Diabetes mellitus: A journey of insulin

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ABSTRACT
Diabetes mellitus is a chronic ailment that impairs the production of or response to insulin, a hormone that helps to convert food into energy. Its complications are responsible for excess morbidity and mortality, loss of independence and reduce quality of life. Among the major cause of disablement and early death are ischemic heart disease, retinopathy, nephropathy, peripheral vascular disease and neuropathy. Insulin replacement therapy has been used in the clinical management of diabetes mellitus for more than 85 years. As subcutaneous injection is a painful episode so various approaches like transdermal, pulmonary, intranasal, colon targeted delivery, oral delivery is tried as an alternative way. Among them oral delivery is the challenging one because insulin cannot administered orally due to rapid enzymatic digestion in stomach. For oral delivery various technology, formulation and various modification approaches are going on. It is high time to invent an acceptable non-invasive insulin delivery for the diabetes to improve patient compliance and decrease the morbidity.

Key Words: Insulin, Approaches, Obstacles, Route of administration, Non-invasive.

INTRODUCTION
Diabetes mellitus is a common disease and its complications are responsible for excess morbidity and mortality, loss of independence, and reduced quality of life (Giriraj et al., 2003; Ahmed et al., 2006). Diabetes mellitus is a serious pathologic condition that is responsible for major healthcare problems worldwide and costing billions of dollars annually. The prevalence of diabetes continues to increase steadily as more people live longer and grow heavier. Type-1 diabetes comprises those forms of diabetes that are primarily due to insulin deficiency. Type-2 diabetes comprises those forms that result from a primary defect in insulin resistance (often associated with obesity), coupled with a relative insulin deficiency. Eventually, progressive loss of insulin producing β-cell of pancreas function in type-2 diabetes creates an absolute insulin deficiency and complicated by glucose (glucosamine) and lipid mediated toxicities.

The American Diabetes Association recently recommended an etiological classification of diabetes (2003). Type I diabetes normally occurs in childhood, has relatively acute onset, and requires insulin for survival. Insulin is a hormone made by the pancreas. With each meal insulin is released to help the body use or store the glucose (sugar) it gets from food. People with type I diabetes make no insulin. People with type II diabetes make some insulin. For many people with type 2 diabetes the insulin has a harder time working.

THE HISTORY OF INSULIN
Nearly 100 years have passed since Von Mering and Minkowski first demonstrated that pancreatectomized dogs exhibited signs and symptoms characteristic of diabetes mellitus (Banting et al., 1922; Dhawan et al., 2009). The brief history of different approaches regarding insulin is tabulated in table 1.

ROUTE OF ADMINISTRATION OF INSULIN
Subcutaneous route is the present mode of administration of insulin. Other non-invasive mode of administration is under investigation though
pulmonary delivery show similar efficacy to injected insulin.

Subcutaneous route
The present mode of insulin administration is by the subcutaneous route by which insulin is presented to the body in a non-physiological manner. Insulin injected subcutaneously at least twice a day is having many inherent disadvantages include local pain, inconvenience of multiple injections, and occasional hypoglycemia as a result of overdose, itching, allergy, hyperinsulinemia, and insulin lipodystrophy around the injection site. Lastly, clinical trials have shown that even on injectable insulin treatment, a significant percentage of patients fail to attain lasting glyemic control due to non-compliance (Pamnani et al., 2008).

Approaches for Non-invasive Insulin Delivery
Despite the newer insulin formulations and strategies that allow the clinician to mimic normal endogenous insulin secretory profiles, intensive insulin therapy has not achieved widespread acceptance because of barriers to its use from both patients and physicians. Specifically, there may be concerns from the patient about fear, inconvenience, pain or the anxiety of insulin injections (Graff et al., 1998; Maisey et al., 1999). Furthermore, the patient may feel as if they are advancing to insulin therapy because they have been noncompliant with their treatment regimen (Hunt et al., 1997).

Transdermal approach
There are several methods for transdermal delivery of insulin. Pulsatile insulin uses microjets to pulse insulin into the patient, mimicking the physiological secretions of insulin by the pancreas (Arora et al., 2007).

<table>
<thead>
<tr>
<th>Year</th>
<th>Events</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1921</td>
<td>Fredrick G. Banting, Charles H. Best, J.J.R. Macleod and James B. Collip discovered insulin, a peptide which lowers blood sugar.</td>
<td>Bliss et al., 1982</td>
</tr>
<tr>
<td>1922</td>
<td>Bovine insulin was first administered to human.</td>
<td>Bliss et al., 1982</td>
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<tr>
<td>1936</td>
<td>Development of protamine, slow release insulin.</td>
<td>Jersild et al., 1956</td>
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<tr>
<td>1944</td>
<td>Standard syringe was released.</td>
<td>Maheux</td>
</tr>
<tr>
<td>1950</td>
<td>Isophane NPH (neutral protamine Hagedorn) insulin.</td>
<td>Jersild et al., 1956</td>
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<tr>
<td>1951</td>
<td>Amorphous ‘lente’ insulins (IZS) – semilente, lente and ultra-lente – were developed.</td>
<td>Jersild et al., 1956</td>
</tr>
<tr>
<td>1956</td>
<td>First antidiabetic oral drug – sulfonamide was invented.</td>
<td>Spencer et al., 1956; Ho et al., 1991; Balsells et al., 1997</td>
</tr>
<tr>
<td>1963-1966</td>
<td>Human insulin was chemically synthesized.</td>
<td>Meienhofer et al., 1963; Kung et al., 1966; Katsoyannis et al., 1966</td>
</tr>
<tr>
<td>1970</td>
<td>Insulin pump was first used.</td>
<td>Teuscher et al., 1974</td>
</tr>
<tr>
<td>1974</td>
<td>Highly purified animal insulin (less than 1 pmol/L of protein impurities) was introduced.</td>
<td>Maheux</td>
</tr>
<tr>
<td>1975</td>
<td>Fully synthetic insulin (CGP 12 831) was synthesized.</td>
<td>Teuscher et al., 1979</td>
</tr>
<tr>
<td>1978</td>
<td>Insulin production started from E. Coli.</td>
<td>Keen et al., 1980</td>
</tr>
<tr>
<td>1980</td>
<td>First recombinant DNA ‘human’ insulin.</td>
<td>Keen et al., 1980</td>
</tr>
<tr>
<td>1982</td>
<td>FDA approved Humulin R (rapid) and Humulin N (NPH).</td>
<td>Maheux</td>
</tr>
<tr>
<td>1986</td>
<td>Insulin pen was first introduced.</td>
<td>Maheux</td>
</tr>
<tr>
<td>2006</td>
<td>Pfizer invented inhaled insulin - Exubera®.</td>
<td>Imam, 2011</td>
</tr>
</tbody>
</table>

Figure 1: Distribution of diabetic patients according to age group.
Intranasal Approach
Delivery of insulin using an intranasal approach was first suggested over 65 years ago, but it was not until the 1980s that this approach was seriously evaluated (Major et al., 1995; Saudek et al., 1997). Feasibility has been demonstrated, as intranasal insulin (60 or 120U) given pre-meal to 17 patients with type 2 diabetes and compared with placebo resulted in reductions in postprandial glucose at both 60 and 120 minutes (Coates et al., 1995). However, the major limitation of this approach is poor bioavailability across the mucous membranes. This was demonstrated in studies by Hilsted et al. (1995) as they reported doses of intranasal insulin that were approximately 20 times higher than those needed with subcutaneous injection. To overcome the problem of limited bioavailability, absorption-enhancing compounds such as bile salts and polyethylene ether derivatives have been evaluated for nasal insulin and have resulted in increased absorption and effective biological activity. It appears, however, that the chance of nasal irritation has increased with these changes (Gizurarson et al., 1991; Jacobs et al., 1993). The feasibility of intranasal insulin has been demonstrated, but limitations do exist and further studies are needed to establish long-term safety and efficacy.

Colon-targeted delivery systems
Proteolytic enzymes in the stomach degrade insulin, but in intestines peptidase activity is low and drainage into lymph is maximized. Researchers are exploring colon-specific delivery for insulin. To achieve colon specific delivery of insulin, Hideyuki prepared azopolymer-coated pellets containing...

Figure 2: Route of administration of Insulin (Cefalu et al., 2004; Dhawan et al., 2009; Kinesh et al., 2010).

Figure 4: Different types of transdermal approaches (Golden et al., 1988; Mitragotri et al., 1995; Saudek et al., 1997; Stieber et al., 1998; Kanikkannan et al., 1999; Bohannon et al., 1999; Rosenstock et al., 2001; Dixit et al., 2007).

Figure 5: Intranasal route for insulin delivery.
In vitro drug-release experiments were carried out according to Japanese Pharmacopoeia XII (rotating basket method). The release of FD-4 from the pellets in phosphate buffered saline was very small. However, the release of FD-4 was markedly increased in the presence of rat caecal contents. The pharmacodynamic studies of the azopolymer-coated pellets containing these peptides with camostat mesilate (protease inhibitor) were carried out by measuring the hypoglycemic effects. A slight decrease in plasma-glucose levels was observed following the oral administration of these pellets containing 12.5 IU of insulin compared with the same dose of insulin solution. The authors concluded that azopolymer-coated pellets with protease inhibitor might be useful carriers for the colon-specific delivery of insulin.

Yakugaku Zasshi developed two types of microcapsular devices containing new acrylate-based nanogels with a specific solute-permeability for the delayed- or thermosensitive-release of peptide drugs (Ichikawa et al., 2007). A nanogel-particle of acrylic terpolymer, ethyl acrylate-methyl methacrylate-2-hydroxy-ethyl methacrylate, was newly synthesized by emulsion polymerization to construct delayed-release microcapsules. The insulin-loaded lactose particles were spray coated with the acrylic terpolymers. These microcapsules showed a pH-in-dependent delayed-release profile.

**Pulmonary approach**

Finally, insulin delivered through the oral cavity can also be considered to have its uptake in the pulmonary bed. However, the idea of pulmonary delivery of insulin is not a new idea, as the first report of inhaled insulin was noted in 1925 (Über et al., 1925) truly remarkable given that this was reported very shortly after the first clinical use of insulin. (Banting et al., 1922) The high permeability of the lung’s large surface area makes it an ideal route for the administration of insulin. The lung has hundreds of millions of alveoli that are richly vascularised and where drug absorption takes place. In addition, the surface area is quite large, as the alveolar capillaries provide a total surface area of 50-140m² for absorption (Heinemann et al., 2002).

Insulin delivered in this way is believed to be transported across the alveolar cells by transcytosis, but this has yet to be conclusively proven. Once
deposited in the alveoli, the inhaled insulin molecules are taken up into vesicles, transported across the epithelial cells and then released into the interstitial fluid between the epithelium and the alveolar capillary endothelium. The insulin is once again taken up into vesicles, transported across the capillary endothelium and released into the bloodstream, where it exerts a rapid systemic effect (Wigley et al., 1971; Pilcher et al., 1987; Klonoff et al., 1999). This process is extremely rapid and pulmonary uptake results in a very rapid peak in insulin levels, that is, after 15-20 minutes (Enzmann et al., 1984; Adams et al., 1992). Therefore, the physiological and anatomic barriers that limit successful implementation of other routes of non-invasive insulin delivery do not appear to be a major concern when one considers the feasibility of pulmonary delivery of insulin, based in large part on the favorable anatomy of the lung.

Inhaled insulin claimed to have similar efficacy to injected insulin, both in terms of controlling glucose levels and blood half-life. Currently, inhaled insulin is short acting and is typically taken before meals; an injection of long-acting insulin at night is often still required (Nice et al., 2006). When patients were switched from injected to inhaled insulin, no significant difference was observed in HbA1c levels over three months. Accurate dosing was a particular problem, although patients showed no significant weight gain or pulmonary function decline over the length of the trial, when compared to the baseline (Cefalu et al., 2001).

The Exubera® insulin formulation is a spray-dried, amorphous insulin powder containing 60% insulin in a buffered, sugar based matrix. In January 2006, Pfizer and its partner Nektar Therapeutics received marketing approval for Exubera®, their insulin DPI. It was available from September 2006 to October 2007 in the United States. It is licensed for use by both type 1 and type 2 diabetes patients. As of October 18, 2007, Pfizer has announced that it will no longer manufacture or market Exubera®, because it failed to gain acceptance of patients and physicians (Imam, 2011).

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**Table 2: Characteristics of modern insulin formulation** (Illinois Extension, 2003; Cefalu et al., 2004; Modi et al., 2007).

<table>
<thead>
<tr>
<th>Insulin formulation</th>
<th>Mechanism of action</th>
<th>On set of action</th>
<th>T&lt;sub&gt;max&lt;/sub&gt;</th>
<th>Duration of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro/Aspart®</td>
<td>Dissociates into monomeric formulation leading to rapid absorption</td>
<td>5-15 min</td>
<td>1-2 hr</td>
<td>4-6 hr</td>
</tr>
<tr>
<td>Human regular®</td>
<td>Unknown</td>
<td>30-60 min</td>
<td>2-4 hr</td>
<td>6-10 hr</td>
</tr>
<tr>
<td>NPH/Lente®</td>
<td>Produces insulin through hormone conversion</td>
<td>1-2 hr</td>
<td>4-8 hr</td>
<td>10-20 hr</td>
</tr>
<tr>
<td>Human ultralente®</td>
<td>Unknown</td>
<td>2-4 hr</td>
<td>Unpredictable</td>
<td>16-20 hr</td>
</tr>
<tr>
<td>Glargine®</td>
<td>Unknown</td>
<td>1-2 hr</td>
<td>Flat</td>
<td>Up to 24 hr</td>
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</table>
Table 3: Different approaches of oral insulin delivery.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Approaches</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depending on barrier</td>
<td>Enzyme Inhibitors</td>
<td>Fuji et al., 1985; Saffran et al., 1986; ziv et al., 1987; Yamamoto et al., 1994; Patki et al., 1996; Chang et al., 1999; Agarwal et al., 2001; Shah et al., 2002; Liu et al., 2003; Tiesca et al., 2006</td>
</tr>
<tr>
<td>Penetration Enhancers</td>
<td>Koosaput et al., 1999; Schiling et al., 1999; Soltero et al., 2001; Thanou et al., 2001; Eaimtarakam et al., 2002; Plate et al., 2002; Gowthamarajan et al., 2003; Salamat-Miller et al., 2005; Torisaka et al., 2005; Rieux et al., 2006; Lin et al., 2007</td>
<td></td>
</tr>
<tr>
<td>Dosage form stability</td>
<td></td>
<td>Pearlman et al., 1991; Agarwal et al., 2001</td>
</tr>
<tr>
<td>Technology dependent</td>
<td>Liposomes</td>
<td>Choudhari et al., 1994</td>
</tr>
<tr>
<td></td>
<td>Coated liposomes</td>
<td>Cantenys et al., 1983; Ramadas et al., 2000; Ye et al., 2000; Wu et al., 2004; Zhang et al., 2005</td>
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<td></td>
<td>Hydrogel</td>
<td>Yung et al., 2001; Dorkoosh et al., 2002; Nakamura et al., 2004; Kavimandan et al., 2006</td>
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<td></td>
<td>Nanoparticle</td>
<td>Damage et al., 1997; Attivi et al., 2005; Sarmento et al., 2006; Tiyaboonchai et al., 2006; Damage et al., 2007; Chalasani et al., 2007; Lin et al., 2007; Cui et al., 2007; Simon et al., 2007</td>
</tr>
<tr>
<td></td>
<td>Erythrocytes</td>
<td>Al-Achi et al., 1998</td>
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<tr>
<td></td>
<td>Nanocubicles</td>
<td>Chung et al., 2004</td>
</tr>
<tr>
<td></td>
<td>Microparticles</td>
<td>Lowman et al., 1999; Tozaki et al., 2001; Peppas et al., 2004; Qi et al., 2004; Senthil et al., 2004; kim et al., 2005; Reis et al., 2007; Ubaidulla et al., 2007</td>
</tr>
<tr>
<td></td>
<td>Mucoadhesive system</td>
<td>Whitehead et al., 2004</td>
</tr>
<tr>
<td>Formulation dependent</td>
<td>Tablet</td>
<td>Krauland et al., 2004</td>
</tr>
<tr>
<td></td>
<td>Microemulsions</td>
<td>Cho et al., 1989; Ritschel et al., 1992; Torisaka et al., 2005</td>
</tr>
<tr>
<td></td>
<td>Oral insulin pills</td>
<td>Kinesh et al., 2010</td>
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<tr>
<td></td>
<td>Oral spray</td>
<td>Kinesh et al., 2010</td>
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</table>

**ORAL DELIVERY: THE CHALLENGE**

**Obstacles of Oral insulin Delivery**

Generally, peptides and proteins such as insulin cannot be administered via the oral route due to rapid enzymatic degradation in the stomach, inactivation and digestion by proteolytic enzymes in the intestinal lumen, and poor permeability across intestinal epithelium because of its high molecular weight and lack of lipophilicity (Nakamura et al., 2004; Jain et al., 2005; Sajeesh et al., 2006). The oral bioavailability of most peptides and proteins therefore is less than 1%. The challenge here is to improve the bioavailability to anywhere between 30-50% (Lee et al., 1991).

**Enzymatic Barrier**

The harsh environment of the gastrointestinal tract (GIT) causes insulin to undergo degradation. This is because digestive processes are designed to breakdown proteins and peptides without any discrimination (Tuesca et al., 2006). Insulin therefore undergoes enzymatic degradation by pepsin and pancreatic proteolytic enzymes such as trypsin and α-chymotrypsin (Patki et al., 1996; Agarwal et al., 2001). Overall, insulin is subjected to acid catalyzed degradation in the stomach, luminal degradation in the intestine and intracellular degradation. The cytosolic enzyme that degrades insulin is insulin-degrading enzyme (IDE) (Chang et al., 1999). Insulin is however not subject to proteolytic breakdown by brush border enzymes (Agarwal et al., 2001). Insulin can be presented for absorption only if the enzyme attack is either reduced or defeated.

**Intestinal Transport of Insulin**

Another major barrier to the absorption of hydrophilic macromolecules like insulin is that they cannot diffuse across epithelial cells through lipid bilayer cell membranes to the blood stream (Lin et al., 2007). In other words, insulin has low permeability through the intestinal mucosa (Torisaka et al., 2005). There is no evidence of active
transport for insulin (Schilling et al., 1999). It has been found however that insulin delivery to the midjejunum protects insulin from gastric and pancreatic enzymes and release from the dosage form is enhanced by intestinal microflora (Koosapur et al., 1999; Schilling et al., 1999). Various strategies have been tried out to enhance the absorption of insulin in the intestinal mucosa and in some cases; they have proven successful in overcoming this barrier.

**Dosage form Stability**
The activity of proteins depends on the three dimensional molecular structure. During dosage form development, proteins might be subject to physical and chemical degradation. Physical degradation involves modification of the native structure to a higher order structure while chemical degradation involving bond cleavage results in the formation of a new product (Agarwal et al., 2001). Proteins must be characterized for change in conformation, size, shape, surface properties, and bioactivity upon formulation processing. Changes in conformation, size, and shape can be observed by spectrophotometric techniques, X-ray diffraction, differential scanning calorimetry, light scattering, electrophoresis, and gel filtration (Pearlman et al., 1991).

**Approaches for oral insulin delivery**
Most peptides are not bioavailable from the GIT after oral administration (Kinesh et al., 2010; Cho et al., 1989). Therefore, successful oral insulin delivery involves overcoming the enzymatic and physical barriers (Tuesca et al., 2006) and taking steps to conserve bioactivity during formulation processing (Agarwal et al., 2001). In developing oral protein delivery systems with high bioavailability, three practical approaches might be most helpful (Morishita et al., 2006):

1. Modification of physicochemical properties such as lipophilicity and enzyme susceptibility.
2. Addition of novel function to macromolecules.
3. Use of improved carrier systems.

**CONCLUSION**
Insulin is the only treatment for type-2 diabetes patient. From 1922 to till date various attempt have been made to achieve different route of administration of insulin. After subcutaneous route, inhalation route has comparable bioavailability but inhaler insulin is rejected by patient and physician. Now-a-days a lot of research subjected for oral delivery of insulin. Liposome, microemulsion, hydrogels, nanoparticles etc. have been investigated and prepared for the oral delivery of insulin.

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