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REVIEW ARTICLE: A COMPARATIVE REVIEW ON VARIOUS NON-INVASIVE TECHNIQUES OF INSULIN

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ABSTRACT

There is a continuing search for improved insulin formulations in order to imitate as closely as possible the physiological pattern of insulin secretion, and thereby to minimize the complications of diabetes mellitus. This review article covers all the most relevant non-invasive insulin delivery methods under development, respective technology and clinical data available according to their status of development. Great efforts have been made in searching for noninvasive modes of insulin administration that will avoid the need for parenteral administration. These include: oral, colonic, rectal, nasal, ocular, buccal, pulmonary, uterine and transdermal routes of administration.

Key words: Diabetes, Insulin, Modes of Administration, Drug Delivery.

INTRODUCTION

Diabetes has been a serious pathological condition which has created major healthcare problems worldwide and costing billions of dollars annually. The mortality rate due to this disease is expected to increase up to approximately 50% till the next decade. At present, 347 million people worldwide have diabetes (Danaei G *et al*., Lancet, 2011). More than 80% of diabetes deaths occur in low- and middle-income countries(Mathers C.D,2006).WHO projects that diabetes will be the 7th leading cause of death in 2030 (Global status report on noncommunicable diseases, 2010).

Diabetes is a metabolic disorder characterized by hyperglycaemia, glycosuria, hyperlipaemia, negative nitrogen balance and sometimes ketonaemia. In normal individuals, the increase in the blood glucose levels triggers the secretion of insulin by pancreatic islet beta cells. The insulin binds to insulin receptors located on cells, and hence signals them to increase the rate of glucose uptake from the plasma into the cells. As the blood glucose returns to normal levels, the amount of insulin in the blood again drops. Therefore, in the absence of insulin, blood glucose levels would rise to dangerously high levels, often resulting in death. The WHO recognises two main forms of diabetes mellitus: type 1 and type 2.

Type 1 diabetes or insulin-dependent diabetes mellitus (IDDM) is characterised by the lack of insulin production and usually develops in childhood. It is often categorised as autoimmune disease (Somers *et al*., 2004). Type 2 diabetes, or non-insulin dependent diabetes mellitus (NIDDM), generally occurs in middle aged people. It is the far more common form of diabetes, comprising 90% of the worldwide population of diabetic patients.

Insulin Replacement Therapy has been used in the clinical management of Insulin-dependent diabetes mellitus for more than 84 years. The glucose level of the patient is monitored and when hyperglycaemia occurs insulin is injected by the subcutaneous route. The saline solution of insulin is gradually absorbed into the bloodstream via the dermal capillaries, where it reaches its maximum activity at 2 to 3 hours following injection Certain slow-acting formulations of insulin such as Lente insulin show an even more prolonged effect (Varshosaz J, 2007). The traditional treatment of Diabetes Mellitus by subcutaneous route has shown inconvenience which led to various attempts production, purification, formulation and methods of delivery of insulin but then too have met

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limited success. Various alternative routes and strategies for insulin administration such as rectal, ocular, nasal, pulmonary and oral (aerosols, hydrogels, micro-capsules, dry powder inhalers, nanospheres, micro-needles, etc.) have been exploited (Cefalu WT, 2004).

Insulin Drug Delivery

Major route of insulin administration is through subcutaneous route where it is presented to the body in a non-physiological manner. This subcutaneous route of administration of insulin has remained the basis of insulin therapy since its introduction. Still this feature is central to the problem of glycaemic control, as the pharmacokinetics of conventional insulin preparation that are given by this route make it difficult to replicate the normal pattern of nutrient-related and basal insulin secretion. The subcutaneous administration of insulin is quite inconvenient and painful. Its overdose may lead to hyperinsulinaemia as insulin is administered in a non-physiological way, targeting mainly extrahepatic insulin-dependent tissues (Silvaa *et al*., 2006).

Insulin delivery is a vast area of research; various factors such as administration routes, form of delivered insulin, dose, etc affect the efficacy of insulin.

Approaches for Insulin Delivery

The oral route for insulin administration is of practical interest as oral drug administration results in less pain, greater convenience, higher compliance and reduced Infection risk as compared to subcutaneous injections (Liu L *et al.*, 2003).

Some recent pharmacokinetics and pharmacodynamics studies on *type 1* diabetic patients, have illustrated that the oral insulin spray showed peak insulin concentrations in relatively shorter time periods, and a more rapid onset of action as compared to regular subcutaneous insulin (Cernea S *et al*., 2004). Some other studies on *type 1* diabetic patients on multiple daily insulin injections and in insulin-treated *type 2* diabetic patients showed that the oral insulin was effective in controlling postprandial glucose levels (Modi P *et al*., 2002).

The major disadvantages associated with this route of administration are low bioavailability due to relatively low passage of active agents across the mucosal epithelium, rapid insulin degradation due to action of digestive enzymes in the GI tract, enzymatic proteolysis, and acidic degradation of orally administered insulin in the stomach(Lin YH *et al*., 2007) .Various approaches have been made to overcome these disadvantages using permeation enhancers(Carino GP *et al*., 2000; Mesiha M *et al*., 1994), protease inhibitors(Yamamoto A.*et al*.,1994) ,enteric coatings (Morishita I *et al*., 1993) and (bio) polymer micro-/ nano-sphere formulations (Sarmento B *et al.*, 2007; Jain D *et al*., 2005).

Clinical significance of the oral delivery of insulin

Physiological insulin that is secreted by the pancreas enters portal circulation and inhibits hepatic glucose production. It undergoes metabolism in the liver to a significant extent (50%) The ratio of plasma insulin in portal circulation versus that in peripheral circulation is two. The physiological hypoglycemic effect of insulin occurs due to the absence of hepatic glucose production that is enhanced by the increase in glucose use caused by lower insulin levels in peripheral circulation. When insulin is injected subcutaneously, the plasma insulin concentration in portal circulation and in peripheral circulation is almost equal. The hypoglycaemic effect of insulin is a result of its action on peripheral tissues. Oral delivery of insulin can mimic the physiological fate of insulin and may provide better glucose homeostasis. This will reduce the incidences of peripheral hyperinsulinaemia, which is linked to neuropathy, retinoendopathy, and so forth (Agarwal V *et al*., 2001).

Challenges associated with the oral delivery of insulin

The various challenges associated with the oral delivery of proteins usually are evaluated by determining the fate of the protein in the gastrointestinal tract (GIT). The main challenges reported are enzymatic degradation and a lack of sufficient insulin permeability through the GIT.

Enzymatic degradation of insulin

Upon ingestion, insulin is subjected to acid-catalyzed degradation in the stomach, luminal degradation in the intestine, and intracellular degradation. The pancreatic enzymes that degrade insulin are trypsin and α-chymotrypsin (Ginsburg A. *et al*., 1960; Young JD *et al*., 1961). The rate of degradation was found to be 10 times higher in the presence of α-chymotrypsin when compared with that in the presence of trypsin (Schilling RJ *et al*., 1991).The cytosolic enzyme that degrades insulin is insulin-degrading enzyme (IDE) (Chang LL, 1997).The rate of degradation of insulin also depends on its associated state in solution. Insulin is a monomer at low concentration (0.1 mM) and dimerizes in a pH range of 4–8 at higher concentrations. At concentrations greater than 2 mM, the hexamer is formed at neutral Ph (Hansen JF, 1991). The associated state affects the rate of degradation of insulin. In the presence of bile salts, the rate of degradation may increase close to six times (Li Y *et al*., 1992).

Dosage form stability issues

The activity of proteins depends on the three-dimensional molecular structure. The dosage form development of proteins may expose the proteins to harsh conditions that may alter their structure. This may affect the efficacy of the protein and its immunogenic responses.

During dosage form development, proteins are subjected to physical and chemical degradation. Physical degradation involves modification of the native structure of a protein which may be due to adsorption, aggregation or precipitation. Chemical degradation is due to the cleavage of the bond and lead to formation of new product. Deamidation, oxidation, disulfide exchange, and hydrolysis are mainly responsible for chemical degradation.

Proteins must be characterized for change in conformation, size, shape, surface properties, and bioactivity upon formulation processing. Changes in conformation, size, and shape can be observed by the use of spectrophotometric techniques, X-ray diffraction, differential scanning calorimetry, light scattering, electrophoresis, ultracentrifugation, and gel filtration (Pearlman R *et al*., 19991).

Selection of a particular technique is based on the sensitivity of the technique, the system under study, and the availability of equipment. Theory about selected techniques used for the characterization of proteins has been reviewed (Pearlman R *et al*., 1991; Hoffmann H, 2000). Some examples of characterization of insulin are discussed in the following paragraphs.

Size-exclusion chromatography with reversed phase–high performance liquid chromatography (HPLC) was used to determine the formation of covalent insulin dimers with trace amounts of high molecular-weight transformation products after microencapsulating insulin in a mixture of poly (DL-lactide-co glycolide) and poly (L-lactide) (Shao PG *et al*., 2000). Differential scanning calorimetry was used to differentiate denaturation endotherms of amorphous and crystalline insulin (Pikal MJ *et al*., 1997).

Strategies for improved oral delivery of insulin

Various strategies have been worked out to overcome the barriers of enzymatic degradation and taking steps to conserve the bioactivity during formulation processing.

The various approaches for oral delivery of insulin are as follows:-

Enzyme inhibitors

Researchers have evaluated the use of protease inhibitors with an aim to slow the rate of degradation of insulin. They hypothesized that the slow rate of degradation will increase the amount of insulin available for absorption. As discussed previously, enzymatic degradation of insulin is mediated by serine proteases trypsin, α-chymotrypsin, and thiol metalloproteinase IDE. Consequently, stability of insulin has been evaluated in the presence of excipients that inhibit these enzymes.

Representative inhibitors of trypsin and α-chymotrypsin include pancreatic inhibitor (Laskowski M.J., 1958), soybean trypsin inhibitor, FK-448 (Fujii S.,1985), camostat mesylate (Tozaki H *et al*,1997), and aprotinin(Yamamoto A.*et al*.,1994) .Inhibitors of insulin-degrading enzyme include 1,10 phenanthroline (Bai JP *et al*., 1996) and bacitracin (Bai JP *et al*., 1999).

Permeation enhancers

Permeation enhancers improve the absorption of proteins by increasing their paracellular and trans-cellular transports. An increase in paracellular transport is mediated by modulating tight junctions of the cells, and an increase in transcellular transport is associated with an increase in the fluidity of the cell membrane. Permeation enhancers included in the former category are calcium chelators, and those included in the latter category are surfactants. Calcium chelators act by inducing calcium depletion, thereby creating global changes in the cells, including disruption of actin filaments, disruption of adherent junctions, and diminished cell adhesion (Citi S,1992) .Surfactants act by causing exfoliation of the intestinal epithelium, thus compromising its barrier functions. The enhancement caused by permeation enhancers is dose and time dependent. Examples of permeation enhancers used include sodium laurate and cetyl alcohol (Touitou E *et al*., 1986), sodium cholate (Ziv E *et al*., 1994), and zonula occludens toxin (ZOT) (Fasano A *et al*., 1997) .

Use of polymer systems

The use of polymer systems both alone and concurrent with absorption modifiers such as enzyme inhibitors and permeation enhancers has been evaluated. In the former system, the drug is released after uptake of the polymer system intact from the GIT. In the latter system, the drug is released in the lumen before being absorbed. Polymeric dosage form with absorption modifiers: Researchers have attempted to use polymers in various controlled-release applications. Depending upon the addition of the modifier, the reported preparations can be grouped into the following:

- Insulin has been incorporated in dosage form with an absorption modifier. The dosage form is then coated with an enteric polymer to release the contents depending on pH or enzymatic conditions of the GIT.
- Insulin has been microencapsulated with polymers and then administered with absorption modifiers. These dosage forms have dual protective properties. The polymer protects the drug from immediate exposure to the enzymes, and the absorption modifier may increase the enzymatic stability or enhance the permeability (Agarval V *et al*., 2001).

Chemical modification

Modifying the chemical structure of protein or peptide is another approach to enhance bioavailability by

increasing its stability against enzymatic degradation or its membrame permeation. For example: substitution of D-amino acids for L-amino acidsin primary structure can improve the enzymatic stability of peptides. A diacyl derivative of insulin maintains its biological activity and also increases absorption from the intestine (Giriraj KG *et al*., 2003).

Pulmonary route

Since insulin has a high molecular weight, numerous formulation approaches have been tried to improve its absorption through the nasal mucosa. Pulmonary drug delivery systems offer an alternate and a better route of insulin administration as compared to the other non-invasive routes. The studies to demonstrate the feasibility of protein crystals for the pulmonary delivery of a sustained release protein drug formulation were performed using Insulin as the model protein. . The hypoglycaemic effects of the microcrystal suspension were prolonged over 7 h. These results could be attributed to the sustained release of insulin from the micro-crystals, which were deposited widely throughout the entire lung. They get readily absorbed through the alveoli directly into blood stream because of large surface area (~140 m^2 in adults), high permeability, and vast vascularisation of the lung; and hence provide higher drug efficacy (Cernea S *et al*., 2005).

Other advantages include relatively simple self-administration, no first-pass liver effect of the absorbed insulin, reduced enzymatic activity and pH mediated drug degradation. One of the most important advantage of this route is higher absorption; the surface area for absorption of the alveolar region of the lung is relatively higher (~140 m^2) as compared to that of the nasal absorption region (~150 cm^2) (Mygiand N *et al*., 1985). The other advantage of the pulmonary administration is that drugs have longer residence time in the alveolar region of lungs due to minimal clearance mechanisms; as compared to the intranasal administration where the drug needs to be absorbed quickly (in approximately 15 to 20 minutes) or they are removed by the rapid mucociliary clearance mechanisms in the nose and if swallowed(Byron PR *et al*., 1986) .In addition, the alveolar region has an extremely thin (0.1 µm) and vesiculated cell barrier which enhances the absorption of drugs that are deposited there(Gil J, 1983). Pulmonary route has also proved to be more beneficial than the subcutaneous route. Some studies have shown that intrapulmonary delivery of nebulized insulin showed the average time to peak insulin levels between 50 and 60 minutes (Jendle P *et al*, 1996), while those injected subcutaneously, the average time to peak insulin levels was 144 minutes (Galloway JA *et al*, 1987). Commonly used devices for pulmonary insulin administration are metered dose inhalers (MDIs) and nebulizers which contain volatile chemical propellants such as hydrofluoroalkanes (HFAs) (Palton J, 2006).

The great challenge for researchers remains the full optimization of the delivery system, which is the culmination of all those particle properties required for therapeutic applications: good encapsulation efficiency, the prevention of protein degradation, and the predictable release of the drug. This breakthrough in the availability of inhaled insulin is certain to have exceptions. It must be recognized that inhaled insulin may not be ideally suited to all 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. However, as a substitute for short-acting insulin, inhaled insulin appears to be safe, efficient, and satisfactory for clinical use and acceptable to patients at this early stage in its development (Granado M, 2006; Defronzo RA, 2005; Rosenstock J, 2005; Skyler JS, 2005; Barnett AH, 2005; Himmelman A, 2003; Henry RR, 2003; Gale EAM *et al*., 2002).

Transdermal drug delivery systems

Transdermal drug delivery systems can be generally divided into physical, biochemical, and chemical methods. Although the skin is easily accessible and has a large surface area (~1–2 m^2), it is relatively impermeable to large, hydrophilic polypeptides such as insulin. Several methods have been tested to improve transdermal transfer, including iontophoresis (Stephen RL *et al.*, 1984; Sage BH, 1997; Siddiqui O *et al.*, 1987; Langkjaer *et al.*, 1998), low-frequency ultrasound (sonophoresis) (Tachibana K, 1992; Mitragotri S, 1995) and drug-carrier agents, such as transfersomes.

Insulin is reported to be transported across the skin with a relatively high degree of efficiency (≥ 50%) when it is incorporated into lipid-based transfersomes (phosphatidylcholine- based drug carriers). Transfersomal insulin (Transfersulin) that is applied to intact human skin can reduce plasma glucose concentration by ~20% within 3–4 hours. The effect lasts for 10 hours or more, and is equivalent to 75–100% of the hypoglycaemic action of soluble insulin injected subcutaneously (Cevc G *et al.*, 1996).

Transdermal route proves to be an alternative route for insulin delivery and further development that include chemical and physical delivery mechanisms could lead to further progress in this area.

Iontophoresis

More recently, one of the most advanced technologies that have been developed in the 20th century to overcome low skin permeability to insulin is iontophoresis. Iontophoresis is a technique used to enhance the transdermal delivery of compounds through the skin by the application of a small electric current. Using the processes of electro migration and electro-osmosis, iontophoresis increases the permeation of charged and neutral compounds. Combinations of iontophoresis with absorption enhancers, electroporation, and sonophoresis have been tested to increase transdermal drug permeation. Recently, it has been demonstrated that the effectiveness and mechanism of a transdermal drug delivery system using iontophoresis plus an absorption enhancer. A combination of absorption enhancer pretreatment and iontophoresis delivered drugs more effectively than iontophoresis alone. The proposed theory is that iontophoretic drug delivery may be easiest through the dilated intercellular spaces of the stratum corneum, which have lowered electrical impedance following absorption enhancer pre-treatment (Panchagnula R *et al*., 2000; Mao XM *et al*., 1995).

Sonophoresis (ultrasound)

For the past two decades, sonophoresis (ultrasound) has been used to enhance the delivery and activity of drugs. Ultrasound has an ever-increasing role in the delivery of therapeutic agents, including genetic material, proteins, and chemotherapeutic agents. There is a tremendous corpus of literature on the use of ultrasound to enhance the permeability of the skin for transdermal drug delivery. Therapeutic levels of ultrasound (1–3 MHz, 1–3 W/cm^2) have been used for years to drive small hydrophobic molecules, like steroids, into or through the skin. It was showed that low frequency ultrasound was much more effective than higher frequencies, and provided evidence of the mechanism involved. Skin permeability increased with decreasing frequency, and with increasing time of exposure and intensity (beyond a certain threshold), thus identifying collapse cavitation as a causative mechanism. The current theory is that cavitation events open reversible channels in the lipid layers of the stratum corneum and provide less tortuous paths of transport for proteins such as insulin. Tezel and Mitrogotri have formulated a model of shock-wave and microject cavitation events and their impact upon skin permeability. Although their model can be fitted to their data, there are many assumptions and parameters in the model, and more direct evidence is needed to identify conclusively the mechanisms of ultrasound enhanced transdermal protein delivery (Mao XM *et al.*, 1995; Pitt WG *et al.*, 2004; Mitrgotri S *et al.*, 2004).

Micro-needles

It involves the use of micro-needles that pierce the skin and create micrometer scale openings that increase the Transdermal transport. Micro-needles of micrometer dimensions can create transport pathway large enough for transfer of small drugs, macromolecules, nanoparticles and fluid flow. It reduces pain and facilitates highly localized and even intracellular targeting. The microelectronic revolution has provided tools for highly precise, reproducible, and scalable methods to fabricate structures of micrometer dimensions. Arrays of micrometer-scale needles could be used to deliver drugs, proteins and particles across skin in a minimally invasive manner. Practical micro-fabrication techniques have been developed to yield micro-needle arrays of silicon, metal, and biodegradable polymers of micrometer dimensions in various geometries.

Micro-needles array having solid or hollow bore with tapered tips may provide minimally invasive method to increase skin permeability for diffusion based transport of large molecules such as proteins (Pandey S, 2007). Hollow micro-needles have permitted the flow of microliter quantities into skin in-vivo, including the microinjection of insulin to reduce blood glucose level in diabetic rats. These results suggest that micro-needles are useful approach to Transdermal drug delivery.

Ocular route

Another non-invasive route of insulin delivery is ocular route where insulin can be delivered into the systemic circulation through the instillation of eye drops, for which the major absorption site of insulin is located in the nasal cavity (Lee YC *et al*., 1997). Systemic delivery of insulin through the ocular route offers many advantages such as convenient administration of drug as eye drops, accurate dose due to the fact that eyes can hold only one drop of ophthalmic solution regardless of the volume instilled, faster absorption, avoidance of hepatic first pass metabolism, more economical than injections as does not require syringes and needles (Chiou GCY, 1991).

Rectal route

Administration of insulin by the rectal route is potentially advantageous because most of the insulin enters the systemic circulation through the lymphatic system, circumventing the hepatic extraction of insulin that occurs by other routes (Caldwell *et al*.,1982). However, absorption of insulin from the rectum is poor and inconsistent, and requires the incorporation of enhancers into suppositories or gels to improve the absorption rate (Brange J *et al.*, 1997; Chetty DJ, 1998; Matsudo H, 1999; Yun MO *et al*., 1999).In addition, bioavailability in humans is low (4 –10%), and compared with subcutaneous injection, rectally delivered insulin acts more rapidly and is shorter lived (Yamasaki Y *et al.*,

1981; Hildebrant R *et al*., 1984). An improvement in short-term glycaemic control has been shown with either a single or repeated doses during one day, but long-term acceptance of this route of delivery among patients is unlikely (Raz I *et al.*, 1984).

ATTEMPTED INSULIN THERAPY APPROACHES

Aerosols

The inconvenience and discomfort caused by delivery of insulin by inhalation has led to research into aerosols. Research has focused on developing medicaments for treating respiratory and nasal disorders by aerosolized drugs that could be delivered by either mouth or nose. These formulations are made effective by adding surface-active materials to the aerosolized solution being introduced to the respiratory tract. The controlled systemic or local delivery of insulin results in enhanced absorption, less nasal irritation and congestion. The aerosol is formulated by suspending the drug as fine powder in a liquefied gas (such as hydrofluoro alkanes). These formulations are than administered to patients through pressurized metered dose inhalers. The major disadvantages associated with this route of administration are protein denaturation during aerosolisation (Mumenthaler M *et al.*, 1994), excessive loss of inhaled drug into oropharyngeal cavity (Heinemann *et al.*, 2001), loss of reproducibility of therapeutic results (Schultz *et al*., 1998). Prolonged storage of proteins and peptides in aqueous medium results in their instability leading to storage problems (Laube *et al*., 1993). Due to all these disadvantages, new formulations for insulin aerosols are being developed.

Dry Powder Inhalers

Dry powder inhalers are used to deliver insulin by combining it with an absorption enhancer, to enhance the systemic absorption of the drug and introducing into the lung in the form of powder of appropriate particle size (< 10 microns).

The dry powder formulation consists of insulin (~ 60%) and excipients, such as mannitol which also acts as a stabilizer. The powdered insulin is dispersed in the form a blister (containing 1-3 mg of insulin) by the inhaler into an aerosol cloud held in a chamber. These aerosol clouds, containing insulin particles, are then inhaled by the patient at the beginning of a slow, deep breath during which draws air into the chamber and thus releasing the aerosol into the lungs.

An ideal DPI formulation should have uniform distribution, small dose variation, sufficient physical stability in the device before use and good performance in terms of emitted dose and fine particle fraction (Chougule *et al*., 2007). Many clinically tested and approved devices for dry powder formulations available in the market, areas Nektar / *Exebura*® device (Nektar Therapeutics Inc., San Carlos, CA, Aventis, Bridgewater, NJ, Pfizer, NY), or liquid aerosols formulations in the AERx® Insulin Diabetes Management System (Aradigm Corp., Hayward, CA, Novo Nordisk A/S, Copenhagen, Denmark) and in the Aerodose® Inhaler (Aerogen Inc., Sunnyvale, CA, USA) (Naryani R, 2001).

Nanospheres

Insulin-loaded nanospheres were prepared by polymerization of Isobutyl cyanoacrylate(IBCA) in an acidic medium. These nanospheres displayed a mean size of 145 mm and an association rate of 1U of insulin per milligram of polymer (Damge *et al*., 1997). These nanospheres were dispersed in an oily medium (Miglyol 812) containing surfactant (Polox-amer 188 and deoxycholic acid) and evaluated for in-vivo and in-vitro degradation. No degradation due to proteolytic enzymes was observed in-vitro. When these nanospheres (100U per kilo gram of body weight) were administered preorally in streptozotocin-induced diabetic rats, a 50% decrease in fastened glucose levels from the second hour upto 10-13 days was observed. These effects were shorter (2 days) or absent when nanospheres were dispersed in water. Using ^{14}C-labeled nanospheres loaded with (^{125}I) insulin, it was found that nanospheres increased the uptake of (^{125}I) insulin or its metabolites in the gastrointestinal tract, blood and liver while the excretion was delayed when compared to (^{125}I) insulin non-associated to nanospheres.

Microcapsules

Microencapsulation offers various benefits over other drug delivery systems in terms of controlled release of insulin, increased stability, and protection of insulin from the various digestive enzymatic actions in the GI tract and enzymatic proteolysis and acidic degradation of orally administered insulin in the stomach, using a biodegradable polymeric material which makes it a suitable system for pulmonary delivery. In addition, the controlled release preparation of insulin can continuously exhibit pharmaceutical efficacy in vivo in a stable manner for an extended period of time. Drug bioavailability can be further enhanced by conjugating it to molecules that can recognize specific receptors on the epithelial cells and get transported across the intestinal epithelium. This approach eliminates the side effects associated with prolonged opening of cross-linked junctions. This also avoids the unspecific transport of toxic compounds due to passage across cell barrier by transcellular mechanism (Yadav *et al*., 2009).

Hydrogels

These are cross-linked network of hydrophilic polymers, which are able to absorb large amount of water and swell while maintaining their three dimensional structure. Complexation hydrogels are suitable for oral

delivery of proteins and peptides due to their ability to respond to changes in pH in GI tract and provide protection from harsh environment of GI tract. pH-sensitive hydrogels have been extensively researched to develop controlled release formulations for oral delivery of insulin. These ionic hydrogels show sudden or gradual changes in their dynamic and equilibrium swelling behaviour as a result of changing the external pH. There are two main types of pH-sensitive hydrogels, acidic hydrogels and basic hydrogels. Acidic hydrogels get charged and swell at high pH due to ionization and shrink at low pH (Nagarsekar A, 2002). While, basic hydrogels show opposite swelling behaviour in response to Ph (Harland, 1992).

The disadvantage associated with hydrogels is the low water solubility of many drugs which affects the gel loading process in a drug concentrate. in the case of therapeutic proteins, the non-aqueous solvents used to make concentrated low-molecular mass drug solutions often denature most bioactive proteins.

Therefore, hydrogels can be used as the basis of the design of closed-loop drug delivery devices for therapeutic agents used for the management of diabetes mellitus (Gehrke *et al.*, 1998).

Liposomes

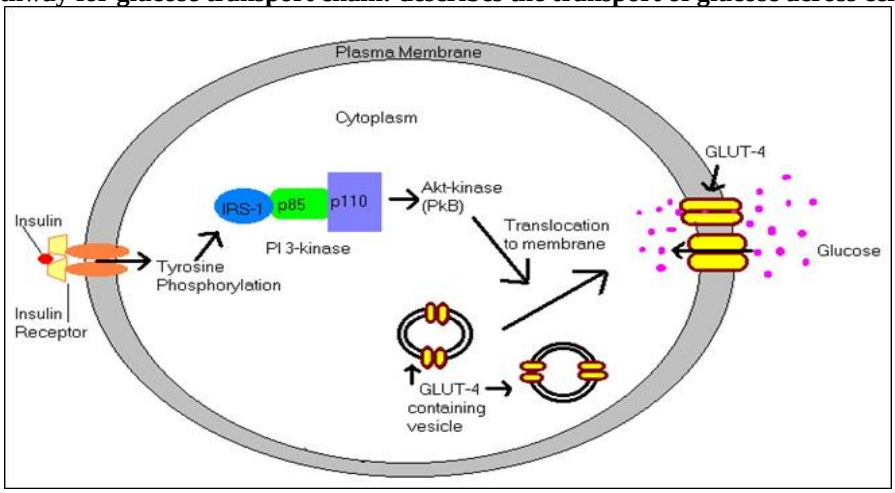
Insulin entrapped liposomes cause dose dependent hypoglycaemia. Researchers have developed liposomes with varying composition by two methods: solvent evaporation hydration and solvent spherule evaporation (Choudhari *et al.*, 1994). Liposomes containing lecithin 100 mg, cholesterol 20 mg and Tween 1% v/v were found to be most effective. The effect of insulin-liposome was prolonged in diabetes- induced rabbits than that of normal rabbits. The pharmacodynamics of the insulin–liposome system was comparable with the action of 1U/kg of insulin administered subcutaneously.

CURRENT AND FUTURE DEVELOPMENTS

Several attempts have been made to adopt various effective measures for the surveillance, prevention and control of diabetes and its complications, particularly in low and middle- income countries. In the attempt to make the diabetes treatment more acceptable, many alternative delivery systems and routes of insulin administration have been explored and many challenges are undertaken. Insulin delivery by alternative route is the area of current interest in the design of drug delivery system. In the endeavour to develop alternative insulin delivery technologies, most of the global pharmaceutical companies are showing encouraging progress. It appears that years of persistent research into non-injectable methods of insulin delivery have resulted in some clinically available routes of insulin administration. Among the various routes of insulin administration pulmonary route appears to be the most clinically viable non-invasive system with the advent of new delivery devices such as dry powder and liquid aerosol formulations. This route of administration has proved to be as effective and well tolerated as the subcutaneously injected regular insulin, and also has a pharmacodynamic profile better suited for mealtime insulin therapy. Other methods of insulin delivery (especially oral) may prone to be a potential choice for prandial replacement. Although the absorption efficiency across epithelial surfaces of the mouth, gastrointestinal tract, skin and nose has increased by using absorption-enhancing techniques, bioavailability of drugs through these routes still has low clinical value.

The ultimate goal for the treatment of diabetes remains the development of a fully automated glucose controlling device. Although the search for alternative routes to subcutaneous insulin administration has been relatively unsuccessful, recent approaches seem to hold potential for effective insulin therapy.

Figure 1. Insulin pathway for glucose transport chain: describes the transport of glucose across cell



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