

EMERGING TRENDS IN ORAL BIOAVAILABILITY ENHANCEMENT

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REVIEW ARTICLE

Talegaonkar, S*., Ahmad, Z., Tariq, M., Khan, Z. I., Negi, L. M., Khan, A. M. and Negi, P

Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard, New Delhi

*Corresponding Author's E-mail: stalegaonkar@gmail.com

ABSTRACT:

Oral route is one of the most accepted and convenient mode of drug administration, however low oral bioavailability of many drugs is a major concern which limits their oral administration. Optimum solubility and permeation of a drug across the intestinal epithelium is a prerequisite to reach the systematic circulation in the active form for effective action at the desired site. Physicochemical properties of the drug, physiological factors and pharmacokinetic factors are mainly responsible for their low solubility, low permeability and high metabolism which in turn into low oral bioavailability of the drug molecules. In this review, various factors which affect bioavailability of drugs and possible approaches to overcome this problem have been discussed. The review identifies various areas for research that can be focused for improving oral bioavailability of therapeutic molecules for different classes of drugs, thus making the oral route of administration of the drugs more effective and useful.

Key words: pKa, pH, bioavailability, Polymorph, NSAIDs, Liposomes, NEs.

Introduction

The ultimate goal of drug therapy is to reverse a disease condition by eliciting a pharmacological response. For this to happen, the drug molecule must enter the systemic circulation and reach the desired receptor site. To achieve the intended goal, drugs can be administered via various routes like oral, Parenteral, transdermal, topical, rectal and vaginal etc. Out of these, oral drug delivery system is the most preferable and convenient system due to patient compliance. It has received most attention due its flexibility in dosage form design in comparison to other route. Currently, more than 60% of the marketed products are intended for oral use. However, oral route of administration has got its own limitation because of pH variability and structural diversity throughout the gastro intestinal tract that affects the absorption of the drugs consequently resulting in decreased bioavailability. (1-4) It is further hampered by physicochemical properties of drugs itself leading to poor solubility, poor penetrability or poor permeability or both. (5) Oral

administration of many drugs is limited by their poor penetration across intestinal barrier. In addition, intestinal permeability of the drug could also be a very important factor because it is the major site of absorption. Intestine performs two major functions that are contradictory in nature. It provides the platform for efficient absorption of nutrients, fluids and electrolyte and drugs, simultaneously, it expulses the potentially antigenic or toxic inflammatory substances that can be a therapeutically active agent. The ability of the intestinal epithelium to provide a barrier to the absorption of these potentially harmful compounds is often referred to as permeability. In this aspect P-glycoprotein (P-gp)-mediated efflux plays a vital role. High first pass metabolism (gastric, intestinal and hepatic first pass metabolism) of drugs is another factor which limits the oral administration of drugs. (6-8) Various factors which influence the bioavailability of drug after oral administration have been summarized in table 1.

Table: 1 Factors affecting oral bioavailability of drugs

Physicochemical properties	Physiological factors	Pharmacokinetic Factors
Solubility and Lipophilicity	GI motility	GI and liver metabolism

pKa of drugs and pH of GIT	Stomach emptying	Distribution & elimination
Molecular size and shape	Disease state	
Hydrogen-bonding Potential		
Particle size and Dissolution rate		
Crystal form (polymorphism)		

Physicochemical Properties

It reflects the intrinsic properties of drugs which impart a vital role in absorption of drugs subsequently bioavailability. Various physicochemical properties which affect the bioavailability of drugs are discussed below:

Solubility and Lipophilicity

An important prerequisite for the absorption of a drug by all mechanisms except endocytosis is that it must be present in solution form (molecular form). This in turn depends on the drug's aqueous solubility. Drug's aqueous solubility depends on the intrinsic solubility which can be defined as the maximum amount of drug which dissolves in a constant volume of solvent under standard condition of temperature, pressure and pH. Highly hydrophilic drugs fulfill one requirement i.e. they are available in solution form however they are unable to cross the GI membrane due to the low permeability. Therefore, lipophilicity of drugs is also an important factor that affects the absorption of drugs in GIT. It governs the partitioning of the drug from aqueous solvent to the lipoidal membrane subsequently effecting absorption. Hence, a drug candidate must have optimum hydrophilic and lipophilic nature for efficient oral absorption. As a general rule of thumb, $\log P$ value of 2 – 3 provides a good balance with respect to solubility and permeability.(9)

Degree of ionization (pKa) and pH of GIT

Most of the drugs are either weak acids or weak base. The amount of drug that exists in unionized or ionized form is a function of dissociation constant (pKa). The degree of ionization as well as solubility of drugs depends on the pH of the surrounding solvent at the absorption site. It is a fact that unionized form of drug is more lipophilic in nature and gets absorb more than its ionized form. Therefore, pKa and pH at the site of absorption highly

influence the absorption of drugs. Weak acidic drugs (pKa>8) remain unionized throughout the GIT and shows pH independent absorption ex. barbiturates. Mild acidic drugs (pKa 2.5-7.5) such as NSAIDs are greatly affected by pH, as they largely exist in ionized form in acidic pH and get absorbed more in the stomach. Strong acidic drugs (pKa<2.5) are remain poorly absorb as they remain in ionized form throughout the GI tract. Similarly weak basic drug (pKa<5) like benzodiazepines are remain unionize throughout GI tract and shows pH independent absorption. Mild basic drugs (pKa 5-11) are mainly absorbed at basic condition i.e. in the small intestine. Similar to strong acidic drugs, strongly basic drugs (pKa> 11) also remain ionized throughout the GI tract and are poorly absorbed.(10-12)

Molecular weight and size

Compounds of molecular weight ≤ 500 are primarily transported across the bio-membrane by passive diffusion. The drug to be permeable across the intestinal epithelium should have molecular weight less than or equal to 500. However, compounds having molecular weight greater than 500 are usually absorbed through carrier mediated transport. The carriers have special affinity for certain drugs of specific chemical structure only. Therefore, molecular weight, size and chemical structure are important factor for carrier mediated transport. (12, 13)

Hydrogen-bonding potential

Hydrogen bonding potentially describes the polarity of the drug which is measured by the number of H-bond acceptors and number of H-bond donors of the molecule. For optimum absorption number of H-bond acceptors should be less than or equal to 10 and number of H-bond donors should be less than or equal to 5. (14-15)

Particle size and dissolution rate

The rate at which the drug enters the aqueous solvent is known as dissolution rate. It is an important parameter for drugs of low solubility (class 2 and class 4 drugs). The dissolution of drug is the primary requirement for the absorption of the drug because before being absorbed the drug has to be in molecular form in the aqueous solvent. Particle size and surface area are inversely related to each other. Smaller the particle size, greater is the surface area. Reduction in particle size leads to an increment of surface area. Greater the surface area, more intimate is the contact between the particle and the aqueous solvent, resulting in higher dissolution rate. The dissolution rate of the drug can be modified by using various fabrication techniques consequently enhancing the bioavailability of drugs.(13,16)

Polymorph

Depending upon the internal structure solids can exist in many forms i.e. crystalline or amorphous. The state in which a crystalline solid exist in more than one form is termed as polymorph which differ in their physical properties like solubility, melting point, hardness and compression characteristics. Polymorph may exist in stable and metastable forms. A stable form possesses lowest energy and low aqueous solubility and high melting point while metastable forms show opposite properties. As different polymorphic form show different solubility, therefore, polymorphic form of drug imparts a great role on its bioavailability For example riboflavin exists in polymorphic form I and III. Form III is 20 times more soluble than form I and more bioavailable. (17-19)

Physiological Factors

Physiological factors are those which are dependent on the physiological condition of the gastro intestinal tract of the patient. They differ greatly from patient to patient according to age, sex, disease condition etc and affect the bioavailability of drugs. They are as following;

Stomach emptying

The stomach is a bag-like organ lined with a relatively smooth epithelial surface. After ingestion of the oral dosage form, stomach is

the place where it reaches and starts releasing the drug from the dosage form unless it is not an enteric coated or a pH sensitive dosage form. Few mild acidic drugs like aspirin are absorbed from the stomach. Although drugs can be absorbed from it, however the contribution of this organ in absorption of drugs is modest. The time spent in the stomach and the amount of drug released in the stomach has a prominent influence on the drug absorption. It is a rate-limiting step in controlling drug absorption. Stomach emptying is complex and is controlled by nervous and hormonal stimuli. It also affected by fed and fasted state. It is a function of rhythmic contractions; its usual frequency is approximately three per minute in a fasted person, and less when food enters the stomach. Food passes from the stomach into the duodenum as a result of these rhythmic contractions. The heavier the meal and the higher the fat content, the longer time to absorb meal as well as drugs ingested with it. (19, 20)

GI motility

Absorption of drug is greatly influenced by GIT motility. GIT motility is responsible for gastric transit time. Any compound or physiological or pathological conditions that increases or decreases the GIT motility may have influence on the drug absorption. There are many compounds that affect the intestinal motility like Anticholinergics drugs retard GI motility and promote absorption of drugs such as ranitidine and digoxin, while decreasing the absorption of Paracetamol and Sulphamethaxazole. Metoclopramide promotes GI motility and enhances absorption of tetracycline, Pivampicillin and levodopa. From the above discussion it can be concluded that GI motility may increase or decrease the absorption. In addition, co-administration of drugs may synergize or antagonize the absorption of each other. (19, 20)

Disease state

There are several diseases which can alter the GI motility, rate of gastric emptying, impair the metabolism, and blood circulation to the organs. It is well known all these states can alter the rate and extent of absorption and consequently bioavailability of drugs. Gastrointestinal, cardiovascular, hepatic diseases are major class

of disease which affects the bioavailability of drugs.

In the earlier section the effect of rate of gastric emptying and GI motility on drug absorption have been discussed. Most of Gastrointestinal diseases alter the gastric emptying and GI motility which influence the rate of absorption of drugs and hence bioavailability. Gastroenteritis, gastric ulcer, pyloric stenosis retard the gastric emptying while gastrectomy duodenal ulcer promote gastric emptying. The state of achlorhydia reduces the absorption of acidic drugs like aspirin. Steatorrhea impairs the bile acid secretion which affects the absorption of lipophilic drugs and vitamins. Celiac disease characterized by destruction of villi and microvilli and abnormalities associated with it are increased gastric emptying and GI permeability which affect the drug absorption and metabolism. Crohn's disease is associated with altered population of gut wall microflora, reduced gut surface area and intestinal transit rate which are responsible for altered absorption of drugs. Cardiovascular diseases may results into intestinal oedema, reduced GIT blood circulation, altered gastric emptying, pH, secretion and microflora which impair the absorption of drugs. Hepatic disease influence the metabolism of drugs subsequently bioavailability, the drugs which undergoes considerable first pass hepatic metabolism showed improved bioavailability in hepatic disease state. Enhanced oral bioavailability of propranolol was observed in hepatic cirrhosis. (21-22)

Pharmacokinetic Factors

A number of drugs are there which have favorable physicochemical properties for oral administration still suffer from low bioavailability problem most probably due to the pharmacokinetic factors. For example remoxipride gets absorb rapidly and completely through the intestinal wall. However, the bioavailability was low in the rodents (< 10% in mice and hamsters and < 1% in rats) due to extensive first pass metabolism. (12)

GI and liver metabolism (first pass effect)

Metabolism of a drug can either inactivate an active drug or convert an inactive drug into active metabolite. Metabolic alteration of a drug

can occur in a variety of tissues consequently altering the pharmacokinetics. The drug administered orally, before reaching the systematic circulation has to pass through organs of elimination namely GIT and the liver. The loss of drug through biotransformation by such eliminating organs during its passage to systematic circulation is called as first pass or pre-systemic metabolism. Drugs which are substrate for first pass effect either in the lumen or tissue of the intestine or liver show reduced oral bioavailability. (23) Important factors responsible for reduced bioavailability are:

Luminal enzymes

- a) Digestive enzymes
- b) Bacterial enzymes

Gut wall/ mucosal enzymes

Hepatic enzymes

Most of orally administered compounds get absorbed from the stomach and intestines enter the splanchnic circulation subsequently to the portal vein, then liver followed by general circulation. Therefore, a large fraction of any orally administered drug that is highly susceptible to liver metabolism will be cleared during the initial first pass. Drugs like acebutolol, alprenolol, desipramine, isoproterenol, and lidocaine get efficiently absorbed from the GI tract and yet poorly available to the general circulation as a consequence of first-pass hepatic clearance. (19,23)

Distribution and elimination

When drug molecules come in systemic circulation it gets exposed to a number of processes called as "disposition process". It tends to lower the plasma concentration of drug. The two major drug disposition processes are distribution and elimination. Distribution which involves reversible transfer of a drug between compartments and elimination involves irreversible loss of drug from the body. Pharmacological action of a drug depends upon its concentration at the site of action. Therefore, distribution and elimination play a significant role in onset, intensity and duration of action. (24)

Approaches to enhance oral bioavailability

With the advancement of new technologies in pharmaceutical sector it has become more prominent that innovation of new molecules only is not sufficient to ensure effective therapy. Often there is failure in drug therapy due to one or more of the following. (25)

1. Poor bioavailability due to poor absorption, rapid metabolism and elimination.
2. Drug distribution and accumulation to particular organ or tissue leading to drug toxicity (e.g. anticancer agent).
3. Poor drug solubility excluding the I.V. formulation of aqueous solutions.
4. Unpredictable fluctuation of drug plasma concentration after peroral administration (e.g. cyclosporine).

Approximately 40% of new drug candidates are restricted to parenteral administration because of their low oral bioavailability, high intra- and inter-subject variability, and a lack of dose proportionality. (26) Therefore, enhancement of oral bioavailability, to maintain the drug concentration within the therapeutic window which is required to suppress diseased conditions, is a great challenge to pharmaceutical industries. A suitable drug delivery system has to be developed to enhance the bioavailability of the active pharmaceutical agent. Same active moiety can be used in different ways by changing the drug delivery system. Approaches that can be applied for the enhancement of oral bioavailability are broadly divided into three categories (**Table 2**).

Table: 2 Approaches for the oral bioavailability enhancement

Physical Methods	Chemical Methods	Biological Methods
Complexation Micronization Solid dispersion Colloidal Carrier	Pro-drug Approach Polymer conjugates	By P-gp Modulation By P-gp inhibition By passing CYP450
Lipid based colloidal carrier Liposome SLN SMEED SNEDDS Microemulsion Nanoemulsion NLC	-----	-----
Polymer based colloidal carrier Nanospheres Nanocapsules Dendrimers Polymeric micelles	-----	-----
Surfactant based colloidal carrier Niosomes		
Miscellaneous Nanosuspension Nanocrystal	-----	-----

Physical Methods

Physical methods employ various techniques to improve the solubility of the drug in biological fluid to improve the absorption of the drug through the intestinal epithelium. These

methods particularly deal with the drug's physicochemical properties and fabrication of dosage form.

Complexation

Complexation involves the interaction between two or more molecules to form a non-bonded entity. The most commonly used complex to increase the solubility of drugs in aqueous media are stacking and inclusion. Stacking complexes are formed by the overlap of the planar regions of aromatic molecules, while inclusion complexes are formed by the insertion of the non-polar region of one molecule into the cavity of another molecule. (27) It is a well known fact that solubility of compounds directly affects their bioavailability. Complexation has a long history to improve oral bioavailability. Naringenin showed a wide clinical application however, its clinical relevance is limited by its low solubility and minimal bioavailability owing to its largely hydrophobic ring structure. Its complex with β -cyclodextrin have been investigated to improve the bioavailability. β -cyclodextrin-Naringenin complex demonstrated 400 fold enhanced solubility of Naringenin and 7.4 fold higher bioavailability. (28)

Micronization

It is well known fact that drug solubility directly affects the rate of absorption of drugs consequently effecting bioavailability. (29) The drugs belonging to BCS class II pose dissolution rate as a rate limiting step in absorption of drugs. (30) Improvement in the dissolution rate of these drugs can increase the plasma drug concentration up to a clinically suitable level. Particle size reduction can be an effective approach to enhance the dissolution rate due to enhanced total surface area which results in improved absorption. (31) Several methods for particle size reduction have been suggested including milling, grinding and micronisation. However, non-uniformity in particle size is a problem associated with grinding and milling. (32) Micronisation is a most common method for particle size reduction of hydrophobic drugs. (33) It is a suitable technique to achieve particle size less than 10 microns. *Chaumeil* described the improvement in dissolution rate and bioavailability using micronization technique of many sparingly water soluble drugs. (34) Gliclazide (GL) is a second-generation

sulfonylurea, widely used for the treatment of non-insulin-dependent diabetes mellitus. It has a low solubility in water (55 mg/L) as well as in gastric fluids, a common characteristic of this group. Due to low dissolution rate; it showed inter-individual variability. (35-36) Rasenak and Müller prepared microcrystal by using micronisation techniques employing stabilizing polymer which covers the hydrophobic surfaces of the precipitated substances and prevents the crystal growth. Developed microcrystal showed an improved oral absorption and pharmacokinetic profile. It can be concluded that micronization is an effective approach for the oral bioavailability enhancement of BCS class II drugs.

Solid dispersion

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous and drug can be dispersed in it in the molecular form. (37) It is the technology that is used to enhance the oral bioavailability of drugs which are poorly water-soluble and highly permeable to biological membranes as these drugs show dissolution rate as a rate limiting step. Hence, it can be hypothesized that rate of absorption will be concurrently accelerated with an increase in the rate of drug dissolution. The solubility or dissolution of poorly water soluble drugs can be improved by changing the physical state, wettability, porosity and particle size. Solid dispersion techniques are able to bring all the above mentioned changes in the drugs. Karavas et al., reported a strong contribution of drug wettability in enhancement of drug solubility. (38) Carrier like urea, cholic acid and bile salt are reported to improve dissolution profile by increasing wettability of drugs. (39-41) In addition particles porosity has a profound effect on the drug solubility. Solid dispersions have been found to have a higher degree of porosity and increased porosity hastens the drug release profile. (42) Further, it was also observed that solid dispersion brings changes in the physical state of drugs i.e. conversion of crystalline form into amorphous. (43-44) The enhancement of drug release can usually be achieved by converting the crystalline drugs into amorphous

state, because no energy is required to break up the crystal lattice during the dissolution process. (45) In addition, solid dispersions forms a supersaturated solution after its dissolution and it is speculated that, if drugs get precipitate, it turn into a metastable polymorphic form with higher solubility than the most stable crystal form. (38,46) Solid dispersion is also termed as molecular dispersion because drugs are dispersed in molecular form into the matrix which represents last state of particle size reduction. After dissolution of carrier, drug directly converts into the molecular form that is the prerequisite for the absorption of drugs. It can be concluded that mixing of poorly water soluble drug into water soluble matrix enhances the dissolution rate consequently, improving bioavailability.(41,46)

Colloidal systems

The term colloid refers to a state of subdivision, implying that the molecules or poly-molecular particles dispersed in a medium have dimension in one direction in the range of 1-1000 nm. Recently, the physicochemical properties of colloidal systems are exploited in pharmaceuticals for various purposes. Various studies have been revealed that oral bioavailability of drugs can be enhanced significantly by nanoparticulate systems such as liposome, niosome, nanoparticles, solid lipid nanoparticles, nanoemulsions, self micro or nanoemulsifying systems and dendrimers etc. These systems are able to incorporate both lipophilic and hydrophilic drugs. The enhanced oral bioavailability might be attributed to protection of drug from hostile environment of GI tract, release of drug at the surface of enterocytes or at the tight junction of intestinal epithelia, avoid the recognition by P-gp and cytochrome P-450 and endocytosis of encapsulated vector via enterocytes or M cells of Peyer's patches at the intestinal lymphatic tissues. (47-49) These systems are described below.

Liposomes

Liposomes are lipoidal spherical vesicle with a membrane composed of a phospholipid bilayer used to deliver drug or genetic material into cells. It is under extensive investigation as drug carriers for improving the delivery of

therapeutic agents. It is composed of phospholipids that combine with water molecules and immediately forms a vesicular structure because one end of each molecule is water soluble, while the opposite end is water insoluble. Water soluble medications are added to the aqueous phase that traps inside central aqueous core while the fat soluble medications are added into the lipids which get entrap into the phospholipid layers.

Currently, liposomes are being investigated to enhance oral bioavailability. It interacts with intestinal epithelial cells by different mechanisms that are responsible for its intracellular uptake that results into enhancement of oral bioavailability. First it interacts with the cell surface either by nonspecific weak hydrophobic or electrostatic forces or by specific interactions with cell-surface components then fusion with the plasma cell membrane by insertion of the lipid bilayer of the liposome into the plasma membrane, with simultaneous release of liposomal content into the cytoplasm that leads to transfer of liposomal contents or uptake of liposome.(50) Sun et al., reported a 9.76 fold increment in oral bioavailability of Hexamethylmelamine incorporated into the liposomes than its free drug solution. (51) Curcumin is associated with low oral absorption or bioavailability problem; however liposome-encapsulated curcumin showed faster and better absorption of curcumin as compared to the other forms. Oral administration of liposome-encapsulated curcumin showed higher C_{max} and shorter T_{max} values, as well as a higher value for the area under the plasma concentration-time curve (AUC), at all time points i.e high bioavailability of curcumin. (48) Improved oral bioavailability of cyclosporine A was also reported by using liposome as a carrier. (49)

Niosomes

A novel drug delivery system is composed of a bilayer of non-ionic surface active agents and hence the name niosomes. A typical niosome usually comprises of vesicle forming amphiphile i.e. a non-ionic surfactant such as Span-60, which is usually stabilized by addition of cholesterol and a small amount of anionic surfactant such as diacetyl phosphate. Diacetyl

phosphate also acts as a charge inducer and also helps in stabilizing the vesicle. (52) The way of drugs incorporation into vesicle is similar to liposomes. Niosome is an alternative delivery system equivalent to liposome in term of size, shape and structure with several obvious advantages like being less expensive than liposome. Phospholipids, the heart of liposome are chemically unstable because of their susceptibility to oxidative degradation and hence special storage and handling. In addition purity of natural phospholipids varies from source to source. Niosomes are free from above mentioned shortcoming but retains the functionality similar to liposomes. Like liposomes, niosomes also increase the bioavailability of the drug and reduce the blood clearance. Recently niosome are being investigated to improve transdermal delivery, targeting of drugs and improvement of oral bioavailability. Niosomal preparation of Grieseofulvin, a poorly water soluble drug showed two fold increments in oral bioavailability in comparison of free drug solution. (47) Paclitaxel niosomal preparation showed an improved oral bioavailability as well as its better intestinal stability. (53) Therefore, niosome could be a better replacement of liposomal drug delivery systems.

Polymeric nanoparticles

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10- 1000nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation either nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen.

It has been found that the size of the nanoparticles plays a key role in their adhesion

to and interaction with the biological cells. The possible mechanisms for the particles to pass through the gastrointestinal (and other physiological) barriers could be (1) paracellular passage— particles “kneading” between intestinal epithelial cells due to their extremely small size, endocytotic uptake—particles absorbed by intestinal enterocytes through endocytosis and lymphatic uptake—particles adsorbed by M cells of the Peyer’s patches. (54) Various studies have revealed the potential of polymeric NP in oral bioavailability enhancement. The apparent permeability (Papp) of paclitaxel (PTX) was found to be 12-fold higher in PTX-HPCD NP than as compared to Taxol® (control). (55) When the anticancer agent 5-fluorouridine, substrate of the CYP3A4 was encapsulated in these nanoparticles, the resulting bioavailability was found to be approximately 80%. (56) The doxorubicin loaded nanoparticles demonstrated superior performance in vivo as evident by enhanced bioavailability and lower toxicity. (57) Tamoxifen (Tmx), an anticancer agent is commercially available as tablet and oral solution dosage form. However its citrate salt showed poor oral bioavailability (20-30%). However, Tmx loaded PLGA NPs showed 3.84 and 11.19 fold increased oral bioavailability as compared to the free Tmx citrate and Tmx base, respectively. In vivo oral antitumor efficacy of Tmx-NPs was carried out in DMBA induced breast tumor model and tumor size was reduced up to 41.56% as compared to untreated groups which showed an increase in tumor size up to 158.66%. In addition Tmx-NPs showed the marked reduction in hepatotoxicity when compared with free Tmx citrate. (58) The data above discussed revealed the potential of polymeric NPs in oral bioavailability enhancement as well as to reduce toxicity of drugs.

Nanoemulsions and microemulsions

NEs are a group of dispersed particles used for pharmaceutical and biomedical aids and vehicles that show great promise for the future of cosmetics, diagnostics, drug therapies, and biotechnologies. NEs can be defined as oil-in-water (o/w) emulsions with mean droplet diameters ranging from 50 to 1000 nm. Usually, the average droplet size is between 100 and 500

nm. The particles can exist as water-in-oil and oil-in-water forms, where the core of the particle is either water or oil, respectively. The main application of NEs is in the preparation of nanoparticles using a polymerizable monomer as the disperse phase (the so-called miniemulsion polymerization method) where NE droplets act as nanoreactors. Another interesting application which is experiencing an active development is the use of NEs as formulations, namely, for controlled drug delivery and bioavailability enhancement through transdermal and oral route. Vyas et al investigated potential of NEs as a carrier for oral administration of saquinavir, the drug concentration was observed 3 fold higher in the systematic circulation. (59) Similarly, oral bioavailability of colchicine increased by 1.6 times when co administered with eugenol in comparison to free colchicine solution while it was increased by 2.1 times when administered in nanoemulsion dosage form. (60)

Self emulsifying drug delivery system

Self-emulsifying drug delivery systems (SEDDS) are one of the lipid formulations which represent an attractive alternative to orally administered emulsions since they are physically stable lipid solutions or dispersions. (61) SNEDDS are isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, and, alternatively, one or more hydrophilic solvents and co-solvents/surfactants. (62) Drug substances with adequate solubility in lipid/surfactants/co-solvent (or co-surfactant) blends are candidates for this formulation concept. SEDDS spread readily in the gastrointestinal tract, while the digestive motility of the stomach and intestine provides the agitation necessary for self-emulsification–dispersion process. Benita *et al.* described SEDDS as systems that produce emulsions with a droplet size between 100 and 300 nm while self-microemulsifying drug delivery systems (SMEDDS) form transparent microemulsions with a droplet size less than 50 nm. (62)

Generally, SEDDS are either administered as liquid dosage forms or incorporated in a soft gelatin capsules. However, it is a fact that solid dosage forms are preferred more than liquid preparations for many reasons including:

facility of manufacturing process, convenience to the patient, accuracy, and stability. Incorporation of lipid formulations into solid dosage forms combines the advantages of lipid-based drug delivery systems with those of solid dosage forms thus overcoming the drawbacks of liquid formulations. Some trials were made to formulate liquid SEDDS into solid dosage forms. (63-65) One of the most known techniques, liquid compact, is used to transfer liquid medication into acceptably flowing and compressible powders. Exemestane which has problem of limited solubility was formulated in self microemulsion drug delivery system (SMEDDS) to enhance its solubility and oral bioavailability. The absorption of exemestane from SMEDDS resulted in about 2.9-fold increase in bioavailability compared with the suspension. (66) Mahmoud et al prepared SNEDDS of transcutool HP containing carvedilol and evaluated its P-gp activity on Human colon carcinoma cells (HCT-116). There was decrease in the IC₅₀ indicating the inhibition of P-gp activity which may lead to a decrease in carvedilol efflux from the intestinal cells with consequent improvement in its absorption. (67) Oral bioavailability of valsartan SMEDDS was evaluated for its oral bioavailability by using rabbit model. The AUC and T_{max} were found to be 607 ng h/mL and 1 h revealing significant improvement for SMEDDS in comparison to 445.36 and 1.36 h for market formulation suggesting significant increase ($p < 0.01$) in oral bioavailability of valsartan. (68)

Solid lipid nanoparticles

Solid Lipid Nanoparticles (SLN) is one of the most emerging systems for drug delivery. Both hydrophilic and lipophilic drugs can be incorporated in this system. SLN consist of solid core of lipid with drug either dissolved or dispersed in the matrix. The release of the drug is in a time dependent manner from the matrix by lipid partitioning of the drug or hydrolysis of lipid when given orally. Use of solid lipid matrices in sustained drug delivery has been well established for many years. Literature review showed that, solid lipid nanoparticles might prolong the release of drug. SLN have shown a prolonged in vitro release of prednisolone for up to 5 weeks which made it a

potential candidate to achieve long-term treatment. Sufficient data implicates that bioavailability of poorly water soluble drugs can be improved when these drugs are encapsulated in lipid-base vehicles and given by the peroral route. Various molecules like clozapine, nitrendipine, quecetin and vinpocetin were investigated for their oral bioavailability enhancement via SLN, 3-5 fold enhancement in oral bioavailability was observed when clozapine, nitrendipine, quecetin and vinpocetin were administered in the form of SLN. (69-72)

Dendrimers

Dendrimer is a repetitively branched molecule, typically symmetric around the core, and often adopts a spherical three-dimensional morphology and are monodisperse in nature. It can be roughly divided into low-molecular and high-molecular weight species. The characteristics of dendrimers mainly depend on functional groups on the molecular surface, however, in some cases it depends on internal functionality. Dendrimers have a very compact structure and high surface charge density, therefore dendrimic polymers can be modified to permeate across intestinal epithelial membrane. Polymers like poly(lysine), and poly(amido amine), are the most commonly used polymer for dendrimer preparation and have been observed to cross g.i.t. epithelium, making them a promising carriers for oral drug delivery.

PAMAM dendrimers have been studied most widely for oral drug delivery system. PAMAM dendrimers have an ethylene diamine core and amido amine branching structure. In each step ethylene diamine and methacrylic acid attach covalently to each other alternatively forming a radiating structure. It has a very open internal structure which makes it suitable to trap drug molecules and surface charge of dendrimer play a vital role in uptake by intestinal epithelia. Ke and co-workers investigated the PAMAM dendrimer for the oral delivery of doxorubin and reported 300 fold increased in bioavailability. (73)

Chemical Approaches

Chemical modification in the drug molecules or the formulation surface can have a very

prominent effect on the absorption of the drug and bioavailability.

Prodrug approach

A prodrug, chemically modified inert drug precursor, can be used to modify the solubility and permeability which upon biotransformation liberates the pharmacologically active parent compound. Basically, prodrug is an approach which was developed in concern of optimization of drug delivery. Prodrug is a result of covalent linkage between pro-moiety to the active moiety, that is designed to overcome the barriers which restricts the optimal use of the active principle. Most drugs are absorbed by passive diffusion for which lipophilicity is an important prerequisite. A big advantage of increased bioavailability through increased lipophilicity is the reduction in dose. Bacampicillin is as more lipophilic congener of ampicillin which is more effective in just one-third of the dose of ampicillin. Palmitate, acetate and maleate esters of chloramphenicol, tocopherol, and enapril respectively were found to be more bioavailable in comparison their respective parent drugs. (74-76)

Polymer Conjugates

Various studies have revealed that colloidal drug delivery systems have a great potential for effective delivery of drugs. However, it suffers from low retention time in GI tract which reduces its efficacy. It would be advantageous to increase the retention time that will lead to increment in intracellular uptake i.e. oral bioavailability. Modification of the polymers or the surface of the formulation by substance like PEG or lectin enhances intracellular uptake i.e. absorption of the drug. This may be attributed to the increased gastric transition time and hydrophilic surface which increases the wettability and penetrability of the systems. Another approach is specific and nonspecific bioadhesion to overcome low transit time of delivery systems in GIT by exploiting a receptor mediated process within gastrointestinal tract. (77) Poor bioadhesion of conventional nanoparticles, binding and uptake into intestinal cells may be facilitated by surface modification with lectins, which occur widely in nature and have the unique ability to recognize and bind to specific carbohydrate

residues intestinal cells. (78) Numerous studies have established the ability of lectins to bind to intestinal mucosa and their ability to enhance the intestinal uptake of orally administered particles. (78-84) Yin et al prepared lectin conjugated PLGA nanoparticles and reported 1.4–3.1 folds more uptake across the intestine compared to the unconjugated ones. Fluorescence microscopy further elucidated that the binding sites of WGA-conjugated nanoparticles were ubiquitous, from the non-lymphoid villous tissue to Peyer's patches. (85) The surface engineering of nanoparticles with

lectins opens a receptor-mediated pathway for oral uptake of nanoparticles which can improve the cytoadhesion as well as cyto-invasion of nanoparticles which in turn to improved oral bioavailability. (86)

Biological Approach

There are certain proteins (P-glycoproteins) and enzymes (Cytochrome 450) which hamper delivery of drug across the intestine. Biological methods are those which emphasize on the inhibition of enzymes or proteins or by pass these enzymes or proteins (Fig 1).

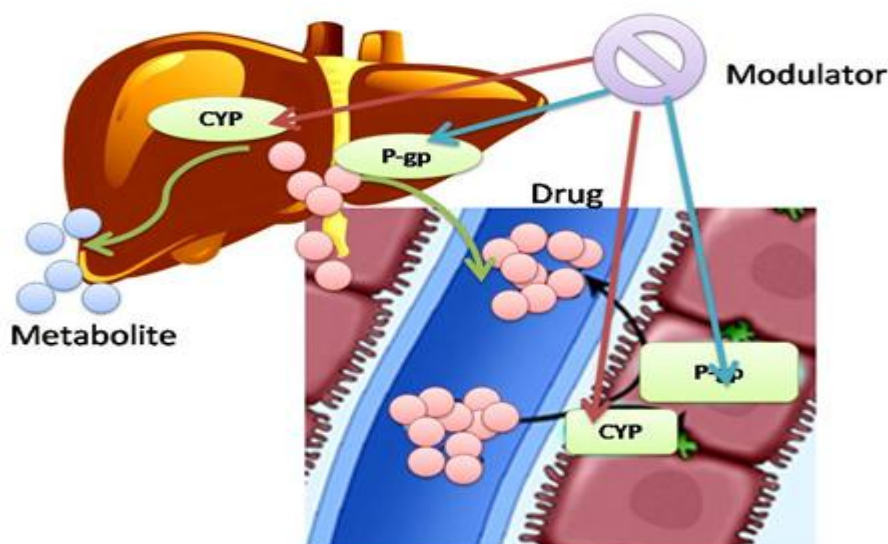


Fig1. Biological methods to increase oral bioavailability

P-glycoprotein inhibition or modulation

Classic multidrug resistance (MDR) is attributed to the elevated expression of the ATP-dependent drug efflux pumps ABCB1 (Pgp), ABCC1 (Multidrug resistance associated protein) and ABCG2 (Breast cancer resistance protein). P-glycoproteins is a member of the ABCB transporter subfamily. It mediates the ATP-dependent export of drugs from cells. It is expressed in the luminal membrane of the small intestine and blood–brain barrier, and in the apical membranes of excretory cells such as hepatocytes and proximal tubular epithelia of kidney, at pharmacological barrier sites, in adult stem cells and in assorted cells of the immune system. (86-88) P-gp has an important role in limiting entry of various drugs into the central nervous system. In addition, it also plays a role in the intestinal absorption and in the biliary and urinary excretion of drugs. The level of

expression and functionality of P-gp can be modulated by inhibition and induction, which can affect the pharmacokinetics, efficacy, safety or tissue levels of P-gp substrates drug molecules. (89-94)

In this prospect, a lot of effort has been made in order to find suitable Pgp-inhibitors to enhance the oral bioavailability, but either due to their poor modulatory activity, toxicity at high concentration, or unpredictable pharmacokinetic interactions in the presence of chemotherapeutic agents. (95-99) only a few significant advances have been made. Clinical trials with 3rd generation Pgp-inhibitors developed specifically for MDR reversal are ongoing but a number of investigations have demonstrated that they also display cross-reactivity at least with MXR and drug-metabolizing enzymes. (100)

There are numerous pharmaceutical excipient such as Tweens, Triton X-100, Cremophor EL,

PEG 400, Pluronic, benzyl alcohol, chloroform and diethyl ether have been reported to have P-gp modulating activity. (101-104) Pluronic P85, chloroform, benzyl alcohol, Tween-20, Nonidet P-40 and Triton X-100 inhibits the ATPase activity of Pgp located in either microsomes or reconstituted vesicles. (105) Pluronic block copolymers, benzyl alcohol, chloroform and various non-ionic detergents accelerate passive movement of doxorubicin across artificial membranes. (106, 107) It has been assumed that anesthetics and nonionic detergents modulate P-gp mediated MDR by inhibition of P-gp. (101) In our laboratory, SMEDD formulations for different anticancer drugs, based on Pgp modulation by using excipient having P-gp modulation activity, have been developed and showed many fold higher oral bioavailability. (108-109) These studies revealed that the bioavailability of drugs can be improved by pgp modulation.

Bypass cytochrome P450

The cytochrome P450 superfamily (officially abbreviated as CYP) is a large and diverse group of enzymes. The function of most CYP enzymes is to catalyze the oxidation of organic substances. The substrates of CYP enzymes include metabolic intermediates such as lipids and steroidal hormones, as well as xenobiotic substances such as drugs and other toxic chemicals. CYPs are the major enzymes involved in drug metabolism and bioactivation, accounting for about 75% of the total number of different metabolic reactions. Unfortunately, the

oral bioavailability of many drugs is extremely low in animals and humans. This is mainly due to the effect of the multidrug efflux transporter P-glycoprotein (P-gp) and its affinity for the intestinal and liver cytochrome P450 metabolic enzymes. (110, 111) In spite of effective permeation of the drug, the bioavailability is poor due to hepatic first pass metabolism. Certain drugs also cause acute hepatic and systematic toxicity due to their metabolites after liver metabolism. Many approaches have been suggested to bypass first pass metabolism of the drug after its oral administration. One is the absorption through the lymphatic system. Lipophilic drugs in oils and lipids are absorbed through lymphatic system and thus avoid first pass metabolism. Other lipidic formulation SMEDDS, SNEDDS, nanoemulsion, and microemulsion follow similar mechanism of absorption and are of interest for improving bioavailability through lymphatic absorption. Another approach is the direct inhibition of CYP to enhance the bioavailability. Simvastatin and cyclodextrin have been reported to have P-gp and CYP inhibition property. 27-33 fold increment in oral bioavailability of paclitaxal was reported using paclitaxal-cyclodextrin complex NPs. (112)

Following aforementioned approaches, a number of studies have been performed in an attempt to bring injectables into oral form. Outcomes some of the recent studies have been summarized Table 3.

Table 3: Outcomes of studies conducted for oral bioavailability enhancement

Drug	Approaches	Improved AUC/ bioavailability	Reference
Physical Methods			
Astragaloside	Complexation	4.45 Fold AUC	113
Artemisinin	Complexation	3.2 fold	114
Nobiletin	Solid dispersion	7 fold	115
Tranilast	Solid dispersion	52 fold	116
Chelerythrine	Liposome	4.83 fold	117
Alendronate sodium	Liposome	12 fold	118
Rhaponticin	PEG liposome	2.41 fold	119
Paclitaxal	Niosome	3.8 fold	120
Flurbiprofen	PACA NPs	211.63%	121
Diadzin	Zein NPs	2.64 fold	122
Albendazole	Chitosan NPs	146.05%	123

Lopinavir	SLN	3.56 fold	124
Diacerein	SLN	2.7 fold	125
Rosuvastatin	SNEDDS	167%	126
Simvastatin	Nanoemulsion	369%	127
Cefuroxime Axetil	Nanoemulsion	1.97 fold AUC	128
Puerarin	Dendrimer	1.93 Fold AUC	129
Sylibin	Dendrimer	178%	130
Chemical Methods			
Tenofovir	Prodrug	20% higher	131
Alamifovir	Prodrug	3 fold	132
Docetaxel	Polymer Conjugate	6.73 fold plasma level	133
Biological Methods			
Sulfasalazine	P-gp Modulation	2-4 Fold	134
Etoposide	P-gp Modulation	3.2 Fold	108
Camptothecin derivative	P-gp Modulation	4 Fold	109
Paclitaxel	CYP 450 inhibition	27-33 fold	112
Ditiazam	CYP 450 inhibition	1.21-1.45 fold	135

Conclusion

Various techniques are being used for successful oral administration of drugs including physical, chemical and biological. Nanoparticulate drug delivery systems offer various advantages over conventional drug delivery systems. As they provide protection along with controlled release and better pharmacokinetic profile. Currently, researchers are focused on biological methods i.e. P-gp modulation and bypass of CYP450 for bioavailability enhancement. From the results of reported studies it can be concluded that combination of both colloidal carrier systems and biological approach could be the most effective approach for bioavailability enhancement.

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