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Review Article

ENHANCEMENT OF BIOAVAILABILITY THROUGH INCREASE IN DRUG PERMEATION, STABILITY AND RETENTION TIME

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ABSTRACT

The rate and extent to which an unchanged drug reaches the systemic circulation is called as bioavailability (BA). Bioavailability, a subcategory of absorption is one of the principal pharmacokinetic parameter determined for an active substance form a pharmaceutical product. It also indicates the fractional extent to which a dose of drug reaches its site of action or biological fluid from which the drug has access to its site of action. Physical properties of drug, drug formulation, route of administration, gastric emptying rate etc. are several factors affect the bioavailability of drug from its drug product. Poor solubility, enzymatic and transporters barrier, drug stability and short retention of the drug in stomach due to peristaltic movement are several factors decrease the bioavailability of the drug. This review deals with the bioavailability improvements techniques from poor permeation, lesser stability and short retention of the drug in stomach. Lipid based formulations; ion pairing and use of permeation enhancer are different methods to enhance the bioavailability through increase in permeation. Enteric coating, complexation and metabolism inhibitors lead to increase in drug stability. Bioadhesive polymers in formulation improve the gastro retention time serve as improved bioavailable product.

Key words: Bioavailability, Lipid based formulations, Enteric Coating, Gastro retentive Drug Delivery System.

INTRODUCTION

Bioavailability is a measurement of the rate and extent to which an unchanged drug reaches the systemic circulation. It is denoted by the letter f (Shargel L. 1999). It also indicates the fractional extent to which a dose of drug reaches its site of action or biological fluid from which the drug has access to its site of action. Figure 1, illustrates that a drug given orally must be absorbed initially from the stomach and intestine, but this may be limited by the characteristics of the dosage form and the drug's physicochemical properties. In addition, drug then passes through the liver, where metabolism and biliary excretion may occur before the drug enters the systemic circulation. Accordingly, a fraction of the administered and absorbed dose of drug will be inactivated or diverted before it can reach the general circulation and be distributed to its sites of action. If the metabolic or excretory capacity of the liver for the drug is large, bioavailability will be reduced substantially (the first-pass effect). This decrease in availability is a function of the anatomical site from which absorption takes place and the choice of the route of drug administration must be based on an understanding of these conditions (Goodman G. 2006).

Necessity of Bioavailability Enhancement

Enhancement of bioavailability is essential for many drugs like penicillin, atropine, chloramphenicol palmitate, griseofulvin etc., which have poor bioavailability due to

- Poor aqueous solubility and/or slow dissolution rate in biological fluids
- Poor stability of the dissolved drug at the physiologic pH.
- Poor permeation through bio membrane due to inadequate partition coefficient.

Approaches to overcome these problems

Pharmaceutics approach

This involves modification of formulation, manufacturing process or the physicochemical properties of the drug without changing the chemical structure.

Pharmacokinetic Approach

Pharmacokinetics of the drug is altered by modifying its chemical structure. The approach of chemical structure modification has a number of hitches of being very expensive and time consuming. The requirement of repeated clinical studies and longer period for regulatory approval further makes the approach deplorable.

Biological Approach

Alteration in the route of drug administration such as changing from oral to parental route, also alter the bioavailability. The limitations of pharmacokinetic approaches to enhance bioavailability, the optimization of the formulation, manufacturing process or the physicochemical properties of the drug without changing the chemical structure are mainly aimed at enhancement of dissolution rate which lead to increase in bioavailability as it is the major rate limiting step in the absorption of most drugs (Brahmankar D. M, 2006). The Pharmaceutical approach for bioavailability enhancement can be applied by following techniques

- Enhancement of drug solubility and dissolution rate
- Enhancement of drug permeability
- Enhancement of drug stability
- Enhancement of gastrointestinal retention

Bioavailability enhancement through increase in drug permeability across biomembrane

Lipid technologies

Lipid-based formulations encompass a diverse group of formulations with very different physical appearance, ranging from simple triglyceride vehicles to more sophisticated formulations such as self-emulsifying drug delivery systems (SEDDS). Lipid-based drug delivery systems may contain a broad range of oils, surfactants and co-solvents. They represent one of the most popular approaches to overcome the absorption barriers and to improve the bioavailability of poorly water-soluble drugs. Oral lipid-based products entered the market in 1981 and presently having well commercially

availability in oral formulations. Lipids open a wide area of different formulations for oral administration because they can be manufactured as solutions, suspensions, emulsions, self-emulsifying systems and micro-emulsions. Lipids offer the potential for enhancing drug absorption and oral bioavailability.

Factors taken into consideration for lipid-based formulations

Lipid Digestion

If the drug possesses high affinity to the lipid vehicle, it can be assumed that the API moves apparently together with vehicle in the GI-tract, revealing that digestibility of lipid would be as important as gastric emptying rate of the same. Thus, careful selection of the lipid vehicle can control the absorption rate of drug. GI lipid digestion consists of three sequential steps: (i) the dispersion of fat globules to yield a fine emulsion, (ii) the enzymatic hydrolysis of fatty acid esters at the emulsion-water interface and (iii) the desorption and dispersion of insoluble lipid products for subsequent absorption .

Mean Emulsion Droplet Diameter

The mean emulsion droplet diameter is a parameter indicating the quality of self-emulsifying formulations. The droplet size of SEDDS upon dilution with aqueous media is primarily influenced by the type and concentration of emulsifier. The higher the concentration of emulsifier, the smaller the emulsion droplet and the faster the drug release. Two techniques are commonly used to determine the mean emulsion droplet diameter: low angle laser light diffraction is applied for emulsions with droplet sizes > 1µ and quasi-elastic light scattering for investigations of submicron dispersions. In addition, the mean emulsion droplet diameter seems to be a very critical factor for prediction of the in-vivo performance of undigested lipid-based formulations, such as long chain triglycerides in case of Cyclosporine (Neoral® versus Sandimmune®). Nevertheless, in case of predigested lipids such as medium chain monoglycerides or propylene glycol monoester of C8-C10 fatty acids, the mean emulsion droplet diameter may not be crucial in-vivo.

Lipophilicity of Drug

Highly hydrophobic drugs (log P > 6) can be taken up into the lymphatic system by partitioning into chylomicrons in the mesentery vein which has been demonstrated to be crucial for the absorption of the anti-malaria compound halofantrine. Furthermore, highly lipophilic retinoids are known to be transported in the intestinal lymph after oral administration.

Type of Lipids

The digestible lipids may influence absorption with differing method from that of non-digestible lipids. Commonly used digestible lipid vehicles are listed in Table 1. The lower the melting point of the fatty acid, the higher is the amount of drug absorbed.

Drug Release

Primarily, the characteristics of drug and lipid as well as their aqueous solubility are key factors to control drug release and absorption from lipid based formulations. Other issues to be considered are whether the drug is formulated in oil, SEDDS or emulsified form, the absorption pathway of the drug, the droplet size of the emulsion present in the intestine, the type of surfactants, the metabolic pathway of the lipids and the changes in gastric motility due to presence of lipids.

Novel Lipid Formulations

The carrier systems that have been most extensively studied to control the release of the incorporated substances are

- Lipid solutions & suspensions
- Micro emulsions
- Self emulsifying drug delivery system (SEDDS)
- Solid lipid nanoparticles (SLN)
- Nanostructured lipid carriers (NLC)
- Lipid – drug conjugate (LDC)
- Liposomes (Basavaraj K 2011)

Lipid Solutions & Suspensions

The simplest lipid-based formulations contain only one excipient such as oleic acid, α-tocopherol, corn oil, peanut oil, sesame oil, medium chain triglycerides, or medium chain mono- and diglycerides. Many of the over-the-counter sold products contain polyethylene glycol or medium chain triglycerides as the solubilizing excipients. Some lipophilic drugs like steroids have good solubility in triacylglycerols. Table 2 illustrates some over the counter or some marketed formulations of Lipid Solutions. Therefore it is better to formulate a drug in an oily liquid and achieve good absorption which leads to enhanced bioavailability (Maulik Patel, 2011).

Microemulsions

The concept of microemulsion was introduced by Hoar and Schulman in 1943. They prepared first microemulsions by dispersing oil in an aqueous surfactant solution with addition of alcohol as a co-surfactant, leading to a transparent, stable formulation Some Patents of Microemulsions is shown in Table 3. The existence of this theoretical structure was later confirmed by use of various technologies. Thus as Shown in Figure 2 the microemulsions are defined as “a system of water, oil and amphiphilic compounds (surfactant and co-surfactant) which is a transparent, single optically isotropic, and thermodynamically stable liquid (Attwood D.1994) (Singh V. 2012).

Self Emulsifying Drug Delivery System (SEDDS)

The most popular approach for enhancing the bioavailability is the incorporation of the active lipophilic component into inert lipid vehicles, surfactant dispersions, self-emulsifying formulations with every formulation approach having its special advantages and limitations. Self-emulsifying drug delivery systems (SEDDS) are mixtures of oils and surfactants, ideally isotropic and sometimes containing co-solvents which emulsify spontaneously to produce fine oil-in-water emulsions when introduced into aqueous phase under gentle agitation. SEDDS have also been formulated using medium chain tri-glyceride oils and nonionic surfactants, the latter being less toxic. Some excipients and product formed by these excipients are listed in Table 5. Upon peroral administration, these systems form fine emulsions (or micro-emulsions) in gastro-intestinal tract (GIT) with mild agitation provided by gastric mobility. Some examples of Marketed formulations of SEDDS are Listed in Table 4 which have Potential advantages of enhanced oral bioavailability enabling reduction in dose, more consistent temporal profiles of drug absorption, selective targeting of drug(s) toward

specific absorption window in GIT and protection of drug(s) from the hostile environment in gut.

Table 1: Vehicles Used For Lipid Formulations

Class	Lipophilic vehicles
Fatty acids	Oleic acid, Myristic acid, Caprylic acid, Capric acid
Triglycerides of mediumchain fatty acids	Miglyol® 812, Captex® 355, Labrafac®
Triglycerides of long-chain fatty acids	Soybean Oil, Peanut Oil, Corn Oil

Table 2: Marketed Lipid Solutions Formulations

Brand Name	API	Manufacturer	Country
Heminevrin	Clomethiazole	AstraZeneka	UK
Marinol®	Dronabinol	Solvay Pharmaceuticals	USA
Epadel®	Ethyl icosapentate	Mochida Pharmaceuticals	Japan

Table 3: Patents of Microemulsions

Patent No.	Issue date	Original Assignee	Title	Reference
US5023271	Jun 11, 1991	California Biotechnology Inc	Pharmaceutical microemulsions	Vigne J.L 1991
US5055303	Oct 8, 1991	KV Pharmaceutical Company	Solid controlled release Bioadherent Emulsions	Riley T.C *et al*, 1991
US5744155	Apr 28, 1998	Friedman, Doron, Schwartz, Joseph, Amselem, Shimon	Bioadhesive emulsion preparations for enhanced drug delivery	Friedman *et al*, 1998
US5925626	Jul 20, 1999	Fidia S.p.A.	Hyaluronic acid fractions having pharmaceutical activity, and pharmaceutical compositions containing the same	Valle F.D *et al*, 1999
US6551605	Apr 22, 2003	Haarmann & Reimer	Diesters or polyesters of naphthalene dicarboxylic acid as solubilizer/stabilizer for retinoids	Bonda C.A *et al,* 2003
US20020102280	Jan. 08, 2002	Anderson, David M.	Solvent systems for pharmaceutical agents	Anderson D.M, 2002

Table 4: Marketed Preparation of SEDDS

Name of product	Company name	Active drug
VITA-SEDDS	Summit Vitamins USA	MULTI VITAMIN
SEDDS VIT. D3 + Ca	Summit Vitamins USA	CALCIUM + VIT. D3
SEDDS CoQ10	Summit Vitamins USA	CoQ10
SANDIMMUNE	Novartis USA	CYCLOSPORINE
NORVIR	Abbott India Limited	RITONAVIR
FORTOVASE	La Roche New Zealand	SAQUINAVIR

http://www.iherb.com/Summit-Vitamins

Table 5: Surfactants, Co-Surfactant and Co-Solvent (Patel P. 2008)

Excipients	Commercial products
Surfactants/co-surfactants	
Polysorbate 20 (Tween 20)	Targretin soft gelatin capsule
Polysorbate 80 (Tween 80)	Gengraf hard gelatin capsule
Sorbitan monooleate (Span 80)	Gengraf hard gelatin capsule
Polyoxy-35-castor oil(Cremophor RH40)	Gengraf hard gelatin capsule,
(Cremophor RH40)	Sandimmune soft gelatin capsules
Co-solvents	
Ethanol	Sandimmune soft gelatin Capsules
Glycerin	Nerol soft gelatin Capsule,
Polypylene glycol	Agenerage Oral solution ,
Polyethylene glycol	Gengraf hard gelatin capsule
Lipid ingredients	
Corn oilmono,di,,tri-glycerides	Targretin soft gelatin capsule,
DL-alpha-Tocopherol	Agenerase soft capsule,
Fractionated triglyceride of coconut oil	Agenerase oral solution
(medium-chain triglyceride)	
Mixture of mono-and di-glycerides of caprylic/capric acid	Nerol soft gelatin Capsule, Nerol Oral
Medium chain mono-and di-glycerides	Solution
Corn oil	Rocaltrol soft gelatin capsule,
Olive oil	Avodat soft gelatin capsule
Oleic acid	Fortavase soft gelatin capsule
Sesame oil	Sandimmune soft gelatin capsule,
Hydrogenated soyabean oil	Depakene capsule
Hydrogenated vegetable oils	Sandimmune oral solution
Soyabean oil	Ritonavir soft gelatin capsule,
	Norvir soft gelatin capsule

Table 6: Patents of Enteric Coating Technology

Patent No.	Issuing Date	Original Assignee	Description	Reference
US4857337	Aug 15, 1989	American Home Products Corp. (Del)	Enteric coated aspirin tablets	Miller *et al*, 1989
US5209933	May 11, 1993	Syntex (U.S.A.) Inc.	Long acting calcium channel blocker composition	Macfarlane *et al*, 1993
US5326586	Jul 5, 1994	BASF Aktiengesellschaft	Coating of drug forms	Grabwoski *et al*, 1994
US5393333	Feb 28, 1995	Societe Anonyme Societe D'Exploitation De Produits Pour Les Industries Chimiques S.E.P.P.I.C.	Film-forming product for coating solid forms, process for its manufacture and products coated with this film-forming product	Trouve *et al*, 1995
US5643868	Jul 1, 1997	Autoimmune, Inc	Method of treating or preventing type 1 diabetes by oral administration of insulin	Weiner *et al*, 1997
US5733575	Mar 31, 1998	BPSI Holdings, Inc	Enteric film coating compositions, method of coating therewith, and coated forms	Mehra D.K *et al*, 1998
US5877309	Mar 2, 1999	ISIS Pharmaceuticals, Inc.	Antisense oligonucleotides against JNK	McKay R. 1999
US7122207	Oct 17, 2006	Bristol-Myers Squibb Company	High drug load acid labile pharmaceutical composition	Ullah *et al*, 2006

Table 7: Patents of FDDS (Rabadia N. 2012)

Drug	Dosage form	Patent no.	Reference
Valsartan	Swelling tablet	WO PCT 2008027945	Javant N. *et al*, 2008
Theophylline	Multi layered tablet	US PATENT 5783212	Fassihi R. *et al* 1998
Amoxicillin	SR floating capsule	US PATENT 2006121106	Kerc J. *et al*, 2006
Cimetidine, Ranitidine	Powder, tablet	US PATENT 5288506	Spickett R. G *et al*, 1994
Methotrexate	SR tablet	US PATENT 2008268045	Dervieux T *et al*, 2008

Table 8: Marketed preparations of FDDS (Shruti s. 2011)

Brand name	Delivery	Active drug	Company
Madopar HBS	Floating capsule	Benserazide (25mg) and L-Dopa (100mg)	Roche Products, USA
Topalkan®	Floating liquid alginate preparation	Al – Mg antacid	Pierre Fabre Drug, France
Cifran OD®	Gas-generating floating form	Ciprofloxacin (1gm)	Ranbaxy, India
Conviron®	Colloidal gel forming FDDS	Ferrous sulphate	Ranbaxy, India
Liquid Gaviscon®	Effervescent Floating liquid alginate preparations	Al hydroxide (95 mg), Mg Carbonate (358 mg)	GlaxoSmithkline, India

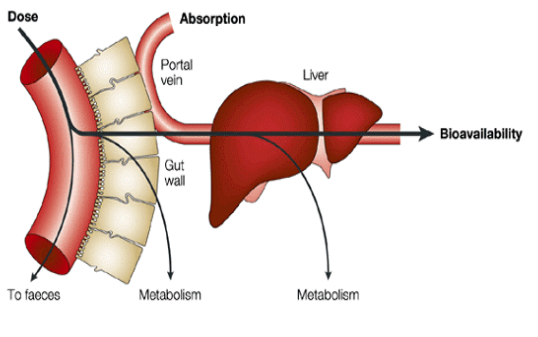

Figure 1: Schematic Representation of Bioavailability

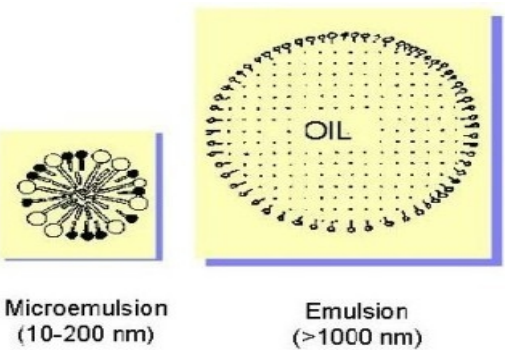

Figure 2: Particle Size of Emulsion & Microemulsion

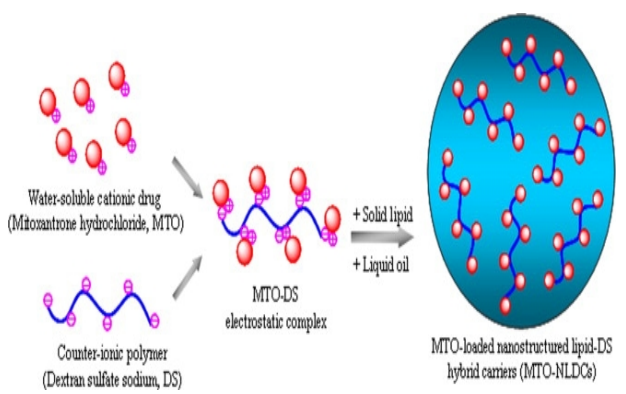

Figure 3: NLC of Mitoxantrone Hydrochloride

Figure 4: Representation of Floating Drug Delivery System

Merits of SEDDS

Selective targeting of drug(s) toward specific absorption window in GIT, Protection of drug(s) from the hostile environment in gut, Enhanced oral bioavailability enabling reduction in dose, More consistent temporal profiles of drug absorption, Control of delivery profiles, Reduced variability including food effects.

Research Materialized in SEDDS

- Gattefosse Corporation, France, has patented SEDDS formulation of Indomethacin which offered two fold increase in bioavailability in rats compared to conventional formulations (Crison J. *et al*, 1999)
- Charman *et.al* reported improvement in pharmacokinetic parameters of Halofantrine (highly lipophillic antimalarial drug) and reduction in inter-subject variability when administered as SEDDS (Charman *et al*, 1998)
- K Itoh observed improvement in biopharmaceutical properties of N-4472, an investigational lipophillic drug having lipolytic activity in SEDDS formulation. (Itoh K. *et al*, 2003)
- Nazzal *et al* observed improvement in pharmacokinetics and two-fold increase in bioavailability of Ubiquinone, a lipophillic drug used as an anti-anginal agent and as antioxidant when given as SEDDS (Gupta N. 2009)

Solid-Lipid Nanoparticle

Solid lipid nanoparticles (SLN) represent an alternative carrier system to tradition colloidal carriers such as - emulsions, liposomes and polymeric micro and nanoparticles. This system was introduced in 1991. Nanoparticles made from solid lipids are attracting major attention as novel colloidal drug carrier for intravenous applications as they have been proposed as an alternative particulate carrier system. SLN are sub-micron colloidal carriers ranging from 50 to 1000nm, which are composed of physiological lipid, dispersed in water or in aqueous surfactant solution. SLN offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interface and are attractive for their potential to improve performance of pharmaceuticals (Ekambaram P.2012). In order to overcome the disadvantages associated with the liquid state of the oil droplets, the liquid lipid was replaced by a solid lipid, which eventually transformed into solid lipid nanoparticles. Even due to the several reasons viz Lipids enhance oral bioavailability and reduce plasma profile variability, Better characterization of lipoid excipients & An improved ability to address the key issues of technology transfer and manufacture scale-up, lead to the increased interest in lipid based drug delivery system.

Merits of SLN

Small size and relatively narrow size distribution which provide biological opportunities for site-specific drug delivery by SLNs. SLNs shows controlled release of active drug over a long period and can be sterilized by autoclaving or gamma irradiation, ability to be lyophilized as well as spray dried, easy to produce in industrial scale by hot dispersion method, no toxic metabolite and economical as compared to other dosage forms (Sailaja K. 2011).

Research Materialized in SLNS

- SLNs have been reported to be useful as drug carriers to treat neoplasms. Tumour targeting has been achieved with SLNs loaded with drugs like methotrexate and camptothecin. Tamoxifen an anticancer drug is incorporated in SLN to prolong release of drug after i.v. administration.
- Mitoxantrone-loaded SLN local injections were formulated to reduce the toxicity and improve the safety and bioavailability of drug41. Efficacy of doxorubicin (Dox) has been reported to be enhanced by incorporation in SLNs. In the methodology the Dox was complex with soybean-oil-based anionic polymer and dispersed together with a lipid in water to form Dox-loaded solid lipid nanoparticles. The system has enhanced its efficacy and reduced breast cancer cells (Vishvajit A. 2010).

Nanostructured Lipid Carriers

The application of NLC as a drug delivery system is enhanced by eliminating the use of organic solvents in the preparation stage and using the hot high-pressure homogenization technique an example of NLC of mitoxantrone hydrochloride is shown in Figure 3. Polysorbate20 and polysorbate80 are non-ionic surfactants commonly used as excipients and emulsifiers in medications for parenteral administration. However, their efficiency in the stabilization of NLC is yet to be elucidated.

Research Materialized in NLC

- Souto and Müller, 2006 reported that among the nanostructured lipid carriers that contain solid lipids together with liquid oils are Miglyol®, α-tocopherol etc. (Muller *et al*. 2006)
- Müller *et al*. 2002 reported that the presence of liquid lipids with different fatty acid C-chains produces NLC with less organized crystalline structure and therefore provides better loading capacity for drug accommodation. Liquid lipids are better solubilizers of drugs than solid lipids. (Müller *et al*. 2002)

Lipid – Drug Conjugate (LDC)

The major problem of SLN is the low capacity to load hydrophilic drug due to partitioning effect during the production process. Only highly potent low dose hydrophilic drug may be suitably incorporated in the solid lipid matrix, in order to overcome this problem, the LDC nanoparticles with drug loading capacity up to 33% have been developed. An insoluble drug- lipid conjugate bulk is first prepared either by salt formation or by covalent linking. This LDC is further processed with an aqueous surfactant solution such as tween to a nanoparticle formulation, using high pressure homogenization. Such matrices may have potential application in brain targeting of hydrophilic drug in serious protozoal infections. Increase in bioavailability is achieved by LDC with the advantage of control & targeted drug release. LDCs are easy to validate, scale up & sterilize (Patidar A. 2010).

Ion Pairing

Ion-pair, a single unit, is a pair of oppositely charged ions held together by Coulomb attraction without formation of a covalent bond. Hydrophobic ion pairing technique has been used to increase the hydrophobicity of molecules containing ionizable groups by stoichiometric replacement of the polar counter ions with more hydrophobic ones. Ion-paired delivery has emerged as a viable approach for enhancing solubility of ionic molecules in non-polar solvents, augmentation of protein and DNA transport and addressing

the poor bioavailability issues of hydrophilic drugs. Ion-pairing can be a valuable tool for enhancing solubility and stability in an organic solvent. The complexes formed can be formulated into particulates with higher drug loading. This technique has found unique opportunities in delivery of polyelectrolytes (e.g. peptide, proteins and polynucleotide) by using them as hydrophobic ion-paired moieties for designing particulates and microemulsions that during formulation require direct solubilization in organic solvents. Additionally, this approach can also improve stability and permeability across biological membranes. Formation of ion pairs normally does not entail an alteration in the structure and function of drug. Thus, this approach can assist in designing better dosage forms for alternative routes of administration (Preeti K. 2011).

Research Materialized in Ion Pairing

- Sarveiya *et al.* (2004) reported a 16-fold increase in the steady-state flux of ibuprofen ion-pairs across a lipophilic membrane. They determined the influence of pH and ion-pairing on the permeation of ibuprofen across polydimethylsiloxane (PDMS) membrane. Diffusion studies at different pH values (4.0, 5.0, 6.0, 7.0 and 8.0) indicated that ibuprofen sodium flux increased significantly with increasing pH from 4.0 to 7.0. Above pH 7.0, a decrease in diffusion was observed. The permeability coefficient increased with an increase in the amount of unionized acid.(Sarveiya et al.2004)
- Sineerat *et al.* (2008) investigated a water insoluble complex of cationic propranolol HCl with anionic sodium lauryl sulfate. They concluded that the 'propranolol-sodium lauryl sulfate complex' provided promising sustained drug delivery and were feasible to be encapsulated in microparticles for a more sustained drug release effect. (Sineerat *et al.*2008)

Penetration Enhancers

Peroral delivery of hydrophilic drugs is one of the greatest challenges in biopharmaceutical research. Hydrophilic drugs usually present low bioavailability after oral administration. One of the causes of this low bioavailability is their poor intestinal permeation through the paracellular pathway. This pathway is actually restricted by the presence of tight junctions at the apical side of the enterocytes. In the last few years, great interest has been focused on the structure and cellular regulation of tight junctions, materializing in more in-depth knowledge of this intestinal barrier. Regular efforts are being made to develop agents that can modulate tight junctions and magnify the paracellular permeability of hydrophilic compounds without causing significant intestinal damage. These compounds are called as penetration enhancers or promoters. Based on the research conducted in the last decade it has become clear that several sodium salts of medium chain fatty acids [caprylate C8 (CH 3-(CH2)6-COOH), caprate C10 (CH3- (CH2)8-COOH) and laurate C12 (CH3-(CH2)10-COOH)] are able to enhance the paracellular permeability of hydrophilic compounds (Jose M. 2005).

Bioavailability enhancement through increased drug stability

Enteric coating

Oral site-specific drug delivery systems are widely used for the treatment of a variety of bowel diseases along with the improved systemic absorption of drugs, which are unstable in the stomach. However, the micro-environment in the gastrointestinal tract and varying absorption mechanisms usually creates barrier for the formulation development and optimization of oral drug delivery. An enteric coating on a solid dosage form can be used for delivery of therapeutic agent into the intestinal region. Such systems are designed to provide protection to tablets in the stomach. A thick coat on solid dosage form causes a delay in the drug release in the small intestine and slows down drug release, which is both pH and time-controlled. This ensures drug delivery to be colon specific. For the preparation of such tailor-made formulations, the selection of a polymer with a suitable coat level is the major factor to be considered. Most of the commercially available systems for colon specific drug delivery utilize Eudragit (L-100/ S-100) or cellulose acetate phthalate (CAP), shellac (SH) and ethyl cellulose (EC). Eudragit S-100 (ES) is a methacrylic acid methyl methacrylate co-polymer, which is soluble at a pH of 7. CAP is also an effective enteric coating material as it dissolves at a pH of 6. It is used at a concentration of 0.5-0.9%. Patents of Enteric Coating Technology is Enlisted in Table 6. (Punia S. 2012).

Complexation

Complexation of drug can be used to increase the drug stability in gastro intestinal tract (GIT). This objective can be served predominantly with Cyclodextrin. The central cavity of the cyclodextrin molecule is lined with skeletal carbons and ethereal oxygen's of the glucose residues. It is therefore lipophilic. The polarity of the cavity has been estimated to be similar to that of aqueous ethanolic solution. It provides a lipophilic microenvironment into which suitably sized drug molecules may enter and be included. No covalent bonds are formed or broken during drug-cyclodextrin complex formation, and in aqueous solutions, the complexes are readily dissociated. Free drug molecules are in equilibrium with the molecules bound within the cyclodextrin cavity. Measurements of stability or equilibrium constants (*K*c) or the dissociation constants (*K*d) of the drug-cyclodextrin complexes are important since this is an index of changes in physicochemical properties of a compound. (Thorsteinn L. 1996)

Metabolism Inhibitors

Administration of a drug with its metabolism inhibitor, results in increase fractional absorption & higher bioavailability. This approach seems to be promising approach to overcome enzymatic barriers of drugs such as peptides & proteins. Important example of a metabolic inhibitor is grapefruit juice. This can produce several clinically significant drug interactions through enzyme inhibition. These include a reduction in the metabolism of cyclosporin, calcium channel blockers and simvastatin.

Bioavailability Enhancement through Gastrointestinal Retention

Gastro-retentive drug delivery systems (GRDDS) are designed on the basis of delayed gastric emptying and are intended to localize the drug in stomach or within the upper part of small intestine until the entire is released. Excipients that are bioadhesive; swell on hydration can promote gastric retention and ultimately absorption.

Types of GRDDS

Floating drug delivery system (FDDS)

Floating systems or hydrodynamically controlled systems as shown in Figure 4 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. This system lead to increased gastric retention time (GRT) and control of the fluctuations in plasma drug concentration. A minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. A minimal gastric content is also required to allow the proper achievement of the buoyancy retention. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres which are listed in Table 8 along with some Patent in FDDS which are listed in Table 7. (Mayavanshi A. 2008). Cook JD *et al*, 1990 reported that the bioavailability of riboflavin controlled release-gastro retentive dosage form (CR-GRDF) is significantly enhanced in comparison to the administration of non-GRDF CR polymeric (Goyal M. 2011).

Bioadhesive Drug Delivery System

The relatively short gastric emptying time in humans, which normally averages 2-3 hrs through the major absorption zone (stomach or upper part of the intestine), can result in incomplete drug release from the drug delivery system leading to diminished efficiency of the administered dose. Localization of a drug delivery system in a specific region of the GIT offers numerous advantages, especially for drugs having narrow absorption window. The intimate contact of the dosage form with the absorbing membrane has the potential to maximize drug absorption and may also influence the rate of drug absorption. These considerations have lead to the development of oral sustained release dosage forms possessing gastric retention potential. The primary concern in the development of once daily oral sustained release dosage form is not just to prolong the delivery of drugs for 24hrs but also to prolong the presence of dosage forms in the stomach or somewhere in the upper small intestine. Gastroretentive dosage forms through local drug release will greatly enhance the pharmacotherapy of the stomach leading to high drug concentrations at the gastric mucosa, which are sustained over a long period of time. Gastroretentive delivery system leads to Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose e.g. Furosemide, Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics. e.g. Beta-lactam antibiotics (penicillin's and cephalosporin's), Retention of drug delivery systems in the stomach, prolongs overall gastrointestinal transit time thereby increasing bioavailability of sustained release delivery systems intended for once-a-day administration. e.g. Ofloxacin (Zate S.U, 2011).

CONCLUSION

Poor solubility, enzymatic and transporters barrier, drug stability and short retention of the drug in stomach due to peristaltic movement are several factors decrease the bioavailability of the drug. This Problem can be overcome by using Lipid based formulations, ion pairing and use of permeation enhancer, to enhance the bioavailability through increase in permeation. Enteric coating, complexation and metabolism inhibitors lead to increase in drug stability. Bioadhesive polymers in formulation improve the gastro retention time serve as improved bioavailable product.

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