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Advancement in Insulin Delivery Over the Period

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KEYWORDS

Insulin, Insulin delivery devices, Do- it-yourself Artificial pancreas, Insulin inhalers, Transdermal route, Oral insulin delivery.

ABSTRACT:

Insulin is a peptide hormone that regulates blood glucose in the body and is secreted from the β-cells of the pancreas, an organ situated behind the stomach, and is the primary source of insulin in the body. The year 2021 has completed 100 years in the discovery of insulin. The discovery of insulin proved to be a lifesaving phenomenon for people suffering from diabetes. Diabetes is a condition that may occur in two states: when the pancreas is not able to produce enough insulin or when the body is not able to use it. Delivery of insulin in the body was quite a typical task earlier because it cannot be directly administered orally like any other medicament. Therefore, various delivery devices are developed and chosen for the successful delivery of insulin in the body, the most promising devices are insulin syringes, jet injectors, pumps, and pens. In addition to this, a DIY-APS (Do-It-Yourself Artificial Pancreas) represents a significant milestone in diabetes treatment. This review centers on the progress and transformation of insulin delivery devices throughout history up to the present day.

1. Introduction

Insulin is a peptide hormone which means it is made of a small chain of 51 amino acids.[1] It is secreted from the pancreas, a leaf-shaped organ present under the liver, and close to stomach.[2] Insulin was successfully discovered in 1921 to treat diabetes at Toronto General Hospital.[3] The human body produces basal insulin continuously and bolus insulin after meals, regulating blood sugar. Diabetes results from insulin issues, causing potential organ damage and hyperglycemia.[4] It is essential to recognize individuals with diabetes, especially those in the early stages of type 2 diabetes, may not manifest any symptoms. If left unaddressed, unmanaged diabetes can result in severe consequences, such as coma, stupor, and, in rare instances, even fatality or ketoacidosis.[5] Insulin therapy is vital for individuals with type 1 diabetes due to inadequate natural insulin production. Type 2 and gestational diabetes may also require insulin when other treatments are ineffective.[6] Doctors hesitate to prescribe insulin due to complex dosing and patient fears, including needle aversion, elderly limitations, and misconceptions about insulin safety.[7]

2. History

Frederick Banting, a plastic surgeon, devised a groundbreaking method in 1921 to isolate islets by clamping a dog's pancreatic duct, rendering acini dead while keeping islets alive. Collaborating with John McLeod, an anatomist and director of the University of Toronto, and student Charles Best, they initiated

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experiments using ten dogs to discover that insulin effectively lowered blood sugar. Biochemist J.B. Collip joined the team to make islets available to people. On January 11, 1922, Banting and Best administered insulin to a 14-year-old boy, successfully reducing blood sugar and marking a significant medical breakthrough. This accomplishment led to the Nobel Prize awarded to Banting, Best, and MacLeod in 1923.[7,8] The structure of insulin is shown in Fig.1

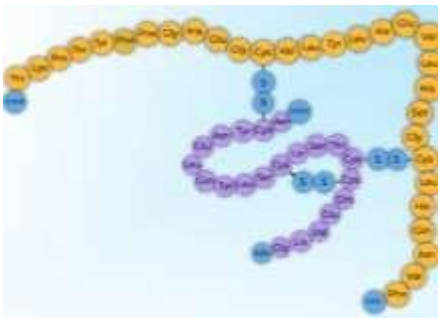

Fig.1 Structure of Insulin

3. Diabetes

Diabetes is a state that affects the body's ability to effectively process glucose, a type of sugar. This condition can be chronic and long-term. When there is not enough insulin being produced by the pancreas or when the body's cells cannot use insulin efficiently, blood sugar levels increase. If not handled correctly, this could cause major health issues.[9]

Diabetes is divided into four categories:

I. **Type-1 Diabetes-** Around 5-10% of diabetics experience type-I diabetes, characterized by β-cell destruction due to immune responses. Often called "juvenile diabetes," it affects youth and requires lifelong insulin management, primarily linked to genetic predispositions. Type-I diabetics may also be at risk for other autoimmune conditions.[10]

II. **Type-2 Diabetes-** Type-II diabetes mellitus (T2DM), a prevalent metabolic disorder globally, results from disrupted insulin secretion and sensitivity. Factors like high-calorie diets, obesity, aging, and medical history contribute to its widespread prevalence.[11]

III. **Latent autoimmune diabetes in adults (LADA)**- This unique diabetes variant is identified by autoantibodies targeting islet antigens. Around 10% of type II diabetes cases exhibit such autoantibodies. It often manifests early due to beta-cell loss and insulin resistance. Immunomodulator therapy is the primary treatment option for this condition.[12]

IV. **Gestational diabetes mellitus (GDM)-** Gestational diabetes mellitus, a condition of chronic high blood sugar in pregnancy, often results from pancreatic beta-cell dysfunction. Risk factors include obesity, older age, and family history of diabetes. Management involves diet, exercise, and medications like Metformin, and insulin.[13]

4. History of Insulin Delivery Devices

Healthcare professionals face continuous growth as more people with insulin-managed diabetes seek out or utilize automated insulin delivery (AID) systems.[14] Insulin delivery devices and techniques have evolved largely over the past few years. These devices have been developed to ease the self-administration of insulin for diabetic patients. Below are the discoveries made in insulin delivery devices from the beginning till date.[15,16]

Table 1: History of Insulin Devices

Years	Discovery
1921	Discovery of insulin.
1924	First specialized insulin syringe.
1954	First disposable glass syringe 'HYPAK'
1963	First insulin pump.
1985	First insulin pen 'Novopen' by NovoNordisk.
1990	Introduction of smart pumps.
2015	Artificial pancreas, first DIY-APS.
2017	Insulin pump + Guardian 3 sensor.
2020	FDA approval for Tandem-control-IQ-AP
2023	iLet Bionic pancreas

5. Types of insulin delivery devices:

I. **Insulin Syringes**

In 1924, scientist Becton Dickinson (BD) pioneered the inaugural customized insulin syringe. In 1925, Novo Nordisk unveiled its "Novo Syringe," marking

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a transition from unwieldy metal and glass syringes, prone to degradation and breakage.[17] Therefore, Hypak™ the first glass syringe was developed in th e year 1954. Disposable plastic syringes were made available in the market in the 1960.[18]

Fig. 2 Insulin Syringe

Insulin Syringe Size:

Insulin syringes are available in a variety of sizes in the market as mentioned in Table 1. The size of the syringe prescribed to a patient by a doctor depends on the amount of insulin dose required in the body. The majority of syringes are available in 30-unit (0.3 ml), 50-unit (0.5 ml), and 100-unit (1 ml) sizes. Insulin syringe sizes and markings facilitate accurate insulin dosage measurement, but patient needle apprehension hinders their preference despite various size options.[18]

Table 2: Dosing of Insulin

S.No.	Dose in units	Dose in ml	The use of dose is
1.	30 units	3/10 ml	Less than 25 mg
2.	50 units	1/2 ml	Between 25-40 mg
3.	100 units	1 ml	Greater than 40 mg

Drawback of Insulin syringes:

1. Patients find it hard to inject insulin multiple times daily.
2. Inaccurate dosing.
3. Educating people about how to inject syringes was time-consuming.[17]

II. Insulin Pens

V The delivery of insulin through a syringe proved challenging due to issues like painful injections and needle thickness. In 1985, Novo Nordisk introduced the Novopen®, a reusable insulin pen, offering a more convenient alternative for patients using long-acting or frequent short-acting insulin injections.[19] Insulin pens, favored by diabetics, provide convenient subcutaneous insulin dosing with minimal discomfort. These compact devices feature fine needles and pre-mixed insulin, superseding traditional syringes for basal and short-acting insulin delivery. The groundbreaking NovoPen® debuted in 1988.[19]

Fig. 3 Insulin Pen

Types of Insulin Pens:

Insulin pens are categorized into two parts:

- Reusable (durable) insulin pens.
- Prefilled (disposable) insulin pens.

Reusable pens are also known as durable pens, as they contain 1.5 ml of replaceable insulin cartridges, which get inserted in pen devices and are changed only after it is entirely utilized or after a month from the time the pen was first initiated.[20]

Prefilled pens, also known as disposable pens, are prefilled with insulin. Once it is entirely used, the pen is discarded and a new pen is prescribed. Usually, these pens typically last 28 to 32 days after being opened.[20]

Length of insulin needle:

Insulin pen needles range in length from 4 to 12.7 mm, with shorter needles found to be less intimidating, less painful, and less prone to injecting insulin into muscle tissue. These needles often have a gauge between 29 and 32, ensuring precise dosing without the need to pinch the skin.[21]

Smart Connected Insulin Pens:

The FDA-approved first insulin smart pen was launched on December 14, 2017, addressing the growing diabetes population. Advanced second-gen pens now offer USB/Bluetooth, improving patient health management through wireless data transmission, dose tracking, and app-based recommendations for medical professionals.[22]

IoT (Internet of Things) technology is used by smart insulin pens to monitor and control the supply of insulin to diabetic patients. They aid in treatment monitoring by wirelessly transmitting dose and schedule data.[23] Smart insulin pens (SIPs) have the potential to help diabetic patients with improved

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drug retention, glucose control, and management, time in a specific glucose range, dose precision, and a reduction in glycemic variability.[24]

Smart pens on the market store insulin injection data, offer bolus dose calculation, reminders, and compatibility with glucose monitors, aiding diabetes management.[25]

III. Insulin Pumps (Continuous Subcutaneous Insulin Infusion):

Insulin pumps are innovative tools for insulin delivery, suitable for interested patients. These pager-sized devices, connected through an infusion set, provide continuous insulin administration, featuring disposable reservoirs and infusion sets with cannulas for subcutaneous infusion, enhancing patient care.[26]

Arnold Kadish, a physician from Los Angeles, invented the very first insulin pump in the early 1960s. The initial version had to be carried like a backpack since it was so large. To give users better control over their insulin dosage and more effective blood sugar monitoring, more user-friendly versions with technologies like bolus planners and compatibility with laptops started to emerge in 1974 by Dr. Ernst Friedrich Pfeiffer. The device proved closed-loop glucose control but was too big for outpatient use.[27]

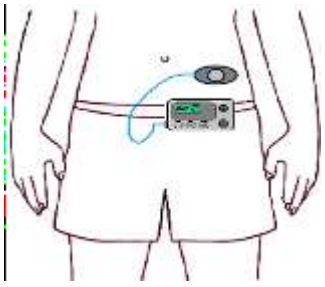

Fig. 4 Insulin Pump

Sensor-Augmented Pump Therapy (SAP):

The 2006 innovation by MiniMed, the MiniMed Framework, merges an insulin pump with CGM for real-time diabetes management. This technological fusion marks a pivotal step towards the development of a closed-loop insulin delivery system, as it combines two distinct technologies through the SAP platform.[28] SAP therapy surpasses other medications in reducing hypoglycemia and enhancing glycemic control. It employs the Low Glucose Suspend feature by Medtronic, halting insulin when glucose levels drop, marking a step toward closed-loop systems, and promising SAP therapy advancements.[29]

IV. Artificial Pancreas*:*

The closed-loop regulation of glucose levels in diabetes, or simply the artificial pancreas (AP), is a system that combines a sensor for measuring glucose, a control strategy, and an insulin delivery device.[30] In 1974, Albisser et al. introduced the concept of an "artificial endocrine pancreas," emphasizing the need for insulin secretion to maintain blood sugar levels within physiological norms, depicting it as a computerized system closely replicating pancreatic endocrine functions.[31,32]

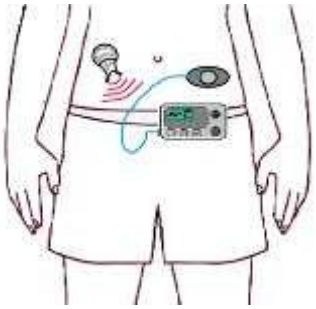

Fig. 5 Artificial Pancreas

Do-It-Yourself Artificial Pancreas:

People with T1D have been waiting for an affordable and effective treatment option for this disease for years. The T1D community has been frustrated by the lack of available data, the cost of existing systems, and the long-term development of medical devices. The phrase "#WeAreNotWaiting" was coined at the DiabetesMine D-Data ExChange event at Stanford University in 2013 to express the emotions and frustrations of people with T1D seeking help. The DIAPS movement started as a result of this.[33,34]

The OpenAPS project was started in 2014 by Dana Lewis, Scott Leibrand, and Ben West. Provides plans and instructions for the patient to create a DIY Artificial Pancreas System (APS). OpenAPS, commonly known as the open-source version, was released in 2015. As of January 31, 2020, more than 1776 disabilities worldwide are using various DIAPS configurations.[35]

V. Insulin Inhalers:

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Exubera® is a dry powder inhaler developed by Aventis and Pfizer for treating type 1 and type 2 diabetes as the first inhalable insulin preparation commercially available. Although technically a cutting-edge method for delivering insulin without needles, it was taken off the market in 2007 due to poor sales (Mack, 2007), a lack of clinician and patient acceptance, and a lack of cost-effectiveness (Black et al., 2007). Exubera's failure was due to high cost, dosing confusion, bulky size, and an FDA alert about lung cancer risk.[36]

Fig. 6 Insulin Inhaler

The FDA approved Afrezza inhalation powder in 2014 for T1DM and T2DM. The new Gen2 inhaler used by Afrezza is more compact and user-friendly than the previously accessible Exubera gadget. Afrezza® inhalation powder is a fast-acting insulin that is delivered through a breath-powered oral inhaler called Technosphere®.[37]The dosing of Alfrezza usually prescribed by doctors in terms of units is mentioned in Table 3

Table 3: Dosing for Alfrezza

Insulin Injected Dosing	Alfrezza Inhaled Dosing
Upto 4 units	4 units
5 to 8 units	8 units
9 to 12 units	12 units
13 to 16 units	16 units
17 to 20 units	20 units
21 to 24 units	24 units

VI. Transdermal Routes for insulin delivery:

Patients with diabetes typically receive instructions for self-administering subcutaneous insulin multiple times daily, requiring regular dose adjustments based on glucose levels and rigorous adherence to self-care guidelines. Nonetheless, this method carries inherent risks like microbe contamination, local tissue damage, and nerve injuries, potentially leading to decreased treatment compliance.[38] It offers several advantages over oral, pulmonary, and nasal delivery methods. It can alter digestive tract breakdown, provide sustained release, and encourage patient compliance for better glycemic control.[39]

Classification of Transdermal Insulin Delivery:

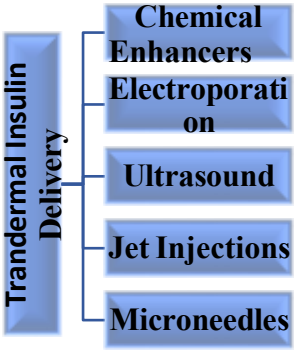

Fig. 7 Classification of Transdermal Insulin Delivery

- **Chemical Enhancer:**

Chemical enhancers can increase skin permeability for delivering medicines. They come in various forms, including chemical compounds, peptides, and vehicles. These enhancers can be added to the lipid bilayer to break down molecular stacking and extract molecules. According to Sintov et al.'s research, iodine effectively deactivates natural sulfhydryls, such as glutathione and gamma-glutamylcysteine, reducing disulfide bond formation and preserving insulin's efficacy as it enters the bloodstream through the skin.[39,40] The structure of a chemical enhancer is shown in Fig.8.

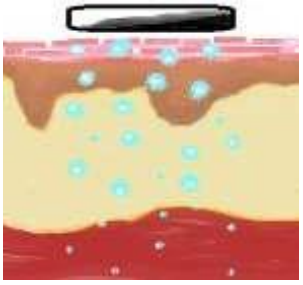

Fig. 8 Chemical Enhancers

- **Electroporation:**

Electroporation temporarily creates pathways through the stratum corneum using brief, high-voltage pulses. This enables the transportation of medications through the skin, making it an effective method for transdermal

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medication delivery.[40] The structure of electroporation is shown in Fig.9.

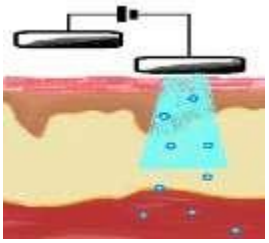

Fig. 9 Electroporation

Fig. 9 Electroporation

- **Ultrasound:**
  Ultrasound is used in biomedicine to transport drugs through the skin via sonophoresis. Smith et al. have developed a lightweight and energy-efficient transducer array for LFS-aided transdermal insulin delivery. The array uses cymbal-shaped transducers in a 3*3 multi-element array design, providing an alternative to bulky ultrasound equipment.[40] The structure of ultrasound is shown in Fig.10

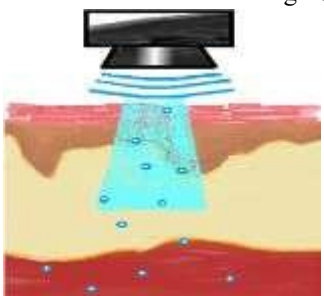

Fig. 10 Ultrasound

- **Jet Injection:**
  Jet injection is a needleless way to administer transdermal insulin. It uses a high-speed spray to create a small hole in the skin and deliver insulin, with over 90% delivery efficiency.[40] In the 1860s, the jet injection technique was introduced. In the 1940s, it was relaunched as "Hypospray" for patient self-use. The US military created the Ped-O-Jet in the 1950s for mass immunization, but it was terminated in 1997 due to contamination concerns from MUNJI use. Jet injection's drawbacks include bruising, bleeding, and pain. Mitragotri's microjet infusion minimizes these issues by using nanoliter volumes. While cost and size hinder adoption, enhancements may increase accessibility.[40] The structure of jet injection is shown in Fig.11

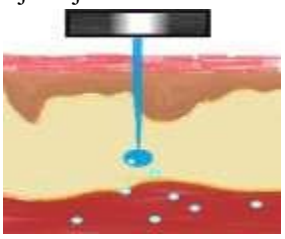

Fig. 11 Jet Injection

- **Microneedle:**
  Microneedle (MN) techniques are gaining popularity as a non-plagiarized approach for transdermal protein distribution, gently disrupting the stratum corneum using micro-scaled needles to deliver drugs into skin layers.[41] Microneedle equipment is categorized by material and drug delivery method. These tiny needles, known as Microneedles (MNs), can administer drugs through the skin via solid, hollow, or dissolving types. Solid MNs enhance drug delivery by penetrating the skin, while hollow MNs inject liquid drugs through the puncture, and dissolving MNs, composed of pharmaceutical-containing polymers, dissolve upon skin contact.[41] The structure of the microneedle is shown in Fig.12

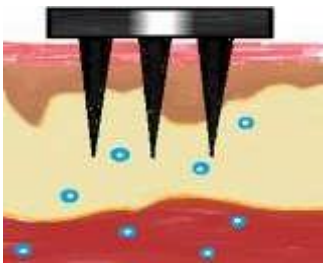

Fig.12 Microneedle

VII. Oral Insulin Delivery:

The creation of an oral formulation of physiologically active insulin has been approached using a variety of different methods. It is widely accepted that a significant challenge is preventing the protein medicine from degrading due to the harsh gastrointestinal environment. Orally administered insulin closely replicates natural insulin pathways, enhancing glucose control. It traverses the intestinal route to the liver via the portal circulation,

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reducing systemic levels, preventing hypoglycemia, and mitigating weight gain concerns. Innovative formulations, such as poly(fumaric-co-sebacic) anhydride and poly(lactide-co-glycolide) (PLGA) nanospheres, have shown promise by traversing the intestinal epithelium within hours.[42]

4. Future Framework:

There is ongoing research in the field of insulin delivery devices. Below are some recent developments:

a) Engineers at MIT University in America have recently developed an implantable device for Type-1 diabetic patients. This device comprises a built-in oxygen generator and a sensor capable of measuring the body's oxygen level. It also includes an incorporated nerve that can produce insulin. The device has undergone successful testing on mice, yielding a positive response.[43]

b) A United States-based company has recently introduced the FreeStyle Libre Sensor to measure blood sugar levels in the body. This sensor is a sticker that adheres easily to the patient's hand and can accurately measure sugar levels for up to 14 days. It is waterproof and suitable for patients as young as 7 years old. Additionally, it is effective for geriatric patients and pregnant women. The cost of this sensor ranges from Rs. 6000 to Rs. 5000.[44]

c) Researchers at Pennsylvania's Penn State University have developed a wearable patch for monitoring patient health. This patch utilizes human sweat to measure glucose levels, pH, and body temperature. In addition to measuring sugar levels, the patch can detect hydration levels, anxiety, and nutrition levels in the body. The patch utilizes laser-induced graphene material to measure the rate of oxidation occurring on the surface of the skin during sweating. It should be replaced with new patches every 3 weeks.[44]

5. Marketed Preparations of Insulin available globally:

Table 4: Marketed Preparations of Insulin available globally

S. No.	Delivery Device	Product Name	Manufacturing Company
1.	Insulin Pen	Novo Pen	Novo Nordisk
2.	Prefilled Insulin Pen	Flex Touch	Novo Nordisk
3.	Insulin Pumps	MiniMed	Medtronic
4.	Artificial Pancreas	MiniMed 530G	Medtronic
5.	Insulin Inhalers	Afrezza	Mannkind Corp.
6.	Insulin Syringes	Bd Insulin Syringe 3ml	BD
7.	Transdermal Insulin Delivery	V-Go®	Valeritas, Inc.
8.	Oral Insulin Delivery	Oralis (Type 2 Diabetes)	Oramed

6. Conclusion:

The lifespan of people with diabetes has increased and their quality of life has increased thanks to the rapid progress of diabetes technology during the past ten years. The existing available devices had some commendable advancements, but many of them were unreasonably expensive. Injection set dealing with, Bluetooth connectivity, cannula obstructions, and user-friendliness were other severe problems. Innovations in pumps, CGMs, and algorithmic forecasting may render the closed-loop system as healthy as feasible with more than 90-95% TIR and the minimal amount of time spent in hypoglycemia while the search for more precise and user-friendly approaches continues. Subjects that use DIY-APS have reported some positive results. All the device companies have released ACE pumps along with compatible sensors in response to the DIY revolution. The ultimate goal is to create a cost-effective artificial pancreas that can perform 100% TIR and 0% time below range. The mission can revolutionize diabetes treatment, despite the significant time and commitment

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requirements. Extensive studies are still being performed for the development of successful oral insulin delivery for treating diabetes with ease and in compliance with patients.

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