration, C_{max}) of its product to that of the "brand name drug is within the limits of 80% to 125%. Where AUC refers to the concentration of the drug in the blood over time t = 0 to t = ∞, C_{max} refers to the maximum concentration of the drug in the blood. When T_{max} is given, it refers to the time it takes for a drug to reach C_{max}.[10] 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.[11]

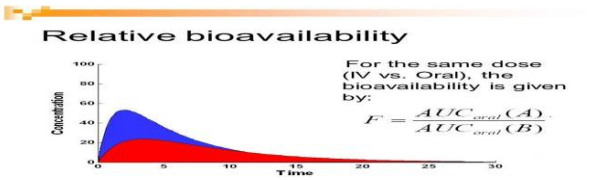

Figure 2: Relative bioavailability

1.2 Factor influencing bioavailability

The absolute bioavailability of a drug, when administered by an extravascular route, is usually less than one (i.e., F< 100%). Various physiological factors reduce the availability of drugs prior to their entry into the systemic circulation. Whether a drug is taken with or without food will also affect absorption, other drugs taken concurrently may alter absorption and first-pass metabolism, intestinal motility alters the dissolution of the drug and may affect the degree of chemical degradation of the drug by intestinal microflora. Disease states affecting liver metabolism or gastrointestinal function will also have an effect.[12]

Other factors may include, but are not limited to

1.2.1 Physical properties of the drug (hydrophobicity, pKa, solubility).
1.2.2 The drug formulation (immediate release, excipients used, manufacturing methods, modified release – delayed release, extended release, sustained release, etc.).
1.2.3 Whether the formulation is administered in a fed or fasted state.
1.2.4 Gastric emptying rate.
1.2.5 Circadian differences.

1.2.6 Interactions with other drugs/foods:
a) Interactions with other drugs (e.g., antacids, alcohol, nicotine)
b) Interactions with other foods (e.g., grapefruit juice, pomello, cranberry juice, brassica vegetables)
1.2.7 Health of the gastrointestinal tract
1.2.8 Enzyme induction/inhibition by other drugs/foods:
a) Enzyme induction (increased rate of metabolism), e.g., Phenytoin induces CYP1A2, CYP2C9, CYP2C19, and CYP3A4
b) Enzyme inhibition (decreased rate of metabolism), e.g., grapefruit juice inhibits CYP3A → higher nifedipine concentrations
1.2.9 Individual variation in metabolic differences
a) Age: In general, drugs are metabolized more slowly in fetal, neonatal, and geriatric populations
b) Phenotypic differences, enterohepatic circulation, diet, gender

1.2.10. Disease state

a) E.g., hepatic insufficiency, poor renal function Each of these factors may vary from patient to patient (inter-subject variation), and indeed in the same patient over time (intra-subject variation). In clinical trials, inter-subject variation is a critical measurement used to assess the bioavailability differences from patient to patient in order to ensure predictable dosing.

1.3 Effects of Poor Bioavailability

Drugs which are having less oral bioavailability fail to reach the minimum effective concentration required to achieve the theraputical action. The oral dose of the drugs showing less bioavailability is usually very high as only a fraction of the administered dose reaches the systemic circulation and hence the target organ. A classic example of such drug is saquinavir, a highly potent HIV protease inhibitor, whose minimum effective concentration is only 100 ng/ml, but in order to achieve this concentration, the oral dose required is 1200 mg/day (taken as six 200-mg capsules).[13] The reason behind this is the very poor oral bioavailability of saquinavir due to extensive hepatic first pass metabolism. Such a high dose leads to gastrointestinal side effects such as diarrhea, nausea, abdominal discomfort, dyspepsia, flatulence, vomiting, and abdominal pain. Another example of such drug is Danazol, which is used in the treatment of endometriosis at a recommended therapeutic dose of 600-800 mg/day in two divided doses. These high doses of Danazol are required because the absolute bioavailability of commercially available Danazol is very low (6.2%), due to low solubility of Danazol in aqueous medium and also due to first pass hepatic metabolism.[14] The high dose of Danazol used in various therapies causes side effects such as weight gain, virilism, and decreased bone mineral content. Moreover, high dose of the drug ultimately leads to its wastage which is not economical (as most of these drugs are very costly). In order to be effective, an orally delivered drug must avoid several potential barriers. For example, it must avoid degradation by stomach acid and gut lumen digestive enzymes; dissolve in the aqueous environment of the gut lumen; cross the lipophilic environment of the gut wall cell membrane; avoid metabolism by enzymes in the gut wall cell; and avoid first-pass extraction by the liver.

1.4 Reasons of Poor Bioavailability

1.4.1 Poor aqueous solubility

Poor solubility of a drug is in most cases associated with poor bioavailability.[15] The contents of gastrointestinal tract are aqueous and hence a drug having poor aqueous solubility has a low saturation solubility which is typically correlated with a low dissolution velocity, resulting in poor oral bioavailability.[16] About 10% of the present drugs are poorly soluble, about 40% of the drugs in the pipeline possess a poor solubility, and even 60% of drugs coming directly from synthesis have a solubility below 0.1 mg/ml. Out of the research around 40% of lipophilic drug candidates fail to reach the market although exhibiting potential pharmacodynamic activities. No matter how active or potentially active a new molecular entity (NME) is against a particular molecular target, if it is not available in a solution form at the site of action, it is not a viable development candidate. As a result, the development of many exciting NMEs has stopped before their potential is realized.[17] Low bioavailability is the most common with oral dosage forms of poorly water-soluble, slowly absorbed drugs, which is indicated in Table 1.

Table. 1: Examples of drugs having poor bioavailability because of low aqueous solubility.

Drug	Aqueous solubility (mg/ml)	Absolute bioavailability
Candesartan cilexetil	0.00770 mg/ml	15%
Felodipine	0.01900 mg/ml	15%
Ibuprofen	0.04900 mg/ml	49-73%
Paclitaxel	0.00030 mg/ml	6.5%
Simvastatin	0.00076 mg/ml	5%

1.4.2 In-appropriate partition coefficient

Too hydrophilic drugs would not be able to permeate through the gastrointestinal mucosa and too lipophilic drug will not dissolve in the aqueous gastrointestinal contents. For optimum absorption, the drug should have sufficient aqueous solubility to dissolve in the gastrointestinal contents and also adequate lipid solubility to facilitate its partitioning into the lipoidal

membrane and then into systemic circulation.[18-19] Drugs having partition coefficient (log P) value in the range of 1 to 3 shows good passive absorption across lipid membranes, and those having (log P) greater than 3 or less than 1 have often poor transport characteristics which is indicated in Table 2.

Table. 2: Effect of partition coefficient on absolute bioavailability.

Drug	Octanol/water partition coefficient	Absolute bioavailability
Acyclovir	-1.57	15-30%
Chlorpromazine	3.17	30-50%
Hydrocortisone	1.52	96%

1.4.3 First-pass metabolism: As shown in figure 3, orally administered drugs must pass through the intestinal wall and then through the portal circulation to the liver; both are common sites of first pass metabolism (metabolism of a drug before it reaches systemic circulation).[2O] Thus, many drugs may be metabolized before adequate plasma concentrations are reached resulting in poor bioavailability. The enterocyte expresses many of the metabolic enzymes that are expressed in the liver.[21] These include cytochromes P450, UDP-glucuronyltransferases, sulfotransferases, and esterases.

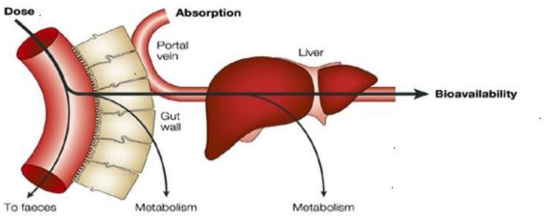

Figure 3: Route of Drug Passage from Stomach to the Systemic Circulation

As shown in table 3, the susceptibility of a drug to first pass metabolism by CYP3A4 has a very high influence on the oral bioavailability, which decreases as the level of first pass metabolism increases.

Table. 3: Effect of level of first pass metabolism of drug on its bioavailability.

Level of first pass metabolism	Drug	Bioavailability
Intermediate	Midazolam	36%
	Verapamil	35%
High	Atorvastatin	12%
	Tacrolimus	11.2%
very high	Ergotamine	5%

1.4.4 Degradation in the gastrointestinal tract

Drug substances used as pharmaceuticals have diverse molecular structures and are, therefore, prone to many and variable degradation pathways. As shown in figure 4, protein drugs, in particular are highly susceptible to inactivation due to the pH and the enzymes present in gastrointestinal tract.[22]

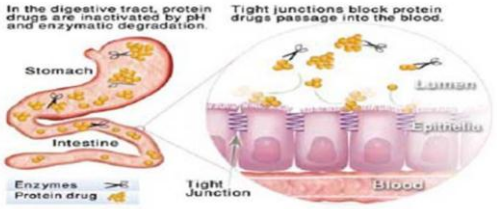

Figure 4: Inactivation of protein drugs in gastrointestinal tract

1.4.4 (a) Degradation due to low pH in stomach

Most drug substances are fairly stable at the neutral pH values found in the small intestine (disregarding enzymatic degradation) but can be unstable at low pH values found in the stomach. Examples of drugs that are very acid-labile are various penicillins, erythromycin and some of its analogs, and the 2´, 3´-dideoxypurine nucleoside anti-AIDS drugs.[23] Knowledge of the stability of a drug in the pH range of 1-2 at 37°C is important in the formulation design of potentially acidlabile drugs. At low pH, foscarnet decomposes via an acid-catalyzed decarboxylation; therefore, poor oral bioavailability (7-9%) might be due to decomposition of foscarnet in gastric acid.

1.4.4 (b) Degradation due to chemical reactions taking place in gastrointestinal tract: Various drugs cannot be administered orally because of their inactivation in gastrointestinal fluids due to chemical reactions. Possible degradation pathways include hydrolysis, dehydration, isomerization and racemization, elimination, oxidation, photodegradation, and complex interactions with excipients, food and other drugs, thiol/disulfide exchange reactions. A hydrolytic cleavage takes place particularly at low pH of the stomach. Various antibiotics, for instance, are hydrolyzed in the stomach. In case of thiol/disulfide bond bearing drugs, thiol/disulfide exchange reactions in particular with glutathione can inactivate them in the gastrointestinal tract.[24]

1.4.4 (c) Enzymatic degradation of drug in gastrointestinal tract: Various classes of drugs such as therapeutic peptides and nucleic acids are enzymatically degraded by proteases/peptidases and nucleases, respectively. Proteases/peptidases are on the one hand based on luminally secreted proteases including pepsin, trypsin, chymotrypsin, elastase and caboxypeptidase A and B and on the other hand on membrane bound peptidases including various endo- as well as amino- and carboxypeptidases.[25] In the colon numerous additional enzymes originating from the local microflora have to be taken into consideration. In terms of nucleases, the enzymatic barrier is much less characterized.

Furthermore ester bonds are cleaved by esterases such as lipases and proteases/peptidases exhibiting also esterase activity. Teriparatide undergoes enzymatic degradation in the intestinal mucosa by enzymes like trypsin, chymotrypsin and pepsin.

1.4.5 Interaction with food

Drugs that undergo a significant first-pass metabolism with a lower bioavailability ranging from 5% to 30% may be affected to a greater degree by grapefruit juice. Calcium, as well as food and dairy products containing high concentrations of calcium, may decrease the absorption of tetracyclines due to chelate formation in the gut.[26]

1.4.6 Insufficient time for absorption

Insufficient time for absorption in the gastrointestinal tract is a common cause of low bioavailability.[27] If the drug (e.g. highly ionized and polar drugs) does not dissolve readily or cannot penetrate the epithelial membrane during its residence time in the gastrointestinal tract, its bioavailability tends to be highly variable as well as low.

2.0 Biopharmaceutical Classification Systems

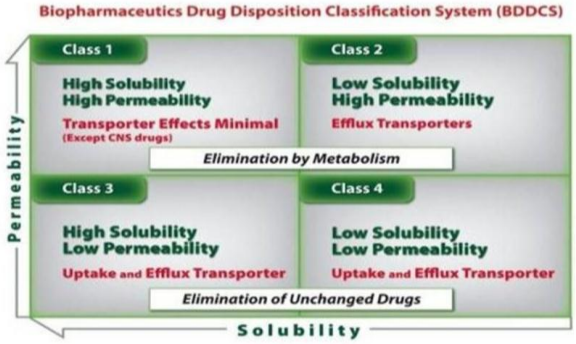

figure 5: Give the (BCS) Biopharmaceutical classification system

The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability (as shown in figure 5). It allows for the prediction of in vivo pharmacokinetics of oral immediate-release (IR) drug products by classifying drug compounds into four classes.[28]

Table. 4. The Biopharmaceutics Classification System.

Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low
V	Not come under the purview of BCP Classification	

Class I: The drugs of this class exhibit high absorption number and high dissolution number. The rate-limiting step is drug dissolution, and if dissolution is very rapid, then the gastric-emptying rate becomes the rate-determining step. These compounds are well absorbed, and their absorption rate is usually higher than the excretion rate. Examples include metoprolol, diltiazem, verapamil, and propranolol.[29]

Class II: The drugs of this class have a high absorption number but a low dissolution number. In vivo drug dissolution is then a rate-limiting step for absorption except at a very high dose number. The absorption for Class II drugs is usually slower than for Class I and occurs over a longer period of time. In vitro–in vivo correlation (IVIVC) is usually accepted for Class I and Class II drugs. The bioavailability of these products is limited by their solvation rates. Hence, a correlation between the in vivo bioavailability and the in vitro solvation can be found. Examples include glibenclamide, phenytoin, danazol, mefenamic acid, nifedinpine, ketoprofen, naproxen, carbamezapine, and ketoconazole.[30]

Class III: Drug permeability is the rate-limiting step for drug absorption, but the drug is solvated very quickly. These drugs exhibit a high variation in the rate and extent of drug absorption [31]. Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors. If the formulation does not change the permeability or gastrointestinal duration time, then Class I criteria can be applied. Examples include cimetidine, ranitidine, acyclovir, neomycin B, atenolol, and captopril.

Class IV: The drugs of this class are problematic for effective oral administration. These compounds have poor bioavailability. They are usually not well absorbed through the intestinal mucosa, and a high variability is expected. Fortunately, extreme examples of Class IV compounds are the exception rather than the rule, and these are rarely developed and marketed. Nevertheless, several Class IV drugs do exist. Examples include hydrochlorothiazide, taxol, and furosemide.[32]

Class V: These are ones that do not come under the preview of BCP classification but includes drugs whose absorption is limited owing to their stability in GI milieu-Gastric instability (omeprazole), Complexation in GIT lumen & First pass metabolism – by intestinal enzymes (peptide drugs), hepatic enzymes, microbial enzymes etc. Class V drugs are those that are metabolically or chemically unstable thus limiting their bioavailability. The various approaches to overcome these problems are aimed at enhancing their stability by the use of methods such as- Pro-drug design, enteric coating (protection from stomach acid), Enzymes inhibition or lymphatic delivery (to prevent presystemic metabolism) & Lipid technologies.

2.1 BCS Class Boundaries: Class boundary parameters (i.e., solubility, permeability, and dissolution) are for easy identification and determination of BCS class.

2.1.1 Solubility: An objective of the BCP approach is to determine the equilibrium in solubility of a drug under approximate physiological conditions. For this purpose, determination of p^H – solubility profiles over a p^H range of 1-8 is suggested. The solubility class is determined by calculating what volume of an aqueous medium is sufficient to dissolve the highest anticipated dose strength.[33] A drug substance is considered highly soluble when the height dose strength is soluble in 250 ml or less of aqueous medium over the p^H range 1-8. The volume estimate of 250ml is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (8 ounces) of water. The ratio of dose/solubility must be less than or equal to 250ml. The volume (250ml = a glass of water) is derived from the minimum volume anticipate in the stomach, when the dosage form is taken in fasted state with a glass of water, as taken from typical bioequivalence study protocol. Since the volume of the solution is fixed. Then the dose of drug (maximum) is taken into account for predictions. A sufficient number of p^H conditions should be evaluated to accurately define the p^H solubility profile. These conditions are based on the ionization characteristics of the drug. When pK^a of a drug is in the range of 3-5, solubility is determined as follows.

$p^H = pK^a$ $p^H = pK^a + 1$
$p^H = pK^a - 1$
$p^H = 1$ $p^H = 7.5$

If these buffer are not suitable for physical or chemical reasons, other buffer solutions can be used. Calculation of dose solubility ratio may not be reliable m because the dose of new drug is not known in the early stages of development. Drugs with low doses may be incorrectly classified into class I/III (example is digoxin). In the calculation, only p^H and volume effects are considered. Some compounds may be inappropriately classified into class II/IV. A few substances have solubility > 100mg/ml, and still exhibited dissolution problems in vivo.

2.1.2 Permeability: Studies of the extent of absorption in human, or intestinal permeability methods, can be used to determine the permeability class membership of a drugs [34]. To be classified as highly permeable, a test drug should have an extent of absorption > 90% in humans. Supportive information on permeability characteristics of the drug substance should also be derived from its physiochemical properties (e.g. octanol: water partition coefficient). Some method to determine the permeability of a drug from the gastrointestinal tract includes.

1. In vivo intestinal perfusion studies in humans.
2. In vivo or in situ intestinal perfusion studies in animals.
3. In vitro permeation experiment using excised human or animal intestinal tissue.
4. In vitro permeation experiment across a monolayer of cultured human intestinal cell.

When using these methods, the experiment permeability data should be correlate with the known extent of absorption data in humans. In many cases, a single method may be sufficient, when the absolute bioavailability is 90% or higher, or when 90% or more of the administered drug is recovered in urine. When a single method fail to conclusively demonstrate the permeability classification, two different methods may be advisable. Chemical structure and/or certain physiochemical attributes of a drug substance (for example partition coefficient in suitable system, n-octanol-water) can provide useful information about the permeability characteristics.

2.1.3 Dissolution

The dissolution class is based on the in- vitro dissolution rate of an immediate release drug product under specified test conditions and is intended to indicate rapid in vitro dissolution in relation to the average rate of gastric emptying in humans under fasting conditions [35]. An immediate release drug products is considered rapidly dissolving when not less than 85% of the label amount of drug substance dissolve within 30 minutes using USP apparatus I at 100 rpm or apparatus II at 50 rpm in a volume of 900ml or less in each of the following media;

1. Acidic media such as 0.1N HCI or simulated gastric fluid USP without enzymes.
2. A p^H 4.5 Buffer
3. A p^H 6.8 Buffer or simulated intestinal fluid USP without enzymes.

3.0 Techniques for improving bioavailability

One approach to improve the systemic availability of the drug is to deliver it by another routes of drug administration such as parenteral, nasal, vaginal, rectal, transdermal or sublingual. However, improvement of the oral bioavailability of the drug is the most realistic approach, as it is the most preferred and convenient route of administration. The techniques to improve oral bioavailability of the drugs are described as follows.

3.1 Enhancement of solubility and dissolution rate

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the methods to improve the solubility are.

3.1.1 Physical modifications

3.1.1.1 Particle size reduction by micronization and nanonization.

3.1.1.2 Drug dispersion in carriers ;eutectic mixtures, solid dispersions and solid solutions

3.1.1.3 Modification of the crystal habit ;polymorphs and pseudopolymorphs

3.1.1.4 Inclusion complexation

3.1.2 Chemical Modifications
3.1.2.1 Change in pH of system
3.1.2.2 Salt formation

3.1.3 Formulation Based Approaches
3.1.3.1 Co-crystallization
3.1.3.2 Hydrotrophy
3.1.3.3 Co-solvency
3.1.3.4 Ultra rapid freezing
3.1.3.5 Addition of solubilizer
3.1.3.6 Porous microparticles technology

3.2 Modification of partition coefficient
3.2.1 Ester formation
3.2.2 Novel formulation approaches like liposomes, niosomes and microemulsion

3.3 Avoidance of hepatic first pass metabolism
3.3.1 Prodrugs to reduce presystemic metabolism
3.3.2 Co-administration with another drug
3.3.3 Use of Novel Drug Delivery Systems like microemulsion, SMEDDS, Solid Lipid Nanoparticles

3.4 Avoidance of degradation in gastrointestinal tract
3.4.1 Avoidance of degradation in stomach – Enteric coating
3.4.2 Avoidance of degradation in intestine – Enhancement of residence time in stomach-
3.4.2.1 Use of bioadhesive (mucoadhesive) polymers
3.4.2.2 Floating drug delivery Systems
3.4.3 Avoidance of degradation in stomach and intestine- Colon Targeted Drug Delivery System

3.5 Novel Drug Delivery system
3.5.1 Nanosuspensions
3.5.2 Solid lipid nanoparticles, polymeric nanoparticles
3.5.3 Vesicular delivery systems such as liposomes, niosomes etc
3.5.4 Microemulsion, Self micro emulsifying drug delivery system

3.6 Emerging Approaches for Improvement of Oral Bioavailability
3.6.1 Phytosomes
3.6.2 Oral Synchronous Drug (OSD) Delivery System
3.6.3 Transient Permeability Enhancer (TPE) technology

3.1 Enhancement of solubility and dissolution rate
3.1.1 Physical modifications
3.1.1.1 Particle size reduction
Particle size reduction leads to increase in the effective surface area resulting in enhancement of solubility and dissolution velocity of the drug. Micronization and nanonization techniques are used to improve dissolution rates of drugs into the biological environment, in order to improve the oral bioavailability. Micronization of drugs is done by milling techniques using jet mill, rotor stator, colloid mills etc. Farinha et. al [36] have found significant increase in the oral bioavailability of micronized Megestrol acetate from in vivo study . As shown in the figure 6, micronization leads to increase in the surface area and hence the dissolution rate but it does not increase saturation solubility, thus bioavailability is not increased. To overcome limitations of micronization, another approach used is nanonization which generally results in formation of nanosuspension- a sub-micron colloidal dispersion of pure particles of drug stabilized by surfactants. It increases dissolution rate due to larger surface area exposed to gastrointestinal fluid and also, absence of Ostwald ripening due to uniform and narrow particle size distribution as in case of micronization. Jia L. et al [37] demonstrated that nanoparticle formulation enhances rat oral bioavailability of the poorly soluble 301029, a thiadiazole derivative. The Cmax and AUC of nanoparticle 301029 were 3- to 4-fold greater than those of microparticle 301029, resulting in a significant increase in oral bioavailability of 301029 as compared with microparticle 301029. Different principles used for nanonization are pearl milling (NanoCrystals®), highpressure homogenization (DissoCubes®), solution enhanced dispersion by supercritical fluids (SEDS), rapid expansion from supercritical to aqueous solution (RESAS), spray freezing into liquid (SFL) and evaporative precipitation into aqueous solution (EPAS) which are patented engineering processes. Rapamune®(drugsirolimus), an immune suppressant agent, is the first FDA approved nanoparticle formulation using NanoCrystals® technology developed by Elan Drug Delivery.[38] The novel approaches for particle size reduction are Sonocrystallisation, supercritical fluid technology and spray drying.

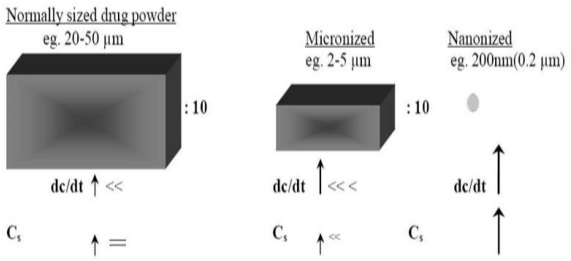

Figure 6: dissolution velocity dc/dt and saturated solubility Cs powder size is ranging from coarse to nanonized drugs

3.1.1.2 Drug dispersion in carriers
The term "solid dispersions" refers to the dispersion of one or more active ingredients in an inert carrier or matrix in a solid state. Firstly, they were introduced to overcome the low bioavailability of lipophilic drugs by forming of eutectic mixtures of drugs with water-soluble carriers. Sekiguchi and Obi [40] suggested that the drug present in a eutectic mixture is in a microcrystalline state. After few years Goldberg et.al. reported that all drugs in solid dispersion might not necessarily be present in a microcrystalline state, a certain fraction of the drug might be as molecular dispersion in the matrix, thereby

forming a solid solution. Once the solid dispersion is exposed to aqueous media and the carrier dissolved, the drug is released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly watersoluble drugs are expected to be high. Two commercial products, a griseofulvin in polyethylene glycol 8000 solid dispersion (Gris-PEG, Novartis) and a nabilone in povidone solid dispersion (Cesamet, Lilly) were marketed during the last four decades. A solid dispersion of poorly soluble REV5901, an antagonist of cysteinylleukotriene receptors, in Gelucire 44/14 under a fasting regimen had much higher bioavailability in human volunteers than that of a tablet formulation, even though the micronized form of drug and a wetting agent were used in the tablet.

3.1.1.3 Modification of the crystal habit

Polymorphism is the ability of an element or compound to exist in more than one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability etc. So, if a drug is known to have polymorphs, it is necessary to detect its metastable form as it has higher energy and thus, higher solubility and subsequently higher bioavailability. Melting followed by a rapid cooling or recrystallisation from different solvents can produce metastable forms of a drug. Similarly, the amorphous form of drug is always more suitable than crystalline form because of its large surface area and less energy requirement to dissolve into a solvent. Generally, the anhydrous form of a drug has greater solubility than the hydrates. This is because the hydrates are already in interaction with water and therefore have less energy for crystal breakup in comparison to the anhydrates (i.e. thermodynamically higher energy state) for further interaction with water. On the other hand, the organic (nonaqueous) solvates have greater solubility than the nonsolvates. J. C. Shah et. al [39] have reported that metastable polymorph of etoposide had an equilibrium solubility and intrinsic dissolution rate of 221 µg/ml and 16.3 µg/min/cm2, respectively; 1.9 and 1.7 times that of etoposide powder at 25°C, respectively.

3.1.1.4 Inclusion complexation: Complexation process, an effective tool to increase solubility of poorly soluble drugs, refers to association between two or more molecules to form a nonbonded entity with a well defined stoichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions. Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). Cyclodextrins and their derivatives have been employed as host for inclusion complex to increase water solubility, dissolution rate and bioavailability of lipophilic drugs for oral or parenteral delivery (as shown in figure 7). Cyclodextrins have a hydrophilic exterior and a hydrophobic internal cavity. This cavity enables cyclodextrins to complex guest drug molecules and hence alters the properties of the drugs such as solubility, stability, bioavailability and toxicity profiles. The solubility enhancement factors of pancratistatin, hydrocortisone, and paclitaxel are 7.5, 72.7 and 99000 by forming complexes with cyclodextrin derivatives. ß-CD, the most widely used native cyclodextrins, is limited in its pharmaceutical application by its low aqueous solubility (1.85 g/100 ml, 25°C), toxicity profile and low aqueous solubility of the formed complexes. P.T Tayade et. al [41] have reported that the maximal plasma concentration of ketoprofen after the oral administration of inclusion complexes to human volunteers increased about 1.5 fold (7.15 Vs 4.65 µg/ml), compared to those of ketoprofen powder alone. Accordingly, derivatives such as hydroxypropyl-ß-CD (HPß- CD; Enapsin®) and sulphobutylether-ß-CD (SE-ß-CD; Captisol®) have been developed to produce more watersoluble and less toxic entities.

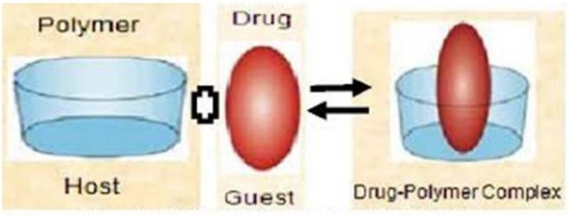

Figure 7: Cyclodextrin/Polymer-Drug Complex

Table 5: Commercially available cyclodextrin based pharmaceutical products.

Drug/cyclodextrin	Trade name	Formulation	Company(country)
Cefotiam-hexetil HCl /α Cyclodextrin	Pansporin T	Tablet	Takeda (Japan)
Nimesulide/ β-Cyclodextrin	Nimedex	Tablet	Novartis (Europe)
Itraconazole /2-Hydroxypropyl-β-cyclodextrin (HP-β-CD)	Sporanox	Oral solution	Janssen(Europe, USA)

3.1.2 Chemical Modifications

3.1.2.1 Change in pH of system

For organic solutes that are ionizable, changing the pH of the system may be simplest and most effective means of increasing aqueous solubility. Under the proper conditions, the solubility of an ionizable drug can increase exponentially by adjusting the pH of the solution. A drug that can be efficiently solubilized by pH control should be either weak acid with a low pKa or a weak base with a high pKa. The complexation of the

practically insoluble drug Furosemide (acidic pKa 3.22) with lower generation polyamidoamine dendrimers showed a significant release dependence on the ionization state of the drug. The dendrimers amine, amide and ester groups, demonstrated pH-dependent ionization as did the drug carboxylic acid group and it was proven that the most efficient drug complexation was achieved in slightly acidic conditions (pH 4.0–6.0). At this pH, amide groups in the dendrimers cavities were at least partially ionized to expose a positive charge whilst the furosemide carboxylic acid ionized to great extent (pH > pKa) resulting in electrostatic Complexation.[42] Furosemide (pKa of 3.9) is unstable at an acid pH, but is very stable under alkaline conditions. In dogs, the oral bioavailability is approximately 77%.

3.1.2.2 Salt formation

Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. It can lead to changes in solubility and permeability of the parent molecule, which can lead to improved bioavailability. The use of salt forms is a well known technique to enhance dissolution rates. Generally, an alkaloidal base is slightly soluble in water, but if the pH of medium is reduced by addition of acid, the solubility of the base is increased as the pH continues to be reduced. The solubility of slightly soluble acid increases as the pH is increased by addition of alkali, the reason being that a salt is formed [43]. The monoethanolamine salt form of piroxicam may be used to shorten the onset of reaction and to improve the bioavailability of piroxicam.

3.1.3 Formulation Based Approaches

3.1.3.1 Co-crystallization

Pharmaceutical co-crystals are alternative option to salt formation, particularly for neutral compounds or those having weakly ionizable groups, to modify the chemical and/or physical properties of an active pharmaceutical ingredient (API) without making or breaking covalent bonds. It is also referred as molecular complexes. Daniel P. McNamara demonstrated use of a Glutaric Acid Cocrystal to Improve Oral Bioavailability of a Low Solubility API 2-[4-(4-chloro-2-fluorophenoxy) phenyl]pyrimidine-4-carboxamide which belongs to the pharmacologic class of sodium channel blockers. They performed single dose dog exposure studies and confirmed that the co-crystal increased plasma AUC values by three times at two different dose levels. So far, only three co-crystallizing agents, saccharin, nicotinamide and acetic acid have been tried for bioavailability improvement. However, the promising results obtained indicate its potential for further studies.[44]

3.1.3.2 Hydrotrophy

The term “Hydrotropy” indicate the increase in aqueous solubility and dissolution velocity of various poorly water soluble compounds due to the presence of a large amount of additives like concentrated solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotropic agents (sodium benzoate, sodium acetate, sodium alginate, and urea) and the solute. Maheshwari et al [46] have found enhancements in aqueous solubilities of metronidazole, tinidazole, norfloxacin, and nalidixic acid in 2.0 M sodium benzoate solution, as compared to solubility in distilled water, which were more than 5, 6, 40 and 98 fold, respectively . Solubilisation of Theophylline with sodium acetate and sodium alginate is also an example of hydrotrophy.

3.1.3.3 Co-solvency

Weak electrolytes and nonpolar molecules frequently have poor water solubility which can be improved by altering polarity of the solvent, usually by the addition of water miscible solvent in which the drug has good solubility. It is well-known that the addition of an organic cosolvent to water can dramatically change the solubility of drugs [45]. This process is known as cosolvency, and the solvents used are known as cosolvents. This system works by reducing the interfacial tension between the predominately aqueous solution and the hydrophobic solute, commonly referred to as solvent blending. Currently, the water-soluble organic solvents used are polyethylene glycol 400 (PEG 400), ethanol, propylene glycol, sorbitol and glycerin. For example, Procardia® (nifedipine) developed by Pfizer contains glycerin, peppermint oil, PEG 400 and sodium saccharin in soft gelatin capsules.

3.1.3.4 Ultra rapid freezing

Ultra-rapid freezing is a novel, cryogenic technology that creates nanostructured drug particles with greatly enhanced surface area. It has the flexibility to produce particles of varying particle morphologies, based on control of the solvent system and process conditions. The technology involves dissolving a drug in a water miscible or anhydrous solvent along with a stabilizer acting as a crystal growth inhibitor. The drug/stabilizer solution is then applied to a cryogenic substrate. The solvent is removed by lyophilization or atmospheric freeze-drying, resulting in highly porous, agglomerated particles. An additional feature is that polymer adsorption on the crystal surface upon freezing aids reduction of Ostwald ripening. Evans J. C. et al. [48] have demonstrated improved bioavailability of ketoconazole nanostructured powder prepared by ultra-rapid-freezing by a 4- to 7-fold increase in AUC with a corresponding 2- to 3.5-fold increase in Cmax as compared to plain drug.

3.1.3.5 Addition of solubilizer

Surfactants are molecules with distinct polar and nonpolar regions in which hydrocarbon segment is connected to a polar group which may be anionic, cationic, zwitterionic or nonionic. When small apolar molecules are added, they can accumulate in the

hydrophobic core of the micelles. This process of solubilization is very important in industrial and biological processes. The presence of surfactants may lower the surface tension and increase the solubility of the drug. Poloxamers, gelucire, lecithin, capmul, myrj, labrasol, polysorbate etc. are examples of surface-active carriers used for dissolution enhancement. Microemulsions and SEDDS are drug delivery systems based on this concept and have been explained under novel drug delivery system. Attivi D. et al [47] developed microemulsion of mitotane and reported the relative bioavailability of that formulation 3.4 fold higher, compared with that of the conventional form (Lysodren (R) after oral administration in rabbits.

3.1.3.6 Porous microparticles technology

In this technology, the poorly water soluble drug is embedded in a microparticle having a porous, water soluble, sponge like matrix. When mixed with water, the matrix dissolves, wetting the drug and leaving a suspension of rapidly dissolving drug particles [49]. This is the core technology applied as HDDSTM (Hydrophobic Drug Delivery System). These drug particles provide large surface area for increased dissolution rate. The solid form has a proprietary spray drying technology that allows the size and porosity of the drug particles to be engineered as desired. The Hydrophobic Solubiization Technology (HST) for insoluble or poorly soluble drugs uses a lecithin and gelatin based water soluble coating to improve dissolution rate and hydration of lecithin-gelatin coat forms micelles which improve the oral bioavailability of the insoluble drugs. Dissolution rate for cyclosporine coated with lecithin/gelatin was shown to be significantly greater than for bulk cyclosporin powder resulting in doubling of the relative bioavailability of cyclosporin given orally in dogs for lecithin/gelatin coated cyclosporine compared to bulk cyclosporin powder.

3.2 Modification of partition coefficient

3.2.1 Ester formation

This strategy refers to improvement in the oral bioavailability of poorly water-soluble drugs by chemical derivatization to a water-soluble prodrug. It utilizes esterification of a hydroxyl, amine or carboxyl group of a drug with a moiety (progroup) designed to introduce an ionizable function or reduce intermolecular interactions responsible for low solubility [50]. The use of spacer groups to introduce derivatizable functions and/or to position ionizable progroups for unhindered hydrolysis is also described. Amprenavir (APV) is expected to have low oral bioavailability due to less aqueous solubility. Prodrug derivatization of APV led to enhanced oral bioavailability, which is attributed by increase in aqueous solubility. Both in vitro and in vivo studies demonstrated dipeptide prodrug derivatization of APV may be an effective strategy to improve oral bioavailability.

3.2.2 Novel formulation approaches like Liposomes, Niosomes and Microemulsion*:*

Various delivery systems such as liposomes, niosomes, microemulsion and mixed micelles have been used to modify the partition coefficient and hence improve bioavailability of hydrophilic drugs. These systems are discussed in detail under the heading "Novel Drug delivery systems"

3.3 Avoidance of hepatic first pass metabolism

Hepatic first pass metabolism is a major cause of poor bioavailability. Several approaches used to avoid first pass metabolism are.

3.3.1 Co-administration with another drug

In general, if a drug has a high first-pass hepatic metabolism, one can expect a marked increase in its plasma concentration if it is co-administered with another drug which inhibits its metabolism [51]. When administered alone, lopinavir has insufficient bioavailability (25%); however, like several HIV protease inhibitors, its blood levels are greatly increased by low doses of ritonavir, a potent inhibitor of cytochrome P450. The absolute oral bioavailability of docetaxel is 8% +/- 6% which was increased to 90% +/- 44% when coadministered with cyclosporine.

3.3.2 Prodrugs to reduce presystemic metabolism

Systemic absorption after oral dosing requires the compound to pass through a series of potential sites of metabolism the intestinal lumen, the intestinal epithelium, and the liver. If the structural position at which presystemic metabolism of a drug occurs is known and, if presystemic metabolism is mediated primarily by a single enzymatic reaction at a single site of the molecule, then it may be possible to design prodrugs to block metabolism at that site [52]. The prodrug is therefore intended to pass through the site of metabolism (intestinal membrane or liver) intact and then be hydrolyzed upon reaching the systemic circulation. An illustration of this prodrug strategy is given in Figure 8.

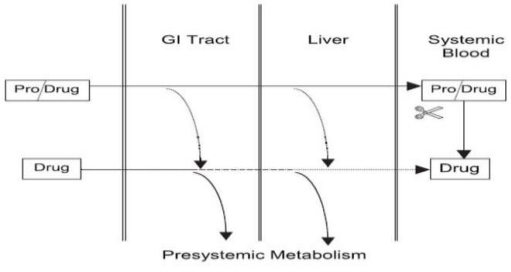

Figure 8: Prodrugs to Reduce Presystemic Metabolism

Nalbuphine is an opioid analgesic that has incomplete oral bioavailability in animals and humans due to presystemic metabolism. The route of presystemic metabolism is primarily conjugation on the phenolic hydroxyl group. Two prodrugs were identified that markedly improved oral bioavailability in preclinical

studies, the acetylsalicylate (Increased oral F<2-fold in rats) and anthranilate esters (increased oral F 8-fold in dogs).

3.3.3 Use of Novel Drug Delivery Systems like microemulsion, SMEDDS, Solid Lipid Nanoparticles

Recent advancement to improve bioavailability is the utilization of lymphatic circulation upon the oral delivery as it circumvents the hepatic first pass effect. The drugs with higher lipophilicity, poor solubility and poor oral bioavailability serve as the potential candidate for lymphatic targeting. Such drugs could be effectively transported through the intestinal lymphatics via thoracic lymph duct to the systemic circulation, joining at the junction of the jugular and the left subclavian vein. This avoids presystemic hepatic metabolism and thus enhances the concentration of orally administered drugs in the systemic circulation. At the capillary level, the intercellular junctions between endothelial cells of lymphatic capillaries are more open compared with blood capillaries that results in molecular sieving of colloidal particles of large size directly into lymphatics, avoiding the blood capillaries. By utilizing this property of lymphatic system, absorption of long chain fatty acids could be facilitated via chylomicrons formation, thus bypassing the portal circulation. Accomplishment of lymphatic targeting can be achieved through lipid-based carrier systems such as microemulsion, SMEDDS and solid lipid nanoparticles (SLNs) which have been discussed under topic Novel Drug Delivery System [53].

3.4 Avoidance of degradation in gastrointestinal tract

3.4.1 Avoidance of degradation in stomach – Enteric coating

An enteric coating is a barrier applied to oral medication that resists the destructive action of the gastric fluid and disintegrates in the intestinal tract thereby releasing the drug in the intestine. Reasons for enteric-coating a drug product include:

1. Preventing destruction of the drug by gastric enzymes or by the acidity of the gastric fluid
2. Preventing nausea and vomiting caused by the drug's irritation of the gastric mucosa
3. Delivering a drug that is primarily absorbed in the intestines to that site at the highest possible concentration. Most enteric coatings work by presenting a surface that is stable at the highly acidic pH found in the stomach, but breaks down rapidly at a less acidic (relatively more basic) pH. For example, they will not dissolve in the acidic juices of the stomach (pH ~3), but will dissolve in the higher pH (above pH 5.5) environment present in the small intestine [54]. Materials used for enteric coatings include fatty acids like stearic acid, hydrogenated castor oil, waxes like carnauba wax, cellulose acetate phthalate and shellac. The enteric materials may be used to coat tablets, capsules or granules to be compressed into tablets or filled into capsules. Enteric coating to certain drugs with azoles groups (esomeprazole, omeprazole, pantoprazole and all grouped azoles), which are acid-unstable, have been found to improve the bioavailability. E. A. Hosny et al found that the bioavailability of diclofenac sodium fromenteric-coated beads filled in hard gelatin capsules was significantly higher (197.54 % increase) than that from the commercial voltaren tablets.

3.4.2 Avoidance of degradation in intestine - Enhancement of residence time in stomach: Many drugs are stable in the acidic environment of stomach but cannot resist the pH and enzymatic conditions of the intestine. An increase in the residence time of such drugs in stomach leads to the absorption of significant amount in stomach before it reaches the intestine. They are designed for retention in the stomach for longer time than usual (~about 8 hours). Some drugs which have narrow zones of absorption in gastrointestinal tract, weakly basic drugs that are poorly soluble in intestinal pH and have better dissolution in the acidic medium of stomach or relatively short residence time in stomach and small intestine are suitable candidates for this system. These systems work on mainly three mechanisms: floatation, size expansion and mucoadhesion.

3.4.2.1 Use of bioadhesive (mucoadhesive) polymers

Mucoadhesive polymeric systems are the most promising approach among several approaches. Mucoadhesive properties can provide an intimate contact with the mucosa at the site of drug uptake preventing a presystemic metabolism of peptides on the way to the absorption membrane in the gastrointestinal tract. Additionally, the residence time of the delivery system at the site of drug absorption is increased. Most of the current synthetic bioadhesive polymers are either polyacrylic acid like carbopol, polycarbophil, Polyacrylic acid (PAAc), polyacrylate, poly (methylvinylether-co-methacrylic acid), or cellulose derivatives like Carboxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, sodium Carboxymethyl cellulose, methylcellulose, and methylhydroxyethyl cellulose. In addition, Seminatural bioadhesive polymers include chitosan and various gums such as guar, xanthan, Poly (vinylpyrrolidone) and poly (vinyl alcohol). Khalid Mahrag Tur et al. [58] performed in vivo absorption study. The results indicates that the addition of poly(acrylic acid) crosslinked with 2,5-dimethyl-l,5-hexadiene (PADH) to griseofulvin can increase the total absorption by 2.9-, 4-, and 2.9-folds when compared with drug powder, aqueous suspension and emulsion, respectively. Avoidance of enzymatic and absorption barriers for protein and peptide delivery Various strategies currently under investigation for proteins and peptides delivery include chemical modification, formulation vehicles and use of enzyme inhibitors, absorption enhancers and mucoadhesive polymers.

3.4.2.2 Floating drug delivery Systems: Floating systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the

stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system [55]. After release of drug, the residual system is emptied from the stomach.

There are two types of floating dosage forms: Effervescent floating dosage forms are matrix types of systems, which may be volatile liquid containing systems or gas-generating Systems, prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g, sodium bicarbonate, tartaric acid, and citric acid.[56] They are formulated in such a way that when in contact with the acidic gastric contents, carbon dioxide is liberated and entrapped in swollen hydrocolloids which provides buoyancy to the dosage forms. V.K. Kakumanu et al.[57] developed an effervescent floating gastroretentive dosage form for cefpodoxime proxetil(CP) and evaluated in rats. The gasroretentive dosage form improved the oral bioavailability of CP significantly by about 75%, hence providing a proof-of-concept. The Tmax value increased to 1.43 +/- 0.24 hours from 0.91 +/- 0.23 hours of pure drug, while Cmax values of 4735 +/- 802 ng/ml and 3094 +/- 567 ng/ml were obtained for the gastroretentive dosage form and pure drug respectively.

Non-effervescent Floating Dosage Forms use a gel forming or swellable cellulose type hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density less than one. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass. Floating tablets of propranolol hydrochloride containing HPMC K4 M gave the best in vitro release of 92% in 18 h. X-ray technique showed that tablet retention in the stomach for 4 hours . Table 6 shows list of drug formulated as single and multiple unit forms of floating drug delivery systems [57]. Table 7 indicates details of marketed products of floating drug delivery systems.

Table. 6: List of Drugs Formulated as Single and Multiple Unit Forms of Floating Drug Delivery Systems.

Dosage form	Drug
Tablets	Cholrpheniramine maleate, Theophylline, Furosemide, Ciprofloxacin
Capsules	Nicardipine, chlordizepoxide HCI, Ursodeoxycholic acid
Microspheres	Verapamil, Aspirin, Griseofulvin, Ketoprofen, Iboprufen, Terfenadine
Granules	Indomethacin, Diclofenac sodium, Prednisolone.
Films	Cinnarizine

Table. 7: Marketed Products of Floating Drug Delivery systems (FDDS).

Brand name	Drug(dose)	Company, Country	Remarks
Madopar	Levodopa(100mg) Benserazide(25mg)	Roche products, USA	Floating, Controlled Release capsule
Valrelease	Diazepam(15mg)	Hoffmann- Laroche, USA	Floating capsule
Cytotech	Misoprolol(100mcg/200mcg)	Pharmacia, USA	Bilayer floating capsule
Conviron	Ferrous sulphate	Ranbaxy, India	Colloidal gel forming FDDS
Cifran OD	Ciprofloxacin(1 g)	Ranbaxy, India	Gas generating floating system

3.4.3 Avoidance of degradation in stomach and intestine - Colon Targeted Drug Delivery System

There are many drugs which are not stable both in stomach as well as intestine. For such drugs, following approaches can be used. A further strategy in order to overcome the enzymatic barrier is a targeting to the colon, where the enzymatic activity is comparatively low.

1). Prodrug approach: This approach involves covalent linkage between the drug and its carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine. Biotransformation is carried out by a variety of enzymes, mainly of bacterial origin, present in the colon. The enzymes that are mainly targeted for colon drug delivery include azoreductase, galactosidase, xylosidase, nitroreductase, glycosidase deaminase, etc [59].

2).pH-dependent approach: This approach is based on the pH-dependent release of the drug from the system. In this case, the pH differential between the upper and terminal parts of gastrointestinal tract is exploited to effectively deliver drugs to the colon [60]. Commonly used copolymers of methacrylic acid and methyl methacrylate have been extensively investigated for colonic drug delivery systems. Commercially available systems are mesalazine (5-ASA) (Asacol® and Salofalk®) and budesonide (Budenofalk® and Entrocort®) for the treatment of ulcerative colitis and Crohn's disease, respectively.

3).Time-dependent approach: Usually, time-dependent drug delivery systems are designed to deliver drugs after a lag of five to six hours. This approach is based upon the theory that the lag time equates to the time taken for the dosage form to reach the colon [61]. An example of such a dosage form would be an impermeable capsule

body containing the drug, fitted with a hydrogel plug that is used to deliver the drug after a predetermined time. This dosage form, for example Pulsincap®, releases the drug once the hydrogel plug hydrates and swells in aqueous media and is ejected from the device, thereby allowing the release of the drug from the capsule. Another example describes use of a hydrophobic material and surfactant in the tablet coating. The release of drug from the Time Clock® depends mainly on the thickness of the hydrophobic layer and is not dependent on the pH of the gastrointestinal environment.

4). Bacteria-dependent approach (Polysaccharides as matrices): The use of gastrointestinal microflora as a mechanism of drug release in the colonic region has been of great interest to researchers in recent times. The majority of bacteria are present in the distal gut although they are distributed throughout the gastrointestinal tract [62]. Endogenous and exogenous substrates, such as carbohydrates and proteins, escape digestion in the upper gastrointestinal tract but are metabolized by the enzymes secreted by colonic bacteria. Sulphasalazine, a prodrug consisting of the active ingredient mesalazine, was the first bacteria-sensitive delivery system designed to deliver the drug to the colon. Use of polysaccharides offers an alternative substrate for the bacterial enzymes present in the colon. Pectin alone and in combination with other polymers has been studied for colon-specific drug delivery. A coating composition of a mixture of pectin, chitosan and hydroxypropyl methylcellulose was proven to be very efficient as the tablets coated with this composition passed intact through the stomach and small intestine and broke in the colon.

5). Pressure/osmotically-dependent approach

Gastrointestinal pressure is another mechanism that is utilized to initiate the release of the drug in the distal part of the gut. The muscular contractions of the gut wall generate this pressure, which is responsible for grinding and propulsion of the intestinal contents. The pressure generated varies in intensity and duration throughout the gastrointestinal tract, with the colon considered to have a higher luminal pressure due to the processes that occur during stool formation. Systems have therefore been developed to resist the pressures of the upper gastrointestinal tract but rupture in response to the raised pressure of the colon. Capsule shells fabricated from a water-insoluble polymer such as ethyl cellulose have been used for this purpose. The performance of these systems may be affected by the administered food as it may disintegrate the capsule in stomach. Pharmacokinetic evaluation of guar gum-based colontargeted drug delivery systems of Dextran ester prodrug was performed and *in vitro* release revealed that release of naproxan from prodrug was several folds higher in caecum homogenates than in control medium or homogenates of the small intestine of pig. The bioavailability of naproxan after oral administration of a dextran T-70-naproxan ester prodrug in pigs was assessed by Harboe et al. [63]. Compared to the administration of an oral solution of an equivalent dose of naproxen the average absorption fraction for the conjugate amounted to 91%.

3.5 Novel Drug Delivery System

3.5.1 Nanosuspensions

Nanosuspension formulation approach is most suitable for the compounds with high log P value, high melting point and high dose. In case of drugs that are insoluble in both water and in organic media instead of using lipidic systems, nanosuspensions are used as a formulation approach [63]. Atovaquone, an antibiotic indicated for treating opportunistic *Pneumocystis carinii* infections in HIV patients, non-complicated *P. falciparum* malaria and leishmanial infections , shows poor bioavailability (10–15%) because of its dissolution- rate limited absorption and has to be administered in high doses (750 mg twice daily). Administration of atovaquone as a nanosuspension resulted in a 2.5-fold increase in oral bioavailability as compared to the commercial product Wellvone, which contains the micronized drug. Table 8 shows some marketed nanotechnology based approaches to improve bioavailability.

Table. 8: Marketed Nanotechnology based approaches to improve bioavailability.

Company	Nanoparticulate Technologies	Description
Elan	NanoCrystal	NanoCrystal drug particles (<1,000 nm) produced by wet-milling and stabilised against agglomeration through surface adsorption of stabilizers
Baxter	Nanoedge	Nanoedge technology: drug particle size reduction to nanorange by platforms including direct homogenisation, microprecipitation, lipid emulsions and other dispersed-phase technology
SkyePharma	IDD	Insoluble Drug Delivery: micro-nm particulate/droplet water-insoluble drug core stabilised by phospholipids; formulations are produced by high shear, cavitation or impaction
Eurand	Biorise	Nanocrystals/amorphous drug produced by physical breakdown of the crystal lattice and stabilised with biocompatible carriers (swellable microparticles or cyclodextrins)
BioSante	CAP	Calcium Phosphate-based nanoparticles: for improved oral bioavailability of hormones/proteins such as insulin; also as vaccine adjuvant
PharmaSol	NLC	Nanostructured Lipid Carriers: nanostructured lipid particle dispersions with solid contents produced by high-pressure homogenisation; lipid-drug conjugate nanoparticles provide high-loading capacity for hydrophilic drugs for oral delivery

3.5.2 Solid lipid nanoparticles (SLNs), polymeric nanoparticles

SLN are widely used to improve bioavailability and to achieve sustained release. To overcome hepatic first passmetabolism and to enhance bioavailability, intestinal lymphatic transport of drugs can be exploited [65]. Transport of drugs through the intestinal lymphatics via the thoracic lymph duct to the systemic circulation at the junction of the jugular and left subclavian vein, avoids presystemic hepatic metabolism and therefore enhances bioavailability. Highly lipophilic compounds such as longchain triglycerides reach systemic circulation via the lymphatics. Lovastatin (whose water solubility is 0.4 × 10−3 mg/mL) is considered to be a reasonable substrate for intestinal lymphatic transport because of its high log P value (4.3) and good solubility in oils (38 and 42 mg/ml in carbitol and propylene glycol monocaprylate, respectively) . Lipid-based drug delivery systems enhance the bioavailability of lipophilic drugs such as halofantrine and ontazolast by lymphatic transport of biosynthesized chylomicrons associated with the drugs. The AUC0→∞ values of vinpocetine after oral administration of SLN was 4.17-fold higher than those obtained with the vinpocetine solution.

3.5.3 Vesicular delivery systems such as liposomes, niosomes etc.

Liposomes, one of the most extensively investigated colloidal carriers in particular to improve the therapeutics of potent drugs, can be used to control retention of entrapped drugs in the presence of biological fluids and enhanced vesicle uptake by target cells. With respect to oral administration, liposome formulations are targeted to reduce toxicity and enhance bioavailability. Different mechanisms for improved oral bioavailability by liposomes has been suggested. For acid labile drugs, such as cefotaxime, entrapment by liposomes might provide a temporary protection for the drug from the hostile acidic environment of the stomach. Also, increase in the intestinal permeability is induced by the lipid components of liposomes. The oral bioavailability of cefotaxime liposomes was approximately 2.7 and 2.3 times higher as compared to that of aqueous solution and the physical mixture, respectively. Iwanaga et al. [66] suggested that liposomes accumulated at brush-border membrane of enterocytes and increased the gradient of drug concentration across the intestinal epithelium, thus enabling the absorption of significant amount of insulin into the systemic circulation. Niosomes are nonionic surfactant vesicles that are well recognized as drug delivery vehicles. They can carry hydrophilic drugs by encapsulation and are quite stable. Preliminary studies indicate that niosomes may increase the absorption of certain drugs from the gastrointestinal tract following oral ingestion. The improved oral bioavailability may be owing to the lipophilic nature of the niosomal formulation and the effect of the non-ionic surface-active agent on the permeability of the gastrointestinal membrane. Improved partioning of the lipophilic system to the mucosa, a direct effect of the surface active agent on the barrier function of the mucosa, and prolonged localization of the drug-loaded niosomes at the site of absorption may be possible reasons for the improved bioavailability [67]. In a study performed to check influence of niosomal formulation on the oral bioavailability of acyclovir in rabbits, the average relative oral bioavailability of the aciclovir from the niosomal dispersion in relation to the free solution was found to be 2.55 indicating more than 2-fold increase in drug bioavailability.

3.5.4 Microemulsion, Self micro emulsifying drug delivery system (SMEDDS): Microemulsions and SMEDDS have demonstrated a great potential in improving the oral bioavailability of therapeutic agents. Some of the microemulsion components such as surfactants can inhibit the Cytochrome P450 metabolizing enzymes. Whereas some lipidic components such as glyceryl monooleate, long-chain triglycerides have been shown to promote the lymphatic absorption of the therapeutic agents from gastrointestinal tract which prevent the first –pass metabolism of the drugs. The SMEDDS have been found to be useful in improving the oral bioavailability of drugs like carvedilol which undergo high degree of firstpass metabolism [64]. The developed SMEDDS formulations significantly improved the oral bioavailability of carvedilol significantly, and the relative oral bioavailability of SMEDDS compared with commercially available tablets was 413%. For very lipophilic Active Pharmaceutical ingredients (API), the coadministration with long chain fatty acids will promote lymphatic transport. After absorption into the enterocytes, the API will be incorporated into chylomicrons with re-esterified fatty acids from the formulations. Primarily, APIs with a log P above 5 and triglyceride solubility above 50 mg/g will show a significant lymphatic transport. Active Pharmaceutical Ingredients transported via the lymph will avoid first pass metabolism in the liver resulting in an increased bioavailability.

Table. 9: Summarizes some work done on microemulsions and self-emulsifying systems.

Drug	Work done	Result obtained
Docetaxel	Docetaxel microemulsion for enhanced oral bioavailability: Preparation and in vitro and in vivo evaluation	Oral bioavailability of the microemulsion formulation in rats (34.42%) rose dramatically compared to that of the orally administered Taxotere® (6.63%) .
Cefpirome and Cefodizim	Microemulsion and mixed micelle for oral administration as new drug formulations for highly hydrophilic drugs	Up to 64% absolute bioavailability of Cefpirome and Cefodizim was obtained by their combination with Microemulsion and mixed micelle .
Halofantrine (Hf)	Formulation design and bioavailability assessment of lipidic self-emulsifying formulations of halofantrine	The lipid-based formulations of Hf base afforded a six- to eight-fold improvement in absolute oral bioavailability relative to previous data of the solid Hf.HCl tablet formulation.

3.6 Emerging Approaches for Improvement of Oral Bioavailability

3.6.1 Phytosomes: Phytosome is a complex between a natural product (botanicals and nutraceuticals) and natural phospholipids. As shown in figure 9, no chemical bond is formed in liposomes. In the case of liposomes, hundreds or even thousands of phosphatidylcholine molecules surround the water-soluble compound whereas with the phytosome, the phosphatidylcholine and the plant components actually form a 1:1 or a 2:1 molecular complex depending on the substance(s) complexed, involving chemical bonds (hydrogen bonds). This result in better absorption and bioavailability of phytosome compared to the liposomes. Standardized plant extracts or mainly polar phytoconstituents like flavonoids, terpenoids, tannins, xanthones when complexed with phospholipids like phosphatidylcholine give phytosome (or herbosome) showing much better absorption profile following oral administration owing to improved lipid solubility which enables them to cross the biological membrane, resulting enhanced bioavailability. A standardized extract from *Silybummarianum* (milk thistle) is an excellent liver protectant but very poorly absorbed orally. Yanyu et al. [68] prepared the silymarin phytosome and studied its pharmacokinetics in rats. In the study the bioavailability of silybin in rats was increased remarkably after oral administration of prepared silybin-phospholipid complex due to an impressive improvement of the lipophilic property of silybin-phospholipid complex and improvement of the biological effect of silybin.

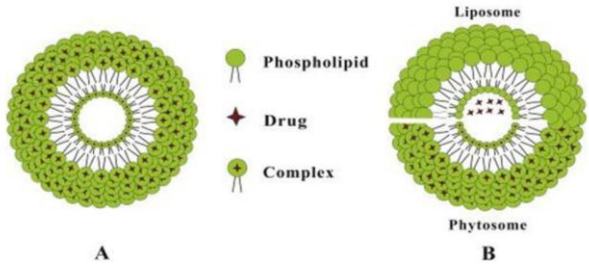

Figure 9: Difference between structure of Liposome and Phytosome

3.6.2 Oral Synchronous Drug (OSD) Delivery System

Combining the understanding of gastrointestinal physiology and the acquaintance with industrial pharmacy, Delivery Therapeutics Ltd. has developed a novel approach to increase the bioavailability of protein drugs, poorly absorbed drugs and drugs susceptible to efflux pumping incidents. This approach has been tested over 4 years in a variety of biological models and resulted in the design of the oral synchronous delivery system (OSD). Comparison between the functioning of conventional tablet and OSD tablet is depicted in figure 10. The concomitant release provided by the OSD allows continuous action of the functional adjuvant (absorption enhancer, enzyme inhibitor, or solubilizing agent) throughout the whole length of the intestine, or at predesigned intestinal segments over predetermined time slots. The outcome is an improved bioavailability of the drug of interest compared with the bioavailability accomplished when administered in non-synchronous carriers [68].

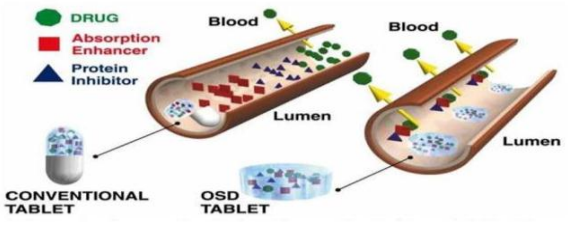

Figure no 10: Comparison between functioning of Conventional tablet and OSD tablet

Pre-clinical advanced animal studies indicate that the Delivery Therapeutics' OSDT (Oral Synchronous Delivery) breakthrough technology is feasible. Pre-clinical studies performed in beagle dogs, three OSD platforms of sCT, sodium decanoate (absorption enhancer) and bacitracin (protease inhibitor) were tested against control formulation (containing similar ingredients, without the ability to synchronize their release). A significant increase in the oral bioavailability of sCT after OSD administration was observed.

3.6.3 Transient Permeability Enhancer (TPE) technology

Transient permeability enhancement (TPE) technique enables the drug to be switched from injectable to oral by temporarily increasing the permeability of the gastrointestinal tract and aiding its absorption. It can also result in new indications or improved labels by reducing side effects. This technology is applicable to macromolecules that to-date can be administered only by injection. TPE can be utilized also with small molecules that are already orally available but are poorly absorbed. This system facilitates intestinal absorbance of drug molecules with limited intestinal bioavailability [69]. It is compatible with peptides, small proteins (up to 20kDa), saccharides and poorly absorbed small molecules. TPE protects the drug molecule from inactivation by the hostile gastrointestinal environment and at the same time acts on the GI wall to induce permeation of its cargo drug molecules. These two attributes ensure that when delivered in TPE formulation, the drug reaches the bloodstream effectively in its native active form, as described in the diagram below. TPE permeation activity is the result of a unique combination of excipients assembled in a process leading to an oily suspension of solid hydrophilic particles in a hydrophobic medium. To date, the TPE system demonstrated results in animal models using various drug molecules (e.g. peptides, small proteins, saccharides and small molecules). The mechanism of action appears to be paracellular, via opening of the tight junctions between adjacent epithelial cells for a short period of time, which seems to be less damaging than disruption of cell membrane structure. The mechanism of permeability enhancement by materials such as sodium caprate was via phospholipase C activation and upregulation of intracellular Ca 2+, leading to contraction of calmodulin dependent actin-myosin filaments and opening of tight junctions. The permeation enhancement effect of the TPE is transient and reversible in animals and lasted for 60-90 minutes after administration. In addition, the absorption enhancement is similar throughout the length of the intestine (in duodenum, jejunum, ileum and colon) [70] as shown in figure 11.

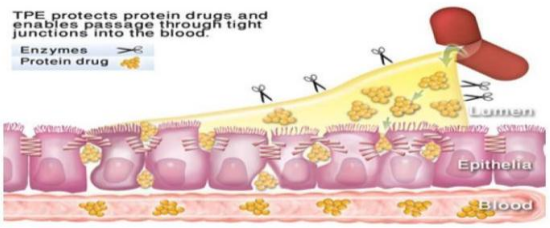

Figure 11:Protection of protein drugs and their passage through tight junctions in blood by TPE

4.0 Future prospects: Poor bioavailability is a major limitation in successful oral drug delivery system. Lot of research work is done to improve oral bioavailability of the poorly absorbed drugs. It is very important to understand the reason behind the poor bioavailability before developing a new delivery system. The positive results obtained with the use of various delivery systems or different approaches of bioavailability enhancement seem to be promising. However, the commercial development of the product demands much more research for overcoming the challenges such as scale up, cost effectiveness and instability of some of the formulations.

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