Review Article

Int J. Pharm. Drug. Anal, Vol: 9, Issue: 2, 2021; 66-70

International Journal of Pharmaceutics and Drug Analysis

Availabe at www.ijpda.com ISSN: 2348:8948

Oral insulin delivery for treatment of diabetes mellitus

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Received: 11 April 2021 Revised: 04 May 2021 Accepted: 13 May 2021

Abstract

Diabetes mellitus is characterized by a condition known as hyperglycemia which may be controlled through medication and insulin. Current insulin therapy for diabetes mellitus involves frequent dosing of subcutaneous injections, causing local discomfort, patient incompliance, hypoglycemia, and hyperinsulinemia, among others, one of the approaches to overcoming these issues is to administer insulin through oral route. An oral form of insulin has been the elusive goal for many investigators since the protein initial discovery by Banting and Best in 1922. Oral delivery of insulin is one of the promising and anticipated areas in the treatment of diabetes, primarily because it may significantly improve the quality of life of patients who receives insulin regularly. However, there are several challenges in developing an oral route for insulin delivery; include low bioavailability due to rapid enzyme degradation in the stomach, inactivation, and digestion by proteolytic enzymes in the intestinal lumen, poor permeability, and poor stability. Several companies have developed technology platforms that protect polypeptides and proteins from enzymatic hydrolysis, enable their transport across the epithelial lining, and promote their absorption from the GI tract. Most notably, the use of permeation enhancers, protease inhibitors, enteric coatings, and polymer microsphere formulation will be covered, including commentary on which methods hold more promise towards the successful development of oral insulin. This review, considers the current literature on the advances, methods, needs, and challenges in the development of oral insulin.

Keywords: Proteins, permeations enhancers, enteric coatings, polymer microsphere.

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DOI: https://doi.org/10.47957/ijpda.v9i2.463

Produced and Published by

South Asian Academic Publications

Introduction

Diabetes mellitus is a metabolic disorder characterised by hyperglycaemia, glycosuria, hyperlipidaemia, and sometimes ketonemia. Two major types of diabetes mellitus are Type 1 or insulin dependent diabetes mellitus and Type 2 or non-insulin dependent diabetes mellitus. Diabetes mellitus is a common disease and its complications are responsible for excess morbidity and mortality, reduced quality of life. Diabetes mellitus is a major healthcare problem worldwide. Diabetes can be controlled through medication and insulin. In addition, the oral route of insulin delivery provides ease of administration, eliminates the pain caused by injection, the decreases chances of infection, improves the absorption rate and mimics the normal route of insulin secretion. A major challenge is to deliver protein drugs like insulin appropriately and effectively. Administration of insulin is limited to the subcutaneous route as it requires one or more daily injections which may lead to peripheral hyperinsulinemia [1]. Thus, several research studies are seeking for the progress of new formulation of insulin which can be given by oral route. Therefore, oral novel formulations of insulin will prove to be successful key for management of insulin. Oral insulin is delivered directly into the liver via portal circulation, which is similar to endogenously produced insulin. This review aims to provide an update on the oral insulin approaches under development. This article focuses on oral insulin delivery via the GI tract because this has highest patient compliance and avoids the

discomfort and disadvantages of the subcutaneous route of insulin delivery [2].

Current routes of insulin delivery and their problems

The present mode of insulin administration is by subcutaneous route. Insulin is injected subcutaneously having many inherent disadvantages includes

1. Raises the risk of hypoglycaemia
2. Can promote weight gain
3. Some people may be uncomfortable about injecting
4. Pain at injection site
5. Expensive

Benefits of Oral Insulin

1. Patient compliance
2. Convenient mode
3. Painless
4. Easy for self-medication
5. Cost effective
6. Reduce hypoglycaemia

Needs of Oral Insulin

Resistance to injectable insulin has been identified as a major reason for clinical inertia and lack of achievement of target glycaemic goals. Physicians as well as patients fear the complexity of insulin regimens, the risk of hypoglycaemia, and the chances of weight gain, as well as the necessity of a needle prick, with insulin therapy. Insulin is perceived to have a high index of intrusion as the conventional insulins need to be given prior to meals. Patients anticipate the early development of an oral insulin, as it will be easy to administer, have a lower index of intrusion, be more convenient, and have more compliance or adherence from the patient, and finally lead to better glycaemic control and thus prevention of complications of diabetes.

Oral insulin may improve b-cell function by providing diabetes via induction of oral tolerance or immune modulation. Oral insulin is able to achieve a high proto-systemic insulin exposure and may obviate the excessive weight gain sometimes seen with subcutaneous insulin. Oral insulin may also be able to correct the blunting of first-phase release of insulin, which is difficult with conventional subcutaneous insulins [3].

Potential Problems With Oral Insulin

While oral insulin may have physiological advantages, it may raise problems inherent to oral medication. 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 condition.The optimal timing for oral insulin ingestion depends at least in part on the technology 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 harbinger 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 [4]. Finally, while insulin per 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.

Approaches For Oral Insulin

Numerous approaches have been applied in order to increase the bioavailability of oral insulin designed both at preserving the insulin towards enzymatic degradation in the GIT and improving their permeability throughout the intestinal epithelial layer. The main approaches are

- Chemical modification to insulin
- Mucoadhesive system
- Protease inhibitors
- Absorption enhancers
- Particulate delivery system

Chemical Modification

A number of researches have been conducted to change or add particular molecules to the structure of insulin to improve in bioavailability and solubility in the GIT and offer prevention of proteolytic enzymes. Insulin-

transferrin conjugates undergo receptor-mediated endocytosis throughout intestinal epithelial cells, that contributes to a substantial hypoglycaemic response in comparison to insulin control [5].

Emisphere established a technique, which involves a non-covalent complexation with non-acyl amino acids that leads to unfolding of the insulin structure to expose hydrophobic side chains that stimulates excellent translocation across the lipid bilayer. When insulin passes across the membrane layer, the complex dissociates, and the insulin comes back to its native conformation. Even though emisphere technological innovation has demonstrated promising outcomes for oral delivery of several therapeutic macromolecules, the formulation is known to trigger nausea in individuals and the quantity of the delivery agent is orders of magnitude higher than the peptide/protein drugs, making it clinically ineffective.

Other researches have evaluated site specific oligomeric modification, which are believed to improve half-lives in vivo and offer higher enzymatic resistance when compared with native insulin have also been researched to improve cellular translocation. It was discovered that CPP-insulin conjugates improved transport by 6-8 times throughout a Caco-2 cell line [6].

Protease Inhibitors

Because trypsin and chymotrypsin are the proteolytic enzymes mainly accountable for the breakdown of insulin in the GIT, researches have focused on neutralizing these enzymes particularly. Co-administration of insulin with enzyme inhibitors provides a viable means to avoid the enzymatic barrier in obtaining the delivery of insulin and to increase bioavailability in the GIT. The selection of enzyme inhibitors will rely on the structure of insulin. Information on the specificity of proteolytic enzyme is important to assure the stability of the insulin in the GIT.

Some permeation enhancers like taurocheno deoxycholate, dimethyl-a-cyclodextrin or glycoholic acid enhanced the bioavailability of insulin and capric acid, fatty acid, was most effective against a-chymotrypsin. A number of researches have indicated that while the use of protease inhibitors improves oral insulin bioavailability, there is still the problem of low permeability, and therefore these strategies must frequently be coupled with other methods. For instance, fatty acids and bile salts have been explored as a method to retard enzymatic degradation and after translocation across the intestinal epithelium. This is considered to happen by modifying the nature of the cellular membrane or facilitating paracellular uptake by opening tight junctions. A new category of enzyme inhibitor, which is known as duck ovomucoid demonstrated 100% protective effect against trypsin and alpha-loading of destruction of insulin in vivo for one hour at 1:2 ratio of enzyme inhibitor. Moreover, polymer-inhibitor conjugates for example CMC Bowman- birk inhibitor and CMC-elastinal have provided in vitro protection against elastase, alpha chymotrypsin and trypsin. Particularly CMC Ela exhibited higher inhibitory activity towards elastase, such that almost 33% of insulin remained stable against proteolytic attack even after 4hour of incubation.

Permeation Enhancers

Mucosal absorption enhancers have also been explored and co-administered with insulin to enhance paracellular permeability. Cyclodextrins, bile salts, trisodium citrates, chelating agents like EDTA, surfactants, fatty acids and terpenes have all been demonstrated to improve translocation across the intestinal mucosa.

Many of these permeation enhancers have been used to insulin delivery systems. Surfactants assist in improving transcellular transport by increasing the fluidity of the cell membrane and calcium chelators assist to enhance paracellular transport mediated by modulating the tight junction of the cells by complex formation with calcium ions.

Mucoadhesive Systems and Mucus Penetration

The mucoadhesive properties of certain polymers have been applied to extend the residence time of the insulin at its absorption site by increasing the contact with mucosa which infact enhance the concentration gradient of the insulin. In polymeric mucoadhesive initial intimate contact between polymer and mucus, diffusion appears to play an important role in the establishment of adhesive interactions; polymers diffuse and entangle with mucin fibres, while bonding is concurrently established, interaction could be either covalent [example; disulphide bridging with cysteine residue of mucin] or non-covalent [example; hydrogen bonding, electrostatic forces, hydrophobic interactions, van der waals bonding]. The dynamic balance between diffusion, physical entanglement and repulsive/adhesive interactions contributes to the consolidation of adhesion. The surface properties of the micro/nanoparticles will affect its transport through the mucus [1,2]. The

micro/nanoparticles mobility also appears to be highly influenced by surface charges. Transport rates were inversely associated with micro/nanoparticles surface potentials, with negatively charged micro/nanoparticles showing substantially greater transport rates than near neutral, or positively charged micro/nanoparticles whose transport was severally restricted, probably by particle aggregation and electrostatic adhesive interaction with mucin fibres [6].

A balance between mucoadhesion and mucus penetration is essential for successful oral delivery. Since particles immobilized by mucus are cleared from the mucosal tissue, the elaboration of mucus-penetrating systems is a primary concern to enhance mucosal drug delivery. Particles have to be small enough to avoid substantial steric inhibition by the fibre mesh and should avoid adhesion to mucin fibres. Concurrently, they should have mucoadhesive properties to prolong retention time and contact with intestinal mucosa [7,8].

Particulate Carrier Delivery System

Encapsulation is the phrase used to indicate the inclusion of an active agent into a particle of various wall material, like a phospholipid or polymer. Two of the main reasons to encapsulate an active agent in drug delivery are for protection and to control release. The active agent can be preserved from PH extremes hydrolytic conditions, or the individual may be protected from the active agent, which could possibly present toxicity and health problems or possess an unpleasant taste or odour. The target location for release and the release profile can be determined by excipient selection, formulation optimization and particle engineering. For instance, in mucosal drug delivery system, materials are usually chosen to enhance epithelial permeability by reversibly opening tight junctions between cells or by improving contact time with the mucosa via bioadhesive forces. Chitosan is one of the biopolymers that can both reversibly open tight junctions and possess high mucoadhesion.

Micro/nanoparticles is the term for describing the incorporation of the active material into micro and nano sized particles respectively. This method is often used in the pharmaceutical industry to influence the pharmacokinetics of a therapeutic, enhance stability and minimize toxicity. Microspheres and nanoparticles are typical terms including both micro or nanospheres and micro or nano capsules. Micro or nanospheres have a matric structure in which the peptides/protein can be absorbed either at the surface or throughout the internal of the particle. Micro or nano capsules, in constract, possess a shell type structure in which the therapeutic is coated in the center of the particle and surrounded by a protein or polymeric coating. When selecting formulation techinques for encapsulating drugs, factors like shear stress, temperature and PH have to be considered to prevent denaturation of the active materials. In addition, an effective method must be scalable to produce industrial levels while reducing cost.

Several Companies Work on Oral Insulin Are

Apprasiment of the status of each of these oral insulin developments in 2014 is a rather challenging task in light of the fact that only 6 out of 13 companies that claim clinical development of an oral insulin formulation published new clinical trial results within the past 5years. Subsequently the focus will be on the progress made by the companies that did publish new clinical trial reports.

In comparison to the situation 5 years ago, new companies like Aphios, Diasome, Jordanian pharmaceutical manufacturing, Novo Nordisk, Oshadi, Oramed, NOD pharmaceuticals/ Shanghai Biolaxy, Tamarisk technologies/ Deliv-RX, and transgene biotek has declared to have started a clinical development programm or oral insulin.

Current Status of Oramed Company Oramed Pod Tm Technology

Oramed pharmaceuticals is a technology pioneer in the field of oral delivery solution for drugs currently delivered via injections. Established in 2006, Oramed protein oral delivery technology is based on more than 30 years of research by top scientists at jerusalems madassah medical center. Oramed is seeking to revolutionize the treatment of diabetes through its proprietary flagship product, an orally ingestible insulin capsule [ORMD-0801]. The company completed multiple phase-2 clinical trial under an investigational new drug application with the U.S food and drug administration. In, addition, Oramed is developing an oral GLP-1 analog capsule [ORMD-0901]. Oramed initiated phase3 trail of oral insulin [9,10].

Conclusion

Oral insulin is promising approach because of enhanced disease management and improvement in patient compliances. Oral delivery of insulin in the future

because it can survive within the GIT, as well as having longer shelf life. The initial cost of the insulin could be high, but with developments in biosimilar, the cost could be reduced. Improved patient compliance with oral insulin has attracted companies like Novo Nordisk, Oramed, Emisphere, and Biocon to put their endeavour in bringing it to market in near future.

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