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Review Article

A BRIEF PERSPECTIVE ON NON-INVASIVE ALTERNATIVE DELIVERY SYSTEMS FOR INSULIN THERAPY

Bhanu Chander Bejgum*

Frontida Biopharm, Inc.,1100 Orthodox st, Philadelphia, PA, 19124, USA

ABSTRACT

Development of patient compliant non-invasive insulin delivery systems has been an elusive goal for several decades. Though current insulin injection therapy is effective, the discomfort caused by repeated injections make patient compliance a major issue. An "insulin tablet" is a long awaited dream of several diabetic patients. However, no commercial per-oral delivery system of insulin is available in the market due to poor bioavailability of insulin administered per-orally. Several alternative non-invasive delivery routes were studied to improve the patient compliance, including mucosal routes such as buccal, pulmonary, nasal and vaginal routes. Some of these systems were shown to be clinically effective, however, could not mimic the physiological insulin secretions and showed variable bioavailability. Significant effort is in progress to develop alternative delivery systems with the improved bioavailability of insulin. This short review will give readers a brief knowledge on the progress of insulin alternative delivery systems and the challenges associated with these routes.

Keywords: Insulin; Alternative routes; Pulmonary insulin; Oral insulin spray; Transdermal insulin, Diabetes.

INTRODUCTION

According to World Health Organization (WHO) survey, there are around 422 million people affected with diabetes mellitus and WHO projects that by 2030 diabetes would be the

seventh leading cause of death (World Health Organization, 2011). Insulin is a peptide secreted by the pancreas and is the principle hormone that controls the glucose uptake by the cells from blood. A constant supply of insulin is necessary for the glucose homeostasis in the body. Insulin deficiency (type I) or insensitivity of its receptors (type II) leads to diabetes mellitus (Kang, S, *et al*., 1991). Insulin therapy is the main line treatment to maintain near-normal blood glycemic levels of diabetes patients. Currently, insulin injections are administered either subcutaneously or intravenously. Though these therapies are effective, patient compliance is the biggest issue because of the frequent need of injections. Several invasive technologies with minimum discomfort were developed for insulin delivery including insulin pumps, jet injectors, pens and IV injection systems (Owens, DR 2002 and Jeandidier, N, *et al*., 1999). More advanced systems such as Omnipod® insulin pumps are also available, and these pumps act in a closed loop that monitors blood glucose levels, and releases required amount of insulin automatically, mimicking natural insulin secretion from pancreas (Zisser, HC 2010). Recently FDA gave clearance to Companion Medical Inc novel first ever smart insulin delivery device, InPen® system, a wireless-enabled insulin pen with proprietary mobile application (Saint, S, *et al*., 2017). This smart system combines the features of insulin pumps and insulin pens with smart mobile features, which makes it easy and affordable to use. Even though these invasive routes are efficient, the need for frequency of administration and the need to educate patients about the delivery systems decrease patient compliance. The development of alternative non-invasive insulin delivery systems via buccal, sublingual, transdermal, pulmonary routes has been an elusive goal over past 70 years. Some of the progress and also the challenges involved in the delivering insulin through non-invasive alternative routes are briefly discussed in this report.

Per-oral route

The per-oral bioavailability of insulin is very low due to degradation in the acidic environment of the stomach and also by digestive enzymes in the intestine. As the molecular size of insulin is relatively larger than the small molecules, its absorption is limited by the permeability through the gastric mucosa (Jintapattanakit, A, *et al*., 2007). Several strategies to improve the stability of insulin in gastro intestinal tract were studied to increase intestinal absorption of insulin, including co-administration with permeation enhancers with/without

enzyme inhibitors, liposomal delivery systems, delivery through drug carriers, mucoadhesive systems, emulsions, polymer-based systems, nanoparticles and complexes (Khan Ghilzai, NM 2003 and Misra, GP, *et al*., 2015). For example, a novel drug-carrier molecule monosodium N-(4-chlorosalicyloyl)-4-aminobutyrate (4-CNAB) with insulin was formulated as capsules for oral delivery. This system was tested in ten male patients with type 2 diabetes and observed that absorption of insulin through GI was feasible with this delivery system under fasted conditions (Kapitza, C, *et al*., 2010). However, the inclusion of permeation enhancers and/or enzyme inhibitors would compromise barrier function of gastric mucosa and promote absorption of unwanted compounds. Much work with combinational delivery systems is in progress to improve per-oral absorption of insulin. Hence, the dream of "insulin tablet" is still a big challenge.

Oral (buccal and sublingual) delivery of insulin

The oral mucosa has relatively a large surface area (100-200 cm^2) to facilitate drug absorption and is easily accessible for patients (Washington, N, *et al*., 2000). Being larger in size, insulin and other peptide absorption from the oral mucosa is limited by poor permeation through the mucosal epithelium, which is the primary safety barrier for limited absorption of unwanted compounds in the oral cavity. Degradation of peptides by proteolytic enzymes present in the mucosa is another major reason for poor permeability of insulin (Lassmann-Vague, V, *et al*., 2006). Various permeation enhancers such as bile salts, surfactants, chelators, alcohol and fatty acids were used alone or in combination with bio adhesive delivery systems to improve the delivery of insulin (Owens, DR, *et al*., 2003). To maintain constant insulin levels in the blood, delivery systems should be in contact with buccal mucosa during the entire period of delivery, but involuntary swallowing of saliva reduces the retention time of the dosage form in the buccal cavity. Mucoadhesive patches were developed to keep these patches in contact with mucosa for an extended period. Gums, patches, sponges, tablets, films and gels are the various mucoadhesive systems that were studied with and without permeation enhancers (Kumria, R, *et al*., 2011). All these systems showed increased bioavailability of insulin to a certain extent (Gordon Still, J 2002) but few of them failed to show the prolonged duration of action and also the results were not reproducible primarily because of subject-to-subject variability. An interesting system developed by Generex was

Rapidmist™ technology to deliver drugs through the buccal route. Oral-Lyn™ is oral insulin spray that is available in the market in many countries (Brange, JJ, *et al*., 1997). Oral-lyn is a liquid formulation of human insulin placed in a metered dose inhaler. Rapidmist sprays insulin directly into buccal cavity in the form of micelles (<7 μm) that gets rapidly absorbed by the buccal mucosa. A kinetic study in type 1 and type 2 patients comparing insulin spray and subcutaneous injection showed that prandial (meal-time) glucose levels were similar to regular subcutaneous injection for a short period after the meal (Pozzilli, P, *et al*., 2005), thus making insulin spray a better alternative non-invasive system (Guevara-Aguirre, J, *et al*., 2007). This product is still in clinical trials and shows that there is an alternative to injectable insulin delivery for patients to control the glycemic levels during mealtime.

Pulmonary route

The pulmonary route has shown to be an effective route for delivery of several therapeutic agents due to the availability of large surface area of around 100 m^2 (Labiris, NR, *et al*., 2003). In addition, the alveolar region in lungs is highly vascular, and the thickness of the epithelium in this region is relatively smaller (0.1 to 0.2 μm), which makes this region a preferable site for absorption of molecules (<40kD) like insulin into the systemic circulation (Washington, N, *et al*., 2000 and Patton, J, *et al*., 2006). Also, the absence of peptidases and mucociliary clearance in this region are additional advantages for improving the bioavailability of compounds deposited in the alveolar region. The deposition of the inhaled particles is largely dependent on the median mass aerodynamic dynamic (MMAD) of aerosol particles. It is well known that particles with MMAD of 1.5-3 μm predominantly deposit in deeper airways and larger particles deposit in upper airways (Patton, JS, *et al*., 2007). Hence it is encouraging to design aerosols that deposit insulin in deeper lung regions.

Aerosol delivery of insulin was started in 1920, but the mechanism of drug delivery through lung was not very well studied at that time (Wigley, FM, *et al*., 1971). However, in recent years a significant development was seen in delivering insulin through the pulmonary route. Insulin was formulated into dry powder inhalers (DPI), metered dose inhalers (MDI), and aqueous mist inhalers (AMI) (Edwards, DA, *et al*., 1998). There were few products that made to clinical trials and one of them even made into the market. The dry powder inhaler of

insulin, Exubera® (White, S, *et al*., 2005) developed by Pfizer was thought to be a blockbuster device for alternative non-invasive delivery of insulin, however, it was recalled from the market due to safety issue. A brief description of this product will be helpful for readers to understand the benefits of the pulmonary route. Exubera® was a novel inhaler with base, transjector and mouthpiece components. Upon actuation, an individual insulin blister will be punctured, and air pump in the base would release compressed air through valve in the transjector and push the drug into the chamber. The released jet of compressed air disperses cohesive insulin powder into fine particles that would be inhaled by the patient. This unique mechanical device produced particles of < 5 μm which were deposited in the alveolar regions for systemic delivery with little patient inspiratory effort. The inhaler was reusable and delivered reproducible doses of insulin.

This system showed several advantages including greater chemical and physical stability of insulin, better patient compliance and easy method of administration. Exubera®, like subcutaneously administered rapid-acting insulin analogs, has a more rapid onset of glucose-lowering activity than subcutaneously administered regular human insulin. In healthy volunteers, the duration of action was comparable to subcutaneous injection of regular human insulin and longer than subcutaneously administered rapid-acting insulin analogs (Schachner, H 2008). However, Exubera® induced lung cancer in six patients who were smokers. After about one year after launch, Pfizer recalled this product from the market. Exubera®'s failure raised several questions about the long-term safety of inhaled insulin, and many companies stopped development of inhalers (Heinemann, L 2008).

Due to the availability of sophisticated aerosol delivery devices which decrease interpatient variability and increased patient compliance, there is a good chance of increasing the life cycle of the aerosol system in the market and thereby make profits. It is well known that dry powders and liquid formulations show long-term safety and efficacy of many drugs for pulmonary delivery (Edwards, DA, *et al*., 2002). Dry powders can be prepared by several well-established techniques including, spray drying and ball milling. Characterization of these dry powders for effective deposition in deeper lungs is critical. The MMAD of the particle determines the mechanism of deposition and the area of the deposition (Carvalho, TC, *et al*., 2011). Powder particle size before and after actuation can be studied using cascade

impactor and thus can predict the deposition of the powders. Large scale manufacture of the dry powders require through knowledge about the powder flow characteristics, density, and segregation. Morphology and geometry of the powder also affect the deposition area (Chow, AH, *et al*., 2007). Also, the physical and chemical stability of powders is higher than liquid formulations. Aerodynamic diameter of particles can be easily controlled by various methods like spray drying. Hence, insulin powder of particles with MMAD < 3 μm that would deposit in the deeper lungs and be absorbed rapidly can be manufactured. Nebulizers and MDIs lack exact coordination of inhaler actuation and patient inhalation. So it is critical to invent devices like Exubera® that doesn't depend on patient coordination. Application of this knowledge in making efficient insulin formulations can result in the development of safe novel devices with increased patient compliance.

The major limitation of DPIs of insulin would be long-term safety, the high cost of production and low reproducibility (erratic bioavailability) (Islam, N, *et al*., 2008). DPIs would pose problems in special population of patients with lung disorders and smokers. The lung physiology of specific population would be impaired and DPIs would not be effective. Another limitation would be correct usage of devices that require patients to be educated, this would be a major issue in developing countries where the market is big but the literacy is low (Islam, N, *et al*., 2008). There always exists continuous debate between the risks and the benefits of inhalation medication and it is necessary to balance the risk by improving the health of individuals. Though much research and development is needed to advance pulmonary delivery systems of insulin with minimum side effects, it is worthy to note that pulmonary route proved to be a better alternative to injectable insulin.

Transdermal delivery of insulin

Unlike other non-invasive routes, the skin has lower proteolytic activity and a large surface area (1-2 m^2), but it is relatively impermeable to few molecules mainly due to their hydrophilic nature and large size of the molecule (Brown, L, *et al*., 1988 and Harwood, RJ 1980). The major barrier in transdermal delivery of large hydrophilic molecules is the lipid layer of the stratum corneum. It was observed that delivery of insulin alone through the intact skin was not efficacious and so many researchers showed that co-administration with

permeation enhancers such as trypsin that disrupt the stratum corneum enhanced the delivery of insulin through the skin (Li, YZ, *et al*., 2008). With the stratum corneum being the main barrier for permeation of macromolecules, several varieties of physical, chemical and electrical methods were developed to disrupt the lipid layer and thus make a passage for insulin. These techniques include iontophorosis, microneedles, sonophorosis, nanoparticulate and vesicular systems (Zhao, X, *et al*., 2010; Martanto, W, *et al*., 2004; Pillai, O, *et al*., 2003; Haga, M, *et al*., 1997 and Park, EJ, *et al*., 2007). For example, Banga *et al*. tried to deliver insulin through iontophorosis but the amount of insulin reaching blood was not adequate to maintain therapeutic levels (Banga, AK, *et al*., 1993). The iontophorotic delivery of insulin is difficult because the isoelectric point (pI 5.3) of insulin is in the same range as pH of skin, so there is a possibility for insulin to form a depot in the skin during iontophorotic delivery. Also, ionotophorotic delivery depends on several factors like pH of the delivery system, the concentration of buffer species (which would compete with insulin during delivery), adsorption to electrodes, aggregation, time of iontophorotic induction and bacterial degradation (Pillai, O, *et al*., 2003).

Microneedle delivery seemed to be a promising route for insulin delivery. A study using micro fabricated metal microneedles showed that transdermal delivery of insulin lowered blood glucose levels in diabetic rats by 80%. Also, these reductions in glucose levels were similar to subcutaneous injections (Martanto, W, *et al*., 2004). But the use of metal microneedles poses safety issues and the time of insertion may not be compatible with good patient compliance. So there is a need for the development of a biologically safe needle with optimum delivery conditions. Several other formulation strategies either alone or in combination showed only certain increase in bioavailability of insulin with minimal long term efficacy and reproducibility, among which microneedle systems showed relatively promising results.

Other alternative delivery systems of insulin

Several other alternative routes including nasal, rectal, vaginal and ocular routes were explored to administer insulin (Owens, DR, *et al*., 2003). However, this hydrophilic macromolecule absorption was shown to be problematic due to the lipid bilayer barrier for all

the above routes. The rectal route has shown to increase the absorption to a certain extent. It was observed that rectal insulin absorption without an absorption enhancer was more efficacious than other mucosal routes (Owens, DR, *et al*., 2003). Much work was done in the 1980's on the rectal administration of insulin, suppositories of insulin with sodium salicylate as an adjuvant were tested in healthy, human, male volunteers and showed a significant decrease in serum glucose levels for longer periods of time (Toshiaki, N, *et al*., 1986). Another interesting study by Hosny *et al*. observed that administration of insulin suppositories with bile salts as permeation enhancers increased the insulin absorption significantly compared to the subcutaneous injection (Hosny, EA 1999). Similarly, several groups are studying rectal delivery due to its advantages including bypassing first-pass metabolism and low protease activity. But the main limitations of rectal delivery are poor bioavailability compared to subcutaneous injections and disruption of membranes due to surfactants resulting in increase in reabsorption of toxic agents from the rectum. Also, pain or discomfort associated with suppository administration and inconvenience for patients make this route an unfavorable and decreases the patient compliance.

Delivery of insulin through nasal route along with permeation enhancers has shown to be another alternative route for insulin delivery, and it was also observed that nasal absorption of insulin was comparable to rectal and sublingual absorption. Also the nasal and rectal routes were about half efficacious as intramuscular insulin (Henkin, RI 2010). Although the nasal cavity has a low surface area (~180 cm^2) compared to the pulmonary region, delivery through this route has several advantages (Washington, N, *et al*., 2000). Also, it is known that there exists direct nose to brain pathways through the olfactory pathway and trigeminal pathway. So nasal administration not only decreases blood glucose levels but can also aid in delivering insulin to the brain to treat some central nervous system disorders such as Alzheimer's disease (Benedict, C, *et al*., 2007). Nasal delivery of insulin is affected by several factors like mucociliary clearance and enzymatic degradation. Another major limitation of the nasal route is that the limited volume of nasal cavity, unlike other routes nasal route can hold relatively less amount of dosage forms and so mimicking the physiological insulin secretion is very promising (Washington, N, *et al*., 2000). The viscosity of the formulation is also an important factor to increase the residence time avoiding

mucociliary clearance (Costantino, HR, *et al*., 2007). Hence it is necessary to mitigate the physiological and formulation factors to optimize insulin delivery via the nasal route.

CONCLUSIONS AND FUTURE DIRECTIONS

Even after significant progress in knowledge on alternative delivery systems, non-invasive insulin therapy is still challenging, and there is a need for research on developing these systems. Most of the non-invasive delivery systems developed have the problem of erratic bioavailability, poor reproducibility, and issues with long-term efficacy and safety. A better alternative to currently available inulin injection therapy would not only improve the patient compliance but also would help the quality of life. This review would give readers an insight on the importance of alternative routes along with progress and challenges associated with developing alternative insulin delivery systems compared to currently available invasive painful insulin injection therapies.

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Correspondence Author:

Dr. Bhanu Chander Bejgum, Ph.D.

Frontida Biopharm,

Inc.,1100 Orthodox st, Philadelphia, PA, 19124

Email: bhanucbejgum@gmail.com

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