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Oral Insulin Delivery: Facts, Developments and Challenges

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Abstract

Diabetes mellitus is a group of syndromes characterized by hyperglycemia which could be managed and controlled through medication and Insulin The current advocacy of intensive insulin therapy regimens involving multiple daily subcutaneous injections places a heavy burden of compliance on patients and 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 which will help eliminate the pain caused by injection, psychological barriers associated with multiple daily injections and possible infections. Oral delivery of Insulin as a non-invasive therapy for Diabetes Mellitus is still a challenge to the drug delivery technology, since it is degraded due to the presence of enzymes in the acidic environment of stomach and also its absorption through the gastrointestinal mucosa is questionable. In developing oral protein delivery systems with high bioavailability, various practical approaches might be most helpful like protecting insulin from enzymatic degradation, use of penetration enhancers , chemical modification, Bioadhesive delivery system, use of microspheres and nanoparticales to improve bioavailability of insulin. Despite, various techniques each having its own limitation and advantages, the oral route scores over the others for the ease of comfort with which the therapeutic agents can be administered to the patients work on attempts to deliver insulin orally has definitely gathered momentum and is no longer considered with pessimism to develop the oral insulin drug delivery system.

Key words: Diabetes mellitus, Insulin, Oral delivery system, Lipodystrophy.

Introduction

Diabetes mellitus is a group of syndromes characterized by hyperglycemia, altered metabolism of lipids, carbohydrates and proteins, and an increased risk of complications from vascular disease. Diabetes mellitus is a major disease characterized by derangement in carbohydrate, fat

and protein metabolism, affecting nearly 10% of the population. In the recent past many hypoglycaemic agents are introduced, still the diabetes and the related complications continue to be a major medical problem not only in developed countries but also in developing countries.
It can, however, be managed and controlled through medication. Insulin is a protein hormone secreted by the β -cells of the islets of Langerhans in the pancreas. It is secreted in response to elevated blood glucose and amino acid levels, and promotes the efficient storage and utilization of these fuel molecules by controlling the transport of metabolites and ions across the cell membrane. Insulin promotes the entry of glucose, fatty acids and amino acids into cells and enhances glycogen, protein and lipid synthesis. Therapeutic Insulin is typically administered via subcutaneous injection. However, some important issues are related to this approach to diabetes management. First, a patient diagnosed in early adolescence might require more than 50,000–60,000 separate injections over his or her lifetime. Second, therapeutic insulin and blood glucose profiles due to injected insulin differ from physiological profiles, which include basal and glucose-responsive insulin secretion. [1, 2] Subcutaneous (S.C.) injections of identical insulin doses may lead to considerable intra- and inter-individual differences in the current metabolic control of patients with diabetes mellitus. This well-known variability of the metabolic effect of insulin hampers practical insulin therapy considerably. A number of studies have been published describing the variability of insulin absorption from the S.C.depot. Only in a few published studies has the variability of insulin action after S.C. administration been quantified. [3]

Viable non-injectable insulin delivery route would thus dramatically improve both compliance and quality of life in patients with diabetes. Alternative routes for insulin delivery that have been investigated include intrapulmonary [4] intrauterine,[5] oral[6] ocular, nasal, [7] buccal,[8] and transdermal [9] systems. However, results to date indicate problems related to poor absorption, high proteolytic degradation, and/or variable delivery times. Consequently, bioavailability is low, and response times are difficult to predict accurately. Attempts at replicating physiological insulin secretion by means of restoring the normal metabolic milieu and thereby minimizing the risk of diabetic complications, has become an essential feature of insulin treatment. However, despite advances in the production, purification, formulation and methods of delivery of insulin which have occurred in recent years, this has met with limited success. The current advocacy of intensive insulin therapy regimens involving multiple daily subcutaneous injections places a heavy burden of compliance on patients and has prompted interest in developing alternative, less invasive routes of delivery. To date, attempts to exploit the nasal, oral, gastrointestinal and transdermal routes have been mainly unsuccessful. [10]

The oral route is considered to be the most convenient and desired route of drug delivery, especially when repeated or routine administration is necessary [11].Insulin is usually administered to diabetic patients through subcutaneous injection. However, the problems encountered with S.C. insulin injections are pain, allergic reactions, hyperinsulinemia, and insulin lipodystrophy around the injection site [12]. Insulin if administered via the oral route will help eliminate the pain caused by injection, psychological barriers associated with multiple daily injections such as needle anxiety [13] and possible infections [14]**.** In addition, oral insulin is advantageous because it is delivered directly to the liver, its primary site of action, via the portal circulation, a mechanism very similar to endogenous insulin; subcutaneous insulin treatment however does not replicate the normal dynamics of endogenous insulin release, resulting in a failure to achieve a lasting glycemic control in patients. [15, 16] In light of the above distinct

benefits, pharmaceutical technologist has been trying to design an oral delivery system for insulin.

Challenges to Oral Insulin Delivery:

Oral delivery of Insulin as a non-invasive therapy for Diabetes Mellitus is still a challenge to the drug delivery technology, since it is degraded due to the presence of enzymes in the acidic environment of stomach and also its absorption through the gastrointestinal mucosa is questionable. **[**17] Generally, peptides and proteins such as insulin cannot be administered via the oral route due to rapid enzymatic degradation in the stomach, inactivation and digestion by proteolytic enzymes in the intestinal lumen, and poor permeability across intestinal epithelium because of its high molecular weight and lack of lipophilicity. [18, 19, 20] 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%. [21]

Enzymatic Barrier: [*22, 23]*

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. Insulin can be presented for absorption only if the enzyme attack is either reduced or defeated.

Intestinal Transport of Insulin:

Insulin has low permeability through the intestinal mucosa [15]. There is no evidence of active transport for insulin. [24] 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. [25, 26] 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.

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. [22] 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.

Approaches towards 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 [23] and taking steps to conserve bioactivity during formulation processing. [27] In developing oral protein delivery systems with high bioavailability, various practical approaches might be most helpful:

1. Protecting insulin from enzymatic degradation by using antiproteolytic agents.
2. Promoting the gastrointestinal absorption of insulin through simultaneous use of a multitude of different penetration enhancers.
3. Chemical modification of insulin to improve its stability.
4. Bioadhesive delivery systems for enhancement of contact of the drug with the mucous membrane lining the gastrointestinal tract.
5. Carrier systems such microspheres and nanoparticles which can improve the bioavailability of insulin.

Enzyme Inhibitors:

Insulin is 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. [22] Administration of insulin via microspheres, together with the protease inhibitors like aprotinin, trypsin inhibitors, chymotrypsin inhibitors, Bowman –brik inhibitors could be found to be the most efficacious combination involving protease inhibitors. The simultaneous release of these inhibiters and insulin in the intestine will prevent the proteolytic degradation and increases the bioavailability of insulin in one such study gelatin microspheres containing trypsin inhibitors caused greater hypoglycaemic effect than microspheres without the same [28, 29]

Limitations: Formulations of insulin with protease inhibitors such as aprotinin have typically shown inconsistent effects; with *in vitro* and *in vivo* effects often being different. 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.[30]

Penetration Enhancers:

Penetration enhancers can increase the absorption of peptides and proteins in the gastrointestinal tract by their action on transcellular and paracellular pathways of absorption. Even if the intact molecule of insulin reaches the intestine, due to the large molecular size and relatively impermeability of the mucosal membrane it might not absorbed in sufficient concentration to produce the required biological effect. One possible approach to overcome this drawback is to use penetration enhancers. **[**31] A number of absorption enhancers are available that causes 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. [32]

These substances include bile salts, surfactants, trisodium citrates, chelating agents like EDTA [33] labrasol [34] Insulin transport across Caco-2 cells was shown to be dramatically increased by conjugation of insulin with TAT, a cell penetrating peptide (CPP). [35] Surfactants and fatty acids affect the transcellular pathway by altering membrane lipid organization and thus increase the absorption of drugs consumed orally. Bile salt micelles, EDTA and trisodium citrate have been reported to increase the absorption of insulin. Cyclodextrins have also been used to enhance the absorption of insulin from lower jejunal and upper ileal segments of rat small intestine

Limitations: 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 [36] and risk to mucous membranes by surfactants and damage of cell

membrane by chelators **[**37] Surfactants can cause lysis of mucous membrane and may thus damage the lining of the gastrointestinal tract. Similarly, chelators such as EDTA cause depletion of Ca^{2+} ions, which may in turn cause disruption of actin filaments and thus damage the cell membrane.

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.

Liposomes:
These are tiny spheres formed when phospholipids are combined with water. Encapsulating insulin in liposomes results in enhanced oral absorption of insulin. [37]

Limitations: The high doses of liposome-entrapped insulin required coupled with variability in glycemic response limits its use. [38] Other drawbacks include instability, leakage of entrapped drug, and low drug carrying capacity**.**

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) [38, 39] 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 [40, 41] studied the oral co-administration of insulin enteric microspheres with sodium N-(8-2-hydroxybenzoyl amino) caprylate (SNAC). In a recent study, Eudragit S100 microspheres on oral administration protected insulin from proteolytic degradation in the GIT and produced hypoglycemic effect. [42] 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. [43]

Nanoparticles :
Nanoparticles have been extensively studied as carriers for oral insulin delivery. [44] The nanoparticles protect insulin against in vitro enzymatic degradation. [45] Synthetic polymers used for nanoparticle formulation include polyalklylcyanoacrylate [46] polymethacrylic acid [47] polylactic-co-glycolic acids (PLGA) **[**48] Natural polymers used include chitosan [49] alginate, gelatin, albumin [50] and lectin. [51] Chitosan has been the proven to have good permeation enhancing abilities via the paracellular pathway [52]

Limitations*:* The nanocapsules of insulin prepared using polyisobutyl cyanoacrylate as polymeric carrier showed initial low plasma concentration followed by higher plasma concentration after sometime, with no significant net enhancement of absorption. Hence, from carrier systems, insulin gets released slowly into intestinal lumen, with small amounts being absorbed.

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 2 (HIM-2) wherein a short chain polyethylene glycol (PEG) linked to an alkyl group is in turn linked to LYS-29 of the beta chain of insulin.[53] Alteration of the physicochemical characteristics leads to enhanced stability and resistance to intestinal degradation of oral insulin [54]**,** Xia CQ et al recently demonstrated improved efficacy of orally administered insulin by conjugating insulin with transferrin through disulfide linkages. [55]

Limitations: Chemical modification does not always lead to improved oral absorption. For example, diacyl derivatives of insulin exhibited a higher proteolysis than native insulin in the small intestine of rat under *in vitro* conditions

Bioadhesive Systems:
Bioadhesive drug delivery systems anchor the drug to the gastrointestinal tract, and have been widely investigated to prepare sustained release preparations for oral consumption of drugs. The anchoring of the drug to the wall of the gastrointestinal tract increases the overall time available for drug absorption because the delivery system is not dependent on the gastrointestinal transit time for removal. Moreover, a drug administered through this method does not need to diffuse through the luminal contents or the mucus layer in order to reach mucosal epithelium lining the gastrointestinal tract. Because of intimate contact with the mucosa, a high drug concentration is presented for absorption, and there is also the possibility of site-specific delivery if bioadhesion can be targeted to occur at a particular site in the gastrointestinal tract. Numerous mucoadhesive delivery systems like chitosan [56] sodium salicylate, and polyoxyethylene-9-lauryl ether [57] have been reported to improve the oral absorption of insulin. Carrier systems such as nanoparticles, microspheres and liposomes can also be used to improve the oral absorption of peptides and proteins.

Limitations: The bioadhesive systems may be affected by the mucous turnover of the gastrointestinal tract, which varies based on site of absorption. Moreover, directing a delivery system to a particular site of adhesion in the gastrointestinal tract is yet to be achieved. **[**58]

Emulsions:
Cho and Flynn [59] 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. Invivo studies showed substantial reduction in blood glucose. These responded to changes in external environment suggesting potential application for oral insulin delivery. [60]

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. [61]

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. [62] A notable advancement is the completion of phase II trials of oral insulin product, hexyl-insulin monoconjugate 2 (HIM 2) which has been found to be safe and well tolerated. [63]

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 noncovalently 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**. [**15] Magnetic responsive particles were designed for use in oral delivery of insulin. Magnetite nanoparticles (12 nm average size) were synthesized and co-encapsulated with insulin into poly(lactide-co-glycolide) (PLGA) resulted in 66% reduction of blood glucose level in the presence of external magnetic field.[64] Another recent advance in the creation of an oral insulin delivery system is insulin delivered in liquid form as oral drops were testing at a pre-clinical level by The Transgene Biotek Ltd, in conjunction with the Pharmacology Division of the Indian Institute of Chemical Technology, Hyderabad, India.[65] Nobex has completed five exploratory Phase II studies in both Type I and Type II diabetic patients to evaluate the safety and efficacy of its rapid-acting oral insulin for controlling blood glucose. [66] The development of oral insulin using the eligen(®) technology represents a significant advance in insulin administration which is expected to improve the quality of life of diabetic patients. As clinical studies progress, a great deal of interest has focused on the process by which this technology enables insulin absorption from the intestinal lumen into the bloodstream. The eligen(®) technology employs low molecular weight compounds (termed drug delivery agents or carriers) which interact weakly and non-covalently with insulin, increasing its lipophilicity and thereby its ability to cross the gastrointestinal epithelium. [67]

Conclusion

Among the various route of insulin administration, each having its own set of favorable and unfavorable properties, the oral route scores over the others for ease of comfort with which the therapeutic agents can be administered to the patients work on attempts to deliver insulin orally has definitely gathered momentum and is no longer considered with pessimism. [68] Since the discovery of insulin more than 70 years ago, injection has been the only method of delivery. The benefits of intensive injected insulin therapy to control blood glucose have been validated in large clinical studies but the risk of hypoglycemia from the intensive use of insulin has increased as a result. In addition, diabetic patients who depend on insulin must endure the discomfort, inconvenience, and social awkwardness of injections, often resulting in inadequate patient compliance that can lead to serious complications. Moreover, many Type II diabetic patients who are advised by their physician to initiate insulin therapy are reluctant to start insulin injections**.** There is a great need for a needle-free insulin delivery device that fulfils the criteria of being safe, efficient, user friendly, cost effective and that mimics the secretion of insulin from

the healthy pancreas. Current guidelines for the management of type 2 diabetes advocate the initiation of oral hypoglycaemic agents, with insulin as a treatment of last resort. Earlier initiation of insulin may reduce morbidity and mortality from the complications of diabetes. [69] The results of such clinical trials only can predict whether this new millennium would witness the replacement of needles by oral insulin tablets, capsules and liquids.

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