Diabetes is one of the leading diseases in current scenario and its incidence is increasing. It is a non curable disease but can be managed. Since it is a deficiency of insulin in one’s body, insulin is to be supplied externally for controlling the blood glucose levels in the body. Earlier insulin was obtained from animals naturally but due to the vast developments it is now possible to prepare different derivatives of insulin by changing the sequence of amino acids in insulin structure which act as precursors of insulin, and are converted to insulin in vivo. Moreover to overcome the pain caused during administration of insulin through syringe and needles, many researches carried on alternative methods of insulin delivery. The advancement in the field of research has lead to the development of new insulin delivery methods which are less painful and more effective than syringes and needles and provide good bioavailability and faster action. Several new approaches to the method have been adopted to decrease the suffering of the diabetic patients including the use of supersonic injector, infusion pump, sharp needles and pens. While some of them eased the pain encountered by the diabetic patients, they offer incomplete convenience. Even though the ultimate goal would be to eliminate the need to deliver insulin exogenously and regaining the ability of patients to produce and use own insulin, new concepts are currently explored to deliver insulin using oral, pulmonary, nasal, rectal and ocular routes. The success of the route of administration is judged on the basis of its ability to elicit effective and predictable lowering of blood glucose level and therefore minimizing the risk of diabetic complications.

**Keywords:** Insulin, Diabetes, Devices.

**INTRODUCTION**

In 2000, according to the World Health Organization, at least 171 million people worldwide suffered from diabetes. Its incidence is increasing rapidly, and it is estimated that by the year 2030, this number will double. Diabetes mellitus is of two types, insulin dependent diabetes mellitus and non insulin dependent diabetes mellitus. Insulin administration is essential for type 1 patients while it is required at later stage by he patients of type 2. Insulin is a hormone secreted from the beta cells of islet of langerhans, a specific group of cells in the pancreas. It is a protein consisting of two polypeptide chains one of 21 amino acid residues and the other of 30, joined by two disulfide bridges. It was isolated in 1921 with its first clinical use in 1922. Nowadays, the major advances achieved in this area include the human insulin analogue synthesis from the recombinant DNA techniques which was prepared by extraction method in early days from animal origin. (2, 3)

Insulin is a key player in the control of intermediary metabolism. It has profound effects on both carbohydrate and lipid metabolism and has significant influence on protein and mineral metabolism. Consequently, abnormal insulin level or responses have wide spread and devastating effects on many organs and tissues. Inadequate lowering of blood glucose level to normal level results in diabetes. Normal people have fasting sugar level less than 110 mg/dl as set by the American Diabetes Association. Diabetes is either type 1 as a result of frank deficiency of insulin or type 2, due to resistance of tissue to respond insulin. The former onset happens in the childhood while the latter in adulthood. In type 1 diabetes patients, the treatment is based on administering insulin and diet control. For type 2 diabetic patients, although insulin is not required initially, but may require the administration of insulin because of decrease in the insulin secretion. These accounts for 7 % of type 2 diabetic patients

The patients requiring insulin may have to take more 60,000 injections throughout their life. In type 1 diabetes, good glycemic control usually requires at least two or more often three or more daily insulin injections. Such invasive and intensive technique urges the search for alternative more pleasant methods for administering insulin. It is predicted that as soon as non/invasive insulin delivery technology becomes available, 2.5% of total diabetic population will use it with projected rapid increase by time.

The traditional and most predictable method for the administration of insulin is by subcutaneous injections. This method is often painful and hence, deterrent to patient compliance especially for those requiring multiple dose injections of four times a day. Also, there have been reports of hypoglycemic episodes following multi dose injections of insulin. It is clear that several difficulties have to overcome with the use of formulation and application devices technology. The various explored routes are reviewed in this review article.
newer devices are easy to use and carry and provide a small subcutaneous depot of unabsorbed insulin. The pump devices allow the patient to achieve a very tight control of blood plasma glucose levels and enhance the overall quality of life. However, if and when insulin delivery is interrupted by infusion set malfunction, needle displacement, pump dysfunction or lack of insulin in the reservoir, circulating insulin concentration drops rapidly causing problems. It is however beneficial for patients having hypoglycemic episodes. When compared with optimized multiple daily insulin injections, CSII resulted in a modest but worthwhile improvement in blood sugar in adults with type I diabetes. The therapy with insulin pump is very expensive as compared to the use of traditional syringes and vials. In a clinical study, the cost / benefit ratio was found to be favorable only in patients who were prone to frequent hypoglycemia. This is because of lower hospitalization rate of such patient population. Also the health and management benefits of the use of insulin pump outweighed that of multiple dose injections as it provides more freedom, flexibility, and spontaneity in the person’s daily life. (4, 5)

Advantages: Insulin pumps deliver insulin more accurately than injections. Using an insulin pump usually results in fewer large swings in your blood glucose levels, insulin pump makes diabetes management easier – if your glucose level is high or you feel like eating, figure out how much insulin you need and push the little button on the pump. Insulin pumps allow you to be flexible about when and what you eat, an insulin pump can improve your quality of life, it reduces severe low blood glucose episodes, it eliminates unpredictable effects of intermediate- or long-acting insulin. Insulin pumps allow you to exercise without having to eat large amounts of carbohydrate

Disadvantages: Can cause weight gain, Can cause diabetic ketoacidosis (DKA) if your catheter comes out and you don’t get insulin for hours. Can be expensive, Can be bothersome since you are attached to the pump most of the time

Insulin jet Injectors
Jet injectors, {introduced in the 1980s} are designed to deliver a fine stream of insulin subcutaneously at high speed and high pressure to penetrate the skin without the needle the use of force on a fluid under considerable pressure through a very opening allows such systems to deliver insulin without a needle to pierce the skin. The dose is controlled by a dial a dose operation through a single component design in comparison to the conventional multicomponent syringe and vial method. The available jet injectors allow a dose range of two to 50 units of insulin and can deliver insulin in half unit increments. Insulin that is administered by the jet injector method is absorbed rapidly without the risk of subcutaneous infection.In gestational diabetes, jet injection therapy is associated with less antiinsulin antibody [AIA] production and better postprandial glycemia.(6) (Fig3)

Advantages: No needle required. This is definite benefit to folk with a real needle phobia or who are just plain scared of needles, as many children, naturally it also removes the problems of bent and broken needles. Simple to use. Just wind, dial, fill, and inject. They can be used with all brands of U-100 insulin in standard 10 ml vials. You are able to mix insulins so eliminating the need for multiple injections that occur with
an insulin pen. This is done by attaching a separate Vial Adapter to each insulin bottle, drawing in the first dose from the one bottle then changing to the second bottle and continue to fill until you have the correct dosage. No disposal problems because there are no ‘sharps’ involved, No needle removes the danger of needle-stick injuries to a person giving insulin to someone who is unable to do it for themselves. Versatility - Due to the ability in some brands to change nozzles a single device can be adjusted to suit different peoples needs in relation to skin thickness and body mass. Other manufacturers offer versatility by offering different pens for different situations. This method of delivery produces a better spread of insulin into the subcutaneous tissue. With a needle the insulin forms a round pool at the tip of the needle and absorption only takes place from the edge of this pool. With a jet injector the pressure causes the insulin to penetrate the tissue and flow through it via the easiest routes (like most of us it takes the path of least resistance). This results in a net like distribution of insulin over a large area of tissue. The insulin automatically goes to the correct depth, no more decisions needed on what length needle to use and no chance of intra-muscular injections. Speed of injection. From the time you depress the actuator the time taken to complete the injection is around 300 milliseconds. With a syringe or pen you have to keep the needle in place for at least 6 seconds to prevent the risk of insulin leaking back through the injector site. Disadvantages:- Cost, this definitely tops the list. Compared to syringes the initial cost of these devices is high, bruising as one can get bruising from a needle puncture so one can get the same from these devices. However you look at it you are forcing a foreign substance into your body - you cannot blame it for fighting back. There is more to do in setting up the injector than there is in a syringe, so it takes more time. They are not widely used so the disposable bits can be more difficult to find. If you travel you will have to take sufficient supplies with you because it is likely you will not be able to find pieces for your particular injector in foreign countries. Sterilisation issues were a big problem with the older models and even some of the newer ones advocate cleaning every two weeks. Not as convenient as an insulin pen. You still have to carry around the device, the insulin vial, which needs to be kept refrigerated, the vial adapter and possible the disposable nozzle. Some people do not like the noise the injector makes when it delivers its insulin.

**Insulin pens**

An insulin pen is an insulin delivery system that generally looks like a large pen. Uses an insulin cartridge rather than a vial, and uses disposable needles. (Fig 4)

In using insulin pens, the patient must attach a needle, prime the pain, set the dose by a dial and depress the plunger to administer the selected dose. A study has shown that using insulin pain needles could help in reducing the economic burden of diabetes without leading to needle tip deformity and increased pain. (7, 8)

**Pens with Replaceable Cartridges**

A replaceable cartridge pen reuses the pen portion. When the insulin is empty, the vial is replaced by inserting a new one. Insulin cartridges for pens come in 3.0 ml and 1.5 ml sizes, with 3.0 being the predominant size. The 1.5 ml size is being phased out and availability may be limited. (Fig 5)

**Prefilled Pens**

A prefilled pen is entirely disposable. When the insulin is gone, the entire unit is discarded. Prefilled pens using pre-mixed insulin are usually marketed for use by people with type 2 diabetes. The fixed ratio of insulins does not provide the flexibility needed to accommodate varying food and exercise. (Fig 6)

**A Pen with Memory**

In February, 2007, Eli Lilly announced a new concept to the US market: ‘HumaPen MEMOIR is the first and only insulin pen with a memory. HumaPen MEMOIR records the date, time, and amount of your last 16 doses (including priming doses). You can see exactly when and how much insulin you last took. With HumaPen MEMOIR, you simply “dial” your dose by turning the dose knob in one-unit increments (up to 60 units) after initial set-up. If you dial too many units, you can correct the dose without wasting any insulin. HumaPen MEMOIR is a reusable pen for use only with Humalog (insulin lispro injection [rDNA origin]) 3 mL insulin cartridges. (Fig 7)

**Advantages:-**

Disposable and Refillable insulin pens are convenient, discreet and easier to use than a syringe and needle. Refillable insulin pens are especially useful for people who use very low doses of insulin. Disposable insulin devices with large numbers on the dial are easier to hold and control than traditional insulin pens or syringes and needles. This may be helpful if your fingers are numb, stiff or shaky.

**Disadvantages:-**

Disposable and Refillable insulin pens cost more than syringes and needles. You may need to give yourself two injections if you use more than one type of insulin.

**Insulin Spray**

The buccal route is another promising alternative for insulin delivery. With the buccal area having an abundant blood supply, it offers some advantages such as a means to deliver the acid labile insulin, and elimination of insulin destruction by first pass metabolism. The device delivers insulin for buccal absorption with no lung deposition. According to a company news release, the oral formulation is intended to offer a safe, simple, convenient, fast, and effective alternative to prandial insulin injections. Two forms of mouth spray (rapid mist, oralin) are being developed by Generex Biotechnology. (Fig 8)

Buccal absorption can be achieved by using a dome shaped the phase mucosal adhesive device prepared by dispersing insulin crystals with sodium glycocholate, an absorption promotor, in an oleaginous core and then overlaying the medicated core by adhesive dome. A systemic bioavailability of only 0.5% was achieved when no absorption promoter was used, which can be improved by co-administration of bile salts, as absorption promoters. Though the systemic bioavailability was very low, therapeutically effective plasma concentrations of insulin were achieved and blood glucose levels were substantially reduced. (11)

**Insulin Inhalers**

Insulin has been studied extensively for systemic delivery by intranasal administration. Insulin has poor oral absorption it can be better absorbed through nasal mucosa. The process of transport across the nasal membrane involves either diffusion of drug molecules through the pores in nasal mucosa or participation of some non passive path-
Fig 1: Syringe; Consisting of Cap, Needle, Barrel and Plunger

Fig 2: Insulin Pumps; consists of a reservoir filled with insulin, a small battery operated pump and a computer chip that allows the patient to control the insulin delivery.

Fig 3: Insulin Jet Injectors; Designed to deliver a fine stream of insulin subcutaneously at high speed and high pressure to penetrate the skin without the needle.

Fig 4: Insulin Pen; Uses an insulin cartridge rather than a vial, and uses disposable needles

Fig 5: Pens with Replaceable Cartridges

Fig 6: Prefilled Pens

Fig 7: A Pen with memory; records the date, time, and amount of your last 16 doses (including priming doses)

Fig 8: Oral Insulin Spray

Fig 9: Pfizer-Exubera; Insulin Inhaler
way before they reach the blood. The transnasal permeability nasal absorption of insulin was found to be enhanced by the co-administration of absorption promoters, such as bile salts, naturally occurring surfactants, or synthetic surfactants. Dose required to be administered by intranasal application is larger than that for subcutaneous injection (9, 10).

Inhaled insulin appears to be a non-invasive, well-tolerated and liked modality of treatment with potential for both type 1 and type 2 diabetics. Results of short-term studies indicate that glycemic control achieved with an inhaled insulin regimen is comparable with a subcutaneous insulin regimen in patients with type 1 and type 2 diabetes. It has been determined in patients with type 1 diabetes that improvement in overall patient satisfaction with inhaled insulin is rapid and sustainable compared with conventional subcutaneous insulin, and the reduced treatment burden has a positive impact on psychological well-being. Inhaled insulin greatly enhances patient satisfaction, quality of life and acceptance of intensive insulin therapy in a diabetic patient.

The rationale behind developing a pulmonary drug delivery system is to ensure that insulin powder is delivered deep into the lungs, where it is easily absorbed into the bloodstream, in a hand-held inhalation device. The device converts the insulin powder particles into an aerosol cloud for the patient to inhale. Advanced PEGylation technology is used to develop a dry powder-inhaled polyethylene glycol (PEG) formulation for delivering peptides efficiently across the lungs and to promote prolonged serum concentration of the peptide.

Exubera represents a novel prandial insulin delivery method. Good glycemic control, comparable to modern subcutaneously administered insulin preparations, has already been demonstrated, and no unexpected safety concerns have been reported with inhaled insulin. After intranasal administration, insulin enters the cerebrospinal fluid compartment and alters brain function. Insulin acts in CNS to reduce food intake and body weight and is considered a major adiposity signal in men. (Fig 9)

**Insulin Oral Pill**

There is strong evidence suggesting that an oral insulin product would provide insulin in a more physiological manner, with a resultant decrease in peripheral insulin concentration and that it would more adequately insulinize the liver. Azopolymer coated pellets to deliver insulin to the colon region were studied earlier. The azopolymer protects the entrapped therapeutic agent till the pellets reach the colon. As only the bacteria inhabiting the colon secrete enzymes that can breakdown the azopolymer, insulin release will be initiated once the pellets reach the large intestine. (12)

Microencapsulation of insulin in polymeric microspheres coated with pH responsive polymers such as alginate is also known. Alginate coating protects the spheres in the acidic pH of the stomach but dissolves in the intestine where the pH increases to above 7 and liberates the entrapped insulin. Recently several biotech companies have been conducting pilot trials in the effort to develop an insulin pill as a potential alternative to injected or pumped insulin. The attempt requires the development of novel delivery technology. Initially small enough to be easily swallowed by the patients, the pill swells following its ingestion. Simultaneously, the system begins a period of extended drug release. This sustained delivery could some day lead to an insulin pill that provides steady release into the bloodstream, minimizing the number of doses required per day. (13)

**Insulin Transdermal Patches**

Though the skin is a formidable barrier, companies are developing various active transdermal delivery technologies to overcome this challenge. The hope is to open up the transdermal market to the delivery of products that were previously considered undeliverable via this route.

Insulin patches are another drug delivery system in development. Patches would release insulin continuously into the bloodstream. Users would pull a tab on the patch to release more insulin before meals. The transdermal insulin application does not result in a reproducible and sufficient transfer of insulin across the highly efficient skin barrier. The challenge is finding a way to have insulin pass through the skin. Chemical enhancers, iontophoresis, electroporation and ultrasound increase skin permeability by making submicron alterations in skin microstructure for continuous delivery over time. The efficacy of passive transdermal versus electrically-enhanced delivery of insulin was studied in diabetic rats, showing low levels of electrical current can induce changes in stratum corneum permeability that are sufficient to produce the transdermal absorption of physiologic doses of a protein such as human insulin. In another study using diabetic rats, iontophoresis of bovine insulin was not effective in decreasing the plasma glucose level when given alone, but application of a depletory cream for hair removal (24 h before the experiment), followed by iontophoresis of bovine insulin produced a concentration-dependent fall in plasma glucose level, indicating the necessity of permeation enhancer for iontophoretic delivery of insulin. But, the precise delivery of insulin is still to be realized by this approach.

**FUTURE TRENDS IN INSULIN DELIVERY SYSTEMS**

**Intraperitoneal Insulin**

There are many benefits to adding insulin via the intraperitoneal (IP) route for the diabetic peritoneal dialysis (PD) patient. They include resemblance between physiological insulin secretion and the response from IP insulin administration; reduction in episodes and severity of hypoglycemia due to the continuous absorption of insulin during the entire PD dwell; minimization of hyperinsulinemia; desirable control of the serum glucose that can be gained and avoidance of subcutaneous injections. (14)

**Rectal gels**

The purpose of this investigation was to first screen for potential effectiveness. Several rectal gels as insulin delivery systems and to select one promising dosage form as candidate for further evaluation in rabbits and man. The rectal gels consisted of emulsion systems prepared from pH 8 buffer solution containing insulin, an oleaginous phase, a surface active agent and a viscosity increasing agent. The finally selected rectal gel was tested in rabbits both in a parallel and a crossover design in nondiabetic and diabetic animals.

**Insulin suppositories**

Oramed pharmaceuticals, a developer of alternative drug delivery system are conducting phase IA trials on eight healthy human volunteer for ORMD 0802, company's newly developed suppository. Phase IA trials on its insulin suppositories mark an important step in history of insulin delivery as it will provide a painless option for diabetic who
seek an alternative to current delivery methods. An insulin suppository is especially important for small children and seniors who often struggle with injection. This is to ensure that the diabetic will be able to receive insulin in the form which is most suitable to their lifestyle and age. Thus this route bypasses the harsh portion of GI system. Based on research the insulin suppositories showed rapid absorption through colon and actively lowered blood glucose levels. These results were well tolerated by participants and no adverse symptoms were seen.

**Insulin toothpastes**

GenoMed Inc. filed for a patent on insulin-laced toothpaste which could replace the use of insulin shots for some diabetics. The recently submitted patent application includes a system whereby drugs are delivered to the bloodstream through specially formulated toothpastes. The insulin-laced toothpaste would be available by prescription and is expected to come in different strengths. The challenge is to find a way for the large insulin proteins to get into a toothpaste form, thus bypassing the need for a needle. Insulin cannot survive the harsh acidic environment of the stomach and must be injected into the bloodstream to be effective. Flossing, which often causes some bleeding of the gums, could help to speed the drug’s delivery to the bloodstream.

**Gene therapy**

Two recent reports describe research into gene therapy for different aspects of diabetes. As scientists identify specific genes whose absence or improper functioning are associated with specific conditions, more possibilities for gene therapy are offered. Scientists have identified a gene called SHIP2 that appears to regulate insulin. Such findings make SHIP2 a potential gene therapy target for the treatment of type 2 diabetes aimed at improving the individual’s insulin regulation. Scientists have developed a gene therapy strategy, applied in diabetic rats, to retool certain cells within digestive glands that already are capable of sensing blood sugar levels to produce and deliver insulin into the bloodstream and normalize blood sugar levels. The insulin-delivery process occurs automatically when food is eaten.

**Islet Cell Transplant**

In contrast to conventional insulin treatment, islet transplantation is far superior for achieving a constant normoglycaemic state and avoiding hypoglycaemic episodes. Using a novel protocol established by the Edmonton Centre, Canada, the insulin dependence rates have improved, reaching 50-80% level. Thus, islet transplantation typically offers stabilization of blood glucose control and elimination of problematic hypoglycaemia and is being increasingly used worldwide. Islet transplantation is done by suppressing the immune response followed by transplantation for normal functioning of islet cells. (15)

**CONCLUSION**

Diabetes mellitus is the third leading cause of death and perhaps in the top 5, of the most significant disease in the developed world. Diet, exercise, hypoglycemic drugs and insulin are being used for diabetes management. Previously insulin obtained from animal origin was used, which has now been shifted to insulin obtained from rDNA technology. There has been development in delivery devices for insulin from traditional syringes to pens, jet injectors, pumps, sprays, inhalers, patches etc. Oral administration of insulin using products such as tablet or capsule would be the major technological breakthrough if approved for marketing. Such a goal necessitates intensive work and commitment from pharmaceutical companies. Inhalation delivery system for insulin [Exubera] is the first alternative method of insulin delivery that has recently been introduced to the market after FDA approval. The product would need time to gain acceptance from other health authorities, to provide long term safety profile and gain popularity among health care professionals and patients. Some unfavorable aspects have to be circumvented to make this alternative insulin delivery system a reality and make them to reach the market. Insulin analogues are also being developed to substitute insulin.

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