



Review Article

NOVEL APPROACHES IN INSULIN DRUG DELIVERY

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ABSTRACT

The drug delivery systems are interdisciplinary approaches that combine polymer science, pharmaceutics, biconjugate chemistry and molecular biology. In today's era, injections remain the most common means for administering therapeutic proteins and peptides such as insulin because of their poor bioavailability designing and formulating a polypeptide drug delivery is still a challenge due to their poor membrane permeability and large molecular size. Diabetes mellitus is a chronic metabolic disorder caused by deficiency of pancreatic hormone insulin (Type I diabetes mellitus) or due to resistance of cells to insulin secreted by the body (Type II diabetes mellitus). It is an increasing serious condition which evokes a lot of global concern due to the inconvenience of insulin injection. Various approaches have been attempted to formulate insulin for administration by non-injectable route. Several non-invasive approaches for insulin delivery are being pursued by pharmaceutical companies to reduce the pain and hypoglycaemic incidences associated with injections in order to improve patient compliance. A well designed controlled drug delivery system by using insoluble or biodegradable natural and synthetic polymers lipoproteins, liposome's, ribosome's etc. can overcome some of the inconvenience of conventional therapy to enhance the therapeutic efficacy of drug. These newer generations of drug delivery systems are advantageous over conventionally available drug delivery systems. This review summarizes different pharmaceutical approaches which overcome various physiological barriers that help to improve bioavailability that achieve the formulation goals for insulin delivery by a patient friendly route.

INTRODUCTION

As per the WHO, Diabetes Mellitus (DM) is defined as a heterogeneous metabolic disorder characterized by common feature of chronic hyperglycemia with disturbance of carbohydrate, fat and protein metabolism. DM is a leading cause of morbidity and mortality world over. It is estimated that approximately 1% of population suffers from DM. The incidence is rising in the developed countries of the world at the rate of about 10% per year, especially of type 2 DM, due to rising incidence of obesity and reduced activity levels. DM is expected to continue as a major health problem owing to its serious complications, especially end-stage renal disease, IHD, gangrene of the lower extremities, and blindness in the adults¹. It is of two types. Type 1 Diabetes Mellitus which is due to the atrophy of pancreatic β cells, causes insufficient insulin secretion and thus makes the patient completely dependent on exogenous insulin supply for his survival, and type 2 diabetes mellitus, in which peripheral cells become resistant to the insulin secreted by the patient's body. Selective individuals with type 2 diabetes mellitus or those at a later stage of type 2 diabetes mellitus require exogenous insulin supply.² This insulin is used to control the level of blood glucose in patient with DM. It is an essential therapy for patients suffering from T1DM, and T2DM (especially in late-stage disease). Insulin was discovered in 1921 by Frederick Banting and Charles Best, went through its first clinical use in 1922²⁻⁴, and helped revolutionize the treatment of T1DM which was fatal at that time. Initially, insulin was isolated from bovine and porcine pancreata, until the 1980s. Later on, recombinant DNA techniques allowed the manufacture of human insulin. Modifications of the amino acid sequence of the insulin molecule by rDNA and protein engineering methods have recently allowed the production of monomeric insulin analogues (e.g. lispro, aspart) which have a more rapid absorption profile.⁵ The current insulin treatment involves exogenous administration, with the aim of achieving effective glycaemic control (i.e. prevention of hyper- and hypoglycaemia) and avoidance of the complications of DM⁶.

Current modes of delivering insulin include intravenous (IV) infusion and subcutaneous (SC) injections. SC insulin preparations, which are more commonly used, include rapid-, intermediate- and long-acting insulin, which are used in different combinations (1 to 4 times or more daily). Despite its worldwide use, conventional subcutaneous insulin injection is relatively painful and inconvenient, with poor patient acceptability. Alternative methods of insulin delivery have been the focus of research for the past few decades.⁷ The increased biochemical and structural complexity of proteins compared with conventional drug based pharmaceutical make formulation design for delivery of the therapeutic proteins (including insulin) a very challenging task. The key to the success of protein as pharmaceutical is to have in place an efficient drug delivery system that allow the protein drug to gain access to their target sites at the right time and for the proper duration.⁸

Four factors that must be considered to fulfil this goal are route of administration, pattern of drug release, method of delivery and fabrication of formulation. Insulin administration has been a prominent topic for researchers in last few decades. A large number of significant work has been published in this regards. A formulation for oral administration of

insulin was designed by Kidron et al. A proposed pharmaceutical compositions for the oral administration of insulin included insulin, a bile acid or alkali metal salt thereof, the bile acid being selected from the group consisting of cholic acid, chenodeoxycholic acid, taurochenodeoxycholic acid, taurocholic glycocholic acid, glycochenocholic acid, 3 beta-hydroxy-12-ketocholic acid, alpha-3, beta-dihydrocholic acid and ursodesoxycholic acid and a protease inhibitor.

The composition was provided with an enter coating to assure passage through the stomach and release in the intestine. The pharmaceutical compositions include insulin and fatty acids having 8 to 14 carbon atoms and nontoxic salts⁸.

INSULIN THERAPY

The indispensable factor in achieving good glycemic control is treating with insulin. The main goal of treating hyperglycemic is delaying the development of complication associated with in the condition^{9, 10}. To maintain near to normal glycemic condition in patients with hyperglycemia the exogenous insulin should have the same pharmacokinetic properties as the pancreas secreted insulin. The more development in the field of insulin development is such a way that to remodel insulin molecule to change its pharmacokinetic properties to more favorable in controlling hyperglycemic condition¹¹. As a result, more than thousands of insulin derivatives are developed from these twenty of them are tested in humans¹².

Fig -1 Insulin Therapy



The conventional form of insulin delivery is through subcutaneous injections (Fig -1) and more than 60000 injections are taken by an average hyperglycemic patient. The main problems with these injections¹³

local pain
multiple injection in same day
occasional hypoglycemia.

Clinical trials data reveal that patients cannot achieve long last in glycemic control because of noncompliance¹⁴ and also reports of hypo glycaemic episodes following multi dose injections is also seen¹⁵. The new methods of insulin delivery are developing to decrease the suffering of diabetes patients, include insulin small pens, sharp needles, jet injectors, infusion

pump. Even though these techniques reduce the pain encountered to the diabetic patients but they offer inconvenience. New concepts are presently investigated to deliver insulin using oral, pulmonary, nasal, ocular and rectal routes, but the eventual goals would be to eradicate the need to deliver insulin exogenously and regaining the ability of patient to produce and use own insulin. The success of the route of administration is judged on the basis of its ability and lowering of blood glucose level, thereby minimizing the risk of dietetic complications. Various noninvasive routes of delivery of insulin have also been investigated. The most significant are oral, ocular, rectal, pulmonary buccal, trans dermal of Nasal.

NOVEL DRUG DELIVERY SYSTEMS FOR INSULIN

Ocular Delivery

Eye, as a portal for drug delivery is generally used for the local therapy as against systemic therapy in order to avoid risk of eye damage from high blood concentration of drugs, which are not intended for eye ¹⁶. The rate of absorption was seen fast in the ocular route than the injection and it also bypasses the first pass effect. The limitations of the ocular delivery are low bioavailability and irritation ¹⁷. Moreover, tissues in the eye are less likely to develop immunological reactions, compared to other tissues. Problems with this route of delivery are local irritation, as well as loss of drug molecules via, blinking, tearing, and drainage. Due to the limited bioavailability of insulin delivered through the ocular route, numerous absorption enhancers have been experimented upon. Fusidic acid and glycolate were proven to increase ocular insulin absorption in rabbits, especially when administered at higher pH levels. Insulin delivered through the ocular route seems possible with no significant toxicity. It is important that the release of insulin from ocular devices is constant and reproducible, Further studies need to be carried out before ensuring that ocular insulin can be used clinically in diabetic patients.

Rectal insulin Delivery

This route involves absorption in the GIT, but differs from oral route, as it bypasses the proximal areas that are actively involved in digestion ¹⁸. It avoids the local enzymatic degradation. Insulin enters through the lymphatic system thereby bypassing the hepatic first pass metabolism as there are Porto- systemic anastomoses in rectal vessels. These vessels connect the portal system to systemic system, hence allowing absorbed drugs to directly enter the systemic circulation. Suppositories containing 100 U insulin and 200mg sodium salicylate as an absorption enhancer's were tested in human studies. Hypoglycemic effects were achieved by 15 minutes and lasted up to 90 minutes' post administration. The technique to improve rectal absorption of insulin is by creating an adhesive interaction between the delivery system and rectal mucosa, increasing drug residence time at the absorption sites. Rectally delivered insulin seems to be a possible alternative for less invasive insulin therapy. However, insulin administered

through this route appears to have lower bioavailability and efficacy compared to SC forms. For long term therapy, it is worth considering the potential adverse effects of using such as increased permeability of rectal mucosa to toxic substances present in the GIT lumen. The disadvantages may be the local adverse reactions, and local irritation ^{19, 20}.

Pulmonary Delivery:

Inhaled drugs are absorbed into the alveolar capillary network, (Fig -2) which has the advantage of having a large surface area, thin diffusion barrier, as well as being non-invasive. Drugs can be aerosolized and delivered with aerodynamic diameter smaller than 5 micrometer pulmonary delivery bypasses digestive enzymes and first pass metabolism associated with oral delivery insulin micro crystals with mean diameter of 3 μ m were prepared and administered to STZ induced diabetic rats by using a sieve type ultrasonic nebulizer. Prolonged hypoglycemic effects were absorbed over 7hrs. Further studies on insulin micro crystals found that the addition of zinc caused an enhancement of the hypoglycemic effect a dry powder form of insulin was found to have a higher bioavailability than a pH 7.4 than a pH 7.4 insulin solution however citric acid added to insulin dry powder increased the hypoglycemic effect with bioavailability of 42 and 53 for dry powder containing 0.025 and 0.036mg/dose citric acid respectively more over citric acid was not found to cause acute to lungs cells

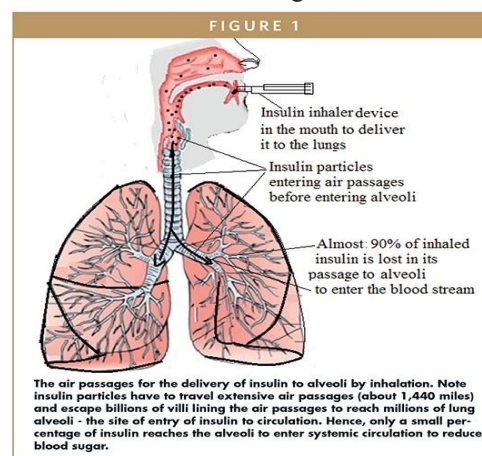


Fig -2 Pulmonary Delivery System of Insulin

Liposomes are another method to improve pulmonary transport of insulin. Studies have found that liposome's can be made and insulin encapsulated within them. Nano particulate delivery systems have helped improve pulmonary insulin delivery as well. One such formulation involves insulin loaded poly nanospheres with a mean diameter of 400nm, prepared by modified emulsion solvent diffusion method in water. These NP were prepared as aqueous dispersions nebulized by a sieve type ultrasonic nebulizer and administered to fasted guinea pigs through a spacer by using a constant volume respirator for 20 min. Administration of 3.19u/kg insulin caused substantial prolonged hypoglycemic responses over 48 hrs. in contrast to 6 hrs. by nebulized aqueous insulin solution

the pulmonary delivery system would have good insulin loading efficiency avoidance of insulin break down, predictable and reproducible release profile as well as minimal effects. It is responsible to consider the adverse effects of inhaled insulin including the greater weight gain and mild to moderate cough in 25% of patients. Insulin doses are also dependent on patient co-morbidities as smokers and asthmatics require lower and higher doses respectively further more to achieve a comparable glycemic response inhaled insulin needs to be given at much higher doses compared to SC administration. Pulmonary delivery was through aerosols, metered dose inhaler systems powder and nebulizers which contain Nanoparticles, Liposomes, micelles and Dendrimers. The advantage which exhibited in this is the high permeability because of large surface area, lack of mucociliary clearance and immune tolerance. But still the bioavailability was only 9-22% that of SC insulin injection. Variation in absorption was due to the age difference, respiratory tract infection and smoking. Other side effects which existed in this delivery were cough, sore throat, shortness of breath and dry mouth^{21, 22, 23}.

Buccal Insulin

Buccal delivery of insulin involves aerosol delivery of the drug into the oral cavity (Fig -3) after which absorption occurs through the inner surface of the cheeks on the back of the mouth^{24, 25}. This distinguishes from the oral delivery which is absorbed further along the GIT, as well as the pulmonary delivery which is absorbed from the lungs. The Buccal formulations are placed in the mouth between the upper gingivae and the cheek for local and systemic circulation. The absorption from the mucosa is due to the molecule weight, hydrophilicity, electrostatic charge, immunogenicity solubility and partition coefficient of the peptides and proteins' including insulin²⁶. The molecules absorbed via the buccal route enter the internal jugular vein and then send into the systemic circulation by passing hepatic first metabolism leading to improved bioavailability. Furthermore, Buccal administration is convenient and painless, easily accessible. Mucoadhesive delivery allows improved buccal absorption without the side effect associated with absorption enhancers.

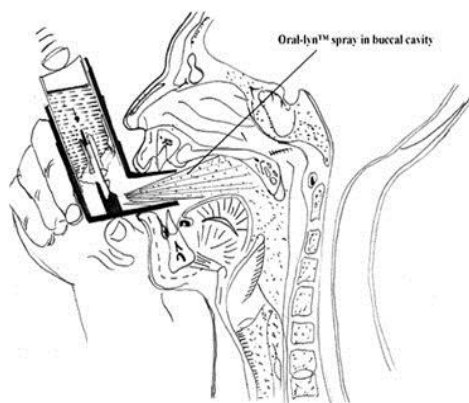


Fig -3 Insulin Delivery through Buccal Cavity

Transdermal Insulin:

The main disadvantage of this route is the lower bioavailability due to the low passage of active agent across the mucosal epithelium in the absence of absorption enhancers. Buccal insulin in the enhancers showed maximum 12% pharmacological activity. It was also found that when certain time was taken by the insulin molecules to adhere to the Buccal mucosa the activity was increased²⁷. The various bio adhesive formulations include gels, films, tablets, Nanoparticles, vesicles, sponges, Sprays and transferases.

For more than 80 years, pharmaceutical companies, government agencies, and universities have researched in hopes of developing an oral form of insulin. It is something of a holy grail of medical innovation: an oral form of insulin would prevent the unpleasantness of insulin injections, make insulin therapy less complicated, and, most importantly, hopefully increase the rate at which insulin users comply with their insulin therapy schedule. Unfortunately, no forms of oral insulin are currently available in the United States.

Another method to deliver insulin into the blood stream in a non-invasive manner is through the skin surface into the underlying capillary network (Fig -4). This method of delivery is convenient, which would lead to better patient's compliance. This delivery of insulin is a needle free technique which is convenient with good patient compliances such as gastro intestinal irritation, metabolism, and interference due to the presence of food. It bypasses first pass metabolism and also suitable for unconscious patients. Many methods have been developed to enhance the skin barrier, some of which include chemical absorption enhancers, iontophoresis, sonophoresis / phonophoresis, electroporation, use of micro needles, and laser ablation^{28, 29}.



Fig -4 Transdermal Insulin

A study involving insulin loaded micro-emulsion has shown promising results in achieving transdermal insulin transport through goat skin. Another potential formulation for transdermal insulin delivery is via transferosomal gels containing insulin, which showed transdermal adsorption with zero order kinetics through porcine ear skin, as well as prolonged hypoglycemic effects in diabetic rats. Insulin emulgel has also been tested for transdermal delivery. Although a potential non-invasive route for effective insulin therapy, transdermal insulin delivery requires further investigation, including clinical studies, to improve insulin bioavailability, as well as ensuring safety of the drug preparation. The main benefit of transdermal drug delivery is

large surface area is available for administration. The permeability of insulin is increased by microbial approach. The main advantage of transdermal insulin delivery is iontophoresis and sonophoresis techniques can be applied³⁰. But some hydrophilic molecules like insulin is relatively impermeable to skin. On administration of several patients it makes patient compliance such as irritation, itching etc. the formation of skin rashes and infections are occurred in some elderly patients, it is a serious complication in condition like diabetes as inflammation and healing are prolonged. Variability in dosing is also another factor making this route limited in clinical application^{31, 32}.

Nasal insulin:

Nasal delivery of the insulin is a route for long term systemic delivery when the drug is ineffective due to the first pass metabolism when given orally^{33, 34}. The nasal cavity is lined by an epithelial layer that has a large surface area due to the existence of microvilli on the epithelial cells. Together with the high blood total flow and porous endothelial membrane, this facilitates absorption of molecule into the sub epithelial capillary beds, directly into the general circulation. It was also enhanced by using sodium glycolate or sodium tauro fusidate as an absorption promoter³⁵. This route also bypasses the liver and avoids first pass metabolism. All together, these can allow fast absorption (comparable to intramuscular or even IV injections) and onset at lower doses, and fewer side effects. Nasal administration is also convenient and less invasive, which can lead to better patient compliance. Considering all these advantages, intranasal insulin has great potential to be used in the treatment of patients with T1DM and T2DM.



Fig -5 Delivery of Insulin through Nasal Cavity

Difficulties faced by nasal delivery include mucociliary clearance, enzymatic activity, as well as the epithelial lining itself that prevents passage of peptide molecule with higher molecular weights and hydrophilic nature. Nasal bioavailability can be increased by use of absorption enhancers, proteolytic enzyme inhibitors, muco-adhesive formulations, as well as dry power system to delivery insulin via the nasal route. The disadvantages which exist due to this delivery system is irritation, low bioavailability, Degradation of proteolytic enzymes, mucociliary clearance.

Oral Delivery

Oral route is the most attractive and convenient route of administration for patient compliance and economical issues. The difficulties encountered in the oral delivery of insulin include degradation of the protein at lower PH of stomach and

by different digestive enzymes in stomach and small intestine. This causes a decrease in bioavailability (1%)^{36, 37}. Proteolytic degradation in GIT and high resistance offered by intestinal epithelial barriers due of high molecular weight with lack of lipophilicity. The challenge is to improve the bioavailability to 30-50%³⁸.

Nanotechnology based insulin like polymeric nanovesicles, Solid lipid Nanoparticles. Nanoparticles can improve the bioavailability absorption. The enzymatic degradation can be prevented by brush border enzymes³⁹ and enzyme inhibitors like sodium cholate along with aprotinin which improved the insulin absorption in rats⁴⁰. The amount of drug release can be enhanced by intestinal micro flora⁴¹. Protection of insulin from gastric environment can be achieved by coating the Nanoparticles with PH sensitive polymers. Complexation hydrogels significantly enhances the absorption of insulin⁴². Recombinant human insulin can be delivered by using niosomal formulations⁴³.

OTHER APPROACHES IN INSULIN THERAPY

Islet Cell Transplantation:

Technological advancements have led to the development of a latest technique called Edmonton protocol in which islet transplantation from a donors pancreas in to the type I diabetes recipients liver takes place for achieving a constant normoglycemic state and avoiding hypoglycemic episodes. Once transplanted, the donar islets begin to make and release insulin, actively regulating the level of glucose in the blood⁴⁴. The transplantation can provide the following benefits as eliminating the need for frequent blood glucose measurements and the need for daily insulin (Fig -6). It can provide more flexibility with meal planning and it protects against the serious long –term complications of diabetes, including heart Disease, kidney disease, stroke, and nerve and eye damage⁴⁵.

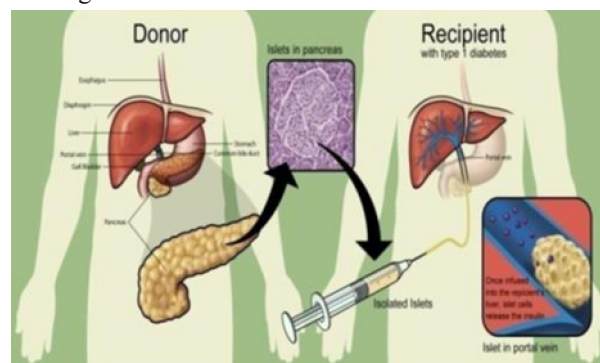


Fig -6 Process of islet transplantation injections

Gene Therapy:

Researches are being done on gene therapy for different aspects of diabetic patients. A gene named SHIP 2 which regulates the insulin has been recognized for treatment of type 2 diabetes in regulating the insulin⁴⁶.

Gene therapy is the use of DNA as a pharmaceutical agent to treat disease. Fig. 7 illustrates gene therapy using an adenovirus vector.

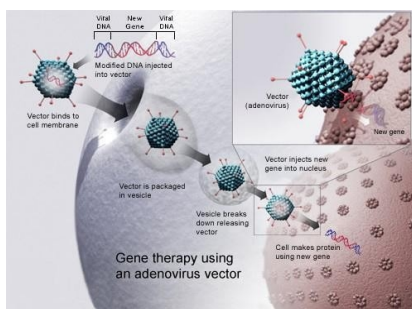


Fig -7 Gene therapy using an adenovirus vector

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 disease⁴⁷. To regulate insulin a gene called SHIP2 has been identified which provides a potential gene therapy target for the treatment of type 2 diabetes⁴⁸. The first FDA-approved gene therapy experiment in the United States occurred in 1990, when Ashanti DeSilva was treated for ADA-SCID⁴⁹. Since then, over 1,700 clinical trials have been conducted using a number of techniques for gene therapy⁵⁰.

Erythrocytes:

Erythrocytes, abundant cell in the today can be used as effective carriers of different drugs. Biocompatibility, Bio degradability, long circulation half-life and the ability to get loaded with a variety of chemically and biologically active compounds make resealed erythrocytes excellent carriers of therapeutic agents⁵¹. Similarly, Dendrimers are also used for successful delivery of insulin

Insulin Analogues

An insulin analogue is an altered form of insulin, available to the human body to control the glucose levels same as insulin. To alter its ADME (absorption, distribution, metabolism, and excretion) characteristics the amino acid sequence of insulin can be changed by genetic engineering of the underlying DNA to produce insulin analogues⁵². Table 1 shows different insulin analogues and their duration of action. Analogue insulin is available in two main forms, rapid acting and long acting, as well as premixed combinations⁵³.

Rapid-acting insulin analogue

They are the fastest-working insulins. Rapid acting insulin analogues include: Aspart, Glulisine, Lyspro. As they enter the blood stream within minutes, it is important to inject them within 5 to 10 minutes of eating. They have a peak action period of 60-120 minutes, and fade completely after about four hours.

Long-acting injected insulin analogue

Long-acting insulin works for the longest period of time and provide relatively constant insulin levels that plateau for many hours after injection. They are also called as “peakless” insulins. They have an onset of action within 60-90 minutes, maximum affect in around 5 hours that gradually wanes over the next 12-24 hours. They include: Insulin detemir (Levemir®), Insulin glargine (Lantus®)⁵⁴. NPH (Neutral Protamine Hagedom) insulin may need to be administered up to three times daily in type 1 patients to provide sufficient insulin

supply throughout the day as its duration of action is 14 h and plasma insulin peak level is achieved 4-6 h after administration⁵⁵.

Premixed analogue

Premixed analogue insulins combine a ratio of rapid acting and long acting insulin. For example, Humalog Mix 25 consists of 25% rapid acting and 75% long acting insulin. The rapid acting insulin works as soon as it is injected and long acting insulins have no peak activity, these are the primary benefits of analogue insulin. Rapid acting insulin minimises sharp rises (spikes) in blood sugar shortly after eating and hence useful for insulin dependent patients. The lack of a peak activity period gives some people more confidence that they will avoid night time hypos, this made long acting analogue insulins quite popular.

ADVANCES IN INSULIN DELIVERY SYSTEM

Insulin Pen Device

One of the accurate method of insulin delivery system. The first insulin pen was introduced by Nova Nordisk in 1987. The main goal of insulin pen devices are improving the quality of life of diabetic patients and making the insulin administration less difficulty. Mainly two types of insulin pens (Fig-8) are developed they are Prefilled insulin pen device – They are of small size and light weight and are accepted in the bedtime insulin regimen for type 2 diabetic patients. Due to the fine and short needle it causes less pain and they are quick and easy to use⁵⁶. Reusable insulin pen device- They are durable, flexible to carry for 5 days supply and eradicate the need of cartridge refrigeration⁵⁷.



Fig-8 Two types of modern prefilled insulin syringes

Insulin pen devices are easy to use^{58,59}. Due to its high accuracy and portability it is widely accepted among elderly patients and adolescents. A study has shown that reusing insulin pen needles help in reducing the burden of economic difficulties in patients. On administration of several diabetic patients, it doesn't make much discomfort as insulin injections^{60,61,62}. Therefore insulin pen devices show preference among patients than syringes. Even though insulin pen devices make these benefits, it is not available for oral insulin types. Patient education is another key factor in using insulin pen devices, particularly in changing of cartridge. Apart from being highly expensive it cannot mix insulin types. Therefore, its use is limited to

developed countries and patients with high economic status. But still it is important that health care providers are aware of the benefits of insulin pens, and the role they play in increasing the adherence. The health care professionals have to keep up to date latest developments in pen devices and teaching approaches in order to assist the patients.

Insulin Jet Injectors

Jet injectors were developed in 1980's Jet injectors deliver insulin by high pressure stream of insulin to the sub cutaneous tissue without needles. The dose of insulin delivery can more precisely determine in jet injectors than subcutaneous injections (Fig -9). The challenges jet injectors are their time of action intermediate acting insulin may be affected. However the discomfort caused by these jet injectors is less than the subcutaneous injections. Insulin jet injectors deliver insulin rapid absorption and decrease the chance of subcutaneous infection. But it is difficult to use on daily basis. Pain or bruising may occur at site of administration. It makes difficulty in adjusting pressure on day to day uses ⁶³.



Fig -9 Insulin Jet Injectors

On administration in several patients, it shows decreased absorption in repeated use. It is mainly used in patients with needle phobia and also for patient who suffer from serious insulin induced lipotrophy ⁶³. These techniques are more appreciated in patients with problems in other insulin delivery routes. Insulin pumps were developed in 1974, imitates the physiological functioning of daily insulin secretion ⁶⁴. The insulin pumps have three parts i.e. the insulin filled reservoir, pump operated on battery and computer chip that permits the patient in controlling insulin delivery.

Insulin Pumps: An insulin pump is a small device about the size of a small cell phone that is worn externally and can be discreetly clipped to your belt, slipped into a pocket, or hidden under your clothes. It delivers precise doses of rapid-acting insulin to closely match your body's needs:

Basal Rate: Small amounts of insulin delivered continuously (24/7) for normal functions of the body (not including food). The programmed rate is determined by your healthcare professional.

Bolus Dose: Additional insulin you can deliver "on demand" to match the food you are going to eat or to correct a high blood sugar. Insulin pumps have bolus calculators that help you

calculate your bolus amount based on settings that are determined by your healthcare professional. The insulin pumps are associated with a computer chip and battery that allows patient to control insulin delivery (Fig- 10). The continuous supply of insulin supply is facilitated by the preset clock in the insulin pump. The more advancement can lead to the making of much smaller insulin pumps, so that they are easy to administer and operate ⁶⁵.

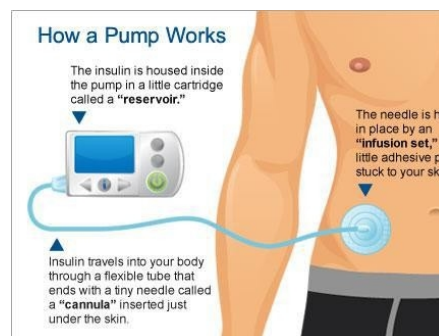


Fig- 10. Working of an insulin pump

It is mainly used for intensive insulin management. A tight control of plasma glucose level can be maintained by this method. Thereby enhancing the quality of life in patients. Another benefit in insulin pumps is that needle is only inserted once every three to four days ⁶⁶. When insulin pumps are followed by recommended procedures they demonstrate efficacy alike from insulin injection in achieving glycemic control ⁶⁵. Based on several patient reviews about insulin pump, it shows that, it makes discomfort in wearing the pump for the whole day. In some patients it may develop infections and lipo hypertrophy. Ketoacidosis is also observed in some patients. Therefore insulin pumps are mainly used in patients who are hospitalized with high pretreatment glycosylated hemoglobin values and patient with poor long term glycemic control.

Insulin Inhalers

These are similar to asthma inhalers and deliver insulin in pre mealtime. These are inhaled through in a form of dry powder and into the lungs through a portable hand held inhaler (Fig - 11). In case of post prandial hyperglycemia, it can be used more effectively ⁶⁷.

Exubera is the first USFDA approved human insulin in powder form. It is used widely in patients with type 1 and type 2 diabetes mellitus ⁶⁸. It was developed by Pfizer pharma and Sanofi Aventis which use they used powdered insulin formulation and an inhalation device developed by Nektar therapeutics, ⁶⁹

The main advantage of insulin inhaler is there is no need of injection and associated local pain. The risk of hyperglycemia is also low. It can be even used in pre meal time ⁷⁰. But it makes frequent cough and cold at initial use. Only fast acting insulin analogues can be delivered in this route with continuous monitoring ⁷¹.



Fig -11. Insulin inhaler

Clinically it shows contraindications such as poorly controlled lung disease and it is not recommended for patients with asthma coronary pulmonary disease and FEV 1. If the patient have smoking habit it should be stopped before six months of treatment. Insulin shows growth promoting properties, so the possibility of long term side effects from the intra alveolar depositions of insulin within the lungs is a matter of concern among clinical practitioners. Patient reviews and administration is limited due to it is not completely developed.

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 as shown in the (Fig. 12) 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 [72-77].



Fig -12 Insulin spray

NEWER INJECTABLE INSULINS

Insulin degludec

Insulin degludec is a novel ultra-long acting basal insulin which is similar to human insulin in structure except for the last amino acid deleted from the B-chain and addition of a glutamyl link from LysB29 to a hexadecanoic fatty acid ⁷⁸. Ultra-long action profile with half life more than 24 h can be achieved by

subcutaneous injection which transforms insulin into soluble multihexamers.

VIAject™

VIAject is faster than that of human soluble insulin and insulin lispro. It is a recombinant human insulin with ultra fast onset of action ^{79, 80}. Insulin degludec, a novel ultra-long acting basal insulin, is almost identical to human insulin in structure except for the last amino acid deleted from the B-chain and addition of a glutamyl link from LysB29 to a hexadecanoic fatty acid ⁸¹. This insulin forms soluble multihexamers after subcutaneous injection, resulting in an ultra-long action profile with half life more than 24 h. Insulin degludec has proven to be non inferior to insulin glargine in clinical trials carried out in both type 1 and type 2 DM. Exploratory studies in type 1 diabetes have shown insulin degludec to be safe with reduced rates of hypoglycemia and comparable glycemic control to long acting insulin analogue insulin glargine ⁸². Phase 3 clinical trials in adults with type 1 DM ⁸³ and type 2 DM glycemic controls was comparable to insulin glargine at one year follow up with fewer hypoglycemic episodes. As insulin degludec has an ultra-long acting profile, insulin degludec was studied using injections three times a week compared with insulin glargine once a day and found to have comparable response ⁸⁴. The advantages of insulin degludec were reviewed in several recent publications ⁸⁵⁻⁸⁷. Comparative studies of efficacy and safety of insulin degludec and insulin glargine, both administered once daily with mealtime insulin aspart, in basal-bolus therapy for type 1 diabetes and type 2 diabetes ⁸⁸ noted effective glycaemic control with a lower risk of nocturnal hypoglycemia than insulin glargine. Similar studies comparing insulin degludec along with aspart insulin compared to insulin detemir with aspart insulin noted improved overall glycemic control while lowering the risk of nocturnal hypoglycemia and fewer injections ⁸⁹. Insulin degludec is not yet approved by Food and Drug Administration.

VIAject™: VIAject is recombinant human insulin with ultra fast onset of action. Pharmacodynamic and pharmacokinetic studies have shown the onset of action of VIAject is faster than that of human soluble insulin and insulin lispro ⁹⁰. VIAject was reported to have less within-subject variability of plasma insulin compared to human regular insulin ⁹¹, and has a faster absorption/onset of action than insulin lispro ^{92, 93}. Two pivotal phase III clinical studies in both type 1 and type 2 DM are ongoing with VIAject. As the amount of insulin circulating several hours after a meal is low, a possible reduction in hypoglycemia and prevention of weight gain are predicted.

CHALLENGES IN MAKING ORAL INSULIN

The main reason that developing an oral insulin therapy hasn't been so easy is due to the inability of potential oral insulin delivery systems to make it through your digestive system unharmed. Your digestive system is designed to break proteins down into amino acids, in order to prevent the absorption of dangerous forms of protein. Part of this process includes

maintaining a very low pH level in your stomach. This low pH level destroys, or breaks down, all peptides. Oral insulin is a type of protein that contains complex peptide bonds. Therefore, the acids in your stomach break down oral insulin before it can get to the liver. Another risk associated with oral insulin involves your ability to absorb it from your gut. Due to the fact that the mucus layer in your intestines is very thick and does not flow easily, the possibility of insulin passing through this lining and into your blood is believed to be relatively low, according to a research review published in the May 2009 issue of *The Journal of Diabetes Science and Technology*. Only a small amount of insulin effectively reached the liver in the studies used in this May 2009 review. In clinical trials, there has been no significant health risks associated with oral insulin compared to regularly administered insulin. However, because large amounts of insulin are required to make it through the digestive system, and because insulin is a growth-promoting substance, researchers are concerned that oral insulin could raise the risk of certain types of cancer.

CONCLUSION

Recent developments in insulin therapy have potential for reducing some of the negative aspects of current methods. The current improvement in insulin delivery provides opportunity to overcome the limitations of present insulin regimens. Transmucosal insulin delivery has shown promising result and soon allowed delivery of non-invasive insulin delivery in hyperglycemic patients. Orally delivering insulin is a ideal formulation in which various companies and institutions are researching extensively. Erythrocytes, which are the most abundant cells in the body, can be used as effective carriers of many different drugs including insulin. Biocompatibility, biodegradability, long circulation half-life and the ability to get loaded with a variety of chemically and biologically active compounds make resealed erythrocytes excellent carriers of therapeutic agents. Dendrimers are macromolecules with highly branched 3D structure. They also are used for successful delivery of insulin. However, the alternate routes of insulin delivery should be explored cautiously, as it may produce unwanted side effects. The currently using subcutaneously injection is known for damaging subcutaneous adipose tissue and local lipodystrophy. Insulin is a growth factor; its prolonged exposure should be done with caution due to its mutagenic property. Increased use of absorption enhancers for increased absorption of drug molecules can lead to penetration of toxic and pathogenic organism. In conclusion much work needs to be done for achieving safe and convenient insulin formulation. Increase in the advancement of nano particle delivery of insulin and ideal insulin tablet can be realized soon, thus improving the quality of life of diabetic patient

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