A REVIEW ON ALTERNATIVE ROUTES FOR INSULIN ADMINISTRATION

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ABSTRACT

Many routes were tried to administer insulin into the body. Intramuscular, intravenous and subcutaneous routes were first tried. Among them, subcutaneous and intravenous routes are commonly used routes of administering insulin. These routes need injectible methods to deliver insulin which causes lot of pain and discomfort to the patient. To make insulin delivery in an easier and simpler way and to increase comfort in patients, other routes of administration were also tried. These include oral, buccal, sublingual, rectal, transdermal, ocular, intrapulmonary, and intranasal routes. This article gives a bird’s eye view of research carried out till date to administer insulin in a convenient route other than injectible route.

KEYWORDS: Insulin, Diabetes, Intra pulmonary route, Intra nasal route.

INTRODUCTION

Diabetes is a serious, chronic disease that occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. Globally, an estimated 422 million adults are living with diabetes mellitus, according to 2016 data from the World Health Organization (WHO). The number of diabetes patients is likely to rise to 101 million in India by 2030, estimates the World Health Organisation (WHO). Insulin is a hypoglycaemic agent and was discovered by Banting and Best in 1921.[1] This hormone is very effective in treating diabetes mellitus. Insulin effectively lowers blood sugar in patients with type 1 and 2 diabetes. Many routes were tried to administer insulin into the body. Intramuscular, intravenous and subcutaneous routes were first tried. Among them, subcutaneous and intravenous routes are commonly used routes of administering insulin.
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To make insulin delivery in an easier and simpler way and to increase comfort in patients, other routes of administration were also tried. These include oral, buccal, sublingual, rectal, transdermal, ocular, intrapulmonary, and intranasal routes.

In the present article, some of the physiological basis, advantages and disadvantages of alternate routes of insulin administration are discussed.

**Oral insulin:** Many attempts were made to develop an oral insulin product, but none of them were successful. Researchers reported that insulin had very low oral bioavailability. The reasons for low bioavailability are, low gastro intestinal permeability of the large insulin molecule, lack of lipophilicity and rapid degradation of insulin by gastrointestinal enzymes.[2] Research is being done to encapsulate insulin to prevent its gastro intestinal degradation. In addition, some companies are using permeability enhancers to enhance the trans-epithelial transport of insulin in GIT.[3,4,5]

**Buccal insulin:** Buccal administration is a topical route of administration, insulin product is held in the buccal pouch. In recent years, buccal mucosa has emerged as a favourable site for insulin delivery as buccal mucosa offers rich vasculature, relatively immobile mucosa and an expanse of smooth muscle.[6] Insulin diffuses through the oral mucosa and enters directly into the blood stream. Buccal route of insulin has an advantage over oral insulin in that it bypasses the gastro intestinal degradation.[7]

Generex a Canadian - and U.S.-based Company developed Oral-lyn, buccal insulin for prandial insulin therapy.[3] This preparation is the only marketed buccal insulin formulation till date. It is a proprietary liquid formulation of human regular insulin that delivers insulin directly to the buccal mucosa utilizing the rapid mist technology.[8] This system allows fast access of the drug into systemic circulation but it showed low bio availability.[9] A larger dose of insulin needs to be applied for achieving therapeutic concentration for desired results.

**Sublingual insulin:** In this route, the product is placed under the tongue. The sublingual absorption of insulin has been increased by use of appropriate permeation enhancers.[10][11][12] The East Gate Biotech developed EGP-1214, a compressed tablet containing human recombinant insulin and designed for sublingual administration. Initial experiments of EGP-
1214 demonstrated that the developed sublingual insulin tablet is easy and convenient to use. It does not irritate the sublingual mucosa and has a fast and reproducible onset of glucose lowering action (within 30 minutes). Further studies have to be carried out on this product to establish proper pharmacokinetic data. Sublingual insulin tablet can become a product of choice for diabetic patients.

**Rectal insulin:** Rectal gels and suppositories for insulin delivery were prepared and they gave good results. Direct insulin absorption through buccal, sublingual, oral, rectal, and intra muscular routes without an absorption promoter has demonstrated that rectal absorption is more efficacious than any of the other routes. The only disadvantage is, this route is practically difficult. Till now there is no insulin marketed product for rectal route.

**Transdermal insulin:** The large surface area of the skin makes it a convenient route for insulin delivery, but the main problem is inefficient delivery of insulin through skin. The outer most layer of the skin, stratum corneum restricts the absorption of insulin. Many methods like Iontophoresis, Sonophereis, electroporation, micro dermal abrasion have been developed to increase the absorption of insulin Trans dermally. A device named Insupatch™, was developed which is supplied along with transdermal insulin pump. This pump increases the absorption of insulin by applying local heat to the skin. These techniques cause skin injury, significant pain and discomfort in patients. Research works has to be carried out to prove the long term safety and usefulness of this route of administration.

**Ocular delivery of insulin:** Systemic absorption of insulin through ocular route has been reported to be effective using absorption enhancers. A Gelfoam ® based eye device has been tested to prolong insulin delivery through eye. This device needs to be inserted to the lower conjunctival sac which is not so convenient. Till now, no human trial has been reported with this route and an animal study failed to achieve significant plasma insulin concentration.

**Pulmonary route delivery of insulin:** Many Devices have been developed for delivering insulin to the alveolar space and are examined clinically. The bioavailability of inhaled insulin for each of the devices varies. An ideal device should deliver insulin in an appropriate manner to achieve optimal glycemic control. It should also be convenient for patients. Devices are usually nebulizers that are metered-dose inhalers or drug-powder
inhalers.\cite{28} Currently dry-powder inhalers are most commonly used devices to deliver pulmonary insulin.\cite{29}

The distal lung has a large surface area (145 m$^2$) with a thin (0.2 μM) alveolar epithelium for absorption of insulin.\cite{31} The various factors which influence the distribution of insulin to the distal lung include size, shape, density, charge, particle speed, and ventilator parameters. In order for particles to be deposited in the alveolar space, their size should be between 1 and 3 μM; smaller particles are exhaled and particles >5 μM are deposited in the upper airways or swallowed.\cite{32} Patient cooperation and appropriate ventilator technique are important to ensure proper delivery of drug to the deep lung.\cite{33,34}

Nektar Therapeutics developed EXUBERA, the first inhaled insulin product which is marketed by Pfizer in 2006.\cite{35} Launching of EXUBERA (EXU), to the market raised hopes that inhaled insulin would pave the way for other alternative routes of insulin administration (ARIA), i.e. oral insulin, nasal insulin or transdermal insulin. EXU was withdrawn from the market as it did not gain sufficient market success. Poor sales led Pfizer to withdraw it in 2007.\cite{36} There after many other attempts to develop inhaled insulin were ended.

AFREZZA, a monomeric inhaled insulin developed by Mannkind, was approved by the FDA in 2014. It is new, quicker acting inhalable insulin with a different and safer pharmacokinetic profile in comparison to previously failed inhaled insulin.\cite{37} AFREZZA uses technosphere technology. In June, 2014, the FDA approved AFFREZA for both Type I and Type II adult diabetics, with a label restriction for patients having asthma, active lung cancer or Chronic Obstructive Pulmonary Disease (COPD).\cite{38}

Technosphere technology contains recombinant human insulin dissolved with powder fumaryl diketopiperazine.\cite{39} Once inhaled, technosphere insulin is rapidly absorbed upon contact with lung surface.\cite{40} It is delivered with a thumb size inhaler. Both components, insulin and powder (fumaryl diketopiperazine) are almost completely cleared from the lungs of healthy individuals within 12 hours of inhalation. In contrast to Exubera (8-9%) only 0.3% of insulin of inhaled insulin remained in lungs after 12 hours. Inhaled insulin successfully ruled out subcutaneous insulin resistance syndrome (a rare condition due to rapid degradation of insulin in subcutaneous tissue).
Intranasal Route: Much interest is given to intranasal insulin administration because nasal region has more complex plexus of small blood vessels which increases the absorption of drug. The surface area for intranasal insulin inhalation is much smaller (~180 cm$^2$) than intrapulmonary insulin but still intranasal insulin administration is more suitable for drug administration because of the characteristics of the upper airways.$^{[41]}$

The factors effecting delivery of intranasal insulin include nasal mucus concentration, character of the nasal mucus,$^{[42]}$ speed of mucociliary clearance, character and thickness of the mucociliary membrane, nasal mucus enzymes. The bacteria present in the nose may also affect the absorption of insulin. One of the key factors for successful development of an intranasal insulin formulation is an absorption enhancer$^{[43]}$ that would deliver insulin efficiently across nasal membranes without causing damage to mucosa. A protein transduction domain (PTD) derived from human translationally controlled tumor protein, was used as absorption enhancers. The newly designed formulations with PTD represented a useful platform for intranasal delivery of insulin and other biomolecules.$^{[44]}$

Nasal delivery avoids the major action of liver metabolism, which is observed with the subcutaneous route administration. Many clinical studies proved that this route of insulin administration is successful in long-term control of plasma glucose.$^{[45-50]}$ Many absorption enhancers such as aminoboronic acid derivatives, amastatin, and enzyme inhibitors improved intra nasal absorption.$^{[51]}$ Inhibition of the action of proteolytic enzymes present in nasal mucus has increased absorption of insulin by intranasal route. Use of surfactants,$^{[52]}$ gelified insulin,$^{[53]}$ bio adhesive microspheres,$^{[54]}$ phospholipids,$^{[43]}$ chitosan nanoparticles$^{[54]}$ and other enhancers increased absorption of intra nasally delivered insulin. Intranasal insulin delivery has little toxic effects. It has been well tolerated without any long-term side effects.$^{[55]}$ In some cases increased cough, nasal irritation, inflammation was noticed. An immediate but not long-term hypertension has been reported with intranasal use.$^{[56]}$ Insulin resistance has also occurred after intranasal insulin administration as in case of all other methods of insulin administration.

CONCLUSION

Some patients are hesitant to introduce injections in their daily routine. Diabetic patients will readily accept an effective non-injectable insulin dosage form. The market success of the dosage form will depend on ease and convenience of administration, and its cost.
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