A REVIEW OF RECENT TRENDS IN NON-INVASIVE INSULIN THERAPY FOR DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus is generally a chronic condition associated with abnormally high levels of sugar (glucose) in the blood. Insulin is used for treating diabetes particularly of type I DM and selectively of type II DM patients. Presently available methods of administration of insulin are insulin syringes, insulin infusion pumps, jet injectors, insulin pens and the traditionally used method of administration i.e.; subcutaneous route are of invasive in nature. In order to reduce the pain of the patients, several approaches of non-invasive delivery of insulin are being developed. The newer non-invasive methods available are inhaled insulin, oral insulin, buccal insulin and transdermal delivery of insulin. This paper reviews the recent developments in noninvasive delivery of insulin with their formulation aspects and their advantages over invasive delivery of insulin. (DM- DIABETES MELLITUS).

KEY WORDS: Diabetes Mellitus, insulin, inhaled insulin, oral insulin, buccal route and transdermal route.

INTRODUCTION

Diabetes mellitus is a chronic condition associated with abnormal high blood sugar (glucose) levels. Normally diabetes is of two types. Type I DM/Insulin Dependent Diabetes Mellitus (IDDM) is due to body’s inability to produce insulin due to the autoimmune destruction of the beta cells in the pancreas. Type II DM/Noninsulin Dependent Diabetes Mellitus (NIDDM) is due to insulin resistance, inadequate insulin secretion and excessive or
inappropriate glucagon secretion. The former happens often in childhood, but it can also develop in adults in their late 30’s and early 40’s. While the latter mostly in adulthood and observed in children of about 2 years who is having a family history.[1] In type I diabetic patients, the treatment is based on administering insulin and diet control. For type II diabetic patients, although insulin is not required initially, but may require the administration of insulin because of decrease in the insulin secretion.[3, 4] These accounts for 7% of type 2 diabetic patients.[2]

Diabetes is emerging as a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with diabetes.[5, 6] In 2000, India (31.7 million) topped the world with the highest population with diabetes followed by China (20.8 million) with the United States (17.7 million) in second and third place respectively.[7] Globally, as of 2013, an estimated 382 million people have diabetes worldwide, with type 2 diabetes making up about 90% of the cases. This is equal to 8.3% of the adults population, with equal rates in both women and men. Worldwide in 2012 and 2013 diabetes resulted in 1.5 to 5.1 million deaths per year, making it the 8th leading cause of death.[8, 9] Diabetes overall at least doubles the risk of death.[10] The number of people with diabetes is expected to rise to 592 million by 2035. The economic costs of diabetes globally were estimated in 2013 at $548 billion and in the United States in 2012 $245 billion.[8]

Insulin is a hormone secreted from the β cells of the islets of Langerhans of pancreas. Insulin is a protein consisting of two polypeptide chains, one of 21 amino acid residues and the other of 30, joined by two disulfide bridges.[2] Insulin therapy is effective at lowering blood glucose in patients with diabetes. Insulin is a key player in the control of hyperglycaemia for type 1 diabetes patients and in selective patients with type 2 diabetes.[11] Discovery of insulin was considered as the most successful step in the history of diabetes treatment. It was isolated in 1921 and clinically used in 1922.[12] The major achievements in this area include the synthesis of human insulin analogues by recombinant DNA technology.[11] Insulin which is very close to human insulin is porcine insulin.

Currently available forms of insulin delivery include insulin syringes, insulin infusion pumps, jet injectors and pens.[11] Subcutaneous route is the most commonly used route of administration of insulin. The main drawback of these methods is of invasive nature and generally in type I diabetes, a patient should take insulin two to three times daily and also may be taken in the form of multiple injections. Due to this there is a chance of developing
hypoglycaemia and cases of hypoglycaemia are observing very often. In order to decrease the suffering of patient, new ways of administration are developed such as supersonic injectors, infusion pumps, sharp needles, and pens [13]. But they are also of invasive type and in turn develop a problem of patient compliance, medication adherence and patient inconvenience in administering insulin. So, there is a need of developing alternative methods of administration and this leads to the development of non-invasive methods of insulin administration in order to increase the patient compliance, medication adherence etc. Generally the route of administration is said to be succeeded when its ability to increase effectiveness and lowering the blood glucose levels and finally reducing the diabetic complications. [13]

This review discuss about the recent developments in the non-invasive routes of administration of insulin for diabetes mellitus.

**Inhaled Delivery Of Insulin**
Generally lungs are having a larger surface area (approximate of about 100 square metres) and acts as an ideal target for insulin delivery [13]. The first attempt to deliver insulin by inhalation was made more than half century ago [14]. 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 [15, 16]. In this mode of administration the drug has a relatively faster onset of action than subcutaneous route. Inhaled insulin has longer glucose lowering activity [17]. Generally insulin inhalers work as asthma inhalers. These products are generally available in two forms as dry powder formulations and solutions [11]. Each of these formulations is prepared basing on regular human insulin [18].

**Exubera** is a rapid acting insulin product for pulmonary delivery in powder form approved by FDA (food and drug administration). It consists of mainly mannitol as stabilizer. This powder is packed into single-dose blisters containing 1 or 3 mg of insulin [19]. The bioavailability of this product is about 10% when compared to regular human insulin given by subcutaneous route with duration of action between 5-10 hours [14]. A patient preference study, by comparing utility scores of two groups of control and test showed that a majority prefers the inhaled route is more convenient than injectable route [20]. But there are minor problems which stopped the development of this new method of administration such as high cost of the inhaler, size of the device and mostly of fear about lung safety [21, 22].
Afrezza is recombinant human insulin, using the technosphere concept. It is administered with the help of a mankind’s next generation inhaler called as Dreamboat. Technosphere is a drug delivery system created by micro particles (2-3 µm), which form microspheres, which are then lyophilized into a dry powder for inhalation\textsuperscript{[23]}. Technosphere insulin is an inhaled form of regular human insulin with a rapid onset of action (15 min) that is being considered for approval for the treatment of type 1 and type 2 DM and is currently in phase 3 clinical trials. Technosphere insulin was reported to be well tolerated by the patients in clinical trials. Rates of hypoglycemia and weight gain were similar to other insulin regimens\textsuperscript{[11]}.

The AERx insulin Diabetes Management System (AERx iDMS) delivers a liquid form of human insulin. In this single use insulin stripes are combined with a hand-held, breathe activated, microprocessor-controlled device which delivers a low velocity, fine particles aerosol spray\textsuperscript{[24]}. The need for holding breath for better drug delivery is not required with this method. The bioavailability is shown to be about 13-17\textsuperscript{%}\textsuperscript{[18, 24]}. Aerodosis insulin is designed to deliver the proprietary liquid formulation with dose adjustment facilities according to dose requirements\textsuperscript{[18]}. A study in type II DM patients showed relative bioavailability of about 21\textsuperscript{%} with this device\textsuperscript{[25]}.

Inhaled insulin is more rapidly absorbed when compared to a insulin given by subcutaneous route with peak concentrations achieving within 49-65 min. This can be compared with lispro and aspart. The duration of action is slightly less than the subcutaneously administered insulin\textsuperscript{[18]}, so a patient may inhale the dose 5-10 min before a meal to achieve beneficial glycemic control but should be used in combination with a once daily injection of long acting insulin\textsuperscript{[19]}. The major drawbacks of inhaled insulin are:

1. The loss of drug within the inhaler and mouth during inhalation.
2. Rate of absorption varies with age differences, respiratory tract infections an smoking.
3. Also a risk of developing anti insulin antibodies against inhaled insulin.
4. Very high doses of insulin may need to achieve the beneficial glycemic control, since the bioavailability of inhaled insulin is relatively low.
5. It can increase the financial burden on patients.

Some side effects are also reported with inhaled insulin (Exubera) are mild to moderate cough which disappears with increase of exposure. Others include shortness of breath, sore throat and dry mouth. As there is a problem of hypoglycaemia patients should carefully monitor their blood sugars regularly\textsuperscript{[19]}. 
Setter et al. studied the clinical pharmacokinetics, tolerability, adverse events, dosage and administration, comparative efficacy, and cost of inhaled dry powder insulin. They concluded that it provides a better control of HbA1c\textsuperscript{[26]}. Leal et al. compared the role of rapid-acting insulin analogues and inhaled insulin in the treatment of diabetes. They concluded that use of rapid-acting insulin analogues gives a good control of higher glucose level. They also concluded that it also reduces the cardiovascular risk conditions\textsuperscript{[27]}. Skyler et al. studied the safety of pulmonary route when exubera, that is, inhaled human insulin is administered by the young patients with insulin dependent diabetes mellitus. They concluded that exubera had no adverse effect on lung function\textsuperscript{[28]}.  

**Oral Delivery Of Insulin**

Since the initial discovery of insulin by Banting and Best in 1922, an oral form of insulin was the main goal. Generally for any drug oral route is the most convenient method of administration and best patient complying method. Development of oral delivery of insulin is still under research. Administration of insulin through oral route avoids the pain due to injection (in subcutaneous administration), anxiety due to needle, and infections which may be developed due to the contamination of the needle.

Insulin as a protein encounters difficulty to be delivered in oral form due to degradation by acidic pH of the stomach and many digestive enzymes in the stomach and small intestine. This leads to less bioavailability of insulin. Metabolism or degradation of insulin takes place by Insulin degrading enzymes (IDEs) like pepsin, trypsin, chymotrypsin which are also known as cytosolic enzymes. To overcome these problems three approaches could be possible by changing the physicochemical properties of the insulin for example lipophilicity, cross linking with macromolecules, use of carrier systems.\textsuperscript{[17]}

Different types of enzyme inhibitors, like sodium cholate, camostatmesilate, bacitracin leupeptin, FK-448, have been used to prevent insulin metabolism so that more amount of insulin is available for absorption\textsuperscript{[29-33]}. Different types of penetration enhancers can be used to increase the absorption of insulin \textit{via} intestinal epithelium. Excipient such as surfactants (ethylenediaminetetraacetic acid) has been used to increase the absorption of insulin. In some study intestinal permeation enhancers like mucoadhesive polymers have been used for mucosal delivery of insulin\textsuperscript{[34]}. Different types of carriers like liposomes, microspheres, and nanoparticles have been used for delivery of protein. Insulin was incorporated in these carriers to prevent its gastrointestinal degradation. By this approach the absorption and
bioavailability of insulin can be enhanced \[^{35}\]. Hydrogels have also been used as carrier that protects insulin degradation in acidic environment of stomach and allows safe transportation in the intestine.\[^{36}\]

Nanoparticles are used as insulin carriers and this technology is a new and developing subject to deliver insulin. The percentage of insulin and polymer in this mode of administration plays an important role in therapeutic efficacy of insulin. In vitro studies showed that nanoparticles protect the insulin through enzymatic degradation. Polymers mainly used in formulation of nanoparticles are polyalkylcyanoacrylate, polymethacrylic acid, and polylactic-co-glycolic acids (PLGA). Polymers like chitosan, alginate, gelatin, albumin, lectin, and so forth are also used which are found naturally. Among these chitosan has a good permeation property. In a diabetic rat model nanoparticle with chitosan significantly reduces the blood glucose level \[^{37}\]. Emulsions or double emulsion technique, solvent evaporation, or spray drying are the presently available methods of preparation of these devices. Some factors should be optimized during preparation of these devices like release rates and encapsulation efficiency to improve their therapeutic efficacy \[^{38}\]. Insulin delivery from oral delivery devices is a better approach to overcome the frequent administration of subcutaneous injections of insulin. Polymeric devices have been widely used for oral insulin delivery through hydrogels, nanoparticles, or microparticles.

Biocon (Bangalore, India) is manufacturing IN-105, which is in late phase 3. IN-105 is human recombinant insulin conjugated with polyethylene glycol via an acetyl chain. It is orally bioavailable and stable at ambient conditions. Preclinical studies in different species have shown good levels of efficacy and safety. Its maximal circulating insulin levels after oral administration of 5 mg were observed after 20 minutes, and the maximum drop in glucose occurred at 40 minutes after oral administration. Phase 1 and phase 2 trials demonstrated that the absorption of IN-105 and the reduction in blood glucose levels were proportional to the dose administered.\[^{39}\]

Prusty et al. prepared the nanoparticles incorporated with insulin by the complex coacervation method. They have been studied antidiabetic activity of orally administered insulin in rats. These nanoparticles have been evaluated for efficiency, particle size, and \textit{in vitro} release studies, \textit{in vivo} pharmacological studies, pharmacokinetic evaluation, and biochemical parameters. \textit{In vivo} antidiabetic studies showed the significant reduction of serum glucose level. This serum glucose level was sustained for longer period of time. Oral
bioavailability was found to be less than 50% but the pharmacological effects of insulin have been noticed for a longer period of time with the nanoparticle as compared to parenteral insulin administration. They concluded that 10 IU/Kg of orally administered insulin given to diabetic rats which is incorporated in nanoparticles shows a maximum change in glucose level of at a time period of 5 hours \(^{[40]}\).

Najafzadeh et al. evaluated efficacy of formulation of insulin having polar and nonpolar ingredients which has been administered by oral route. They concluded that novel excipients used in formulation prevent the degradation of insulin from gastric enzymes. This formulation significantly reduces the concentration of glucose in blood plasma in healthy and diabetic rats \(^{[41]}\).

Elsayed et al. investigated possibility of administration of insulin by oral route by using nanocapsulation and use of vehicle having oily phase. They concluded that orally administered nanoparticles increase effectiveness of insulin administered by oral route \(^{[42]}\).

Mundargi et al. investigated that copolymeric hydrogels which are pH sensitive synthesized from N-vinylcaprolactam and methacrylic acid monomers through free radical polymerization result in 52% encapsulation efficiency. In in vivo studies diabetic rats, those induced by alloxan, showed 50% biological inhibition and 44% inhibition by glucose tolerance test \(^{[43]}\).

**Buccal Delivery Of Insulin**

The inner lining of cheeks is called as buccal mucosa and transmucosal delivery is a suitable form for noninvasive administration of insulin. In this route the drug is delivered through an aerosol spray into the oral cavity. This makes the difference from normal inhalers. Factors that influence the absorption potential are molecular weight, hydrophilicity, conformation stereo specificity, solubility, electrostatic charge, and partition coefficient of proteins and peptides \(^{[44]}\). In this type of delivery the insulin is absorbed in mouth and throat through a device which delivers the insulin in spray form \(^{[48-52]}\). In the buccal mucosa the blood supply in reticulated veins is very high, so absorption will be also high and this route prevents hepatic first pass metabolism. Delivery by inhaler containing high pressure droplets of insulin to the back of the throat is beneficial. Due to low permeability of buccal mucosa more puffs are required for optimum drug delivery \(^{[45]}\).
In vivo studies performed on diabetic rats showed promising results with stable blood glucose profile with a significant hypoglycemic response after 7 h \cite{46}. Similar studies in the rabbit and rat have shown that buccal spray of insulin is an effective insulin delivery system, which is promising for clinical trial and future clinical application \cite{47}. Though results are promising in rat models, rats are not appropriate models as rats have a keratinized buccal mucosa. The only animal models comparable to the human buccal permeability are pigs. The continuous, but variable, saliva flow and the robust multilayered structure of the oral epithelium constitute another effective barrier to penetration of drugs.

Pelleted nanoparticles have been used for buccal administration of insulin due to their 3D structural conformity and coherence and also facilitate buccal application and adherence \cite{53}. At present buccoadhesive tablets using compression of powder mixes (carbopol 934, hydroxylpropyl methylcellulose, and few absorption promoters) have been used for insulin delivery by buccal route, but patches are considered to be better than tablets as these are thin and flexible. It also consists of drug reservoir and bioadhesive surface. In this enhancer, sodium deoxycholate is used for better permeation. Next to the patches, films are also better than adhesive tablets but the main drawback observed was they are very weak in nature and breaks in the mouth. Bilayered system of insulin delivery is sponges. These sponges are also mucoadhesive (chitosan layer and impermeable ethyl cellulose layer), porous, and flexible. By modifying formulation variables, for example, type of chitosan salt insulin content molecular weight, we can control \textit{in vitro} release properties from sponges. For insulin buccal spray soybean lecithin and propanediol are used. Studies show that intracellular and paracellular, both routes, have been used in the passage of FITC (fluorescein isothiocyanate) insulin through buccal mucosa \cite{54–56}.

Oral-lynTM

Generex Biotechnology Corporation (Toronto, Canada) is developing a buccal insulin formulation based on RapidMistTM, an advanced buccal drug delivery technology \cite{39}. Only marketed buccal insulin formulation is Oral-lyn. It is a liquid formulation and is used with a propellant. Rapidmist technology is used for insulin delivery which sprays insulin directly in the mouth towards throat and it delivers aerosols of high velocity so that it is absorbed rapidly by buccal mucosa into the systemic circulation \cite{54–56}. Prasanth et al. developed a buccal insulin drug delivery system by using a mucoadhesive polymer, locust bean gum to increase the permeability and effectiveness of insulin. Therapeutically this has been acting as
adsorbent, demulcent, and stabilizer. Buccal tablets of insulin were prepared by using a direct compression method. By using various evaluation parameters like in vitro bioadhesion study, drug release, drug permeation, and in vivo study, it has been concluded that locust bean gum, DME500 (dimethyl ether), and PEG (polyethylene glycol) were suitable enhancers for buccal insulin drug delivery.[57]

**Transdermal Delivery Of Insulin**

Transdermal insulin delivery is a very attractive non-invasive, needle-free alternative choice for the invasive parenteral route and other alternative routes such as pulmonary and nasal routes of administration. The main strategy of transdermal insulin delivery includes passive delivery of insulin, usage of patch, cream, and spray forms are recommended and it requires a day to diffuse through the skin and to show systemic effect. The outermost layer of the skin, Stratum corneum limits the permeability of compounds to small, lipophilic molecules and acts as the major barrier for permeability of other drugs. In order to overcome this problem and enhance the permeability of skin, there is a healthy development in physical and chemical enhancement techniques. They are

**Iontophoresis**, is a technique that enhance the transdermal delivery of compounds through the skin via the application of a small electric current.

**Ultrasound/Sonophoresis**, uses ultrasound and it has been shown to increase skin permeability to various low and high molecular weight drugs, including insulin. However, its therapeutic value is still being evaluated.

**Microneedles**, offers a cost-effective, minimally invasive, and controllable approach to transdermal insulin delivery. It involves the creation of micronized channels in the skin, and therefore disturbs the stratum corneum barrier. Upon creation of the microchannels, interstitial fluid fills up the channels, resulting in hydrophilic pathways. Microneedles deliver the drug into the epidermis without causing any damage or disruption of nerve endings [60]. Microneedles have been regarded as a healthy technology approach to be used either alone or with other enhancing techniques such as Electroporation and Iontophoresis, as well as with different drug carriers (lipid vesicles, micro- and nanoparticles) [58]. As Microneedles inserted into the skin of human subjects are reported to be painless, microneedles are considered as a promising technology to deliver drugs into the skin [59].

**Microdermabrasion**, is a method to increase skin permeability for transdermal drug delivery by damaging or removing skin’s outer layer, stratumcorneum. Microdermabrasion can increase skin permeability to deliver insulin [61].
The advantages of transdermal delivery of insulin includes
1. Convenience
2. Good patient compliance
3. Prolonged therapy and
4. Avoids liver’s first-pass metabolism and degradation in the gastrointestinal tract.

The main drawback of the transdermal drug delivery is that insulin molecules are large enough to penetrate the skin at therapeutically useful rates. This requires the usage of Microneedles as said above as one of enhancing techniques available.[11]

CONCLUSION
The main aim of insulin therapy is glycemic control. Presently available methods lead patient to fear about increased risk of hypoglycaemia due to multiple injections, and also raises medication adherence issues. Additionally, the invasive nature of the traditionally used methods remains as an obstacle for patients. Recent alternatives developed in insulin therapy have potential for reducing some of the negative aspects of current methods. Oral insulin in particular could prove to be promising alternative method, especially with nanotechnology allowing for several types of encapsulations to bypass the gastric acidic environment. Oral delivery offers the benefits of ease of administration by increasing the acceptance of patient, improved absorption rates, and mimicry of the normal route of insulin through the liver.

Apart from few drawbacks, inhaled insulin is also a good achievement in the field of noninvasive delivery of insulin due to its good absorptive nature, fast onset of action, longer blood glucose lowering activity and also has a potential to treat postprandial hyperglycemia effectively when compared to traditionally administered subcutaneous route.

Oral-lyn which is a liquid formulation, is presently marketed buccal route insulin product. In this rapidmist technology is used for insulin delivery which sprays insulin directly in the mouth towards throat and it delivers aerosols of high velocity so that it is absorbed rapidly by buccal mucosa into the systemic circulation.

Transdermal delivery of insulin is also a beneficial development in noninvasive therapy of insulin in improving the patient convenience, compliance, prolonged therapy, also avoids liver’s first pass metabolism and degradation of insulin in gastrointestinal tract. The main drawback of the transdermal drug delivery is that insulin molecules are large enough to penetrate the skin at therapeutically useful rates, hence it requires the usage of Microneedles.
as an enhancing technique. From this review we have concluded that there is a need of developing noninvasive therapy of insulin for diabetes mellitus, as it has greater advantages than existing invasive therapy of insulin.

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