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INSULIN DELIVERY SYSTEM: A SYSTEMIC REVIEW OF CURRENT TECHNOLOGIES AND FUTURE PROSPECTS

Mohammed Mateen Maaz[1]*, Dinesh Kumar V.[2] and Umea Hani B.[3]

[1,2,3] Pharm D, Sree Siddaganga College of Pharmacy, Tumakuru, Karnataka, India.

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***Corresponding Author: Mohammed Mateen Maaz**
Pharm D, Sree Siddaganga College of Pharmacy, Tumakuru, Karnataka, India.
Email ID: mateen2481@gmail.com

ABSTRACT
Diabetes mellitus is a major worldwide health burden that requires efficient treatment techniques to lessen its effects on patients and healthcare systems. Insulin therapy is a fundamental component of diabetes management, and in order to maximize treatment results, ongoing innovation in insulin delivery methods is required. This systematic study addresses the opportunities for future injectable innovation while offering a thorough assessment of the state-of-the-art insulin delivery systems. Insulin and pens, which are considered traditional approaches, are contrasted with sophisticated systems like insulin pumps, inhaled insulin, and new developments like patch pumps and smart insulin pens. The evaluation assesses these technologies' cost-efficiency, safety, effectiveness, and patient convenience while emphasizing their influence on patient outcomes and glycemic management. Potential solutions to problems including affordability limits, challenges associated to devices, and adherence concerns are presented. Prospects for the future that look promise for bettering diabetes management include closed-loop systems, implantable technologies, smart insulin pens, and uses of nanotechnology. In order to satisfy the changing demands of people with diabetes, regulatory concerns, market trends, and accessibility difficulties are also looked at. These points highlight the need of ongoing innovation and fair distribution of insulin delivery systems.

KEYWORDS: Diabetes, Insulin, Insulin pumps, Insulin Delivery systems.

INTRODUCTION
Elevated blood glucose levels are a hallmark of diabetes mellitus, a chronic metabolic disease caused by either insufficient insulin synthesis, inefficient insulin utilization, or both. The pancreas secretes the hormone insulin, which is essential for controlling blood sugar levels and promoting the absorption of glucose by cells for energy synthesis.[1]

Type 1 diabetes, type 2 diabetes, and gestational diabetes are the three most prevalent forms of diabetes mellitus. In type 1 diabetes, the pancreatic beta cells that produce insulin are accidentally attacked and destroyed by the immune system, resulting in a complete lack of insulin. Usually developing in infancy or adolescence, type 1 diabetes requires lifelong insulin treatment in order to survive.

Conversely, insulin resistance, or the body's cells becoming less sensitive to the effects of insulin, is a hallmark of type 2 diabetes. As a result, blood sugar levels rise and cells absorb less glucose. Genetic predisposition, obesity, and sedentary lifestyles are frequently linked to type 2 diabetes. Type 2 diabetes is characterized by insulin resistance, but the pancreas may also gradually lose its capacity to generate enough insulin over time, which exacerbates the disease.

Elevated blood sugar levels that develop or are initially detected during pregnancy are the hallmark of gestational diabetes, which happens throughout pregnancy. In addition to raising the risk of difficulties for both the mother and the unborn child, gestational diabetes may put women at risk for type 2 diabetes in the future.[2,3]

In order to avoid both long-term problems and acute issues like hyperglycemia (high blood sugar) and hypoglycemia (low blood sugar), the therapy of diabetes mellitus centers on obtaining and maintaining appropriate blood glucose levels. This usually entails a mix of pharmaceutical interventions, such as insulin therapy or oral drugs to reduce blood sugar levels, together with lifestyle changes, such as dietary adjustments, frequent physical exercise, and weight control. To minimize variations in blood sugar levels and to alter treatment regimens, it is imperative to continuously monitor blood glucose levels using continuous glucose monitoring devices or self-monitoring. To identify and treat problems early, diabetes treatment also includes routine medical exams and preventative care.[4,5]

IMPORTANCE OF INSULIN DELIVERY SYSTEMS

Systems for delivering insulin are essential for managing diabetes mellitus, a long-term metabolic disease marked by high blood sugar. The pancreas secretes the hormone insulin, which is vital for controlling glucose metabolism and preserving appropriate blood sugar levels. But in people with diabetes, hyperglycemia results from either the pancreas' inability to generate enough insulin (type 1 diabetes) or the body's cells' resistance to insulin (type 2 diabetes).

The main objective of insulin treatment is to replicate the body's natural insulin release in response to variations in blood glucose levels. This will help to achieve strict glycemic control and avoid problems related to diabetes. Insulin delivery systems are the means by which patients get exogenous insulin; they provide accurate dosage and timing of insulin administration to correspond with customized treatment plans.

There are some important considerations that help explain the significance of insulin delivery systems:

1. Glycemic Control: Preventing both short-term and long-term problems from diabetes requires maintaining appropriate blood glucose levels. Insulin delivery systems provide a consistent supply of insulin to manage blood sugar levels throughout the day, including during fasting, postprandial, and nocturnal periods, allowing persons with diabetes to achieve tight glycemic control.

2. Adaptability and Personalization: Different diabetics require different amounts of insulin depending on their age, weight, level of physical activity, food preferences, and length of illness. Because insulin delivery systems provide for flexibility in dosage and mode of administration, medical professionals may customize treatment plans to suit the individual needs of each patient. This personalization enhances glycemic management.

3. Patient Adherence: Reaching treatment objectives and averting complications need patient adherence to insulin administration. Convenient, user-friendly insulin administration devices that blend in well with everyday life might increase patients' adherence to treatment plans. For instance, the inconvenience of administering insulin can be lessened by using devices like insulin pens and patch pumps, which provide discrete and easy-to-use alternatives to traditional insulin injections.

4. Lessened Difficulties: It has been demonstrated that effective insulin therapy lowers the risk of complications connected to diabetes, such as nephropathy, neuropathy, retinopathy, and cardiovascular disease. Insulin delivery systems assist lessen the negative consequences of chronic hyperglycemia on different organ systems by preserving stable blood glucose levels within goal ranges, which enhances overall health outcomes and quality of life for diabetics.

5. Improved Quality of Life: Diabetes is a chronic illness that needs constant attention and self-care. The quality of life for people with diabetes can be improved by insulin delivery devices that reduce treatment-related difficulties and expedite treatment administration. These devices let patients to live more active, meaningful lives by lowering the frequency of injections, streamlining the insulin dosage, and providing useful features like dose reminders and data recording.[6,7,8]

HISTORY OF INSULIN AND INSULIN DELIVERY SYSTEMS

The development of insulin and insulin delivery devices is a narrative of scientific advancement, human inventiveness, and the never-ending search for new diabetes therapies. Let's examine the significant turning points in the evolution of insulin delivery technologies and the development of insulin:

1. Discovery of Insulin

- The discovery of the pancreas' function in glucose metabolism at the beginning of the 20th century marked the beginning of the insulin saga. A ground-breaking discovery was made in 1921 by Canadian researchers Sir Frederick Banting and Charles Best when they separated insulin from the pancreas of dogs and showed that it could reduce blood sugar levels. This groundbreaking discovery made it possible to produce insulin, a life-saving medication for diabetes, which was once thought to be an incurable illness. For their groundbreaking study, Banting and his associates were granted the 1923 Nobel Prize in Physiology or Medicine.[9,10]

2. Early Techniques for Insulin Delivery

- The next issue after insulin's discovery was figuring out how to give it to patients in a way that worked. Originally, insulin was purified for injection by removing it from the pancreases of animals. Reusable needles and glass syringes were frequently used to administer insulin. These early insulin delivery techniques did have several drawbacks, though, including as the requirement for repeated injections, the fluctuation of insulin potency, and the possibility of injection site infections. Despite these difficulties, insulin therapy represented a major breakthrough in the treatment of diabetes, allowing individuals to live healthy lives despite their illness.

3. Introduction of Insulin Pens

- During the 1980s, pens for administering insulin became a more practical and user-friendly option than conventional needles and vials. Insulin pens provide benefits including precise dosage, increased portability, and less risk of needle stick injuries. Insulin pens are prefilled with insulin cartridges and include disposable needles, making them easier to use and carry. They became well-liked by patients and medical professionals right away, and many diabetics chose them as their preferred insulin administration system.[11,12]

4. Development of Insulin Pumps

- The development of insulin pumps is a noteworthy achievement in the history of insulin delivery systems. Over time, programmable basal rates, bolus calculators, and integrated continuous glucose monitoring (CGM) systems have become features of insulin pump technology. The first insulin pump was introduced in the 1970s and offered continuous subcutaneous insulin infusion to mimic the physiological secretion of insulin by the pancreas. These developments have enhanced the precision and adaptability of insulin administration, improving patients' quality of life and glucose management.[13]

5. Developments in Insulin Delivery Technology

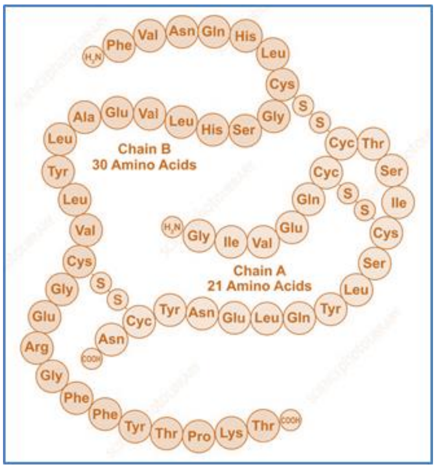
- With the advent of cutting-edge gadgets like patch pumps, closed-loop systems, and smart insulin pens, insulin delivery technology has undergone further advancements in recent times. While closed-loop systems automate insulin dosing based on real-time glucose monitoring data, patch pumps provide discrete and convenient insulin delivery; smart insulin pens with Bluetooth connectivity and dose tracking capabilities allow patients to track treatment adherence as well as insulin usage. These gadgets easily link with digital health systems, giving patients and medical professionals access to insightful data.[14,15]

STRUCTURE OF INSULIN

The pancreatic beta cells generate insulin as a preprohormone precursor, which then travels through a number of processing stages to become the mature insulin molecule. Two polypeptide chains, referred to as the A and B chains, are joined by two interchain disulfide bonds and further stabilized by an extra intrachain disulfide bond to form the mature insulin molecule.

Thirty amino acids make up the B chain compared to twenty one in the A chain. The configuration of disulfide bonds and amino acid residues is essential for preserving insulin's structural integrity and pharmacological action. The N-terminal region of the B chain's alpha-helical domain and the remaining B chain and the whole A chain's beta-sheet domain are the two domains that fold together to form the three-dimensional structure of insulin.

Insulin takes on a tight, spherical shape that isolates its hydrophobic core from the surrounding aqueous medium. Because of its structural characteristics, insulin may selectively bind to its receptor and start intracellular signaling cascades that control the absorption, use, and storage of glucose in target organs.[16,17]



Structure of Insulin

SYNTHESIS OF INSULIN

The transcription of the insulin gene (INS) in pancreatic beta cells initiates the manufacture of insulin. Many exons and introns make up the insulin gene, which is translated into a precursor mRNA molecule. A mature mRNA molecule encoding the preproinsulin protein is produced by splicing the precursor mRNA in order to eliminate the introns.

A signal peptide located at the N-terminus of the 110-amino acid polypeptide preproinsulin directs the developing polypeptide to the endoplasmic reticulum (ER) for translocation. Proinsulin, an 86-amino acid precursor protein made up of the A chain, B chain, and C-peptide section, is created in the ER when the signal peptide is cleaved.

After being delivered to the Golgi apparatus, prohormone convertases (PC1/3 and PC2) proceed to further process proinsulin in order to eliminate the C-peptide section and produce the mature insulin molecule. Insulin and the C-peptide are produced during this processing phase by the particular breaking of peptide bonds at the intersections of the A and C-peptide and B and C-peptide segments.

Within the pancreatic beta cells, mature insulin molecules are encapsulated into secretory granules, where they await release in response to various stimuli, including rising blood glucose levels. Insulin attaches to its receptor on target cells after it is secreted into the circulation, starting a series of intracellular signaling processes that control the absorption, use, and storage of glucose.[18,19]

MECHANISM OF INSULIN ACTION

The mechanism of insulin action is a highly orchestrated process that begins with insulin binding to specific receptors on target cells. This interaction triggers a cascade of intracellular signaling events, ultimately leading to various metabolic effects. Insulin promotes glucose uptake into cells, enhances glycogen synthesis, inhibits gluconeogenesis, and regulates lipid and protein metabolism. Dysfunction in insulin signaling pathways can lead to insulin resistance and metabolic disorders such as diabetes. Understanding the mechanism of insulin action is essential for developing targeted therapies and interventions to manage these conditions effectively.[20,21]

Step	Description
1. Insulin Binding	Insulin binds to insulin receptors (IR) on the surface of target cells, primarily muscle, adipose, and liver cells.
2. Activation of IR	Binding of insulin to its receptor activates the tyrosine kinase activity of the insulin receptor.
3. Phosphorylation of IRS	Activated insulin receptors phosphorylate insulin receptor substrates (IRS), such as IRS-1 and IRS-2.
4. Activation of PI3K Pathway	Phosphorylated IRS proteins activate phosphoinositide 3-kinase (PI3K), leading to the production of PIP3.
5. Generation of PIP3	PIP3 serves as a second messenger that recruits and activates protein kinase B (Akt) at the cell membrane.
6. Activation of Akt	Akt activation promotes various cellular processes, including glucose uptake, glycogen synthesis, and more.
7. Translocation of GLUT4	Activated Akt phosphorylates proteins that facilitate the translocation of glucose transporter 4 (GLUT4) to the cell membrane.
8. Glucose Uptake into Cells	GLUT4 allows the uptake of glucose from the bloodstream into the cell, where it can be utilized or stored.

TYPES OF INSULIN

Type of Insulin	**Onset of Action**	**Peak Action**	**Duration of Action**	**Examples**
Rapid-Acting Insulin	15 minutes	1-2 hours	3-4 hours	Insulin lispro (Humalog), insulin aspart (NovoLog), insulin glulisine (Apidra)
Short-Acting Insulin	30 minutes - 1 hour	2-3 hours	6-8 hours	Regular insulin (Humulin R, Novolin R)
Intermediate-Acting Insulin	1-2 hours	4-8 hours	12-16 hours	NPH insulin (Humulin N, Novolin N)
Long-Acting Insulin	1-2 hours	Steady over 24 hours	18-24 hours	Insulin glargine (Lantus, Basaglar), insulin detemir (Levemir), insulin degludec (Tresiba)
Premixed Insulin	Varies depending on composition	Varies depending on composition	Varies depending on composition	70/30 (70% NPH insulin, 30% regular insulin), 75/25 (75% insulin lispro protamine, 25% insulin lispro)
Ultra-Rapid-Acting Insulin	5-15 minutes	2-3 hours	2-3 hours	Insulin lispro-aabc (Lyumjev)
Inhaled Insulin	Rapid	Varies	Shorter than subcutaneous insulin	Afrezza

TRADITIONAL METHODS IN INSULIN DELIVERY

For many years, traditional insulin administration techniques have been the mainstay of diabetes care, offering vital ways to provide people with diabetes exogenous insulin. Despite their effectiveness, these techniques have developed throughout time to provide greater patient adherence, ease, and accuracy. Comprehending the conventional techniques of insulin administration is essential to grasping the past background of diabetes treatment and the basis on which contemporary insulin delivery systems have been constructed.

1. Insulin Injections

- Insulin injections entail the subcutaneous injection of insulin with the use of a needle and syringe. Insulin is normally injected into the subcutaneous fat, where it enters the bloodstream and is absorbed. Insulin pens can be used to make insulin injections more convenient, or the patient or caregiver can deliver the shot by hand.

- Different insulin formulations, such as rapid-acting, short-acting, intermediate-acting, and long-acting insulin, can be administered via injection. The demands of each patient, including mealtime coverage, basal insulin requirements, and blood glucose control objectives, determine the kind and schedule of insulin to use.

- **Advantages**
- Easily accessible and reasonably priced.
- Permits accurate dosage modifications in accordance with each person's unique insulin needs.
- It is compatible with all insulin formulations

- **Challenges**
- Manual injection is necessary, which some patients may find frightening or uncomfortable.
- May cause bruising, soreness, or discomfort where the injection was made.
- The possibility of needle stick injuries and using the wrong injection method.

2. Insulin Pens

- Insulin pens are pen-shaped devices that come with a disposable injection needle and an insulin cartridge. They provide an easy-to-use, discrete substitute for standard syringe and needle injections, enabling accurate dosage. Insulin pens with features like dosage memory, dose modification, and dose increments to make insulin administration easier can be purchased prefilled or reusable.

- There are many different kinds of insulin pens on the market, including reusable, disposable, and smart pens with cutting-edge features like dosage tracking, reminders, and connection to mobile apps.

- **Advantages**
- It is portable and easy to use, making it ideal for administering insulin while on the road
- It allows for accurate dosage and dose modifications, especially for individuals with poor dexterity or visual acuity.
- Promotes better patient adherence and lessens the stigma attached to insulin shots.

- **Challenges**
- The initial outlay could be more than with conventional syringes and needles.
- Needs pen cartridges and needles to be changed on a regular basis.
- Less formulation and type flexibility than vials of insulin.
- Possibility of pump-related problems, such as blockages in the infusion set, infections at the site, or difficulties with the pump.
- For certain patients, adoption may be hampered by the initial expense and learning curve.[22,23,24,25,26]

ADVANCED DELIVERY SYSTEMS IN INSULIN DELIVERY

Modern insulin delivery systems provide creative ways to improve accuracy, convenience, and adherence to insulin administration, which is a major advancement in the treatment of diabetes. These systems make use of state-of-the-art technology to improve glycemic control, optimize insulin delivery, and improve the quality of life for people with diabetes. A thorough explanation of a few cutting-edge insulin delivery devices is provided below:

1. Insulin Pump Therapy

- **Description:** Insulin pump treatment, often referred to as continuous subcutaneous insulin infusion (CSII), is a method of delivering insulin continuously throughout the day by means of a tiny electronic device called an insulin pump. This mimics the basal insulin production that occurs naturally. Insulin pumps are programmable devices that provide accurate control of mealtime boluses and basal insulin rates according to lifestyle variables and individual insulin requirements.

- **Features:** A reservoir to store insulin, a pump to administer insulin, a programmable interface to set bolus dosages and basal rates, and a catheter or infusion set to inject insulin subcutaneously are the standard components of insulin pumps. Other aspects of certain sophisticated insulin pumps might be automated insulin delivery (closed-loop systems), predictive algorithms, and integration with continuous glucose monitoring (CGM)

- **Advantages:** Insulin pump therapy has a number of advantages over conventional insulin injection techniques, including as better glycemic control, a lower risk of hypoglycemia, increased flexibility in when to eat and exercise, and easier insulin delivery. Those with type 1 diabetes, those with unstable glycemic control, and those in need of intense insulin therapy benefit most from insulin pumps.

2. Patch Pumps

- **Description:** Adhesive to the skin, patch pumps are wearable insulin delivery devices that give continuous subcutaneous insulin infusion. Patch pumps have an integrated design with a self-contained reservoir and infusion mechanism, in contrast to typical insulin pumps, which require tubing and infusion sets. Patch pumps provide more mobility and discretion while administering insulin since they are covert, lightweight, and waterproof.

- **Features:** Typically, patch pumps have an adhesive backing to stick to the skin, an infusion mechanism to distribute insulin, and a reservoir to store insulin. Automated insulin administration algorithms, touchscreen interfaces, and Bluetooth connectivity are additional features that some sophisticated patch pumps may have.

- **Advantages:** Compared to standard insulin pumps, patch pumps provide a number of benefits, including as a discreet and small design, ease of application and removal, a lower risk of problems from the tubing (such kinking or disconnection), and better adherence to insulin administration. For those who would like a more covert and convenient way to administer insulin, patch pumps are a great choice.

3. Smart Insulin Pens

- **Description:** Pen-shaped gadgets that incorporate cutting-edge technology to improve insulin delivery and tracking. More accurate and convenient insulin dosage is made possible by the capabilities that these devices often incorporate, such as dose memory, dose tracking, Bluetooth connectivity, and smartphone compatibility.

- **Features:** To record insulin dosages, time stamps, and injection locations, smart insulin pens may include built-in memory. This information is useful for diabetes control and insulin dose titration. Some sophisticated smart pens can also manage insulin dosages, check blood glucose levels, and give customized information for medical professionals by syncing with smartphone apps or cloud-based systems.

- **Advantages:** Compared to conventional insulin pens, smart pens provide a number of benefits, such as increased adherence to insulin therapy, better dosage precision, real-time data recording and analysis, and interaction with digital health platforms. With the help of smart pens, people with diabetes may participate more actively in their care and give medical professionals useful information for tailoring treatment plans.

4. Closed-Loop Systems

- **Description:** Closed-loop systems, sometimes referred to as artificial pancreas systems or hybrid closed-loop systems, automate the supply of insulin in response to real-time glucose readings by combining insulin pump therapy with continuous glucose monitoring (CGM) technology. These devices attempt to maintain stable blood glucose levels without the need for personal intervention by using algorithms to modify basal insulin rates and provide automatic correction boluses.

- **Features:** In closed-loop systems, an insulin pump delivers insulin, a control algorithm modifies insulin administration based on glucose readings, and a CGM sensor measures interstitial glucose levels. To improve glucose management and reduce the risk of hypoglycemia, certain sophisticated closed-loop systems may also include configurable settings, adaptive learning, and predictive algorithms.

- **Advantages:** Compared to traditional insulin therapy, closed-loop devices have a number of benefits, including as better glycemic control, a lower risk of hypoglycemia, easier insulin administration, and more flexibility with regard to meal planning and physical activity. Closed-loop systems are especially helpful for those with type 1 diabetes, those whose blood sugar levels fluctuate, and people who want to make managing their diabetes easier.[27,28,29,30,31]

EFFICACY OF INSULIN DELIVERY TECHNOLOGIES

- The goal of insulin delivery systems is to give the appropriate quantity of insulin at the appropriate time to provide optimal glycemic control. The ability of these technologies to keep steady blood glucose levels within the desired range serves as a proxy for efficacy.

- Compared to conventional techniques, accurate insulin dosage is made possible by advanced delivery devices such insulin pumps and closed-loop systems, which enhance glycemic control. According to studies, using insulin pumps for continuous subcutaneous insulin infusion can lower HbA1c levels and lessen the risk of both hyperglycemia and hypoglycemia.

- Targeted and sustained insulin administration, which reduces blood glucose swings, is a potential improvement for implantable devices and insulin formulations based on nanotechnology.[32.33]

SAFETY OF INSULIN DELIVERY TECHNOLOGIES

- The safety of insulin delivery systems is crucial in order to reduce the possibility of hypo- or hyperglycemia as well as other unfavorable outcomes. It is important to deliver insulin treatment with the least amount of risk of problems or adverse effects.

- By modifying insulin administration based on glucose patterns, advanced delivery systems with features like automated dosing algorithms and real-time glucose monitoring help prevent hypoglycemia. When compared to traditional insulin administration, closed-loop devices have been demonstrated to lessen the incidence and severity of hypoglycemia episodes.

- Dose-tracking smart insulin pens improve safety by encouraging patients to follow their insulin regimen and avoiding missing doses.

PATIENT CONVENIENCE OF INSULIN DELIVERY TECHNOLOGIES

- In terms of overall diabetes control and adherence to insulin treatment, patient convenience is crucial. Technologies for delivering insulin should be portable, easy to use, and flexible enough to fit into patients' daily routines.

- More flexibility in insulin dose schedules and mealtime bolusing is provided by advanced delivery devices like as insulin pumps, which let patients to tailor their treatment plans to their daily routines and eating preferences.

- Bluetooth-enabled smart insulin pens and mobile app integration facilitate smooth data management and remote monitoring, improving patient and healthcare provider comfort.

COST-EFFECTIVENESS OF INSULIN DELIVERY TECHNOLOGIES

- When making decisions about healthcare, cost-effectiveness is very important, especially when managing chronic illnesses like diabetes. Technologies for delivering insulin should add value by enhancing patient outcomes and reducing medical expenses.

- Research has demonstrated that, despite their higher initial costs, modern delivery systems like as insulin pumps and closed-loop systems can result in long-term cost benefits by lowering the rate of hospitalizations and problems associated with diabetes.

- As an affordable substitute for separate glucose monitors and a significant source of data insights to enhance insulin therapy, smart insulin pens are a great option for administering insulin.[34,35]

ADHERENCE ISSUES OF INSULIN DELIVERY TECHNOLOGIES

- Maintaining stable blood glucose levels and avoiding complications from diabetes depend on adherence to insulin therapy. However, poor glycemic control might arise from adherence problems, which are frequent among diabetics.

- The inconvenient nature of administering insulin, injection anxiety, and trouble sticking to complicated dosage schedules are all factors that lead to low adherence. Furthermore, psychological variables that affect adherence include anxiety, sadness, and suffering connected to diabetes.

- Adherence problems may be made worse by insulin administration methods that are difficult to use or need frequent modifications. If patients feel that the technology is obtrusive or onerous, they may be less inclined to stick with their treatment plan.

DEVICE-RELATED COMPLICATIONS OF INSULIN DELIVERY TECHNOLOGIES

- The use of insulin delivery systems, such as insulin pumps, infusion sets, and injectable devices, may result in issues associated to the device. Insulin pump problems, infusion site reactions, and site infections are common consequences.

- Poor cleanliness habits, insufficient site rotation, and incorrect device insertion or positioning can all raise the risk of problems. Problems with the device might cause disruptions in the supply of insulin, which would cause fluctuations in blood sugar levels and make people more vulnerable to hypo- or hyperglycemia.

- To reduce the chance of issues, education and training about the correct use and maintenance of devices are crucial. In order to address any worries or issues patients may have with insulin delivery devices, healthcare practitioners should collaborate closely with patients.

AFFORDABILITY CONSTRAINTS

- In low- and middle-income nations where access to healthcare resources may be restricted, affordability restrictions represent a substantial obstacle to the use of insulin delivery systems. Individuals and families impacted by diabetes may find it financially difficult to pay the high out-of-pocket expenses for insulin, insulin pumps, and related supplies.

- Wide variations in insurance coverage and reimbursement policies result in unequal access to insulin delivery technologies among various populations. Individuals without sufficient insurance coverage may find it difficult to pay for necessary diabetic supplies, to the point where they ration insulin or stop taking their medication entirely.

- Financial limitations also apply to the continuous upkeep and replacement of insulin delivery systems. Insulin treatment may be interrupted if patients have trouble getting timely replacements for damaged or broken equipment.[36,37]

NOVEL DRUG DELIVERY SYSTEMS FOR INSULIN DELIVERY

Significant progress has been achieved in the creation of innovative drug delivery methods for the administration of insulin in recent years. These devices address issues with conventional insulin administration techniques and seek to increase the convenience, safety, and effectiveness of insulin therapy. Novel medication delivery systems, which make use of cutting-edge technology, present new ways to improve glycemic control and maximize diabetes care. A thorough explanation of a few recently developed innovative insulin delivery medication delivery systems may be found below.

1. Oral Insulin Delivery Systems

- **Description:** These systems seek to provide insulin orally, obviating the requirement for subcutaneous injections. These systems make use of a variety of techniques to improve insulin absorption into the bloodstream and shield it from deterioration in the digestive system. Methods include co-administration with protease inhibitors or permeability enhancers, formulation with absorption enhancers, and encapsulation in polymer matrix.

- **Advantages:** There are a number of possible benefits of oral insulin delivery, such as non-invasive administration, enhanced patient adherence, and a lower risk of injection-related problems. Additionally, oral insulin may more closely resemble physiological insulin production, resulting in improved glucose control and more physiologic insulin action.

- **Challenges:** Poor oral bioavailability, variable absorption, and vulnerability to breakdown by digestive enzymes are issues with oral insulin administration. Innovative formulation techniques, efficient delivery methods, and thorough preclinical and clinical testing are needed to overcome these obstacles.

2. Transdermal Insulin Delivery Systems

- **Description:** By avoiding the need for subcutaneous injections, transdermal insulin delivery devices allow for the non-invasive administration of insulin via the skin. These devices improve the penetration of insulin across the skin barrier by utilizing a variety of technologies, including ultrasound, iontophoresis, and microneedles. Specifically, microneedle patches have become a viable method for transdermal insulin administration that is both painless and effective.

- **Advantages:** Potential benefits of transdermal insulin delivery include painless administration, a lower chance of needle stick injuries, and better patient acceptability and adherence. In comparison to subcutaneous injections, transdermal administration offers a more regulated and prolonged release of insulin, which results in more stable blood glucose levels.

- **Challenges:** The use of transdermal insulin administration presents several difficulties, such as the requirement for an ideal patch design, improved skin penetration, and exact control over insulin release kinetics. It will take interdisciplinary cooperation, creative materials science, and thorough preclinical and clinical testing to overcome these obstacles.

3. Inhalable Insulin Delivery Systems

- **Description:** Insulin may be delivered non-invasively to the lungs by inhalable devices, which facilitate quick absorption of the insulin into the circulation. These methods use insulin formulations that are either aerosolized or dry powder and are inhaled via specialized equipment. When it comes to lunchtime insulin administration, inhalable insulin provides a simple and needle-free substitute for subcutaneous injections.

- **Advantages:** There are several possible benefits associated with inhalable insulin delivery, such as quick start of action, ease of administration, and enhanced patient acceptability and adherence. When compared to subcutaneous injections, inhalable insulin may potentially offer more physiological insulin kinetics, simulating the sharp peak and fall of natural insulin production.

- **Challenges:** Optimizing pulmonary deposition, maintaining constant dosage precision, and lowering the risk of pulmonary consequences are among the difficulties in using inhalable insulin administration. To tackle these obstacles, sophisticated aerosolization techniques, meticulous formulation development, and comprehensive safety assessment in clinical trials are necessary.

4. Implantable Insulin Delivery Systems

- **Description:** Implantable insulin delivery systems allow for the long-term, regulated release of insulin by inserting insulin-releasing devices or reservoirs into the body. These methods can administer insulin intraperitoneally or subcutaneously using biodegradable polymers, osmotic pumps, or microfluidic devices. Long-term insulin administration without the need for frequent injections is a benefit of implantable devices.

- **Advantages:** There are several possible benefits associated with implantable insulin delivery devices, including as continuous insulin administration, decreased treatment burden, and enhanced patient compliance. In order to maximize glycemic control, implantable devices can deliver insulin continuously or pulsatilly, imitating the rhythm of natural insulin production.

- **Challenges:** The risks of device-related consequences including infection or mechanical failure, as well as biocompatibility and foreign body reaction, are challenges that come with implanted insulin delivery devices. Innovative materials engineering, biocompatible coatings, and strong implanted device design are necessary to overcome these obstacles.

5. Smart Insulin Delivery Systems

- **Description:** To improve insulin dose and administration in real-time, smart insulin delivery systems incorporate cutting-edge technology such sensors, microcontrollers, and feedback control algorithms. These devices constantly check blood sugar levels and modify insulin dosages according to a person's specific needs, food consumption, amount of physical activity, and other pertinent variables. The goal of intelligent insulin delivery systems is to minimize the chance of hypoglycemia while maintaining strict glycemic control.

- **Advantages:** The use of smart insulin delivery systems has several potential benefits, such as tailored insulin therapy, flexible dosage algorithms, and instantaneous glucose monitoring. By using predictive algorithms to alter insulin dosage proactively, these systems can lessen the strain of managing diabetes and enhance patient outcomes.

- **Challenges:** Smart insulin administration systems have several challenges, such as sensor accuracy, algorithm improvement, and user acceptability. Human factors engineering, comprehensive clinical validation, and interdisciplinary cooperation are necessary to integrate various components into a smooth and user-friendly system.[38.39,40,41,42]

Future Prospects and Innovations in Insulin Delivery

The field of insulin administration is constantly changing due to developments in engineering, technology, and medicine. Looking ahead, a number of exciting opportunities and cutting-edge discoveries are set to revolutionize the insulin delivery industry and open up new paths for bettering patient outcomes and diabetes treatment. Below is a thorough analysis of several significant upcoming opportunities and advancements in insulin delivery.

1. Targeted Insulin Delivery Systems

- **Prospects:** Localized insulin administration to certain tissues or organs is a potential benefit of targeted insulin delivery systems, which also minimize systemic exposure and lower the possibility of adverse consequences. Targeted insulin administration to the liver, muscle, or adipose tissue may be helpful in disorders including type 1 diabetes, insulin resistance, and diabetic complications. These devices may find use in these settings.

- **Innovations:** Targeting tissue-specific insulin receptors, microencapsulation technologies, and nanoparticle-based carriers are some of the novel techniques to tailored insulin delivery. By maximizing insulin bioavailability, extending insulin action, and reducing off-target effects, these tactics hope to provide more accurate and efficient insulin administration.

2. Gene Therapy for Insulin Production

- **Prospects:** By facilitating the direct synthesis of insulin in the body's cells, gene therapy presents a promising new avenue for the administration of insulin. To encourage endogenous insulin production and release, gene therapy procedures entail introducing insulin-producing genes into target cells, such as muscle or pancreatic beta cells.

- **Innovations:** Viral and non-viral vectors, as well as genome editing tools like CRISPR-Cas9, have recently been used in gene therapy to produce insulin. These methods seek to increase insulin sensitivity, repair pancreatic beta cell function, and provide diabetics a long-term insulin therapy option.

3. Biomimetic Insulin Delivery Systems

- **Prospects:** Biomimetic insulin delivery methods provide improved biocompatibility, stability, and efficacy by imitating natural mechanisms of insulin production and action. The intricate interactions between insulin and glucose in the body are replicated in these systems, improving glycemic control and resulting in more physiologic insulin kinetics.

- **Innovations:** Insulin microspheres, glucose-responsive insulin formulations, and insulin analogs with altered pharmacokinetic profiles are examples of innovations in biomimetic insulin delivery systems. By imitating the dynamic control of insulin production in response to variations in blood glucose levels, these technologies seek to improve the accuracy and adaptability of insulin therapy.

4. Personalized Insulin Delivery Strategies

- **Prospects:** The goal of personalized insulin delivery techniques is to adjust insulin dosage based on the needs, preferences, and metabolic profiles of each patient. In order to maximize therapy results and enhance patient adherence, these techniques include variables such insulin sensitivity, glucose variability, meal patterns, levels of physical activity, and comorbidities.

- **Innovations:** Patient-specific insulin formulations, integrated decision support systems, and algorithm-based insulin dosage algorithms are examples of novel methods to customized insulin administration. With the help of these technologies, patients may take charge of their diabetes treatment and receive personalized insulin therapy based on data from wearables, digital health platforms, and continuous glucose monitoring.

5. Using Nanotechnology to Deliver Insulin

- **Prospects:** Innovative approaches to improving insulin's stability, effectiveness, and tailored administration are provided via nanotechnology. Utilizing nanoparticles and nanoscale devices to get around the drawbacks of conventional insulin formulations and improve treatment results for diabetics is how nanotechnology in insulin administration will develop in the future.

- **Innovations:** Nanoparticle-Based Formulations: By improving insulin stability, bioavailability, and tissue specificity, nanoparticle-based insulin formulations will allow for more accurate and prolonged insulin administration. Glucosensors Enabled by Nanotechnology: These glucose sensors will monitor blood glucose levels continuously and in real time, allowing for customized insulin dosage and improved glycemic control. Nanofiber-Based Delivery Devices: Providing a continuous and regulated release of insulin via the skin, nanofiber-based insulin delivery devices will provide a non-invasive and painless substitute for conventional injection techniques.[43 to50]

CONCLUSION

Finally, a thorough overview of both the state-of-the-art and the bright future prospects in the field of insulin delivery systems has been presented by the systemic review. We have looked at how insulin administration has changed over time, from simple syringes to sophisticated closed-loop devices, emphasizing the cost-efficiency, patient convenience, safety, and effectiveness of each approach in the management of diabetes.

This study has shown that, with to developments in technology, research, and patient-centered care, insulin delivery methods are still being rapidly innovated. The development of smart insulin pens and implantable devices, together with the incorporation of nanotechnology and tailored therapy, present enormous opportunities for optimizing patient outcomes and glycemic control in the future of insulin administration

But these developments also bring with them new difficulties, such problems with adherence, complications from the device, and financial limitations, which need to be resolved to provide fair access to and the best possible use of insulin delivery systems. The availability and acceptance of these technologies are significantly shaped by regulatory factors, market trends, and accessibility concerns, highlighting the significance of ongoing innovation and stakeholder engagement.

In conclusion, we can further develop the area of insulin administration and enable people with diabetes to better control their disease and lead healthier lives by adhering to current trends, embracing innovation, and placing a high priority on patient-centered care.

REFERENCES

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care, 2009 Jan; 32 Suppl 1(Suppl 1): S62-7. D
2. Wondmkun YT. Obesity, Insulin Resistance, and Type 2 Diabetes: Associations and Therapeutic Implications. Diabetes Metab Syndr Obes., 2020 Oct 9; 13: 3611-3616.
3. Chen YK, Liu TT, Teia FKF, Xie MZ. Exploring the underlying mechanisms of obesity and diabetes and the potential of Traditional Chinese Medicine: an overview of the literature. Front Endocrinol (Lausanne), 2023 Aug 1; 14: 1218880.
4. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B; American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care, 2009 Jan; 32(1): 193-203.
5. Diabetes Control and Complications Trial Research Group: The effect of intensive diabetes treatment on the development and progression of long-term complications in insulin-dependent diabetes mellitus: the Diabetes Control and Complications Trial. N Engl J Med., 1993; 329: 978–986.
6. Rahman MS, Hossain KS, Das S, Kundu S, Adegoke EO, Rahman MA, Hannan MA, Uddin MJ, Pang MG. Role of Insulin in Health and Disease: An Update. Int J Mol Sci., 2021 Jun 15; 22(12): 6403.
7. Cerasi E. Insulin deficiency and insulin resistance in the pathogenesis of NIDDM: Is a divorce possible? Diabetologia, 1995; 38: 992–997.
8. Rask-Madsen C, King GL. Vascular complications of diabetes: mechanisms of injury and protective factors. Cell Metab., 2013 Jan 8; 17(1): 20-33.
9. Lewis G.F., Brubaker P.L. The discovery of insulin revisited: Lessons for the modern era. J. Clin. Investig., 2021; 131: e142239.
10. 2. Vecchio I., Tornali C., Bragazzi N.L., Martini M. The Discovery of Insulin: An Important Milestone in the History of Medicine. Front. Endocrinol, 2018; 9: 613.
11. Pearson TL. Practical aspects of insulin pen devices. J Diabetes Sci Technol., 2010 May 1; 4(3): 522-31.
12. Keith K, Nicholson D, Rogers D. Accuracy and precision of low-dose insulin administration using syringes, pen injectors, and a pump. Clin Pediatr (Phila) 2004; 43(1): 69–74.
13. Berget C, Messer LH, Forlenza GP. A Clinical Overview of Insulin Pump Therapy for the Management of Diabetes: Past, Present, and Future of Intensive Therapy. Diabetes Spectr., 2019 Aug; 32(3): 194-204.
14. Kesavadev J, Saboo B, Krishna MB, Krishnan G. Evolution of Insulin Delivery Devices: From Syringes, Pens, and Pumps to DIY Artificial Pancreas. Diabetes Ther., 2020 Jun; 11(6): 1251-1269.
15. Shah RB, Patel M, Maahs DM, Shah VN. Insulin delivery methods: Past, present and future. Int J Pharm Investig., 2016 Jan-Mar; 6(1): 1-9.
16. Fu Z, Gilbert ER, Liu D. Regulation of insulin synthesis and secretion and pancreatic Beta-cell dysfunction in diabetes. Curr Diabetes Rev., 2013 Jan 1; 9(1): 25-53.
17. De Meyts P. Insulin and its receptor: structure, function and evolution. Bioessays, 2004; 26(12): 1351–62.
18. De Meyts P, Whittaker J. Structural biology of insulin and IGF1 receptors: implications for drug design. Nat Rev Drug Discov., 2002; 1(10): 769–83.
19. Ataie-Ashtiani S, Forbes B. A Review of the Biosynthesis and Structural Implications of Insulin Gene Mutations Linked to Human Disease. Cells, 2023; 12(7): 1008.
20. Petersen MC, Shulman GI. Mechanisms of Insulin Action and Insulin Resistance. Physiol Rev., 2018 Oct 1; 98(4): 2133-2223.
21. da Silva Rosa SC, Nayak N, Caymo AM, Gordon JW. Mechanisms of muscle insulin resistance and the cross-talk with liver and adipose tissue. Physiol Rep., 2020 Oct; 8(19): e14607.
22. Garg SK. Role of continuous glucose monitoring in patients diabetes using multiple daily insulin injection. Infusystems Int., 2009; 8: 18–21.
23. Bergenstal RM, Tamborlane WV, Ahmann A, Buse JB, Dailey G, Davis SN, et al. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. N Engl J Med., 2010; 363: 311–20. [PubMed] [Google Scholar]
24. Sovik O, Thordarson H. Dead-in-bed syndrome in young diabetic patients. Diabetes Care, 1999; 22(Suppl 2): B40–2. [PubMed] [Google Scholar]

25. Cryer PE. Severe hypoglycemia predicts mortality in diabetes. Diabetes Care, 2012; 35: 1814–6. [PMC free article] [PubMed] [Google Scholar]
26. Brazg RL, Bailey TS, Garg S, Buckingham BA, Slover RH, Klonoff DC, et al. The ASPIRE study: Design and methods of an in-clinic crossover trial on the efficacy of automatic insulin pump suspension in exercise-induced hypoglycemia. J Diabetes Sci Technol, 2011; 5: 1466–71.
27. Bode B, King A, Russell-Jones D, Billings LK. Leveraging advances in diabetes technologies in primary care: a narrative review. Ann Med., 2021 Dec; 53(1): 805-816.
28. Pettis RJ, Muchmore D, Heinemann L. Subcutaneous insulin administration: sufficient progress or ongoing need? J Diabetes Sci Tech., 2019; 13(1): 3–7. [PMC free article] [PubMed] [Google Scholar]
29. Lasalvia P, Barahona-Correa JE, Romero-Alvernia DM, et al.. Pen devices for insulin self-administration compared with needle and vial: systematic review of the literature and meta-analysis. J Diabetes Sci Technol., 2016; 10(4): 959–966. [PMC free article] [PubMed] [Google Scholar]
30. Singh R, Samuel C, Jacob JJ. A comparison of insulin pen devices and disposable plastic syringes - simplicity, safety, convenience and cost differences. Eur Endocrinol, 2018; 14(1): 47–51. [PMC free article] [PubMed] [Google Scholar]
31. Adolfsson P, Hartvig NV, Kaas A, et al.. Increased Time in Range and fewer missed bolus injections after introduction of a smart connected insulin pen. Diabetes Technol Ther, 2020; 22(10): 709–718.
32. Michou P, Gkiourtzis N, Christoforidis A, Kotanidou EP, Galli-Tsinopoulou A. The efficacy of automated insulin delivery systems in children and adolescents with type 1 diabetes Mellitus: A systematic review and meta-analysis of randomized controlled trials. Diabetes Res Clin Pract., 2023 May; 199: 110678.
33. Bassi M, Franzone D, Dufour F, Strati MF, Scalas M, Tantari G, Aloi C, Salina A, d'Annunzio G, Maghnie M, et al. Automated Insulin Delivery (AID) Systems: Use and Efficacy in Children and Adults with Type 1 Diabetes and Other Forms of Diabetes in Europe in Early 2023. Life. 2023; 13(3): 783.
34. Egede LE, Dismuke CE, Walker RJ, Williams JS, Eiler C. Cost-Effectiveness of Technology-Assisted Case Management in Low-Income, Rural Adults with Type 2 Diabetes. Health Equity, 2021 Jul 26; 5(1): 503-511.
35. Sherr JL, Heinemann L, Fleming GA, Bergenstal RM, Bruttomesso D, Hanaire H, Holl RW, Petrie JR, Peters AL, Evans M. Automated insulin delivery: benefits, challenges, and recommendations. A Consensus Report of the Joint Diabetes Technology Working Group of the European Association for the Study of Diabetes and the American Diabetes Association. Diabetologia, 2023 Jan; 66(1): 3-22.
36. Al-Tabakha MM, Arida AI. Recent challenges in insulin delivery systems: a review. Indian J Pharm Sci., 2008 May-Jun; 70(3): 278-86.
37. Chow, Clara & Ramasundarahettige, Chinthanie & Hu, Weihong & Khalid, Fawad & Avezum, Alvaro & Cheng, Xiaoru & Chifamba, Jephat & Dagenais, Gilles & Dans, Antonio & Egbujie, Bonaventure & Gupta, Rajeev & Iqbal, Romaina & Noor hassim, Ismail & Keskinler, Mirac & Khatib, Rasha & Kruger, Iolanthé & Kumar, Raj & Lanas, Fernando & Lear, Scott & Yusuf, Salim. (2018). Availability and affordability of essential medicines for diabetes across high-income, middle-income, and low-income countries: a prospective epidemiological study. The Lancet Diabetes & Endocrinology. 6. 10.1016
38. King MJ, Badea I, Solomon J, Kumar P, Gaspar KJ, Foldvari M. Transdermal delivery of insulin from a novel biphasic lipid system in diabetic rats. Diabetes Technol Ther., 2002; 4: 479–88.
39. Zhao J, Xu G, Yao X, Zhou H, Lyu B, Pei S, Wen P. Microneedle-based insulin transdermal delivery system: current status and translation challenges. Drug Deliv Transl Res., 2022 Oct; 12(10): 2403-2427.
40. Mohanty RR, Das S. Inhaled Insulin - Current Direction of Insulin Research. J Clin Diagn Res., 2017 Apr; 11(4): OE01-OE02.
41. Lee SH, Lee YB, Kim BH, Lee C, Cho YM, Kim SN, Park CG, Cho YC, Choy YB. Implantable batteryless device for on-demand and pulsatile insulin administration. Nat Commun., 2017 Apr 13; 8: 15032.
42. Jarosinski MA, Dhayalan B, Rege N, Chatterjee D, Weiss MA. 'Smart' insulin-delivery technologies and intrinsic glucose-responsive insulin analogues. Diabetologia. 2021 May; 64(5): 1016-1029.
43. Freckmann G, Pleus S, Haug C, Bitton G, Nagar R. Increasing local blood flow by warming the application site: Beneficial effects on postprandial glycemic excursions. J Diabetes Sci Technol. 2012; 6: 780–5.
44. Efrat S. Prospects for gene therapy of insulin-dependent diabetes mellitus. Diabetologia. 1998 Dec; 41(12): 1401-9.
45. Wong MS, Hawthorne WJ, Manolios N. Gene therapy in diabetes. Self Nonself., 2010 Jul; 1(3): 165-175.
46. Mansoor S, Kondiah PPD, Choonara YE, Pillay V. Polymer-Based Nanoparticle Strategies for Insulin Delivery. Polymers (Basel)., 2019 Aug 22; 11(9): 1380.
47. Psoma SD, Kanthou C. Wearable Insulin Biosensors for Diabetes Management: Advances and Challenges. Biosensors, 2023; 13(7): 719.

48. Summers KH, Szeinbach SL, Lenox SM. Preference for insulin delivery systems among current insulin users and nonusers. Clin Ther., 2004 Sep; 26(9): 1498-505.
49. Soares, Sandra & Costa, Ana & Sarmento, Bruno. Novel non-invasive methods of insulin delivery. Expert opinion on drug delivery, 2012; 9: 10.
50. Lakshman R, Boughton C, Hovorka R. The changing landscape of automated insulin delivery in the management of type 1 diabetes. Endocr Connect, 2023 Jul 31; 12(8): e230132.