



Recent Advances in Insulin Delivery Devices and Modes of Insulin Therapy

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The discovery of insulin was 100 years old till 2021. Insulin, the first diabetic medication, is now the safest and most effective glucose-lowering medication available. Despite its efficacy, the most significant challenge with insulin has been the prevalence of hypoglycemia, which has resulted in the majority of patients being prescribed optimum dosages. Insulin delivery devices include syringes, pens, and pumps. Soon, artificial pancreas (AP) by using a very closed-loop delivery method will be a big step towards the advancement of insulin delivery devices. This article looks at the invention of syringes, disposable, long-lasting pens, and smart connected pens, continuous intraperitoneal insulin infusion (CIPII) and patch insulin pumps, artificial pancreas and other medical devices. Hence, insulin administration that is both minimally invasive and non-invasive towards the advancement is required. We review the available information on the evolution of insulin delivery systems, focusing on the advantages and disadvantages of technology as well as anticipated advances. Due to the wide variety of technological solutions accessible via the international platform, only the most common methods essential to the patient's care are detailed here in the article.

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1. INTRODUCTION

Diabetes mellitus is a group of disorders that impact the body's ability to use blood sugar (glucose). Because glucose is a significant source of energy for the cells which make up the muscles and tissues, it is essential to health. It is also the primary source of energy for brain. Diabetes is becoming more common in the world. Diabetes is anticipated to affect 537 million people in 2021, with that figure expected to rise to 643 million by 2030 and 783 million by 2045. Furthermore, in 2021, 541 million individuals are expected to have reduced glucose tolerance. In 2021, about 6.7 million persons aged 20 to 79 are expected to die from diabetes-related causes. Yearly, the number of children and adolescents (those aged 10 to 19) diagnosed with diabetes increases. Type 1 diabetes will affect approximately 1.2 million children and adolescents by 2021. [1] Even though Type 2 diabetes mellitus includes 85-95 percent of all cases of diabetes, the overall number of Type 1 diabetes mellitus patients of various regions of Europe and the United States has escalated by 2-3 percent. [1] As a result, diabetes has become one of the world's most common NCD. In 1997, the American Diabetes Association (ADA) suggested the standard category of diabetes as type 1, type 2, other forms, and gestational diabetes mellitus (GDM), the most generally recognized and used

classification. (1) In most parts of the world, diabetes is becoming a severe public health issue (1).

Insulin is essential for blood glucose control in all patients with type 1 diabetes and a large percentage of those with type 2. Technological innovation and biotechnology have altered the diabetes treatment environment during the last 20 years. There are multiple types of insulin and several injection schedules available. Despite the availability of insulin vials and pens, patient acceptance and glucose readings obtained with single or multiple-dose injection regimens are not to the required level. Many people with severe Type 2 diabetes and all individuals with Type 1 diabetes demand insulin to keep blood glucose levels within the therapeutic range. Insulin injections in subcutaneous route are the most typical mode of administration. However there are various other routes of insulin administration such as Nasal, Transdermal, Oral/Buccal, Inhaled and Intra-peritoneal/Intra-portal Insulin.(Fig. 1). It can be delivered subcutaneously using several methods, which include vials and syringes, pens, and pumps.(2)

There are various treatment options available for diabetes mellitus, with the advancement in technology there have been various emerging modalities for the treating the disease.

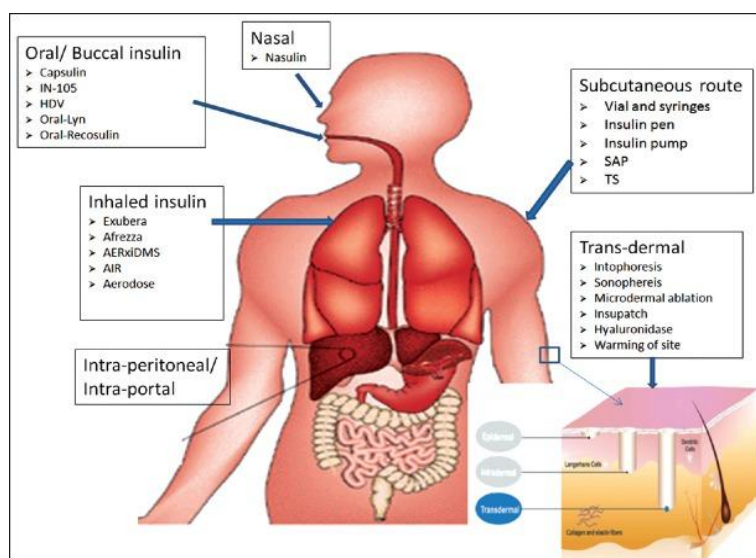


Fig. 1. Various modalities

1.1 Subcutaneous Route

Insulin can be administered subcutaneously in several ways, including vial & syringe, pens, and continuous subcutaneous insulin infusion (CSII).

1.2 Vials & Syringe

One of the earliest parenteral strategies for drug distribution, which employed syringes and needles, was documented in the late 1800s, whereas the injections under the skin route were discovered in the early 2000s. Becton, Dickinson and Company (BD) developed an insulin injection syringe two years later to the discovery. [3] Syringes were made of metals and/or glass, were reusable, and need to be sterilized after every use by boiling. To reduce the number of infections caused by needles, disposable

syringes were developed. The injection port i-port Advance® was recently developed. It's the first device to integrate an i port for injection and an inserter into one device, reducing the number of syringes needed and removing the necessity for skin pricks for each dosage. This gadget is helpful for insulin-dependent people who are afraid of needles but yet want a controlled blood sugar (3,4)

1.3 Limitations

Despite all foregoing advancements, most patients had trouble injecting insulin numerous times per day [4]. Furthermore, the use of syringes has been linked to poor dosage accuracy, a lengthy training time, an unpleasant psychologic impact, and conveyance issues [5].

Table A. Disadvantages and Advantages of pens and pumps

Device	Advantages	Disadvantages
Insulin pen	Discreet Insulin administration that is both efficient and simple Accurate dosing Injection Ease Time saving It is feasible to be versatile due to the disposable and reusable options. Simple to transport Improved treatment adherence Cost-effectiveness over time	In low-income nations, syringes are more costly. For the first time, syringes are more costly. It is not possible to blend various insulin kinds. Dosage is kept low.
Insulin pump	Utilization of a regular insulin regimen Ensures sustained insulin delivery Close similarity to physiologic insulin delivery Allows for greater lifestyle freedom	Cannula and infusion set technical and safety concerns (detachment, crimping, or leaking) Patients may have skin irritation or hypersensitivity because of cannula and infusion set technical and safety difficulties (detachment, crimping, leakage). More patient engagement and compliance are required. More patient engagement and compliance are required. More expensive

1.4 Insulin Pens

Pens, in comparison to syringes, provide simpler, precise, and convenient insulin administration. An insulin pen comprises of three parts: a cartridge for insulin, disposable needle, and a single-click per unit dosage system. The gadget can be reusable or disposable. It gives patients greater freedom, discretion, and long-term cost-effectiveness, all of which help the patients stick to their treatment plan. As a result, insulin pens provide better blood glucose regulation and are becoming more generally adopted [6]. Novo Nordisk introduced the NoVo Pen, the first insulin pen, in 1985. Pens of the first generation have been on the market since the 1990s. Many generations of durable NoVo Pen pens, AllStar (Sanofi), and pre-filled pens like FlexPen and Kwikpen are among the popular insulin pens of this type. The NovoPen 3 is a long-lasting pen with an optimum dose of 70 Units. It was brought to the market in 1992. In 2012, Sanofi India debuted AllStar, the country's first indigenously made reusable insulin pen, particularly tailored for diabetic patients.

Next-Generation Insulin Pens-Since 2007, with memory features, sometimes known as "smart pens," have been on the market. These devices contain a multidose memory feature that saves the date, time, and dosage of prior administrations [7]. These devices provide USB or Bluetooth connectivity for better monitoring and data management.

Smart Connected insulin pens- these pens are the next advancement in the category of pens, which includes properties that go far beyond memory. The InPen System, a Bluetooth-enabled wireless pen with a device interface and advisor about bolus, was introduced by Companion Medical in 2017 [8]. This collection of pens includes Novo Nordisk's "soon to be launched" Novo Pen 6 and Novo Pen Echo Plus.

Disadvantages- The limitations, like the difficulty of combining insulins, the higher cost have all been major sources of concern. Insulin pens are more difficult to use mechanically than insulin syringes, despite their apparent simplicity. Pen device therapy is more expensive than vial therapy when long-term economic effectiveness is ignored, as observed in low- and middle-income nations [9]. Table A highlights some main benefits and drawbacks of pen [10].

1.5 Insulin Pumps (Continuous Subcutaneous Insulin Infusion-CSII)

One of the most efficient ways to supply exact doses of rapid-acting insulin to meet the body's demands to use an insulin pump, also known as CSII. An insulin pump is made up of 3 parts such as an insulin reservoir, infusion set and tube.

The insulin reservoir is linked to an infusion set and a catheter, which constantly injects dosage depending on user-specific programming to meet daily demands. Before meals, the pump can provide insulin in both basal (slow, continuous) and incremental (bolus) dosages.

Multiple Daily Injections (MDI) have been extensively used in the care of diabetes patients since the 1970s, when it was initially introduced as a strategy for establishing and maintaining stringent blood glucose control in people with T1DM [11]. The insulin pump and the MDI have been utilized to treat diabetes in the juvenile and adult populations [12]. Several studies have shown that CSII therapy improves glycaemic control over MDI treatment. Glycaemic management is critical for preventing long-term diabetic consequences. The usage of insulin pumps in pediatric T1DM patients has expanded dramatically, from 1.3 percent in 1995 to 47 percent in 2016 [13]. Pumps are routinely utilized to replace insulin in young T1DM patients [14], but they are also commonly utilized in T2DM patients. In people with diabetes CSII treatment improves glycemic and metabolic control (lowering HbA1c, glycemic fluctuation, and low blood sugar) [15].

The most current external pumps, which debuted in the 1990s, are tiny, compact, convenient, and efficient. Bolus calculators, computer connectivity, and warnings are all included in these "smart pumps." [16]. Medtronic created the first "intelligent" pump in 2003. This system includes a MiniMed Paradigm 512 insulin pump and a BD-developed Paradigm Link glucose monitor. The glucose readings from the glucometer are sent to the pump remotely and automatically in this situation, and the appropriate insulin doses are computed using a Bolus Wizard calculator [17].

Patch pumps- Because of the limitations of infusion sets, "patch pumps" have been developed: pumps that do not require infusion sets, are compact and lightweight with an adhesive that adheres to the skin. Patch pumps

assist patients hence provides more comfort and flexibility, which is important while travelling. In 2011, Insulet introduced the OmniPod, the first insulin pump without a tube. It includes an infusion set and an automated inserter that communicates wirelessly with a blood pressure monitor.

1.6 Continuous Intraperitoneal Insulin Infusion (CIPII)

Since the 1970s, researchers have been looking into the intraperitoneal modes of insulin delivery. Continuous intraperitoneal insulin infusion (CIPII) allows insulin to be infused into the peritoneal cavity. This technique has the benefit of closely resembling physiology more than other conventional treatments [17].

1.7 Sensor-augmented Pump Devices and Continuous Glucose Monitors

In December 2016, the first continuous glucose monitor (CGM) was designed by Dexcom. These devices infer blood glucose by estimating its levels in interstitial fluid of subcutaneous tissue. A thin, biocompatible sensor wire is introduced into the skin and coated with a glucose-reactive enzyme, allowing the device to detect the voltage created and estimate blood glucose based on it. The most significant advantage of a CGM over a traditional fingerstick blood glucose metre is that it can take a new reading as frequently as every 60 seconds (though most only take a reading every 5 minutes), allowing for a sampling frequency that can provide not only a current blood sugar level, but also a list of previous measurements [18].

Since advancements in continuously delivering glucose monitors (CGM), it is possible to make both devices one for diabetes-management systems (pump and CGM). CGMs have improved T1DM patients' blood sugar control, and newer devices are more accurate and smaller [19]. Sensor-augmented pump (SAP) therapy is when CGM data is used to alter insulin dosage using an insulin pump. In T1DM individuals, SAP decreases A1c by 0.7-0.8 percent compared to baseline or MDI treatment [20,21]. In order to modify insulin pump administration based on CGM glucose measurements, SAP requires compliance by the patient. To modify insulin pump administration based on CGM glucose measurements, SAP requires patient participation. Therefore, SAP is susceptible to human error. Further, SAP

medication requires patients' awakening to manage low blood sugar during the night.

1.8 Sensor-Augmented Pumps with Hypoglycaemic Suspend or Threshold Suspend Pumps

In individuals with T1DM, low blood sugar is the most dreaded immediate consequence of treatment with insulin. Most times hypoglycaemia occurs at night, and nocturnal hypoglycaemia is responsible for 6% of mortality in younger people with T1DM [22,23]. Furthermore, the MDI, CSII, and SAP are incapable of eradicating nocturnal hypoglycemia. To decrease nocturnal hypoglycemia, the initial stage in developing an artificial pancreas is to stop treatment once CGM glucose falls below a certain level (usually 70 or 60 mg/dl). If the user fails to respond to a low glucose warning, the device will stop administering insulin for up to two hours. This function's purpose is to reduce the severity and duration of hypoglycemia, not to avoid it [24]. Insulin suspension for two hours does not cause severe hyperglycemia or diabetic ketoacidosis, nor does it increase the risk of ketone generation. [25] The clinical studies showed that, threshold suspended pumps lowered the hypoglycemia severity at night by 30-40% and the time duration of severe hypoglycemia by 30-40% without affecting HbA1c levels [26,27].

1.9 Limitations

The main disadvantages of infusion sets are that they frequently detach, leak, or cause skin irritation, making insulin pumps more difficult to use. The downsides of CSII treatment include a greater price than MDI, a larger risk of subcutaneous infections, the inconvenient nature of being attached to a device, and a theoretically higher risk of diabetic ketoacidosis [28,29]. To avoid these problems, patient education before commencing CSII treatment is critical [30]. Patients experienced irritation and aseptic conditions regularly at the insertion site. Implanted cannulas kinking, bending, or crimping, as well as infusion set leakage, have all been documented [29]. Compared to MDI, pump treatment has higher initial and total yearly expenses.

1.10 Artificial Pancreas

CSII's main goal since its inception has majorly been to create an artificial pancreas that can mimic optimal sugar management with minimum human participation. A "closed-loop" artificial

pancreas combines cutting-edge technology with automation to achieve glycaemic goals. In general,

The AP connects three devices: (1) a sensor, such as a continuous glucose monitor (CGM), that monitors blood sugar levels and sends data to software, (2) a computer program that analyses data and determines the appropriate insulin dosage, and (3) an insulin infusion pump that delivers insulin as directed by the computer. In 2017, the FDA authorized the MiniMed 670G insulin pump with Guardian 3 sensor as the first hybrid closed-loop device for T1D therapy in children aged 7 and higher.

The following will be the next phases in the advancement of the artificial pancreas [28]:

- 1) Using predictive plans to reduce hypoglycaemia before it arises.
- 2) The use of planned methods to keep blood sugar levels within the intended range (hypoglycaemia or hyperglycaemia minimizer).
- 3) Automated basal closed loop
- 4) Fully automated single or multiple (insulin) or multiple (insulin) or multiple
- 5) Dual hormonal close loop (insulin + glucagon).

2. ORAL ROUTE

Oral insulin administration is more patient-friendly and more nearly resembles physiological insulin delivery [31]. Proteolytic enzymes in the gastrointestinal system inactivates it, and lower permeability across Insulin's larger size and hydrophobicity cause damage to the intestinal membrane, produce low bioavailability. Several pharmaceutical firms are working on carriers that shield insulin from GI breakdown and improve intestinal insulin transport, allowing for appropriate bioavailability when delivered to the circulation [32].

As insulin carriers or vehicles, natural and manufactured nanoparticles such as chitosan, liposomes, polymeric nanovesicles, polylactides, polyalkyl cyanoacrylate, and other polymeric hydrogels have been employed [33].

The key turning points in the history of insulin delivery methods are graphically represented here.

2.1 Insulin Inhaling Devices

Because it was closer to physiologic portal delivery, the respiratory mode of insulin administration was the first alternative to the subcutaneous method of insulin administration. Insulin inhaling devices help patients breathe perfectly all right pulmonary insulin (solution-based formulations or powder-based formulations) in the respiratory tract [34]. Inhalable insulin was first offered to the market in 2006 as a critical advancement to combat needle phobia and poor insulin injection processes in systemic insulin delivery systems. Inhalable insulin has a proper treatment of postprandial hyperglycemia [35]. In 2006, the Food and Drug Administration approved Exubera (Pfizer) as the first inhalable insulin to treat T1D and T2D. On the other hand, Exubera use has been linked to an increased risk of low blood sugar. Due to its high cost and dosage error, the drug was removed in 2007. Afrezza, a fast-acting Technosphere insulin powder, is the lone survivor in this group (MannKind Corp.). Afrezza was authorized by the FDA in 2014 for the treatment of prandial insulin [36]. Afrezza's administration method is compact and convenient, and it displays the dose in units [37]. In T1D patients, Afrezza has been proven to enhance glycemic control and minimize hypoglycemia [38]. Insurance restrictions, safety concerns, and rival products further limit the acceptance of inhalable insulins [37].

2.2 Transdermal

The hazards connected with injections are eliminated with transdermal insulin delivery. The skin's enormous surface area makes it an ideal route for insulin delivery [39]. Insulin cannot enter the stratum corneum, the outermost layer of the skin. To get through the stratum corneum barrier, several ways have been investigated [39]. Skin damage, burn or blister development, and seldom substantial pain and suffering restrict transdermal insulin administration systems. The technologies are still in development, and the long-term use, safety, as well as usefulness remain unknown.

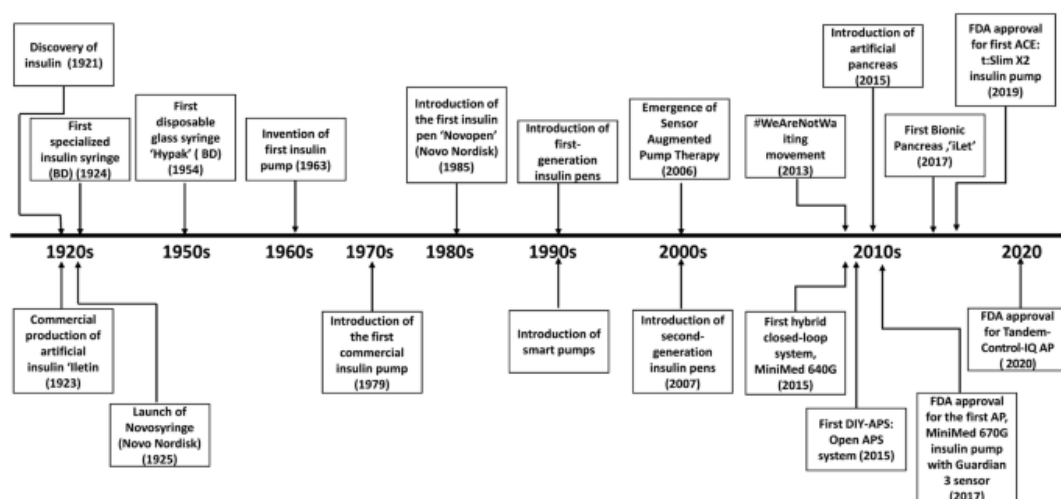


Fig. 2. Block diagram of insulin delivery methods

There are numerous methods for delivering insulin transdermally, including:

- (a) iontophoresis, a technique that employs tiny electric currents, [40].
- (b) Ultrasound waves are used in sonophoresis or phonophoresis.
- (c) Microdermal ablation is possible once the stratum corneum is removed [41].
- (d) Electroporation is a procedure that involves delivering a high-voltage pulse for a brief length of time [42].
- (e) Insulin is contained in a transferosome, an elastic, flexible vesicle that squeezes itself into skin pores to carry drugs [43].
- (f) Insupatch™ is an insulin pump add-on device that uses localized heat to boost insulin absorption [44].

3. CONCLUSION

Even though subcutaneous insulin administration is the most common, it has been linked to injection discomfort, needle phobia, lipodystrophy, noncompliance, and peripheral hyperinsulinemia. As a result, minimally invasive or non-invasive insulin delivery that is also physiological is required. Though there were some laudable advancements in the already available technologies, many of them were unreasonably costly. Each route and delivery technique has its own set of possible benefits and drawbacks. Alternative methods of delivery, if effective, might change the treatment of diabetes mellitus and assist enhance patients' quality of life. This brief essay depicts a shifting dynamic in the insulin delivery devices market's incorporation of digital health technologies.

DISCLAIMER

The products used for this research are commonly and predominantly in our research area and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for litigation but the advancement of knowledge. Also, the research was not funded by the producing company rather, it was funded by the personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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