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A Review Article on Permeability Enhancement

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Abstract: ***Human skin acts as a barrier, thermo regulator and prevents excess water loss from internal organs. Various ways of transferring drugs have been developed by altering the barrier properties of the skin. Improvement of skin penetration, partitioning and solubility effects through hydration of the stratum corneum or the use of chemical enhancers acting on lipids and keratinized structures in the stratum corneum is a promising tool in potential clinical applications. Penetration enhancement is a new emerging technology that has the potential to increase the amount of trans-dermally administered drugs. Also drugs with short biological half-lives can be easily administered. Among the many advantages over other routes, three important ones are avoidance of hepatic metabolism, minimal adverse effects, and increased bioavailability. The stratum corneum prevents the loss of physiologically essential substances and consequently provides penetration resistance by acting as a protective barrier. This is the rate-limiting step for absorption of the drug percutaneously. In this review article, we summarize the various advances made in the field of access enhancers based on a literature survey of various research articles.***
Keywords: Intestinal Permeability, Bioavailability, Permeation, BCS, Drug Delivery System, Bioequivalence.

I. INTRODUCTION

Developments in the field of combinatorial chemistry and high-throughput screening have made it possible to produce a large number of drug candidates but have also produced many poorly soluble and or poorly absorbable drugs. A new trend in drug development based on pharmacogenomics or molecular targeted drug development is also encouraging this trend and not necessarily yielding good results in terms of new drug development. Therefore, better improvement of membrane permeability is required. (Fuyuki et al 2008). Absorption of complex molecules such as oligonucleotides vaccines, chimeric proteins and small peptides is different from traditional synthetic small molecular weight organic compounds. However, in all cases the solubility and permeability of a drug can be related to its absorption profile. Biopharmaceutical Classification All drugs are classified into four categories based on solubility and permeability as per BCS to rationalize the science of drug delivery and to ease the complexities of drug registration of various newly developing compounds for regulatory authorities. Among the various classes of BCS, the oral delivery of class 3 and 4 drags is partially or completely reduced due to their poor intestinal permeability. Due to their unfavorable physicochemical and chemical properties, which are difficult to modify, many drug molecules show poor permeability thus an excipient can be added exogenously to increase permeability transiently, (Pradeep et al 2005).

Oral delivery of the drug is also preferred for its convenience. Tablets and capsules can be produced in large quantities at low cost. Therefore in the lead optimization phase of drug discovery, the oral bioavailability of a drug is important. It depends on various factors, the most common being intestinal permeability. Responsibility for solubility, release from dosage form, efflux and metabolism during gastrointestinal transit. The importance of solubility and permeability is particularly evident in the FDA's adoption of Amidon's Biopharmaceutics Classification System (BCS) in 2000 as the scientific basis for approving bioweavers for in vivo bioavailability and bioequivalence studies. (Kartsen et al 2006).

Over the past few decades, there have been significant medical advances in the field of drug delivery with the development of new dosage forms and techniques. For drugs that are not absorbed orally, other routes of drug delivery such as injection, transdermal, pulmonary or other routes are used. However, among the various possible routes, the oral route is the most preferable as it offers significant advantages in therapeutic efficacy and patient compliance. (Seulki et al 2005).

Various experimental systems are used for permeability enhancement. Although the use of intact animal models has enabled an improved understanding of permeability enhancement, the inherent complexity of the models has hindered definitive experiments to determine biochemical mechanisms. Through the use of in vitro models and techniques, identification of key components of the barrier functions of epithelia has led to a clearer understanding of permeability enhancement. (Edward et al 1996).

In this article we reviewed some of the basic permeability enhancement techniques that are useful for enhancing the permeability of poorly permeable drugs that fall into classes III and IV of the Biopharmaceutics Classification System (BCS) that was accepted by the FDA in 2000 as a scientific basis. Approval of biowaivers for in vivo bioavailability and bioequivalence studies.

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II. CLASSIFICATION

BCS classification system is an important tool for generic drug development. It's give a comparative evidence between test product and RLD (reference listed drug). Without BCS classification it's so tough to design a generic drug development. Because the solubility and permeability of API highly impact on BE study. So to reduce the failure of BE study one should be confirmed the API BCS classification.

Class	Solubility	Permiability	Absorption Pattern	Rate Limiting Step in Absorption	Example of drug
I	High	High	Well absorbed	Gastric emptying	Diltiazem
II	Low	High	Variable	Dissolution	Nifedipine
III	High	Low	Variable	Permeability	Insulin
IV	Low	Low	Poor Absorbed	Case by Case	Taxol

TABLE I: Biopharmaceutics Classification System for Drug

III. PERMEABILITY ENHANCEMENT TECHNIQUES

A. Self-micro-emulsifying Drug Delivery Systems (SMEDDS)

GI absorption of poorly permeable drugs such as BCS class 4 drugs can be enhanced using self-microemulsifying drug delivery systems. Much research has been done in this decade on developing self-micro emulsifying drug delivery systems (SMEDDS). Typically these systems are isotopic mixtures of oils, surfactants and co-solvents/co-surfactants. Once administered into the GI system, they are diluted with gastrointestinal fluid and gastric motility provides agitation to form a fine oil-in-water (o/w) microemulsion (SMEDDS). The difference between SEDDS and SMEDDS is that dilution of the former results in droplet sizes between 100 and 300 nm, while the latter results in droplet sizes below 50 nm. (Mallikarjun et al 2011).

B. Self-double Emulsifying Drug Delivery System (SDEDDS)

Self-double emulsifying drug delivery system (SDEDDS) can be used to increase the oral bioavailability of drugs with high solubility and low permeability, but their industrial use is insufficient due to low stability. A new formulation i.e. self-double-emulsifying drug delivery system can be developed which is stable through formulation optimization. SDEDDS can temporarily emulsify into a water-in-oil-in-water (w/o/w) double emulsion in a diverse aqueous gastrointestinal environment, with drugs incorporated into the water phase within the double emulsion. Water-in-oil-in-water (w/o/w) double emulsions are complex systems consisting of aqueous droplets dispersed within larger oil droplets, which are dispersed in an aqueous continuous phase. Internal aqueous droplets encapsulated by an oil membrane can be viewed as a storage chamber for hydrophilic drugs. This structure can preserve the dissolved drug in an internal aqueous phase and has shown great promise for increasing the oral bioavailability of compounds. Generally w/o/w double emulsion is prepared by modified two-step emulsification method. SDEEDS changed the process of the second emulsification step, which can self-emulsify into a w/o/w double emulsion due to gastrointestinal peristaltic movements in vivo instead of simulated emulsification in vitro. Similar to SEDDS, SDEDDS can be temporarily emulsified in mixed aqueous gastrointestinal environments. But the emulsions formed are oil-in-water (w/o/w) double emulsions and not o/w emulsions, and the drugs are incorporated into the water phase within the double emulsion. Compared to conventional thermodynamically unstable emulsions, SDEEDS are stable formulation systems. Additionally, SDEDDS can be directly filled into soft or hard gelatin capsules for ease of administration and storage. (Xiole et al 2011).

C. Bile Salts

Bile, which contains glycine and taurine conjugates of cholic acid and chenidoxycholic acid, emulsifies dietary fat and accelerates the transport of lipolysis and lipid products through the unstirred aqueous layer of the intestinal mucosa through micellar solubilization. Bile salts escaping active reabsorption in the ileum are metabolized by bacterial flora to the secondary bile salts deoxycholic acid and lithocholic acid. The decreasing order of hydrophilicity is taurine conjugate > glycine conjugate free bile salts. Polarity increases with the number of hydroxyl groups. Bile salts are able to bind calcium, their binding properties decrease with increasing hydrophilicity. No unambiguous data are available on the mechanism of increased absorption of bile salts.

This can be done by affecting mucosal layers and paracellular and transcellular absorption pathways. They affect the intestinal glycocalyx structure and have been reported to thin the gastric and intestinal mucosa. The transcellular absorption-enhancing effect is indicated by the phospholipid-disordering action of conjugated and conjugated bile salts. Colonic tight junction structures appear to be affected by relatively low bile salt concentrations (5 mM and less) in rabbits and rats. This paracellular uptake promoting effect is suggested to be mediated by binding of Ca. Although bile salts have been documented to significantly enhance drug absorption, the application of these compounds as safe absorption promoters in humans poses several complications, due to mucosal damage. On the other hand, 2 years of therapy with oral chenodeoxycholic acid (350–750 mg/day) to dissolve gallstones was accompanied by mild side effects (increased aminotransferase and cholesterol levels, diarrhea). Observations indicate that long-term therapy with bile salts containing formulations may be promising, however, the suggested co-carcinogenic and co-mutagenic effects of secondary bile salts discourage the development of bile salts containing pharmaceutical formulations (Ewoud et al1989).

D. Nano Emulsions

Nanoemulsions can be excellent vehicles for oral delivery of poorly permeable and/or highly lipophilic drugs because they can be formulated from excipients with solubilizing or even permeability-enhancing properties. Oral nanoemulsions with droplet sizes below 150 nm are almost always of the o/w type. Similar to traditional emulsions, they promote increased gastrointestinal absorption and reduce inter- and intra-individual disparities for various drugs. Additionally due to their very large interfacial area, they exhibit excellent drug release properties. Furthermore nanoemulsions can provide some degree of protection against degradation or progress in difficult organoleptic properties of active ingredients. Some nanoemulsions self-emulsify in aqueous media, making them remarkable for oral formulations. Self-emulsifying formulations can be administered as water free preconcentrates that form nanoemulsions in gastrointestinal tract fluids in situ.

Pluronics® are a class of non-ionic surfactants known for their extremely low toxicity. Pluronics®, also known as poloxamersare triblock copolymers of poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) [(EO)x(PO)y(EO)x]. They are mainly used as solubilizers, wetting agents for microemulsions and microcontainers for drugs after micellization. It has been demonstrated that Pluronics® can influence the carrier mediated transport of drugs depending on their structural design. This effect may be beneficial for the treatment of drug-resistant tumors as well as increasing the oral bioavailability of active ingredients. Various Pluronics®-based nanoemulsion systems have been discovered, which can be used to stabilize lipophilic drugs. It has been demonstrated that the formulation influences the intestinal penetration of both transcellularly and paracellularly transported drugs. They may therefore find their use for active substances with low permeability or low solubility or a combination of both problems (BCS class 2, 3 and 4 substances. Furthermore pluronics are known to inhibit p-gp-mediated drug efflux, so they are probably also used in the formulation of actively released drugs such as many cytostatics, as these formulations may find their use, e.g. For dose escalation studies, methods that cannot be tested in vivo in vitro due to their low solubility (Kartsen et al 2006).

E. Cyclodextrin Inclusion Complex

Cyclodextrins (CDs) are cyclic oligosaccharides containing d (+) glucopyranose units linked by (1, 4) glucosidic bonds. With a hydrophilic outer surface and a hydrophobic cavity lined with protons, their special structure has their intrinsic ability to form inclusion complexes with various guest molecules. CDs have the ability to interact with poorly water-soluble drugs and drug candidates to increase apparent water solubility and dissolution rate of the drug. It has also been reported in the literature that CD complexation increases the oral bioavailability of poorly water-soluble drugs. Increasing solubility also affects dissolution rate and improves oral bioavailability. It is possible to move class II drugs and sometimes class IV drugs into class I by cyclodextrin complexation. Cyclodextrin can be considered. CD is practically non-toxic on oral administration due to the lack of absorption through the intestinal tract because it is extensively absorbed in the colon. Use of cyclodextrin inclusion complexes. Eg, Exemestane is a neutral compound with a steroid structure characterized by high lipophilicity. It is freely soluble in N. N-dimethyl formamide, soluble in ethanol and practically insoluble in water (80µg/ml). The Biopharmaceutical Classification System (BCS) is a scientific framework for classifying medicinal substances based on their aqueous solubility and intestinal permeability. According to BCS, aqueous solubility and intestinal permeability are the most important constraints affecting drug bioavailability. EXE is a BCS class IV drug characterized by poor aqueous solubility and low permeability. EXE:CD inclusion complex can be prepared to improve solubility and dissolution rate and increase intestinal permeability EXE and new oral tablet formulation using EXE:CD inclusion complex can be prepared and compared with tablets in pharmaceutical market. In the light of the data it can be concluded that it is possible to prepare effective oral tablets of EXE in terms of intestinal penetration through the aqueous solubility of the drug, high dissolution rate and modified cyclodextrin, methyl cyclodextrin and especially the complexity of the swallowing mechanism.

F. Spray Freeze Dying

Spray freeze drying is another technique to increase permeability e.g. Freeze-drying spray with oleanolic acid (OA) a BCS class 4 compound polyvinyl pyrrolidone-40 (PVP-40) as a stabilizer and sodium caprate (CS) as a wetting agent and penetration enhancer to form a kinetically stable, amorphous solid dispersion system with excellent disintegration in vitro was Performance and better and more uniform absorption compared to commercial OA tablets. SFD processed OA formulations and commercial OA tablets generally exhibit large inter-animal variability in oral bioavailability, consistent with the absorption characteristics of BCS class IV compounds. Substitution of OA with sodium salt (OA-Na) in the inclusion of SC in the formulation showed a significant reduction in absorption discrepancy. The Absorption anomalies of OA can be significantly reduced by incorporating SC and using the sodium salt, OA-Na, in the formulation. The above results indicate that the improvement in both dissolution and intestinal permeability of BCS class IV drugs exemplified by the SFD processed OA-Na/PVP/SC system is uncertain to reduce the significant interindividual variability in oral absorption common with this class of compounds. (Henry et al 2010).

G. Chitosan Derivatives

Chitosan is a non-toxic, biocompatible polymer that has found many applications in drug delivery, including adsorption of hydrophilic macromolecular drugs. Chitosan, when protonated (pH 6.5), is able to increase the paracellular permeability of peptide drugs in mucoepithelia. Chitosan derivatives have been evaluated to overcome the incomplete solubility of chitosan and as absorption enhancers at neutral pH values found in the intestinal tract. Trimethyl chitosan chloride (TMC) has been synthesized at different degrees of quaternization. These quaternized polymers form complexes with anionic macromolecules and gels or solutions with cationic or neutral compounds in aqueous environments and at neutral pH values.

TMC has been shown to significantly increase the penetration and or absorption of neutral and cationic peptide analogs across intestinal epithelia. The mechanism by which TMC enhances intestinal permeability is similar to that of protonated chitosan. It reversibly interacts with components of tight junctions, leading to widening of paracellular pathways. Monocarboxy methylated chitosan (MCC) is a poly ampholytic polymer capable of forming visco-elastic gels with anionic macromolecules in aqueous environments or at neutral pH values. MCC appears to be less potent than the quaternized derivative. However, MCC enhances the penetration and absorption of low molecular weight heparin (LMWH; an anionic polysaccharide) across the intestinal epithelia. Neither of the chitosan derivatives increased cell membrane damage nor did they alter the variability of intestinal epithelia cells. (Thanou et al. 2001).

H. Saponins

Saponins are glycosides of vegetable origin that have surface tension reducing properties and hemolytic activity. They are able to enhance sterols and promote intestinal and transdermal absorption properties. It is conceivable that the absorption support properties of saponins are mediated by their surfactant like properties. On the other hand, interactions with the membrane stabilizer cholesterol may also have a transcellular promoting effect. This shows that saponins exhibit absorption enhancing activity at relatively low concentrations. However; Also for these compounds the safety vs. This issue of efficacy requires further investigation. (Ewoud et al1989).

I. Straight Chain Fatty Acids

Medium chain fatty acids, including long chain fatty acids such as capric acid (C10), lauric acid (C12) and oleic acid (C18), have been shown to increase the permeability of a series of hydrophilic drugs by tightening and/or expanding tight junctions. or altering the cytoskeleton of intestinal epithelial cells without major cytotoxicity. A major advantage of these excipients is their incorporation into conventional oral dosage forms without the need for complex or expensive formulation techniques. (Dimple et al. 2010)

IV. CONCLUSION

Significant research work has been committed to the development of oral, rectal or nasal formulations of poorly absorbed drugs with absorption modifying agents. In recent years a large number of compounds have been clearly demonstrated to have absorption promoting actions. Among these compounds, bile salts, cyclodextrins, chitosan, fatty acids appear to be the first choice candidates for additional studies, given their effective relaxation and preliminary data on their safety profile. Undoubtedly, many more techniques will be discovered in the near future to demonstrate absorption enhancing effects. One such technique is the use of animal viruses. As no unequivocal conclusions can be drawn on this point, additional research into the mechanism of permeability enhancement is highly desirable.

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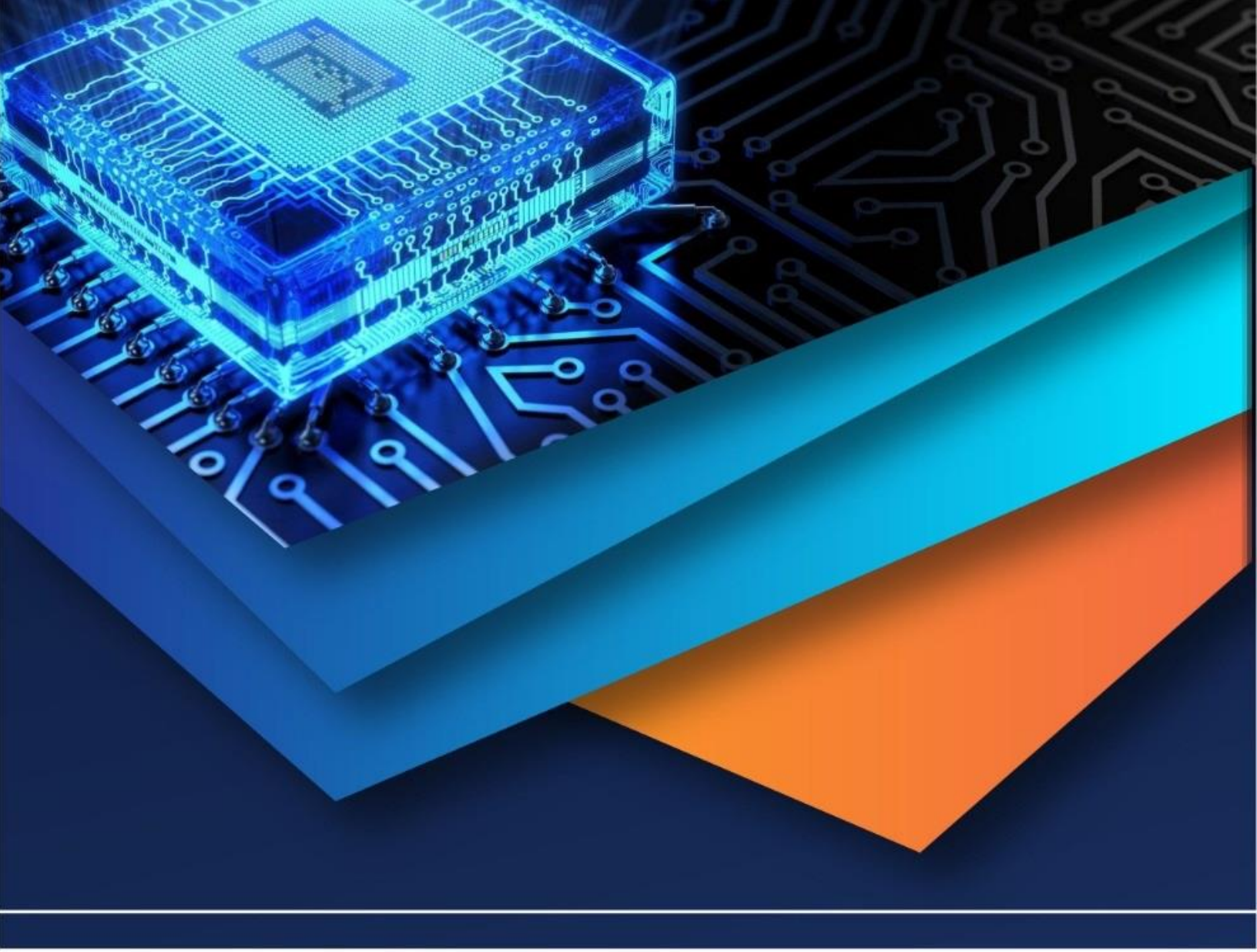

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