



NONINVASIVE INSULIN DELIVERY SYSTEM: A REVIEW

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ABSTRACT

In today's era, insulin delivery by noninvasive route is an area of current interest in diabetes mellitus treatment. Insulin is a hormone produced by the pancreas that reduces the level of blood glucose in the body. In 1921, when insulin was invented by scientist Banting & Macleod, it was first delivered by parenteral route for type-I & type-II diabetes mellitus. As the time passes, there has been need for delivery of insulin by a noninvasive route. Insulin delivery via parenteral route is a painful treatment to the patient. It is an expensive, inconvenient therapy and there is a possibility for developing infection to the patient. Therefore, recently various approaches have been developed for noninvasive delivery of insulin that has shown success in delivering insulin. These deliveries are designed to overcome the inherent barriers for insulin uptake across the gastrointestinal tract, mucosal membranes and skin. This article reviews some recent advances in insulin delivery by noninvasive route and also reviews the potential for using each route.

INTRODUCTION

The term diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances in carbohydrate, fat and protein metabolism that results in defects in insulin secretion, insulin action or both. Diabetes mellitus may present with characteristics symptoms such as thirst, polyuria, blurring of vision and weight loss. Three well known scientists Fedrick Banting, Macleod, and Collip had discovered the insulin in 1921, which is responsible for diabetes mellitus and they received Nobel Prize in 1923. Diabetes mellitus is the sixth most common cause of death in the world and significantly becomes the cause of death for major diseases. When diabetes was discovered, there has been only 10 % of the world population affected by this disease. According to the World Health Organization (WHO), at least 171 million people worldwide suffer from diabetes or 2.8% of the population in 2000 ¹. As estimated by WHO, 135 million peoples worldwide had been detected with diabetes mellitus in 1995, and this number is expected to rise about 300 millions by 2025 ². Diabetes is a major disorder of endocrine system and caused due to deficiency of insulin. Insulin is a peptide hormone composed of 51 amino acid residues and has a molecular weight of 5808 Da. It is composed of two peptide chains referred to as an A chain and a B chain. The A and B chains are linked together by the two disulfide bonds, and an additional disulfide is formed within the A chain. In most species, the A chain consists of 21 amino acids and the B chain consists of 30 amino acids. It is produced in the islets of langerhans in the pancreas. Two major types of diabetes mellitus- type 1 diabetes mellitus and type 2 diabetes mellitus. Type 1 diabetes is an insulin dependent diabetes mellitus (IDDM) and results in an insufficient amount of insulin in body. Type 2 diabetes is a non-insulin dependent diabetes mellitus (NIDDM) and results in an insulin resistance- a condition in which body cells fail to use insulin properly, sometimes combined with reduced amount of insulin secretion. When insulin was discovered, it was first delivered by parenteral route. Insulin is delivered to diabetic patients exclusively via the subcutaneous route. The usual duration of action is relatively short; i.e., 4-8 hrs and therefore daily 2 to 4 injections are required for proper control of severe diabetic condition. The parenteral route is satisfactory in terms of efficacy. However, it may result to some severe adverse conditions like, a peripheral hyperinsulinemia, a smooth muscle cell proliferation, and a diabetic micro and macro angiopathy ³. In addition, the burden of daily injections, physiological stress, pain, inconvenience, cost, and the localized deposition of insulin leads to a local hypertrophy and fat deposition at the injection sites ⁴. Therefore, now a day there has been more focus on noninvasive route of insulin delivery. In 1996 AD, the FDA approved the first recombinant DNA human insulin analogue, lispro (Humalog). In 2001 AD, FDA approved Cygnus' first-generation model of the GlucoWatch Biographer for use by adults - the first frequent, automatic and noninvasive glucose monitor. Research approaches for noninvasive insulin delivery are given in table 1.

Table 1: It shows research approaches for noninvasive insulin delivery

Devices	Method of delivery
Oral route	Uptake of insulin occurring within the gastrointestinal tract or buccal mucosa
Pulmonary	Insulin uptake occurring in the highly vascularized alveoli of the lung
Intranasal	Use of nasal membranes as absorptive surface for insulin
Iontophoresis	Transdermal delivery of insulin by a direct electrical current
Ultrasound	Process by which sound waves increase, by several fold, the permeability of human skin to macromolecules

POTENTIAL OF VARIOUS ROUTES FOR INSULIN DELIVERY

The stress and discomfort of multiple daily injections provoked numerous attempts to develop a safe and an effective noninvasive route for insulin delivery. Potential routes for insulin administration are oral, pulmonary, buccal, rectal, transdermal, nasal and vaginal ⁵.

ORAL ROUTE

Oral is the most effective, safe, and convenient route for administration. It seems that oral administration of insulin may be the most convenient route to deliver insulin in the body. It is known that insulin can easily diffuse across the intercellular tight junctions of intestinal, colonic and rectal mucosa. When it is given orally, insulin is directly channeled from the intestine to the liver and a high level of insulin is reached in the portal blood, simulating the physiological secretion pattern of the pancreas. Since insulin is a large molecular peptide, it is quickly denatured and degraded by proteolytic enzymes in the gastrointestinal tract (GI) ^{6,7}. Proteolytic enzymes like pepsin, trypsin, chymotrypsin and carboxypeptidase, which are located in the stomach and small intestinal lumen. These proteolytic enzymes are responsible for about 20% degradation of ingested proteins. The remaining of the degradation occurs at the brush-border membrane (by various peptidases) or within the enterocytes of the intestinal tract ^{8,9}. A different approaches have been developed to improve the oral bioavailability of proteins like use of (i) permeation enhancers (detergents, fatty acids or bile salts which improve the permeability through the mucus and epithelial layers and open the intercellular tight junctions) (ii) protease inhibitors, (iii) microspheres and (iv) nanoparticles ¹⁰.

1) Peptidase inhibitors and penetration enhancers

A Peptidase or protease inhibitors promotes an oral absorption of therapeutic peptides and proteins by reducing their proteolytic

breakdown in the gastrointestinal tract. The protease inhibitor aprotinin administration with insulin via microsphere is the most efficacious delivery for diabetes mellitus treatment. Penetration enhancers can increase the absorption of peptides and proteins in the gastrointestinal tract by acting in transcellular and paracellular pathways of GI tract. Penetration enhancers include substances like surfactants, fatty acids, bile salts, citrates, and chelators like ethylene diamine tetra acetate (EDTA). Surfactants and fatty acids affect the transcellular pathway by altering membrane lipid organization and therefore increase the oral absorption of insulin. Bile salts like EDTA and trisodium citrate have been reported to increase the absorption of insulin. Cyclodextrins have been used to enhance the absorption of insulin from lower jejunal and upper ileal segments of rat small intestine ¹¹.

Mitra, A.K. *et al.*, have performed the study of enhancement of intestinal insulin absorption by bile salt-fatty acid mixed micelles in dogs. The pharmacokinetics and pharmacodynamics of porcine zinc insulin following intravenous (i.v), intrajejunal, and ileocolonic delivery were evaluated in dogs. Incorporation of mixed micelles containing sodium glycocholate and linoleic acid significantly improved the enteral insulin absorption. Delivery of insulin with mixed micelles has also improved the mean absolute bioavailability and caused significant hypoglycemia in all dogs ¹².

2) Microspheres

Microspheres are solid spherical particles with a size range from 1 to 600 mm and are prepared by double emulsion solvent evaporation technique. The microspheres are prepared using natural biodegradable polymers (gelatin or albumin) or synthetic polymers (polylactic or polyglycolic acid). In emulsion, the dispersed phase consists of droplets of polymer-drug solution and they are linked by entrapment, ionic or covalent bonding. Microspheres can be prepared either by incorporating the drug in a microcapsule or by dispersing the drug with polymer in a suitable vehicle. Microspheres are targeted to lung capillaries or to RES by active targeting ¹³.

Majumdar, D.K. *et al.*, have prepared the Eudragit S100 insulin microsphere using water-in oil-in water emulsion solvent evaporation technique. A polysorbate 20 as a dispersing agent in the internal aqueous phase and a polyvinyl alcohol (PVA)/polyvinyl pyrrolidone as a stabilizer in the external aqueous phase. Authors have reported that an oral administration of PVA stabilized microspheres in the normal albino rabbits (equivalent to 6.6 IU insulin/kg of animal weight) demonstrated a 24% reduction in blood glucose level, with maximum plasma glucose reduction in 2 hours and effect continuing up to 6 hours. The results indicate that an oral administration of Eudragit S100 microspheres can protect insulin from proteolytic degradation in the gastrointestinal tract and produce hypoglycemic effect ¹⁴.

3) Nanoparticles

An oral delivery of insulin via polymer nanoparticles has produced positive result in diabetes mellitus treatment. The first report by Demage *et al.*, in 1988 have suggested that insulin encapsulated in poly(isobutylcyanoacrylate) (PIBCA) nanocapsules had a long-term (up to 20 days) hypoglycemic effect in diabetic rats after oral administration ¹⁵. A recent study by Pan *et al.*, in 2002 have shown that a peroral administration of chitosan-insulin nanoparticles could significantly lower the serum glucose levels of alloxan-induced diabetic rats ¹⁶.

Lee-Yong Lim *et al.*, have performed the effects of formulation parameters on the in vivo pharmacological activity of the chitosan-insulin nanoparticles. Chitosan-insulin nanoparticles formulated with insulin at pH 5.3 and 6.1 were effective in lowering the serum glucose level of streptozotocin-induced diabetic rats. The pharmacological activity of the nanoparticles was not achieved by increases in the serum insulin concentration, but might be ascribed to the local action of the insulin in the intestinal epithelium ¹⁷.

PULMONARY ROUTE

In a wide area of delivery system, a pulmonary route is another alternative route for insulin administration. Inhaled insulin appears

to be a noninvasive, well-tolerated and liked modality of treatment with potential for both type 1 and 2 diabetes mellitus. The pulmonary insulin delivery is becoming a viable alternative to injections in large measure due to its inherent anatomic advantages. Specifically, the lung provides a vast (50–140 m², 500 million alveoli) and well-perfused absorptive surface. The lung lacks a certain peptidases that are present in the gastrointestinal tract and "first pass metabolism" route (i.e., immediate hepatic degradation by the absorbed insulin). In addition, the presence of a very thin alveolar-capillary barrier allows a rapid uptake of peptides in the bloodstream and a rapid onset of action after inhalation. The exact mechanism of insulin absorption across the pulmonary epithelium remains unclear. However, it involves transcytotic and paracellular mechanisms. Various types of formulation have been developed using liposome, pulmonary insulin crystals and absorption enhancers. Citric acid appears to be a safe and a potent absorption enhancer for insulin in a dry powder form. Mishra, A.N. *et al.*, in 2003 have performed the study of influence of absorption promoters on pulmonary insulin bioactivity by the pulmonary route using a combination of absorption promoters. They have concluded that the absorption promoters in combination have significant potential for increasing the pulmonary bioactivity of insulin ¹⁸. Cyclodextrin (CD) derivatives, such as tetradecyl- β -maltoside (TDM) and dimethyl- β -cyclodextrin (DM β CD), may enhance the pulmonary absorption of insulin.

Ungaro, F. *et al.*, have developed the dry powder of insulin for sustained delivery to lungs using cyclodextrins. Large porous particles (LPP) made of poly(lactide-co-glycolide) (PLGA) were produced by the double emulsion-solvent evaporation technique and hydroxypropyl- β -cyclodextrin (HP β CD), used as an absorption enhancer for pulmonary protein delivery. The prepared formulation is an advanced carrier system for a safe and an efficient combined delivery of the protein and HP β CD in the respiratory tract ¹⁹. Technosphere™/Insulin (TI) is a dry powder form of inhaled insulin designed for regular human insulin. It is designed to produce an efficient transport of insulin from the respiratory epithelium into the systemic circulation. Several studies using the euglycemic clamp technique were performed in healthy volunteers and in patients with type 2 diabetes mellitus to assess the pharmacokinetic and pharmacodynamic properties of Technosphere/Insulin. The investigations revealed a very rapid systemic insulin uptake (insulin T (max) approximately 12-14 min), a fast onset of action (maximum activity approximately 20-30 min), and a short duration of action (approximately 2-3 h) in healthy volunteers and in patients with type 2 diabetes ^{20, 21}. Exubera® from Pfizer & Nektar offers the potential for an alternative delivery to insulin injections. Exubera is a fast-acting, dry powder form of human insulin that's inhaled into the lungs to regulate (lower) blood sugar level. It is administered using a hand-held inhaler and offers a new, painless alternative delivery to traditional insulin injections ²².

NASAL ROUTE

A nasal administration of insulin has been investigated and attempts have been made to deliver a large number of peptides and proteins by this route ²³⁻²⁶. The accessibility of the nasal route facilitates self-medication, thus improves patient compliance compared to parenteral route ^{27, 28}. The large surface area available for absorption through nose and its epithelial surface is covered with numerous microvilli. The subepithelial layer is a highly vascularized, and the venous blood from the nose passes directly into the systemic circulation, thereby avoiding the loss of insulin from first-pass hepatic metabolism. It allows lower doses, more rapid attainment of therapeutic blood levels, quicker onset of action and produces fewer side effects. The porous endothelial basement membrane of nose is an easily accessible and the drug is delivered directly into the brain along the olfactory nerves ^{29, 30}. In spite of these advantages, there are some barriers to the nasal absorption, mainly an active mucociliary clearance mechanism and a factors that could influence the bioavailability of intranasal insulin, such as physicochemical properties of the particles, timing, dosing, frequency of administration, type, volume and concentration of insulin or absorption enhancers used in treatment of diabetes ³¹⁻³³. The effects of sodium deoxycholate (SDC) in combination with cyclodextrins

(CD) in insulin nasal absorption have been determined by measuring the blood glucose levels³⁴. The majority of absorption enhancers used to overcome the problem of low bioavailability of insulin³⁵⁻⁴⁰.

Udupa, N. *et al.*, in 2005 have developed nasal insulin as an alternative route to parenteral route. The insulin gel was formulated using the combination of carbopol and hydroxypropyl methylcellulose as a gelling agent. The *in vivo* efficacy of insulin gel administered intranasally was assessed by measuring the blood glucose levels and serum insulin levels at specified time intervals in rats and humans. The study demonstrated that when insulin was administered in a gel form with a penetration enhancer, it traverses through the nasal mucosa and rapidly passes into the systemic circulation. Further, insulin gel delivered via nasal mucosa is a pleasant and a painless alternative to the injectable insulin⁴¹.

BUCCAL ROUTE

A hydrophilic high molecular weight drug, such as peptide that is sensitive to the degradation by the oral route can be administered alternatively by the buccal route. A buccal route is a highly preferable due to high systemic effects, surface area and high vascularity. The buccal epithelium is a non-keratinized in nature and composed of multiple layers of cells, which show different patterns of maturation between the deepest cells and the surface. The basal cells are capable of division and maintain a constant number in the epithelium as cells move toward the surface. A drug administered by the buccal route enters directly into the systemic circulation through the internal jugular vein and bypasses the hepatic first-pass metabolism⁴². The drug transport mechanism through the buccal mucosa involves two major routes: transcellular (intracellular) and paracellular (intercellular) pathways. Peptides that cross the buccal epithelium via paracellular route enter in contact with extracellular enzymes. Recently, it was found that aminopeptidases in the buccal mucosa have proteolytic activity and they are representative of the surface membrane-bound proteases^{43, 44}. One of the disadvantages associated with the buccal route is low bioavailability, which can be enhanced by the use of various permeation and absorption enhancers like polysorbate-80, sorbitol and phosphatidylcholine. A buccal insulin delivery is under clinical development by Genexer and Lilly under the names of Oralyn in Europe and Oralgen in the USA. Administration is similar to an angina spray, with an aerosol (RapidMist®) delivering a fine spray directly onto the buccal mucosa⁴⁵. Oral-lyn™ is human regular insulin in a proprietary liquid formulation utilizing surfactants, absorption enhancers, and other GRAS ingredients in very low quantities. It is delivered to the buccal mucosa using a spray device similar to that used in asthma. RapidMist™ device is designed to propel the liquid formulation into the oral cavity as a fast-moving and a fine-particle aqueous spray. The mixed micelles containing the insulin molecules transverse the superficial layers of oropharyngeal mucosa and with the aid of absorption enhancers, insulin is rapidly absorbed into the blood stream⁴⁶⁻⁴⁸.

Bernstein, G. has suggested the insulin delivery by the buccal route in diabetes mellitus in large number of patient, particularly in type 2 diabetes mellitus⁴⁹.

TRANSDERMAL ROUTE

Transdermal delivery of insulin is an alternative to the subcutaneous injection of insulin in diabetic patients. Apart from being a conventional painless procedure, it can potentially maintain a long lasting effect by producing steady blood insulin levels over a long period of time. During recent years, various experimental methodologies have been developed for facilitating transdermal delivery of insulin. A chemical enhancers based on biphasic lipid system or flexible lecithin vesicles-containing insulin showed good hypoglycemic effect in experimental animals^{50, 51}. An additional approach to facilitate the transdermal delivery of insulin included altering skin characteristics by physical tools such as iontophoresis, sonophoresis, electroporation and photomechanical treatment⁵²⁻⁵⁶. Insulin has a tendency to form dimers and hexamers in pharmacological compositions, which are considered to be too large for transdermal delivery. Brange in 1988 has suggested chemically modifying insulin to produce insulin analogs that resist

intermolecular association and enable improved iontophoretic delivery⁵⁷. Combination of chemical enhancers and iontophoresis also showed facilitated transdermal delivery of insulin^{58, 59}. Jang *et al.* in 1999 have disclosed a patch containing insulin formulated in a gel for the iontophoretically driven transdermal delivery of insulin⁶⁰. Recent novel techniques using ultradeformable carriers (transfersomes) and CaCO₃-nanoparticles encapsulating insulin may also serve as efficient insulin delivery systems^{61, 62}. Clinical use of transdermal drug delivery has been limited because very few drugs can pass by passive diffusion, and able to penetrate the skin at a sufficient rate to produce systemic drug concentration in the patient.

Sintov, A.C. *et al.*, in 2007 have done the study for insulin transdermal delivery by use of topical iodine. It has been found that skin pretreatment with iodine followed by a dermal application of insulin results in reduced glucose level and elevated hormone levels in the plasma. Topical iodine protects the dermally applied insulin presumably by inactivation of endogenous sulfhydryls such as glutathione and gamma glutamylcysteine, which can reduce the disulfide bonds of the hormone. Thus, the effect of iodine is mediated by retaining the potency of the hormone during its penetration via the skin into the circulation⁶³.

RECTAL ROUTE

During the past few years, a considerable interest has arisen in the rectal route for insulin administration. Rectal insulin delivery offers several advantages over some of the other enteral routes. First, the rectal route is an independent of intestinal motility, a gastric-emptying time, and a diet. It is most likely that the presence of degrading enzymes in the gut wall decreases from the proximal end to the distal end of the small intestine and rectum. The most important advantage suggested for the rectal administration of insulin is the possibility of avoiding the hepatic first-pass metabolism⁶⁴. The rectal suppositories can be formulated using a lipophilic or a hydrophilic base. These bases, along with other incorporated absorption promoters and enzyme inhibitors, help in improving the bioavailability of water-soluble compounds⁶⁵⁻⁶⁷. Surfactants are useful absorption enhancers for rectal route. The "effectiveness" of rectal insulin preparations is to be evaluated by four criteria: the pharmacological availability via the area under the % glucose reduction-time profile, the maximum glucose concentration reduction (C_{max}), the time to reach the maximum reduction (t_{max}) and the mean residence time for glucose reduction (MRT). Barichello, J. *et al.*, in 1999 have performed the rectal administration study of insulin using pluronic F-127 (PF127) gel containing unsaturated fatty acids such as oleic acid (18:1), eicosapentaenoic acid (20:5) and docosahexaenoic acid (22:6). Rectal insulin absorption was markedly enhanced, and marked hypoglycemia was induced by all PF127 gels (insulin dose, 5 U/kg) containing different unsaturated fatty acids. PF127 gels containing unsaturated fatty acids presented low t_{max} mean values indicating that the absorption of insulin occurred very rapidly in the rectum⁶⁸.

OCULAR ROUTE

An ocular route is also an alternative route for insulin administration. Insulin delivered through the ocular route by use of nanoparticles, liposomes, ocular inserts and gels^{69, 70}. Chiou, G.C. *et al.*, in 1989 have studied improvement of systemic absorption of insulin through eyes with absorption enhancers. In order to increase the amount of peptides absorbed into systemic circulation, the effects of enhancers on insulin absorption into systemic circulation and reduction of blood glucose concentration have been studied. Insulin eye drops containing an absorption enhancer have been shown to significantly lower the blood glucose levels of animals⁷¹. Jain, S.K. *et al.*, in 1999 have performed the study of effect of insulin delivery by ocular route. Ocular administration of free insulin (400 U/mL) to normal rabbits produced change in blood glucose level using permeation enhancer. The effectiveness of liposomes in aiding ocular absorption of entrapped insulin was also studied in normal rabbits. Administration of insulin entrapped in positively charged liposomes composed of egg phosphatidylcholine with cholesterol and stearylamine (10: 2:1, in weight ratio) to normal rabbits produced substantial reduction in blood glucose concentration 90-120 min after the instillation of the formulation⁷².

Yalkowsky, H. *et al.*, in 1999 have performed in vivo and in vitro dissolution study to determine the dissolution rate of insulin from a Gelfoam® based eye device. The dissolution profiles generated by these two methods are comparable. The in vivo data suggests that there is a direct relationship between the blood glucose lowering and the rate of release of insulin from the device. The in vitro dissolution results indicate that the release of insulin from the device is a flow-rate dependent. The prolonged activity of the insulin is due to the gradual release of insulin from the device, which results from the lachrymal system's slow and constant tear production. This Gelfoam device can be directly inserted into the eye and enhances the therapeutic effect, the duration of action and the better bioavailability of the insulin. The gelfoam suppresses blood glucose level rapidly and can deliver insulin in the systemic circulation without the use of any absorption enhancer. Furthermore, no physical signs of eye irritation (i.e. redness, lachrimation, and restlessness) were observed, when the device was used in rabbits ^{73, 74}.

VAGINAL ROUTE

The vagina has been used for a long time as a route for drug delivery, with the purpose of obtaining a local pharmacological effect. The

advantages of insulin administration via the vaginal route are the avoidance of hepatic first-pass metabolism, a reduction in the gastrointestinal side effects, a decrease in hepatic side effects of drugs such as steroids, an overcoming of pain, tissue damage, and a probable infection observed with parental routes ⁷⁵. Morimoto, K. *et al.*, in 1982 have done the study of insulin administration through the vaginal mucosa using polyacrylic acid aqueous gel bases. The results showed that when these gels were administered to rats and rabbits, the plasma insulin reached a peak, and the hypoglycaemic effects were sustained for 30 min. The sustained release improvement is necessary in order to achieve longer time of hypoglycaemia ⁷⁶.

Ning, M. *et al.*, in 2005, have prepared niosomes with sorbitan monoester as a carrier for vaginal delivery of insulin. Two kinds of vesicles with span 40 and span 60 were prepared by lipid phase evaporation methods with sonication. The hypoglycemic effect and insulin concentrations after vaginal administration of insulin vesicles into rats were investigated and compared with the subcutaneous administration of insulin solution. The results indicated the insulin-Span 60, Span 40 niosomes had an enhancing effect via vaginal delivery of insulin ⁷⁷.

Table 2: It shows potential noninvasive insulin delivery options

Delivery	Potentials
Oral Route 1. Enteric	Oral enteric insulin delivery has limited bioavailability. Insulin is too large and hydrophilic to readily cross the intestinal mucosa. Polypeptides undergo extensive enzymatic and chemical degradation. Only around 0.5% of a dose of oral insulin reaches the systemic circulation. Ongoing phase I and II clinical trials with new formulation suggest a bioavailability of 5%, which may result in an acceptable glucose-lowering effect
2. Buccal	Liquid aerosol insulin is sprayed into the buccal cavity without entering the airways. A liquid formulation of human recombinant insulin with added enhancers, stabilizers, and a non-chlorofluorocarbon propellant delivered via a metered dose inhaler is in clinical trials.
Pulmonary	High permeability and large surface area provide a favorable anatomy for protein/drug uptake. Very rapid absorption of insulin after inhalation mimics time-activity profile of fast-acting insulin; appropriate for pre-meal delivery. Appears comparable to subcutaneous insulin on glycemic parameters for both type 1 and type 2 diabetic patients.
Transdermal- 1. Iontophoresis 2. Low-frequency ultrasound	Electrical current used to enhance transdermal insulin delivery; proof-of-principle from animal studies; human studies needed. Use of low-frequency sound wave to augment delivery of insulin and other macromolecules across human skin.
Nasal	Nasal administration of certain proteins (e.g., oxytocin, desmopressin, and calcitonin) is now well established. Permeability enhancers are generally required to augment insulin bioavailability; insulin bioavailability is typically in the range of 8-15% with enhancers. Nasal irritation is common (e.g., with lecithin, bile salts, or laurth-9 as enhancers). Nasal tolerance and high rates of treatment failure are major limitations.

CONCLUSION

Non invasive delivery of insulin poised to change the statue for treatment of both type 1 and type 2 diabetes mellitus. A much progress has been made since, several decades in the development of noninvasive techniques. Various researches have been done in alternative insulin delivery by using novel formulations and novel devices. Among the entire delivery route, pulmonary route of insulin administration has received much clinical significance due to novel devices. The transdermal and oral route also frequently used and have undergone considerable research. The other delivery routes are also chasing behind that through research in novel formulation and devices. However, the delivery of insulin via non invasive routes has become a challenge due to the poor absorption of insulin and an

enzymatic instability. As these technologies become feasible in the near future, a non invasive, an efficacious and a cost effective treatment for diabetes mellitus patient will be available.

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