



ISSN: 2231-3354
Received on: 10-06-2012
Revised on: 14-06-2012
Accepted on: 19-06-2012
DOI: 10.7324/JAPS.2012.2705

Permeability Enhancement Techniques for Poorly Permeable Drugs: A Review

Shaikh MS I, Nikita D. Derle and Rajendra Bhamber

ABSTRACT

Need for an oral replacement to parenteral delivery has led to renewed attentiveness in excipients like intestinal permeation enhancers which improve oral drug bioavailability. Delivery of a drug by oral route is predominantly restricted by pre-systemic degradation and poor penetration across the gut wall. The major challenge in the oral drug delivery is the development of novel dosage forms to endorse absorption of poorly permeable drugs across the intestinal epithelium. Fifty years ago research on oral absorption enhancers that increases gut permeability was first commenced yet clinical success yet to be achieved. Development has been troubled by lack of adequate reproducibility interest as well as perceived safety concerns. We reviewed some selected permeation enhancement techniques that are advantageous for increasing permeability of poorly permeable drugs.

Keywords: Parenteral drug delivery, permeation, bioavailability, BCS, epithelium.

Shaikh Ms I, Nikita D. Derle,
Rajendra Bhamber
Dept of Pharmaceutics,
MVP's, College of Pharmacy,
Gangapur Road, Nasik (MS, India).

INTRODUCTION

Development in the field of combinatorial chemistry and high throughput screening has made it possible to generate a large number of drug candidates but it has also resulted in a number of poorly soluble and or poorly absorbable drugs. A new trend of drug development based on pharmacogenomics or development of molecular targeted drugs is also encouraging the tendency, and it does not necessarily lead to good output in terms of new drug development. Therefore it is necessary to improve the membrane permeability as well. (Fuyuki *et al* 2008). The absorption pattern of complex molecules like oligonucleotides vaccines, chimeric proteins and small peptides differ from conventional synthetic small molecular weight organic compounds. However, in all cases the solubility and permeability of a drug can be correlated with its absorption profile. All drugs are now classified according to the biopharmaceutical classification BCS into four categories on the basis of solubility and permeability to rationalize science of drug delivery and simplify complications in the drug registration of newly evolving diverse compounds for regulatory authorities.

For Correspondence
Shaikh MS I
Department of Pharmaceutics,
M.V.P.'s' College of Pharmacy,
Nashik-422002,
Maharashtra, India.
Fax No- 0253 2580250
Mob: 09175669336

Among the different classes of BCS the per oral delivery of class 3 and 4 drugs is partially or completely decreased due to their poor intestinal permeability. Due to their inauspicious physicochemical and chemical properties which are difficult to change many drug molecules show poor permeability thus an excipient may be added externally to enhance permeation transiently. (Pradeep *et al* 2005).

During the past few decades, noteworthy medical advances have been made in the field of drug delivery with the improvement of new dosage forms and techniques. For the drugs which are not absorbed by oral route other routes of drug delivery such as injection, transdermal, pulmonary or other routes are employed. However, oral route among different probable routes is most preferable because it offers significant advantages of therapeutic effectiveness and patient compliance. (Seulki *et al* 2005).

Delivering a drug by oral route is also preferred for its convenience. Tablets and capsules can be prepared in large quantity at low price. Therefore in lead optimization step of drug discovery, oral bioavailability of a drug is important. It depends on various factors the most common being intestinal permeability, solubility during gastrointestinal transit, liberation from dosage form, liability to efflux and metabolism. The importance of solubility and permeability is especially reflected in the adoption of Amidon's Biopharmaceutics Classification System (BCS) by the FDA in 2000, devised as a scientific basis to grant biowaivers for *in vivo* bioavailability and bioequivalence studies. (Cartsen *et al* 2006).

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

In this article we reviewed some basic permeability enhancement techniques which are useful for enhancing the permeability of poorly permeable drugs which are included in the class III and IV of the Biopharmaceutics Classification System (BCS) which was adopted by FDA in 2000 as a scientific basis for granting biowaivers for *in vivo* bioavailability and bioequivalence studies.

POTENTIAL ABSORPTION BARRIERS

Review has been done comprehensively to determine the barriers for the intestinal permeability of drugs. The location of these barriers may be in the unstirred water layer, the mucous layer, the apical and basal cell membrane and cell contents, the tight junctions and the wall of lymph and capillaries. Metabolic barriers of the mucosal peptidases are the other barriers which extensively condense the bioavailability of peptides and proteins.

Mucous

A mucous layer consisting of water glycoproteins (mucins), electrolytes, proteins and nucleic acids covers the epithelial cells of the entire intestine. The layer is bound to the apical surface by the glycocalyx, a 500 nm thick glycoprotein structure which is covalently linked to lipids and proteins of the brush border membrane. The unstirred water layer is composed partially of the mucous layer, and it is supposed that the minimal thickness of the unstirred water layer, 100-500µm corresponds with the mucous layer. The mucous layer maintains the pH of the epithelial surface at 6 by acting as a buffer, thus creating an acidic microclimate.

Apical cell membrane

The shape of the apical cell membrane is like a 1µm thick brush border, and it consists of a 10nm thick double layer of polar lipid molecules containing a hydrophobic and a lipophilic part. The main constituents of lipid are phosphatidylcholine, phosphatidyl ethanolamine, sphingomyline (zwitterionic), phosphatidyl serine, phosphatidylinositol, phosphatidic acid (anionic), cholesterol and lipids. For the preservation of membrane structures divalent metal ions may be necessary, Ca²⁺ chalets with negatively charged phospholipids, thus decreasing membrane permeability and lipophilicity. Proteins are entrenched in the lipid bilayer by their hydrophobic segments. For the optimal activities of membrane bound enzymes, fluid state of the membrane is required; cell preserves the membrane transition temperature (T_{in}), the temperature at which the transition from the stiff gel to the fluid liquid crystalline state occurs, below environmental temperature. A regulating action of cholesterol is employed on membrane structure, increasing fluidity of gel-state membrane and decreasing fluidity of liquid crystalline membrane. Sphingomyline has been proposed to enhance the assembling influence of cholesterol. The membrane order is also influenced by natural fatty acids, their cis-double bonds distracting phospholipid organisation. For this reasons fluidity of fluid state membranes may increase with decreasing cholesterol/phospholipid molarratio or increasing total lipid/protein ratio and double bond index thus increasing permeability. In rat colonocytes lipid fluidity decreases from proximal to distal ,transition temperatures amounting to 23-24° C and 26-27° C respectively corresponding with a high enzyme activity in the proximal segment. The transport of molecules across the phospholipid bilayer is commonly correlated with lipid-water coefficient. Subsequently the absorption of strongly hydrophilic substances is restricted by the lipid bilayer e.g. certain antibiotics and peptides. For this reason the transcellular transport of water, ions and polar solutes (e.g. monosaccharides) require other mechanisms e.g. Diffusion through pores and carrier mediated transport.

Basal cell membrane

The basal cell membrane is composed of a 9 nm thick phospholipids' bilayer which contains proteins. The lipid fluidity of the basolateral membrane surpasses apical membrane fluidity

probably because of lower content of glycosphingolipids. Hence the barrier function of the basal membrane is possibly less prominent than that of apical membrane.

Tight Junctions

Tight junctions (zonula occludentes) are regions of close communication between apical ends of epithelial cells. They are constructed of a network of strands, the permeability of tight junction increases with the decreasing strand number, thus determining the 'leakiness' of epithelium. The small intestine contains leaky epithelium, and intestinal permeability decreases in the distal direct ion running parallel with apical cell membrane permeability; the proximal colon is temperately leaky, the distal colon moderately tight. The medium sized solutes (e.g. disaccharides'), ions and water thus establishing route for passive ion permeation.

Tight junctions are cation selective & they have been suggested to be impermeable for cations with a molecular weight higher than 350 nm or a diameter exceeding 0.8 nm. Alternatively, it is conceivable that a distribution of pore sizes exists, with a large number of small pores and a few large ones. The structure of tight junction is destabilized by exposure to hypertonic solutions and by Ca^{2+} depletion. In hamster small intestine sodium coupled solute transports have been suggested to increase junctional permeability towards small peptides, sugars and amino acids.

Capillary wall

The location of capillary wall is 500 nm underneath the basal membrane. The endothelial cell membrane contains small perforations of 0.4-1 nm radius and the blood capillary wall is fenestrated, fenestrate radius amounting 20-30 nm. On the other hand lymphatic capillaries are provided with an intracellular junction of larger size, permitting passage of particles with a radius up to 300 nm. Particles with a radius smaller than 6 nm are not retained by basement membrane surrounding fenestrated capillaries. Due to the existence of large pores, the intestinal blood and lymph capillaries are not considered to execute an important barrier for drug absorption. However, it is conceivable that strongly hydrophilic drugs will be transported slowly across the capillary wall, compared with hydrophilic compounds, as their absorption site will be limited to the pore area. (Ewoud *et al* 1989).

PERMEABILITY ENHANCEMENT TECHNIQUES

Bile salts

Bile, which contains glycine and taurine conjugates of cholic acid and chenodeoxycholic acid, emulsifies dietary fat and accelerates lipolysis and transport of lipid products through the unstirred water layer of the intestinal mucosa by micellar solubilisation. The bile salts which escape from active reabsorption in the ileum are metabolised to secondary bile salts deoxycholic acid & lithocholic acid by the bacterial flora. The diminishing order of hydrophilicity is as follows taurine conjugates > glycine conjugates > free bile salts. Polarity increases with the number of hydroxyl groups. Bile salts are capable to bind calcium, their

binding properties decreasing with increasing hydrophilicity. No unambiguous data is available on the mechanism of absorption enhancement by bile salts. It may be carried out by effects on the mucous layer and on paracellular and transcellular absorption routes. They have been reported to affect the intestinal glycocalyx structure and to diminish gastric and intestinal mucous. A transcellular absorption enhancing effect is suggested by the phospholipid disordering action of unconjugated and conjugated bile salts.

Colonic tight junction structure appears to be influenced by comparatively low bile salt concentrations (5mM and lower) in rabbits and rats. This paracellular absorption promoting effect is suggested to be intermediated by binding of Ca^{2+} . Although bile salts have been validated to enhance drug uptake to a significant extent, applicability of these compounds as safe absorption promoter in man faces many complications, because mucosal damage seems to be correlated with their uptake. On the other hand, 2 year therapy with oral chenodeoxycholic acid (350-750 mg/day) for dissolution of gallstones was concomitant with mild side effects (increase of serum level of amino transferase and cholesterol, diarrhoea). This observation designates that longterm therapy with bile salts containing formulations may be promising in man. However, the suggested co-carcinogenic & co-mutagenic effects of secondary bile salts discourage the development of bile salts containing pharmaceutical formulations. (Ewoud *et al* 1989).

Nano emulsions

The nano emulsions can be outstanding vehicles for oral delivery of poorly permeable and/or highly lipophilic drugs since they can be manufactured from excipients that have solubilising or even permeation enhancing properties. Oral nano emulsions which have a droplet size of less than 150 nm, are almost from the o/w type. Similar to conventional emulsions, they promote enhanced gastrointestinal absorption and reduce inter & intraindividual unevenness for a variety of drugs. Additionally due to their very large interfacial area, they exhibit excellent drug release properties. Moreover nano emulsions may offer a certain degree of protection against degradation or may progress difficult organoleptic properties of the actives. Some nanoemulsions tend to self-emulsify in aqueous media, which makes them remarkable for oral formulations. The self-emulsifying formulations can be administered as water free pre-concentrates which in situ form nanoemulsions in the gastrointestinal tract fluids.

Pluronics® are class of non-ionic surfactants which are very well known for their very low toxicity. The Pluronics®, also known as poloxamers are triblock copolymers of poly (oxy ethylene)-poly (oxy propylene)-poly (oxy ethylene) [(EO)_x(PO)_y(EO)_x]. They are predominantly used as solubilisers, wetting agent for microemulsions and as micro container for drugs after micellization. It has been demonstrated that Pluronics® may influence the carrier mediated transport of drugs depending on their structural composition. This effect might be advantageous for the treatment of drug resistant tumours as well as to enhance the oral bioavailability of actives. Nano emulsion system based on different Pluronics® have been found, that can be used to stabilize lipophilic

drugs. It has been demonstrated that formulations have influence on intestinal permeation of both transcellularly and paracellularly transported drugs. They can, therefore find their use for actives with either low permeability or low solubility or a combination of both problems (BCS class 2, 3 & 4 substances. Furthermore since the Pluronic® are known to obstruct p-gp-mediated drug efflux, they might also be used for formulation of actively effluxed drugs like many cytostatics. Since cytotoxicity is not perceived with these formulations, they can find their use in early formulations, e.g. dose escalation studies, especially for substances that can otherwise not be tested with *in vivo/in vitro* methods due to their low solubility. (Cartsen *et al* 2006).

Cyclodextrin inclusion complex

Cyclodextrins (CDs) are cyclic oligosaccharides comprising of d (+) glucopyranose units which are attached by (1, 4) glucosidic bonds. They have an intrinsic capability of forming inclusion complexes with a variety of guest molecules owing to their special structures, with a hydrophilic external surface and a hydrophobic cavity lined with protons. CDs have the ability to interact with poorly water soluble drugs and drug candidates resulting in an increase in the drug's apparent water solubility and dissolution rates. It is also reported in the literature that CD complexation enhances oral bioavailability of poorly water soluble drugs. The increase in solubility also affects dissolution rate and improves oral bioavailability. It is possible to move the class II drugs and sometimes class IV drugs into class I through cyclodextrin complexation. Cyclodextrins can be considered practically nontoxic upon oral administration due to lack of CD absorption through intestinal tract as they are known to be extensively absorbed in the colon. Use of cyclodextrin inclusion complex.

e. g. Exemestane is a neutral compound with steroidal 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 drug substances based on their aqueous solubility and intestinal permeability. According to the BCS, aqueous solubility and intestinal permeability are the most important constraints affecting drug bioavailability. EXE a BCS class IV drug with characteristic poor aqueous solubility and low permeability.

EXE: CD inclusion complex can be prepared in order to improve the solubility and dissolution rate and enhance the intestinal permeability EXE and a new oral tablet formulation can be designed using EXE:CD inclusion complex and compared with the tablets in the pharmaceutical market. In the light of data it can be concluded that effective oral tablet formulation of EXE in terms of increased aqueous solubility of drug, higher dissolution rate and intestinal permeation by complexation to modified cyclodextrins, methyl cyclodextrin and kneading method in particular can be achieved.

Properties of EXE, which is reported in the literature as a BCS class IV drug, can be transformed by inclusion complexation,

such that EXE can be suggested to be behaving like class I or class III when complexes to cyclodextrins. This phenomenon requires further *in vivo* bioavailability studies to be better elucidated. Thus this is an encouraging approach to improve the poor bioavailability of EXE which is commonly used for long term oral administration in post-menopausal breast cancer chemotherapy. (Burcin *et al* 2010).

Spray freeze drying

Spray freeze drying is another technique for enhancement of permeability e.g. Spray freeze drying of oleonic acid (OA) a BCS class 4 compound polyvinyl pyrrolidone-40 (PVP-40) as stabilizer and sodium caprate (CS) as wetting agent and penetration enhancer produces kinetically stable, amorphous solid dispersion system with superior *in vitro* dissolution performance and better and more uniform absorption in comparison with commercial OA tablet. The SFD processed OA formulation and commercial OA tablet generally exhibit large inter-animal variability in oral bioavailability, consistent with the absorption characteristics of BCS class IV compounds. Inclusion of SC coupled with the replacement of OA with its sodium salt (OA-Na) in the formulation shows considerable decrease in the observed absorption inconsistency.

The observed absorption inconsistency of OA can be significantly decreased by inclusion of SC and the use of sodium salt, OA-Na, in the formulation. Above results suggest that improvement in both dissolution and intestinal permeability of BCS class IV drugs as exemplified by the SFD processed OA-Na/PVP/SC system is precarious to reduce the considerable interindividual inconsistency in oral absorption commonly observed with this class of compounds. (Henry *et al* 2010)

Chitosan derivatives

Chitosan is a non-toxic, biocompatible polymer that has found a number of applications in drug delivery including that of absorption of hydrophilic macromolecular drugs. Chitosan, when protonated (pH 6.5), is capable to increase the paracellular permeability of peptide drugs across mucosal epithelia. Chitosan derivatives have been assessed to overcome chitosan's incomplete solubility and effectiveness as absorption enhancer at neutral pH values such as those found in the intestinal tract. Trimethyl chitosan chloride (TMC) has been synthesized at different degrees of quaternisation. This quaternized polymer forms complexes with anionic macromolecules and gels or solutions with cationic or neutral compounds in aqueous environment and neutral pH values.

TMC has been shown to substantially increase the permeation and /or absorption of neutral and cationic peptide analogue 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 the paracellular routes. Monocarboxy methylated chitosan (MCC) is poly ampholytic polymer able to form visco-elastic gels in aqueous environments or

with anionic macromolecules at neutral pH values. MCC appears to be less potent compared to the quaternized derivative. Nevertheless MCC is found to increase the permeation and absorption of low molecular weight heparin (LMWH; an anionic polysaccharide) across intestinal epithelia. Neither chitosan derivatives aggravates damage of the cell membrane, nor therefore do they not alter the variability of intestinal epithelia cells. (Thanou *et al*2001).

Saponins

Saponins are glycosides of vegetable source with surface tension reducing properties and haemolytic action. They are capable of precipitating sterols and exert intestinal and transdermal absorption promoting properties. It is imaginable that the absorption supporting properties of saponins are mediated by their surfactants like properties. On the other hand, a transcellular promoting effect may also be caused by interaction with the membrane stabilizer cholesterol. This shows that saponins exhibit absorption promoting activity at relatively low concentrations. However; also for these compounds the issue of safety vs. efficacy requires further investigation. (Ewoud *et al*1989).

Straight chain fatty acids

The medium chain fatty acids including capric acid (C10), lauric acid (C12) and long chain fatty acids, such as oleic acid (C18) have been shown to increase the permeability of a series of hydrophilic drugs by dilating the tight junction and/or changing the cytoskeleton of the intestinal epithelial cells without prominent cytotoxicity. One of the foremost advantages of these excipients is the comfort of incorporating into the conventional oral dosage forms without the need for complex or expensive formulation technique. (Dimple *et al*2010)

Self-micro-emulsifying drug delivery systems (SMEDDS)

The GI absorption of poorly permeable drugs i.e. BCs class 4 drugs can be enhanced by using self-microemulsifying drug delivery systems. In this decade a lot of research has been conducted on developing self-micro emulsifying drug delivery systems (SMEDDS). Generally these systems are isotropic mixtures of oils, surfactants and co-solvents /co-surfactants. Once administered in to the GI system, they are diluted with gastrointestinal fluid and the gastric motility provides the agitation for the formation of a fine oil-in-water (o/w) micro emulsion (SMEDDS). The difference between a SEDDS and SMEDDS is that the former when diluted results in a droplet size between 100 & 300 nm and the later results in a droplet size of less than 50 nm. (Mallikarjun *et al* 2011).

Self-double emulsifying drug delivery system (SDEDDS)

The self-double emulsifying drug delivery systems (SDEDDS) can be used for enhancing oral bioavailability of drugs with high solubility and low permeability, but their industrial application is inadequate because of low stability. A novel formulation i.e. self-double-emulsifying drug delivery system can

be developed which is stable through formulation optimization. SDEDDS can extemporaneously emulsify to water-in-oil-in-water (w/o/w) double emulsion in the diversified aqueous gastrointestinal environment, with drugs encapsulated in the internal water phase of the double emulsions.

Water-in-oil-in-water (w/o/w) double emulsions are complex systems consisting of aqueous droplets dispersed within larger oil droplets, which are they dispersed in an aqueous continuous phase. The internal aqueous droplets encapsulated by the oil membrane can be seen as a storage chamber for hydrophilic drugs. This structure can safeguard the drug dissolved in the internal aqueous phase and have shown great promise for enhancing oral bioavailability of compounds.

Generally w/o/w double emulsions are prepared by improved two step emulsification method. SDEDDS changed the process of second emulsification step, which can self-emulsify to w/o/w double emulsions due to gastrointestinal peristaltic movements *in vivo* instead of simulated emulsification *in vitro*.

Similar to SEDDS, SDEDDS can be extemporaneously emulsified in the mixed aqueous gastrointestinal environment. But the formed emulsions are water in- oil-in-water (w/o/w) double emulsions not o/w emulsions, and drugs are encapsulated in the internal water phase of the double emulsions. Compared to conventional thermodynamically unstable emulsions, SDEDDS are stable formulation system. In addition SDEDDS can be filled directly into soft or hard gelatin capsules which are easy for administration and storage. (Xiole *et al* 2011).

CONCLUSION

Substantial research exertions have been committed to the development of orally, rectally or nasally applicable formulations of poorly absorbed drugs with absorption improving agent. In recent years a large variety of compounds have been evidently demonstrated to exercise an absorption promoting action. Of these compounds bile salts, cyclodextrins, chitosan, fatty acids appears to be contenders of first choice for additional studies, considering their effectiveness and the preliminary data on their safety profiles. Unquestionably, in the near future many more techniques will be discovered to exhibit absorption promoting effects. One such technique is use of animal viruses. As no unambiguous conclusions can be drawn on this issue, additional research is highly desirable insight in the mechanism of permeability enhancement.

ACKNOWLEDGMENT

We are thankful to our institute for providing facilities for collection of data and other work. We are also thankful to our mentor **Dr. D. V. Derle** who generously shared his wisdom and expertise with us and has provided an excellent guidance and general interest.

REFERENCES

Burcin Y., Erem B., Imran V., Murat S. Alternative oral exemestane formulation: Improved dissolution and permeation. *Int J Pharmaceutics*, 2010; 398:137-145

- Carsten B., Adrian F., Urte K., Torsten W. Comparison of permeation enhancing strategies for an oral factor Xa inhibitor using the Caco-2 cell monolayer model. *Eur J Pharmaceutics and Biopharmaceutics*. 2006; 64: 229–237
- Dimple P., Fatemeh A., Hossein Z. Intestinal permeability enhancement of levothyroxine sodium by straight chain fatty acids studied in MDCK epithelial cell line. *Eur J Pharm Sci*. 2010, 40:466-472
- Edward L. L., Steven C. S. *In vitro* models for selection of development candidates. Permeability studies to define mechanisms of absorption enhancement. *Advanced Drug Delivery Reviews*. 1997; 23: 163-183
- Ewoud J.V.H., Albertus G. D. B, Douwe D. B. Intestinal drug absorption enhancement: An overview. *Pharmac. Ther*. 1989; 44: 407-443
- Fuyuki M., Koji T., Masateru M., Ken-ichi O., Masaaki O., Kazutaka H., Toshikiro K. Novel oral absorption system containing polyamines and bile salts enhances drug transport via both transcellular and paracellular pathways across Caco-2 cell monolayers. *International Journal of Pharmaceutics*. 2009; 367: 103–108
- Henry H.Y. T., Zhen D., Geng N. W., H.M. Chan H.M., Qi C., Leon C.M. L., Albert H.L. C., Zheng Y. Spray freeze drying with polyvinylpyrrolidone and sodium caprate for improved dissolution and oral bioavailability of oleanolic acid, a BCS Class IV compound. *International Journal of Pharmaceutics*. 2011; 404: 148–158
- Mallikarjun C., Kok K. P., Yusrida D., Muthanna A., Ghassan Z. A., Mohammed J. Q. Intestinal Permeability Studies of Sulpiride Incorporated Into Self-Micro emulsifying Drug Delivery System (SMEDDS). *Pak. J. Pharm. Sci*. 2011; 24:113-121
- Masateru M., Takanori M., Hajime T., Masaaki O., Ken-ichi O., Kazutaka H., Toshikiro K. Importance of bile acids for novel oral absorption system containing polyamines to improve intestinal absorption. *Journal of Controlled Release*. 2006; 115: 130–133
- Pradeep S., Manthena V.S.V., Harmander P.S. C., Ramesh P. Absorption enhancement, mechanistic and toxicity studies of medium chain fatty acids, cyclodextrins and bile salts as peroral absorption enhancers. *Farmaco*. 2005; 60: 884–893
- Seulki L., Sang k. k., Dong Y. L., Kyeongsoon P., Tadiparthi S., Su Y. C., Youngro B. Cationic Analog of Deoxycholate as an Oral Delivery Carrier for Ceftriaxone. *Journal of Pharmaceutical Sciences*. 2005; 94: 2541–2548
- Thanou M., Verhoef J.C., Junginger H.E. Oral drug absorption enhancement by chitosan and its derivatives. *Advanced Drug Delivery Reviews*. 2001; 52: 117–126
- Van der Merwe S.M., Verhoef J.C., Verheijden J.H.M., Kotze A.F., Junginger H.E. Trimethylated chitosan as polymeric absorption enhancer for improved peroral delivery of peptide drugs. *European Journal of Pharmaceutics and Biopharmaceutics*. 2004; 58: 225–235
- Xiaole Q., Lishuang W., Jiabi Z., Zhenyi H., Jie Z. Self-double-emulsifying drug delivery system (SDEDDS): A new way for oral delivery of drugs with high solubility and low permeability. *International Journal of Pharmaceutics*. 2011; 409:245-251