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Review

Recent Advances Using Nano-Drug Delivery Systems in the Management of Diabetes Mellitus

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ABSTRACT

Diabetes mellitus is a global epidemic with significant morbidity and mortality rates. There are numerous ways to provide medications for treating diabetes, including transdermal, oral, nasal, and pulmonary routes. Traditional methods of glucose monitoring and insulin delivery have limitations. The form of diabetes that is principally to blame for the current global epidemic, type 2 diabetes mellitus (T2DM), is the major subject of this perspective article; this review discussed the advancements made in drug delivery systems for the management of diabetes focusing on methods utilizing Nano drug delivery systems, chitosan drug delivery systems, implantable drug delivery systems, micro-particulate drug delivery systems, nanoparticle delivery, micro-needle-based insulin transdermal delivery systems, and intranasal insulin delivery. By examining these drug delivery systems' mechanisms, applications, potential, and limitations, the article provides insights on how these technologies can potentially transform diabetes care by enhancing medication effectiveness, improving adherence, supporting personalized treatment approaches, and presenting innovative solutions for continuous glucose monitoring

Keywords: Drug delivery systems, Micro particulate drug delivery system, Oral insulin, Nanoparticulate, diabetes.

1. Introduction

One of the biggest global epidemics affecting both developed and developing countries is diabetes mellitus. Diabetes mellitus, now recognized as a condition, is classified as a group of illnesses characterized by signs and symptoms associated with chronic hyperglycemia. The three most common varieties of diabetes are type 2 diabetes mellitus (T2DM), type 1 diabetes mellitus (T1DM), and gestational diabetes mellitus; however, several distinct variants are significantly less common (1). Globally, the prevalence of diabetes mellitus has risen in the last several decades. The International Diabetes Federation (IDF) has published its ninth edition of Diabetes Atlas, which projects that there will be 463 million diabetics worldwide in 2019. By 2030, that figure is expected to rise to 578 million; by 2045, it will reach 700 million (2).

Currently, diabetes mellitus ranks alongside cardiovascular disease and malignant tumors as a major non-communicable disease with a high death and morbidity rate. Diabetes mellitus, an endocrine and metabolic disorder marked by hyperglycemia and numerous complications, is one of the most prevalent chronic diseases. The primary causes of diabetes mellitus are genetic, environmental, microbial, immune system, and psychological variables that lead to low insulin secretion and insulin resistance. Diabetes mellitus patients have long suffered from life-threatening complications that have the potential to reduce their quality of life drastically. Long-term metabolic abnormalities, such as diabetic retinopathy (3), diabetic nephropathy (3), and diabetes hypertension (4), will result in persistent progressive lesions and damage to multiple systems and organs (3).

Extremes on the dysglycaemia spectrum, such as hyperglycemia, hyperosmotic state, and diabetic ketoacidosis (5), can also result from severe acute metabolic abnormalities. As a result, diabetes mellitus is currently a major health concern. Type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes, and specific kinds of diabetes are the classifications for diabetes mellitus used by the World Health Organization (WHO). 90% of

patients in China have type 2 diabetes. This represents the majority of patients (6). Over the past 20 years, the number of persons with type 2 diabetes has more than doubled worldwide. According to the International Diabetes Federation's (IDF) most recent estimate, there were 415 million persons worldwide with diabetes mellitus in 2015, and by 2040, that figure is expected to rise to 642 million.

Due to the relatively complex pathogenesis of diabetes mellitus, the key to controlling and treating the disease is to take into account each patient's unique situation and combine medication treatment, appropriate exercise, diet modification, close monitoring of blood sugar, mood assessment, and self-management skills, insulin analogs (7), and non-insulin hypoglycemic medications, which include insulin sensitizers, insulin secretagogues (8), glucose regulators (3), and gene therapy, make up the majority of antidiabetic medication treatments. Oral administration is the most advantageous and promising of them all. Nonetheless, there are numerous obstacles to oral medication delivery (9); these barriers mostly consist of the mucus and intestinal epithelium, the low pH of the stomach's gastric medium, and digestive enzymes in the stomach and small intestine. These challenges severely restrict medications' therapeutic efficacy and bioavailability, particularly those involving insulin and genetics. Consequently, it is crucial to create drug delivery systems that are safe, non-toxic, and biodegradable in order to shield medications from these impediments and enhance blood absorption.

Drugs were often given orally in the past, either as liquids or as powders. In order to circumvent issues that may arise from the oral drug administration route, novel dosage forms containing the drug or drugs were devised, and innovative drug delivery devices that could guarantee a consistent release of the medication to the precise location of action became necessary as time went on, and are implanted these days in place of the conventional approach delivery methods. In order to maximize the therapeutic qualities of pharmaceutical preparations and make them more dependable, safe, and successful, new drug delivery systems were created; in this review will discuss some of these systems, including Nano Drug Delivery Systems, Chitosan drug delivery systems, Implantable Drug Delivery Systems, Microparticulate Drug Delivery System, Transdermal nanoparticle in diabetes, Microneedle-based insulin transdermal delivery system, and Intranasal insulin.

2. Nano drug delivery system for the treatment of diabetes mellitus

Drug delivery systems (DDSs) can carry diverse functional substances to the wound site. Nano-drug delivery systems (NDDSs), benefiting from the features related to their nano-size, overcome the limitations of conventional DDS applications and are considered a developing process in the wound treatment field. Recently, several finely designed nano-carriers efficiently loading various substances (bioactive and non-bioactive factors) have emerged to circumvent constraints faced by traditional DDSs. This review describes recent advances in nano-drug delivery systems that mitigate diabetes mellitus-based, non-healing wounds, as shown in Table 1. Modern drug delivery systems owe their remarkable success to nanoparticles and their characteristics, as they have a high capacity for transporting drugs, very large active surface for the reaction, suitable for small bodies to cross the blood levels, and the ability to accumulate in the target tissue, and Low toxicity (10).

2.1. Types of Nano-drug delivery system

[A] Polymer Nanoparticles

Nanospheres are vesicular systems where the drug within the polymer membrane is confined and transported to the target tissue, as represented in Figure 1. The polymer breaks into lactic acid, and the glycolic acid returns through the carbon dioxide and water cycle. Previous studies have emphasized using natural polymers, such as collagen, cellulose, etc., as biodegradable systems. Cytotoxicity experiments showed that drug release from spherical nanospheres was enhanced and did not harm cells (11–13).

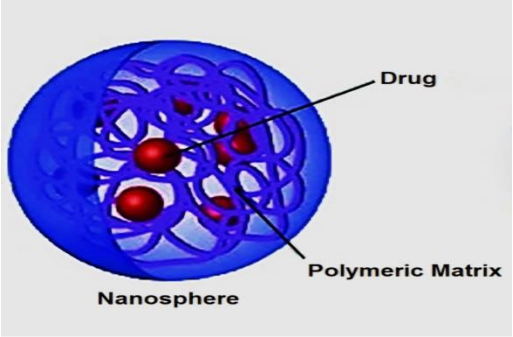

Figure 1. Schematic representation of Nanosphere (14).

Polymer-particles have provided significant material for oral and intravenous dosage forms to achieve efficiency and effectiveness, so polymer nanoparticles can be used in the special situation of administering high concentrations of pharmacological agents; these nanoparticles may be ideal candidates for insulin therapy and insulin delivery; polymeric nanoparticles are used as insulin carriers, these biodegradable polymers with an insulin matrix polymer on the membrane.

[B] Ceramic nanoparticles

Ceramic nanoparticles are made of calcium phosphate, silica, alumina, or titanium. Ceramic nanoparticles have advantages such as easy manufacturing, high biocompatibility, very small size (less than 50 m and high stability in the fourth dimension). These particles can effectively protect drug molecules from denaturation by changing the external pH and temperature. Optical syntheses of water-insoluble anticancer drugs loaded in ceramic nanoparticles are drug delivery systems for photodynamic therapy in cancer treatment. However, their surfaces can be easily modified with different functional groups so that they can be loaded with different ligands or monoclonal antibodies to bind to a specific site.

These nanoparticles can be designed according to the desired porosity size, shape, and quantity. Ceramic nanoparticles caused by environmental changes do not affect inflation or porosity changes. Calcium phosphate nanoparticle core is used as insulin carriers. Recent studies have shown that calcium phosphate nanoparticles can be used for oral insulin (15–18)

2.2.Nanoparticles and oral insulin

In people with diabetes, oral insulin can help reduce injection pain and damage and mimic the fate of physiological insulin (19,20). Oral administration of protein drugs such as insulin faces the problem of low pH, stomach digestive enzymes, and Intestinal epithelium, the main barrier to the absorption of hydrophilic macromolecules (such as proteins, polysaccharides, and nucleic acids) before it reaches the target cell for a specific action. Therefore, improving the transport of hydrophilic molecules in cellular parameters using nanotechnology has been considered in diabetes research. Thus, biodegradable polymers such as s (polyglycolic acid, PLGA) and polycaprolactone have been investigated for oral insulin.

However, these nanoparticles may not be ideal for transporting hydrophobic drugs. However, oral administration of hydrophobic drugs such as insulin remains a major challenge; thus, it was considered to improve the transferability of hydrophilic drug packages (21,22), because if it is administered orally, a carrier system is needed to protect protein drugs in the harsh environments of the stomach and small intestine, various enteric coatings and carriers have been used to facilitate the absorption of hydrophilic molecules, such as chitosan (Cs) (23,24).

Cs nanoparticles increase protein molecules absorbed in the intestine more than aqueous CS solutions in the body; insulin-loaded nanoparticles coated with sticky CS mucus can persist for longer periods, allowing their residues to remain in the small intestine, penetrate the mucosal layer and then transiently open the epithelial cell-mediated tight junction when the condition becomes unstable, due to their sensitivity to PH or degradation; insulin is released from the degrading particles and can enter the cells and travel to the final destination in the bloodstream (25). A nanoparticulate formulation of vitamin B12-dextran was investigated to overcome intestinal digestion of peptide/protein-bound vitamin B12 (26); these nanoparticles prevent insulin from being captured by intestinal proteases. Dextran-Vitamin B12 nanoparticle formulation has a suitable release profile for oral insulin delivery systems. In addition, gold nanoparticles synthesized with chitosan as a regenerative agent have been studied for insulin delivery (14).

Table 1. Applications of nano drug delivery systems in diabetes mellitus (27–38).

Drug-delivery system	**Phytocompound**	**Effects of proposed systems**
Chitosan Nps	Ferulic acid	Bioavailability increased; glucose-lowering effect increased; anti-hyperlipidemic effect increased.
PLGA NPS	Quercetin	Bioavailability increased; sustained release; glucose lowering effects increased; antioxidant effects increased.
Chitosan-alginate NPS	Naringenin	Glucose lowering effects increased; Normalization of pancreatic and hepatic abnormalities increased; Prevention of glycation-induced iron-mediated oxidative stress; increased; No toxicity.

Chitosan-alginate NPs	Quercetin	Glucose lowering effects increased; Anti-hyperlipidemic effect increased; No toxicity.
Gum-rosin nano-capsules	Thymoquinone	Glucose lowering effect's increased; Anti-hyperlipidemic effects increased; HbA1c level increased.
Chitosan-gum arabica NPs	Glycyrrhizin	Glucose lowering effects increased; Anti-hyperlipidemic effects increased.
Micelles	Curcumin	Bioavailability increased; Glucose lowering effects increased; Anti-hyperlipidemic effects increased; Prevention of damage in kidney, liver and pancreas; No toxicity; B-cell regeneration increased; Wound healing effects increased.
Zinc oxide NPs	Docosahexaenoic acid	Glucose lowering effects increased; Insulin lever increased; Insulin resistance decreased; Antioxidant effects increased; Improvement of erythrocyte membrane fatty acids; PI3K level decreased; Anti-hyperlipidemic effects increased.
Selenium NPs	Catathelasma ventricose polysaccharides	Glucose lowering effects increased; Antioxidant effects increased; Anti-hyperlipidemic effects increased.
Selenium-coated NLCS	Berberine	Bioavailability increased; Glucose lowering effects increased.
Mesoporous-silica NPs	16-Hydroxycleroda-3,13-Dine-16, 15-Olid	Glucose lowering effects increased; TG, GOT, and CHOL levels.
Nanocrystals	Curcumin	Glucose lowering effects increased; Gene expression and activities of insulin and insulin receptor increased.

3. Chitosan drug delivery system

Chitosan is a naturally occurring linear bio-polysaccharide obtained from the alkaline deacetylation of chitin, as revealed in Figure 2. Chitin is a major component of the cell walls of certain fungi, including aspergillus and mucor, and the protective cuticles of crustaceans, such as crabs, shrimp, and lobsters (24,25,39). Chitosan is affordable, non-toxic to mammals, and biodegradable. Because of this, it can be used as an antibacterial agent in clinical applications, a moisturizing agent in cosmetics, an additive in the food industry (40), and, more recently, a pharmaceutical agent in the development of biomedicine (41). Chemical technologies, including acid hydrolysis, oxidative degradation, and physical techniques like microwave degradation, UV irradiation, and enzymatic degradation processes, are utilized to produce chitosan (42). Nitric acid, hydrofluoric acid, and hydrochloric acid are the acid reagents utilized in the degradation of chitin; among these, hydrochloric acid is most frequently employed under catalytic conditions at 80 °C for 1-2 hours (43).

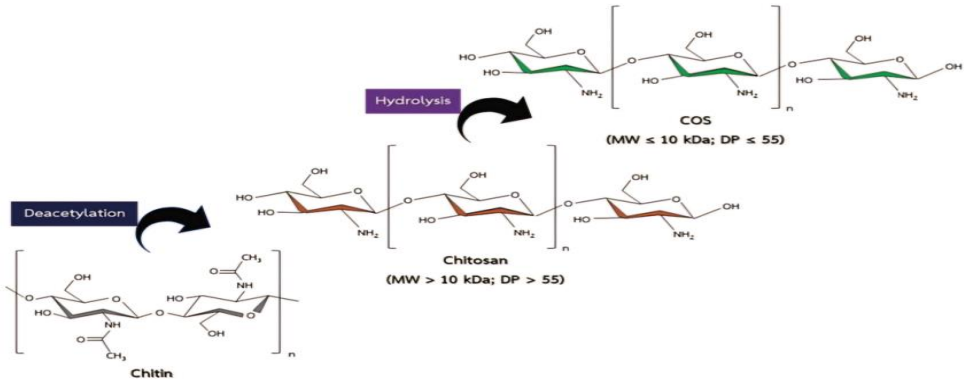

Figure 2 Structure of Cs and its preparation (44).

However, one drawback of chemical degradation is the complexity of the product materials that need to be extracted. Also, these dangerous chemical compounds frequently damage the environment and contribute significantly to producing hazardous waste (45). Because of glucosamine, chitosan has a positive net surface charge at slightly acidic pH levels, which makes it easy for chitosan to bind to the anion protein in the mucus layer; the main mechanisms by which chitosan's mucoadhesion capabilities were achieved were hydrophobic interaction, hydrogen bonding, and electrostatic contact (46), furthermore, the presence of hydroxyl and amino groups

in the chitosan backbone provides a wide range of opportunities for different chemical changes that improve solubility (47), encourage cell absorption, and enable medication release over an extended period. This characteristic makes it possible for intestinal and nasal cells to absorb chitosan and offers an excellent platform for medication delivery (48).

3.1. Chitosan clinical applications: (49,50)

Unexpectedly, several chitosan forms demonstrate the potential for enhancing the metabolism of lipids and carbohydrates linked to diabetes. However, chitosan also made many novel carriers available for the targeted delivery of antidiabetic medications (44). Chitosan is a multifaceted molecule that has become an effective pharmaceutical carrier and an antidiabetic agent due to significant developments in therapeutic research. Chitosan will easily attach to the surface of the mucus and open tight located in the intestinal and nasal passages epithelial cells (51).

a) Chitosan in Scar Differentiation.

b) Practical Applications in Chitosan Hydrogels in Photochemistry and Experimental Surgery.

c) Chitosan activates macrophages for tumoricidal activity and production of Interleukin-1.

d) Chitosan used for scaffold and hydrogel preparation.

e) Chitosan dressings are useful in hemostasis and angiogenesis.

Three types of chitosan nanoparticles, namely insulin-loaded nano chitosan (INCS), insulin-chitosan complex nanoparticles (ICSCN), and enteric insulin chitosan coated complex nanoparticles (EICSCN) for efficient oral insulin delivery, in order to manage issues like loading with low performance, early rush release, and poor bioavailability (52). Chitosan allows peptide drugs to remain in the nasal mucosa for a prolonged period, and it is used as an enhancer of absorption through the epithelium of the nose (53). To attain sustained release, researchers developed a novel hydrogel heat-sensitive system by N-[(2-hydroxy-3-trimethylammonium) propyl] chitosan chloride (HTCC), PEG, and α-β-glycerophosphate (GP) as a drug for nasal administration; HTCC-PEG-GP solution filled with insulin converted into a hydrogel at around 37°C (54).

A single chitosan-zinc-insulin injection (complex did not affect insulin structure, thermal stability is improved, and insulin release has been extended by 84 days) paired with PLA-PEG-PLA (poly (lactic acid), poly (ethylene glycol), and poly (lactic acid) tri-block thermosensitive copolymer with a molecular weight of 4500) demonstrated continuous release of insulin and held blood sugar levels below 200 mg/dL for up to 70 days (55).

4. Implantable Drug Delivery Systems for Diabetes Management

Despite the limitations of conventional insulin delivery systems and glucose monitoring technologies concerning multiple intervals, time constraints, pain, and inconvenience, point-of-care blood tests, which use a portable finger-pricking kit (usually utilizing an enzyme-based glucometer and disposable strips), over the past few decades, have been the most widely used method for self-monitoring blood glucose levels since its introduction in 1974 (56,57). Implantable continuous glucose monitoring (CGM) devices have been used in clinics since the late 1990s to measure blood glucose levels. This has enabled it to identify and forecast hypo- and hyperglycemia and do retrospective analyses (58,59).

These methods, however, are intrusive and necessitate routine recalibration through finger-prick blood tests to correct sensor drift. Time-dependent biofouling growth significantly affects implanted devices, making it difficult to maintain their measurement accuracy (60,61). As a result, there is a growing need for a novel gadget to make it possible for diabetics to continuously and more reliably check their blood sugar levels. The development of mechanically deformable and electrochemically active materials leads to the creation of wearable (i.e., on-body) glucose sensors (62,63). These sensors can discreetly interface with different human body regions, enabling long-term in situ measurement of glucose concentrations from bodily fluids such as saliva, tears, and interstitial fluid.

When developing an implanted medication delivery system, there are several important considerations to consider. Since the technology will be implanted, biocompatibility with the human environment is crucial; a substance needs to meet specific criteria to be considered biocompatible at the implant site; all agents must be mechanically stable, non-carcinogenic, hypoallergenic, and chemically inert. Furthermore, the implant should not induce an inflammatory

reaction at the implantation site, and the material should not be altered chemically or physically by the surrounding tissue (64,65). The process of developing these drugs is intricate and time-consuming, involving numerous studies to ensure stability and biocompatibility. Many undesirable consequences, including capsular contracture, unexpected medication release, platelet adhesion, tissue injury, and infection of the implant's surrounding area, may arise if appropriate biocompatibility is not attained (66).

Medicine implants and implantable pumps containing medicine have historically been the two main categories into which implantable drug delivery systems have been divided. The first major class regulates the kinetics of drug release from delivery systems using different kinds of polymers and polymeric membranes (64). The biodegradable and non-biodegradable systems comprise the two further classifications into which this initial set of implants can be separated. The second major implant class is mechanical pump-type devices that control drug release by acting like an infusion pump. Due to ongoing technological advancements in this field, a third class of unusual implants has been identified.

4.1. Pump systems' drug delivery technique

Pump systems' drug delivery technique sets them apart from other implanted systems. Pump systems release pharmaceuticals by creating a gradient under pressure that causes a controlled bulk flow of the drug (64).

Five distinct implantable pump system types have been tested to date, including:

1- Infusion pump.

2. Peristalsis pumps.

3. Osmotic valves.

4- Pumps with positive displacement.

5. Micropumps with regulated release.

Usually inserted subcutaneously in the lower abdomen, the implanted insulin pumps use a catheter to deliver insulin intraperitoneally. When insulin is administered intraperitoneally rather than subcutaneously, the liver can absorb it more easily through the portal system, resulting in quicker absorption and more stable, long-term glucose control (67,68).

Medtronic MIP

The Medtronic MIP 2007D is the only implanted insulin pump model currently on the market, as shown in Figure 3. Its internal battery can last seven to ten years once implanted under general anesthesia (69). However, depending on patient consumption, a transcutaneous refill of the 15 mL insulin reservoir is needed every three months.

Figure 3. Examples of minimally-invasive CGM systems based on electrochemical sensing technique: (a) A patient wearing a sensor; (b) Medtronic Enlite sensor with dedicated inserter device; (c) Dexcom G5 Mobile with Share technology; (d) Abbott FreeStyle Navigator 2 (58).

In recent years, two implant systems have gained approval for human use. These include a silicone-based device (Norplant®) and a system utilizing lactide/glycolide copolymers to administer a luteinizing hormone-releasing hormone (LHRH) agonist for the treatment of male reproductive tract tumors (70).

5. Micro particulate drug delivery system application in diabetes

Microparticles, also known as free-flowing powders, are small spherical entities with a diameter ranging from 10 μm to 1000 μm (71). They are created from various inorganic, polymeric, and mineral components. Furthermore, MPs can have a variety of structural forms, such as magnetic MPs, lipid vesicles like liposomes and noisomes, micro granules, micro pellets,

microcapsules, micro sponges, and microemulsions (72). The most prevalent kind of MPs are polymeric MPs, which come in two primary forms: MPs and microspheres. The MPs matrix comprises a homogeneous mixture of polymers, copolymers, and active pharmaceutical ingredients (APIs). Microspheres, on the other hand, are composed of a solid or liquid core encased in a layer of material distinct from the core, as shown in Figure 4.

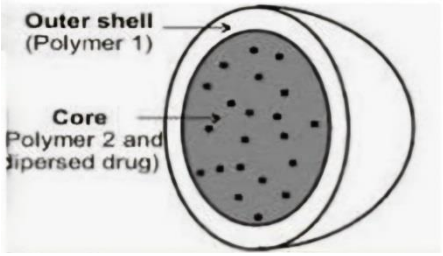

Figure 4. Microsphere cross section (72).

Polymers that determine their structure and greatly influence their qualities make up most of polymeric MPs. Polymers should ideally be inexpensive, biodegradable, safe, stable, and inert (73). In the meantime, a core made of either a liquid or a solid is referred to as a microsphere when it is encased in a layer of materials that are very different from the core. Polymers comprise most polymeric MPs, which determine their structure and greatly influence their qualities. Polymers should ideally be inexpensive, biodegradable, safe, stable, and inert (73). MPs are created using a broad variety of polymers that come from both natural and artificial sources (74). Depending on the polymer's makeup, the medication released from the MPs can be changed, and medicines into the MPs at higher concentrations and high entrapment efficiency can be optimized. Furthermore, research has demonstrated a clear correlation between particle size and drug loading capacity, with a decrease in particle size translating into a decrease in drug loading capacity and vice versa (75).

The microparticulate drug delivery system (MDDS) is gaining popularity because of its many advantageous technological features. When compared to conventional dosage forms, MDDS has many benefits: it guarantees a longer and regulated release pattern; it lowers medication toxicity and dose; it increases drug bioavailability; and because of its large surface area, it improves the solubility of poorly soluble medicines. In addition, they shield the medication from the in vitro and

in vivo surroundings, direct the medication to a particular biological site of action, cover up the undesirable taste and smell, and lower the frequency of dosages, increasing patient compliance (76,77). However, for successful clinical applications, MDDSs must be safe, perform therapeutic functions, provide convenient routes of administration, and be easy to manufacture. The production of MDDS has faced some limitations due to its poor reproducibility, expensive materials and production process, and some of its components and excipients that degrade into hazardous materials that can be harmful to the environment (72).

However, many new microparticulate products are currently in clinical trials. However, some of them were also available in the market. In particular, it has been reported in the literature that microparticle formulations can be promising in controlling blood concentrations of diabetes drugs, improving the dissolution of drug release, and finally improving their pharmacokinetics and bioavailability. In addition, Surface modified and muco-adhesive MPs showed benefits from the protective effect of enzyme degradation and improved peptide stability, in addition to site-specific drug release and gastric retention. The literature revealed that the field of drug delivery moved by unprecedented speed, and several drug delivery systems have been central to the past decade. Therefore, this review comprehensively reviews MDDS and focuses on their therapeutic applications as effective diabetic drug carriers.

5.1. MDDS Production Techniques

[A] Single Emulsion Technology

This method produces natural polymers based on MP, such as proteins and carbohydrates. First, the polymer is dissolved in an aqueous medium and then dispersed as oil in a non-aqueous solution. Cross-linking of the dispersion is then carried out either by heating or using chemical cross-linking agents such as glutaraldehyde. The surfactant type favors particle size, particle charge, surface morphology, drug loading, drug release, and bioactivity of MPs (78).

[B] Double emulsion technology

Double emulsion technology involves the preparation of double emulsions water-in-oil-in-water (w/o/w) or water-in-oil (o/w/o), as shown in Figure 5. Both natural and synthetic polymers can be used in the preparation of MPs. Double emulsion w/o/w is more suitable for water-soluble drugs, peptides, proteins, and vaccines. For example, a luteinizing hormone-releasing hormone (LH-RH) agonist was successfully encapsulated in MP using the double emulsion method (79).

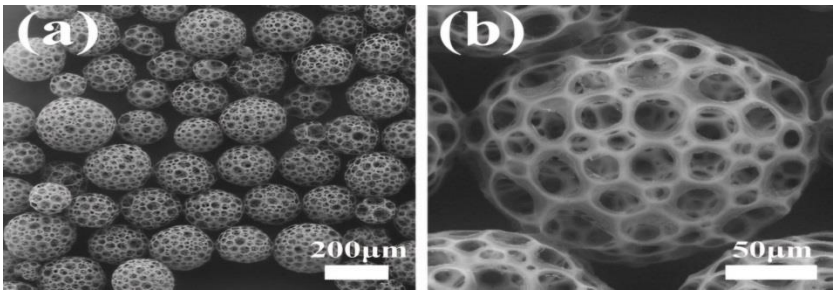

Figure 5. SEM images of PLGA porous microspheres fabricated by the double emulsion-solvent evaporation method. C_{PLGA}: 2.5 %, $C_{\text{ammonium bicarbonate}}$: 1 %, homogenization speed: 3600 rpm.

[C] Spray drying technique

Both polymer and drug are dissolved in a volatile organic solvent and homogenized in a high-speed homogenizer.

5.2. Application of microparticulate drug delivery systems

[A] Yeast microcapsule (YMC)

Saccharomyces cerevisiae microcapsules may incorporate various charged nanoparticles through electrostatic force-mediated spontaneous deposition, as shown in Figure 6. Long-term administration of yeast microcapsules (YMC) has a favorable safety profile in treating chronic diseases (80). YMC can be transferred to the systemic circulation via lymphatic circulation by intestinal M cell-mediated endocytosis. The alginate's excellent biocompatibility, abundance in nature and low cost make it an ideal candidate for protecting insulin from the severe conditions of the GI tract (81). Alginate can form a fragile gel in the presence of multivalent cations like calcium ions in aqueous media (82).

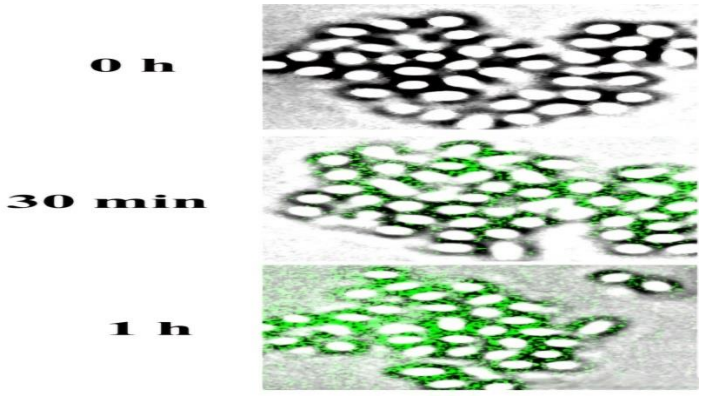

Figure 6. Fluorescence images showing the insulin loading onto YMC. YMC were incubated with FITC-labeled insulin, and the samples were taken at specified time points and processed for imaging. The scale bar represents 15 um (80).

The presence of numerous enzymes in the digestive tract, as well as the low pH of the gastric media, can all contribute to drug breakdown. As a result, a carrier system is required for insulin delivery across the gastrointestinal tract. Saccharomyces yeast microcapsules can be loaded with insulin to provide effective therapy. A promising strategy for hyperglycemia is to use bioinspired IYMC coated with alginate. The alginate coating protects YMC from severe GIT conditions. The 1,3-β-glucan polysaccharide found in the outer shell of baker's yeast allows for receptor-mediated uptake by phagocytic cells via M cell-mediated endocytosis and delivery to the systemic circulation via lymphatic transport.

[B] Microparticulate drug delivery system of Glimepiride

Delayed release dosage forms are necessary to minimize dosing frequency and enhance patient compliance. As a result, there is ongoing interest in and a need for developing controlled-release formulations; the Glimepiride microparticles were created. The impact of various factors on drug content and drug release from microparticles was studied. Encapsulation efficiency, particle size, drug loading, FTIR, DSC, SEM analysis, and drug release tests were all used to characterize microparticles. The solvent evaporation approach was used to create microparticles for oral controlled release and to obtain controlled release of Glimepiride (83).

[C] Insulin-loaded lectin–microparticle

Extensive research has been dedicated to discovering specialized carriers for oral delivery of insulin (84) and their bio-adhesive interactions with the mucosal membrane (85). Bio-adhesion can be achieved through nonspecific or selective interactions with surface ligands on a mucosal membrane. Small colloidal particles (drug carriers) combined with lectins capable of interacting with receptors on the surface of the gastrointestinal mucosa can generate specific bio-adhesive devices (86). Lectins (wheat germ agglutinin, WGA) are non-immunological proteins or glycoproteins that detect sugar molecules and can thus bind to glycosylated membrane components (87). Most lectin-particle conjugates have been described with polystyrene particles, which are unsatisfactory as a drug carrier because of their non-degradability, and there are relatively few researches involving biodegradable particles (88,89). Alginate is a naturally occurring biodegradable polymer with various distinguishing characteristics that have allowed it to be employed as a matrix for the entrapment and transport of proteins, medicines, and cells (90,91). The piezoelectric ejection method was used to create biodegradable microparticles from alginate, and lectin was conjugated to the microparticles to make use of the protective advantages of alginate microparticles and the muco-adhesive qualities of WGA for enhanced insulin oral delivery as shown in Figure 7.

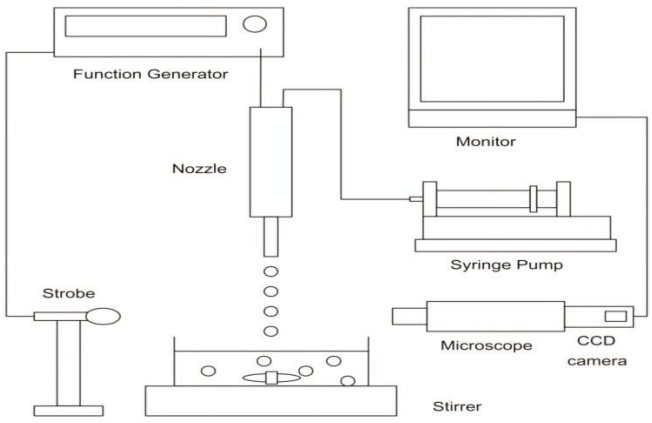

Figure 7. The schematic diagram of the piezoelectric ejection process (92).

The findings demonstrated that alginate-WGA microparticles improved insulin absorption in the intestine. The protective effects of alginate microparticles and the muco-adhesive qualities of WGA appeared to increase insulin administration orally (92).

6. Transdermal/ nanotechnology system in diabetes

Getting beyond the skin's natural barrier is the biggest obstacle in transdermal medication delivery. There is proof that the stratum corneum was the transdermal transport rate-limiting phase site. Various methods have been employed to improve the absorption of medications through the skin; a few transdermal administration attempts successfully provided glucose-responsive insulin dosages (about 20–50 mIU/mL) for brief periods (93). However, there is ongoing debate regarding these systems' place in long-term diabetes management. Techniques that physically or chemically disrupt the skin are particularly dubious since they may result in long-term pathological alterations.

In particular, the transdermal method is a promising option for delivering insulin into the bloodstream steadily and continuously. The stratum corneum is a major obstacle to protein absorption, but once the protein gets beyond it, there are several special benefits to using the transdermal method. First, the skin has comparatively few proteases, contributing to the drug's minimal proteolytic breakdown. Secondly, patch applications that are comfortable, non-invasive, and painless promote good patient compliance. Thirdly, in hyperinsulinemia, patches are likewise simple to remove (94), so it makes sense to employ medication carriers as a transdermal delivery vehicle (95). Drug carriers can alter the encapsulated molecules' physiochemical characteristics and promote percutaneous distribution. The administration of a wide range of active medications shows significant potential for the latest developments in nanoparticulate technologies for enhanced drug delivery (95). Transdermal films filled with polymeric nanoparticles, liposomes, and micro-emulsions have all been the subject of recent reports; it has been demonstrated that solid lipid nanoparticle (SLN) is a superior alternative carrier system to traditional ones. They create a longer-lasting release and shield the medication against deterioration. In addition to having less cytotoxicity than polymeric nanoparticles, since they don't contain a solvent, they are also reasonably inexpensive for excipients, and the straightforward homogenization procedure allows for large-scale synthesis. Reactive oxygen species production and the ensuing oxidative stress in cells and organs are considered one of the NPs' damaging mechanisms. It is advisable to include testing for NPs' interactions with different types of cells and proteins in the toxicological assessment; depending on the properties of the nanoparticle under study, the body may absorb and translocate nanoparticles via oral exposure (ingestion), cutaneous exposure (neuronal uptake,

translocation across lung epithelium, and inhalation exposure), and inhalation exposure. There is still little knowledge on the biological fate of NPs, including their distribution, accumulation, metabolism, and organ-specific toxicity, with the exception of airborne particles that are inhaled and end up in the lungs.

One disadvantage of liposomes is that the body's defense mechanism can ensnare them. Researchers are still testing liposomes' ability to carry drugs, but the results are unclear. Every prior study found that the NPs accumulated in the skin and eyes after treatment; gold nanoparticles (GNPs) often build up in organs and bone joints in order to stop NPs from having negative effects on humans; once they are injected into the body, they need be under external control. It is unavoidable for the NPs to interact and cluster together into a bigger structure, which could impair their ability to transport drugs. These drug carriers are so small that the body's excretory pathways may remove them from the body. Larger NPs have the potential to build up in important organs and cause toxicity that ends in organ failure if they are not eliminated.

6.1.Transdermal insulin

Transdermal insulin delivery eliminates the need for needles. The main obstacle to insulin penetration reaching usable levels is the stratum corneum, the skin's outermost layer. It has also been reported that microneedles work well as transdermal insulin delivery methods. Compounds can only permeate tiny, lipophilic molecules. Several chemical and physical enhancement methods have been investigated to get past the stratum corneum barrier and boost insulin permeability in the skin. These methods include iontophoresis, ultra-sound/sonophoresis, microneedles, electroporation, laser ablation, and chemical enhancers (95). Fluorescent micro/nanoscale devices for glucose sensing can be created, and transdermal monitoring of changes in interstitial fluid glucose levels may be possible by exploiting micro/NPs in the dermis (96). Transdermal patches were prepared using Methocel K100M as a film-forming agent; after soaking the polymer in water for the entire night, 50 mg of ready-made SLN was added and thoroughly mixed, suspension was poured into a glass mold, and once it dried, the patches were divided into tiny pieces and preserved for later research between wax paper sheets in a desiccator.

6.2. Microneedle-based insulin transdermal delivery system

Researchers are dedicated to learning more about non-invasive insulin delivery methods, including nasal, pulmonary, percutaneous, and oral, to increase patient compliance (97). Transdermal delivery systems (TDDS) are appealing to them and have several advantages:

1-Skin has a surface area of around (1-2) m^2, making it a large region for the administration of drugs (98).

2-Compared to painful injections, TDDS is less invasive, which makes it easier to lessen the side effects of repeated injections, improving patient compliance and the quality of life for diabetic patients.

3-The fundamental limitations of insulin oral administration, hepatic first-pass metabolism and gastrointestinal tract degradation can also be overcome by insulin administered through the skin (99,100).

4- TDDS lowers the risk of concentration-related adverse effects by continually releasing insulin to maintain normal glucose levels for a longer time with minimal variations in glucose levels (99,101).

Getting the macromolecules to pass through SC is crucial to the TDDS. A new method for transdermal administration of macromolecular biologics, including as proteins, peptides, and genes, has been made possible recently by advancements in microneedle (MN) technology (102–104). Micro-scaled needles ranging in height from 25 to 2000 μm make up MN arrays (100,105). MNs can enter the SC painlessly and release drugs by reaching the skin's dermis and epidermis. In order to avoid long-term skin injury, the micro-channels created by MNs are only briefly exposed for medication administration and can quickly heal after MNs are removed (106). MNs are classified into five categories based on how they transport drugs: hydrogel MNs, solid MNs, coated MNs, dissolving MNs, and hollow MNs (107). It is challenging to regulate the solid MNs' real delivery dosage; the thickness and level of skin moisture influence the microchannels' resealing time following the removal of solid MNs, which influences how quickly medications are absorbed (108). Coated MNs use solid MN arrays on the needle surface coated with a medication solution

or dispersion (109). The formulation coated on the MNs is deposited after the MNs are applied to the SC. The medication has a very low drug loading and can be rapidly delivered through the skin (110). These two kinds of MNs might not be appropriate for delivering insulin since effective glycemic management while lowering hypoglycemia episodes necessitates accurate dose administration; this article will concentrate on hollow MNs, dissolving MNs, and hydrogel MNs.

Kinds of micro-needle MNs

[A] Hollow MNs

Hollow MNs share the same basic construction as a typical subcutaneous injection needle. Compared to other MN kinds, hollow MNs have a better delivery capacity since their dosage and flow rate can be adjusted with an external auxiliary device. In contrast, coated or dissolving MNs have dosage restrictions based on needle area and number (111,112). An efficient substitute for conventional insulin injections is an intradermal infusion of insulin using hollow microneedles (MNs). It resists discomfort and can greatly lessen both localized and general skin irritation. Many academic publications and clinical investigations have documented superior PK/PD characteristics, rapid onset of action, short duration to reach maximum blood concentration (Cmax), and excellent bioavailability of intradermal insulin infusion over standard subcutaneous injection. Several hollow MN devices are now available in the market (98), and some of them are under clinical evaluation, including MicronJet® (Nanopass Technologies), MicronJet600® (Nanopass Technologies), and Microstructured Transdermal System® (3 M™).

[B] Dissolving MNs

Dissolving MNs have been utilized widely to deliver insulin in literature research. They have garnered increasing interest recently due to their evident advantages, including easy preparation, high drug loading, and one-step application. Slowly releasing insulin by dissolving MNs can give diabetics a stable and long-term blood glucose level, which is ideal for long-acting insulin. However, there are still several issues to take into account. The first is the issue of safety. Polymer deposition in the skin might not be an issue in the event of a single administration. However, it is not negligible for medications like insulin to be taken consistently. In theory, repeatedly applying

dissolving MNs might cause polymer deposition and buildup in skin tissue, which would then cause the body to react immunologically and accumulate in the liver or perhaps throughout the entire body (112).

[C] Hydrogel MNs patch

An insoluble hydrogel MN patch was presented as a solution to the skin's polymer deposition issue (113), as shown in Figure 8. Creating hydrogel MNs involves physically or chemically cross-linking hydrophilic polymers possessing water-swelling characteristics (114). Needles that have been implanted into the skin have the potential to quickly absorb the interstitial fluid in the skin and swell to a hydrogel state, allowing the preloaded medications to release gradually and continuously (98,115). Modifying the cross-linking density of hydrogel polymers can enhance the transdermal delivery efficiency and drug release behavior. As predicted for the frequent delivery of insulin, the hydrogel MNs could completely withdraw from the skin without depositing, thanks to the hardness of the cross-linked matrix (116,117). Hydrogel MNs can achieve a more consistent and controlled insulin release profile without polymer deposition in the skin than dissolving MNs. However, there are still certain issues that need to be resolved. Regulating the final release amount is challenging because of the partial release of loaded insulin from the hydrogel network.

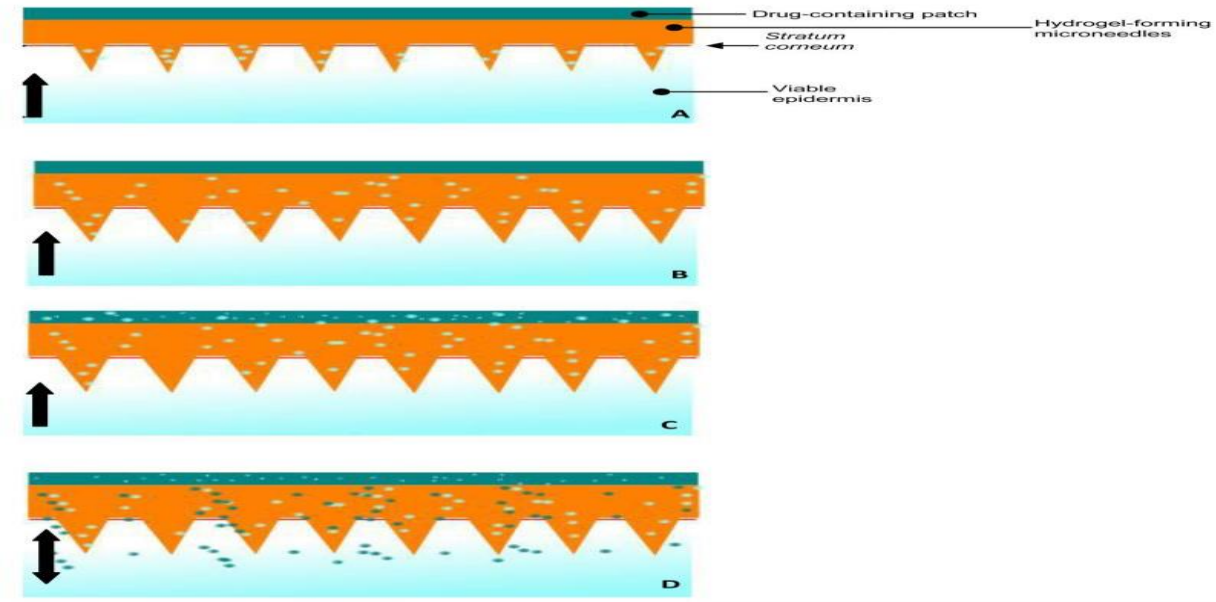

Figure 8. Illustration of phenomena involved in the swelling and subsequent permeation of drug substances from the novel PEG-PMVE/MA-based hydrogel MN arrays. Skin insertion (A), followed by rapid uptake of skin interstitial fluid (B), liberation of drug from the patch (C) and subsequent drug diffusion into the viable epidermis (D) (116).

7. Intranasal insulin

Insulin is a highly effective approach for reducing blood glucose levels and plays a crucial role in diabetes management. Nevertheless, some individuals with diabetes may be reluctant to initiate or adhere to insulin therapy due to concerns such as needle phobia, injection site problems, and discomfort with administering insulin in public settings (118). Patients frequently resist transitioning to subcutaneous insulin administration due to their fears (119,120), concerns around the need to successfully associate carbohydrate consumption with insulin administration, and efficiency with a hypodermic needle (121,122). Intranasal insulin, in a particular form, exhibits rapid efficacy in managing postprandial hyperglycemia. Additionally, it has demonstrated efficacy in mitigating hypoglycemic episodes and insulin resistance, which are primary adverse outcomes associated with regular use of conventional insulin (123). The potential benefits of using intranasal insulin (INI) as a supplement to meals for individuals with non-insulin-dependent diabetes mellitus (NIDDM) were assessed; the results indicated that participants with T2DM who received INI

treatment showed improved walking speed, as well as enhanced executive function and verbal memory compared to those who received a placebo. Furthermore, the study found that INI treatment did not lead to serious adverse events, hypoglycemic episodes, or weight gain (124).

Due to the substantial dosages required and the associated costs, Intranasal Insulin is currently utilized as adjunctive therapy in conjunction with conventional insulin (123). Administering nasal insulin as a single dose at the start of a test meal has decreased post-meal high blood sugar in patients with non-insulin-dependent diabetes. For patients with mild to moderate high blood sugar levels before fasting, nasal insulin helped lower post-meal glucose to an acceptable range. However, post-meal glucose levels, while lower than with placebo, remained unacceptably high for patients with poorly controlled fasting blood sugar (121). Intranasal insulin is regarded as one of the most effective antidiabetic medications for increasing brain insulin levels and reducing insulin resistance, a major issue for many Diabetes Mellitus patients.

Additionally, this insulin delivery method bypasses peripheral circulation and eliminates the adverse effects associated with subcutaneous insulin injections (123). Failure to use the pulmonary route was due to the high insulin doses needed and the low blood insulin levels achieved. To address this, researchers focused on three approaches to maximize the effectiveness of inhaled products. These approaches included using the patients' right formulation, inhaler, and breathing techniques (125,126). Various efforts have been made to develop an inhaled insulin delivery system, including systems in which insulin is delivered as a dry powder (Exubera, AIR, and Technosphere®) or a liquid formulation (AERx® iDMS) (127).

Examples of Intranasal insulin

[A] AERx® iDMS

The AERx Insulin Diabetes Management System (iDMS) results from the collaboration between Aradigm Corporation and Novo Nordisk. This innovative delivery device utilizes pre-prepared liquid insulin blisters and is equipped with electronic controls to ensure consistent and reproducible insulin inhalation. Additionally, the AERx iDMS can record and download dosing, frequency of use, and inhalation patterns, providing valuable data for physicians and patients to monitor treatment progress and adherence to medication (127). The AERx iDMS performance

studies involved patients with type-I diabetes mellitus (T1DM). These studies revealed a faster increase in serum insulin levels in the inhaled group compared to the traditional subcutaneous insulin method (128). However, this study also emphasized that the intrasubject variability for the total insulin exposure was 26% for the inhaled group, indicating that consistent inhalation procedures may play a key role in treating diabetes (127). However, while the AERx® iDMS system was in phase III trials for Food and Drug Administration (FDA) approval, Novo Nordisk decided to discontinue further experiments. Novo Nordisk A/S terminated the development of inhaled-insulin AERx® iDMS because it was unable to deliver significant therapeutic improvements over the present-day insulin pen devices, and not for safety reasons (129); however, AERx® iDMS exhibited nocturnal hypoglycemia and is not advised for youngsters (130).

[B] Technosphere Inhaled Insulin (Afrezza®)

Technosphere insulin (TI) is an inhalation powder developed using recombinant human insulin adsorbed onto Technosphere microparticles created by the inert excipient fumaryl diketopiperazine (FDKP), as shown in Figure 9. At neutral or basic pH, FDKP dissolves readily in water. In mild acidic circumstances, FDKP self-assembles and crystallizes into microparticles with a median diameter of roughly (2.0-2.5) μm (131,132).

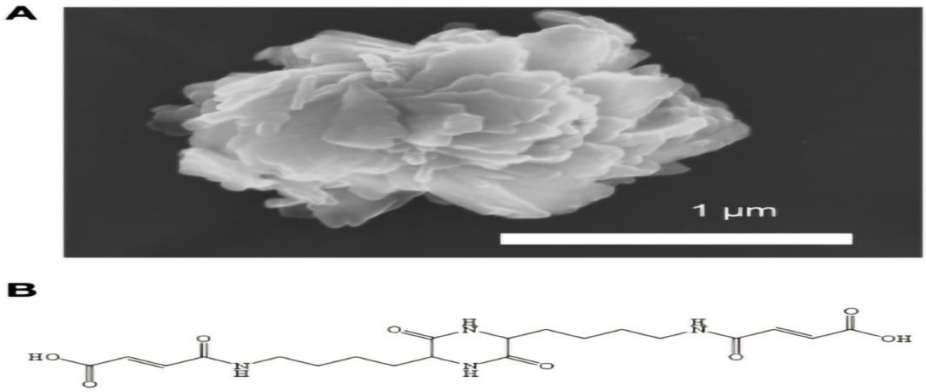

Figure 9. (A) Scanning electron micrograph of a Technosphere particle and (B) the chemical structure of FDKP used to form the particle (131).

These particles are within the optimal size range for transport to the deep lung; larger particles tend to be deposited in the mouth, throat, or upper airways, while smaller particles may be expelled (133,134). The low bulk density and consistent particle size contribute to aerodynamic features

that improve TI transport to the deep lung. Once in the deep lung, the particles rapidly dissolve at the alveoli's neutral or basic physiological pH, allowing quick absorption of insulin and FDKP into the systemic circulation; FDKP is biologically inactive and expelled unaltered in the urine (135). Cough is the most prevalent side event that caused cessation of inhaled TI and the Afrezza Inhaler (136).

[C] Vibrating Mesh Technology

Around 2005, a big innovation was made in the nebulizer market by creating the ultrasonic vibrating mesh nebulizer (VMN) (136,137). Clinical researchers have confirmed the superior performance and cost-saving potential of the Aerogen Aeroneb vibrating mesh nebulizer device compared to other nebulization devices. It has been documented that staff satisfaction experienced a significant increase after transitioning to Aerogen Aeroneb (136).

[D] The Dance 501 VMN Inhaled Insulin

Dance Biopharm created Dance 501, an insulin-specific VMN, using a licensed patent from Aerogen (138). The Dance 501 inhaler, which delivers a unique mild mist of human insulin formulation through inhalation, has shown rapid onset of action and no substantial harm to pulmonary functions in a phase II clinical trial (Clinical Trials Noi.: NCT04100473) (139).

Other Applications of nanotechnology in the management of diabetes

Buccal insulin

Unlike inhalers, the buccal delivery device for insulin dispenses the drug into the oral cavity through an aerosol spray. Rather than going through the lungs, the insulin is absorbed by the back of the mouth and the inside of the cheeks(140). Insulin-administered buccal with absorption enhancers exhibited a maximal % pharmacological activity of 12%. Researchers have looked into a range of bucco-adhesive formulations, including nanoparticles, and recently, the effective use of bioadhesive formulation for insulin buccal mucosal delivery (141). Based on RapidMistTM, Generex Biotechnology Corporation is creating a buccal insulin formulation. Oral-lynTM is a liquid formulation of regular human insulin with a spray propellant for prandial insulin therapy. The mixture produces an aerosol with comparatively big micelles, most of which are too large to

enter the lungs at a mean size of more than 10 μm. It is stated that each puff provides 10 units of insulin. Since 10% of given insulin is absorbed in puff form, 1 U is provided when 1 puff of 10 U is presented; 10 puffs will provide 10 U of insulin for a meal.

Insulin is taken orally; novel insulin carriers are closely related to new methods for administering insulin orally (142). The oral route would be the most practical and recommended option (143). Addressing the issue of daily subcutaneous injections, oral insulin administration is crucial for treating diabetes mellitus. When taken orally, gastric enzymes cause insulin to break down in the stomach (144). Furthermore, in vivo and in vitro bioassays have shown that nano-encapsulated insulin is bioactive (145). Oral insulin administration has the potential to imitate the physiological fate of insulin in diabetes patients while also mitigating the pain and trauma associated with injections (95).

Oral insulin delivery may make use of solid lipid nanoparticles (NPs), liposomes, pro-drugs (insulin-polymer conjugation), micelles, and NPs of biodegradable polymers, among other nanomedicine technologies, because of its advantageous biological features and simplicity of chemical modification, chitosan is being researched extensively for application in oral insulin delivery. It has been discovered that chitosan can shield insulin from gastric juices and improve insulin absorption into the bloodstream (143). Additionally, the chitosan-coated NPs had a greater transport capacity than unmodified and free drug particles. Such polymeric nanoparticles have made significant advancements in oral insulin delivery in recent years. Thus, oral insulin administration has great promise for nano-sized polymeric particles (146) due to the sustained-release properties of the pectin-insulin interaction. Calcium pectinate-insulin NPs, which were created from a combination of pectin and insulin at pH 3, were linked to the release of 12.6% ± 3.2% and 21.7% ± 8.7% insulin at 8 and 24 hours after dissolution in simulated intestinal medium (143).

8. Conclusion

The field of drug delivery systems for diabetes management has shown tremendous advancement in recent years, with innovative technologies offering promising alternatives to improve patient outcomes. These advanced systems provide benefits, including enhanced drug

bioavailability, reduced invasiveness, improved glucose control, targeted delivery, sustained drug release, improved quality of life for patients, and reduced side effects. The previous advantages made them indispensable tools for efficient diabetes therapy. While challenges and limitations such as dosages, costs, variability in insulin exposure, and side effects exist, patients should collaborate with their healthcare professionals to find the best insulin therapy for their specific needs and preferences. The ongoing research and development in this field can potentially improve diabetes care by offering patients safer, more convenient, and more efficient drug administration choices. Additional research and clinical trials are required to evaluate the safety and efficacy of these systems in the real world. By utilizing the prospects of these advanced drug delivery technologies, we can change diabetes care and improve the quality of life for people worldwide.

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