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ISSN: 0975-7538
Review Article

# Insulin drug delivery systems: A review

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**ABSTRACT**

Diabetes Mellitus is a metabolic disorder characterized by hyperglycaemia, glycosuria, and hyperlipidemia. At present, India is considered as the diabetic capital of the world. There are approximately 3.5 crore diabetics in India, and this figure is expected to increase up to 5.2 crore by 2025. Two major types of diabetes mellitus are IDDM and NIDDM. Insulin is a hormone. And like many hormones, insulin is a protein. Insulin is secreted by groups of cells within the pancreas called islet cells. Discovery of Insulin is appropriately attributed to Banting and Best. It is made up of 51 amino acids having two chains. Chain A have 21 and Chain B have 30 amino acids. The more commonly used types of insulin are Rapid-acting (*aspart* or *Lispro),* Short-acting (*regular insulin),* Long-acting (*ultralente insulin),* Insulin glargine and insulin detemir. Insulin delivery systems that are currently available for the administration of insulin include syringes, insulin infusion pumps, jet injectors and pens. Insulin syringe is the most commonly used, and the most economical of all the delivery devices. Insulin pump is known as continuous subcutaneous insulin infusion therapy. A jet injector is a type of medical injecting syringe that uses a high-pressure narrow jet of the injection liquid instead of a hypodermic needle to penetrate the epidermis. Pen is reusable and prefilled device. Many insulin delivery devices are under process. The purpose of this review is to focus more light on the insulin as a prime drug for the treatment of diabetes from historical era to present time.

**Keywords:** Diabetes mellitus; proteins and peptides; Insulin drug delivery systems

## INTRODUCTION

Diabetes Mellitus is a metabolic disorder characterized by hyperglycaemia, glycosuria, hyperlipidemia, negative nitrogen balance and sometimes ketonemia. A wide-spread pathological change is thickening of capillary basement membrane, increase in vessel wall matrix and cellular proliferation resulting in vascular complications like lumen narrowing, early arthrosclerosis, sclerosis of glomerular capillaries, retinopathy, neuropathy and peripheral vascular insufficiency. (Tripathi KD et al, 2004)

### Types of Diabetes Mellitus

Two major types of diabetes mellitus are as follows,

1. Type I or Insulin dependent diabetes mellitus (IDDM)
2. Type II or Non insulin dependent diabetes mellitus (NIDDM)

### 1. Type I or Insulin dependent diabetes mellitus (IDDM)

It is also known as juvenile onset diabetes mellitus. There is β cell destruction in pancreatic islets; majority of cases are autoimmune antibodies that destroy β cells are detectable in blood, but some are idiopathic -- no β cell antibody is found. In all type 1 cases circulating insulin levels are low or very low, and patients are more prone to ketosis. This type is less common and has a low degree of genetic predisposition.

### 2. Type II or Non insulin dependent diabetes mellitus (NIDDM)

It is also known as Maturity onset diabetes mellitus. There is no loss or moderate reduction in β cell mass; insulin in circulation is low, normal or even high, no anti-β-cell antibody is demonstrable; has a high degree of genetic predisposition; generally has a late onset. Over 90% cases are type 2 DM. Causes may be:

- Abnormality in gluco-receptor of β cells so that they respond at higher glucose concentration.
- Reduced sensitivity of peripheral tissues to insulin: reduction in number of insulin receptors. Many hypertensives are hyperinsulinemic but normoglycaemic; exhibit insulin resistance.

Excess of hyperglycemic hormones (glucagon) cause relative insulin deficiency. (Tripathi KD et al, 2004)

At present, India is considered as the diabetic capital of the world. There are approximately 3.5 crore diabetics in India, and this figure is expected to increase up to 5.2 crore by 2025. Every fifth patient visiting a consulting physician is a diabetic and every seventh patient

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Received on: 02-06-2011
Revised on: 05-07-2011
Accepted on: 09-07-2011

visiting a family physician is a diabetic. Keeping in view the alarming increase in the incidence and prevalence of diabetics in India, the World Health Organization (WHO) has declared India as the Diabetic Capital of the world. Studies have shown that increasing patient knowledge regarding disease and its complications has significant benefits with regard to patient compliance to treatment and to decreasing complications associated with the disease. Considering this, we sought to quantify in a population of diabetics visiting our clinic, the level of knowledge with respect to different areas pertaining to the prevention and treatment of associated complications.**(**Gulabani M et al., 2008)

**BIOSYNTHESIS OF INSULIN** (Goodman & Gilman's et al. 2006)

The cells in the islet are connected by tight junctions that allow small molecules to pass and facilitate coordinated control of groups of cells. Arterioles enter the islets and branch into a glomerular like capillary mass in the β-cell core. Capillaries then pass to the rim of the islet and coalesce into collecting venules. Blood flows in the islet from the β-cells to α and 6 cells. Thus, the β cell is the primary glucose sensor for the islet, and the other cell types presumably are exposed to particularly high concentrations of insulin. Insulin is synthesized as a single-chain precursor in which the A and B chains are connected by the C peptide. The initial translation product, preproinsulin, contains a sequence of 24 primarily hydrophobic amino acid residues attached to the N terminus of the B chain. This signal sequence is required for the association and penetration of nascent preproinsulin into the lumen of the rough endoplasmic reticulum. This sequence is cleaved rapidly, and proinsulin is then transported in small vesicles to the Golgi complex. Here, Proinsulin is packed into secretory granules long with the enzyme responsible for its conversion to insulin.

**SYNTHESIS OF INSULIN**

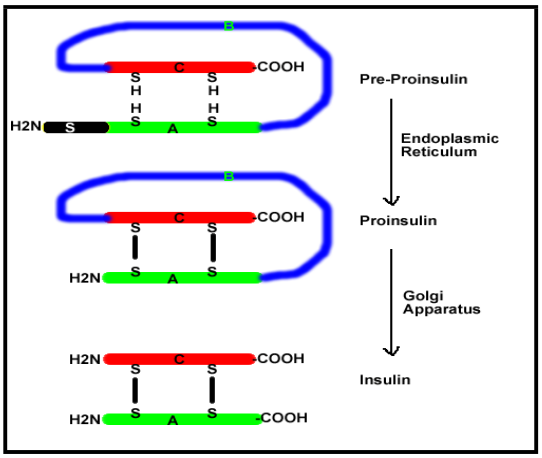


**Figure 1: Synthesis of insulin**

The conversion of Proinsulin to insulin begins in the Golgi complex, continues in the secretary granules, and is nearly complete at the time of secretion. Thus, equimolar amounts of C peptide and insulin are released into the circulation. The C peptide has no known biological function but serves as a useful index of insulin secretion in distinguishing between patients with factitious insulin injection and insulin-producing tumors. Small quantities of Proinsulin and des-31, 32 Proinsulin also are released from β cells. This presumably reflects either exocytosis of granules in which the conversion of Proinsulin to insulin is not complete or secretion by another pathway. Since the half-life of Proinsulin in the circulation is much longer than that of insulin, up to 20% of immunoreactive insulin in plasma is, in reality, Proinsulin and intermediates.

Two distinct $Ca^{2+}$ dependent endopeptidases, which are found in the islet cell granules and in other neuroendocrine cells, are responsible for the conversion of Proinsulin to insulin. These endopeptidases, PC2 and PC3, have catalytic domains related to that of subtilisin and cleave at Lys-Arg or Arg-Arg sequences. PC2 selectively cleaves at the C peptide- A chain junction. PC3 preferentially cleaves at the A chain junction as well. Although there are at least two other members of the family of endoproteases, PC2 and PC3 appear to be the enzymes responsible for processing Proinsulin to Insulin.

**STRUCTURE OF INSULIN**

Insulin is a polypeptide with a molecular weight of about 6000. It is composed of an A-chain (acidic) made up of 21 amino acids, and B-chain (basic) of 30 amino acids, linked by two disulphide (-S-S-) bridges. The immediate precursor of insulin within the pancreatic β cells is Proinsulin in which the A and B chains are joined by the " connecting " peptide (C-peptide) composed in man of 31amino acids. Proinsulin has a molecular weight of 9000. Insulin has been completely synthesized, however the present supplies ware obtained mainly from the pancreas of cattle (bovine).

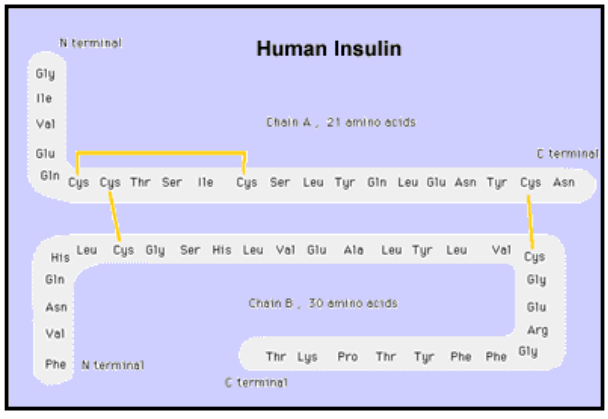


**Figure 2: Structure of Insulin**

**MECHANISM OF ACTION** (Tripathi KD et al 2004)

Like the receptors for other protein hormones, the receptor for insulin is embedded in the plasma membrane. The insulin receptor is composed of two alpha subunits and two beta subunits linked by disulfide bonds. The alpha chains are entirely extracellular and

house insulin binding domains, while the linked beta chains penetrate through the plasma membrane.

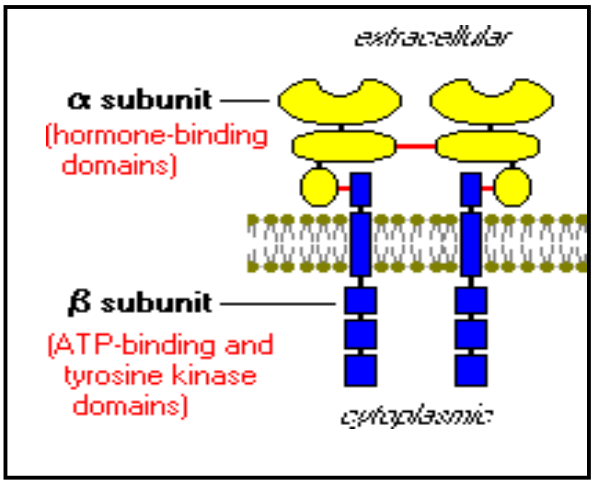


**Figure 3: Mechanism of action (Goldfine ID et al 2002)**

The insulin receptor is a tyrosine kinase. In other words, it functions as an enzyme that transfers phosphate groups from ATP to tyrosine residues on intracellular target proteins. Binding of insulin to the alpha subunits causes the beta subunits to phosphorylate themselves (autophosphorylation), thus activating the catalytic activity of the receptor. The activated receptor then phosphorylates a number of intracellular proteins, which in turn alters their activity, thereby generating a biological response (Goldfine ID et al 2002). The insulin acts on specific receptor consisting of 2 extracellular α and 2 transmembrane β subunits linked together by disulfide bonds. The α subunits carry insulin binding sites while the β subunits have tyrosine protein kinase activity.

Binding of insulin to α subunits induces aggregation and internalization of the receptor along with the bound insulin molecules. This activates tyrosine kinase activity of the β subunits tyrosine residues of the β subunits get autophosphorylated so that the activity of this subunit to phosphorylate tyrosine residues of Insulin Receptor Substrate proteins (IRS1, IRS2) is increased. In turn a cascade of phosphorylation and dephosphorylation reactions is set into motion resulting in stimulation or inhibition of enzymes involved in the rapid metabolic actions of insulin.Insulin stimulates glucose transport across cell membrane by ATP dependent translocation of glucose transporters GLUT4 AND GLUT1 to the plasma membrane as well as by increasing their activity. Over a period of time it also promotes expression of the genes directing synthesis of GLUT.

**CURRENT INSULIN DELIVERY SYSTEMS:** (Tyagi P et al. 2002)

Insulin delivery systems that are currently available for the administration of insulin include syringes, insulin infusion pumps, jet injectors and pens. A concise review of these delivery devices has been described as under.

**1. Insulin Syringes**

**Figure 4: Insulin Syringe**

This is the most commonly used, and the most economical of all the delivery devices. It consists of a vial or a small bottle and insulin syringes. The needles of the syringes are short and thin, making them less painful. Recent advancements have given rise to coated needles that further reduce the pain. The syringes have gradations to help draw the correct dosage of insulin. Insulin syringes are characterized by three factors, i.e. needle gauge, needle length and syringe capacity. The manufacturers of the syringes offer a wide array of sizes and styles. The proper selection of an appropriate syringe is based on many considerations, like chemical composition of the material from which syringes are made, syringe capacity. Insulin syringes that were introduced initially were large and heavy with reusable glass plungers and barrels with a long, large bore needle. Today, many insulin injection syringes are available in the market that is derived from plastics being light in weight, disposable and versatile in use of variety of micro fine needles.

**Advantages**

- It is cheap.
- Its usage is easy to understand especially by the less educated people.
- It can be used by the blind too. This can be done by someone filling the syringes and the patient injecting it at the desired time.
- These syringes increase patient comfort and offer convenience, thus better patient compliance.

**Disadvantages**

- It is uncomfortable to use in parties or get-togethers
- It is more painful to use when compared to other devices such as insulin pens as the syringe needles are slightly thicker than pen needles.
- The procedure is slightly elaborate and time consuming when two types of insulin are required to be mixed and taken.

- It includes their bulky construction and the requirement of time and practice to learn optimal syringe technique.

**2. Insulin Infusion Pumps**

**Figure 5: Insulin Pump**

- An Insulin pump is a medical device used for the administration of insulin in the treatment of diabetes mellitus, also known as continuous subcutaneous insulin infusion therapy. The device includes:

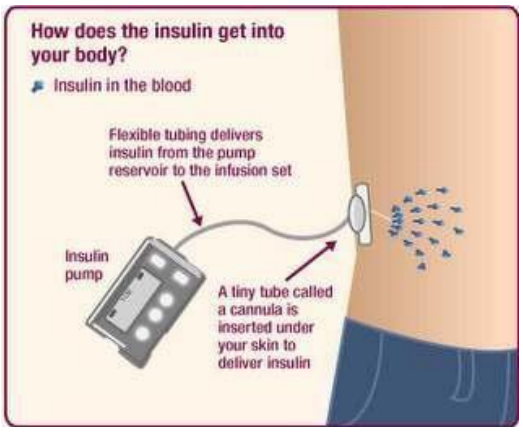


**Figure 6: IIP Mechanism**

The pump itself (including controls, processing module, and batteries) a disposable reservoir for insulin (inside the pump) Disposable infusion set, including a cannula for subcutaneous insertion (under the skin) and a tubing system to interface the insulin reservoir to the cannula. An insulin pump is an alternative to multiple daily injections of insulin by insulin syringe or an insulin pen and allows for intensive insulin therapy when used in conjunction with blood glucose monitoring. Continuous subcutaneous insulin infusion (CSII) is a way to simulate the physiology of daily insulin secretion. The first CSII pump was introduced in the market in 1974.

By design, an insulin pump typically consists of a reservoir filled with insulin (e.g., Velosulin® BR), a small battery operated pump and a computer chip that allows the patient to control the insulin delivery. The pump is designed to provide a continuous supply of insulin infusion around the clock and can be adjusted as per the specific needs of the patient. Appropriate amounts of insulin are delivered into the body by the pump through a thin plastic tube known as an infusion set. Most of the factors that affect the variability of subcutaneous injections such as depth of injection and change of injection sites are avoided with pump systems. In these pumps, the insulin reservoir is connected to a subcutaneous catheter, which is changed every two to three days. Thus, advantageous for people who do not like injections as it is only necessary to insert a needle once every three to four days. These are relatively easier to operate than the earlier ones and can be carried conveniently in a shirt pocket. However, some patients may not like the idea of wearing a pump constantly or disconnecting the catheter before bathing or swimming.

Insulin pumps provide accuracy and greater flexibility in insulin delivery for patients according to their individual requirements, especially during travel. Some of the available infusion pumps have the ability to accurately deliver micro doses (0.1 units) of insulin.

The newer devices are easy to use and carry and provide a small subcutaneous depot of unabsorbed insulin. The pump devices allow a patient to achieve a very tight control of 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. This may be a great concern for some patients. However, patients who experience many hypoglycemic episodes may benefit from infusion pumps.When compared with optimized multiple daily insulin injections.

**Advantages**

- The use of rapid-acting insulin for basal needs offers relative freedom from a structured meal and exercise regimen previously needed to control blood sugar with slow-acting insulin. The alternative basal insulins, such as the long lasting insulins injected once a day, often release their insulin at a very unpredictable rate.
- Many pumpers feel that blousing insulin from a pump is more convenient and discreet than injection.
- Insulin pumps also make it possible to deliver more precise amounts of insulin than can be injected using a syringe. This supports tighter control over blood sugar level and reducing the chance of long-term complications associated with diabetes.
- It provides more freedom, flexibility, and spontaneity in the person's daily life.

**Disadvantages**

- Insulin pumps, cartridges, and infusion sets are far more expensive than syringes used for insulin injection.
- Since the insulin pump needs to be worn most of the time, pump users need strategies to participate

in activities that may damage the pump, such as rough sports and activities in the water. Some users may find that wearing the pump all the time is uncomfortable or unwieldy.

- An episode of diabetic ketoacidosis may occur if the pump user does not receive sufficient fast acting insulin for many hours. This can happen if the pump battery is discharged.
- Possibility of insulin pump breaking and having to resort back to multiple daily injections until new pump arrives.

**3. Insulin Jet Injectors**

**Figure 7: Jet Injector**

A jet injector (Introduced into 1980) is a type of medical injecting syringe that uses a high-pressure narrow jet of the injection liquid instead of a hypodermic needle to penetrate the epidermis.


**Figure 8: Detailed Diagram of insulin jet injector**

It is powered by compressed air or gas, either by a pressure hose from a large cylinder, or from a built-in gas cartridge or small cylinder. Some are multi-shot, and some are one-shot. The use of force on a fluid under considerable pressure through a very small opening allows such systems to deliver insulin without using 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 multi component 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 anti insulin antibody (AIA) production and better postprandial glycemia.

**Disadvantages**

- Force of the spray breaking the skin
- Most people report more pain with injectors than with a syringe
- It is time consuming to prepare and clean the injector (some newer models have disposable injection chambers but they are expensive)
- The potential for a decreased amount of absorbed insulin over repeated administration with jet injectors.
- The size and the cost of these jet injectors are considered unfavorably and often limit their routine use in patients with diabetes.
- Until the recent approval of inhaled insulin, insulin jet injectors were the only insulin delivery device available that did not use a needle or a sharp cannula (needle-like tip to tubing used in an insulin pump).

**4. Insulin Pens**

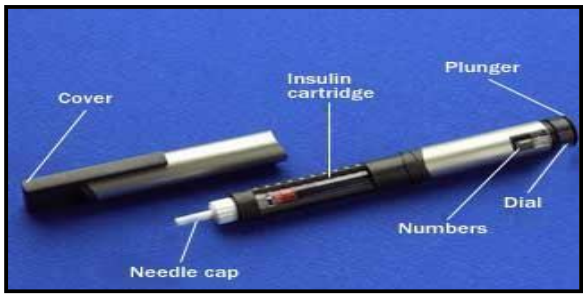


**Figure 9: Insulin Pen**

Pen devices are novel in that they combine the insulin container and the syringe into a single modular unit. Insulin pens eliminate the inconvenience of carrying insulin and syringes. The first insulin pen (NovoPen®) was introduced by Novo Nordisk in 1987. Many pens are available since then in a variety of types and shapes. There are two main types of pens, one that is reusable and the other a prefilled device. In the former case, the patient must load an insulin cartridge prior to use. Regardless of the type, both pens hold cartridges containing from 1.5 ml to 3 ml of U100/ml insulin. The number of steps required to change an insulin cartridge with reusable pens varies between the different pen device manufacturers. Prefilled devices are well accepted in a bedtime insulin regimen for type 2 patients. Reusable insulin pens offer a wide range of advantages such as their durability, eliminating the need of cartridge refrigeration and flexibility in carrying three to five day supply. The refilled insulin pens are smaller in size and lighter in weight. They cause minimal pain due to the finest and shortest disposable insulin needles. In addition, they are quick and easy to use as

they resemble the fountain pen; they are considered to be discreet. The manufacturers of the pen devices recommend keeping the needle separate and attaching only when ready to use. A study has shown that reusing insulin pen needles could help in reducing the economic burden of diabetes without leading to needle tip deformity and increased pain. The needles for pens are available in varying lengths (from 8 mm to 12.7 mm) and varying gauges (from 29- to 31-gauge; the larger the gauge number, the smaller the diameter of the needle bore).The devices can add lifestyle flexibility and may result in better glycemic control. Many newer generation pens are able to deliver 60 U at a time for type 2 patients.Insulin pens have become very popular in some countries such as France where over 50 percent of insulin-treated patients are using insulin pen.

**Advantages**

- More convenient and easier to transport than traditional vial and syringe
- Repeatedly more accurate dosages
- Easier to use for those with visual or fine motor skills impairments
- Less injection pain (as polished and coated needles are not dulled by insertion into a vial of insulin before a second insertion into the skin)
- Insulin pens are smaller in size and lighter in weight.

**Disadvantages**

Unlike the traditional syringe, pens are usually restricted to full or half unit dosing. You are also not able to mix two different insulins in the same pen.

**FUTURE TRENDS IN INSULIN DELIVERY SYSTEMS**

Concise information on some of the prominent insulin delivery systems given as under:

**1. Insulin Inhalers**

**Figure 10: Insulin Inhaler**

The lungs, on account of their large surface area, are an ideal target for drug delivery and inhaled insulin (pulmonary insulin) represents one of the most promising alternatives to injection. The first attempt to deliver insulin by inhalation was made more than half century ago. Clinical experience has shown that inhaled insulin has the potential to be an effective treatment in patients with diabetes, with particular utility in the treatment of postprandial hyperglycaemia. Exubera®, containing rapid-acting insulin in powder form, has been studied extensively in patients with type 1 and type 2 diabetes mellitus. The AERx® Insulin Diabetes Management System (AERx® iDMS) delivers a liquid form of human insulin.Preliminary data indicate that patients converting from insulin injections to inhalation systems showed higher compliance to therapy, demonstrated by improved glycemic control.Other pulmonary insulin delivery systems, including ProMaxx® (Epic Therapeutic- Baxter Healthcare Corporation), AIR® (Alkermes, Eli Lilly), Spiros® (Dura Pharmaceuticals and Eli Lilly), and Technosphere ™ -insulin Med Tone® inhaler (Pharmaceutical Discovery Corp.), are also under investigation . In humans, inhaled regular insulin is more rapidly absorbed than insulin from the subcutaneous injection. However, the efficiency of inhaled insulin is lower than that of subcutaneous injection because pulmonary delivery of insulin involves some loss of drug within the inhaler or mouth during inhalation. Exubera® device [Figure 10] is about 25 cm long, has a base into which a packet of insulin powder is placed and a clear chamber above which the insulin powder is turned into an aerosol cloud for inhalation. The device delivers powdered insulin in 1 and 3 mg doses (approximately 3 and 9 units, respectively). Fine powder particles can stick together and become difficult to inhale effectively, reducing the chances of accurate dosing. Many inhalers (e.g. those used by some asthmatics) rely on a quick inhalation by the patient to try and force the particles apart.However, rather than rely on the ability of the patient to get their breathing right in order for effective treatment. The inhaler uses compressed air traveling at the speed of sound to create a cloud of insulin powder that the patient can then breathe in slowly and deeply to their lungs, where it dissolves into the blood stream. Clinical trials have shown that inhaled insulin delivered by the AERx® iDMS controls blood glucose in the similar way as injected insulin in terms of absorption and onset of action like the rapid acting analogues, making it ideal for dosing immediately prior to a meal. (ARIDA AI et al, 2008)

**2. Mouth Sprays**

**Figure 11: Mouth Spray**

Mouth sprays deliver insulin through an aerosol spray and hence, they differ from inhalers. In mouth sprays, the insulin is absorbed through the inside of cheeks and in the back of mouth instead of lungs. Two forms of mouth spray (Rapid Mist/Oralin) are being developed by Generex Biotechnology. One of the forms is fast-acting whereas, another one covers the basal rate of insulin (the basal rate is the amount of insulin required throughout the day to keep blood sugars stable). **(**ARIDA AI et al., 2008)

**3. Transdermal insulin delivery**

Noninvasive transdermal insulin delivery could provide diabetic patients with sustained physiological levels of basal insulin in a pain-free manner. Patches are the examples to deliver basal insulin rather than fast-acting boli in two steps process.

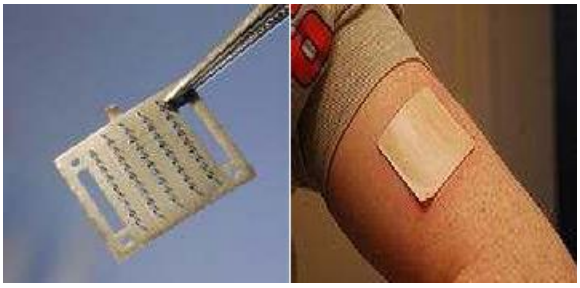

**Figure 12: Insulin trasdermal patch**

First, by a device that would make microscopic holes in the top layer of the skin and secondly, the application of patch over the skin. Altea Development Corporation is planning to introduce a product which will either be a one- or half-day patch, depending on the outcome of testing. **(**ARIDA AI et al, 2008.). One of the skin's primary roles is to provide protection against infection and physical damage. This barrier is so effective that it prevents many pharmaceutical compounds from crossing into the bloodstream. To overcome this defense, both passive and active drug transport across the skin (transdermal) barrier are being developed. Passive transdermal delivery allows a drug to diffuse through the skin and act locally or penetrate the capillaries and have a systemic effect. Passive delivery usually occurs with a patch, cream, or spray. Passive Transdermal delivery only works with small molecule drugs, such as nicotine and aspirin. Insulin is far too large to get through the skin passively.Active transdermal delivery, on the other hand, involves a chemical or mechanical disruption of the skin barrier. By using an applied force, such as ultrasound or an electrical current, active transdermal systems are capable of delivering proteins and other large molecule formulations through the skin and into the bloodstream.Though the skin is a formidable barrier, companies are developing various active transdermal delivery technologies to overcome this challenge. The transdermal insulin application does not result in a reproducible and sufficient transfer of insulin across the highly efficient skin barrier. 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. (Tyagi P et al, 2002)

**4. Nasal Insulin**

**Figure 13: Nasal Insulin**

Nasal insulin application was considered for a number of years as a potential method, because of the rapid absorption of insulin across nasal mucosa. However, relative bioavailability was low and required use of absorption enhancers and more importantly, the metabolic effect lasted too short to be of clinical usefulness. Use of nasally-administered insulin has been tested for up to three months, but so far results have been discouraging because only 10% to 20% of the dose is absorbed.Other probiems associated with nasal insulin include irritation of the nasal passages and upper respiratory infections. While this method may one day be possible, it is not the most promising technique under investigation. (Sircar AR et al ,2002)

**5. Oral Insulin:** Insulin is degraded very quickly by the stomach's acidic environment and proteolytic enzymes. The dream of an "insulin tablet" has also not become a reality, the main problem being digestion and a lack of a specific peptide carrier system in the gut.Researchers are currently examining whether insulin absorbed into a microsphere can bypass these enzymes and pass through the wall of the intestine. But this research is still in its early phases. Provalis is trying to develop an insulin based oral pill (Macrulin®). The technology uses a water-in-oil micro emulsion in which aqueous phase contains insulin and the oil phase contains cholesterol, lecithin and non-esterified fatty acids.Nobex oral insulin is based on a technology of covalent attachment of low molecular weight polymers to insulin creating drug polymer conjugate. This is now in phase II trial in USA. Chemical engineers at Purdue University, USA recently

claimed that they have developed a polymer, to shepherd insulin past the stomach. The polymer in acid collapses into a tight ball that traps the insulin.In about 30 minutes, the pill reaches the non-acidic intestine, where the polymer expands to release the insulin. **(**Sircar AR et al, 2002)

**6. Pills:** The concept of delivering insulin by mouth ("peroral" delivery) for absorption across the intestinal wall into the portal vein has long been regarded as a difficult challenge, but of substantial clinical and commercial potential. Presently, the biggest challenge with insulin pills is posed by the human digestive system. Either the gastrointestinal tract breaks the insulin down or the insulin passes out intact because it is unable to pass through the gastrointestinal membrane.

Attempts have been made to overcome such obstacles. For example, insulin was complexed with cyclodextrins (CD) in order to improve its solubility and stability in the form of a dry powder, after encapsulation into poly (D,L-lactic-co-glycolic acid) (PLGA) microspheres. Other examples include a delivery agent SNAC (sodium N-[8-(2-hydroxybenzoyl)amino] caprylate) that was incorporated with insulin, a hyaluronan-insulin complex was prepared and calcium phosphate-PEG-insulin-casein (CAPIC) particles were produced for oral delivery of insulin.Several manufacturers are working on pills. In these pills, special molecules were attached to the insulin to help to reach its destination either by reducing insulin break down or, escorting the insulin through the gastrointestinal lining, or both. NOBEX Corporation has applied the technology that permits them to deliver insulin orally as an orally absorbed, bioactive conjugate. It has been shown to be safe, rapidly absorbed and demonstrated dose-dependent, glucose-lowering effects in animal models, healthy volunteers and type 1 diabetic patients. Emisphere Technologies are also pursuing oral delivery as such oral route of insulin delivery takes advantage of the portal-hepatic route of absorption, as insulin would be delivered to the liver, hence acting directly on hepatic glucose production in the same way of normal physiological state**.**

## CONCLUSION

Though tremendous work has been done in development of novel insulin delivery, none other than injection (syringe) & insulin pen has gained popularity. However if the oral insulin or inhalation grab the success in development, will definitely replace any other dosage form for insulin.

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