A REVIEW ON TECHNIQUES FOR ORAL BIOAVAILABILITY ENHANCEMENT OF DRUGS

Thakkar Hetal*, Patel Bindesh, Thakkar Sneha
Pharmacy Department, Faculty of Technology & Engineering, The Maharaja Sayajirao University of Baroda, Vadodara-390001, Gujarat, India.
***Email:** hetal_thakkar11@yahoo.com

ABSTRACT

Bioavailability refers to the rate and extent of the drug absorbed in the systemic circulation after administration. Oral delivery, the most convenient mode of drug administration has certain limitations, the most important being the low bioavailability of certain drugs. Drugs having low bioavailability require to be administered at a higher dose as only a small fraction of the administered dose is absorbed in the systemic circulation and reach the target site. Thus, a major amount of the drug is wasted and the unabsorbed drug leads to undesired side effects in the gastrointestinal tract. Various approaches are used for bioavailability enhancement of the orally administered drugs. The present review focuses on the importance of bioavailability, reasons for poor bioavailability and different approaches used for bioavailability enhancement.

Keywords: Bioavailability enhancement, dissolution rate, solubility, P-glycoprotein efflux, gastro retentive systems, Novel Drug Delivery Systems.

1. INTRODUCTION

1.1 Bioavailability and its importance

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). Figure 1 depicts different pathways of drug absorption from gastrointestinal tract to systemic circulation. 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[1].

1.1.1. Absolute bioavailability

Absolute bioavailability measures the availability of the active drug in systemic circulation after non-intravenous administration (i.e., after oral, rectal, transdermal, and subcutaneous administration). 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 (i.v.) and non-intravenous administration. The absolute bioavailability is the dose-corrected area under curve (AUC) non-intravenous divided by AUC intravenous.

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[1].

1.1.2 Relative bioavailability

This measures the bioavailability of a certain drug when compared with another formulation 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[1].

2. FACTORS INFLUENCING BIOAVAILABILITY

The absolute bioavailability of a drug, when administered by an extravascular route, is usually less than one (i.e. *F*<1). Various physiological factors reduce the availability of drugs prior to their entry into the systemic circulation,

Such factors may include, but are not limited to:

- Physicochemical properties of the drug (hydrophobicity, pKa, solubility)
- The drug formulation (immediate release, excipients used, manufacturing methods, modified release - delayed release, extended release, sustained release, etc.)
- Whether the drug is administered in a fed or fasted state
- Gastric emptying rate
- Circadian differences
- Enzyme induction/inhibition by other drugs/foods:
  - o Interactions with other drugs (e.g. antacids, alcohol, nicotine)
  - o Interactions with other foods (e.g. grapefruit juice, pomello, cranberry juice)
- Transporters: Substrate of an efflux transporter (e.g. P-glycoprotein)

- Health of the gastrointestinal tract
    - Intestinal motility-alters the dissolution of the drug and degree of chemical degradation of drug by intestinal microflora.
- Enzyme induction/inhibition by other drugs/foods:
    - Enzyme induction (increase rate of metabolism). e.g. Phenytoin (antiepileptic) induces CYP1A2, CYP2C9, CYP2C19 and CYP3A4
    - Enzyme inhibition (decrease rate of metabolism). e.g. grapefruit juice inhibits CYP3A, so higher nifedipine concentrations obtained
- Individual Variation in Metabolic Differences
    - Age: In general, drugs are metabolized more slowly in fetal, neonatal, and geriatric populations
    - Phenotypic differences, enterohepatic circulation, diet, gender.
- Disease state
    - e.g. hepatic insufficiency, poor renal function
    - stress, disorders (eg, achlorhydria, malabsorption syndromes)
    - previous gastrointestinal surgery (eg, bariatric surgery) can also affect drug bioavailability

Each of these factors may vary from patient to patient (inter-individual variation), and indeed in the same patient over time (intra-individual variation) [1].

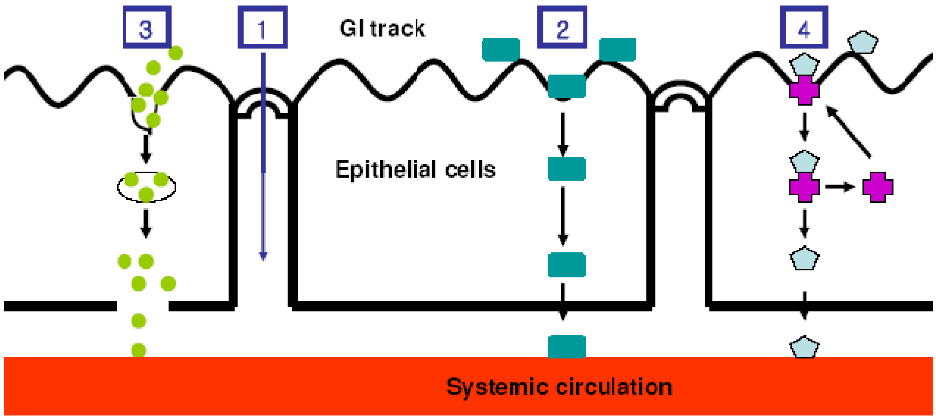

Figure 1: A schematic representation of absoption pathways **1)** paracellular transprt and trancellular transport of drugs or solutes across the epithelial cells of the gastrointestinal tract into the systemic circulation; **2)** transcellular passive diffusion; **3)** trancellular endocytosis; **4)** carrier-mediated transport processes between a specific carrier and a drug [2]

3. EFFECTS OF POOR BIOAVAILABILITY

Drugs which are having poor oral bioavailability fail to reach the minimum effective concentration required to achieve the pharmacological action. The oral dose of the drugs showing poor 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 [3], but in order to achieve this concentration, the oral dose required is 1200 mg/day (taken as six 200-mg capsules). 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 [4]. 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%) [5], due to low solubility of Danazol in aqueous medium and also due to first pass hepatic metabolism. The high dose of Danazol used in various therapies causes side effects such as weight gain, virilism, and decreased bone mineral content [5]. 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.

4. REASONS OF POOR BIOAVAILABILITY

4.1. Poor aqueous solubility

Poor solubility of a drug is in most cases associated with poor bioavailability. 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. 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 [6]. 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. Low bioavailability is the most common with oral dosage forms of poorly water-soluble, slowly absorbed drugs.

4.2. Inappropriate 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. 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 Ps greater than 3 or less than 1 have often poor transport characteristics [17], which is indicated in Table 2.

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

Drug	Aqueous solubility (mg/ml)	Absolute bioavailability
Felodipine	0.01900 mg/ml[7]	15%[8]
Ibuprofen	0.04900 mg/ml[9]	49-73%[10]
Candesartan cilexetil	0.00770 mg/ml[11]	15%[11]
Simvastatin	0.00076 mg/ml[12]	5%[13], [14]
Paclitaxel	0.00030 mg/ml[15]	6.5% [16]

Table 2: Effect of partition coefficient on absolute bioavailability

Drug	Octanol/water partition coefficient	Absolute bioavailability
Acyclovir	-1.57[18]	15-30%[19]
Chlorpromazine	3.17[20]	30-50%[21]
Hydrocortisone	1.52[22]	96%[23]

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

Level of first pass metabolism	Drug	Absolute Bioavailability
Intermediate	Midazolam	36% [25]
	Verapamil	35%[26]
High	Atorvastatin	12%[27]
	Tacrolimus	11.2%[28]
Very high	Ergotamine	5%[29]
	Lovastatin	< 5%[30]

Table 4: Examples of various materials used as carriers for preparation of solid dispersions[54]

Sr. No.	Chemical Class	Examples
1.	Polymeric Materials	Polyvinylpyrrolidone, PEG-4000, PEG-6000, CMC, HPC, HPMC, Guar gum, Xanthan gum, Sodium alginate, Methyl cellulose, Galactomannan
2.	Surfactants	Poloxamers, Tweens and Spans, Deoxycholic acid, Polyoxyethylene stearate, Gelucire 44/14
3.	Sugars	Dextrose, Sorbitol, Sucrose, Maltose, Galactose, Xylitol
4.	Acids	Citric acid, Tartaric acid, Succinic acid
5.	Miscellaneous	Pentaerythritol, Urea, Urethane, Hydroxyalkyl xanthines

Table 5: Commercially available cyclodextrin based pharmaceutical products [58]

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)

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 HCl, 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 sulfate	Ranbaxy, India	Colloidal gel forming FDDS
Cifran OD	Ciprofloxacin(1 g)	Ranbaxy, India	Gas generating floating system

Table 8: Marketed Nanotechnology based approaches to improve bioavailability [98]

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

Table 9: Examples of 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%) [104].
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 [105].
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[106].

4.3. First-pass metabolism

As shown in **figure 2,** 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). 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. These include cytochromes P450, UDP-glucuronyltransferases, sulfotransferases, and esterases.

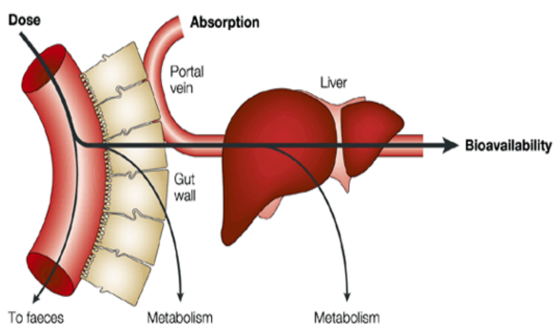

Figure 2: Route of drug passage from stomach to the systemic circulation

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 [24].

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 3**, protein drugs, in particular are highly susceptible to inactivation due to the pH and the enzymes present in gastrointestinal tract.

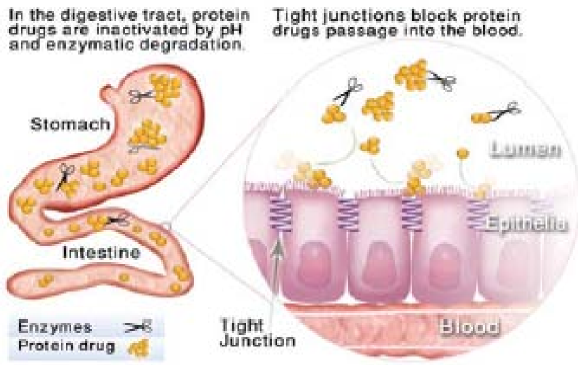

Figure 3: Inactivation of protein drugs in gastrointestinal tract

4.4.1. 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 [31], and the 2´, 3´-dideoxypurine nucleoside anti-AIDS drugs [32]. 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 acid-labile drugs [33]. 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 [34].

4.4.2. 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 [33]. 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 [35].

4.4.3. 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. 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 [35]. Teriparatide undergoes enzymatic degradation in the intestinal mucosa by enzymes like trypsin, chymotrypsin and pepsin [36].

4.4.4. 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 [37]. 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 [38].

4.5. Drug efflux pumps like p-glycoprotein

It is recently identified that drug efflux pumps like P-glycoprotein are playing a major role in altering the pharmacokinetics of various drugs. Due to selective distribution at the port of drug entry and exit, P-glycoprotein has been speculated to play a major physiological role in absorption, distribution and excretion of xenobiotics. As shown in **figure 4 a**, overall P-glycoprotein functions as a biochemical barrier for entry of xenobiotics and as a vacuum cleaner to expel them from the brain, liver, etc. and ultimately from systemic circulation [39]. Apical expression of P-glycoprotein in such tissues like liver, kidney and intestine results in reduced drug absorption from the gastrointestinal tract and enhanced drug elimination into bile and urine [40].

One of the most well- studied P-gp substrates is talinolol, a β-blocker used as antihypertensive, which has moderate lipophilicity and negligible metabolic clearance which are prerequisites for good absorption [41]. Also, the compound is cleared almost exclusively unchanged in the urine and feces. However, oral bioavailability of talinolol is only 54%, which has been ascribed to incomplete absorption from the gastrointestinal tract. In the Caco-2 cell absorption model, talinolol exhibits asymmetric flux with approximately a 10-fold greater flux in the baso-lateral to apical direction [42]. Thus, it appears that the oral bioavailability of talinolol in man is limited by P-glycoprotein-mediated efflux rather than poor membrane permeation or first-pass metabolism [43].

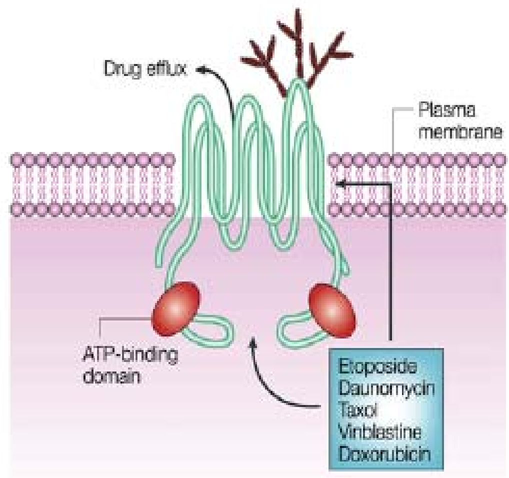

Figure 4a: Mechanism of Drug efflux by P-glycoprotein

Agents that interact with P- glycoprotein: [39], [44]

Lidocaine, quinidine, ceftriazone, erythromycin, itraconazole, Chloroquine, quinacrine, quinine, bepridil, diltiazem, nitrendipine, verapamil, daunorubicin, doxorubicin, mitomycin C, vincristine.

4.6. A combined role for P-glycoprotein and CYP3A4 in the gut wall:

Many authors have suggested that gut wall CYP3A4 and P-glycoprotein act in a concerted manner to control the absorption of their substrates. This is based on the large overlap of substrates between the two and the proximity of their expression within the gut wall, as shown in **figure 4 b**. Thus, it is proposed that P-glycoprotein effectively recycles its substrates, thereby allowing CYP3A4 several opportunities to metabolize compounds in the gut. In this way, a small amount of CYP3A4 in the gut wall (relative to the liver content) can exert a profound extraction of the compound.

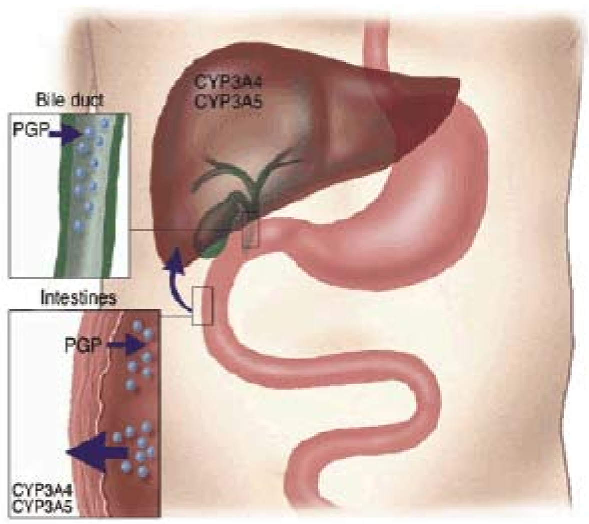

Figure 4b: Expressions of P-gp and CYP3A4

This certainly appears to be the case for cyclosporin, which is a substrate for both CYP3A4 and P-glycoprotein. Intestinal metabolism accounts for up to 50% of oral cyclosporin metabolism following oral administration [45].

4.7. Insufficient time for absorption

Insufficient time for absorption in the gastrointestinal tract is a common cause of low bioavailability. If the drug (eg. 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 [46].

5. TECHNIQUES FOR IMPROVING BIOAVAILABILITY

One approach to improve the systemic availability of the drug is to deliver it by alternative routes of administration such as parenteral, nasal, vaginal, rectal or transdermal. 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:

5.1. 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:

***5.1.1.* Physical modifications**

5.1.1.1. Particle size reduction

micronization and nanonization

5.1.1.2. Modification of the crystal habit

polymorphs and pseudopolymorphs

5.1.1.3. Drug dispersion in carriers

eutectic mixtures, solid dispersions and solid solutions

5.1.1.4. Inclusion complexation

5.1.2. Chemical Modifications

5.1.2.1. Change in pH of system

5.1.2.2. Salt formation

5.1.3. Formulation Based Approaches

5.1.3.1. Co-crystallization

5.1.3.2. Co-solvency

5.1.3.3. Hydrotrophy

5.1.3.4. Addition of solubilizer

5.1.3.5. Ultra rapid freezing

5. 1.3.6. Porous microparticles technology

5.2. Modification of partition coefficient

5.2.1. Ester formation

5.2.2. Novel formulation approaches like liposomes, niosomes and microemulsion

5.3. Avoidance of hepatic first pass metabolism

5.3.1. Co-administration with another drug

5.3.2. Prodrugs to reduce presystemic metabolism

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

5.4. Avoidance of degradation in gastrointestinal tract

5.4.1. Avoidance of degradation in stomach - Enteric coating

5.4.2. Avoidance of degradation in intestine –

Enhancement of residence time in stomach-

5.4.2.1. Floating drug delivery Systems

5.4.2.2. Use of bioadhesive (mucoadhesive) polymers

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

5.5. Inhibition of P-glycoprotein efflux

5.5.1. By using P-glycoprotein inhibitors

5.5.2. Use of surfactant

5.5.3. Use of dendrimers

5.6. Novel Drug Delivery system

5.6.1. Nanosuspensions

5.6.2. Microemulsion, Self micro emulsifying drug delivery system

5.6.3. Solid lipid nanoparticles, polymeric nanoparticles

5.6.4. Vesicular delivery systems such as liposomes, niosomes etc.

5.1. Enhancement of solubility and dissolution rate

5.1.1. Physical modifications

5.1.1.1. 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. A. Farinha et. al have found significant increase in the oral bioavailability of micronized Megestrol acetate from in vivo study [47]. As shown in the **figure 5**, **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 demonstrated that nanoparticle formulation enhances rat oral bioavailability of the poorly soluble 301029, a thiadiazole derivative. The C_{max} 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 [48]. Different principles used for nanonization are pearl milling (NanoCrystals®), high-pressure 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 [49]. Rapamune®(drug-sirolimus), an immune suppressant agent, is the first FDA approved nanoparticle formulation using NanoCrystals® technology developed by Elan Drug Delivery [50]. The novel approaches for particle size reduction are Sonocrystallisation, supercritical fluid technology and spray drying.

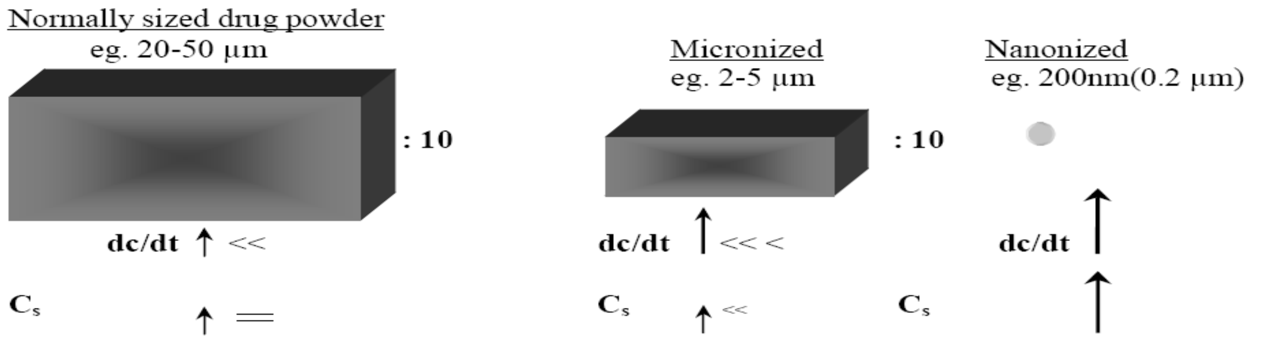

Figure 5: Dissolution velocity dc/dt and saturation solubility Cs as a function of the size of drug powders ranging from coarse to nanonized drugs

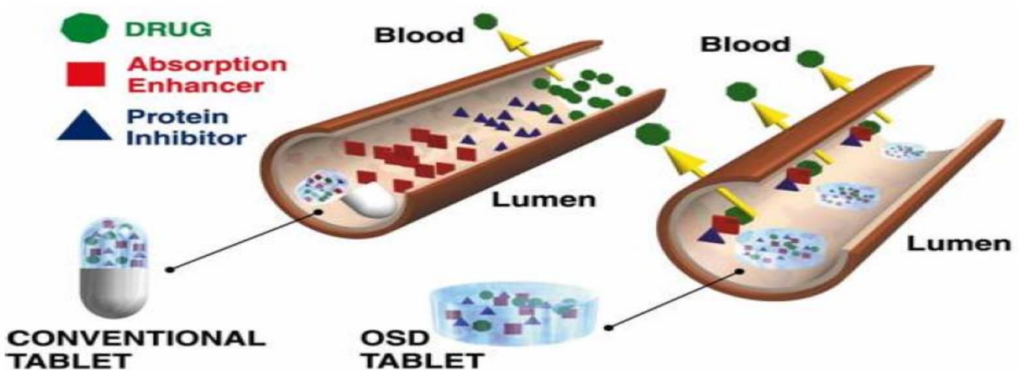

Figure 8 Comparison between functioning of conventional tablet and OSD tablet

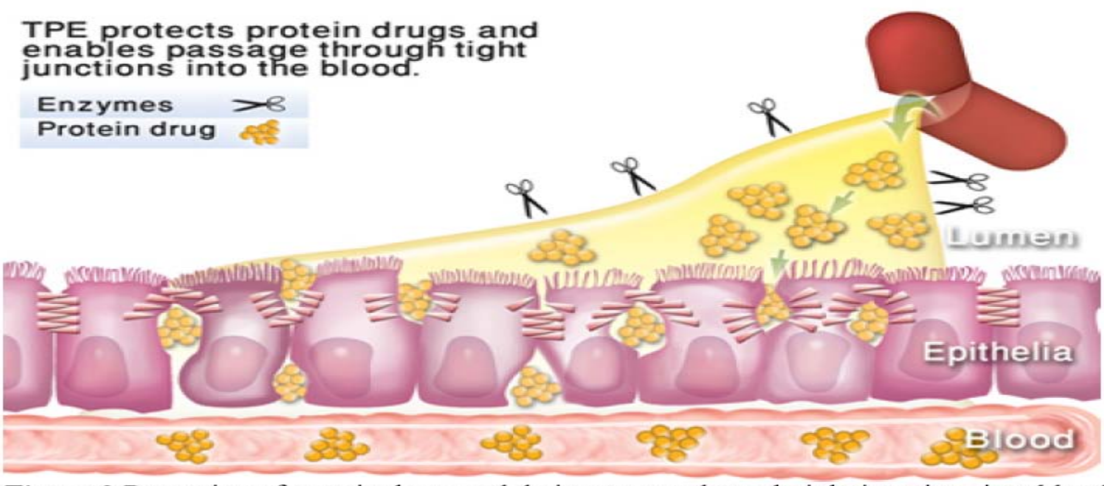

Figure 9 Protection of protein drugs and their passage through tight junctions into blood by TPE

5.1.1.2. 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 have reported that metastable polymorph of etoposide had an equilibrium solubility and intrinsic dissolution rate of 221 µg/ml and 16.3 µg/min/cm^2, respectively; 1.9 and 1.7 times that of etoposide powder at 25°C, respectively [50].

5.1.1.3. 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 suggested that the drug present in a eutectic mixture is in a microcrystalline state [51]. 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 [52]. 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 water-soluble 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 [51]. A solid dispersion of poorly soluble REV5901, an antagonist of cysteinyl-leukotriene 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 [53].

5.1.1.4. 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. 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 [55]. 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 [56]. P.T Tayade et. al 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 [57]. Accordingly, derivatives such as hydroxypropyl-ß-CD (HPß- CD; Enapsin®) and sulphobutylether-ß-CD (SE-ß-CD; Captisol®) have been developed to produce more water-soluble and less toxic entities [56].

5.1.2. Chemical Modifications

5.1.2.1. 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 [59]. 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% [60].

5.1.2.2. 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. The monoethanolamine salt form of piroxicam may be used to shorten the onset of reaction and to improve the bioavailability of piroxicam [61].

5.1.3. Formulation Based Approaches

5.1.3.1. 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 [62]. So far, only three co-crystallizing agents, saccharin, nicotinamide and acetic acid have been tried for bioavailability improvement [63]. However, the promising results obtained indicate its potential for further studies.

5.1.3.2. 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. 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 [64].

5.1.3.3. 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 [65]. Maheshwari et al 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 [66]. Solubilisation of Theophylline with sodium acetate and sodium alginate is also an example of hydrotrophy [65].

5.1.3.4. Addition of solubilizer

The solubility of poorly soluble drug can also be improved by various solubilizing materials. PEG 400 improves the solubility of hydrochlorothiazide [67]. Modified gum karaya (MGK), a recently developed excipients has been evaluated as a carrier for dissolution enhancement of poorly soluble drug, Nimodipine [68]. The nonaqueous formulation of Gelucire 44/14 and DMA (N,N-dimethylacetamide) at a weight ratio of 2:1 solves the stability, solubility, and bioavailability problems for PG301029 (novel antiviral agent). Basically, the solubility of the drug is increased by using DMA as the solvent, its bioavailability is increased by using Gelucire 44/14 as a dispersant [69]. Various surfactants have also been used as solubilizing agents.

Solubilization by surfactants

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 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 [70].

5.1.3.5. 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. 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 [71].

5. 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. 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 [72]. Dissolution rate for cyclosporin 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 cyclosporin compared to bulk cyclosporin powder [73].

5.2. Modification of partition coefficient

5.2.1. 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. 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 [74].

5.2.2. 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" (5.6).

5.3. 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:

5.3.1. 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. When administered alone, lopinavir has insufficient bioavailability (25%) [75]; 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 [76].

5.3.2. 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. 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 6.**

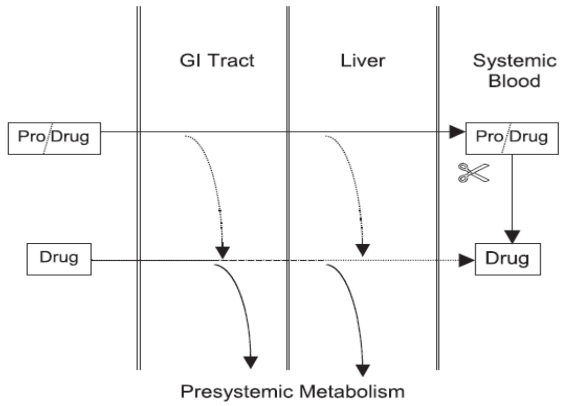

Figure 6: Prodrug strategy

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) [77].

5.3.3. 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 [78]. 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.

5.4. Avoidance of degradation in gastrointestinal tract

5.4.1. 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. 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 from enteric-coated beads filled in hard gelatin capsules was significantly higher (197.54 % increase) than that from the commercial voltaren tablets [79].

5.4.2. Avoidance of degradation in intestine –

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.

Enhancement of residence time in stomach

Gastro Retentive drug delivery system:

They are designed for retention in the stomach for longer time than usual (~about 8 hours) [80]. Some drugs which have narrow zones of absorption in gastrointestinal tract, weakly basic drugs that are poorly soluble in intestinal pHs 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.

5.4.2.1. 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. After release of drug, the residual system is emptied from the stomach [81].

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, eg, sodium bicarbonate, tartaric acid, and citric acid. 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 [81]. V.K. Kakumanu et al. 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 [82].

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 [81]. 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 [83]. Table 6 shows list of drug formulated as single and multiple unit forms of floating drug delivery systems. Table 7 indicates details of marketed products of floating drug delivery systems.

5.4.2.2. 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. 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 [84].

b. 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.

5.4.3. Avoidance of degradation in stomach and intestine

There are many drugs which are not stable both in stomach as well as intestine. For such drugs, following approaches can be used.

Colon Targeted Drug Delivery System

A further strategy in order to overcome the enzymatic barrier is a targeting to the colon, where the enzymatic activity is comparatively low.

Approaches of Colon Targeted Drug Delivery System: [85]

A. 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.

B. 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. Commonly used co-polymers 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.

C. 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. 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.

D. 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. 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.

E. 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 colon-targeted 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 [86]. The bioavailability of naproxan after oral administration of a dextran T-70-naproxan ester prodrug in pigs was assessed by Harboe et al.. Compared to the administration of an oral solution of an equivalent dose of naproxen the average absorption fraction for the conjugate amounted to 91% [87].

5.5. Inhibition of P-glycoprotein efflux

5.5.1. By using P-glycoprotein inhibitors

Several studies have demonstrated the possible use of P-glycoprotein inhibitors that reverse P--glycoprotein -mediated efflux in an attempt to improve the efficiency of drug transport across the epithelia, thus resulting in enhanced oral bioavailability. P-glycoprotein inhibitors may also influence absorption, distribution, metabolism and elimination of P-glycoprotein substrates in the process of modulating pharmacokinetics. Early studies on verapamil to reverse P-glycoprotein mediated resistance to vincristine and vinblastine provided the rationale for its clinical usefulness as P-glycoprotein inhibitor. In addition to this, orally administered Verapamil has been shown to increase peak plasma level, prolong elimination half-life and increase volume of distribution of doxorubicin, another P-glycoprotein substrate, after oral administration [88]. Many natural compounds from medicinal plants have demonstrated capacity to enhance the bioavailability of co-administered drugs by inhibiting efflux pumps or oxidative metabolism, and perturbing the intestinal brush border membrane. These natural compounds include quercetin, genistein, naringin, sinomenine, piperine, glycyrrhizin and nitrile glycoside [89]. Oral bioavailability of paclitaxel was increased from 4.6% to 34.4% when coadministered with P-Glycoprotein Inhibitor KR30031 (Verapamil analog) [90].

5.5.2. Use of surfactant

Surfactants used in certain drug formulations affect P-glycoprotein mediated efflux of drug, leading to altered gastrointesinal tract permeability. Many surfactants such as Vitamin E, Solutol HS 15, Cremophore EL and Polysorbate 80 and oil phases such as Imwitor 742 and Akoline MCM (mono and di-glyceride of caprylic acid) have potential to inhibit P-glycoprotein efflux. Hence, SMEDDS can also inhibit the P-glycoprotein efflux process. Cremophore EL dose-dependently increased C_{max}, AUC (0, 4 h), and AUC (0,∞) of saquinavir as compared to the placebo. For 5000 mg cremophore EL, there was 13-fold increase for both C_{max} and AUC (0, 4 h) and 5-fold increase for AUC (0,∞) [91].

5.5.3. Use of dendrimers

Certain drugs are known substrates for P-glycoprotein; one such drug is propranolol. By conjugating this poorly soluble drug to dendrimers (a class of polymers capable of enhancing the water solubility of certain drugs), a prodrug is created. This prodrug increases the water solubility of propranolol and assists in bypassing drug efflux transporters, such as P- glycoprotein [92].The doxorubicin-PAMAM complex led to the bioavailability that was more than 200-fold higher than that of free doxorubicin (P-glycoprotein substrate) [93] after oral administration which indicated that PAMAM dendrimer is a promising novel carrier to enhance the oral bioavailability of drug, especially for the P-glycoprotein substrates [94].

5.6. Novel Drug Delivery System

5.6.1. 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. Atovaquone, an antibiotic indicated for treating opportunistic *Pneumocystis carinii* infections in HIV patients, non-complicated *P. falciparum* malaria and leishmanial infections [95], 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 [96, 97]. Table 8 shows some marketed nanotechnology based approaches to improve bioavailability.

5.6.2. 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 [99]. 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 [100]. The SMEDDS have been found to be useful in improving the oral bioavailability of drugs like carvedilol which undergo high degree of first-pass metabolism [101]. 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% [102].

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 [103]. 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.

5.6.3. Solid lipid nanoparticles (SLNs), polymeric nanoparticles

SLN are widely used to improve bioavailability and to achieve sustained release. To overcome hepatic first-pass metabolism and to enhance bioavailability, intestinal lymphatic transport of drugs can be exploited. 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 long-chain 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) [30]. 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 [106,107]. The $AUC_{0\rightarrow\infty}$ values of vinpocetine after oral administration of SLN was 4.17-fold higher than those obtained with the vinpocetine solution [108].

5.6.4. 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 [109]. With respect to oral administration, liposome formulations are targeted to reduce toxicity and enhance bioavailability [110]. 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 [111]. Iwanaga et al. 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 [112].

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 nonionic 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 [114]. 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 [114].

6. EMERGING APPROACHES FOR IMPROVEMENT OF ORAL BIOAVAILABILITY

6.1. Phytosomes:

Phytosome is a complex between a natural product (botanicals and nutraceuticals) and natural phospholipids. As shown in **figure 7,** 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 [115]. Yanyu et al. 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 [116].

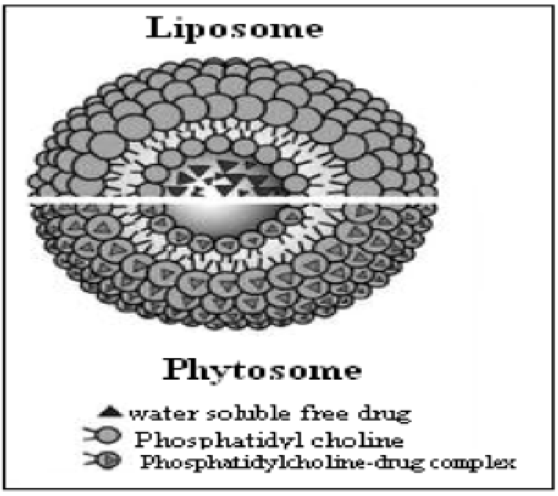

Figure 7: Difference between structure of liposome and phytosome.

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 8.**

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 pre-designed 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 [117].

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 [117].

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. 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) [118].

Future prospects: Poor bioavailability is a major limitation in successful drug delivery by oral route. Lot of research work is focused on oral bioavailability enhancement of the poorly absorbed drugs. It is necessary to understand the reason behind the poor bioavailability before designing a 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.

REFERENCES

1. L. Shargel, A.B. Yu, (1999). *Applied biopharmaceutics & pharmacokinetics* (4th edition) New York: McGraw-Hill. ISBN 0-8385-0278-4
2. N. N. Salama, N. D. Eddington, A. Fasano, Tight junction modulation and its relationship to drug delivery, Adv. Drug Deliv. Rev. 58 (2006) 15-28.
3. C.J.L. la Porte, D.J. Back, T. Blaschke, Updated guideline to perform therapeutic drug monitoring for antiretroviral agents. Rev. Antivir. Ther. (2006) 3:4–14.
4. http://www.medicinenet.com/saquinavir_oral/page3.htm
5. S.I.F. Badawy, M. M. Ghorab, C. M. Adeyeye, Characterization and bioavailability of danazol-hydroxypropyl-β-cyclodextrin coprecipitates, Int. J. Pharm., Vol. 128, No. 1- 2, 1996, 45-54.
6. H. Lennemas, Modeling gastrointestinal drug absorption requires more in vivo biopharmaceutical data : Experience from in vivo dissolution and permeability studies in humans ; Curr. drug metab. Vol. 8, No. 7, 2007, 645-657.
7. http://www.drugbank.ca/drugs/DB01023
8. S. Capewell, J. A. J. H. Critchley, S. Freestone, A. Pottage, L. F. Prescott Reduced felodipine bioavailability in patients taking anticonvulsants, The Lancet, Volume 332, Issue 8609, 1988, 480-482.
9. http://www.drugbank.ca/cgi-bin/getCard.cgi?CARD=APRD00372.txt
10. http://en.wikipedia.org/wiki/Ibuprofen
11. http://www.drugbank.ca/drugs/DB00796
12. http://www.drugbank.ca/drugs/DB00641
13. S.Vickers, C.A. Duncan, K.P. Vyas, In vitro and in vivo biotransformation of simvastatin, an inhibitor of HMG CoA reductase. Drug Metab. Dispos. 1990;18:476–483.
14. S. Vickers, C.A. Duncan, I.W. Chen, A. Rosegay, D.E. Duggan. Metabolic interaction studies on simvastatin, a cholesterol-lowering prodrug. Drug Metab. Dispos. 1990;18:135–145.
15. . Richard , W. L. Liggins , H. M. Burt, Solid-state characterization of Paclitaxel, J. Pharm. Sci. Volume 86 Issue 12**,** Pages 1458 – 1463.
16. http://en.wikipedia.org/wiki/Paclitaxel
17. V. Vemulapalli, N. M. Khan, B. R. Jasti, Physicochemical Characteristics that Influence the Transport of Drugs Across Intestinal Barrier, AAPS news magazine, March 2007, 18-21.
18. A. Kristl, J. J. Tukker, Negative Correlation of n-Octanol/ Water Partition Coefficient and Transport of Some Guanine Derivatives Through Rat Jejunum In Vitro, Pharm. Res., Volume 15, Number 3, 1998, 499-501.
19. http://en.wikipedia.org/wiki/Aciclovir
20. U. Franke, A. Munk, M. Wiese, Ionization constants and distribution coefficients of phenothiazines and calcium channel antagonists determined by a pH-metric method and correlation with calculated partition coefficients, J. Pharm. Sci., Volume 88, Issue 1, 89 – 95.
21. en.wikipedia.org/wiki/Chlorpromazine
22. http://www.cerep.fr/Cerep/Users/pages /Downloads /Documents/Marketing/
23. Pharmacology ADME/Application notes /partitioncoefficient.pdf
24. H. Derendorf, H. Mollmann, J. Barth, C. Mollmann, S. Tunn, M. Krieg, Pharmacokinetics and oral bioavailability of hydrocortisone, J. Clin. Pharmacol., 1991; 31: 473-476.
25. G.K. Dresser, J.D. Spence, D.G. Bailey, Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. Clin. Pharmacokinet. 2000, 38:41-57.
26. M. D. Reed, A. Rodarte, J. L. Blumer, K. C. Khoo, B. Akbari, S. Pou, G. L.Kearns, The single-dose pharmacokinetics of midazolam and its primary metabolite in pediatric patients after oral and intravenous administration, J. Clin. Pharmacol., 41 (12) 1359
27. http://www.mentalhealth.com/drug/p30-i03.html
28. J. Kim, M. Kim, H. J. Park, S. Jin, S. Lee and S. Hwang, Physicochemical properties and oral bioavailability of amorphous atorvastatin hemi-calcium using

spray-drying and SAS process, Int. J. Pharm.,Volume 359, Issues 1-2, 2008, 211-219.

29. M. Antignac, B. Barrou, R. Farinotti, P. Lechat, S. Urien, Population pharmacokinetics and bioavailability of tacrolimus in kidney transplant patients, Br. J. Clin. Pharmacol. 2007 Dec;64(6):750-757.

30. S. W. Sanders, N. Haering, H. Mosberg, H. Jaeger, Pharmacokinetics of ergotamine in healthy volunteers following oral and rectal dosing, Eur. J. Clin. Pharmacol., Volume 30, Number 3, 1986, 331-334.

31. G.Suresh, K.Manjunath, V.Venkateswarlu, V. Satyanarayana, Preparation, Characterization, and In Vitro and In Vivo Evaluation of Lovastatin Solid Lipid Nanoparticles, AAPS PharmSciTech 2007; 8 (1) Article 24, E1-E9.

32. M.S. Gogate, Erythromycin monograph, in chemical stability of Pharmaceuticals: A handbook for Pharmacists, 2nd ed. (K.A. Connors, G. L. Amidon, V.J.Stella, eds), 457-463, John Wiley and sons, Newyork, 1986, and references therein.

33. B. D. Anderson, M. B. Wygant, T. X. Xiang, W. A. Waugh and V. J. Stella, Preformulation solubility and kinetic studies of 2',3'-dideoxypurine nucleosides: Potential antiAIDS agent, Inf. J. Pharm., 1988, 45, 27-37.

34. S. Yoshioka, V. J. Stella, Stability of Drugs and Dosage forms, Chapter 2- Chemical stability of drug substances, pg.no. 4.

35. P. Barditch-Crovo, B.G. Petty, J. Gambertoglio, L. J. Nerhood, S. Kuwahara, R. Hafner, P. S.Lietman, D. M. Kornhauser, The effect of increasing gastric pH upon the bioavailability of orally-administered phosphonoformic acid (foscarnet). Int. Conf. AIDS. 1991 Jun 16-21; 7: 210 (abstract no. W.B.2115).

36. A. Bernkop-Schnürch, Oral Drug Delivery: How do chemical reactions in the Gastrointestinal tract influence the therapeutic potential of drugs?

37. M. Werle, A. Samhaber, A. Bernkop-Schnurch, Degradation of teriparatide by gastro-intestinal proteolytic enzymes, J. Drug Target., Volume 14, Issue 3, 2006, 109 – 115.

38. U. Fuhr, (1998) Drug interactions with grapefruit juice: extent, probable mechanism and clinical relevance. Drug Safe 18, 251-272.

39. H. Poiger, Ch. Schlatter, Compensation of dietary induced reduction of tetracycline absorption by simultaneous administration of EDTA, Eur. J. Clin. Pharmacol., Volume 14, Number 2, 1978, 12-131.

40. V.S. Manthena, A. Varma, Y. Ashokraj, S. Chinmoy, B. Dey, R. Panchagnula, P-glycoproein inhibitors and their screening: a perspective from bioavailability Enhancement, Pharmacol. Res., 48 (2003) 347–359.

41. M.F.Fromm, P-glycoprotein: a defense mechanism limiting oral bioavailability and CNS accumulation of drugs. Int. J. Clin. Pharmacol. Ther. 38(2), 2000, 69-74.

42. B. Trausch, R. Oertel, K. Richter, T. Gramatte, Disposition and bioavailability of the β-adrenoceptor antagonist Talinolol in man, Biopharmaceut. Drug Disp. 1995, 16, 403-414.

43. U. Wetterich, H. Spahn-Langguth, E. Mutschler, B. Terhaac, W. Rosch, P. Langguth, Evidence for intestinal secretion as an additional clearance pathway of Talinolol enantiomers: concentration and dose dependent absorption in vitro and in vivo, Pharm. Res. 1996, 13, 514-522.

44. H. V. Waterbeemd, H. Lennernäs, P. Artursson, Drug Bioavailability-Estimation of solubility, Permeability, Absorption and bioavailability , Chapter 13- The importance of Gut wall metabolism in determining drug bioavailability, Pg. 320.

45. J. Hunter, B. H. Hirst, Intestinal secretion of drugs. The role of P-glycoprotein and related drug efflux systems in limiting oral absorption. Adv. Drug Deliver. Rev., 1997;25:129–57.

46. H. V. Waterbeemd, H.Lennernäs, P.Artursson, Drug Bioavailability-Estimation of solubility Permeability, Absorption and bioavailability , Chapter 13- The importance of Gut wall metabolism in determining drug bioavailability, Pg. 321.

47. The Merck manual, Online Medical library, Section: Clinical Pharmacology, Subject: Pharmacokinetics, Topic: Bioavailability.

48. A. Farinha, A. Bica, P. Tavares, Improved bioavailability of a micronized megestrol acetate tablet formulation in humans, Drug Dev. Ind. Pharm. 2000;26(5):567-70.

49. L. Jia , H. Wong, C. Cerna, S. D. Weitman, Effect of Nanonization on Absorption of 301029: *Ex Vivo* and *In Vivo* Pharmacokinetic Correlations Determined by Liquid Chromatography/Mass Spectrometry, Pharm. Res., Volume 19, Number 8, 2002, 1091-1096.

50. J. Hu, K.P. Johnson, Williams III, R.O., Nanoparticle engineering processes for enhancing the dissolution rates of poorly water soluble drugs, Drug Dev. Ind. Pharm., 30(3), 2004, 233- 245.

51. J. C. Shah, J. R. Chen, D. Chow, Metastable Polymorph of Etoposide with Higher Dissolution Rate, Drug Dev. Ind. Pharm., Vol. 25, No. 1, 1999, 63-67 .

52. K. Sekiguchi, N. Obi, Studies on absorption of eutectic mixture. I A comparison of the behavior of eutectic mixture of sulfathiazole and that of

ordinary sulfathiazole in man. Chem. Pharm. Bull., 1961, 9, 866-872.

53. A. H. Goldberg, M. Galbaldi, K. L. Kanig, Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures III. Experimental evaluation of griseofulvin-succinic acid solution. J. Pharm. Sci. 1966, 55, 487-492.

54. P. C. Sheen, S. I. Kim, J. J.Petillo, A.T.M. Serajuddin, (1991). Bioavailability of a poorly water-soluble drug from tablet and solid dispersion in humans. J. Pharm. Sci., 80: 712-714.

55. W.L. Chiou, S. Riegelman, Pharmaceutical applications of solid dispersion systems, J. Pharm. Sci. 1971, 60, 1281-1302.

56. T. Loftsson, M. E. Brewster, Pharmaceutical applications of cyclodextrins-1. Drug solubilization and stabilization, J. Pharm. Sci., 85, 1996, 1017-1025.

57. B. G. Prajapati, M. M. Patel, Conventional and alternative pharmaceutical methods to improve oral bioavailability of lipophilic drugs, Asian J. Pharm., Volume 1, Issue 1, April – June, 2007.

58. P. T. Tayade, P. R. Vavia, Inclusion complexes of ketoprofen with β-cyclodextrins :Oral pharmacokinetics of ketoprofen in Human, Ind. J. Pharm. Sci., Vol. 68, No. 2, 2006, 164 – 170.

59. M. E. Davis, M. E. Brewster, Cyclodextrin-based pharmaceutics: past, present and future, Nat. Rev. Drug Discov., 2004 , 3, 1023-1035.

60. B. Devarakonda, D.P. Otto, A. Judefeind, R.A. Hill, M.M. Villiers, Effect of pH on the solubility and release of furosemide from polyamidoamine (PAMAM) dendrimer complexes. Int. J. Pharm. 2007; 345(1-2):142-53.

61. http://www.elephantcare.org/Drugs/furosemi.htm

62. H. Gwak, J. Choi, H. Choi, Enhanced bioavailability of piroxicam via salt formation with ethanolamines, Int. J. Pharm., 297 (2005) 156–161.

63. D. P. McNamara, S. L. Childs, J. Giordano, Use of a glutaric acid cocrystal to improve oral bioavailability of a low solubility API, Pharm. Res., vol. 23, No.8, 2006, 1888-1897.

64. N. Blagden, M. Matas, P.T. Gavan, P.York, Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates, Adv. Drug Deliv. Rev., Volume 59, Issue 7, 2007, 617-630.

65. Strickley, R. G., Solubilizing Excipients in Oral and Injectable Formulations, Pharm. Res., Vol. 21, No. 2, 2004, 200-229.

66. R.H. Müller, R. Becker, B. Kruss, K. Peters, Pharmaceutical nanosuspensions for medicament administration as systems with increased saturation solubility and rate of solution 1999. US Patent 5858410

67. R. K. Maheshwari, S. C. Chaturvedi, N. K. Jain, Novel spectrophotometric estimation of some poorly water soluble drugs using hydrotropic solubilizing agents, Asian J. Pharm. Clin. Res., Volume 3, Issue 10, 2010, 43-45.

68. C. Vervaet, J.P. Remon, Bioavailability of Hydrochlorothiazide from Pellets, Made by Extrusion/ Spheronisation, Containing Polyethylene Glycol 400 as a Dissolution Enhancer, Pharm. Res., Volume 14, Number 11 , 1997 , 1644-1646.

69. G. V. Murali Mohan Babu, C.D.S. Prasad, K.V. Ramana Murthy, Evaluation of modified gum karaya as carrier for the dissolution enhancement of poorly water-soluble drug nimodipine, Int. J. Pharm., 2002, 234, 1–17.

70. Y. He, L. H. Johnson, S. H. Yalkowsky, Oral formulation of a novel antiviral agent, PG301029, in a mixture of Gelucire 44/14 and DMA (2:1, wt/wt), AAPS PharmSciTech, Volume 6, Number 1 ,2005, 1530-9932.

71. D. Attavi, A. Imane, A. Alain, D. Béatrice, G. Stéphane, Development of microemulsion of mitotane for improvement of oral bioavailability, Drug Dev. Ind. Pharm., Volume 36, Number 4, 2010 , 421-427(7).

72. J. C. Evans, B. D. Scherzer, C. D. Tocco, G. B. Kupperblatt, J. N. Becker, D. L. Wilson, S. Saghir, E. J. Elder, Preparation of nanostructured particles of poorly water soluble drugs via a novel ultrarapid freezing technology, A.C.S. symposium series, 2006, vol. 924, 320-328.

73. V. Rajesh Babu, S.H. Areefulla, V. Mallikarjun, Solubility and Dissolution Enhancement: An overview, J. Pharm. Res., 2010, 3(1),141-145

74. Water soluble pharmaceutical coating and method for producing coated pharmaceuticals, United States Patent 5851275

75. N. K. Mandava, R. Awasthi, S. Ye1, A.K. Mitra, Prodrug Derivatization of Amprenavir: Strategy to enhance the oral bioavailability, AAPS 2009-0*03847*

76. Lopinavir-Ritonavir: A New Protease Inhibitor: Pharmacokinetic-Pharmacodynamic Profile, Medscape Today, Pharmacotherapy. 2001;21(11)

77. M.M. Malingré, D.J. Richel, J.H. Beijnen, Coadministration of Cyclosporine strongly enhances the oral bioavailability of docetaxel, J. Clin. Oncol., Vol 19, Issue 4, 2001: 1160-1166.

78. B. J. Aungst, M.J. Myers, E. Shefter, E. G. Shami, Prodrugs for improved oral nalbuphine bioavailability: inter-species differences in the disposition of nalbuphine and its acetylsalicylate and

anthranilate esters, Int. J. Pharm., Volume 38, Issues 1-3, 1987, 199-209.

79. S. Baboota, M. S. Shah, A. Javed, A. Ahuja, Effect of poloxamer 188 on lymphatic uptake of carvedilol-loaded solid lipid nanoparticles for bioavailability enhancement, J. Drug Target., Volume 17, Issue 3, 2009 , 249 – 256.

80. E. A. Hosny, G.M. El-Mahrouk, M.W. Gouda, Formulation and in Vitro and in Vivo Availability of Diclofenac Sodium Enteric-Coated Beads, Drug Dev. Ind. Pharm., Vol. 24, No. 7, 1998, 661-666.

81. S. A. Charman, W. N. Charman, Oral Modified Release Delivery Systems, Book: Modified Release Drug Delivery Technology by M. J. Rathbone, J. Hadgraft, M.S. Roberts,1- 10.

82. A. V. Mayavanshi, S.S. Gajjar, Floating drug delivery systems to increase gastric retention of drugs: A Review, Research J. Pharm. and Tech. 1(4): 2008, 345-348.

83. V. K. Kakumanu, V. K. Arora, A. K. Bansal, Gastro-retentive dosage form for improving bioavailability of Cefpodoxime Proxetil in Rats, Yakuguku Zasshi, Vol. 128, No. 3 , (2008), 439-445.

84. S. C. Jagdale, A. J. Agavekar, S. V. Pandya, B. S. Kuchekar, A. R. Chabukswar, Formulation and Evaluation of Gastroretentive Drug Delivery System of Propranolol Hydrochloride, AAPS PharmSciTech, Volume 10, Number 3, 2009 , 1071-1079.

85. M. T. Khalid, C. Hung-Seng, B. Saringat, Use of bioadhesive polymer to improve the bioavailability of griseofulvin, Int. J. Pharm., Volume 148, Issue 1, 1997, 63-71.

86. A. Pareek, K.S. Rathore, Colon Targeted Drug Delivery Systems: An Overview, Articlebase, Nov. 2006

87. M.K. Chourasia, S. K. Jain, Polysaccharides for Colon Targeted Drug Delivery, Drug Deliv., Vol.11, No.2 : 2004,129-148.

88. E. Harboe, C. Larsen, M. Johansen, H. P. Olesen, Macromolecular prodrugs. XIV. Absorption characteristics of naproxen after oral administration of a dextran T-70-naproxen ester prodrug in pigs , Int. J. Pharm., Volume 53, Issue 2,1989, 157-165.

89. Varma, M. V. S., Ashokraj, Y., Dey, C. S., Panchagnula, R., P-glycoprotein inhibitors and their screening: a perspective from bioavailability enhancement, Pharmacol. Res. Volume 48, Issue 4, 2003, 347-359.

90. M.J. Kang, J. Y. Cho, B. H. Shim, D. K. Kim, J. Lee, Bioavailability enhancing activities of natural compounds from medicinal plants, J. Medi. Plants Res. Vol. 3(13), 2009, 1204-1211.

91. J. S. Woo, C. H. Lee, C. K. Shim, S.J. Hwang, Enhanced Oral Bioavailability of Paclitaxel by Coadministration of the P-Glycoprotein Inhibitor KR30031, Pharm. Res., Volume 20, Number 1, 2003, 24-30.

92. M. M. Facklam, J. Burhenne, R. Ding, R. Fricker, G. Mikus, I. Walter-Sack, E. H. Walter, Dose-dependent increase of saquinavir bioavailability by the pharmaceutic aid cremophor EL, Br. J. Clin. Pharmacol., 53, 576–581.

93. A. D'Emanuele, R. Jevprasesphant, J. Penny, D. Attwood, The use of a dendrimer-propranolol prodrug to bypass efflux transporters and enhance oral bioavailability,

94. J. Control. Rel., Volume 95, Issue 3, 2004, Pages 447-453

95. I.C. Van der Sandt, M. C. Blom-Roosemalen, A. G. Boer, D.D. Breimer, Specificity of doxorubicin versus rhodamine-123 in assessing P-glycoprotein functionality in the LLC-PK1, LLC-PK1:MDR1 and Caco-2 cell lines, Eur. J. Pharm. Sci.,11(3), 2000 ,207-214.

96. W. Ke, Y. Zhao, R. Huang, C. Jiang, Y. Pei, Enhanced oral bioavailability of doxorubicin in a dendrimer drug delivery system, J. Pharm. Sci., 97(6), 2008, 2208-2216.

97. S. Looareesuwan, J. D. Chulay, C J. Canfield, D. B. Hutchinson, Atovaquone and proguanil hydrochloride followed by primaquine for treatment of Plasmodium vivax malaria in Thailand. Trans. R. Soc. Trop. Med. Hyg., 1999, 93: 637–640.

98. N. Schöler, K. Krause, O. Kayser, R. H. Müller, K. Borner, H. Hahn, O. Liesenfeld, Atovaquone nanosuspensions show excellent therapeutic effect in a new murine model of reactivated toxoplasmosis. Antimicrob. Agents Chemother., 2001 45: 1771–1779.

99. V. B. Patravale, A. A. Date, R. M. Kulkarni, Nanosuspensions: a promising drug delivery strategy, J. Pharm. Pharmacol., 56, 2004, 827–840.

100. R. Saffie-Siebert, J. Ogden, M. Parry-Billings, Nanotechnology approaches to solving the problems of poorly water-soluble drugs, Drug Discovery World Summer 2005, 71-76.

101. X. Ren, X. Mao, S. Luqin, L. Cao, X. Hui, Q. Jun, D. S. Aaron, Gao, L., Pharmaceutical excipients inhibit cytochrome P450 activity in cell free systems and after systemic administration, Eur. J. Pharm. Biopharm. Volume 70, Issue 1, 2008, 279-288.

102. H. Cai-Xia, , H. Zhong-Gui, G. Jian-Qing, Microemulsions as drug delivery systems to improve the solubility and the bioavailability of poorly water-soluble drugs, Expert Opinion on Drug Delivery, Vol. 7, No. 4, 2010, 445-460.

103. R. R. Ruffolo, D.A. Boyle, R. P. Venuti, Preclinical and clinical pharmacology of carvedilol. J Hum. Hypertens. 1993;7:S2-S15.

104. W. Lanlan, S. Peinan, N. Shufang, P. Weisan, Preparation and Evaluation of SEDDS and SMEDDS Containing Carvedilol, Drug Dev. Ind. Pharm., Vol. 31, No. 8, 2005,785-794.

105. A. Mullertz, Lipid-based Drug Delivery Systems: Choosing the Right In Vitro Tools, Drug Delivery, Am. Pharm. Rev., Vol. 10, Issue 4, 2007, 102-110.

106. Y.M.Yin, F.D. Cui, C.F. Mu, M. K. Choi, J.S. Kim, S. J. Chung, C. K. Shim, D. D. Kim, docetaxel microemulsion for enhanced oral bioavailability: preparation and in vitro and in vivo evaluation. J. Control. Release.,140(2), 2009 ,86-94.

107. Y. Mrestani, L. Behbood, A. Härtl, H. Reinhard, H. Neubert, Microemulsion and mixed micelle for oral administration as new drug formulations for highly hydrophilic drugs, Eur. J. Pharm. Biopharm., Volume 74, Issue 2, 2010, 219-222.

108. S.M. Khoo, A. J. Humberstone, C. J. H. Porter, G.A. Edwards, W. N. Charman, Formulation design and bioavailability assessment of lipidic self-emulsifying formulations of halofantrine, Int. J. Pharm., Volume 167, Issues 1-2, 1 1998, 155-164.

109. D. J. Hauss, S.E. Fogal, J. V. Ficorilli, Lipid-based delivery systems for improving the bioavailability and lymphatic transport of a poorly water soluble LTB_4 inhibitor. J. Pharm. Sci. 1998;87:164-169.

110. Y. Luo, D. Chen, L. Ren, X. Zhao, J. Qin, Solid lipid nanoparticles for enhancing vinpocetine's oral bioavailability, J. Control. Release 114 (2006) 53–59.

111. S. Doktorovova, T. Morsy, V. M. Bãlcao, E. B. Souto, The role of lipids in drug absorption through the GIT, 192-198.

112. A. Samad, Y. Sultana, M. Aqil, Liposomal Drug Delivery Systems: An Update Review, Curr. Drug Deliv. , Vol: 4-(4) , 2007, 297-305.

113. S.S. N. Ling, E. Magosso, N.A. K.Khan, K.H. Yuen, S.A. Barker, Enhanced Oral Bioavailability and Intestinal Lymphatic Transport of a Hydrophilic Drug Using Liposomes, Drug Dev. Ind. Pharm., Vol. 32, No. 3, 2006, 335-345.

114. K. Iwanaga , S.Ono, K. Narioka, K. Morimoto, M. Kakemi, S. Yamashita, M. Nango, N. Oku, N. Oral delivery of insulin by using surface coating liposomes Improvement of stability of insulin in GI tract, Int. J. Pharm., 157, 1997, 73-80.

115. M. N. Azmin, A.T. Florence, R. M. Handjani-Vila, F. B. Stuart, G. Vanlerberghe, J.S.Whittaker, The effect of non-ionic surfactant vesicles (niosome) entrapment on the absorption and distribution of methotrexate in mice. J. Pharm. Pharmacol., 37,1985; 237-242.

116. I.A. Attia, I. S.A. El-Gizawy, M.A. Fouda, A.M. Donia, Influence of a Niosomal Formulation on the Oral Bioavailability of Acyclovir in Rabbits, AAPS PharmSciTech, 8 (4) Article 106, 2007, 206-212.

117. S. Bhattacharya, A. Ghosh, Phytosomes: the Emerging Technology for Enhancement of Bioavailability of Botanicals and Nutraceuticals. The Internet Journal of Aesthetic and Antiaging Medicine,Volume 2, Number 1, 2009.

118. X. Yanyu , S. Yunmei , C. Zhipeng, P. Quineng, The preparation of silybin-phospholipid complex and the study on its pharmacokinetics in rats. Int. J. Pharm., 307 (1), 2006,77-82.

119. BZB Group, Executive summary, The OSD: Oral Synchronous Drug Delivery System

120. http://chiasmapharma.com/technology.

****