

NEWER APPROACHES FOR INSULIN ADMINISTRATION IN DIABETES TREATMENT

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Summary

Diabetes Mellitus is one of the main threats to human health in the 21st century and is going to be an epidemic both in the first and developing world. Insulin a polypeptide hormone responsible for controlling the transport, utilization and storage of glucose in the body, is used as the main drug in treatment of diabetes. Due to the polypeptide nature insulin delivery to biological system is complicated, therefore various investigations have been attempted to formulate insulin for administration with maximum bioavailability. Different approaches to deliver insulin includes subcutaneous, transdermal, transmucosal, pulmonary route using dry aerosols and inhalers, smart hydrogels, nasal delivery, ocular delivery, vaginal delivery and oral delivery. As oral delivery is the most convenient route for drug administration more and more research is needed to deliver insulin orally.

Keywords: Diabetes, Insulin, Liposome, hydrogels, Micro and Nanoparticles,

Introduction

The World Health Organization (WHO) projects that by 2010 the global figure of people infected with Diabetes is going to cross 220 million and by 2025 the figure will approach to 300 million and it will approach to 370 million by 2030. Diabetes mellitus is a heterogeneous disorder and have varying degree of insulin resistance and insulin deficiency, leading to disturbance in glucose homeostasis. There are currently four distinct types of diabetes mellitus. Type I Diabetes Mellitus is characterized by selective pancreatic β cell destruction and severe or complete insulin deficiency and in this case insulin administration is mandatory. (1) Type II Diabetes Mellitus is characterized by tissue resistance to insulin and relative deficiency in insulin secretion. Though insulin is not essential for approximately 70% of type II diabetics but it can change over time and close glucose and side effect monitoring is essential. Type III Diabetes Mellitus occur due to various reasons one such example is side effect to certain drug therapies. The fourth type is gestational diabetes and is diagnosed in approximately 4% of pregnancies in the United States. Although the specific treatments vary for different types of diabetes but the basic goal is to regulate blood glucose in order to prevent the primary and secondary effects of hyperglycemia. (2)

Insulin is a hormone secreted by the beta cells of the pancreatic islets of Langerhans. It stimulates carbohydrate metabolism in skeletal and cardiac muscle and adipose tissue by facilitating transport of glucose. The hormone also stimulates protein synthesis and lipogenesis and inhibits lipolysis and release of fatty acids from adipose cells. Insulin is used as replacement therapy in the management of diabetes mellitus. It supplements deficient levels of endogenous insulin and temporarily restores the ability of the body to properly utilize carbohydrate, fats and proteins. Insulin therapy is indicated in all cases of insulin dependent (type 1) diabetes mellitus and is mandatory in the treatment of diabetic ketoacidosis. Insulin is also indicated in patients with non insulin-dependent (type II) diabetes mellitus when weight reduction and/or proper dietary regulation have failed to maintain satisfactory concentrations of blood glucose in both the fasting and postprandial state. (3)

Insulin has a molecular weight of about 6000 and is composed of 51 amino acids in two chains connected by disulfide linkages. Insulin like other peptide and protein drugs possesses a large number of functional groups and, therefore may undergo a variety of chemical or physical alterations with time depending on storage conditions. The changes that occur may or may not affect the safety and efficacy of the protein as a drug. (4) Small variations in the amino acid sequence of insulin produces insulin analogs having slightly different activity than the parent insulin. Insulin absorption via different routes is given as follows ;(5)

Route	Insulin absorption
Oral	0.05%
Nasal	30%
Buccal	0.5%
Rectal	2.5%
Vaginal	18%
subcutaneous	80%

Insulin Analogs

Insulin analogs are synthetically produced variations of insulin which have difference in amino acid sequence than that of native human insulin. When delivered subcutaneously, normal insulin has an onset of action of 30-60 minutes, a peak at 2.5-5 hours, and duration of effect is 5-8 hours. This profile of action poorly matches that of endogenous insulin secretion. Similar to formulator insulin variations, insulin analogs change the timing and duration for the effect of insulin and they are separated accordingly. (6)

Fast-Acting Insulin Analogs

Natural insulin exhibits some self associative behavior delaying its activity; Fast acting analogs are modified in such a way that the self association behavior is decreases so the monomeric form becomes more stable. Therefore fast-acting insulin analogs were administered near mealtime. (7, 8, 9)

Name	Changes investigated	Effect of change	Pharmacological activity
1. Insulin lispro	Lysine (B 29) and proline (B 28) are substituted for one another.	Reduced tendency to self-associate into dimmers by 200-300 times.	More rapidly work than normal human insulin when administered subcutaneously.
2. Insulin aspart	Proline (B28) is replaced with an aspartic acid residue.	Reduced tendency self-associate into dimmers by 200-300 times.	More rapidly work than normal human insulin when administered subcutaneously.
3. Insulin gulisine	Lysine (B29) is replaced by glutamate and asparagine (B3) is replaced by lysine.	This improves monomer stability, reduced self-association, and an increased rate of absorption.	Have the most rapid rate of onset and clearance.
4. Insulin asp (B10).	Histidine (B10) is replaced by aspartic acid.	It exhibited twice the absorption rate of regular insulin.	Increases affinity for the insulin receptor in cells, inducing increased mutagenic activity.

Long-Acting Insulin Analogs

Long-acting insulin analogs were designed to maintain a healthy blood glucose levels throughout the night in diabetic patients. Regular human insulin has duration of roughly four hours, so a diabetic patient using it had to interrupt their sleep in order to maintain normal glucose levels. Therefore long acting insulin analogs are used to overcome such difficulty.(10,11)

Name	Changes investigated	Effect of change	Pharmacological activity
1. Insulin glargine (Lantus®)	Asparagine (A21) replaced by glycine and addition of two arginine residues at the C-terminus of the B-chain.	The isoelectric point shifted from 5.4 to 6.7 resulting in reduced solubility of insulin glargine at neutral pH levels.	At neutral pH it precipitates forming a subcutaneous insulin depot and releases slowly
2. Insulin detemir (Levemir®)	Threonine (B30) replaced by a C14 fatty acid chain (myristic acid).	Forms hexamers and reversibly binds to albumin.	Slowly released into the bloodstream from the sight of injection

Pulmonary Delivery of Insulin

Pulmonary delivery is an alternative route for insulin administration, best example is the inhaled dry powder insulin formulation from Nektar and Pfizer called as Exubera®. (12, 13) Due to large surface area (100-140 m²), high permeability, and high vascular nature of lung, insulin delivery becomes easier. (14) Insulin can be absorbed efficiently without the help of absorption enhancers or enzyme inhibitors, decreasing side effects. The delivery system shows a rapid onset of action and more rapid clearance than that of subcutaneous injection of regular human insulin. (15) By pulmonary route insulin enters directly to circulation bypassing the first-pass hepatic clearance, resulting in longer pharmacodynamic profile than endogenous insulin. (16) The major disadvantage of pulmonary delivery is the bioavailability, that is only 9-22 % that of subcutaneously injected insulin.

Nasal Delivery of Insulin

The delivery of insulin to the nasal cavity is convenient, due to large absorptive surface, and high vascularity. Drug absorption by the nasal mucosa is fast and directly enters the systemic circulation, bypassing the first-pass hepatic clearance. Major disadvantage in case of insulin is mucociliary clearance, and presence of proteolytic enzymes therefore permeation enhancers, mucoadhesive materials, enzyme inhibitors, or a combination of these methods are used to increase insulin delivery. (18) Another approach is the use of chitosan, a positively charged polysaccharide in the form of nanoparticle to deliver insulin. This approach has highest bioavailability of 17.0 % for insulin delivery. (19)

Transdermal Delivery of Insulin

Transdermal insulin delivery is somewhat same as subcutaneous delivery but without the pain of injection. The main hurdle is relative impermeability of skin to large, hydrophilic molecules such as insulin due to the intracellular lipid layer of the stratum corneum. (20, 21, 22, 23)

Methods used	Impact on insulin delivery
1. Use of micro or nanoneedles.	Low levels of associated pain and increases the permeability of insulin.
2. Iontophoresis (Use of electrical charge to disrupt the stratum corneum).	Pretreatment of the delivery site and still deliver very little insulin into the bloodstream.
3. Sonophoresis (Use of sound waves to disrupt the stratum corneum).	Time taking process.
4. Use of Photomechanical waves or laser generated stress.	Time taking process.

Pumps and implantable devices

Insulin Pumps are being used to deliver insulin subcutaneously to diabetic patients since 1970. The pump is a small, battery-powered, external device that administers insulin through a subcutaneous catheter and insulin can be administered at a slow constant rate as well as bolus doses before meals or at other times as desired. It is having its own demerits. (24)

Other Delivery Routes for Insulin

A number of researches were carried out to investigate other routes like rectal, ocular, vaginal, buccal, and oral for insulin delivery. The rectal insulin delivery system is devoid of enzymatic degradation but has low absorption (4-10 %) of insulin and it does not seem to represent an acceptable alternative route. Both ocular (25) and vaginal (26) insulin delivery routes showed limited absorption levels and severe local adverse reactions indicating little opportunity for insulin delivery. (27) Buccal delivery systems is having the advantages of easier administration, low proteolytic activity, and high vascularization but the main challenges are thick, multilayered structure of the buccal mucosa and constant flow of saliva (28,29) A Canadian company Generex, currently produces Oral-Lyn™ which delivers insulin via the buccal route. The product is intended for those who have pre-diabetes or Type 2 diabetes as an insulin therapy to slow the progression of the disease. (30)

Oral Insulin Delivery

Enzyme Inhibitors

Enzyme inhibitors diminish the action of proteolytic enzymes, thereby reducing the loss of insulin in the gastric and intestinal environments. But the important considerations are the multitude of enzymes in the lumen, brush-border, and intracellular environments make a single approach difficult and by altering the proteolytic activity of the GI tract, natural digestive processes are modified that may induce significant side effects. (31)

Permeation Enhancers

Permeation enhancers modify insulin structure and make it resistant to proteolytic enzymes. Takeyama et al and Komada et al demonstrated that enzymatic insulin degradation was inhibited by the absorption enhancer nafamostat. (32, 33) A variation of permeation enhancers involves covalent attachment of the therapeutic molecule to the delivery agent through prodrug strategies. Clement et al. demonstrated that the covalent attachment of a 7-9 unit length of polyethylene glycol and a hydrophilic hexyl alkyl chain to the lysine B29 residue of insulin to form hexyl insulin monoconjugate-2 (HIM2) that increases the enzymatic resistance of insulin as well as increasing its permeation across a modeled intestinal epithelium using Caco-2 cells (34,35)

Prodrug Systems

Prodrugs are pharmacological substances which are modified from their normal form such that they have a different molecular structure which alters the biological action of the substance.(36) Insulin analogs are sometimes referred to as insulin prodrugs. Prodrugs can also involve the covalent conjugation of a chemical species to the drug which directly alters its absorption, distribution, metabolism, and excretion (ADME) behavior. Prodrugs differ from traditional enzyme inhibitors and permeation enhancers because their action is immediately concentrated in close proximity to the therapeutic protein due to covalent modification. (37)

Active Transport and Receptor-Mediated Endocytosis

Transferrin is an important transmembrane transporters investigated for facilitated absorption of insulin by active transport and receptor-mediated endocytotic pathways.(38) Transferrin (Tf) is an iron transporting glycoprotein with a molecular weight of ~82 kDa expressed in the mucosa of the GI tract.(39,40) Number of investigation were carried out to observe the potential for oral delivery of Tf-conjugated insulin to the bloodstream.(41)

Lipid Based Delivery Systems

Lipid based delivery systems use lipids, bile salts, cholesterol, or a combination thereof to encapsulate a protein in one of several 3-dimensional configurations thereby preventing the orally delivered protein from enzymatic degradation. Liposomes are mostly used for insulin delivery. Liposomes are bilamellar sphere with an aqueous core, surrounded by a lipid bilayer.(42,43) The primary method of absorption was found to be pinocytosis in the Peyer's patches primarily located in the ileum. The Peyer's patches have high concentrations of absorptive M-cells. Absorption in M-cells has been reported to increase with increasing hydrophobicity.(44) The important drawback of liposomes are as follows,

In concentrated form liposomes have a tendency to form large aggregate and difficult to be absorbed in the Peyer's patches. The outer lipid bilayer is digested by the action of bile salts and lipases present in the GI tract (45) A little deviation destroys the stability of the liposome. When a liposome is stored at 4 °C for 3 days it lost around 26 % of incorporated insulin. (46,47)

Polymeric Systems for Oral Insulin Delivery

Numbers of polymeric delivery systems are investigated like micro- and nanoparticles, biodegradable systems, bioadhesive systems, and hydrogels etc for insulin delivery. The polymers are used to entrap or encapsulate insulin and protect it from enzymatic activity of GI tract.

Micro- and Nanoparticles

Micro and Nanoparticles involves both the micro- or nanocapsules and micro- or nanospheres. In Capsules insulin is surrounded by a polymeric shell where as in Spheres the polymers and insulin are dispersed throughout the particle. Xiong et. al used a block copolymer with polylactic acid (PLA), polyethylene oxide (PEO), and polypropylene (PPO) in a PLA-PEO-PPO-PEO-PLA configuration to make polymeric vesicles of 30-100 nm (Pluronic®) The polymeric vesicles were loaded with insulin by forming them in an insulin solution. The indirect method of loading was only able to incorporate 0.08 wt% of available insulin into the nanoparticles. The dosing levels in this study were at least 100-fold greater than that of subcutaneous injection of insulin, so the bioavailability of the protein remained very low.(48) Furtado et al. investigate insulin containing microcapsules from a block copolymer of fumaric anhydride (FA) and sebacic anhydride (SA). In this method phase inversion technique is used for the entrapment of insulin within a hydrophobic polymer shell. Major disadvantage is low bioavailability due to slow rate of insulin release, non-specific rate of release, and the large size of the particles expected to be transported across the intestinal epithelium. (49,50)

Biodegradable Systems

Biodegradable Polymeric materials degraded when exposed to the GI tract. An example of a time-based biodegradable polymer is a copolymer of poly (lactic acid) (PLA) with poly (glycolic acid) (PGA). Both polymers are hydrophobic and can be used to make micro- or nanoparticles containing insulin. The polymeric bonds of each polymer are cleaved by hydrolysis.(51,52) Other biodegradable polymers used for insulin delivery are polysaccharides like dextran and chitosan that are well characterized, easily customizable, plentiful, and highly biocompatible. Dextran is a polysaccharide derived from glucose and chitosan is commercially produced from chitin, a material found in the exoskeleton of shellfish. The degradation of the particles is based on the natural digestion of polysaccharides by the GI tract. Sarmiento et. al. used dextran sulfate with chitosan to make biodegradable nanoparticles for oral insulin delivery(53)

These particles exhibited the ability to maintain high insulin content through the stomach and release it in the small intestine in the presence of amylolytic enzymes. The dosing levels are quite high, though significant bioavailability was observed (5.6 %) due to the extended action of the hypoglycemic effect versus subcutaneous injection.(54) Eudragit® is another biodegradable polymer investigated for oral insulin delivery, it is made from poly(methacrylic acid). Eudragit® is a weak acid with a pKa of ~ 4.8 therefore in acidic pH environments below this pH, the polymer is hydrophobic and insoluble in chyme but in alkaline pH the polymer is hydrophilic and soluble due to loss of hydrogen on the carboxylic acid side group and release insulin. (55)

Mucoadhesive Delivery Systems

Mucoadhesive polymers bind to the mucus layer covering the epithelial cells, and bring insulin within close proximity to the epithelial layer making it easy to cross it in order to be absorbed into the bloodstream. The most commonly investigated mucoadhesive polymers include chitosan, poly(acrylic acid), poly(methacrylic acid), sodium alginate, and cellulose derivatives.(56) The long-term effects of mucoadhesive materials are not yet determined. Concerns over potential buildup in the GI tract or toxicity must be addressed in future work with these materials.

Hydrogels for Oral Protein Delivery

Hydrogels are defined as water-swollen, cross linked polymer structure produced by the reaction of one or more monomers. In comparison to other synthetic biomaterials, they are considered to resemble living tissue because of their high water content and soft texture. (57) Their consistency can range from nearly liquid materials that can flow through syringes to rubbery material with the stiffness of tissues such as cartilage and tendons. The swelling of hydrogels is dependent not only on the intrinsic nature of the polymer, but also on the surroundings. The swelling of hydrogels depend on temperature, light, pH, ionic strength, pressure, electric current, or the presence of particular species such as glucose. Of particular interest to oral insulin delivery are pH-sensitive hydrogels. In a similar fashion as that of Eudragit, pH sensitive hydrogels can restrict release of encapsulated insulin in the stomach due to the low pH levels and allow its release in the neutral environment of the small and large intestines. (58)

Conclusion

Insulin in many forms are available in the market, including newer analogs (Lispro, aspart, glargine). Insulin analogs seem to be more physiologically active, but practically shows similar or slightly increased efficacy to regular insulin. The most clinically viable non-invasive system for insulin administration may be pulmonary delivery. . Among the noninvasive ways for controlling diabetes in the future, the nanoparticulate systems seem to be promising potential drug carriers for oral insulin delivery. In the near future, type 1 diabetic patients will receive insulin in optimal quantities at right times by optimal routes into the body in order to achieve optimal blood glucose control. Therefore more and more research is needed to make insulin available to the biological system orally. These new technologies will facilitate proper treatment of type 1 diabetes and improve the lives of affected patients.

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