Insulin Delivery: An Evolution in the Technology

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Introduction

All patients with type 1 diabetes (T1DM) require insulin due to absolute deficiency, and most type 2 diabetes (T2DM) patients require insulin at one time or the other due to progressive β-cell failure, to sustain life [1, 2]. In people with diabetes, the most efficient therapeutic option available to reduce hyperglycemia continues to be insulin even though they experience numerous challenges with the use of insulin including interference with daily living, financial constraints, the complexity of regimens, injection discomfort, and public embarrassment for injecting insulin [3, 4]. Therefore, to avoid the complications related to diabetes such barriers have to be handled with advanced and proven technologies for insulin delivery [5].

Beginning with the syringe for injecting insulin, progressing to insulin pumps, insulin pens, and sensor-augmented pumps, the growth of diabetes technologies accelerated with the introduction of hybrid closed-loop systems, integration with consumer electronics, and cloud-based data systems [6, 7]. These devices have favorably improved patients' perceptions about insulin therapy along with improving their quality of life [8]. However, the right choice and application of diabetes technologies are essential for positive outcomes.

The first manufactured insulin pump was introduced as early as in the 1970s, whereas the first manufactured insulin pen was introduced only in 1985 [9].

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Insulin Delivery Devices

Insulin Vial and Syringe

In 1924, 2 years after the discovery of insulin, Becton, Dickinson and Company (BD) made a syringe specifically designed for insulin injection [10] (Fig. 69.1). Initially, syringes were made of metals and/or glass, which were reusable and after each use, required boiling for sterilization. In 1925, Novo Nordisk launched the first insulin syringe, the "Novo Syringe" (Fig. 69.2). To reduce the extent of needle-associated infections, disposable syringes were developed. In 1954, BD mass-produced the first glass disposable syringes called the BD Hypak. In 1955, an all-plastic Monoject syringe (Roehr Products Inc) was introduced onto the market. In the 1960s, BD introduced the 1-mL LuerLok insulin syringe available with either a detachable needle or a permanently attached needle. Disposable plastic syringes from numerous vendors were available on the market by the mid-1960s [11]. These syringes reduced pain and the rate of needle-associated infections [12]. In spite of all these advances, many patients did not feel to inject insulin 3–4 times a day due to needle phobia.

By 1970, BD manufactured the first one-piece insulin syringe with an integral needle [13]. Following, U-100 plastic insulin syringes with units marking down the side of the syringe came into use [11]. In 1988, the BD Safety-Lok insulin syringe with advanced safety features was introduced. In 2012, BD introduced the BD Veo insulin syringe with an Ultra-Fine 6-mm needle, offering less pain and reduced plunger force to ease the flow of large insulin doses [14]. Due to the reduced risk of intramuscular injections, this syringe has been widely preferred [15]. The FDA approved a U-500 specific insulin syringe designed by BD to address the dosing errors while administering doses from a U-500 vial with a U-100 insulin syringe in 2016 [16]. Instead of the long, large bore-sized and reusable needles used in earlier years, nowadays, small bore-sized and short-length needles (8 mm, 6 mm, and 5 mm) are used for insulin injection.

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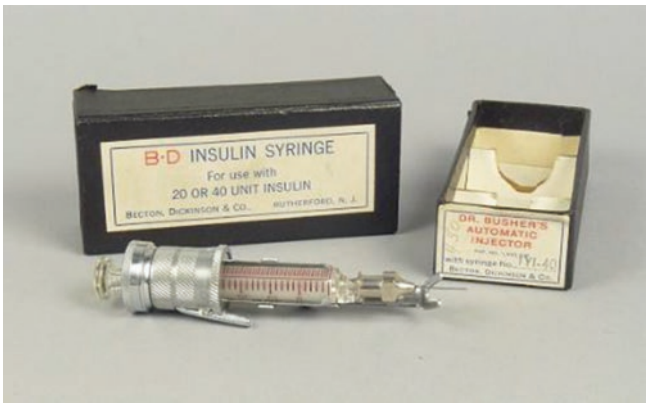


Fig. 69.1 First insulin syringe

Fig. 69.2 Novo syringe

For more than 50 years, vials and syringes have remained as the only option for insulin delivery although "conventional" syringe technology has become less popular in the current era.

Insulin Pen

Due to inconvenience and inaccuracy in preparing the insulin dose, insulin shots using vial and syringe have a lot of challenges [9]. These issues contributed to the development of insulin pens. The introduction of insulin pens was a phenomenal achievement in insulin delivery. In 1985, the first insulin pen, the NovoPen, was launched by Novo Nordisk followed by NovoPen 2 in 1988. NovoPen 2 has a distinct dial-up setting to measure the required dose [17]. In common, pens provide more simple, accurate, and convenient insulin delivery over syringes (Table 69.1). An insulin pen has mainly three components: an insulin cartridge, a disposable short needle, and an incremental "one-click per unit" dosing. These devices can be either reusable or disposable. Reusable insulin pens have a replaceable cartridge whereas disposable pens have a prefilled cartridge and are discarded after use.

Table 69.1 Advantages and disadvantages of insulin delivery methods

Methods	Advantages	Disadvantages
Vial and syringe	• Less expensive compared to insulin pen and pump	• Increased pain at the site of injection versus pen • Inconvenience in carrying • Decreased accuracy when compared to pens • Less patient-friendly
Insulin pen	• Efficient and convenient delivery of insulin • Accurate dosing and flexible because of disposable and reusable options • Ease of injection and time saving • Easy to carry • Better treatment compliance and long-term cost-effectiveness	• More expensive than syringes • Does not allow the mixing of different insulin types • Low dosing
Insulin pumps	• Continuous delivery of insulin • Better glycemic control • Increased patient compliance and acceptance • Decreased hypoglycemia	• More expensive • Increased risk of DKA if pump fails • Injection site infection • Technical and safety issues with the cannula and infusion set (detach, crimp, or leakage) • Can cause skin irritability or hypersensitivity in patients
Intraperitoneal	• Direct insulin delivery to the portal vein • More physiological	• Invasive • More cost • Increased risk of infection and portal vein thrombosis
Inhaled insulin	• Noninvasive • Increased patient compliance • Rapid onset of action (10–15 min) • Better PPBG control	• Reduced bioavailability • Inhalational devices issues • Decreased lung function • Transient cough
Oral insulin	• Increased portal insulin concentration • Noninvasive • Patient-friendly	• Reduced bioavailability
Buccal insulin	• Relatively large surface for absorption • Presystemic metabolism in the GI and liver avoided • The level of vascularization is very high in some areas	• Great variations of permeability among the different areas of the oral mucosa • Reduced bioavailability
Nasal insulin	• No interference with pulmonary functions	• Reduced bioavailability (15–25%) • Local irritation • Nasal irritation
Transdermal insulin	• Needle-free	• Skin irritation, blister, pain and redness • Safety not established

PPBG Postprandial blood glucose

Novo presented the world's first disposable, prefilled insulin pen known as "Novolet" in 1989 [18]. Insulin adsorbs onto the plastic surface of these prefilled pens over time and a precise concentration can be accomplished by legitimate blending. Therefore, the dose accuracy and blood glucose (BG) stability between cartridge changes are increased by pens [19].

The newer insulin pens are more accurate and furnish with safety features such as audible clicks with each dose to improve accuracy and reduce the chances of human errors [9, 20]. Another achievement in the pen device (HumaPen® Memoir™) is integrated with recording the time and date of the last 16 injections [21].

Compared with syringes, pens offer more flexibility, accuracy, discreetness, and long-term cost-effectiveness, providing improved treatment continuity and adherence. Therefore, the use of insulin pens exhibits better glycemic control and has wider acceptance [22, 23]. Despite insulin pens being convenient, less painful, and patient-friendly, they are related with higher cost in comparison with vial and syringe [24, 25].

Technologic refinements over the fundamental features of the earlier versions have produced more advanced insulin pens. Finer and safer needles which are shorter and thinner (31–32 G × 4–5 mm) that offer reduced pain perception and require less thumb force and time to inject insulin have also been developed resulting in improved patient satisfaction [26, 27].

First Generation Insulin Pens

From the 1990s, first-generation insulin pens are available on the market. The prominent insulin pens in this category are multiple generations of durable pens of the NovoPen family, AllStar (Sanofi), and prefilled pens, such as FlexPen, FlexTouch (Novo Nordisk), Humalog Pen, Kwikpen (Eli Lilly), and SoloSTAR (Sanofi) (Fig. 69.3). NovoPen 3, a durable pen allowing a maximum dosage of 70 U, was launched in 1992 (Fig. 69.4). The essential feature of this device was less wastage of insulin while resetting the dose at the dial and push-up buttons. This pen was more economical and was further refined for patient subsegments, such as NovoPen 1.5 and NovoPen Junior. In 1996, NovoPen 1.5 was launched, a shorter version of NovoPen 3, which can hold smaller insulin cartridges. NovoPen3 Demi, the first Novo family member to allow half-unit dose increments, was advertised in 1999. In 2001, FlexPen, a prefilled insulin pen, was introduced. In 2003, NovoPen Junior, with vibrant colors, specifically designed for children with diabetes, was initiated [28]. The NovoPen 4 (dose increments of 1.0 U, maximum dose of 60 U) was launched in 2005. In 2007 and 2008, refilled insulin pens, Kwikpen (Eli Lilly) and SoloSTAR (Sanofi), were launched respectively [29].

Fig. 69.3 First generation insulin pens

Fig. 69.4 NovoPen®

In 2011, Novo Nordisk introduced FlexTouch, a re-engineered version of the original FlexPen. It is the single prefilled insulin pen with an easy touch button, which improves the ease of use and device handling for the patients [30]. In 2012, Sanofi India launched its first indigenously developed reusable insulin pen, AllStar, specifically designed for diabetes patients in India. The key features of this pen are the slim and discreet design, clear dose magnification window, dose arrow on both sides, bayonet cartridge lock, short dial-out distance, penalty-free reverse dialing, audible click sound with every unit dialed and dispensed, and non-rotating dial button during dispensing [31]. In 2017, Junior KwikPen, a prefilled half-unit

insulin pen, was considered to be lighter and smaller than other half-unit insulin pens and was approved on the market.

In 2021, Toustar Reusable Insulin Pen Sanofi was intended to be used in conjunction with the insulin glargine 300 U/mL in a dedicated cartridge (Toujeo® 1.5 mL cartridges) to deliver insulin through subcutaneous injection using commercially available needles. The key features are user can reverse dial without losing insulin and simple "push-to-reset" plunger (no screwing required) [32].

Insulin pen needles of 4 mm, 5 mm, 6 mm, 8 mm, and 12.7 mm lengths are used. The Nano 4-mm pen needle (BD), the shortest pen needle, is more comfortable and easiest to use. These needles require low thumb force and allow higher flow rate and insulin absorption [33].

Next-Generation Insulin Pens

Since 2007, second-generation pen devices or "smart pens" with a memory function were available on the market. These devices have a multidose memory feature that allows storing the date, time, and amount of the previous doses [34, 35]. These devices are unified with USB or Bluetooth features for efficient monitoring and data management. In 2007, Eli Lilly launched HumaPen MEMOIR, the world's first digital insulin pen with memory, and HumaPen LUXURA HD, a reusable pen for people who require insulin dosing in half-unit increments from 0.5 to 30 units. In 2010, Novo Nordisk launched NovoPen Echo, the first insulin pen with memory and half-unit dosing features [36]. In 2012, NovoPen 5, a successor to NovoPen 4 was launched with a simple memory function for use with the 3-mL Penfill cartridge [37].

The newer smart pens are designed to guide the individual with diabetes about the insulin dosage (by means of inbuilt 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 [12].

Connected Pens

Connected pens are next-generation insulin pens with characteristics that go beyond the memory function. In 2017, Pen System was launched by Companion Medical which consists of a Bluetooth-enabled wireless insulin pen with a smartphone interface and bolus advisor [38]. These pens will automatically record the dose of insulin injected, and the data can be shared with collaborating CGM devices and Glooko's Diasend digital diabetes management platforms and are expected to be synced with Roche's mySugr app [39]. Novo

Fig. 69.5 NovoPen 6 and NovoPen Echo Connected pens

Nordisk's NovoPen 6 and NovoPen Echo Plus also fall into this category of pens (Fig. 69.5). These pens will automatically record the dose of insulin injected and the data will be shared with Dexcom G6 CGM, FreeStyle Libre system (Abbott), and Glooko's Diasend digital diabetes management platforms. Connected pens are furnished with NFC (near-field communication) technology that permits scanning of these devices to transfer the data off to another device [40]. Another advanced innovation in pen technology was Bluetooth/internet-connected insulin pen cap that aids the generation of smart dosing systems through a mobile app for the convenience of T1DM patients who do not use an insulin pump [41].

Even though insulin pens offer the convenience of use, less pain, and better treatment adherence and health outcomes, they have limitations such as difficulty in applying a mixture of insulins, higher cost, and lack of universal insurance coverage [42]. Regardless of the ease of use, pens are mechanically more complex than insulin syringes [43].

InPen Smart Insulin Pen

In 2020, Medtronic launched connected smart insulin pen, the InPen, acquired from Companion Medical. The InPen is the only FDA cleared, smart insulin pen system that combines the freedom of a reusable Bluetooth pen with the intelligence of an intuitive mobile app that helps users administer the right insulin dose, at the right time (Fig. 69.6). The InPen sends dose information to a mobile app and the app uses the glucose levels and a carbohydrate estimate to recommend the dose. It even considers the amount of insulin that is still working in the body, to help avoid low glucose.

Fig. 69.6 InPen with Guardian connect and connected app

Injection Aids: I-Port Advance Injection Port

To reduce the frequency of multiple injections and needle phobia in patients with diabetes, injection aids are also used in practice. In 2016, an injection port was designed known as i-port Advance launched by Medtronic. It is a small and discrete patch, which can be attached to the skin and the device remains adhered to the skin for up to 72 h and allows multiple injections. It is the first device to combine an injection port and an inserter in one complete set which helps to eliminate the need for multiple injections without puncturing the skin for each dose. This device is useful for insulin requiring patients having needle phobia and helps them to accomplish glycemic control effectively [44, 45]. Although there was an initial excitement, this device remains unpopular probably because insulin shots with newer needles are virtually painless.

Insulin Pumps

Insulin pumps are small, computerized devices that imitate the way the human pancreas works by delivering small doses of short acting insulin continuously (basal rate). The device is also used to deliver variable amounts of insulin when a meal is eaten (bolus). Pumps are modernized gadgets for the delivery of insulin and can be used for dispensing insulin in any patient who exhibits the desire to initiate pump therapy and fulfills the criteria for a pump candidate [1].

Continuous Subcutaneous Insulin Infusion (CSII)

In normal physiology, a continuous small amount of insulin secretion from the beta cells of the pancreas reduces hepatic glucose output, and when food is ingested a larger amount of insulin is secreted to maintain euglycemia [46]. The CSII therapy was used by DCCT trial in nearly 40% of the participants in the intensive arm [47]. The current generation of insulin pumps are more patient-friendly due to its smaller size and smart features such as built-in-dose calculators and alarms [46]. The main components of an insulin pump are an insulin reservoir, infusion set, and tubing. The insulin reservoir is connected to the infusion set and a catheter helps to continuously deliver insulin to meet the daily requirement. The pump has user-specific inbuilt programs to dispense insulin at basal rates (slow, continuous) and in incremental (bolus) doses before meals [48]. This characteristic helps in the removal of the inherent variations associated with the injection depth and multiple injection sites that are typical of conventional subcutaneous injections. The infusion site needs to be changed only once every 2–3 days. Therefore, insulin pumps terminating the need for multiple injections on a daily basis can lead to less insulin variation [49, 50].

In 1963, the first portable insulin pump was invented by Dr.Arnold Kadish but it was limited by its size and technical issues [51](Fig. 69.7). In 1979, the first commercial insulin pump was introduced in the USA [20]. In 1976, Dean Kamen introduced the first wearable insulin pump, known as the "blue brick" and later the "autosyringe," and led to the introduction of insulin pump therapy in the same year [52]. The first SOOIL insulin pump was clinically evaluated at Seoul National University Hospital in 1979 [53]. In 1983, MiniMed introduced their first insulin pump, MiniMed 502. In 1986, MiniMed introduced the implantable insulin pump to deliver insulin intraperitoneally. Insulin delivered through this device was absorbed quickly and directly to the portal system [54]. In 2000, new versions of the pump with improved memory and battery life were launched on the market. Later in 2007, implantable insulin pump devices were discontinued by Medtronic.

In the 1990s, new-generation external pumps were released which are comparatively small, compact, handy, and effective. These "smart pumps" have characteristics as built-in bolus calculators, personal computer interfaces, and alarms [55]. The insulin pump models which are approved on the global market are Medtronic MiniMed,

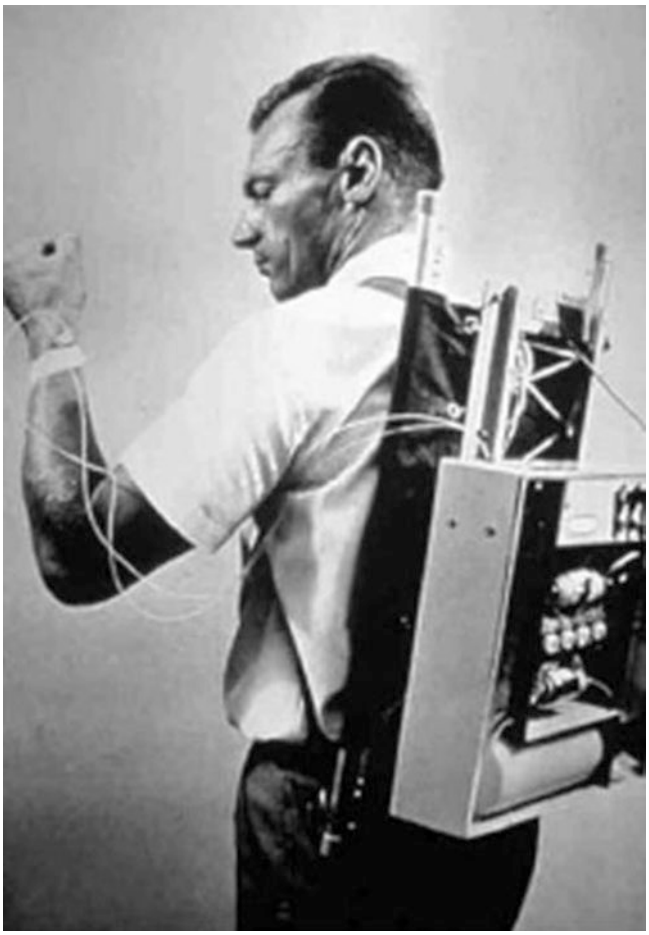


Fig. 69.7 Dr. Arnold Kadish with the first insulin pump

OmniPod (Insulet), T:Slim (Tandem), DANA R (SOOIL), Cellnovo, Accu-Chek Solo Micropump (Roche), and Ypsomed [56].

Medtronic introduced the first-ever "intelligent" insulin pump in 2003. The system comprises a MiniMed Paradigm 512 insulin pump and a Paradigm Link blood glucose monitor. Nowadays, BG readings from the glucometer are wirelessly and automatically transmitted to the insulin pump, and the required insulin doses are recommended by a Bolus Wizard calculator [57].

Insulin pumps are commonly used for insulin replacement in T1DM patients, but it has now been widely used by T2DM patients as well [58]. In patients with hyperglycemia, diabetes management with CSII provides better glycemic and metabolic control (reduces HbA1c, glycemic variation, and hypoglycemia) [59, 60]. The use of insulin pumps contributes to the patients' quality of life. However, the major limitations associated with the infusion sets are that they can exhibit handling issues and can detach, leak, or cause skin irritability, thus undermining the convenient use of insulin pumps [61]. Patient education before starting CSII therapy is of utmost importance to avoid the chances of a "pump failure" [62].

Patch Pumps

The barriers associated with infusion set have led to the development of "patch pumps." These pumps are free of infusion sets, small, lightweight, and attached to the skin through an adhesive. Patch pumps also offer additional comfort and flexibility to users, especially while traveling. Insulet introduced OmniPod, the first tubeless insulin pump in 2011. It consists of an integrated infusion set and automated inserter that converses wirelessly with an integrated BG meter. The Omnipod patch pump provides complete freedom to the users to engage in routine activities [63]. The specific simplified patch pump models available on the market are V-Go (Valeritas) and PAQ (CeQur) [64]. The second-generation Omnipod, which is smaller and more compact was launched in 2013. This version of the patch pump has modern features such as "human factor screens" and improvements in both correction and meal boluses for insulin dose calculation [65].

Continuous Intraperitoneal Insulin Infusion (CIPII)

Continuous intraperitoneal insulin infusion (CIPII) is considered to permit the infusion of insulin into the peritoneal cavity. The advantage of this method is that it more closely coincides the physiology than the other conventional therapies [66]. Two different technologies have been developed in CIPII: implanted intraperitoneal pumps such as MiniMed MIP2007C (Medtronic) and a percutaneous port attached to an external pump such as the Accu-Chek Diaport system (Roche Diabetes Care). The MIP 2007C is implanted under the subcutaneous tissue in the lower abdomen, and from this subcutaneous pocket, the peritoneum is opened, and the tip of the catheter is carefully inserted and directed towards the liver. After implantation, at least every 3 months the pump reservoir is refilled in the outpatient clinic with concentrated insulin transcutaneously. The Accu-Chek Diaport system permits insulin infusion into the peritoneal cavity through an Accu-Chek insulin pump and an infusion set. CIPII has been proven as a viable option for T1D patients with skin problems and unable to securely or efficiently control their diabetes with subcutaneous insulin [67].

The drawbacks of this route of insulin administration include the invasive nature, cannula blockage, higher cost, portal vein thrombosis, and peritoneal infection. Medtronic announced the worldwide termination of the implantable insulin pump in 2007.

Sensor-Augmented Pump Therapy (SAP)

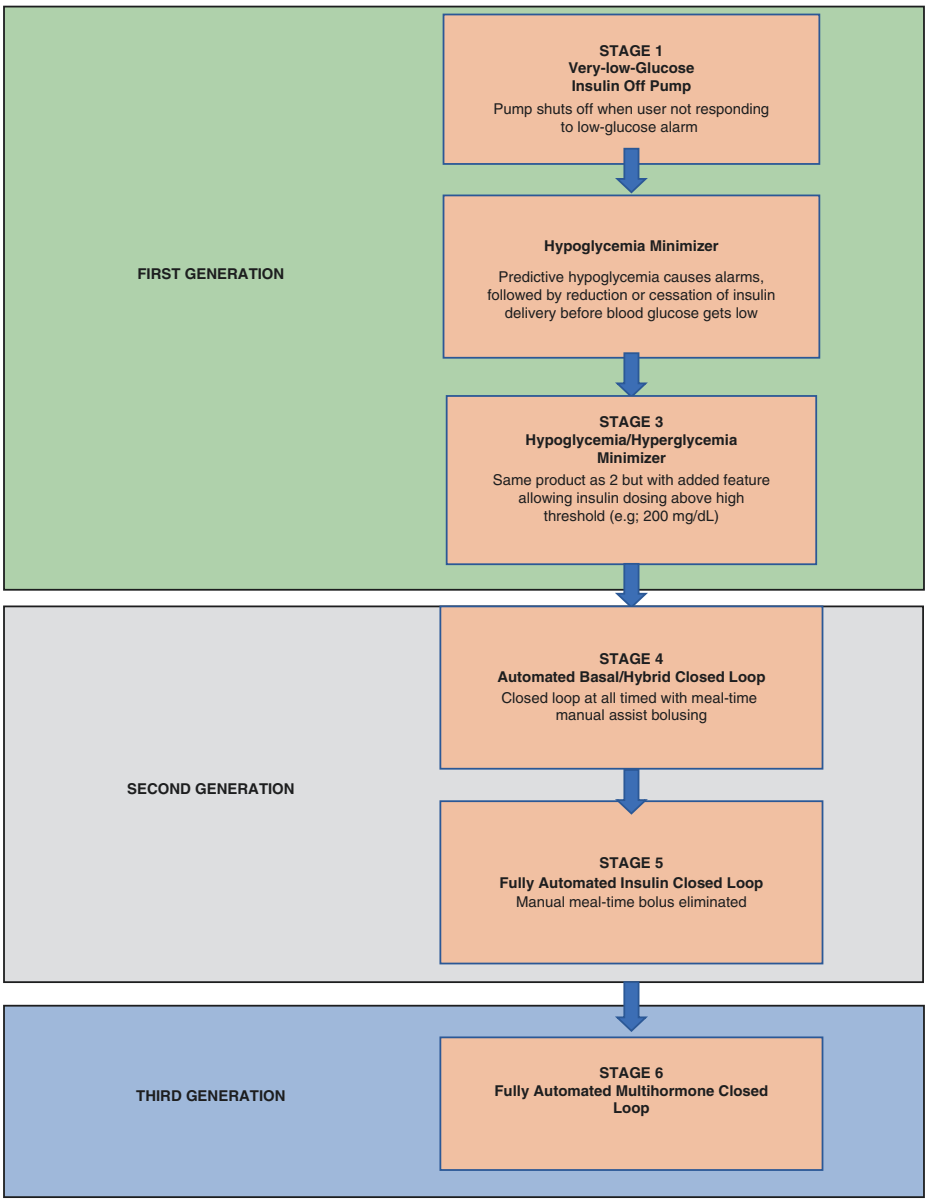
The new generations of CGMs are more accurate, smaller in size, and shown to improve glycemic control in patients with T1DM [68]. When CGM readings are used to adjust insulin

delivery through an insulin pump, it is known as sensor-augmented pump (SAP) therapy [69]. In patients with T1DM, SAP reduces A1c by 0.7–0.8% compared to baseline or MDI therapy. The introduction of real-time, sensor-augmented insulin pumps is considered a major turning point in the development of "closed-loop" insulin delivery or an artificial pancreas (AP) [1]. SAP therapy produces higher-level results in reducing hypoglycemia and achieving glycemic control to conventional therapies [70, 71].

Medtronic launched the MiniMed Veo System in 2009, with a Low-Glucose Suspend feature that automatically halts insulin delivery when sensor glucose levels reach a preset low threshold. This device has been considered the first stepping stone to an AP system [72].

The pump provides more accurate dosing, avoids the need for multiple daily injections, and thus provides convenience and a flexible lifestyle. They can also store a plethora of data that can be transmitted to computer programs or bolus insulin calculators and further analyzed to make insulin dose adjustments. The limitations of pump therapy are technical problems associated with the infusion set and higher acquisition costs. Patients also complained of skin irritations and infections at the insertion sites. Technical issues such as kinking, bending, or crimping of inserted cannulas and leakage of infusion sets have also been observed [61]. SAP requires patient involvement for using CGM glucose readings to adjust insulin pump delivery. This makes SAP susceptible to human errors.

Automation of Insulin Pump



Artificial Pancreas (Closed Loop)

MiniMed 530G with an Enlite sensor has been acknowledged as a first-generation artificial pancreas (AP) device system with Threshold Suspend automation. In 2013, this device was approved by the FDA for diabetes patients >16 years of age [55]. In 2015, Medtronic introduced the MiniMed 640G system, which has been taking one step closer to the artificial pancreas system. This system has integrated smart characteristics such as active insulin tracking, a bolus progress bar, and predictive battery life [73] (Fig. 69.8).

Since the conception of CSII, the main aim was to design an artificial pancreas that mimics exquisite sugar control with minimal human interference. An artificial pancreas or a "closed-loop" is a compilation of progressive technologies to engage automation to achieve glycemic targets. Generally, AP links three devices [74]:

1. A sensor like CGM that measures BG and sends data to a computer algorithm
2. A control algorithm to analyze the data and calculate the required insulin dose
3. An insulin infusion pump to deliver insulin as per the computer instructions

Fig. 69.8 A new-generation insulin pump: MiniMed 640G insulin pump system by Medtronic

Since 2016, safety and efficacy studies have been conducted on the combinational use of the predictive low-glucose suspension algorithm (PLGM) (commercially, "SmartGuard technology") with the MiniMed 640G insulin pump that automatically suspends insulin delivery based on the prediction of low glucose levels [75]. In 2017, the first hybrid closed-loop system, the MiniMed 670G insulin pump with a Guardian 3 sensor, was approved by the FDA (Fig. 69.9). When in auto mode, it functions as a hybrid closed-loop system that automatically controls basal insulin delivery every 5 min based on the CGM values to hold BG levels tightly to the specific target [8]. These systems have been reported to enhance glycemic targets [BG, HbA1c, time-in-range (TIR)] and reduce the incidence of nocturnal hypoglycemia to improve better safety, treatment satisfaction, sleep quality, and cognition in T1D patients [76–78].

In 2018, the FDA approved Insulet's Omnipod Dash System, a CSII system comprising a tubeless, waterproof, Bluetooth wireless technology pump with a capacity of 200 units of U-100 insulin and an advanced personal diabetes manager (PDM) that regulates the pump [79] (Fig. 69.10).

In 2021, Medtronic launched new MiniMed 780G insulin pump designed to work with Medtronic's Guardian sensors to continuously monitor glucose levels throughout the day (Fig. 69.11). Basal insulin adjusts insulin dosage every five minutes as needed based on glucose levels. Bolus is delivered automatically up to every 5 min if maximum auto basal delivery is reached or if glucose level is above 120 mg/dL. This pump helps to achieve the Time in Range goal of >70% and HbA1c goal of 7.0%.

Future steps in the evolution of the artificial pancreas will be [80]:

1. Use of predictive algorithms to minimize hypoglycemia even before hypoglycemia occurs.
2. Use of algorithms to keep blood sugar in target range (hypoglycemia/hyperglycemia minimizer).
3. Automated basal and/or hybrid closed-loop.
4. Fully automated (insulin).
5. Dual (insulin + glucagon) hormonal closed-loop.

Fig. 69.9 First Artificial Pancreas: MiniMed 670G insulin pump system with Guardian 3 sensor

Fig. 69.10 Omnipod DASH pump

Fig. 69.11 MiniMed 780G System

Alternate Controller-Enabled Infusion (ACE) Pumps

Another modern technology in this area has been the arrival of alternate controller-enabled (ACE) infusion pumps. Despite the conventional stand-alone pumps, ACE pumps can be interoperable: used jointly with different components of diabetes technologies, permitting custom-made diabetes management for patients according to individual device preferences. The ACE insulin pump can be combined with automated insulin dosing (AID) systems, CGMs, BG meters, and other electronics. In 2019, the FDA approved the first interoperable t:Slim X2 insulin pump for subcutaneous insulin delivery for children and adults with diabetes [81]. The FDA approved a new-generation, interoperable, control-IQ artificial pancreas system (tandem diabetes) in 2020. A clinical trial that revealed that the use of the control-IQ AP system was linked with a greater percentage of TIR, over the use of SAP, paved the way for this approval [78].

Do-It-Yourself Artificial Pancreas (DIY-APS)

People affected by T1DM have been expecting an affordable and efficient solution for the management of this chronic disease for decades. Lack of accessible and actionable data, unaffordability of the current systems, and long timeline of

medical device development cycles have led to general annoyance in the T1DM community. The first Diabetes Mine D-Data Exchange gathering at Stanford University spotlighted the sentiments and frustrations of patients with T1D and their families/caregivers gathered online under the hashtag "#WeAreNotWaiting" in waiting for their needs to be addressed in 2013. This event marked the beginning of the DIY-APS movement. A major dimension of the #WeAreNotWaiting initiative was that the tech-savvy diabetes followers started self-building their closed-loop systems, also known as "looping." These automated insulin delivery systems are generally known as a "Do-it-yourself" artificial pancreas (DIY-APS) [82, 83]. The basic components of DIY-APS are:

(a) A real-time CGM.
(b) An insulin pump.
(c) A minicomputer or smartphone app.

The diabetes community shared DIY diabetes device-related projects on digital and social media platforms such as Facebook, Twitter, NightScout, and GitHub, which led to the merging of these projects [84]. Through a gradual and systematic method of assembling, merging, and processing data from patients' devices to deliver significant actionable information, there has been a rush in the propagation and convergence of DIY diabetes device-related projects. Dana Lewis, Scott Leibrand, and Ben West launched the OpenAPS project, providing the instructions and outline of a DIY patient-built artificial pancreas system (APS) in 2014. In 2015, the open-source version, also known as OpenAPS, was launched [85]. On January 31, 2020, more than 1776 PWD around the globe have implemented various layouts of DIY-APS [86]. DIY-APS uses individually made unauthorized algorithms to convert CGM data and calculate insulin doses, FDA approved communication devices and insulin pumps. Since it involves the use of unauthorized algorithms, these systems are not FDA approved, commercialized, or regularized. In 2017, another innovation in the DIY-APS evolution was "RileyLink," designed by Pete Schwamb for his daughter Riley, who had T1D. It is a translator device that allows easy communication between the insulin pump and iPhone. This device is considered more user-friendly, and it is easy to set up and maintain procedures [87]. Real-life experiences from patients and caregivers, unscientific data, and published reports from selected cohorts have highlighted the clinical benefits and reductions in self-management burden with DIY-APS [88].

In India, Jazz Sethi, a 26-year-old professional dancer from Ahmedabad, who has been living with T1D since the age of 13, is the first user of Do-It-Yourself (DIY) artificial pancreas. *Diabetes and Metabolic Syndrome: Clinical Research and Review* has narrated her experience with this breakthrough technology, why she decided to use the system, and how the device has produced significant improvement in her quality of life and management of T1D [89].

There are mainly three types of DIY-APS:

1. OpenAPS
2. AndroidAPS
3. Loop

OpenAPS

OpenAPS is a safe, powerful, and easily understandable system that proposes to adjust insulin dosage to manage the BG levels in the recommended range, overnight and between meals. The first Open APS was developed by Dana Lewis, Scott Leibrand, and Ben West, and the code written with the help of Chris Hannemann was on a Raspberry Pi computer and a communication stick to connect to an old Medtronic pump.

Generally, an OpenAPS consists of an insulin pump, a CGM system, and an algorithm running on a microcomputer. The algorithms used in OpenAPS are oref0 (OpenAPS Reference Design Zero), Adjusting for unexpected BG deviation, and Bolus snooze. Recently, an "Advanced Meal Assist (AMA)" feature has been integrated into the OpenAPS algorithm. AMA gives an extremely adaptable algorithm for securely dosing insulin after meals, regardless of broadly differing meal types, and the high variations in rates of digestion between individuals, making it the most widely used postprandial insulin dosing algorithm. The ultimate aim of the OpenAPS system is to completely automate insulin dosing in all situations. In that regulation, an oref1 algorithm has been developed that utilizes small "supermicroboluses (SMB)" of insulin at mealtimes and ensures more rapid and secure insulin delivery in response to BG rises [90].

OpenAPS reads the CGM data every 5 min and queries the insulin pump every few minutes for recent settings and activities such as current and maximum basal rates, recent boluses, insulin on board (IOB), insulin sensitivity factor (ISF), carb ratio (CR), duration of insulin acting (DIA), and BG target/ range. Based on the communication from the insulin pump, OpenAPS updates the bolus wizard calculation and decides upon whether to cancel or supply a temporary basal. OpenAPS accomplishes this function through a physical piece of hardware called a "rig" that implement a sequence of commands to collect the CGM data, runs it through Oref0, and performs the dose calculations based on the pump setting values. The system can guide on changes in insulin to carbohydrate ratios and ISF settings through either Autosens (checking back 8–24 h) or Autotune (check back either 24 h or a user-specified period). However, this was the first developed system; recent users have been preferring AndroidAPS which offers more combinations of compatible devices and in-warranty pumps.

AndroidAPS

AndroidAPS is an open-source app with all properties of OpenAPS but runs on Google Android smartphones. The smartphone receives data from a CGM and transmits it with the insulin pump via Bluetooth. In 2017, the first AndroidAPS was developed in Europe by Milos Kozak and Adrian Tappe and it works with modern in-warranty pumps with Bluetooth capability. The algorithms used here are Oref0 and Oref1. The app is available in different versions particular to geographic locations and languages. The basic elements of the profile include basal rates (BR), ISF, CR, and DIA. AndroidAPS supplies multiple possibilities for remote monitoring of adults and pediatric patients with T1D. NSClient app can be used to check the relevant data by parents and caregivers of kids with T1D on their Android phones. Features like alarms using the xDrip+ app in follower mode, remote monitoring and control with SMS commands, and remote profile switch and temperature targets through the NSClient app provide the kid-friendly convenience of this system.

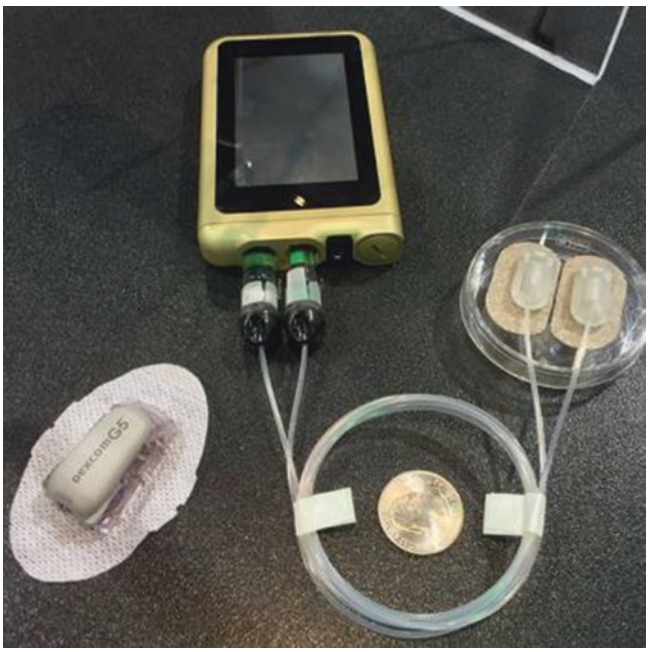


Fig. 69.12 iLet Bionic Pancreas

Loop

The Loop algorithm is different from OpenAPS and runs on an iOS operating system. The Apple iPhone receives CGM data and communicates with the insulin pump via Bluetooth. In 2016, the first loop was developed by Nate Racklyeft and a D-Dad, Pete Schwamb. Loop makes use of a free application, Xcode, to convert the raw code into an iOS application and install it on an iPhone. Loop documentation is available on GitHub and the builders need to register as Apple developers to install the necessary software. The loop makes a forecast using BG values every 5 min from 30 min ago and integrates between that value and the current glucose value to make adjustments in insulin dose and to provide bolus recommendations and temporary basal rates. The app communicates with a small translator device called RileyLink that ensures interaction between the pump, iPhone, and CGM [90]. It is almost the size of a tic-tac box and needs to be carried with you at all times. In a loop system, the pump speaks via radio language and the iPhone speaks via Bluetooth, and RileyLink acts as a translator to loop these parts together.

Bionic Pancreas (BP)

The "bionic pancreas" is a type of closed-loop system consisting of two infusion pumps (separately for insulin and glucagon) and connected to a CGM via a smartphone app. In 2015, the first bionic pancreas, "iLet" (Beta Bionics), exclusively for T1D treatment, was innovated by Dr. Edward Damiano. In this system, based on the appraised CGM data automated dosing assessments of insulin and glucagon levels are made every 5 min (Fig. 69.12). These data are transmitted to pumps to control insulin or glucagon delivery [91]. In 2019, the FDA approved iLet BP as the "breakthrough device designation" [92].

D-Dads

D-Dads are fathers whose fatherhood has been challenged by T1D. Unsatisfied with the disruption and unpredictability of diabetes care, some D-dads thought "outside the box" to ease the burden of diabetes management.

Dr. Edward R. Damiano, a professor of biomedical engineering at Boston University, was determined to develop a bionic pancreas when his 11-month-old son, David, was diagnosed with T1D. Frustrated with the absence of reliable technologies, he created a bionic pancreas with the help of physicians and researchers [93]. The US Food and Drug Administration (FDA) conferred "breakthrough device designation" to the iLet bionic pancreas in 2019 [94]. Pete Schwamb, a software engineer, made innovatory contributions in the field of diabetes technologies. Pete's effort to gain access to the insulin pump data of his 6-year-old daughter, Riley, led to the development of RileyLink, a translator device used to communicate between the insulin pump and iPhone. Later, he developed the first iOS-based automated insulin delivery system, "loop," in association with Nathan Racklyeft [95]. Bryan Mazlish, a Wall Street quantitative analyst and one of the cofounders of Bigfoot Biomedical, made a fully functional homebrew artificial pancreas to manage

his son's T1D. Being a hacker by profession, he has been recognized as a standard-bearer for the DIY-APS hacking mission [93]. Jeffrey Brewer, a past president of the Juvenile Diabetes Research Foundation (JDRF), also known as "the father of the artificial pancreas," has commenced research projects on automated insulin delivery systems. Later, he co-founded Bigfoot Biomedical accompanying Bryan Mazlish to develop its own closed-loop system, the Bigfoot smartloop system [96]. John Costik, the father of a 4-year-old boy, Evan, who had T1D, designed a code to hack his son's CGM, to upload the values into the cloud and remotely acquire those data using a web-based or android interface. He later made the code available as open-source and initiated "Nightscout CGM in the Cloud Project" for wider dissemination of the technology [85, 97]. Lane Desborough, D-Dad of Hayden is the name of an engineer from Medtronic, one of the so-called D-dads in diabetes technology by Nightscout CGM in the Cloud. He was a chief engineer at Medtronic and was one of the advocates of the #WeAreNotWaiting movement. Lane was the first person to get involved in the DIY-APS movement from the industry and later co-founded Bigfoot Biomedical [98]. Tidepool, a non-profitable organization was started by the D-Dads Howard Look and Steve McCanne and has been creating a regulated loop version of DIY-APS. Tidepool is currently on a venture to release a regulated version of the DIY-APS in collaboration with Omnipod and Dexco [99, 100].

D-Dads have been making significant contributions to turn the artificial pancreas dream into reality while focusing on its equitable access and affordability.

Bolus Calculator Apps

Bolus calculator/bolus advisor mobile apps are used for insulin dose calculation available in smartphones. These can function independently or can be integrated into pumps to calculate the accurate insulin dose by incorporating expected carbohydrate intake, measured blood glucose values, and previous insulin doses [101]. The most commonly used bolus calculator apps are Diabetes: M, mySugr (Roche), and PredictBGL. Bolus wizards are built-in automated bolus calculators specific to insulin pumps for insulin dose recommendations. The use of bolus wizards has been correlated with better glycemic control and treatment satisfaction [102]. In 2016, Endocrine Society Clinical Practice Guidelines have strongly promoted patients to use suitably adjusted built-in bolus calculators in CSII to improve glycemic control [103].

Implanted Pancreas

Another novel AP technology was the implanted artificial pancreas, a fully implantable insulin delivery device, which is under development at De Montfort University. It is a gel-based system that responds to BG variation by changing the insulin delivery rate. The performance of this system in glycemic control is well tested in a diabetic domestic pig [104]. It reduces hourly management and human interference to improve user acceptance and quality of life in diabetes patients [105].

Insulin Inhalers

Insulin delivery to the lungs was the first reported substitute for subcutaneous injection. It has long been estimated that insulin delivery by aerosol reduces blood glucose [106]. Insulin inhalers permit patients to breathe fine-inhalable insulin (pulmonary insulin) (either dry powder-based formulations or solution) into their lungs [12].

Advantages of the pulmonary route include a broad and well-perfused absorptive surface, the 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" [107]. Although the exact mechanism of insulin absorption across the pulmonary epithelium remains unclear, it is believed to involve transcytotic and paracellular mechanisms [106].

When introduced to the market, inhalable insulin was considered a remarkable innovation to address needle phobia and incorrect insulin injection techniques pertained to systemic insulin delivery methods [108]. In 2006, the first inhaled product Exubera® was approved by the US FDA. 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 [109]. Exubera® was found to have pharmacokinetic and pharmacodynamic (PK/PD) properties similar to insulin aspart with a faster onset of action (10–15 min) [110]. In clinical trials in patients with uncontrolled T1DM and T2DM, Exubera® was found to reduce postprandial blood glucose and A1c markedly [111] although Exubera® was contraindicated in smokers as it increased the risk of hypoglycemia due to greater absorption compared to nonsmokers [112]. Along with this, patients were required to undergo pulmonary function tests before treatment initiation, after 6 months, and annually thereafter [109, 112]. This product did not flourish well commercially despite the noninvasive route possibly due to higher cost, the bulky delivery device, concerns related to decline in pulmonary function, and less preference by the patients and physicians. In 2007, this product was withdrawn from the market due to poor sales volume.

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 [113]. Initially, the common side effects are transient non-productive cough and a modest

reduction in lung function [114]. In 2014, Afrezza got FDA approval for prandial insulin therapy [115]. The delivery system of Afrezza is small, handy, and displays the dose in units [116]. The use of Afrezza has provided remarkable glycemic control and reduction of hypoglycemia in T1DM patients [117, 118]. The recognition of inhalable insulins is further limited by insurance barriers, safety concerns, and competing products [116].

Jet Injectors

Another possible innovation to the market could be jet injectors, a type of syringe that dispenses insulin subcutaneously with the use of a high-pressure air mechanism. In the 1860s, Pioneer jet injector technology was introduced. Later, it was reintroduced in the 1940s as the "Hypospray," focusing on patients' self-management of insulin. In the 1950s, the US military designed a high-speed system, "Ped-O-Jet" (Keystone Industries), in the category of a multiuse nozzle jet injector (MUNJI) for mass vaccination programs. In 1997, the Ped-O-Jet was discontinued as a result of contamination issues built with the use of MUNJI [119]. During the 1990s, the new-generation, disposable-syringe jet injectors (DSJIs) with disposable dose chambers (insulin cartridge) and nozzles were launched. Even though the idea is not firsthand to the market, the wider acceptance of these devices has been interrupted by the cost, low absorption with the repeated use, and high contamination rates of the previous systems [120]. The jet injectors are a solution for patients with needle phobia [121]. Recent safety and feasibility studies have assessed the treatment efficiency and pharmacokinetic and pharmacodynamic (PK-PD) profiles of the insulin administered by the new-generation jet injectors [122].

Oral Insulin

The oral route of insulin administration may be the most patient-friendly way of taking insulin and it could more closely imitate physiological insulin delivery (more portal insulin concentration than peripheral) [123]. Despite this, the limitations in making oral insulin include inactivation by proteolytic enzymes in the GI tract and low permeability through the intestinal membrane due to the 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 [124–129].

Certain oral insulin preparations such as Capsulin, ORMD-0801, IN-105, oral hepatic directed vesicles, and Eligen have undergone phase 1 and phase 2 trials with promising results [130].

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 achieving systemic therapeutic goals. The large intestine is preferably not suited for absorption processes for drugs but it has certain advantages over the small intestine like long transit time, lower levels of peptidases (prevent the destruction of peptides), and higher responsiveness to permeation enhancers. Accordingly, it has been under extensive inquisition as a possible strategy to enhance 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 [131].

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 and despite its progress, there is still a long way to go before these products will be available on 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 appealing for the delivery of insulin. However, intranasal delivery has disadvantages such as limited permeability of a large molecule through the nasal mucosa and rapid mucociliary clearance resulting in variable absorption [132].

Significantly, intranasal delivery with early porcine and bovine insulins was studied in patients with T1DM [133, 134]. Currently, two technologies are under investigation: Nasulin™ (CPEX Pharmaceuticals) and nasal insulin by Nastech Pharmaceutical Company Inc. Both insulin preparations have a bioavailability of about 15–25% with the onset of action approximately 10–20 min [135, 136]. The substances such as bile salt, surfactant, and fatty acid derivatives are being investigated to improve mucosal permeability of insulin but they increase the risks for local irritation, nasal secretion, sneezing, or burning sensation [137].

Nasal insulin crosses the blood-brain barrier since it has a hypothesized effect on memory function [138]. Treatment with intranasal insulin improved memory, preserved caregiver-rated functional ability, and preserved general cog-

nition without any remarkable hypoglycemic event. These improvements in cognitive functions were combined with changes in the Aβ42 level and in the tau protein-to-Aβ42 ratio in cerebrospinal fluid [139]. Based on these, investigations are ongoing to evaluate the usefulness of this agent for the treatment of Alzheimer's disease.

Buccal Insulin

Buccal delivery of insulin has similar efficacy as oral insulin with the advantage of bypassing GI degradation. In addition, the relatively large surface area results in better bioavailability [140]. 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 (RapidMist™). Eli Lilly and Generex conducted phase 1 and phase 2 trials in patients with T1DM and T2DM with favorable results [141]. Another fragment being developed by Shreya Life Sciences Pvt. Ltd., India, is oral Recosulin® [142].

Another technique for the delivery of insulin is fast dissolving films as a substitute to oral tablets for rapid drug delivery [143]. The Monosol Rx (Pharm Film Drug delivery technology) in collaboration with Midatech Company developed Midaform™ insulin, which is delivered by buccal route.

Transdermal

Transdermal insulin delivery terminates the problems associated with needles and injections and the large surface area of the skin makes it an appropriate route for insulin delivery. Although the perforation of insulin is halted by the stratum corneum, the outermost layer of the skin, numerous methods have been explored to overcome the barrier of the stratum corneum [144].

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

(a) Iontophoresis, the technique that uses small electric currents [145].
(b) Sonophereis or phonopheresis uses ultrasound waves [146].
(c) Microdermal ablation by removing the stratum corneum [147].
(d) Electroporation utilizes high voltage pulses that are applied for a very short time [148].
(e) Transfersulin is the insulin encapsulated in transferosome, an elastic, flexible vesicle, which squeezes by itself to deliver drugs through skin pores [149].
(f) 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 [150].
(g) Recombinant human hyaluronidase (rHuPH20) to increase insulin absorption from subcutaneous tissue [151].

Moreover, microneedles with a 1 μm diameter and of various lengths can deliver insulin in an effective, accurate, and precise manner [152]. 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.

Other Non-conventional Routes

Ocular Route

No human trial has been reported with this route and an animal study failed to achieve significant plasma insulin concentration [153].

Rectal Route

Rectal gels [154] and suppositories [155] showed fair results. However, this route is not commercially viable.

Intra-Tracheal

In 1924, the administration of insulin was reported [156] but is not practical so not taken up for further development.

Conclusion

There is a long history of research focusing on recognizing 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 has its own potential advantages and disadvantages. There has been a high-speed evolution in diabetes technologies to improve the quality of life and to extend the endurance of subjects with diabetes. Though there were commendable developments in the currently available devices, many of those were prohibitively expensive. Additionally, there were serious issues associated with cannula blockages, infusion set handling, Bluetooth connectivity, and user-friendliness. As the search for more accurate and user-friendly methods continues, advances in pumps, CGMs, and predictive algorithms can

make the closed-loop system as physiologic as possible with >90–95% TIR and the least time spent in hypoglycemia. Some of the promising experiences are shared by subjects using DIY-APS. The DIY revolution has prompted all device manufacturers to introduce ACE pumps and compatible sensors. The ultimate dream is to develop an artificial pancreas capable of 100% TIR and 0% time below range and affordable to everyone. Even though the mission demands enormous commitment and time, it has the potential to transform diabetes therapy.

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