

**REVIEW ARTICLE ON NOVEL ROUTES OF INSULIN FOR
DIABETIC TREATMENT****Neha Raut*, Vaishnavi Suryawanshi, Sudarshan Kejkar and Patel A. C.**

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***Corresponding Author****Neha Raut**Student, Barshi Road, Latur,
Maharashtra, India.**ABSTRACT**

Subcutaneous insulin has been used to treat diabetes since the 1920s; however, despite a number of different formulations, intensive insulin therapy with multiple daily injections has not gained widespread clinical acceptance. Attempts to find effective, well-tolerated, nonenteral routes for delivering insulin began in the 1920s, and, over the years, have included ocular, buccal, rectal, vaginal, oral, nasal and uterine delivery systems. Until recently, many researchers believed that insulin delivered noninvasively was associated with too low a bioavailability to offer a realistic clinical approach. However, a growing body of evidence suggests that inhaled insulin is an effective, well-tolerated, noninvasive alternative to subcutaneous regular insulin. Critically, inhaled insulin shows a more physiological insulin profile

than that seen with conventional insulin. Further studies are needed to confirm long-term efficacy and pulmonary safety, to compare the different approaches, and to characterize better their relative places in practice. As a result of the recognition of the importance of tighter control of glycaemia and the growing number of patients with type 2 diabetes who receive insulin, inhaled insulin could become an increasingly integral part of managing diabetes. Many patients with advanced type 2 diabetes mellitus (T2DM) and all patients with T1DM require insulin to keep blood glucose levels in the target range. The most common route of insulin administration is subcutaneous insulin injections. There are many ways to deliver insulin subcutaneously such as vials and syringes, insulin pens, and insulin pumps. Though subcutaneous insulin delivery is the standard route of insulin administration, it is associated with injection pain, needle phobia, lipodystrophy, noncompliance and peripheral hyperinsulinemia. Therefore, the need exists for delivering insulin in a minimally invasive or noninvasive and in most physiological way. Inhaled insulin was the first approved

noninvasive and alternative way to deliver insulin, but it has been withdrawn from the market. Technologies are being explored to make the noninvasive delivery of insulin possible. Some of the routes of insulin administration that are under investigation are oral, buccal, nasal, peritoneal and transdermal.

INTRODUCTION

T2 Diabetes is a class of diseases characterized by elevated blood sugar in the face of inadequate insulin production or insulin action. The disease affects approximately 23.6 million Americans (8% of the population), and fully one-third of those individuals are unaware that they have the disease.^[1] There are two broad categories of diabetes – type 1 (T1DM) and type 2 diabetes (T2DM). Individuals with T1DM are dependent on insulin for survival and rely on subcutaneous administration by injection or continuous infusion. Patients with T2DM may control their disease for a time with lifestyle intervention or oral therapies. However, those who fail these strategies will require insulin to achieve adequate disease control. Delivery of insulin via inhalation is a potential alternative to subcutaneous insulin in the management of diabetes. This review will discuss the rationale for development of pulmonary delivered versions of insulin as well as discuss the role that inhaled insulin may play in improving long-term diabetes care.

Classification of diabetes mellitus It is critical to mention that term diabetes mellitus is used for a group of diseases that leads to prolonged hyperglycemia.

1. **Type 1 diabetes mellitus** It was known previously as insulin dependent diabetes (Juvenile onset diabetes), which can be characterized as autoimmune disorder which involves severe destruction of the beta cell, absolute insulin deficiency. In most cases affect non-obese people. (Joseph, et al., 2010).
2. **Type 2 diabetes mellitus** Type two diabetes is known by its insufficient synthesis of insulin and its secretion, in addition, the body become acquires insulin resistance. It happens due to relative insulin deficiency, it occurs usually to obese patients, as obesity causes down regulation of insulin receptors. Over eating lead to excess insulin release and excess internalization of receptors which lead to decrease the available receptors results to down regulation. The number of available receptors are inversely proportional to serum insulin. (Joseph, et al., 2010).
3. **Gestational diabetes mellitus** Gestational diabetes mellitus is classified as an operational one; identifies the woman who develop diabetes mellitus during the gestation. Gestational

diabetes mellitus develops in women who have type 1 diabetes mellitus during pregnancy and in those who have undiagnosed asymptomatic type 2 diabetes mellitus. In most cases, it happens in the third trimester of pregnancy. (Joseph, et al., 2010) Other specific type (Monogenic diabetes).

4. Other specific types”, a group of diabetes mellitus with known etiologies. It concerns people with genetic defects in beta-cell function, in some cases this type of diabetes called MODY “maturity-onset diabetes in youth”. In addition, it concerns people with defects in insulin action, diseases in the exocrine pancreas, for instance, pancreatitis or cystic fibrosis, and people with dysfunction linked with other endocrinopathies. Furthermore, it affects people with pancreatic dysfunction induced by drugs, chemical or infections. They represent less than 10% of diabetes mellitus cases.

Type 1 diabetes mellitus Type 1 diabetes mellitus is known by autoimmune reduction of insulin producing cells in the pancreas by CD4+ and CD8+ T cells and macrophages which infiltrates the islets.

Various features classify type 1 diabetes mellitus as an autoimmune disease,

1. Immune-competent and accessory cells present and infiltrates in pancreatic islets.
2. The associated susceptibility for the disease with class II genes of major histocompatibility complex and human leucocyte antigen.
3. Islet specific autoantibodies are present.
4. The remarked alteration if T cell mediated immune-regulation, especially in CD4+ T cell compartment.
5. The participation of monokines and TH1 cells which aid in production of interleukins in the disease process.
6. The response of the disease to immunotherapy.
7. Usual occurrence of other organ specific auto-immune disease in the affected person.

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Routes of Administration

Vials and syringe

The intravenous route are the first parental route for drug delivery reported through syringes and needles in the late 17th century, and the subcutaneous route of drug delivery was established in the early 19th century. In 1924, 2 years after the discovery of insulin, Becton, Dickinson and Company (BD) made a syringe specifically designed for the insulin injection. Initial syringes were made of metals and/or glass, were reusable and required boiling after each use to sterilize. To reduce the incidence of needle associated infections, disposable syringes were developed. BD mass produced the first glass disposable syringes in 1954, called the BD Hypak. A number of modifications have been made to the modern insulin syringes and needles over the last five decades. Despite all these advances, many patients do not feel to inject insulin 3-4 times a day as a result of needle phobia. Recently, an injection port has been designed known as i-port Advance. It is the first device to combine an injection port and an inserter in one complete set that eliminates the need for multiple injections without having to puncture the skin for each dose. This device is helpful for the insulin requiring patients having needle phobia and helps them to achieve glycemic control effectively.

Insulin pen

Insulin injections using vial and syringe are limited by inconvenience and inaccuracy in preparing the insulin dose. These issues led to the development of insulin pens. The first insulin pen was manufactured by NovoNordisk in 1985. This was followed by refinements by various pharmaceutical companies over the past 30 years. The newer insulin pens are reusable, more accurate and equipped with safety features such as audible clicks with each

dose to improve accuracy and reduce the chances of human errors. Another advancement in the pen device (HumaPen Memoir) is built-in recording of the time and date of the last 16 injections. Recently, NovoPen Echo has been designed to give children and parents increased confidence, combines dosing in half-unit increments with a simple, easy-to-use. memory function. As such insulin pens are more accurate, convenient. less painful and patient friendly but associated with higher cost in comparison with vial and syringe. The use of insulin pen devices varies widely between countries with higher use in Europe (about 80%) and less in the USA (about 15%) as result of reimbursement issues, patient and physician related factors recently developed pen needles are shorter and thinner (31-32 G x 4-5 mm), less painful and requires less thumb force and time to inject insulin resulting in improved patient satisfaction.

The newer smart pens are designed to guide the individual with insulin requiring diabetes about the insulin dosage (by means of in-built calculators), memory functions to remember the amount and time of insulin dosage and automatic transmission of insulin dose to the mobile logbook through Bluetooth technologies.

Continuous subcutaneous insulin infusion

More physiologic delivery of insulin has been a long-standing goal. In normal physiology, a continuous small amount of insulin secretion from the beta cells of the pancreas reduces hepatic glucose output, and a larger amount of insulin is secreted when food is ingested to maintain euglycemia. Although multiple daily injections (MDI) therapy can effectively achieve hemoglobin A1c (A1c) goals, it does not resemble the insulin secretion pancreatic beta cells. Hence, it is associated with high glycemic variability (hypoglycemia and hyperglycemia). The first portable insulin pump was invented by Kadish in 1963. However, it was limited by its size and technical issues. Since then, modifications have been made to make it more efficient and comfortable to the patient. The first portable insulin pump was invented by Kadish in 1963. However, it was limited by its size and technical issues. Since then, modifications have been made to make it more efficient and comfortable to the patient. The first commercial insulin pump was introduced in 1979 in the USA. The DCCT trial used CSII therapy in nearly 40% of the intensive arm. The current generation of insulin pumps are more patient friendly as a result of smaller size and smart features such as built-in-dose calculators and alarms.

Clinical trials have demonstrated the effectiveness of CSII over MDI therapy in achieving glycemic goals (-0.5% A1c reduction), reduction in insulin dosage (-14%), reduction of

hypoglycemia and glycemic variability and improved patient satisfaction and quality of life. Limitations of CSII therapy include: Higher cost compared with MDI, increased risk for subcutaneous infections, inconvenience of being attached to a device, and a theoretical higher risk for diabetic ketoacidosis. Patient education before starting CSII therapy is of utmost important to avoid these complications.

Sensor-augmented pump therapy

With the improvements in continuous glucose monitors (CGM), it has become feasible to combine two technologies (pump and CGM) in the management of diabetes. The new generations of CGMs are more accurate, smaller in size and shown to improve glycemic control in patients with T1DM. When CGM readings are used to adjust insulin delivery through insulin pump, it is known as sensor-augmented pump (SAP) therapy. The use of SAP reduces A1c by 0.7-0.8% compared to baseline or MDI therapy in patients with T1DM. SAP requires patient involvement for using CGM glucose readings to adjust insulin pump delivery. This makes SAP susceptible to human errors. In addition, SAP therapy requires patients to wake up to manage nocturnal hypoglycemia.

Sensor-augmented pump with low glucose suspend or threshold suspend pump Hypoglycemia is the most feared acute complication of insulin therapy in patients with T1DM. More than half of hypoglycemia occurs during the night and although rare, 6% of deaths are due to nocturnal hypoglycemia in younger individuals with T1DM. In addition, the MDI, CSII and SAP are not able to eliminate nocturnal hypoglycemia. Therefore, the first step in making an artificial pancreas (closed-loop system) is to suspend insulin delivery once CGM glucose is at a low threshold (often 70 or 60 mg/dl) to reduce nocturnal hypoglycemia.

The threshold suspends (TS) system suspends the delivery of insulin for up to 2 h if a patient does not take action with a low glucose alarm. This feature is designed to reduce the severity and duration of hypoglycemia, although it will not prevent hypoglycemia 2 h of insulin suspension is not associated with severe hyperglycemia and/or diabetic ketoacidosis or more likelihood of ketone. In clinical trials, TS reduced the severity of nocturnal hypoglycemia by 30-40% and reduced the duration of severe hypoglycemia without altering A1c values. Recently, the TS system has been approved by US Food and Drug Administration (FDA) after having been approved in 2009 in other countries.

Future steps in the evolution of the artificial pancreas will be;

- Use of predictive algorithms to minimize hypoglycemia even before hypoglycemia occurs. Use of algorithms to keep blood sugar in target range (hypoglycemia/hyperglycemia minimizer)
- Automated basal and/or hybrid close-loop and Fully automated the single (insulin + glucagon) hormonal close-loop.

Novel approaches to deliver insulin

The subcutaneous route of insulin administration is associated with many drawbacks as injection pain, inconvenience, variable compliance and difficulty in achieving postprandial blood glucose control. In addition, subcutaneous insulin administration results in peripheral hyperinsulinemia in contrast to physiologic delivery to the portal vein. Therefore, there is interest in delivering insulin by alternate noninvasive routes. Currently, the pulmonary route of administration is approved and discussed as well as other routes under investigation.

Inhaled insulin

Insulin delivery to the lungs was the first reported alternate to subcutaneous injection. It has long been appreciated that insulin delivery by aerosol reduces blood glucose. Early studies showed that delivering bovine or porcine insulin using a nebulizer produced a prompt hypoglycemia in subjects with and without diabetes.

Advantages of the pulmonary route include a vast and well perfused absorptive surface, absence of certain peptidases that are present in the gastrointestinal (GI) tract that breaks down insulin, and the ability to bypass the "first pass metabolism. However, the exact mechanism of insulin absorption across the pulmonary epithelium remains unclear, but it is believed to involve transcytotic and paracellular mechanisms.

The first inhaled product, Exubera® was approved by the US FDA in year 2006] Exubera was a dry power formulation available as 1 mg and 3 mg doses to be taken with the help of an Inhance™ inhaler device. Exubera® was found to have pharmacokinetic and pharmacodynamic (PK/PD) properties similar to insulin aspart with a faster onset of action (10-15 min). In clinical trials in patients with uncontrolled T1DM and T2DM, Exubera® was found to reduce postprandial blood glucose and A1c significantly. However, Exubera® was

contraindicated in smokers as it increased the risk of hypoglycemia due to greater absorption compared to nonsmokers. In addition, patients were required to undergo pulmonary function tests before treatment initiation, after 6 months and annually thereafter. This product did not do well commercially despite the noninvasive route possibly due to higher cost, the delivery device, concerns related to declining in pulmonary function, and less preference by the patients and physicians. This product was withdrawn from the market by Pfizer in 2007.

Another promising inhaled insulin is Afrezza (Sanofi and MannKind) based on Technosphere dry powdered formulation. The onset of action of Afrezza inhaled insulin is 15 min and duration is 2-3 h, which is ideal for postprandial blood glucose control. Transient nonproductive cough and a modest reduction in lung function initially are the common side-effects. Recently, MannKind completed two large phase 3 clinical trials with the use of this device in patients with T1DM and T2DM and a clinical trial is under investigation in patients with already compromised pulmonary function. This device is in the FDA approval process.

The AERX insulin Diabetes Management System, Aerodose, ProMaxx (protein matrix microsphere) and advance inhalational research are newer inhalational devices being investigated in clinical trials. Recently, Sanofi has launched Afrezza in the United States market for diabetes management in patients with T1DM. Although, the pulmonary route of insulin administration is noninvasive, it is limited by technical issues associated with inhaler devices, higher cost and long-term safety especially pulmonary function.

Oral insulin

The oral route of insulin administration may be the most patient-friendly way of taking insulin and it could more closely mimic physiological insulin delivery (more portal insulin concentration than peripheral). However, the challenges in making oral insulin include: Inactivation by proteolytic enzymes in the GI tract and low permeability through the intestinal membrane due to larger size and hydrophobicity of insulin resulting in poor bioavailability. Several pharmaceutical companies are engaged in developing carriers to protect insulin from GI degradation and facilitate intestinal transport of insulin to deliver insulin to the circulation with sufficient bioavailability.

Natural and synthetic nanoparticles have been used as a carrier or vehicle for insulin such as chitosan, liposomes, polymeric nanovesicles, polylactides, poly-c, poly-alkyl cyanoacrylate and various polymeric hydrogels, although further discussion of these carriers or vehicles is

beyond the scope of this review. Certain oral insulin preparations such as Capsulin, ORMD-0801, IN-105, oral hepatic directed vesicles and Eligen completed phase I and phase 2 with promising results.

Recently, multifunctional polymers and self nanoemulsifying drug delivery system (SNEDDS) has been tried for oral insulin by Sakloetsakun et al. This SNEDDS was based on thiolated chitosan. The formulations in the presence or absence of insulin (5 mg/mL) were spherical with the size range between 80 and 160 nm. Entrapment efficiency of insulin increased significantly when the thiolated chitosan was employed ($95.14\% \pm 2.96\%$), in comparison to the insulin SNEDDS ($80.38\% \pm 1.22\%$). After 30 min, the in vitro release profile of insulin from the nanoemulsions was markedly increased compared with the control. In vivo results showed that insulin/thiolated chitosan SNEDDS displayed a significant increase in serum insulin ($P = 0.02$) compared to oral insulin solution. A new strategy to combine SNEDDS and thiolated chitosan described in this study could therefore be a promising and innovative approach to improve oral bioavailability of insulin.

Colonic insulin delivery

Oral colon delivery is currently considered of importance not only for the treatment of local pathologies, such as primarily inflammatory bowel disease, but also as a means of accomplishing systemic therapeutic goals. Large intestine is ideally not suited for absorption processes for drugs but it has certain advantages over small intestine like, long transit time, lower levels of peptidases (prevent destruction of peptides) and higher responsiveness to permeation enhancers. Accordingly, it has been under extensive investigation as a possible strategy to improve the oral bioavailability of peptide and protein drugs. Oral delivery systems intended for colonic release of insulin were devised according to microflora-, pH- and time-dependent strategies were well described in a review by Maroni et al.) Bioavailability and pharmacological availability data are generally still far from being reliable in terms of magnitude, onset, duration and above all, consistency for this route of administration and it is under investigation.

Despite the enthusiasm and progress in making oral insulin, there is still a long way to go before these products will be available in the market.

Nasal insulin

In theory, intranasal delivery has several advantages over oral (bypass GI peptidases), subcutaneous (noninvasive and painless) and inhalation route (no issue with lung function) which makes this route attractive for the delivery of insulin. However, intranasal delivery has shortcomings such as limited permeability of a large molecule through the nasal mucosa and rapid mucociliary clearance resulting in variable absorption.

Historically, intranasal delivery with early porcine and bovine insulins was investigated in patients with T1DM. Currently, two technologies are under investigation: Nasulin™ (CPEX pharmaceuticals) and nasal insulin by Natestch Pharmaceutical Company Inc. Both insulin preparations have bioavailability of about 15-25% with the onset of action 10-20 min. Results from the phase 2 and 3 clinical trials are awaited. The substances such as bile salt, surfactant and fatty acid derivatives are being investigated to enhance mucosal permeability of insulin but they increase the risks for local irritation, nasal secretion, sneezing or burning sensation.

Nasal insulin crosses the blood brain barrier hence it has a hypothesized effect on memory. In a randomized placebo controlled trial with 104 adults with amnesic mild cognitive impairment or mild to moderate Alzheimer's disease were randomized to receive either placebo or 20 IU or 40 of intranasal insulin. Treatment with intranasal insulin improved memory, preserved caregiver-rated functional ability and preserved general cognition without any significant hypoglycemic event. These improvements in cognitive functions were correlated with changes in the Aβ42 level and in the tau protein-to-Aβ42 ratio in cerebrospinal fluid. Based on this, large randomized controlled trials are ongoing to evaluate the usefulness of this agent for the treatment of Alzheimer's disease.

Buccal insulin

Buccal delivery of insulin has similar benefits as oral insulin with the advantage of bypassing GI degradation. Furthermore, the relatively large surface area results in better bioavailability. Initially, Genex Biotechnology developed Oral-lyn which is a liquid formulation of short acting insulin that is administered using Genex's metered dosage aerosol applicator (RapidMist™). The Eli-Lilly and Genex conducted phase 1 and phase 2 trials in patients with T1DM and T2DM with promising results. However, in 2004 both companies dissolved their development agreements. The phase 2 clinical trial is on-going on and further information is awaited. Another molecule being developed by Shreya Life Sciences Pvt. Ltd. India is oral Recosulin® and the results of the phase 2 and phase 3 trials are awaited.

Another method for delivery of insulin is fast dissolving films as an alternative to the oral tablets for rapid drug delivery. The Monosol Rx (Pharm Film Drug delivery technology) in collaboration Midatech Company developed Midaform insulin, which is delivered by buccal route. No information is available on studies using this formulation. Another formulation "insulin loaded orally dissolved films" is undergoing PK/PD investigation.

Transdermal

Trans-dermal insulin delivery eliminates the problems associated with needles and injections and large surface area of the skin makes it a convenient route for insulin delivery. However, the penetration of insulin is halted by the stratum corneum, the outer most layer of the skin. Numerous methods have been explored to overcome the barrier of stratum corneum.

There are several ways insulin can be delivered transdermally such as:

Iontophoresis, the technique that uses small electric current

Sonophoresis or phonophoresis uses ultrasound waves

Microdermal ablation by removing the stratum corneum Electroporation utilizes high voltage pulses that are applied for a very short time

Transfersulin is the insulin encapsulated in transferosome, an elastic, flexible vesicle which squeeze by itself to deliver drugs through skin pores.

Insupatch™, a device developed as an add-on to an insulin pump that applies local heat to the skin in order to increase the absorption of insulin, and Recombinant human hyaluronidase (rHuPH20) to increase insulin absorption from subcutaneous tissue

Additionally, micro needles with 1 um diameter and of various lengths can deliver insulin in effective, accurate and precise manner. Micro needle technology also can be combined as a transdermal patch. The transdermal insulin delivery techniques are limited by skin injury, burn or blister formation and rarely significant pain and discomfort. These technologies are still evolving and their long-term utility, safety and usefulness are not known at present.

Intra-peritoneal (Intra-portal)

As discussed, the intravenous and subcutaneous route of insulin delivery are associated with peripheral hyperinsulinemia and considered nonphysiological. Direct delivery of insulin in the portal vein mimics the high portal insulin concentration. This route of insulin delivery has been investigated since the 1970s. The pump (The MIP 2007C Medtronic/Minimed. Northridge, CA, USA) is implanted beneath the subcutaneous tissue in the lower abdomen

under general anesthesia. From this subcutaneous pocket, the peritoneum is opened, and the tip of the catheter is carefully inserted and directed towards the liver. After implantation, the pump reservoir is refilled in the outpatient clinic transcutaneously at least every 3 months, depending on the individual insulin requirement. Clinical trials have shown safety and efficacy of intraperitoneal insulin delivery. The limitations of this route of insulin administration include it is invasive, may be associated with subcutaneous infections, cannula blockage, higher cost, portal-vein thrombosis and peritoneal infection.

Other nonconventional routes Ocular route

Until date, no human trial has been reported with this route and an animal study failed to achieve significant plasma insulin concentration.

Rectal route

Rectal gels and suppositories showed fair results. However, this route is not commercially viable.

Intra-tracheal

Administration of insulin was reported in 1924 but is not practical so not taken up for further development.

CONCLUSION

In humans, the method is widely used to administer chemotherapy drugs to treat some cancers, particularly ovarian cancer. Although controversial, intraperitoneal use in ovarian cancer has been recommended as a standard of care.^[1] Fluids are injected intraperitoneally in infants, also used for peritoneal dialysis.

Intraperitoneal injection or IP injection is the injection of a substance into the peritoneum (body cavity). It is more often applied to non-human animals than to humans. In general, it is preferred when large amounts of blood replacement fluids are needed or when low blood pressure or other problems prevent the use of a suitable blood vessel for intravenous injection.

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