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NEWER STRATEGIES FOR INSULIN DELIVERY

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ABSTRACT
Insulin is a proteinaceous hormone produced in the islets of Langerhans in the pancreas and used as a treatment in the diabetes mellitus. Successful oral insulin delivery involves overcoming the enzymatic and physical barriers and taking steps to conserve bioactivity during formulation processing. Newer strategies for insulin delivery include insulin pen injector, Refillable insulin injection pen, Insulin Syringe, Transfersome and Implantable insulin pumps.
Keywords: Newer Strategies for insulin delivery, Insulin injection pen, Insulin syringe, Transfersome, Implantable insulin pumps.

INTRODUCTION

Insulin is a proteinaceous hormone, required to be taken from externals sources in case of some patients suffering from Diabetes Mellitus. Insulin causes most of the body's cells to take up glucose from the blood (including liver, muscle, and fat tissue cells), storing it as glycogen in the liver and muscle, and stops use of fat as an energy source. When insulin is absent (or low), glucose is not taken up by most body cells and the body begins to use fat as an energy source (i.e. transfer of lipids from adipose tissue to the liver for mobilization as an energy source). As its level is a central metabolic control mechanism, its status is also used as a control signal to other body systems (such as amino acid uptake by body cells). It has several other anabolic effects throughout the body. When control of insulin levels fails, diabetes results. It is produced in the islets of Langerhans in the pancreas. The name comes from the Latin insula for "island". Insulin's structure varies slightly between species of animal. Insulin from animal sources differs somewhat in 'strength' (i.e., in carbohydrate metabolism control effects) in humans because of those variations. Porcine (pig) insulin is especially close to the human version[1-5].

Newer Strategies for Insulin Delivery

The goal for delivering exogenous insulin in patients with diabetes is to mimic as closely as possible the normal physiological insulin secretion seen in non-diabetic individuals. In order to achieve optimal glycemic control, a more intensive insulin therapy both for patients with TYPE-1 diabetes and TYPE-2 diabetes[7,8] .

Oral Approach

Despite the different approaches being investigated for insulin delivery, the development of oral delivery, the development of oral delivery system of insulin has been the elusive goal since the discovery of insulin.

Insulin if administered via the oral route will eliminate the pain caused by injection, physiological barrier 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, 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. In light of the above distinct benefits, pharmaceutical technologists have been trying to design an oral delivery system for insulin. Such is the interest in oral insulin delivery that some pharmaceutical companies are solely focused on it. [10-18]

Challenges to Oral Insulin Delivery

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. 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%.

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. 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 micro flora. 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[20,21].

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 [25]. In developing oral protein delivery systems with high bioavailability, three practical approaches might be most helpful:

(1) Modification of physicochemical properties such as lipophilicity and enzyme susceptibility.

(2) Addition of novel function to macromolecules.
(3) Use of improved carrier systems.
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 Inhibitor

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. The earliest studies involving enzyme inhibitors were carried out with sodium cholate along with a protein which improved insulin absorption in rats. Significant hypoglycemic effects were also obtained following large intestinal administration of insulin with camostat mesilate, 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 azo aromatic 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 [28-32].

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. 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 zonula occludens toxin, chitosan, thiolated polymers, and Pz-peptide have all demonstrated capacity to increase macromolecular drug absorption. Combinational strategies involving enzyme inhibitors and absorption enhancers have been effective in increasing bioavailability of insulin. Combinations like sodium cholate and soybean trypsin inhibitor sodium lauryl sulphate and aprotinin have resulted in reduction in blood glucose in dogs.[33]

Formulation Approaches

A third strategy to circumvent the carrier system is the formulation approach. Here the peptides or protein drug is housed within a delivery system that is designed not only to protect the drug from contact with luminal proteases, but also to release the drug only on reaching an area favorable for its absorption.

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, micro spheres and nanoparticles have been developed for use as carrier systems for insulin.[34]

Emispheres

These are proteinoids prepared by the condensation of polymers produced by polymers produced by the assembly of natural/synthetic amino acids in order to facilitate oral delivery of certain peptides. These Emispheres/carriers bind to transportable conformations capable of crossing the cell membrane. This acts effectively as a prodrug. Once it crosses membrane the complex dissociates and the drug molecule returns to its therapeutic active conformational state.[36]

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 polyalklylcyanoacrylate, polymethacrylic acid, polylactic-co-glycolic acids (PLGA). Insulin encapsulation with nanoparticles (Table 1)

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[40] .

Use of surfactants in formulation

One of the most effective ways of formulating a protein is to decrease the adsorption to delivery matrix by incorporating surface active agents such as polysorbates or sodium dodecyl sulphate or by addition of protein (albumin) to compete for adsorption sites. thus, surfactants stabilize insulin preparation.

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. Alteration of the physicochemical characteristics leads to enhanced stability and resistance to intestinal degradation of oral insulin.[42]

Other approaches

1. Cholera protein may increase oral delivery of insulin: Research at University of Maryland reported that a Vibrio cholera protein called "Zonula occludens toxin" modulates intestinal epithelium permeability, and thus be used to enhance the intestinal absorption of orally administered macromolecules through the paracellular pathway.
2. Natural mechanism for oral uptake of vitamin B12 to co-deliver insulin: Vitamin B12 is absorbed across the intestinal barrier and insulin may be passively co-transported as a part a co-transport system.
3. Transferrin receptor mediated trancytosis
4. Oral delivery of genes that encode therapeutic protein.

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 2 (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 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. The oral route for insulin delivery might be possible in the near future with the use of using superior materials as carriers for insulin delivery systems. However, only further research into delivery systems can make it possible 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 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 in the foreseeable future[47-57].

Buccal/sublingual delivery

Buccal delivery involves a device a spray of insulin, which is absorbed in the lining at the back of the mouth and throat. Drugs are absorbed through thin mucosa into the reticulated veins and enter into the systemic circulation directly, thus bypassing the hepatic metabolism.

Upcoming Diabetes Medications

Buccal (cheek) delivery of insulin: On May 11, 2005, Generex released a a press release that indicates "Oral-lyn™ has been approved for commercial marketing and sale by the Ecuadorian Ministry of Public Health for the treatment of both Type-1 and Type-2 diabetes**.**

The buccal inhaler delivers a high-pressure stream of insulin to the back of the throat. Like the nasal mucosa, the buccal mucosa offers limited surface area. Because the mucosa has low permeability, many puffs may be required for effective dosing. One study demonstrated efficacy for buccal insulin used as an add-on therapy for postprandial control in patients who were failing on oral therapy, but research overall has been limited to a very small number of subjects.

TRANSDERMAL APPROACH

The portability of this drug delivery system is designed to improve the quality of life for many patients afflicted with chronic diseases requiring the constant delivery of therapeutic medicines.Passive transdermal delivery allows a drug to diffuse through the skin and act locally or penetrate the capillaries and have a systemic effect. Passive delivery usually occurs with a patch, cream, or spray. Passive Transdermal delivery only works with small molecule drugs, such as nicotine and aspirin. Insulin is far too large to get through the skin passively. Though the skin is a formidable barrier, companies are developing various active transdermal delivery technologies to overcome this challenge.

Insulin pen injector

These are one of the major advances in insulin delivery that has made self-injection easier, portable and convenient. These are small devices that consist of the syringe and insulin cartridge and make use or smaller gauge needles that may result in less painful injections. Another advantage of this device is that desired dose of insulin can be precisely selected with a dial. Turn the dial to align the arrow with the amount of insulin need. Then insert the needle underneath the skin and press a spring-loaded plunger to inject the insulin. Once the insulin is used in the cartridge, dispose of the entire pen. However, disposable pens cost more than syringes. If require more insulin than is left in a partially used cartridge. (Figure 1)

Syringe and needle

Mostly disposable insulin syringes and needles are use to inject insulin. This method costs less than insulin injection devices such as pumps and pens. But, withdrawing insulin from a bottle isn't as convenient or discreet as using some devices. (Figure 2)

Transfersome

When carriers are employed to administer macromolecules epicutaneously, the drugs must be associated with specifically designed vehicles in the form of highly deformable aggregates and applied on skin non-occlusively. As demonstrated, the application of insulin-laden transfersomes over 40cmsq would provide the daily basal insulin needs of a typical patient with type 1 diabetes. Transfersomes mediated drug delivery through the skin is little affected by the molecular size of the carrier associated active ingredient.

Dermisonics has integrated microelectronics and ultrasonic science into a skin pad called the U-Strip™. It uses alternating ultrasonic waveforms to enlarge pore diameter sufficiently for large molecules like insulin to proceed through the skin and ultimately reach the bloodstream. The system consists of 4 parts: the Medi-Cap, Ultrasonic Applicator, the dose controller and the dose report for the physician. (Figure 3)

The Medi-Cap, the transdermal patch that holds the insulin, is applied to the skin. The Ultrasonic Applicator and Dose Controller generates ultrasonic transmissions to dilate the pores and allow large molecule drugs to enter the blood stream. It adjusts rate and frequency to vary dose delivery, records the dose delivered, and keep this in memory for 60 days.

OTHER UPCOMING METHODS

Implantable Insulin Pumps

It is implanted just under and insulin is delivered into the peritoneal cavity not into the subcutaneous tissue. The primary advantage of an insulin pump is that person able to achieve normal or near-normal blood sugar levels (tight control), which can help prevent long-term diabetes complications. (Figure 5)

Transdermal Patch

The Altea Therapeutics PassPort™ System was the first product in development shown in US FDA clinical trials to provide a non-invasive, controllable and efficient way to deliver insulin via a patch on the skin. The PassPort™ System enables fast, controlled drug delivery without the pain of an injection or the possible complications associated with inhaled medications. It also avoids the first-pass gastro-intestinal and liver metabolism that occurs often after oral administration.

Intra-Nasal Approach

An insulin inhaler is used to take powdered insulin. This device offers a quick, easy way to take short-acting insulin. Advantages to inhaled insulin include the convenience of carrying the compact inhaler and its fast-acting nature. Inhaled insulin can be taken minutes before meals to control blood sugar increases.[58-59](Figure 5.)

CONCLUSION

The advanced methods of insulin delivery systems would gradually progress toward physiological insulin replacement and reduce the long-term complications of diabetes mellitus.

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Table 1: Insulin encapsulation with nanoparticles

Polymer	Size (nm)	Species	Observations
Chitosan- (γ-PGA)	110-115	Rat	Significant reduction of blood glucose level up to 10 hours
Lectin-modified solid NP	300	Rat	
Poly(isobutylcyanoacrylate)	270-340	Rat	Bioavailability of 4.46% and 4.49%
Chitosan	270-340	Rat	Decrease of glycemia from 300mg/dl to 125 mg/dl
Acrylic-based copolymer	200-2000	Rat	
Poly(ε-caprolactone)-Eudragit RS	358	Rat	Effective glycemic control at doses of 50 U/kg and 100 U/kg
	200	Rat	Significant reduction in serum glucose
Soybean phosphatidylcholine (SPC)	250-400	Rat	Bioavailability of 13% over 24h with maximal effect at 100 U/kg
Chitosan			Oral bioavailability of 7.7%
			Pharmacological availability of 14.9%

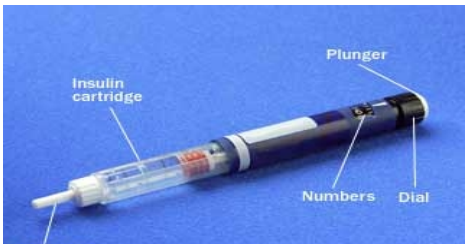

Figure 1. Insulin pen injector

Figure 2. Insulin syringe

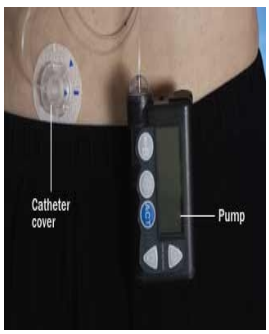

Figure 3. Implantable insulin pump

Figure 4. Dermisonics U-stripes

Figure 5. Insulin inhaler