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Approaches for Enhancement of Oral Bioavailability of Oral Formulation with Special Emphasis on Absorption.

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ABSTRACT:

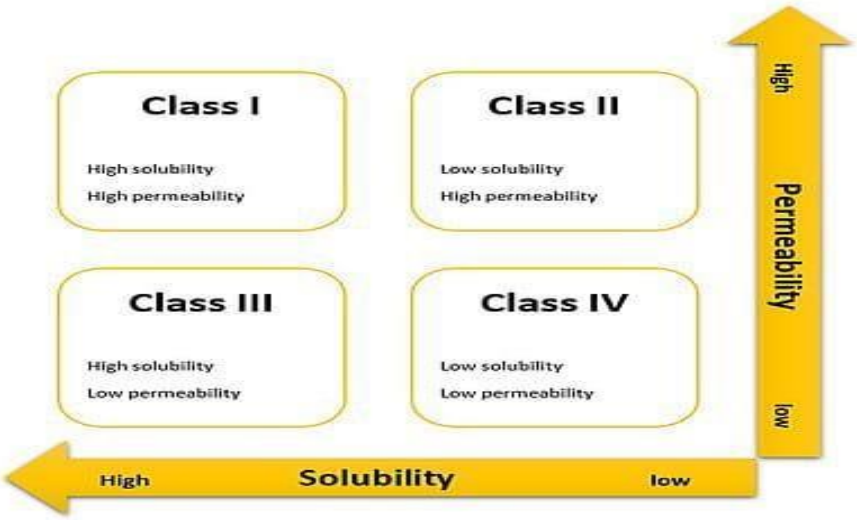
Oral dosage forms are most preferred by physician because better patient compliance and cost effectiveness but bioavailability of oral dosage form mainly depend upon absorption and metabolism of the drug if there is poor absorption and higher pre systemic metabolism then such drug are poor candidate for the formulation of the oral dosage. In the process of absorption of oral dosage there are many barrier which limit the use the oral dosage form in this article approaches regarding enhancement of oral bioavailability have been discussed with special focus on absorption

Keywords: Bioavailability, absorption, substrate, drugs, metabolism.

Introduction:

bioavailability is amount of drug reach into the systemic circulation in its unchanged form and the bioavailability of the drug is mainly depend upon the absorption and pre systemic metabolism of that drug. Drug with poor absorption is one with

1. Poor aqueous solubility leading to the poor dissolution of the drug in biological fluid
2. Poor permeability of the drug from the biological membrane this may be due to the greater molecular size of the drug such as peptide e. g insulin



The effectiveness of a drug can only be assessed by its concentration at the site of action. However, it is difficult to measure the drug concentration at such a site. Instead, the concentration can be measured more accurately in plasma. There always exist a correlation between the plasma concentration of a drug and the therapeutic response and thus, absorption can also be defined as the process of movement of unchanged drug from the site of administration to the site of measurement i.e. plasma. This definition takes into account the loss of drug that occurs after oral administration due to Presystemic metabolism or first-pass effect. Not only the magnitude of drug that comes into the systemic circulation but also the rate at which it is absorbed is important. A drug that is completely but slowly absorbed may fail to show therapeutic response as the plasma concentration for desired effect is never achieved. On the contrary, a rapidly absorbed drug attains the therapeutic level easily to elicit pharmacological effect. Thus, both the rate and the extent of drug absorption are important. Such an absorption pattern has several advantages:

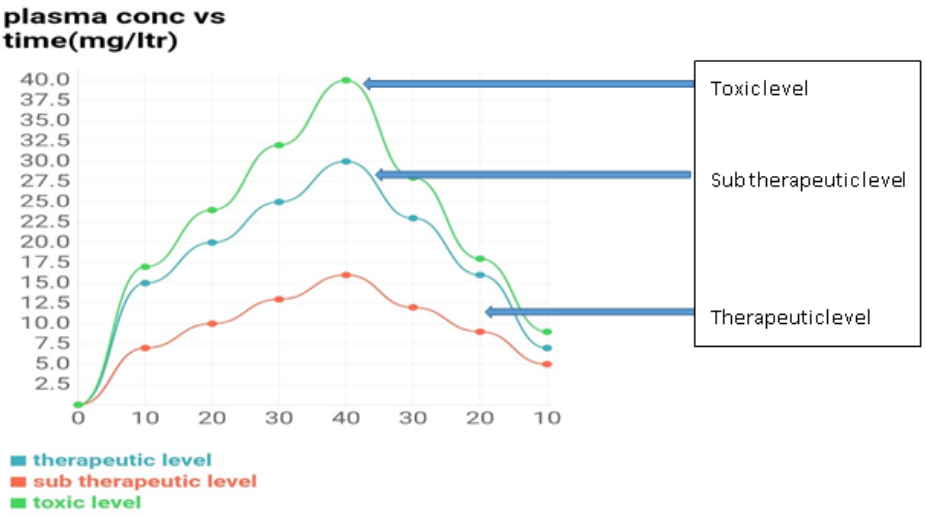
1. Lesser susceptibility of the drug for degradation or interaction due to rapid absorption.

2. Higher blood levels and rapid onset of action.
3. More uniform, greater and reproducible therapeutic response.

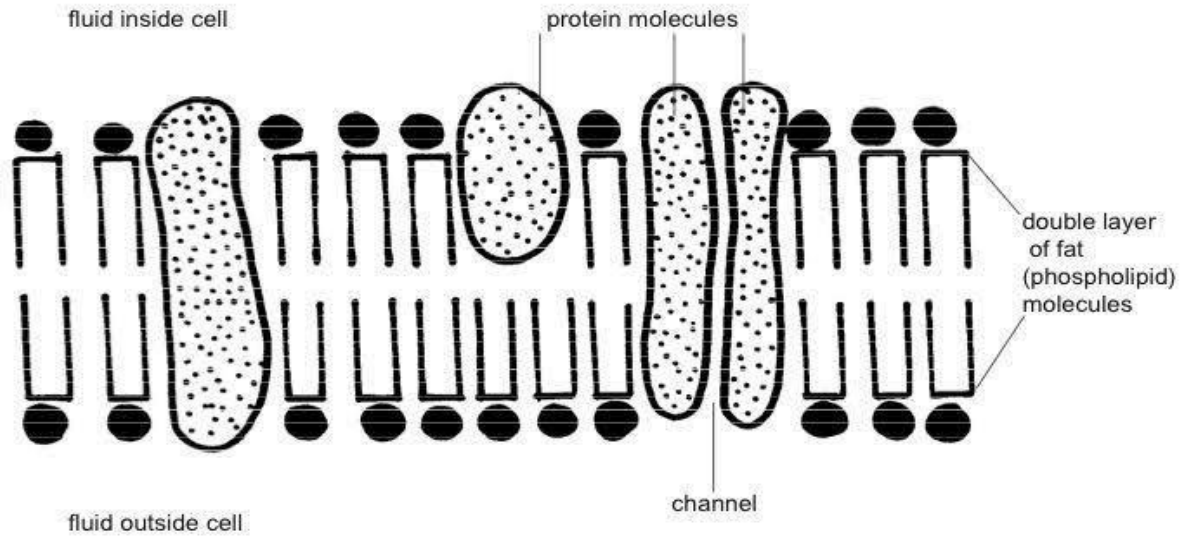
Drugs that have to enter the systemic circulation to exert their effect can be administered by three major routes:

1. The Enteral Route: includes per oral i.e. gastrointestinal, sublingual/buccal and rectal routes. The GI route is the most common for administration of majority of drugs.
2. The Parenteral Route: includes all routes of administration through or under one or more layers of skin. While no absorption is required when the drug is administered i.v., it is necessary for extravascular parenteral routes like the subcutaneous and the intramuscular routes.
3. The Topical Route: includes skin, eyes or other specific membranes.

The intranasal, inhalation, intravaginal and transdermal routes may be considered enteral or topical according to different definitions.



Cell Membrane Structure and Physiology:



Cell Membrane: Structure and Physiology

For a drug to be absorbed and distributed into organs and tissues and eliminated from the body, it must pass through one or more biological membranes/barriers at various locations. Such a movement of drug across the membrane is called as drug transport.

The cellular membrane consists of a double layer of amphiphilic phospholipid molecules arranged in such a fashion that their hydrocarbon chains are oriented inwards to form the hydrophobic or lipophilic phase and their polar heads oriented to form the outer and inner hydrophilic boundaries of the cellular membrane that face the surrounding aqueous environment. Globular protein molecules are associated on either side of these hydrophilic boundaries and also interspersed within the membrane structure. In short, the membrane is a mayonnaise sandwich where a bimolecular layer of lipids is contained between two parallel monomolecular layers of proteins. The hydrophobic core of the membrane is responsible for the relative impermeability of polar molecules. Aqueous filled pores or perforations of 4 to 10 Å in diameter are also present in the membrane structure through which inorganic ions and small organic water-soluble molecules like urea can pass. In general, the biomembrane acts like a semipermeable barrier permitting rapid and limited passage of some compounds while restricting that of others. The GI lining constituting the absorption barrier allows most nutrients like glucose, amino acids, fatty acids, vitamins, etc. to pass rapidly through it into the systemic circulation but prevents the entry of certain toxins and medicaments. Thus, for a drug to get absorbed after oral administration, it must first pass through this biological barrier.

Mechanisms of Drug Absorption

The three broad categories of drug transport mechanisms involved in absorption are –

A. Transcellular/intracellular transport

B. Paracellular/intercellular transport

C. Vesicular transport

A. Transcellular/Intracellular Transport – is defined as the passage of drugs across the GI epithelium. It is the most common pathway for drug transport. The 3 steps involved in transcellular transport of drugs are –

i. Permeation of GI epithelial cell membrane, a lipoidal barrier – this is the major obstacle to drug absorption.

ii. Movement across the intracellular space (cytosol).

iii. Permeation of the lateral or basolateral membrane- this is of secondary importance.

The various transcellular transport processes involved in drug absorption are –

1. Passive Transport Processes – These transport processes do not

require energy other than that of molecular motion (Brownian motion) to pass through the lipid bilayer. Passive transport processes can be further classified into following types –

a. Passive diffusion.

b. Pore transport.

c. Ion-pair transport.

d. Facilitated- or mediated-diffusion.

2. Active Transport Processes – This transport process requires energy from ATP to move drug molecules from extracellular to intracellular milieu. These are of two types –

a. Primary active transport.

b. Secondary active transport – this process is further subdivided into two –

i. Symport (co-transport).

ii. Antiport (counter-transport).

B. Paracellular/Intercellular Transport – is defined as the transport of drugs through the junctions between the GI epithelial cells. This pathway is of minor importance in drug absorption. The two paracellular transport mechanisms involved in drug absorption are –

1. Permeation through tight junctions of epithelial cells – this process basically occurs through openings which are little bigger than the aqueous pores. Compounds such as insulin and cardiac glycosides are taken up this mechanism.

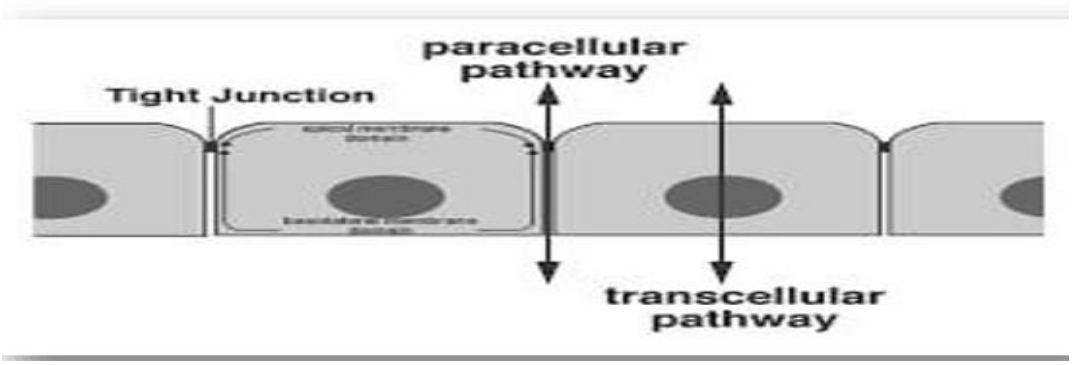
2. Persorption – is permeation of drug through temporary openings formed by shedding of two neighbouring epithelial cells into the lumen.

Paracellular transport differs from pore transport in that the former involves transfer of drug across epithelium and through the cellular junctions whereas in the case of latter, the molecules are transferred from outside of the epithelial cell into the cell through pores present in the cell membrane.

C. Vesicular or Corpuscular Transport (Endocytosis) – Like active transport, these are also energy dependent processes but involve transport of substances within vesicles into a cell. Since the mechanism involves transport across the cell membrane, the process can also be classified as transcellular. Vesicular transport of drugs can be classed into two categories –

1. Pinocytosis.

2. Phagocytosis.



Bioavailability Enhancement Through Enhancement of Drug Solubility or Dissolution Rate

There are several ways by which drug solubility or the dissolution rate can be enhanced.
Some of the widely used methods are discussed briefly.

1. Micronization: The process involves reducing the size of the solid drug particles to 1 to 10 microns commonly by spray drying or by use of air attrition methods (fluid energy or jet mill). The process is also called as micro-milling. Examples of drugs whose bioavailability have been increased by micronization include griseofulvin and several steroidal and sulpha drugs.
2. precipitation or crystallization. This can be prevented by use of inert polymers such HPMC, PVP, PVA, PEG, etc. which act by one or more of the following mechanisms -Increase the viscosity of crystallization medium thereby reducing the crystallization rate of drugs. Provide a steric barrier to drug molecules and inhibit crystallization through specific intermolecular interactions on growing crystal surfaces.Adsorb onto faces of host crystals, reduce the crystal growth rate of the host and produce smaller crystals.
3. Alteration of pH of the Drug Microenvironment: This can be achieved in two ways—in situ salt formation, and addition of buffers to the formulation e.g. buffered aspirin tablets.
4. Use of Amorphs, Anhydrates, Solvates and Metastable Polymorphs: Depending upon the internal structure of the solid drug, selection of proper form of drug with greater solubility is important. In general, amorphs are more soluble than metastable polymorphs, anhydrates are more soluble than hydrates and solvates are more soluble than non-solvates.
5. Solvent Deposition: In this method, the poorly aqueous soluble drug such as nifedipine is dissolved in an organic solvent like alcohol and deposited on an inert, hydrophilic, solid matrix such as starch or microcrystalline cellulose by evaporation of solvent.
6. Precipitation: In this method, the poorly aqueous soluble drug such as cyclosporine is dissolved in a suitable organic solvent followed by its rapid mixing with a non-solvent to effect precipitation of drug in nanosize particles. The product so prepared is also called as hydrosol.
7. Selective Adsorption on Insoluble Carriers: A highly active adsorbent such as the inorganic clays like bentonite can enhance the dissolution rate of poorly water-soluble drugs such as griseofulvin, indomethacin and prednisone by maintaining the concentration gradient at its maximum. The two reasons suggested for the rapid release of drugs from the surface of clays are—the weak physical bonding between the adsorbate and the adsorbent, and hydration and swelling of the clay in the aqueous media.
8. Solid Solutions: The three means by which the particle size of a drug can be reduced to submicron level are—

Use of solid solution

Use of Eutetic micture

Use of solid desperation

In all these cases, the solute is frequently a poorly water-soluble drug acting as the guest and the solvent is a highly water-soluble compound or polymer acting as a host or carrier.A solid solution is a binary system comprising of a solid solute molecularly dispersed in a solid solvent. Since the two components crystallize together in a homogeneous one phase system, solid solutions are also called as molecular dispersions or mixed crystals. Because of reduction in particle size to the molecular level, solid solutions show greater aqueous solubility and faster dissolution than eutectics and solid dispersions. They are generally prepared by fusion method whereby a physical mixture of solute and solvent are melted together followed by rapid solidification. Such systems, prepared by fusion, are often called as melts e.g. griseofulvin-succinic acid The griseofulvin from such solid solution dissolves 6 to 7 times faster than pure griseofulvin.Binary phase diagram for continuous solid solution of A and B. TA and TBare melting points of pure A and pure B respectively.If the diameter of solute molecules is less than 60% of diameter of solvent molecules or its volume less than 20% of volume of solvent molecule, the solute molecule can be accommodated within the intermolecular spaces of solvent molecules e.g. digitoxin-PEG 6000 solid solution. Such systems show faster dissolution. When the resultant solid solution is a homogeneous transparent and brittle system, it is called as glass

solution. Carriers that form glassy structure are citric acid, urea, PVP and PEG and sugars such as dextrose, sucrose and galactose.Solid solutions can be classified on two basis –

A. Miscibility between the drug and the carrier – on this basis the solid solutions are divided into two categories –
   1. Continuous solid solution is the one in which both the drug and the carrier are miscible in all proportions. Such a solid solution is not reported in pharmaceutical literature.
   2. Discontinuous solid solution is the one where solubility of each of the component in the other is limited .

B. Distribution of drug in carrier structure – on this basis the solid solutions are divided into two categories –
   1. Substitutional crystalline solid solution is the one in which the drug molecules substitute for the carrier molecules in its crystal lattice. This happens when the drug and carrier molecules are almost of same size.
   2. Interstitial crystalline solid solution is the one in which the drug molecules occupy the interstitial spaces in the crystal lattice of carrier molecules. This happens when the size of drug molecule is 40% or less than the size of carrier molecules

Types of crystalline solid solution

The two mechanisms suggested for enhanced solubility and rapid dissolution of molecular dispersions are:When the binary mixture is exposed to water, the soluble carrier dissolves rapidly leaving the insoluble drug in a state of microcrystalline dispersion of very fine particles, andWhen the solid solution, which is said to be in a state of randomly arranged solute and solvent molecules in the crystal lattice, is exposed to the dissolution fluid, the soluble carrier dissolves rapidly leaving the insoluble drug stranded at almost molecular level.

Bioavailability Enhancement Through Enhancement of Drug Permeability Across Biomembrane

On several occasions, the rate-limiting step in drug absorption is transport through the intestinal epithelium owing to poor permeability. Several approaches besides the use of lipophilic prodrugs that increase the drug permeation rate are discussed below. 1. Lipid Technologies: With an increase in the number of emerging hydrophobic drugs, several lipid-based formulations have been designed to improve their bioavailability by a combination of various mechanisms briefly summarized as follows:

Physiochemical—Enhanced dissolution and solubility.

Physiological —potential mechanisms include -

Enhancement of effective luminal solubility by stimulation of secretion of bile salts, endogenous biliary lipids including phospholipids and cholesterol which together form mixed micelles and facilitate GI solubilization of drug.

Reduction in gastric emptying rate thereby increasing the time available for dissolution and absorption. Increase in intestinal membrane permeability. Decreased intestinal blood flow. Decreased luminal degradation. Increased uptake from the intestinal lumen into the lymphatic system (and a reduction in first-pass hepatic and GI metabolism).The various lipid-based dosage forms include – lipid solutions and suspensions, micelle solubilization, coarse emulsions, microemulsions, multiple emulsions, selfemulsifying drug delivery systems (SEDDS), self-micro emulsifying drug delivery systems (SMEDDS), nanoparticles and liposomes. The reasons for the increasing interest in lipid-based systems are due to the several advantages they offer and include:

Physiochemical advantages: Such as

1. Solubilization of drug with low aqueous solubility
2. Solubilization of labile drugs against hydrolysis or oxidation

Pharmaceutical advantages: such as

1. Better characterization of lipidic recipients
2. Formulation versatility and the choice of different drug delivery system

Pharmacokinetics advantages: Such as

1. Reduce Plasma profile variability
2. Potential for drug targeting application

Pharmacodynamic advantages:Such as

1. Reduce toxicity
2. Consistency in drug response

a) Lipid solutions and suspensions: Some lipophilic drugs such as steroids have appreciable solubility in triacylglycerols alone. It is therefore comparatively straightforward to administer the drug in an oily liquid (e.g. encapsulated) and thereby achieve satisfactory absorption. One disadvantage of this formulation approach, however, is that oil alone rarely provides the solubilizing power to dissolve the required dose in a reasonable quantity of oil. This limits the option of using a simple drug/oil formulation system.

b) Coarse emulsions, microemulsions, SEDDS and SMEDDS: The ability of oil to accommodate a hydrophobic drug in solution can be improved by the addition of surfactants. The surfactants also perform the function of dispersing the liquid vehicle on dilution in gastrointestinal fluid. Hence, the drug is present in fine droplets of the oil/surfactants mixture which spread readily in the gastro-intestinal tract. Self-emulsifying/microemulsifying systems are formed using an oily vehicle (or a mixture of a hydrophilic phase and a lipophilic phase) a surfactant with a high HLB and if required, a co-surfactant. Unlike emulsions, the resultant liquid is almost clear. These pre-concentrates form spontaneously an emulsion/microemulsion in aqueous media (e.g. gastro-intestinal tract).

c) Solid lipid nanoparticles: To overcome the disadvantages associated with the liquid state of the oil droplets, the liquid lipid is replaced by a solid lipid leading to the formation of solid lipid nanoparticles. In contrast to emulsions, the particles consist of a solid core made from solid lipids. They are characterized by a mean diameter between approx. 100 to 1000 nm.

There are two basic production techniques for solid lipid nanoparticles –

1. Homogenization of melted lipid at elevated temperature
2. Homogenization of a suspension of solid lipids at or below room temperature.

d) Liposomes: Liposomes are broadly defined as lipid bilayers surrounding an aqueous space. Liposoluble drugs can be embedded in the ―fatty‖ regions, while hydrophilic substances are held in the aqueous internal spaces of these globular vesicles.

2. Ion Pairing: The ion pairing approach involves co-administration of a hydrophilic or polar drug with a suitable lipophilic counterion, which consequently improves the partitioning of the resultant ion-pair (relatively more lipophilic) into the intestinal membrane. In fact, the approach seems to increase the oral bioavailability of ionizable drugs, such as atenolol, by approximately 2fold. However, it is important that a counterion possess high lipophilicity, sufficient aqueous solubility, physiological compatibility, and metabolic stability.

3. Penetration Enhancers: Compounds which facilitate the transport of drugs across the biomembrane are called as penetration/permeation enhancers or promoters. This method is used mainly in cases of hydrophilic drugs which are expected to have difficulty in penetrating the lipid structure of the biomembrane. Penetration enhancers act interaction of its lipid part with the polar component of membrane phospholipids.

Penetration enhancers can be divided into three categories –

1. Substances that act very quickly have a strong effect and cause injury to the membrane (which is reversible), e.g. fatty acids such as oleic, linoleic and arachidonic and their monoglycerides.
2. Substances that act quickly, cause temporary injury but have average activity, e.g. salicylates and certain bile salts.
3. Substances having average to strong activity but cause sustained histological changes, e.g. SLS, EDTA and citric acid.

Bioavailability Enhancement Through Enhancement of Drug Stability

The various ways by which improvement of stability of drug in the GIT has a positive impact on bioavailability are discussed below.

1. Enteric Coating: Enteric-coated systems utilize polymeric coatings that are insoluble in the gastric media and therefore, prevent or retard drug release in the stomach. Such systems release the drug in the alkaline milieu of intestine. Bioavailability of drugs that are unstable in the gastric milieu, for e.g. erythromycin, penicillin V, pancreatin and benzimidizoles such as omeprazole can be improved by enteric coating.
2. Complexation: Complexation, in certain instances, can be used to increase the stability of drug in the GI milieu, particularly those of ester drugs and thus enhance their oral availability. Generally speaking, β-cyclodextrins are potential carriers for achieving such objectives but other complexing agents, such as caffeine, sodium salicylate, sodium benzoate, and nicotinamide, may also be used.

Use of Metabolism Inhibitors: Co-administration of a drug with low bioavailability and its metabolism inhibitor, which can selectively inhibit any of the contributing processes, would result in increased fractional absorption and hence a higher bioavailability. In fact, this approach seems to be a promising alternative to overcome the enzymatic barriers to oral delivery of metabolically labile drugs such as peptides and proteins. Current novel approaches in this area include: Bioadhesive system that can reduce the drug degradation between the delivery system and absorbing membrane by providing intimate contact with GI mucosa. Controlled-release microaencapsulated systems that can provide simultaneous delivery of a drug and its specific enzyme inhibitor at the desired site for required period of time.Interestingly, the intestinal wall metabolism (prehepatic metabolism) may also be inhibited by co-administration of certain drugs and diet, which act by selectively inhibiting an enzyme present in enterocytes. An illustrative example is that of cyclosporin, which undergoes extensive intestinal metabolism, resulting in low bioavailability ranging between 30–40%. Studies have shown that co-administration of ketoconazole and grapefruit juice, which contains the inhibitory components, can

significantly decrease the presystemic metabolism (both act via selective inhibition of intestinal, not hepatic, CYP3A4) and consequently increase the oral bioavailability of cyclosporin. In a differential manner, however, ketoconazole moderately inhibits P-gp, whereas grapefruit juice activates P-gp-mediated efflux of cyclosporine, which is a well-characterized substrate of P-gp, thereby partially counteracting the CYP3A4-nhibitory effects of grapefruit juice.Grapefruit juice is reported to be a powerful inhibitor of enzyme CYP3A4 and is known to enhance the bioavailability of several drugs. It could be argued that extraction of such components from grapefruit juice (thought to be flavonoids) and their inclusion as excipient in the dosage form would lead to not only more complete but also more consistent systemic levels by counteracting inconsistencies brought about by enzyme inhibitors in food and drink. Co-administration of a drug that can selectively inhibit an enzyme in the liver may lead to increased bioavailability of another drug. For

example, coadministration of erythromycin can result in inhibition of hepatic metabolism and thereby significantly increase the oral bioavailability of cyclosporin. As a matter of fact, this attribute of erythromycin appears to be selective, which permits a noninvasive measurement of the in vivo hepatic CYP3A4 activity, popularly known as erythromycin breath test. Many examples also exist related to the inhibitory effects of diet on hepatic first-pass metabolism.

Bioavailability Enhancement Through Gastrointestinal Retention

Gastro-retentive drug delivery systems (GRDDS) are designed on the basis of delayed gastric emptying and CR principles, and are intended to restrain and localize the drug delivery device in the stomach or within the upper parts of the small intestineuntil the entire drug is released. Excipients that are bioadhesive or that swell on hydration when incorporated in an oral dosage form, can promote gastro-retention and absorption by –

Increase contact with epithelial of GI

Prolonging residence time in the stomach

Delaying intestinal Transit

Cellulose ethers, gums of natural origin, and

synthetic acrylic acid polymers have been evaluated for such purposes. The range of materials available and their differing viscoelastic and rheological behaviours mean that it is possible, by judiciousad mixture, to develop delivery units with balanced properties so that adhesion, density, hydration, drug release rate, etc. can be tailored to the drug in question and the physiological characteristics of the target delivery site.

Conclusion:

There are various factors that determine the bioavailability of the drug however bioavailability of drug can be enhanced by using novel approaches which ultimately help to reduce dose of drug as well as frequency of drug administration,In this paper we have discussed some techniques that can be used in enhancement of drug bioavailability.

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