**Abstract**

Diabetes mellitus is a group of syndromes characterized by hyperglycemia. This can be controlled through medication and insulin. The current insulin therapy regimen involving multiple daily subcutaneous injections places a heavy burden of compliance on patients. It has prompted interest in developing alternative, less invasive routes of delivery. The oral route is considered to be the most convenient and desired route of drug delivery. Oral delivery eliminates the pain caused by injection, psychological barriers associated with multiple daily injections. Oral delivery of Insulin as a non-invasive therapy for Diabetes Mellitus is still a challenge to the drug delivery technology, because insulin is degraded by the enzymes in the acidic environment of stomach. Its unconvinced absorption through the gastrointestinal mucosa brings a challenging environment for pharmaceutical scientist. For developing oral protein delivery systems with high bioavailability, various approaches are mostly helpful in protecting insulin from enzymatic degradation. Using several approaches such as penetration enhancers, chemical modification, bio adhesive drug delivery systems, use of microspheres and nanoparticles improves bioavailability of insulin. Even though various techniques have their own limitation and advantages, the oral route scores more than others. Attempts have been made to deliver the insulin orally due to ease of administration by patients. So there is no doubt to develop the oral insulin drug delivery system. This review is an attempt to illustrate the use of oral insulin drug delivery in diabetes management benefiting many diabetic patients with promising patient compliance.

**Keywords:** Diabetes mellitus, Insulin, non-invasive delivery systems, Oral delivery system

**Introduction**

The oral route is considered to be the most convenient and desired route of drug delivery, especially when repeated or routine administration is necessary. Insulin is usually administered to diabetic patients through subcutaneous injection. However, the problems encountered with subcutaneous insulin injections are pain, allergic reactions, hyperinsulinemia, and insulin lipodystrophy around the injection site.

Insulin if administered through the oral route will help to eliminate the pain caused by injection, psychological barriers associated with multiple daily injections such as needle anxiety and possible infections. In addition, oral insulin is advantageous because it is delivered directly to the liver, its primary site of action, via the portal circulation, ultimately leads towards better patient compliance. Looking towards a novel formulation owing to the above distinct benefits, pharmaceutical technologists have been trying to take it as a challenge to formulate an oral delivery system for insulin as a frontier area of research. As a result pharmaceutical companies are in a race and solely focusing in oral insulin delivery which seems to produce a fruitful result and will add a new era for the management of Diabetes in near future.\(^2\)

![Fig. 1: It shows Structure of Insulin \(^3\)](image)

**Potential Problems with Oral Insulin:**

Though oral insulin may have physiological advantages, it may raise problems innate to oral...
medication in general. For instance, the rate and extent of absorption of an oral drug are often affected by food and may differ if the drug is administered shortly before a meal or after a meal as compared to administration under fasting conditions. The optimal timing for oral insulin ingestion depends at least in part on the tools used for drug delivery and will need to be determined for each oral insulin in development. The food effect is likely to determine how the oral insulin will be used and for what indication. One other issue is that all the polypeptide and protein delivery platforms developed thus far have relatively low bioavailability. Low bioavailability is a forerunner of significant inter- and intrasubject variability. A way to reduce variability is to increase the amount of insulin in the dosage form. Until recently such a proposition was impractical for insulin because of commercial considerations. At the present time, however, the supply of insulin and its price can support such a strategy. Low bioavailability also implies that most of the insulin ingested is not absorbed and remains in the gastrointestinal tract. It is most likely that insulin retained in the gastrointestinal tract will be degraded by peptidases and proteases. Nevertheless, a concern that will need to be addressed in long-term safety studies is whether insulin, a known mitogen implicated in an increased risk of several cancers, including colon cancer, will increase the incidence of cancer when given orally. Finally, though insulin may not be toxic, the chemical compounds employed in the various delivery systems as excipients or absorption promoters need to be deemed safe and effective in long-term toxicological and clinical studies.[4]

Challenges to Oral Insulin Delivery:
Administration of peptides and proteins such as insulin through Oral route is not recommended as the stomach degrades the enzymes very quickly which ultimately leads to inactivation and digestion of proteolytic enzymes in the intestinal lumen, poor permeability across intestinal epithelium because of its high molecular weight and lack of lipophilicity. The oral bioavailability of most peptides and proteins therefore is less than 1%. The challenge here is to improve the bioavailability to anywhere between 30 – 50%.[5, 6]

Enzymatic Barrier:
The harsh environment of the gastrointestinal tract (GIT) causes insulin to undergo degradation. This is because digestive processes are designed to breakdown proteins and peptides without any discrimination. Insulin therefore undergoes enzymatic degradation by pepsin and pancreatic proteolytic enzymes such as trypsin and α-chymotrypsin. Overall, insulin is subjected to acid-catalyzed degradation in the stomach, luminal degradation in the intestine and intracellular degradation. The cytosolic enzyme that degrades insulin is insulin-degrading enzyme (IDE). Insulin is however not subject to proteolytic breakdown by brush border enzymes. Insulin can be presented for absorption only if the enzyme attack is either reduced or defeated. [7, 8, 9]

Intestinal Transport of Insulin:
Another major barrier to the absorption of hydrophilic macromolecules like insulin is that they cannot diffuse across epithelial cells through lipid-bilayer cell membranes to the blood stream. In other words, insulin has low permeability through the intestinal mucosa. There is no evidence of active transport for insulin. It has been found however that insulin delivery to the mid-jejunum protects insulin from gastric and pancreatic enzymes and release from the dosage form is enhanced by intestinal microflora. Various strategies have been tried out to enhance the absorption of insulin in the intestinal mucosa and in some cases, they have proven successful in overcoming this barrier. [10, 11]

Fig.3: It shows Barriers to absorption of drug in the intestine.

Dosage form stability:
The activity of proteins depends on the three-dimensional molecular structure. During dosage form development, proteins might be subject to physical and chemical degradation. Physical degradation involves modification of the native structure to a higher order structure while chemical degradation involving bond cleavage results in the formation of a new product. If a protein needs to survive transit through the stomach and intestine, knowledge and assessment of stability parameters during formulation processing is of utmost importance.

Attempted Oral Insulin Delivery Systems:
Most peptides are not bioavailable from the GIT after oral administration. Therefore, successful
oral insulin delivery involves overcoming the enzymatic and physical barriers and taking steps to conserve bioactivity during formulation processing. In developing oral protein delivery systems with high bioavailability, three practical approaches might be most helpful:

- Modification of physicochemical properties such as lipophilicity and enzyme susceptibility.
- Addition of novel function to macromolecules.
- Use of improved carrier systems. [11, 12]

The various oral delivery systems which have been attempted to deliver insulin orally either singly or in a synergistic approach can be categorized as follows:

**Enzyme Inhibitors:**

Insulin degraded in the GIT by pepsin and other proteolytic enzymes. Enzyme inhibitors slow the rate of degradation of insulin which increases the amount of insulin available for absorption. The earliest studies involving enzyme inhibitors were carried out with sodium cholate along with aprotinin which improved insulin absorption in rats. Significant hypoglycemic effects were also obtained following large intestinal administration of insulin with camostatmesilate, bacitracin. Other inhibitors which have shown promise are leupeptin, FK-448, a potent and specific inhibitor of chymotrypsin and chicken and duck ovomucoid. In one study, polymers cross-linked with azoaromatic groups formed an impervious film to protect insulin from digestion in the stomach and small intestine. Upon reaching the large intestine, the indigenous microflora degraded the polymer film, thereby releasing the drug into the lumen of the colon for absorption. The use of enzyme inhibitors in long-term therapy however remains questionable because of possible absorption of unwanted proteins, disturbance of digestion of nutritive proteins and stimulation of protease secretion. [13, 14, 15]

**Penetration Enhancers:**

Another strategy for oral insulin delivery is to promote absorption through the intestinal epithelium by permeation enhancement. Hydrophilic molecules like insulin are adsorbed to the apical membrane and are internalized by endocytosis. Another theory suggests absorption via paracellular transport.

Tight junctions between each of the cells in the epithelium prevent water and aqueous soluble compounds from moving past those cells. Hence, approaches for modulating tight-junction permeability to increase paracellular transport have been studied. A number of absorption enhancers are available that cause these tight junctions to open transiently allowing water-soluble proteins to pass. Absorption may be enhanced when the product is formulated with acceptable safe excipients. These include substances like bile salts, surfactants, trisodium citrates, chelating agents like EDTA, labrasol. Insulin transport across Caco-2 cells was shown to be dramatically increased by conjugation of insulin with TAT, a cell penetrating peptide (CPP). The drawbacks with penetration enhancers include lack of specificity, i.e., they allow all content of the intestinal tracts including toxins and pathogens the same access to the systemic bloodstream, and risk to mucous membranes by surfactants and damage of cell membrane by chelators. Mucoadhesive polymers have been proven to be safe and efficient intestinal permeation enhancers for the absorption of protein drugs. The zonulaoccludens toxin, chitosan, thiolated polymers, and Pz-peptide have all demonstrated capacity to increase macromolecular drug absorption.

Combination strategies involving enzyme inhibitors and absorption enhancers have been effective in increasing bioavailability of insulin. Combinations like sodium cholate and soybean trypsin inhibitor, sodium laurel sulphate and aprotinin have resulted in reduction in blood glucose in dogs. [16]

**Carrier Systems:**

The oral bioavailability of insulin can be enhanced by the use of novel carrier systems which deliver insulin to the target site of absorption. Liposomes, microspheres and nanoparticles have been developed for use as carrier systems for insulin. [2]

**Liposomes:**

These are tiny spheres formed when phospholipids are combined with water. Encapsulating insulin in liposomes results in enhanced oral absorption of insulin. However, the high doses of liposome-entrapped insulin required coupled with variability in glycemia response limits its use. Other drawbacks include instability, leakage of entrapped drug, and low drug carrying capacity. [2, 17]

**Fig.4:** It shows Encapsulation of insulin in liposomes.
Microspheres:
Insulin can be encapsulated in a microcapsule or dispersed in a polymer matrix. Microspheres are prepared by emulsification using natural (gelatin or albumin) or synthetic polymers (polylactic or polyglycolic acid). Morishita et al used microspheres for insulin delivery in rats. Their study showed that L-microspheres carrying insulin and aprotinin enhanced insulin absorption. Insulin-loaded alginate microspheres complexed with cyclodextrins have an absorption enhancing effect leading to increase in bioavailability.

Qi and Ping studied the oral co-administration of insulin enteric microspheres with sodium N-(8-2-hydroxybenzoyl amino) caprylate (SNAC). EDTA was administered before the insulin oil solution was given to rats. A decrease in glucose levels, which primarily resulted from EDTA’s enzyme inhibiting properties, was observed. In a recent study, Eudragit S100 microspheres on oral administration protected insulin from proteolytic degradation in the GIT and produced hypoglycemic effect. Microspheres encapsulated with chitosan phthalate polymer protect the insulin from enzymatic degradation with an insulin-loading capacity of 62% and may be a potential carrier for oral insulin delivery. \[2, 18, 19, 20, 21\]

Nanoparticles:
Nanoparticles have been extensively studied as carriers for oral insulin delivery. Polymeric nanoparticles (nanocapsules and nanospheres) are of special interest from a pharmaceutical point of view. The biological effect of insulin nanocapsules depends on the amount of both insulin and polymer. The nature of polymers strongly influences the nanoparticle size and release profile.

The intensity and duration also depends on the site of administration (65% ileum, 59% stomach, 52% duodenum and jejunum, 34% colon). The nanoparticles protect insulin against enzymatic degradation in vitro. Synthetic polymers used for nanoparticle formulation include polyalkylcyanoacrylate, polymethacrylic acid, polylactic-co-glycolic acids (PLGA).

Natural polymers used include chitosan, alginate, gelatin, albumin and lectin. Chitosan has been the proven to have good permeation enhancing abilities via the paracellular pathway. A recent study showed that insulin-loaded nanoparticles shelled with chitosan could effectively reduce the blood glucose level in a diabetic rat model. An exhaustive review of nanoparticles as a potential oral delivery system for proteins has been done by Rieux et al. \[22, 23, 24\]

Chemical Modification:
Modifying the chemical structure and thus increasing its stability is another approach to enhance bioavailability of insulin. An example of chemical modification is that of hexyl-insulin monoconjugate (HIM-2) wherein a short chain polyethyleneglycol (PEG) linked to an alkyl group is in turn linked to LYS of the beta chain of insulin. Alteration of the physicochemical characteristics leads to enhanced stability and resistance to intestinal degradation of oral insulin. Shen et al recently demonstrated improved efficacy of orally administered insulin by conjugating insulin with transferrin through disulfide linkages. \[25, 26\]

Bioadhesive Systems:
Mucoadhesive delivery systems adhere to the mucous gel layer covering mucosal membranes. A high drug concentration is therefore present for absorption due to the intimate contact with the mucosa. As a result, numerous mucoadhesive delivery systems like chitosan, sodium salicylate, and polyoxyethylene-9-laurylether have been proposed. The bioadhesive systems may however be affected by the mucous turnover of the GIT, which varies based on the site of absorption. \[2, 27\]

Emulsions:
Cho and Flynn developed water-in-oil microemulsions in which the aqueous phase is insulin and oil phase is lecithin, non-esterified fatty acids and cholesterol in critical proportions. In vivo studies showed substantial reduction in blood glucose. Recent studies have focused on enteric-coated dry emulsion formulations prepared from solid-in-oil-in-water emulsions. These responded to changes in external environment suggesting potential application for oral insulin delivery. \[28\]

Hydrogels:
These are cross-linked networks of hydrophilic polymers, which are able to absorb large amounts of water and swell, while maintaining their three-dimensional structure. Complexation hydrogels are suitable candidates for oral delivery of proteins and peptides due to their abilities to respond to changes in pH in the GI tract and provide protection to the drugs from the harsh environment of the GI tract.
Oral administration of insulin has been an attractive concept in research. The lining of the mouth and throat. The advantage from oral spray is indistinguishable to an insulin injection in its ability to lower blood glucose levels.

**Other Approaches:**

**Tablets**

Thiolated chitosan insulin tablets: The efficacy of orally administered insulin has also been improved using thiolated chitosan. 2-Iminothiolane was covalently linked to chitosan and the resulting chitosan-TBA (chitosan-4-thiobutylamidine) conjugate exhibited 453.5 ± 64.1 µmol thiol groups per gram of polymer (A.H. Krauland et al., 2004). Two enzyme inhibitors Bowman-Birk-Inhibitor (BBI) and Elastatinal were covalently linked to chitosan. Chitosan-TBA conjugate (5 mg), insulin (2.75 mg), the permeation mediator reducer glutathione (0.75 mg), and the two inhibitor conjugates (in each case 0.75 mg) were compressed to make chitosan-TBA-insulin tablets. Control tablets were also prepared using chitosan and insulin. Chitosan-TBA-insulin tablets showed a controlled release of insulin over 8 h. In vitro mucoadhesion studies showed that the mucoadhesive/cohesive properties of chitosan were at least 60-fold improved by the immobilization of thiol groups on the polymer. [30, 29]

**Oral insulin pills**

Insulin administration in the form of a pill has always been an attractive concept in research. Due to abundant limitations of this mode of insulin administration, efficacy has been hard to demonstrate. Research has focused on overcoming these limitations by stabilising the degradation, improving the permeability, and adding absorption promoters to protect the insulin as it passes through the stomach.

**Oral spray**

A substitute to injected insulin that is currently being explored by researchers is a mouth spray containing insulin that would be absorbed through the lining of the mouth and throat. The liquid formulation allows the insulin to be absorbed by the mucus membranes in the cheeks, tongue, and throat. The advantage from oral spray is indistinguishable to an insulin injection in its ability to lower blood glucose levels.

**Pulmonary or inhaled insulin**

The inhaled insulin system delivers a dose of insulin, either in liquid or dry powder form, through the mouth, directly into the lungs, where it enters the blood circulation as quick-acting insulin. With inhaled insulin, the highly permeable alveolar epithelium and large surface area of the lungs provide a useful, efficient portal for macromolecular delivery.

**Developments in oral insulin delivery:**

The oral delivery of insulin has always been a significant challenge for pharmaceutical researchers. The development of oral insulin is at different stages for different companies and covers a broad spectrum from pre-clinical testing to Phase II clinical trials. A notable advancement is the completion of phase II trials of oral insulin product, hexyl-insulin monoconjugate (HIM 2) which has been found to be safe and well tolerated. Human clinical trials with conjugated insulin are a clear demonstration that proteins can be developed into therapeutically viable products. In October 2006, Emisphere announced preliminary results of Phase II trials of oral insulin product developed with Eligen™ technology. Emisphere’s Eligen™ technology makes use of small hydrophobic organic compounds that interact non-covalently with macromolecules, increasing their lipophilicity and enhancing absorption. Covalent and non covalent drug modifications for increasing membrane permeability are currently employed by two companies, Nobex (now Biocon) and Emisphere Technologies. Clinical trials with type 1 and type 2 diabetic patients have demonstrated initial efficacy, but low bioavailability (estimated at 5%) continues to be a problem. [2]

**Market Status of Oral Insulin Products:**

IN-105 (Biocon, Bangalore):

Biocon is developing the IN-105 conjugated insulin molecule, administered as a tablet. This oral insulin pill has polymers added at specific locations...
in the B chain of the insulin to prevent insulin from getting destroyed in the stomach (insulin is made up of two polypeptide chains namely, chain-A with 21 amino acids and chain-B with 30 amino acids, which are held together by two disulfide bonds). Biocon’s R&D group has successfully developed a carefully selected formulation to give consistent absorption through the intestines, delivering the glucose-lowering effect. In the clinic, this molecule has completed phase I trials and is expected to enter phase II in India later this year to illustrate proof of concept. The encouraging results of the phase Ia and Ib studies represent a pivotal hurdle crossed in the development of IN-105 as a product. IN-105 will enter phase I trials in Europe towards the end of the year.

Oral-lyn (Generex Biotechnology, Canada)

Oral-lyn is the company’s proprietary oral insulin spray product. The liquid formulation is absorbed into the body by the lining of the inner mouth using the company’s proprietary Rapid Mist device. Since it is buccally absorbed, no insulin is deposited in the lungs by the Oral-lyn RapidMist. August 2007 saw the commercial launch of Oral-lyn in the Indian market. Generex Biotechnology entered into Master Product Licensing and Distribution Agreement of Oral-lyn with Shreya Life Sciences, the fourth largest distributor of insulin in India. In April 2008, Generex entered into a similar agreement for the distribution of Oral-lyn in China, Hong Kong, and the following additional countries: Indonesia, South Korea, Malaysia, the Philippines, Singapore, Thailand, and Vietnam. Presently, Generex Oral-lyn is in phase III clinical trials at several sites around the world – US, Canada and Ukraine.

Transgene (Biotek, Andhra Pradesh)

Transgene has developed an oral delivery technology which combines several oral delivery approaches into a single drug delivery system. Unique in its approach, this technology involves using biodegradable novel polymeric nanoparticles loaded with insulin as a new carrier to ferry the insulin across the intestinal epithelial tissues. Nanoparticles are solid spherical particles with a size range of 10 and 1,000 nm containing dispersed drugs. Transgene has attempted to improve the intestinal absorption of insulin and other peptides. The technology has been well proven in animal models, and human clinical studies are in progress. Drug companies are obviously interested in the potential of oral insulin to net a massive share of the market, and therefore, investment in research is substantial and ongoing. Biocon, Transgene Biotek and Generex Biotechnology have proven to be insightful in the race to enhance the treatment of diabetes, and are definitely ahead of the pack. [30]

**Conclusion**

The oral route for insulin delivery is possible in the now with the use of superior materials as carriers for insulin delivery systems. Maximization of the absorptive cellular intestinal uptake and stabilization of insulin at all stages before it reaches its target will determine its final efficiency. The chances for a market launch will depend on several factors such as efficacy and safety as well as economic reasons. Although considerable efforts have been already made to deliver insulin orally, extensive and continuous comparison of in-vitro and in-vivo studies are essential to develop oral insulin delivery systems.

**References**


17. Spangler RS. Insulin administration via liposomes. Diabetes Care, 13(9), 911-922.


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