Research Article

RECENT ADVANCED INSULIN DELIVERY METHOD FOR FUTURE

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ABSTRACT

Diabetes mellitus (DM) is a chronic metabolic illness estimated to have affected 451 million individuals to date, with this number expected to significantly rise in the coming years. There are two main classes of this disease, namely type 1 diabetes (T1D) and type 2 diabetes (T2D) 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 non-invasive and in most physiological way. Inhaled insulin was the first approved non-invasive and alternative way to deliver insulin, but it has been withdrawn from the market. Technologies are being explored to make the non-invasive delivery of insulin possible. Some of the routes of insulin administration that are under investigation are oral, buccal, nasal, peritoneal and transdermal. This review article focuses on the past, present and future of various insulin delivery techniques. This article has focused on different possible routes of insulin administration with its advantages and limitation and possible scopes for the new drug development.

Keywords: Diabetes mellitus, inhaled insulin, insulin delivery, oral insulin, technology, closed-loop system, artificial pancreas.

INTRODUCTION

The prevalence of diabetes is increasing throughout the world. The International Diabetes Federation estimated 366 million people had diabetes in 2011 and is expected rise to 552 million by 2030. Though type 2 diabetes mellitus (T2DM) accounts for 85-95% of diabetes, the prevalence of T1DM has increased by 2-3% in certain parts of Europe and USA. Thus, diabetes has become one of the most common no communicable diseases worldwide. Discovery of insulin was one of the greatest medical discoveries of the last century. All patients with T1DM and many patients with long standing T2DM require insulin therapy to achieve good glycaemic control. The early insulin's were derived from bovine and porcine pancreas and were associated with immunological reactions, lipodystrophy and unpredictable insulin absorption from subcutaneous tissue. Hence, initial research focused on the purification of insulin. There has been marked progression in the development of insulin's such as rapid and long acting insulin analogs in the last five decades. The landmark Diabetes Control and Complication Trial (DCCT), demonstrated the importance of intensive insulin therapy (IIT) in T1DM for prevention of micro- and macro-vascular complications. However, IIT results in increased risk for hypoglycaemia, which is a major obstacle in achieving glycaemic targets. Therefore, emphasis has evolved to achieving tight glycaemic control with minimal hypoglycaemia by focusing on delivering insulin that mimics endogenous insulin secretion by the pancreas. Insulin is a peptide hormone, therefore, destroyed by gastric acid if taken orally. Intradermal absorption of insulin is not reliable, and it cannot mimic physiological insulin secretion. In addition, intradermal, intramuscular and intravenous therapy is not suitable for self-administration daily. Subcutaneous route of administration is widely preferred method for administration of insulin because of the ease of self-administration. It has limitations like pain at injection site, lipodystrophy, noncompliance by the patient, etc. The newer methods of insulin delivery aim to deliver insulin with minimal invasiveness in an accurate and precise manner and to reduce patient burden.

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This review article focuses on the development of the past and present methods to deliver insulin with a perspective on anticipated developments.

INSULIN DELIVERY METHODS-FROM PAST TO PRESENT

Insulin can be administered subcutaneously via various methods such as vial and syringe, insulin pen and continuous subcutaneous insulin infusion (CSII). The advantages and disadvantages of each subcutaneous insulin delivery system are reviewed.
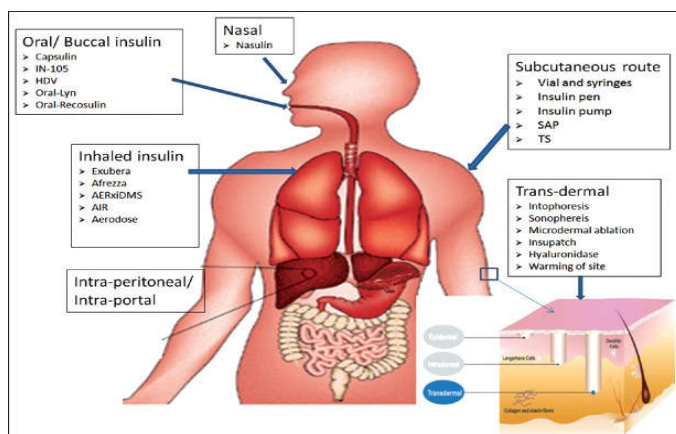
Vial and syringe

The word syringe came from the Greek "syrinx," which means "tube." The development of syringes dates back to 1853. One of the earliest syringes was the Fergusson syringe that paved the way for the development of the modern syringes. The intravenous route was the first parenteral 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)

Methods	Advantages	Disadvantages	Remarks
Insulin delivery through subcutaneous route			
Vial and syringe	↓Expensive versus pen and CSII	↑Pain versus pens Psychosocial issues Inconvenience to carrying it ↓Accurate versus pens ↓Patient friendly	Most frequently used method
Pen device	Convenient ↓Pain versus syringes More accurate, precise versus syringes Easier to use	More expensive versus syringes Can't mix two insulins	No superiority of pen devices versus syringes for glycemic control
CSII (Accu-Chek® Spirit, OneTouch Ping MiniMed Paradigm, DANA Diabecare IIS, OmniPod, Nipro Amigo, T-slim)	Continuous delivery of insulin Better glycemic control ↑Patient compliance and acceptance	↑Cost ↑Risk of DKA if pump fails injection site infection	Successful CSII needs patients education and requires motivation
SAP (any of the above pumps+Dexcom G4, Minimed, FreeStyle Navigator)	Same as CSII+better glycemic control ↓Hypoglycemia	Same as CSII CGM accuracy	Better glycemic control requires contentious CGM use
TS (Paradigm Revel 2.0 insulin pump and Enlite glucose sensor)	All the advantage of SAP+reduce hypoglycemia by 30% versus CSII	Same as CSII and SAP Hypoglycemia algorithms not predictive	Approved recently by FDA Phase 4 survey underway
Intra-pentoneal (MIP 2007)	Direct insulin delivery to the portal vein More physiological	Invasive ↑Cost Infection, portal vein thrombosis risk↑	Long-term data not available
Inhaled (Exubera, Technosphere, AERx, insulin Diabetes Management System)	Noninvasive ↑Patient compliance Rapid onset of action (10-15 min) Better PPBG control	↓Bioavailability Inhalational devices issues ↓Lung function Transient cough	Exubera withdrawn from the market Technoshere under FDA review
Oral (Capsulin, ORMD-0801, IN-105)	↑Portal insulin concentration Noninvasive Patient friendly	GI degradation of insulin ↓Bioavailability	Result of phase 3 trial awaited-IN-105
Buccal (Oral-Lyn, Recosulin)	Same as oral+bypass GI degradation	↓Bioavailability	Phase 3 trial result awaited
Nasal (Nasulin)	Same as oral and buccal+no interference with pulmonary functions	Bioavailability (15-25%) Local irritation Nasal irritation	Phase 2 and 3 clinical trials awaited
Transdermal (Microneedles, iontophoresis, electrophoresis, sonophoresis microdermalabration)	Needle free	Skin irritation, blister, pain and redness	No long-term trials Safety not established

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 know 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 glycaemic 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 Novo Nordisk 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 (Huma Pen® Memoir™) is built-in recording of the time and date of the last 16 injections. Recently, Novo Pen 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 × 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 haemoglobin A1c (A1c) goals, it does not resemble the insulin secretion from pancreatic beta cells. Hence, it is associated with high glycaemic variability (i.e., hypoglycaemia and hyperglycaemia).The first portable insulin pump was invented by Kaddish 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 glycaemic goals (~0.5% A1c reduction), reduction in insulin dosage (~14%), reduction of hypoglycaemia and glycaemic 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 glycaemic 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 hypoglycaemia.

Sensor-augmented pump with low glucose suspend or threshold suspend pump

Hypoglycaemia is the most feared acute complication of insulin therapy in patients with T1DM. More than half of hypoglycaemia occurs during the night and although rare, 6% of deaths are due to nocturnal hypoglycaemia in younger individuals with T1DM. In addition, the MDI, CSII and SAP are not able to eliminate nocturnal hypoglycaemia. 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 hypoglycaemia. 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 hypoglycaemia, although it will not prevent hypoglycaemia. 2 h of insulin suspension is not associated with severe hyperglycaemia and/or diabetic ketoacidosis or more likelihood of ketone. In clinical trials, TS reduced the severity of nocturnal hypoglycaemia by 30-40% and reduced the duration of severe hypoglycaemia 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 hypoglycaemia even before hypoglycaemia occurs.
- Use of algorithms to keep blood sugar in target range (hypoglycaemia/hyperglycaemia minimizer).
- Automated basal and/or hybrid close-loop and
- Fully automated the single (insulin) or
- Dual (insulin + glucagon) hormonal close-loop.

Novel approaches to deliver insulin

The subcutaneous route of insulin administration is associated with many drawbacks such 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 non-invasive 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 hypoglycaemia 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 transcytosis 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 Enhance™ inhaler device. Exubera® was found to have pharmacokinetic and pharmacodynamic (PK/PD) properties similar to insulin apart 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 hypoglycaemia due to greater absorption compared to non-smokers. 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 non-invasive route possibly due to higher cost, the bulky 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 Arezzo (Sanofi and Mankind) based on Technosphere® dry powdered formulation. The onset of action of Arezzo inhaled insulin is 15 min and duration are 2-3 h, which is ideal for postprandial blood glucose control. Transient non-productive cough and a modest reduction in lung function initially are the common side-effects. Recently, Mankind 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, Aero dose, ProMax (protein matrix microsphere) and advance inhalational research are newer inhalational devices being investigated in clinical trials. Recently, Sanofi has launched Arezzo in the United States market for diabetes management in patients with T1DM. Although, the pulmonary route of insulin administration is non-invasive, 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-ε, 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 Eigen completed phase 1 and phase 2 trials with promising results. Recently, multifunctional polymers and self-nanoemulsifying drug delivery system (SNEDDS) has been tried for oral insulin by Salkowski et al. This SNEDDS was based on thiolate 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 thiolate chitosan was employed (95.14% ± 2.96%), in comparison to the insulin SNEDDS (80.38% ± 1.22%). After 30 min, the in vitro release profile of insulin from the nano emulsions was markedly increased compared with the control. In vivo results showed that insulin/thiolate chitosan SNEDDS displayed a significant increase in serum insulin ($P = 0.02$) compared to oral insulin solution. A new strategy to combine SNEDDS and thiolate 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 (non-invasive 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 muco-ciliary clearance resulting in variable absorption. Historically, intranasal delivery with early porcine and bovine insulin's was investigated in patients with T1DM. Currently, two technologies are under investigation: Nasulin™ (CPEX pharmaceuticals) and nasal insulin by Nastech 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 function. In a randomized placebo-controlled trial with 104 adults with amnestic 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, Generex Biotechnology developed Oral-lyn™ which is a liquid formulation of short acting insulin that is administered using Generex's metered dosage aerosol applicator (Rapid Mist™). The Eli-Lilly and Generex 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 (NCT00948493 and NCT00668850). 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 MedTech 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 trans dermally such as:
- Iontophoresis, the technique that uses small electric currents,
- Sonophoresis or phonophoresis uses ultrasound waves,
- Micro dermal 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,
- Ins patch™, 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, microneedles with 1 μm diameter and of various lengths can deliver insulin in effective, accurate and precise manner. Microneedle 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 no physiologically. 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/Misnamed, Northridge, CA, USA) is implanted beneath the subcutaneous tissue in the lower abdomen under general anaesthesia. 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 transcutaneous 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 gelsand suppositories showed fair results. However, this route is not commercially viable.

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

CONCLUSION

There is a long history of research focusing on identifying a route of administration for insulin that is minimally or non-invasive, effective, safe, convenient and cost-effective for patients. Each route and delivery method have its own potential advantages and disadvantages. However, if successful, alternative routes of administration could revolutionize the treatment of diabetes mellitus and help improve patients' quality of life.

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