EMERGING TRENDS IN INSULIN THERAPY

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***Abstract*- Over the past few decades, insulin therapy has progressed remarkably. Insulin therapy can help individuals lower their blood sugar levels because it is essential for managing hyperglycemia in people with diabetes mellitus. Syringes, infusion pumps, jet injectors, and pens are presently used to administer insulin. In recent years, there have been several emerging trends in insulin therapy that aim to improve outcomes for patients. Worldwide, a serious study effort has been made to find more accurate, non-invasive alternatives to authentic methods. Insulin mimics with ultra-rapid and ultra-long actions are now marketed. Transdermal insulin, Inhaler insulins, Implants, Insulin spray, Transferosome, Islet cell transplant, Gene therapy and Non-invasive treatment are some of the more recent techniques being investigated. This review discusses novel therapies currently being developed as well as recent emerging patterns in insulin therapy.**

***Keywords*: Insulin, Diabetes Mellitus, Non-invasive treatments, Ultra-rapid insulin, Ultra-long insulin.**

1. INTRODUCTION:

Insulin was first discovered by Bating Best in 1921 and its crystalline form was first observed in 1926. Insulin therapy is used for treatment of diabetes, it controls hyperglycemia in type 1 diabetes patients while in patients with type 2 diabetes it may be required in selective individuals or in later stages. Major drawback of current forms of insulin therapy is its invasive nature. In order to decrease the suffering and improve the adherence in insulin regimens, Modern and Non-Invasive approaches for insulin delivery are being pursued. The demand for novel drug delivery technologies is ever increasing. These drug delivery technologies can be broadly classified into four principle routes like oral, transdermal, inhalation and parenteral. The major advances achieved in this area include the synthesis of human insulin analogues by recombinant technology, Insulin pen injectors, External infusion pumps, Transferosomes, Insulin inhalers, Insulin sprays, Insulin pill, Transdermal patch, Iontophoresis, Islet cell transplant and Gene therapy.

Synthesis and Release of Insulin

It was released from the endocrine part of pancreas i.e. islets of Langerhans. Insulin is synthesized as preproinsulin and processed to proinsulin. Proinsulin is then converted to insulin and C-peptide and stored in secretary granules awaiting release on demand.

History and Types of Disease:

About 40% of people with diabetes rely on insulin to maintain control of their blood glucose levels. Patients with Type-1 diabetes are completely dependent on insulin injections. For patients with Type-2 diabetes, which comprises 90% of the world's diagnosed cases of diabetes, about one-third of them rely on insulin as part of their regimen for controlling their blood glucose levels. Normal blood sugar is around 90 to 120mg/dL.

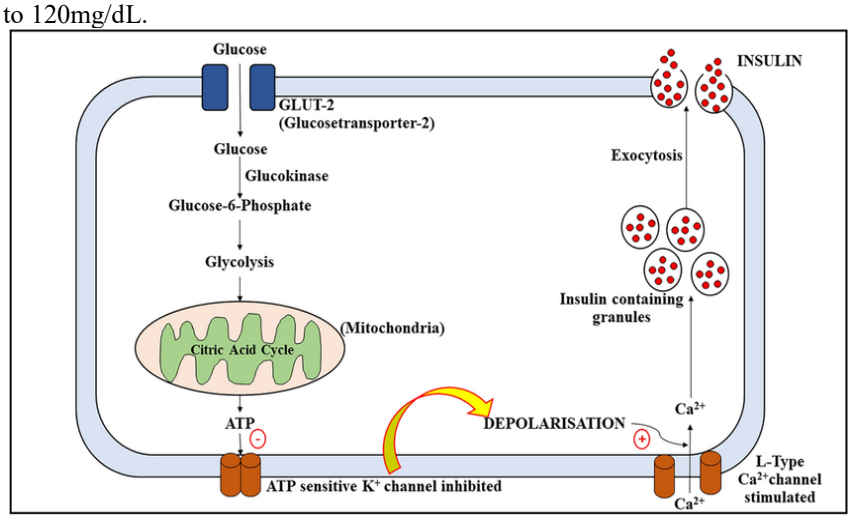

Fig 1. Release of Insulin from Pancreas

Insulin Structure and Chemistry:

The basis of all modern insulin analogs/derivatives and insulin formulations is human insulin, a small protein of 51 amino acids consisting of 2 chains, the A-chain, composed of 21 amino acids, and the B-chain, composed of 30 amino acids. Two interchain disulfide bridges (CysA7 to CysB7 and CysA20 to CysB19) covalently link chains A and B. Chain A also contains an intrachain (CysA6 to CysA11) disulfide bridge. In the pancreatic β-cells, the active 2-chain insulin molecule is generated from a single-chain proinsulin precursor by the proteolytic excision and release of C-peptide, which circulates and is used as a measure of endogenous insulin secretion. Proinsulin is secreted at the same time as insulin, but has low biological activity. Insulin is stored within the

pancreatic β-cells as hexamers stabilized by zinc ions; 6 monomers readily form 3 dimers that assemble into hexamers in the presence of zinc. When secreted from the β-cells, the zinc-insulin hexamers are diluted in the blood stream, causing the zinc to be released, which results in the hexamers disassembling into monomers—the active state of insulin. Ultimately, the insulin monomers are carried to the peripheral tissues where they act primarily on muscle and fat, imparting a variety of biochemical processes, including stimulation of glucose uptake, inhibition of adipose triglyceride breakdown, and fuel utilization.

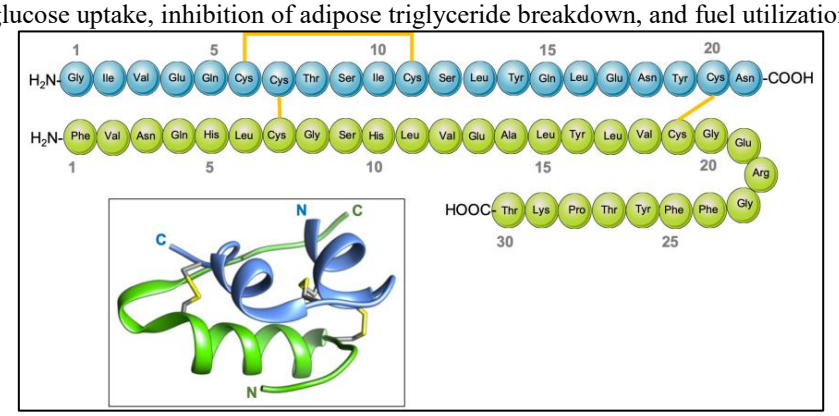

Fig 2. Structure of Human Insulin

Barriers to Conventional Insulin Injection Therapy:

1.Psychological Insulin Resistance

Psychological insulin resistance, defined as reluctance to initiate insulin injection therapy, is common among healthcare professionals and patients with diabetes mellitus. Despite ample evidence that many patients with type 2 diabetes do not achieve glycemic control with oral therapy alone, some physicians are still reluctant to initiate insulin therapy. Koro and colleagues found that despite frequent failure to achieve glycemic targets, the use of insulin declined from the 24% reported in the National Health and Nutrition Examination Survey (NHANES) III (1988-1994) to 16% in the initial release of NHANES IV (1999-2000), whereas the use of oral glucose-lowering monotherapy increased. This may in part reflect the availability of more oral medications for diabetes, but it may also be the result of the perceived complexity and inconvenience of the therapeutic regimen, the belief that it is not effective in type 2 diabetes, and fears of hypoglycemic episodes and weight gain. In addition, clinicians may perceive that initiation of insulin therapy will require more practice resources than are readily available. The relationship between psychological barriers to medication adherence and glycemic control can have important therapeutic implications. In a systematic literature review covering 1985 to 2007, Brodd and colleagues evaluated 116 peer-reviewed articles to assess the impact of psychological insulin resistance on diabetes management. The investigators concluded that this phenomenon is affected by the following components:

• Patients' beliefs and knowledge about diabetes and insulin
• Negative self-perceptions and attitudinal barriers • Fear of side effects and complications of insulin use
• Lifestyle adaptations
• Restrictions required by insulin use
• Social stigma.

These factors may lead to delayed treatment initiation and compromised glucose control.

2. Reduced Medication Adherence

Decreased adherence because of injection-related anxiety can influence glycemic control and quality of life in patients with insulin-treated diabetes. Adherence to a daily regimen of multiple injections can be difficult to maintain, interfering with lifestyle, compromising optimal glycemic control, and potentially resulting in CV complications. In one study of elderly patients (aged ≥65 years) with type 2 diabetes who were treated in a managed care setting, an inverse correlation was observed between blood glucose–lowering medication adherence and healthcare service utilization (e.g., emergency department visits, outpatient visits, hospitalizations). In this longitudinal cohort study, an increased medication possession ratio (MPR) for diabetes medications was the strongest predictor of decreased total annual healthcare costs: between 8.6% and 28.9% decrease in annual costs for every 10% increase in the MPR (P <.001).

2.MODERN INSULIN DELIEVERY SYSTEMS

2.1 Insulin pen injectors

These are the one of major advances in the insulin delivery that has made self-injection easier and convenient. These are smaller devices that consist of syringe and insulin cartridge and make use of smaller gauge needles that may result in less painful injections. There are two pen systems: durable and prefilled. A durable pen uses a replaceable insulin cartridge. A prefilled pen is entirely disposable. Fig 3 shows types of prefilled insulin syringes. Insulin pens have a number of advantages: it is more convenient and easier to transport than traditional vial and syringe and repeatedly more accurate dosages can be obtained through it. The **disadvantage** of insulin pen is that unlike with the traditional syringe, two different insulins cannot be mixed by the user in an insulin pen.

Fig 3. Two Types of Insulin Pens

2.2 External Insulin Pumps

External insulin pumps are small devices the size of a pager that can be attached to your belt or placed in your pocket. They are made up of an insulin reservoir connected to a tube, ending in a cannula or catheter, which is inserted under the skin of your abdomen. The working of an insulin pump is shown in fig 4. They can be set to deliver insulin at a slow, continuous rate throughout the day, or to release larger quantities at meal times or when blood sugar levels are high. The main advantage of pump is that it closely mimics the slow but continual release of insulin by the pancreas. The **drawback** is the risk of episodes of low blood sugar (hypoglycemia) is higher and there is also the risk of ketoacidosis if the catheter blocks.

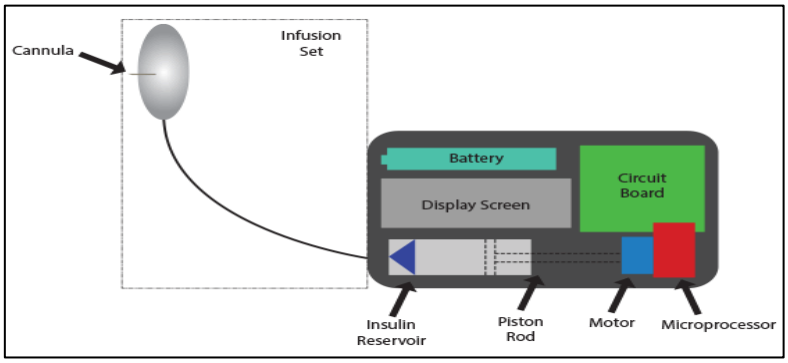

Fig 4. Insulin Infusion Pump

2.3 Transferosome

Transferosome means “carrying body”. A Transferosome carrier is an artificial vesicle designed to exhibit the characteristics of a cell vesicle or a cell engaged in exocytosis, and thus suitable for controlled and, potentially, targeted drug delivery. The carrier aggregate consists of at least one amphipath (such as phosphatidylcholine), which in, aqueous solvents self-assembles into a lipid bilayer that closes into a simple lipid vesicle. By addition of at least one bilayer softening component (such as a biocompatible surfactant or an amphiphile drug) lipid bilayer flexibility and permeability are greatly increased. Transferosomes can be prepared by (a) thin film hydration technique and (b) modified hand shaking, lipid film hydration technique. Transferosomes are advantageous as phospholipids vesicles for transdermal drug delivery. Because of their self-optimized and ultra-flexible membrane properties, they are able to deliver the drug reproducibly either into or through the skin, depending on the choice of administration or application, with high efficiency. The vesicular transferosomes are more elastic than the standard liposomes and thus well suited for the skin penetration. The application of insulin-loaded transferosomes over 40 cm2 would provide the daily basal insulin needs of a typical patient with type 1 diabetes. Transferosomes mediated drug delivery through the skin is little affected by molecular size of carrier associated over the ingredient. Systemic normoglycemia that lasts at least 16 hours has been achieved using a single non-invasive, epicutaneous administration of insulin in Transferosomes. Transferosomes are chemically unstable because of their predisposition to oxidative degradation lack of purity of the natural phospholipids comes in the way of adoption of transferosomes as drug delivery vehicles and transferosomes formulations are expensive to prepare.

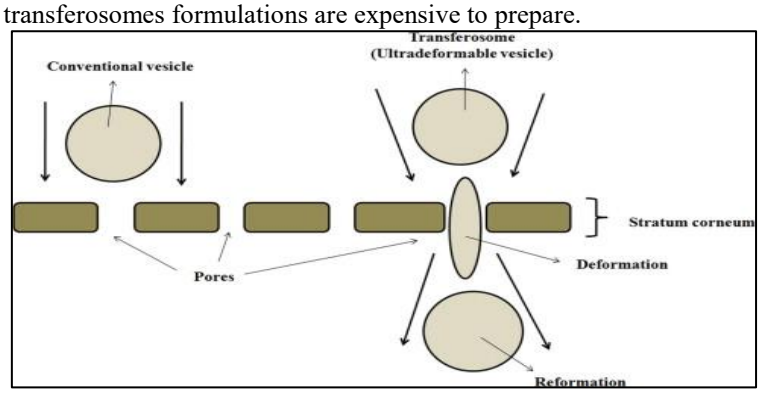

Fig 5. Transferosome

2.4 Insulin Inhalers

Inhalable insulin is not a modern method of insulin delivery as it was withdrawn from the market in October 2007 due to concerns of lung cancer. However, it has been included here only for lesson. However, a new inhalable insulin product was approved for sale in the United States by the FDA in June of 2014, and hence may become available. Non-invasive, well-tolerated with potential for both type 1 and 2 diabetes are advantages of inhaled insulin. Comparable results for glycemic control for inhaled insulin with subcutaneous insulin were indicated in short term studies. A type of insulin inhaler is shown in Fig. 6. As compared to conventional subcutaneous insulin, rapid and sustainable patient satisfaction and a positive impact on psychological well-being in patients with type 1 diabetes was obtained with inhaled insulin. Patient satisfaction, quality of life and acceptance of intensive insulin therapy are the advantages of inhaled insulin. The pharmacokinetic profile of inhaled insulin has both advantages and disadvantages compared with subcutaneous insulin injection. Because inhaled insulin is more quickly absorbed, pulmonary insulin delivery may reduce the time necessary between insulin administration and mealtimes. However, because the duration of action of inhaled regular insulin is short, a once daily injection of long-acting insulin should be administered to patients who previously required multiple insulin injections daily. The bioavailability of inhaled insulin is less than 20%; thus, dosage requirements and cost per treatment are increased in comparison with insulin administered by subcutaneous injection. Patients receiving inhaled insulin had more episodes of hypoglycemia and gained more weight than did patients treated with oral agents. Mild to moderate cough was also reported in up to 25% of patients receiving inhaled insulin. Uncontrollable factors also affect pulmonary absorption, and smokers need lower and asthmatics higher doses. The pulmonary insulin dose required for a similar glycemic effect is approximately 20 times that required for a subcutaneous injection, and insulin directed antibodies are an issue.

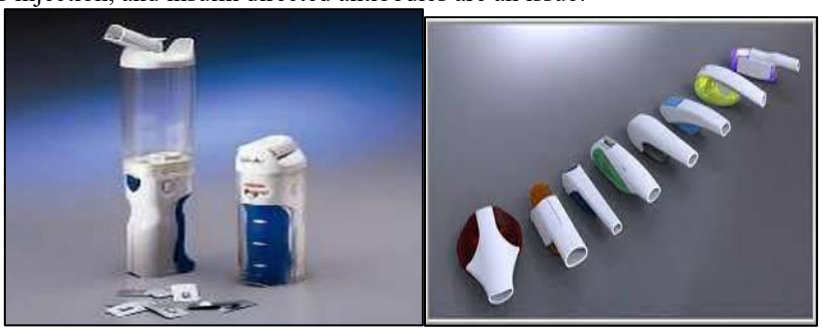

Fig 6. Insulin Inhalers

2.5 Insulin Spray

Another promising alternative for insulin delivery is the buccal route. Delivery of the acid labile insulin, and elimination of insulin destruction by first pass metabolism are the advantages of buccal area as it has an abundant blood supply. The patient does not inhale with the buccal spray device as the formulation is delivered as fine spray onto the buccal mucosa. Rapid absorption into the bloodstream is allowed with high-speed spray. Inhaled insulin formulation shows the risks to lung tissue, this can be avoided as the drug gets deposited onto the buccal mucosa.

2.6 Insulin Pill

Controlling postprandial glycaemia requires several daily injections of insulin. Treatment using insulin through subcutaneous or other parenteral route results in peripheral hyperinsulinemia, this may also include coronary artery disease, hypertension, dyslipidemia and weight gain along with the risk of hypoglycemia. An oral insulin product has proved to adequately insulinize the liver as it provides insulin in more physiological manner, with a resultant decrease in peripheral insulin. Researchers have found that insulin can be protected in a chemical coating known as a novel polymer, bringing the chance of oral insulin, an insulin capsule, ever closer. The coating is a key step to ensure that insulin taken in pill form is not broken down by enzymes and rendered useless before entering the blood stream.

Azopolymer coated pellets entrap therapeutic agent till the pellets reach the colon and hence used for delivering the insulin to the colon region. The bacteria inhabiting the colon, secrete enzymes which can breakdown the azopolymer, this initiates the release of insulin from pellets. Insulin is microencapsulated using pH responsive polymers. Alginate is one such polymer, its coating protects them in the acidic pH of the stomach but dissolves and liberates the entrapped insulin in the intestine.

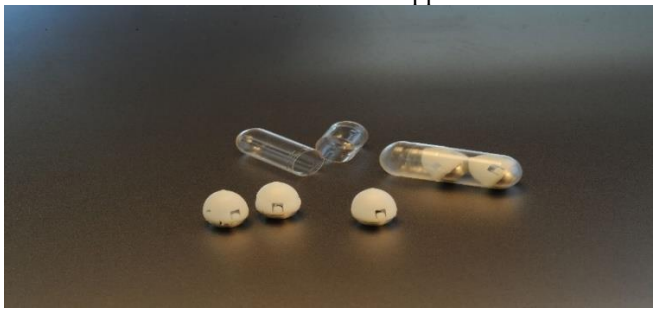

Fig 7. Insulin Pill

2.7 Transdermal Patch

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin into the bloodstream. The Altea Therapeutics Pass Port™ System was the first product to provide a non-invasive, controllable and efficient way to deliver insulin via a patch on the skin. It consists of an applicator and a reservoir patch; the latter is placed on

the skin and provides for painless delivery of insulin. It 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 gastrointestinal and liver metabolism that occurs often after oral administration. It creates an effective economical and patient-friendly delivery of insulin as well as the delivery of drugs for a wide variety of conditions. However, the transdermal patch system has its own limitations in which the drug that require high blood levels cannot be administered and may even cause irritation or sensitization of the skin. The adhesives may not adhere well to all types of skin and may be uncomfortable to wear. Along with these limitations the high cost of the product is also a major drawback for the wide acceptance of this product.

2.8 Iontophoresis

It refers to transdermal delivery of insulin or other peptides by direct electric current. A weak current carries drug ion through the skin to cause vasodilation and increased blood perfusion. Fig. 8 shows an iontophoresis patch used for the transdermal delivery. Iontophoresis differs from transdermal medication patch by using a low-level electrical current in the process, enhancing the delivery of drug ions into the skin and surrounding tissues. Depending on the net charge of the insulin molecule, the applied electrical potential has been shown to increase the rate of insulin transfer across skin. It offers the option of a programmed drug delivery technique that physically facilitates the transport of permeates across the skin. Gels are considered the most suitable delivery vehicle for iontophoresis, because they can easily be amalgamated with the iontophoretic delivery system and match the contours of the skin.

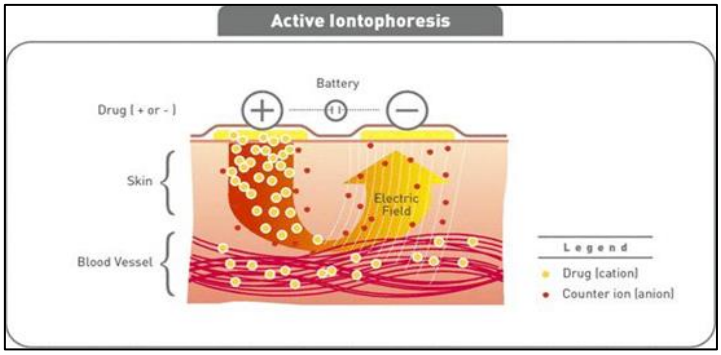

Fig 8. Iontophoresis patch

2.9 Islet Cell Transplant

Constant normoglycemic state and avoiding hypoglycemic episodes can be achieved by islet transplantation which is far superior compared to conventional insulin treatment. Insulin-producing beta cells are taken from a donor's pancreas and transferred into a person with diabetes. Once transplanted, the donor islets begin to make and release insulin, actively regulating the level of glucose in the blood. Fig. 9 depicts the process of islet cell transplantation for the treatment of diabetes mellitus. Procedure for islet transplantation involves enzymatic digestion of the pancreatic tissue, purification of the islets from exocrine tissue infusion of the islets into the portal vein and implantation in the liver. The percutaneous trans hepatic approach for the implantation of islet cells into the portal vein is a safe procedure. Successful transplantation can provide the following benefits:

(1) Need for daily insulin injections and frequent blood glucose measurements are eliminated

(2) Flexibility with meal planning

(3) Provides protection against heart disease, kidney disease, stroke and nerve and eye damage which are the long-term complications of diabetes

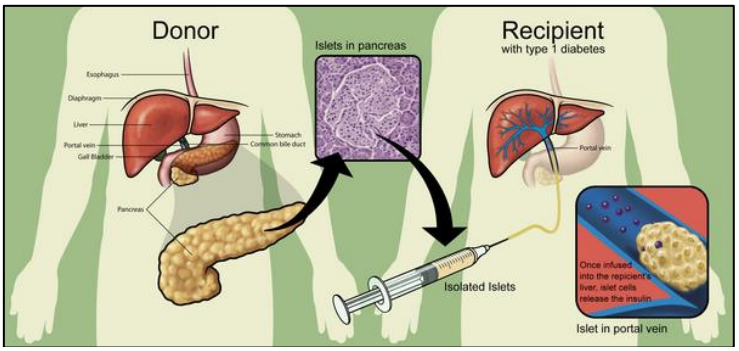

Fig 9. Islet Cell Transplant

2.10 Gene Therapy

Gene therapy is the use of DNA as a pharmaceutical agent to treat disease. Fig. 10 illustrates gene therapy using an adenovirus vector. A new gene is inserted into a cell using an adenovirus. If the treatment is successful, the new gene will make functional protein to treat a disease. To regulate insulin a gene called SHIP2 has been identified which provides a potential gene therapy target for the treatment of type 2 diabetes. The first FDA-approved gene therapy experiment in the United States occurred in 1990, when Ashanti DeSilva was treated for ADA-SCID. Since then, over 1,700 clinical trials have been conducted using a number of techniques for gene therapy

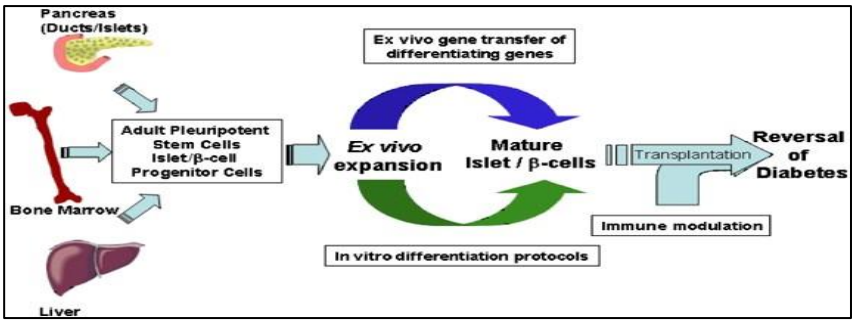

Fig 10. Gene Therapy for Diabetes

3. NON-INVASIVE INSULIN DRUG DELIVERY SYSTEMS

3.1 Insulin-loaded Bio adhesive PLGA Nanoparticles for Oral Drug Delivery

Poly (D, L-lactide-co-glycolide) nanoparticles (PLGA-NP) have been extensively used as a drug delivery system for proteins and peptides. CS-PLGA-NP was prepared using a water-in-oil-water solvent evaporation technique. Chitosan PLGA nanoparticle has attractive properties, such as a positive charge, mucosal adhesion, and absorption promotion, which prolong the duration of residence of insulin in vitro and improve its bioavailability in vivo for oral delivery. The toxicity of nanoparticle drug delivery systems has been a prominent concern. Related studies have shown that nanoparticles enhance therapeutic effects but can also increase toxicity. But the positive properties of CS-PLGA-NP do not increase the cytotoxicity because chitosan is biocompatible, biodegradable, and has low cell toxicity. This is why it has been widely applied in tissue engineering, gene therapy, drug delivery, and other fields.

In another study, insulin was encapsulated in poly (lactic-co-glycolic acid) (PLGA) nanoparticles (NPs) by using double-emulsion/solvent evaporation technique and analyses on its release kinetics were carried out using both in vitro and in vivo methods. Blood glucose decreased and the concentration of insulin in animal blood increased. The experimental results indicated that oral insulin-loaded poly (lactic-coglycolic acid) nanoparticles are able to deliver insulin effectively and decrease animal blood sugar. In conclusion, this may be a promising delivery system for the treatment of diabetes.

3.2 Polymeric Hydrogels for Oral Insulin Delivery

Hydrogels are cross-linked networks of hydrophilic polymers, which are able to absorb large amounts of water and swell, while maintaining their three-dimensional structure. For oral delivery of proteins and peptides complexation hydrogels are suitable due to their ability to respond to changes in pH in the GI tract and provide protection to the drugs from the harsh environment of the GI tract. Polymeric hydrogels protect insulin from enzymatic degradation in acidic stomach and delivers effectively in the intestine. Swelling and deswelling mechanisms of the hydrogel under varying pH conditions of the body control the release of insulin. Combining enzyme inhibitors within polymeric systems represents the potential to increase the potency of orally administered insulin. Several insulin derivatives with increased physicochemical and biological stability such as alkylated / acylated insulin, PEGylated and polyciliate insulins have been the most promising candidates for oral administration.

In a study, Polyelectrolyte crosslinked hydrogel was synthesized using gamma radiation-induced copolymerization of methacrylic acid (MAA), N, N-dimethyl aminoethyl methacrylate (DMAEMA) in aqueous solution to utilize for oral delivery of insulin. Drug release studies showed that the increasing content of MAA in the copolymer enhances release in simulated intestinal fluid to design and improve insulin release behavior from these carriers.

In another study, cationic hydrogel sub microparticles based on poly dimethyl amino ethyl methacrylate for oral insulin delivery were synthesized and evaluated in vitro. Polymerization of dimethyl amino ethyl methacrylate was carried out in aqueous medium with potassium persulfate as the initiator. cationic surface groups were introduced by the quaternization of the resulting hydrogel and the derivatization was confirmed by zeta potential measurements, nuclear magnetic resonance and infrared spectroscopies. Insulin-loaded particles were subjected to in vitro release experiments at gastric and intestinal pH.

3.3 Acrylic Polymers for Oral Insulin Delivery

Acrylic polymers are synthetic mucoadhesive polymers, principally used for oral drug delivery. Synthetic polymers can be generated by diverse techniques such as nanoprecipitation, solvent evaporation, freeze–drying or spray drying of emulsions and supercritical fluid technology. The efforts to develop an oral insulin nanotech delivery system started in the late 1980s with poly alkylcyano acrylate Nano capsules, for which a remarkable hypoglycemic effect has been reported. Recent studies have demonstrated the potential of poly alkyl cyano acrylate (PACA) as a colloidal carrier of drugs. PACA not only enhances the oral absorption of insulin but also prolongs its action in the presence of protease inhibitors. Capric acid & glycyrrhizin can be used as oral absorption enhancers. pH- sensitive copolymeric hydrogels prepared from N-vinylcaprolactam and methacrylic acid monomers by free radical polymerization offered 52% encapsulation efficiency and evaluated for oral delivery of human insulin. The formulations of this study are the promising carriers for oral delivery of insulin.

Nanospheres of crosslinked networks of methacrylic acid grafted with poly (ethylene glycol), and acrylic acid grafted with poly (ethylene glycol) nanospheres for use as oral insulin delivery devices were developed. Free radical precipitation/dispersion was used for the synthesis of copolymer nanospheres. By partitioning from concentrated insulin solution, insulin was loaded into the copolymers at levels of 9.33 and 9.54 mg per 140 mg solid sample. In vitro studies were performed to study the passage of the insulin-loaded copolymer samples in the gastrointestinal tract. In studies with diabetic rats, the serum glucose level was lower for the animals that received the insulin loaded copolymers than control values and lasted for at least 6 h. The insulin loaded copolymer nanospheres caused a significant reduction of serum glucose with respect to that of a control animal.

3.4 Aerosolized Liposomes for Pulmonary Delivery of Insulin

Pulmonary route for systemic delivery of therapeutic agents (mainly peptides and proteins) is paid more attention because it's a non-invasive method of administration and hence valuable for the delivery of large molecular proteins. The lungs provide good blood supply, a large absorptive surface area with extremely thin absorptive mucosal membrane. The anatomic structure of the human respiratory system and the effect of disposition exerted by the respiration process makes the pulmonary delivery of peptides and proteins is complicated. Aerosolized liposomes with phosphatidylcholine enhance pulmonary insulin delivery by opening the epithelial cells space in pulmonary mucosa and not mucosal cell damages and, also, a smaller liposomal particle size is advantageous for enhanced pulmonary delivery.

3.5 β-Cyclodextrin Grafting Hyperbranched Polyglycerols as Carriers for Nasal Insulin Delivery

Insulin-loaded HPG-g-CD nanoparticles had the ability to significantly decrease the blood glucose concentrations. CDs are believed to enhance nasal absorption of peptides and proteins by inhibiting their enzymatic degradation, disrupting the epithelial membrane by extraction of phospholipids and proteins, and/or opening tight junctions and the positive charge of the nanoparticles might also play an important role, since the interaction of positively charged material with the negatively charged epithelium membrane would be helpful for opening the tight junction and facilitating the absorption of drugs across the paracellular pathway.

3.6 Chitosan–zinc–insulin Complex Incorporated Thermosensitive Polymer for Controlled Delivery of Basal Insulin

Nanoparticles composed of naturally occurring biodegradable polymers have emerged as potential carriers of various therapeutic agents for controlled drug delivery through the oral route. Chitosan, a biodegradable polymer and a cationic polysaccharide, has been extensively exploited for the preparation of nanoparticles for oral controlled delivery of many pharmaceutically active agents. Chitosan derivatized polymers that improve drug retention capability, provide improved permeation, enhanced mucoadhesion and sustained release of therapeutic agents are more important. Thermosensitive polymeric delivery system (PLA-PEG-PLA) loaded chitosan–zinc–insulin complex was designed for continuous in vivo insulin delivery at basal level for prolonged period after a single subcutaneous injection. Chitosan–zinc–insulin complex was optimized to restrict the diffusion of insulin from the delivery system by forming large complexes and thereby reducing the initial burst release. The insulin released from the delivery systems did not provoke any immune response. The delivery systems demonstrated excellent biocompatibility both in vitro and in vivo and were non-toxic. In vitro release studies indicated that the increased size of chitosan–zinc–insulin complex helped to reduce complex diffusion from the thermosensitive polymer gel matrix, and prolonged the insulin release in vitro. This slow diffusion of insulin resulted in reduced initial burst release, stabilize insulin during release and storage, while providing controlled release over extended duration in vitro. The polymeric delivery system containing chitosan was biodegradable, biocompatible in vivo. This signifies that the chitosan–zinc–insulin complex incorporated in the thermosensitive polymeric delivery system can be used as an alternative to the conventional daily multiple dose basal insulin therapy

3.7 Semi-interpenetrating Network (SIPN) Co-electro spun Gelatin/insulin Fiber Formulation for Trans buccal Insulin Delivery

Insulin can be fabricated into a semi interpenetrating network co-electro spun gelatin/ insulin fiber (SIPN-GIF) formulation following coelectrospinning and cross-linking without losing bioactivity. Gelatin was electro spun into fibers and converted into a SIPN following eosin Initiated polymerization of polyethylene glycol diacrylate (PEG-DA). Insulin was co-electro spun with gelatin into fibers and converted into a SIPNGIF using this suitable formulation. ELISA was used for the in vitro release kinetics of insulin. In vitro porcine oral mucosa model was used to determine the trans buccal permeability of released insulin. Degradation half-life of 49 min which is a moderate degradation rate, significant enhancement in mechanical properties and no cytotoxic effects were found in the SIPN-GF formulation of GF cross-linked by PEG-DA (1% w/v) with eosin Y (5% v/v). Insulin release was extended up to 4 h by using This formulation to fabricate SIPN-GIF. Intracellular AKT phosphorylation and induced adipocyte differentiation in 3T3-L1 preadipocytes were successfully started by the released insulin.

3.8 Films Loaded with Insulin-coated Nanoparticles (ICNP) as Potential Platforms for Peptide Buccal Delivery

Insulin-coated nanoparticles (ICNPs) can be obtained by a new antisolvent co-precipitation fabrication process. The ICNPs were embedded in polymeric films containing a cationic polymethacrylate derivative (ERL) or a combination of ERL with hydroxypropyl methylcellulose (HPMC). ICNPs with 40% (w/w) insulin load was successfully obtained by the antisolvent co-precipitation method, 323±8 nm particles with a high zeta potential of 32.4±0.8 mV, indicating good stability were achieved. One-month storage did not decrease the insulin content. ICNP-embedded films using ERL as the polymer matrix presented excellent mucoadhesive and insulin release properties. ICNP-loaded ERL formulations are a promising delivery system for buccal administration of a peptide such as insulin, as they were found to be more effective in terms of film performance and insulin permeation through the human buccal mucosa model.

4. FUTURE INVENTIONS

4.1 Radiation technologies for non-invasive glucose monitoring

The use of various electromagnetic radiation, such as infrared radiation, Raman, thermal or photoacoustic spectroscopy, as well as millimeter waves, allow remote measurement of blood glucose concentration, either punctually or continuously, without stinging. Some solutions are already on the market, such as the GlucoTrack device, which is placed on the earlobe. Others are in advanced development, such as GlucoWise, which is used between the thumb and index finger, K'Watch, a connected watch, or Sugar Beat, a patch that attaches to the arm. The debate on whether these devices should be adopted by non-insulin-dependent patients, who make up the vast majority of diabetic patients, remains open. Demonstrating the real clinical benefit of continuous glucose monitoring for these patients could encourage their adoption, along with a reimbursement of these devices by healthcare systems

4.2 Smart insulin that responds to rising blood glucose levels

Smart insulin is a form of insulin that is designed to stay in the blood for a long time but activates when blood glucose levels rise. This solution would make blood glucose monitoring obsolete, greatly simplifying the daily life of diabetic patients. There are

currently two possibilities: the development of an insulin molecule chemically modified to be reactive to glucose, or the encapsulation of insulin within a glucose-reactive material. The Juvenile Diabetes Research Foundation (JDRF) is very involved in this field, as well as other companies such as Thermalin Diabetes, Glycostasis, Ziylo, Sensulin or Zenomics.

4.3 The bioartificial pancreas to treat insulin resistance

Another promising lead would provide the pancreas with new cells capable of producing insulin. To date, three types of cells have shown promising results: stem cells, mature human cells and beta cells (insulin-producing pancreatic cells) from pigs. These cells must then be protected from the immune system by means of an encapsulation system, which simultaneously allow insulin to come out and oxygen to be supplied. Viacyte is one of the most advanced companies in this field, with a new treatment currently in Phase I clinical trials.

4.4 Immunotherapy as a vaccine for type 1 diabetes

As with other autoimmune diseases, immunotherapy could prevent the onset of Type 1 diabetes by preventing, or at least delaying, the self-destruction of pancreatic cells. This therapy could be particularly relevant for all people with a genetic predisposition to the disease. Different approaches are currently being developed: use of the tuberculosis vaccine by the Massachusetts General Hospital, development of a monoclonal antibody by the biopharmaceutical company Provention Bio, or use of synthetic peptides modified by the Belgian startup Imcyse. Clinical studies are multiplying, much to the benefit of future diabetic patients.

4.5 The intestinal microbiota, an army against type 2 diabetes

Finally, several recent studies show a clear link between the intestinal microbiota and Type 2 diabetes: the absence of a combination of bacteria, still unknown to this day, would strongly contribute to the development of obesity, and ultimately to Type 2 diabetes.

5. CONCLUSION

The long-term complications of diabetes mellitus can be reduced by the advanced methods of insulin delivery systems. Efforts have been undertaken to replace the invasive subcutaneous route by a non-invasive route. There has been a significant progress in the delivery of insulin via pulmonary, buccal and oral route. Each route has their own set of advantages and disadvantages. Of all the non-invasive methods, oral route seems to be the most promising as nanotechnology allows the various encapsulations to pass through the gastric acid environment. Oral route also provides improved absorption rates and ease of administration and thus, improves patient compliance. Of the various emerging trends, artificial pancreas may prove to be a valuable therapy for the patients of type 1 diabetes, particularly if the lag period is shortened through improved glucose sensors and the use of ultra-fast acting insulin.

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