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# Technological Innovation In Insulin Delivery: A comprehensive Review of Emerging solutions for Diabetes Management

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## ABSTRACT

The bad and ugly part of metabolic fuel in human body is the health impairment termed Diabetes which is non-infectious silent killer that has subjected human galaxy to high morbidity and mortality. Synthetic insulin delivery methods for ameliorating the effect caused by diabetes remains in the fore-front of development geared towards miniaturizing and getting user-friendly approach in curbing the pain and penury associated with Diabetes. There is evolution over the years from the crude insulin delivery tools to present day technological advancement of delivery system that dispense insulin to the systemic circulation which mimic the natural and physiological potency in management of the glycemic level in real time. The future landscape is aimed towards providing an automated technological panacea that is cost effective, efficient in monitoring and maintenance of

the physiological level of glucose in real time scenario.

**Key words:** Glucose metabolism, Insulin therapy, New Technology, Type 1 and Type 2 Diabetes.

## 1.0 INTRODUCTION

Diabetes is considered to be a combination of metabolic impairments, linked with a persistently increasing level of sugar with a tendency of manifesting some deleterious effects in organs (nerves, kidneys, eyes, blood vessels) of great physiological relevance in the human body (WHO, 2019.). Its incidence has a coverage of over 200 million individuals both in developed and low-income countries that are affected by this glucose-driven impairment, which is of concern to public health (Wais *et al.,* 2012). The disruption of the endocrine gland or the inability of cells to take up glucose remains the major hallmark of Diabetes, causing the systemic level of glucose to be heightened beyond normal and culminating in alterations in cellular homeostasis. Glucose, which is the key driver of diabetes, when not judiciously harnessed, will cause a compromise in body function, and this can be expressed as type 1 diabetes, in which insulin loses its capacity to aid the conversion of excess glucose to glycogen or mediate the availability of glucose for cellular utilization, and Type 2 diabetes, which is associated with the inability of cells to take up glucose despite the presence of insulin (insulin resistance) (Hovens *et al.,* 2005; Velho and Froguel, 2002). In type 1 diabetes, the beta cells of the Islets of Langerhans fail to produce insulin due to an autoimmune menace that can be affected by viruses (Jasser-Nitsche *et al.,*2017). About 90 percent of people suffering from Diabetes globally are those with the case of type 2 diabetes, which is chronic in nature, and the management measures require a concerted dietary scheme and engaging in regular exercise. The phenomenon of glucose intolerance can be seen in women during pregnancy. In this case, there is insulin resistance in the cells of the peripheral origin. This type of diabetes is referred to as Gestational diabetes mellitus which return to normal after birthing of new born.

Prolonged effects of Diabetes mellitus may result in blockage of the blood vessels, kidney failure, blindness, ischemic heart disease, neuropathy, stroke, and destruction of nerves, coupled with reduced life expectancy (ADA, 2009). According to the World Health Organization, the incidence of diabetes has increased geometrically from approximately 30 million to over 170 million in the year 2000. There could be a 50 percent increment by 2030 if the disease conditions persist over time, with elderly people between the ages of 45-64 years becoming more vulnerable (Garg *et al.,*2013).

Insulin is grouped as chemical messenger (hormone) secreted by the beta cells that are contained within the Islet of Langerhans of the pancreatic gland. Insulin with growth factors (Insulin growth factor 1 and insulin growth factor 2) are expressed by family of similar genes **(**Jin and Steiner,2000**).** The discovery of insulin has played a pivotal role in the management of Diabetes mellitus. Its discovery serves as a major breakthrough, presenting the possibility for treatment of diabetes and a chance of survival for individuals afflicted with this unpalatable health condition. Insulin is one of the most efficacious vehicles for the management of diabetes to this present epoch. Patients with type 1 diabetes mellitus and those with type 2 diabetes mellitus need insulin therapy in order to achieve a balance level of glucose in their body (Shah *et al.*,2013) Diabetic patients who use oral glucose-attenuating drugs often experience a resurfacing of symptoms within ten years, which requires therapy to be optimized by insulin administration. Due to the scarcity of specialists in diabetes management, general physicians are seldom involved in recommending insulin therapy for the treatment of type 2 diabetes mellitus. This might be a result of a hypoglycemia manifestation, lack of confidence or knowledge in initiating insulin therapy (Wright *et al.,*2002).

The unveiling of clinical trials has supported the usefulness of insulin in treatment of patients affected by type 2 diabetes. The usefulness linked with management of diabetes based on insulin therapy at early onset are beta-cell functioning integrity, toxicity of sugar(glucose) prevention and vascular complication delay (Tanenberg,2004). Patients with new cases of diabetes can be enlightened on the severity of the consequence associated with insulin therapy such as hypoglycemia which is not life threatening if effectively managed using tool like needles (less painful), insulin analogue and insulin pen and these tools are becoming wholly acceptable by patients. The management of glucose level in the blood is very important using insulin procedure however the need for proper formulation so as mimic the endogenous biphasic insulin produced by the pancreas is very important in order to overcome any bizarre circumstances arising from the synthetic therapeutic approach for diabetes management and in the same vein to strike a balance between baseline and peak level of glucose that is utilized by the body through hormonal (insulin) control. The first route for insulin delivery was the parenteral route for diabetic patients. The duration of action for adequate control of glycemic level is 2 days with 2-4 injections via the subcutaneous route. This route is considered efficient but the major challenges include hyperinsulinemia, proliferation of the smooth muscle and angiopathy (Ekam *et al.,*2013). The key objective of intensive management of the level of glucose is to obtain the minimal possible hemoglobin that is glycosylated without stimulating low level of blood glucose. This can be achieved through the use of insulin analogs, with a design to elicit a proportionate effect of the natural insulin function.

Having identified the relevance of insulin in fixing the abnormality associated with glucose metabolism in a synthetic form, the vehicle for delivery is crucial for diabetes management and prevention of complications. The crude or traditional methods, which include the use of insulin pens and syringes, have been effective to some extent. However, they are implicated with some bottlenecks in regulating glucose levels with the precision essential for minimizing future complications. The vehicle for insulin delivery in the modern era is aimed at eliciting the same effect as physiological endogenous insulin with consistency and controlled glucose levels in the blood. The use of syringe, pen, insulin infusion pumps and jet injectors are the major means for insulin delivery. The constrain linked with the use of these approaches are destructive (invasive) effect and mainly for type 1 diabetes with patient taken the synthetic hormone(insulin) multiple times on daily basis (Maniatis *et al.*, 2001). New approaches are designed in order to achieve precision with insulin delivery in the non-invasive way with aim of patience adaptability, and improved medical acceptance. The route of administration is considered effective when there is an increase in the effectiveness of the insulin in attenuating the concentration of glucose in the blood and ultimately lowering complication geared by diabetes (Veuillez *et al.*, 2001).

This review herein aims to delve deeply into the evolving phenomenon of various technologies in insulin delivery, with a critical examination of traditional and modern approaches, the mechanisms, advantages, and challenges of the different delivery systems. Furthermore, the advancements in technology, which include the automation of systems for insulin delivery, smart pens with high levels of precision, nasal passage insulin, and fast-growing innovations, will be reviewed. Evaluation of the technologies in line with their effect on patient outcomes, Economic considerations, and healthcare system integration will provide a clear understanding of the present framework and the long-term potential of insulin delivery.

## 2.0 Traditional Methods of Insulin Delivery

### 2.1 Syringes and Vials

The utilization of both vials and syringes is considered the first traditional method for insulin delivery, invented in the first half of the 1920s. The route of administration for insulin is through the subcutaneous layer, where a syringe is used to take insulin contained in a vial for sufferers of glycemic fluctuation. This approach is cost-effective, involving manual skills and a high level of accuracy. A lot of patients subscribe to this method since it is less expensive. It is adaptive to diverse forms of insulin, allowing for different insulin doses. The key challenges are the time consumption in getting insulin from the vial compared to new methods. The issue of parallax error can be associated with taking the right dose of insulin, posing difficulties for the elderly or those who are visually impaired. There is a tendency for improper fat distribution at the injection site and incessant pain. Reduction of side effects can be achieved by changing the injection site. (Pickup & Williams, 2011; Owens, 2002).

### 2.2 Insulin Pens

This method has been in existence since 1980s. they are made up cartridge that are pre-loaded with insulin and a controlled mechanism for fixing the dosage to be administered. They are small and can be disposed after being used or in some cases can be reused. Dosage adjustment is made possible due to dialing process that is fix to the pen which minimize the risk of error presentation. It does not require much technicalities for its operation which makes it useful for diabetic patients that have issues with their sight. This vehicle for insulin delivery is relatively expensive compared to syringe and vials, this can be of challenge to patients who cannot afford the cost. There is a need to change the sites of injection and yielding to instruction of the producers is also required for proper use of the pen. Patients need to fix new needles, evacuate air bubbles and get the dose adjusted for effective usage (Bergenstal *et al.,* 2008; Davies *et al.,* 2008).

### 2.3 Insulin Pumps

It applies an automation mechanism for its utilization. It uses the subcutaneous route to carry out its function of insulin delivery. The pump works like the body's natural insulin by dispensing and maintaining the normal physiological level of insulin. The insulin pump provides efficient regulation, resulting in a better level of glucose in the body. It minimizes the need for continuous daily use of insulin and hence improves adherence to insulin therapy. It allows for varying doses of insulin administration on a daily basis and even during physical engagement. This traditional technique is highly exorbitant, and its usage requires proper training to fix any technical or faulty issues. This technique can subject patients to infections, and ketone bodies can be generated due to a breakage in insulin availability. Injection sites can be modified on a routine basis with constant monitoring for optimization of its operation (Jeitler *et al.,* 2008).

### 2.4 Inhaled Insulin

This is a non-invasive approach to insulin delivery with a swift mechanism of action. It works almost in the same way as an asthmatic inhaler. The powdered form of insulin is infused into the hub of gaseous exchange (lung) in the body, followed by diffusion into the systemic circulation. It aids in the regulation of glycemic levels during meals. It overcomes the burden and pain associated with the use of injections. In comparison with subcutaneous delivery, this approach elicits a faster effect in carrying out its physiological role. Patients afflicted with lung problems like chronic obstructive pulmonary disease or asthma are not allowed to use this delivery process to avoid undesirable effects. Therefore, it is essential to conduct proper diagnostic checks for lung inflammation before using this method. Prior to feeding, this vehicle should be used to give insulin to patients at accurate dosages (Rave *et al.,* 2008).

### 2.5 Jet Injectors

The thermal route is utilized by jet injectors with air of intense force (pressure) rather than needle puncturing. This approach has been in existence for many years and is meant to deliver insulin through a route that is void of pain. The force used in this process can inflict physical tension (pain) around the injection site. They are relatively heavy and exorbitant for fixing problems associated with diabetes. The level of absorption of insulin using jet injectors is uncertain, presenting a challenge in the regulation of blood glucose. They are seldom used for insulin delivery as it requires some level of expertise for operation (Berveiller *et al.,* 2005; Hirsch, 2006).

## 3.0 Modern Methods of Insulin Delivery

### 3.1 Continuous Glucose Monitoring (CGM) Systems

This method marks a landmark advancement in the management of aberrations linked with carbohydrate metabolism by providing actual readings of sugar levels during morning and night hours. This system consists of a detector that is fixed in the skin, a signal receiving device, or an adaptive smart tool. It provides details of glucose changes over time. It gives a real-time result of the glucose level and allows the person using it to provide accurate information on the level of insulin to use, nutrient allowance, and exercise. It indicates the glycemic volume at every point in time, permitting proper intervention schemes and preventing any form of side effect (Bergenstal *et al.*, 2008; Davies *et al.*, 2008). Calibration difficulties, high cost, and supply challenges make it difficult for patients to subscribe to the use of this insulin delivery approach (Rodbard, 2016; American Diabetes Association, 2019).

### 3.2 Insulin Pumps with Continuous Glucose Monitoring (CGM) Integration

This system functions as an unnatural pancreas. The system is integrated in such a way that it permits adjustment in the delivery of insulin, which depends on incessant glucose monitoring. The looping functionality of this design allows for adequate delivery of the correct dose, attenuating the challenges of diabetes management. It provides a better outcome and works as a customized system for insulin availability and concerted control of glucose levels by reducing hypoglycemic incidence (Bergenstal *et al.,* 2013; Kovatchev *et al.,* 2014; Weinzimer *et al.,* 2008). The technology of this method is complex and expensive, hence making it difficult for patients to adopt it (Rodbard, 2016; American Diabetes Association, 2019).

### 3.2 Patch Pumps

The skin serves as the route of administration of insulin when using a patch pump. These pumps are tiny, wireless, and highly efficient for day-to-day use. They prevent attachment and allow for reproducibility. Due to the portable size of the pump, there is a need for proper regular refilling of the insulin tank. Side effects can manifest among some individuals who adapt to using the patch pump due to its adhesive nature (Rini & Goldberg, 2010; American Diabetes Association, 2019).

### 3.3 Smart Insulin Pens

This is a modified form of the native insulin pens utilizing technology that allows for tracking of the dosing data and are linked to electronic application. Analysis of the tracked information can be done with mobile device. The pen has a memory for reminding of gap in dose intake depending on the level of glucose in circulation (Foster *et al.,* 2014; American Diabetes Association, 2019). The smart pens are quite expensive, reducing the chance of accessing them for use (Foster *et al.,* 2014; American Diabetes Association, 2019).

### 3.4 Mouth spray:

In this case, the delivery of insulin is achieved via the cheek and posterior part of the oral cavity using an aerosol spray. There are two types of mouth spray: the fast-acting form, which determines the quantity of insulin needed to maintain glucose stability within 24 hours. This method allows for quick absorption of insulin into the bloodstream (Arida *et al.,* 2008).

### 3.5 Electroporation:

This approach allows the delivery of chemical substances through the skin with the passage of a minute current of electricity. It is one of the major technological mainstays of this dispensation that has helped to minimize the challenge of poor diffusion of insulin via the skin. It allows for the migration of both neutral and charged compounds and aids the physical delivery of drugs in a programmed way.

### 3.6 Ultrasound/Sonophoresis:

This method allows for both small and large molecular weight compounds, such as insulin, to permeate through the dermal route with the aid of ultrasound. The application of ultrasound as a vehicular means for transporting biological material spans a broad spectrum of applications. Ultrasound plays a pivotal role in increasing the fluidity of the skin, allowing for improved transport of chemicals.

| Categories | Traditional Delivery method | Modern Delivery methods |
|---|---|---|
| **Different forms** | Vials and Syringes | Insulin Pens, Insulin Pumps, Continuous Glucose Monitoring systems Inhalers, Smart Insulin Pens, Patch Artificial Pancreas Systems. |
| **Description** | Insulin delivery utilizing vial and syringes | Delivery of insulin is achieved at the same time, through nasal air |

| | | | |
|---|---|---|---|
| | | intake, or utilizing GCM with looping mechanism | |
| **Route of delivery** | Insulin is sucked using vial and transferred into a syringe. | Delivery is done by automation using subcutaneous or inhalation process. | |
| **Precision** | It relies on individual techniques with precision in dosing | Automation aids high level of delivery process | ( Heinemann *et al.,*2020) |
| **Adaptability** | Requires a detailed process for dosing and delivery | It is highly easy as it consists of automated framework and Preparation process is simple. | (Pettus *et al.*, 2018). |
| **Bottleneck** | There is tendency for inconveniences and discomfort | It is not painful when compared to the crude method. | (Bergenstal *et al.,*2017; Peyrot *et al.,*2013) |
| **Compactness** | There is a need for mobility of syringe and vials though it is simple and portable. | It is made up of portable system such as pumps and pens | (Kalra *et* al.,2015; Evans *et* al.,2019**)** |
| **functionality** | It needs physical skills for it to function | It is easy to use and a programmed dose is design with automatic functionality. | (Bremer *et* al.,2019) |
| **Regulation** | Not efficient in the creating a balance in the amount of glucose in systemic circulation. | It enables qualitative control of the operational process which produce an ideal regulation of glucose with minute variation | (Edelman *et* al.,2018) |

## 4.0 NON-INVASIVE DRUG DELIVERY SYSTEM

### 4.1 Liposomes:

This consists of multiple compartments of lamellar structure, with a double space of vesicular compartments containing a hydrophilic solution. The membrane contains phospholipids that are both natural and synthetic. Liposomes can be used for the direct delivery of peptide-containing compounds to specific organs or tissues in the body (Wu *et al.*, 2004). The challenge of instability associated with the use of liposomes for conveying compounds within the gastrointestinal tract can be overcome with the use of polyethylene glycol. Lyophilization is needed to increase the stability of liposomes, allowing them to be stored for long periods. Lambkin detailed the process for setting the formulation of insulin to be delivered through the oral route using different diameters of liposome design.

### 4.2 Nanoparticles:

Nanoparticles have great relevance in various fields including agriculture, environment, biotechnology, medicine, and food. They can be used in wastewater treatment, monitoring environmental constraints, as components of functional foods, and for drug delivery (Zahra *et al.*, 2020; Chen *et al.*, 2023). Nanoparticles are a group of particles with sizes ranging between 1 to 100 nm. They are characterized by large surface area and minute size, possessing distinctive features compared to larger molecular-sized compounds (Hasan, 2015).

Nanoparticles have been employed for the delivery of peptide-containing compounds such as insulin due to their high stability and exceptional capacity to uptake both aqueous and hydrophobic compounds. They demonstrate a high degree of drug delivery with increased bioavailability at the site of physiological action. Patches are used for incorporating insulin into nanoparticles for delivery to the intestinal compartment. Nanoparticles made with chitosan used in pre-clinical trials have been shown to lower glucose levels in experimental rats. Optimization of parameters such as release rate and encapsulation efficiency should be conducted to enhance the bioavailability of insulin at the site of action.

### 4.3 Microsphere

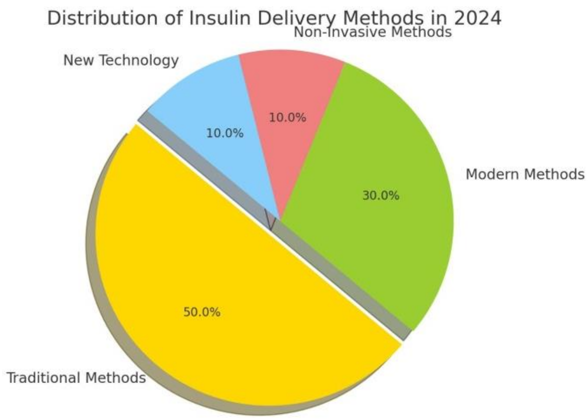
These particles are spherical solids that are prepared using solvent evaporation from natural polymers that are biodegradable, such as albumin, or from unnatural polymeric sources, which include polyglycolic acid. Microspheres range in size from 1 to 600 nanometers. Microspheres are also formed by encapsulating them in small capsules. Insulin can be incorporated into these microspheres using sodium alginate or mucin. This insulin delivery system can also be infused with polyfumaric anhydride (Furtado *et al.,* 2007).

### 4.4 Niosomes:

This is in the form of a liposome containing a surface tension-reducing substance that is inactive. The function of the surfactant present in the liposome is to enhance the easy delivery of drugs. The hydrophobic surfactants belong to the alkyl or polyglycerol ether families and include steroids (such as cholesterol), which further hydrate in a hydrophilic solution. They play a pivotal role in reducing the clearance time of peptide-containing compounds like insulin in systemic circulation. Genetically engineered insulin can be delivered to cells using formulations made with niosomes (Mehanna, 2005).

### 4.5 Hydrogels:

This drug delivery system consists of a colloid where the chemical agent is dispersed in a hydrophilic solution. It is composed of several components that form a three-dimensional polymeric framework (Kahyap *et al.,* 2005). Water is primarily used to disperse the macromolecules transported by this system. The hydrogel can reversibly change its form, especially from sol to gel, and it self-regulates the drug transfer process. Hydrogels exhibit a high level of compatibility with biological systems, possess flexible physical characteristics, and have the ability to encapsulate chemical compounds such as drugs. These attributes make hydrogels a promising agent for insulin delivery, facilitating effective management of diabetes.




## 5.0 Emerging and Future Technologies in Insulin Delivery

### 5.1 Implantable Insulin Delivery Devices

This novel technology is essential for making insulin available in systemic circulation directly having homogeneous effect as the natural hormone secreted by the pancreas. It consists of insulin storage system, a pumping system and glucose monitoring network. The level of glucose is incessantly watched and there is a need for regular pumping of glucose to maintain the physiological benchmark. The abnormal effect caused by the use of injection is wholistically substituted with the use of this technology. The architecture of this framework is to enhance precision in the delivery of insulin in a compacted and dose-efficient manner. The Insulin reservoir system can be changed over time and refilling is also allowed. The pump dispenses insulin based on signal detected in a real time circumstance. the technological automation of this system is to permit for intermittent dispensing of insulin as a function of level of glucose in the body. In recent time, insulin delivery system that can be inserted into human body is in the clinical trial stage with a target of fixing issues of potency of the technology, usability and biosafety of the system. Improving the functionality of the device through side reduction, efficient battery durability, recruitment of other technology to form a unit remains a key pursuit with the utilization of this method for human diabetic management. New technology is aimed towards having automatic looping system that monitor the glycemic level in a real time scenario. (American Diabetes Association, 2020). The need for machine learning algorithm will be so pivotal in improving the automation and efficiency of the device in discerning the hormonal (insulin) needs of a diabetic patient and in same vein helps in the regulation of dose at every single point of glycemic alteration.

## 5.2 Smart Insulin (Glucose-Responsive Insulin)

The dimension of smart insulin design is targeted towards dispensing insulin as the need arise which is a function of the amount of glucose in the blood. The technology is made in such a way that it resembles the innate insulin need. The formulation of this system has compounds with affinity for glucose that stimulates the dispensing of insulin as the level of glucose get heightened in the systemic circulation. This innovation is still on the pipeline of development with a great prospect in curbing the challenge associated with diabetes (Shulman and Rothman, 2020).

## 5.3 Gene Therapy and Stem Cell Research

The advantages set with the use of gene therapy for biological purpose are unquantifiable ranging from diseases management, biomedicine, crop improvement and chemical industry. It involves the utilization of foreign gene for enhancing the quality of endogenous protein which impacts the physiology of diverse cellular components. In the case of insulin improvement, gene therapy involves the injecting a foreign functional gene that encodes for insulin into the cell of the pancreas using a vector as a vehicle for delivery without causing any immunological aberration. The goal of this procedure is to prevent the side effect attached to the use of synthetic insulin via injection. This process is still in the clinical trial stage towards improving its biosafety and potency of the technique (American Diabetes Association, 2020). The gene SHIP2 has been found useful in the management of type 2 diabetes by regulating the expression of insulin secreted by the pancreas (Valerie, 2018).

Stem cell therapy requires the stem cell differentiation into pancreatic cells (beta cells) and subsequent integration into the body of sufferer of the health impairment. The transplanted cell can be derived from induced pluripotent stem cells and then developed the capacity to produce insulin hence reducing the constrain of exogenously synthesized insulin. The ongoing research is focus on increasing the survival of the transplanted cell, improved differentiation of the stem cells and reduced immune response.

## 6.0 Challenges and Considerations

The major bottlenecks of the novel advancement of insulin delivery process are precision and usability of the technology. There is a need for the innovative devices to give correct amount of insulin needed in a real time and the glycemic level must also be attained at different point correctly in order to cushion any deleterious anomaly in the level of glucose. Machine learning algorithm and the development of insulin sensor are filling the gap of the problem (Shulman & Rothman, 2020). There is ongoing research towards improving the calibration of the device for effective usage and also working on increasing the durability of the device.

## Conclusion

Diabetes remains one of the non-infectious diseases that is of public health concern. The need to set in new technology towards delivering insulin for the management of diabetes is gaining new ground with the emergence of technologies with a real-time effect in maintaining glucose homeostasis. The traditional method of insulin delivery still presents some complications such as hypoglycemia and constant pain inflicted on patients when they are injected. The novel technologies, such as gene therapy and non-invasive monitoring of glucose, are all aimed at controlling the level of glucose among diabetics and reducing the mortality caused by diabetes. The future cannot be far-fetched with the scientific strides and evolving innovations for improving the health of diabetic patients utilizing scalable and user-friendly technology for delivering insulin needed in restoring a balance in the physiological metabolic fuel

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