Review Article

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ORAL INSULIN DELIVERY: AN OVERVIEW

Swamy P V *, Phanisri D D, Prasanna Rani G

Department of Pharmaceutics, Shri Vishnu College of Pharmacy, Bhimavaram, West Godavari District, Andhra Pradesh, India

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*Corresponding author

E-mail: vspadavala@svcp.edu.in

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ABSTRACT

Oral insulin is an exciting space of research and development within the field of diabetology. The oral route is taken into account to be the foremost convenient and desired route of drug delivery, particularly, when repeated or routine administration is necessary. Diabetes mellitus is a serious pathologic condition that is to blame for major healthcare problems. Insulin replacement therapy has been employed in the clinical management of diabetes mellitus for over 90 years. So, the development of oral insulin remains an ultimate goal to both enhance ease of use and to produce therapeutic benefits rooted in its direct delivery to the portal vein and liver. This brief review covers the importance, novel approaches of oral insulin delivery as well as challenges, market status and future perspectives of oral insulin products.

Keywords: Oral insulin, insulin replacement therapy, diabetology, diabetes mellitus, hypoglycemia, hyperinsulinemia.

INTRODUCTION

Insulin has saved the lives of infinite individuals, since its discovery in 1922. The primary oral Insulin preparations were tried, with poor results, by Joslin, in 1922 and 1923. Since then, several researchers have worked on this idea, with no success. Diabetes mellitus may be a common disease and its complications are responsible for excess morbidity and mortality, loss of independence and reduced quality of life. Diabetes happens due to either the pancreas not producing enough insulin, the maximum amount needed by the body or the cells of the body not responding properly to the insulin made, i.e., cells desensitized of insulin made (Figure 1). Current insulin medical care for diabetes mellitus involves frequent dosing of subcutaneous injections inflicting native discomfort, patient noncompliance, hypoglycemia and hyperinsulinemia. Thus, novel approaches for insulin delivery are being explored and investigated.¹

Oral insulin is one among the foremost exciting areas of development within the treatment of diabetes as a result of its potential advantages in patient convenience, speedy insulinization of liver, adequate insulin delivery avoiding peripheral hyperinsulinemia whereas probably avoiding adverse effects of weight gain and hypoglycemia. Growing proof that earlier initiation of intensive insulin therapy produces sustained tight glycemic management leading to substantial delay in complications makes a good oral insulin product even important for the management of patients with diabetes. The aim of this review is to summarize and emphasize the challenges that precipitate via oral route of administration of insulin in conjunction with novel approaches and to review the current state of affairs in relevance of oral insulin.²⁻⁵

Importance of Oral Insulin

Earlier, the stress of oral delivery was a lot because of convenience and avoidance of needles. With the present understanding of diabetes, extra stress has additionally been

placed on the physiological importance of the hepatic route of delivery.⁶

Accessible insulin preparations fail to mimic the endogenous insulin pathway wherever the injectable insulin analogues area unit delivered on to the peripheral circulation, thus reversing the insulin concentration gradient in traditional physiology and as a result, insulin reaches the liver at a lot of lower concentrations than those in non-diabetic people.⁷

Resistance to injectable insulin has been known as a significant reason for clinical inertia and lack of fate of target glycemic goals. Moreover, oral insulin, devoid of the apprehension and distress related to insulin injections, could bring this drug from expedient medical care to the forefront.⁸⁻¹²

However, oral administration is thought to be a stronger route of administration owing to its cost-effectiveness and well established satisfactoriness and particularly as a result, it permits avoiding the needle.¹³ In fact, oral delivery of insulin permits high portal vein concentrations, with no sustained peripheral hyperinsulinemia, that is related to neuropathy and retinopathy.¹⁴

Additionally, oral insulin is advantageous as a result of its delivery on to the liver, its primary site of action, by mechanism very similar to endogenous insulin; subcutaneous insulin treatment,¹⁵⁻¹⁷ however doesn't replicate the conventional dynamics of endogenous insulin release, leading to a failure to achieve a long-lasting glycemic management in patients.¹⁸

Rationale of Oral Insulin

Physiological Rationale

Orally administered insulin better replicates the normal physiological insulin pathway and leads to better glucose homeostasis.⁷ After its absorption from the intestinal lumen, insulin is transported via the portal circulation to the liver (Figure

2 and Figure 3). Interestingly, oral insulin plays a significant role in protection of β -cells of the pancreas from autoimmune destruction.¹⁹⁻²²

Pharmaceutical Rationale

It has been suggested that oral insulin offers induction of oral tolerance or immune modulating effect which is likely to help in prevention of diabetes.²³⁻²⁵ The theory behind this phenomenon is that oral administration of a low dose of antigen alters responsiveness of systemic T cell to that antigen which seems to inhibit autoimmune diseases.^{26,27} Despite its lower bioavailability, oral delivery of peptides showed high level of acceptance by patients with improved level of compliance.⁷

Barriers to Oral Insulin

However, the fundamental barrier to the oral delivery of proteins or oral insulin delivery is the gastrointestinal tract (GIT), which functions as an absorptive and protective organ. Some existing barriers could be categorized into 3 main sub-types, namely physical, biochemical and formulation based.⁷

Physical Barriers

Mucous Barrier

Mucus is the first barrier which functions as both diffusion and enzymatic barrier encountered by polypeptides. Mucus is continuously secreted and probably because of its negative charge, it filters out positively charged drugs and proteins by electrostatic interaction.²⁸

Intestinal Epithelium

The intestinal epithelium is composed of a single layer of columnar epithelial cells. Passive diffusion is limited to lipophilic drugs less than 700 Daltons in molecular weight, and because the molecular weight of insulin is 5800 Daltons, this renders transcellular passive diffusion of insulin into cells very difficult.^{29,30}

Tight Junctions

This dynamic structure is selectively permeable to small hydrophilic molecules (nutrients, ions and certain drugs). Solutes of molecular radius more than 15 Å are usually excluded from crossing this barrier.^{31,32}

Biochemical Barriers

Luminal pH

pH varies from highly acidic (1.2-3.0) in the stomach to slightly basic (6.5-8.0) in the intestine. Such pH variation can cause pH-induced oxidation and deamination of protein drugs.^{33,34}

Enzymatic Degradation

Insulin is predominantly degraded by trypsin, α -chymotrypsin and carboxypeptidases in the mucous layer as well as intestinal lumen, with research also showing the existence of a specific insulin-degrading enzyme (IDE) on the brush-border membrane. These types of drugs that do cross the intestinal epithelial barrier then undergo further degradation in the liver (hepatic first-pass metabolism).³⁵

Formulation Barriers

The fabrication method could be the last barrier in formulation of peptide drugs. Being a sensitive polypeptide hormone and any conformational changes to insulin structure would affect its biological activity.³⁶ Better ways for formulation of oral peptide drugs have been tackled by many scientists through various approaches by focusing on overcoming of intestinal hurdles and ensuring high bioavailability.³⁷ Then emerging techniques are basically aiming to improve pharmacokinetic and pharmacodynamic characteristics of the hormone.⁷

Oral insulin outlook

Several research groups have attempted to deliver insulin orally with a limited degree of success.³⁸ Typically, depending on the formulation approach, the pharmacokinetics (PK) of the oral insulin's have been either rapid (onset of action within 20 min) or delayed release (onset of action within 1-3 h). In all the published studies of oral insulin formulations, duration of action typically corresponds to the PK and is either short or intermediate acting.⁴

Short-acting Oral Insulin

Early attempts were made to understand if insulin could be absorbed via the portal vein by directly injecting insulin in the intestinal loop.³⁹ In another study, a hexylresorcinol solution containing insulin was administered to 10 healthy volunteers.⁴⁰ The study successfully showed a reduction in blood glucose levels, but concluded that oral delivery of insulin exhibits great variability and poor bioavailability. Recently, short-acting oral insulins with varying times of onset are being developed by Emisphere Technologies and Biocon. Emisphere's oral insulin uses a proprietary polyethylene (PE) which helps in absorption of insulin. The rapidity of absorption in PK studies indicated a time to insulin C_{max} of ~20 min from the time of administration and the plasma insulin levels return to baseline within 80-120 min.⁴¹⁻⁴³

Intermediate or Delayed-acting Oral Insulin

There are several reports on the encapsulation of insulin using nanoparticles and it has been successfully shown to reduce the glucose levels in animal models.⁴⁴ IntesulinTM, long-acting oral insulin, involves encapsulation of insulin in nanoparticles made of bioadhesive polymers. A study conducted in streptozotocin induced diabetic rats showed a statistically significant reduction in glucose levels in 15 min from the time of administration all the way up to 300 min. Another company Oramed has developed an oral insulin capsule, which has been tried in early phase clinical trials. The technology involves an enteric coated capsule where the insulin is released in the intestine; absorption is promoted by use of a PE.⁴⁵ A study in 8 normal healthy volunteers showed administration of an oral form of insulin in the fasted state demonstrated a reduction in blood glucose (7-37%) and a significant decrease in C-peptide levels in all formulations (13-87%).^{46,47}

Novel Approaches for Oral Insulin Delivery

Various workers have tried different approaches to overcome the above-mentioned barriers. The suggested approaches trialed for oral insulin delivery can be classified into as follows.²

Attempted oral insulin delivery systems

Generally, bioavailability of most of the peptides is very negligible or not possible after oral administration in gastrointestinal tract. While developing oral protein delivery

systems with high bioavailability, three practical approaches might be most helpful.⁴⁸ These are: effectively modifying physiochemical properties such as lipophilicity and enzyme susceptibility; addition of novel functions to macromolecules (proteins and peptides) and using improved carrier systems.

Following approaches can be categorized as various oral delivery systems which have been attempted for oral delivery of insulin either singly or in a synergistic manner.¹⁸

Penetration Enhancers

Insulin is a hydrophilic molecule adsorbed to the apical membrane and is internalized by endocytosis. Tight junctions present between each of the cells in the epithelium prevent transport across the cell of water and aqueous soluble compounds.⁴⁹ Hence, approaches designed for modulating tight-junction permeability to increase paracellular transport have been studied. A countless absorption enhancers are available that cause these tight junctions to open transiently allowing water soluble proteins to pass. In a study, work on penetration enhancers has proven mucoadhesive polymers to be safe and efficient intestinal permeation enhancers for the absorption of proteinaceous drugs.^{2,18}

Enzyme Inhibitors

Enzyme inhibitors can be used to avoid the rapid enzymatic degradation of insulin by enzyme pepsin in stomach and other pancreatic proteolytic enzymes in gastro-intestinal tract.⁵⁰ Enzyme inhibitors slow down the rate of degradation of insulin in gastrointestinal tract which in turn increases the amount of insulin available for absorption.⁵¹ The use of enzyme inhibitors in long term therapy however is considered to be highly risky because of possible absorption of unwanted proteins. In a study, polymers cross-linked with azo-aromatic groups formed a resistant or withstanding film to protect insulin from digestion in the stomach and small intestine.⁵²

Chemical Modification

Effective modification in the chemical structure of proteins and peptides may result in appreciable enhancement in bioavailability by increasing its stability against possible enzymatic degradation or its membrane penetration.⁵³ Since proteins are structurally having more complex chemical structure as compared to peptides, this approach is more applicable to peptides as compared to proteins. The covalent attachment of polyethylene glycol (PEG) to therapeutic peptides has been utilized previously; the technology is called PEGylation. Another example of structural modification has been pioneered by Emisphere's EligenTM.⁵⁴

Various carrier systems

Liposomes

Dose-dependent hypoglycemia is observed in case of insulin-entrapped liposomes. Liposomes with varying composition have been prepared by researchers via two methods. Those are solvent evaporation, hydration and solvent spherule evaporation. Liposomes which contain lecithin 100 mg, cholesterol 20 mg, insulin 150 units and 1% v/v Tween 80 were found to be most effective for this purpose. The effect of insulin-liposome was extended in diabetes-induced rabbits than that of normal rabbits.⁵⁵

Hydrogels

These are cross-linked networks of hydrophilic polymers, which are able to absorb large amounts of water and swell, while maintaining their 3D structure. Complexation hydrogels are preferential or useful candidates for oral delivery of proteins and peptides because of their ability to respond to changes in pH in the GI tract and provide protection to the drugs from the disturbing environment of the GI tract.⁵⁶

Nanospheres

Insulin-loaded nanospheres were prepared by polymerization of isobutyl cyanoacrylate in an acidic medium. These nanospheres showed a mean size of 145 nm and an association rate of 1 unit of insulin per milligram of polymer. These nanospheres were placed in an oily medium containing surfactant and evaluated for *in vitro* and *in vivo* degradation. No *in vitro* degradation was observed due to proteolytic enzyme. These nanospheres were administered per orally in streptozotocin induced diabetic rats and observed that 50% decrease in fasted glucose levels up to 10-13 days.⁵⁷

Erythrocytes

Human RBCs have been studied as oral carrier systems for human insulin. In a study, Male Wistar rats were made diabetic by a single intra-peritoneal injection of Streptozocin (100 mg/kg). Rats received orally one of the following: an insulin solution (100 U/2 ml), a ghosts-insulin suspension, a vesicles-insulin suspension, a liposome-ghosts-insulin suspension, or a liposome vesicles-insulin suspension. Free-carrier suspensions or sodium chloride solution (0.9% w/v) were used as controls. Blood glucose concentration was noted before administration and at 1, 2, 3, 4, 5, 6, and 7 h after administration. Results showed that all treatment groups, except liposome-ghosts-insulin, were appreciably different statistically from their respective controls.⁵⁸

Nanocubicles

A liquid formula that can be easily dispersed in water to produce particles termed as "Nanocubicles" was developed. These Nanocubicles holding insulin were administered to fasted streptozotocin induced diabetic rats. To contrast, an aqueous solution of insulin in water was also administered. Nanocubicles without insulin and with insulin in phosphate buffered saline were administered as controls. Blood glucose concentration and insulin concentration were measured at 1, 2, 3, 4 and 6 h after administration of insulin formulation. It was observed in these studies that the serum glucose concentration was controlled for more than 6 h after oral insulin administration but returned to the basal concentration in 3 h when 1 IU/kg of insulin was injected through intravenous route.⁵⁹

Microspheres

Insulin-loaded microspheres composed of chitosan 3% (w/v) and loading 120 IU insulin were produced by emulsion cross-linking method. Cross-linking time for it is almost 5 h and glutaraldehyde 3.5% (v/v) was used as cross-linker. To predict release of insulin from chitosan microspheres, swelling ratio studies were conducted. Chitosan is a polymer with mucoadhesive properties that increases the contact with mucosa, where drugs are absorbed, resulting in a concentration gradient required for its absorption. Microspheres of chitosan are extensively used for providing a controlled release of peptides and proteins, such as insulin. It helps in enhancing the bioavailability of peptide, as well as the uptake of other hydrophilic substances through epithelial layers

with improved protection against the unfavorable and disagreeing environment of stomach upon oral administration.⁶⁰

Other Approaches

Tablets

Thiolated chitosan insulin tablets: Another approach for improving efficacy of orally administered insulin is by using thiolated chitosan. 2-Iminoethanol was covalently linked to chitosan to produce chitosan-TBA (chitosan-4-thiobutylamine) conjugate. Bowman-Birk inhibitor (BBI), a soybean-derived protease inhibitor, and Elastatinal two enzyme inhibitors, were covalently linked to chitosan. Chitosan-TBA-insulin tablets were compressed by using Chitosan-TBA conjugate (5 mg), insulin (2.75 mg), glutathione (0.75 mg), and the two inhibitors conjugates (in each case 0.75 mg). Control tablets were also developed by using chitosan and insulin. Chitosan-TBA insulin tablets produced a controlled release of insulin over 8 h. *In vitro* mucoadhesion studies suggest that the mucoadhesive/cohesive properties of chitosan were at least 60-fold improved by the immobilization of thiol groups on the polymer.⁶¹

Micro-emulsions

Water-in-oil micro-emulsions in which, aqueous phase is insulin and oil phase is lecithin, non-esterified fatty acids and cholesterol in critical amounts was developed. *In vivo* studies demonstrated that micro-emulsions produced substantial reduction in blood glucose level. Recent research has focused on enteric-coated dry emulsion formulations prepared from solid-in-oil-in water emulsions. These modes of administration responded to changes in external environment suggesting potential application for oral insulin delivery.⁶²

Oral Insulin pills

This mode of insulin administration has so many limitations associated with it and efficacy regarding it has been hard to demonstrate. Main focus of research regarding this mode of administration is to overcome these limitations by stabilizing the degradation, improving the permeability, and adding absorption promoters to protect the insulin as it passes through the stomach.⁶³

Oral Spray

Oral mouth spray containing insulin when administered 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 benefit from oral spray is similar to an insulin injection in its capacity to lower blood glucose levels.^{64,65}

Pulmonary or inhaled insulin

In case of inhalational delivery system of insulin, a dose of insulin, either in liquid or dry powder form, delivered through the mouth, directly into the lungs, where it enters the blood circulation as rapid-acting insulin. The mostly permeable alveolar epithelium and large surface area of the lungs impart an effective,

efficient portal for macromolecular delivery, i.e., inhaled insulin.⁶⁶⁻⁶⁸

Market Status of Oral Insulin Products

IN-105 (Biocon, Bangalore)

Biocon is developing the IN-105 conjugated insulin molecule, administered as a pill. This oral insulin pill has polymers accessorial at specific locations within the B chain of the insulin to stop insulin from being degraded within the stomach by detrimental surroundings. Biocon's R and D cluster has with success developed a carefully chosen formulation to allow consistent absorption through the intestines, delivering the glucose-lowering effect. During this clinic, the 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 part 1a and 1b studies represent a crucial hurdle crossed within the development on IN-105 as a product.² IN-105 will enter phase I trials in Europe towards the end of the year.

Oral-Lyn (Generex Biotechnology, Canada)

Oral-Lyn is that the proprietary oral insulin spray product of company Generex Biotechnology, Canada. Oral-Lyn contains a liquid formulation that is absorbed into the body by the lining of the inner mouth using the company's proprietary Rapid Mist device. Because it is buccal absorbed, no insulin is deposited within the lungs by the Oral-Lyn Rapid Mist. The Oral-Lyn was launched in Indian market on August 2007. Generex Biotechnology entered into market product licensing and contract of Oral-Lyn with Shreya Life Sciences, which is the fourth largest distributor of insulin product in India. Generex entered into an analogous agreement for the distribution of Oral-Lyn in China, Hong Kong and also the following countries: Indonesia, South Korea, Malaysia and The Philippines in April 2008. Generex Oral-Lyn is in phase III clinical trials at many sites round the world US, Canada and Ukraine.¹⁸

Transgene (Biotek, Andhra Pradesh)

Transgene has developed an oral delivery technology which mixes many oral delivery approaches into one drug delivery system. Unique in its approach, this technology involves utilizing biodegradable novel polymeric nanoparticles loaded with insulin as a replacement carrier to move the insulin across the intestinal epithelial tissues. Nanoparticles are unit solid spherical particles with a size range of 10-1000 nm containing distributed drugs. Transgene has tried to enhance the intestinal absorption of insulin and alternative peptides. The technology has been well tested 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.¹⁸

Transgene Biotek, Biocon and Generex Biotechnology have proven to be insightful in the race of oral insulin delivery and undoubtedly doing a revolutionary work in history of insulin replacement medical care.²

Figure 1: Epicatechin in the control of glucose homeostasis: Involvement of redox-regulated mechanisms

Figure 2: Absorption mechanisms of orally administered insulin

Figure 3: Orally administered insulin better replicates the normal physiological insulin pathway and leads to better glucose homeostasis

CONCLUSION

Non-invasive hormone and peptide administration have been a motivating challenge for an extended time within the pharmaceutical drug delivery field. Oral insulin delivery has been a motivating and promising research field that guarantees to revolutionize the way diabetes is treated. Many studies have achieved some advanced results, and a few delivery systems are units in advanced stages of development. The route of insulin administration by subcutaneous route into the body of patient is an exceedingly non-physiological manner. There is a massive body of data within the literature outlining completely different techniques and methods to boost oral insulin bioavailability, as well as proof-of-concept. Studies are indicating the potential feasibility of productive oral insulin administration; whereas the primary century of insulin medical care targeted on providing, purification and improved pharmacokinetics.

Research in the long run, can probably concentrate on development of additional easy and physical formulations that may minimize the chance of hyperglycemia, weight gain and different insulin medical care associated complications. The most focus of research in oral insulin delivery is targeted towards overcoming insulin degradation and enhancing its absorption in GIT. However, solely any research into delivery systems can make it feasible for the oral route to represent a viable route of administration. Maximization of the absorptive cellular intestinal uptake and stabilization of insulin at all stages before it reaches its target can verify its final potency.

The possibilities for a market launch can rely on many factors like efficacy and safety yet as economic reasons. Though good enough efforts are already created to deliver insulin orally, intensive and continuous comparison of *in vitro* and *in vivo* studies are unit essential to develop oral insulin delivery system within the predictable future.

Future perspective

Recent reports, together with proof-of-concept studies, and early clinical studies, however, are a good reason for optimism that oral insulin can presently become a reality.¹ Insulin modification looks to be a very promising approach for the oral delivery of insulin within the future as a result of it will survive inside the GI tract, also as having a longer shelf life. The initial cost for the changed insulin can be high; however, with the developments in biosimilars, these costs can be reduced.³

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