Original Article

Recent Advances In Nanoparticles For Anti-Diabetic Therapy

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Abstract

The use of nanoparticles in diabetes research has facilitated the creation of new insulin delivery systems that have the potential to significantly enhance diabetics' quality of life. The development of nanoparticle drug delivery systems for the treatment of diabetes has made it possible to deliver small molecule medications more effectively, which could significantly enhance the quality of life for diabetics. The use of nanoparticles in drug delivery to target the tissue for the treatment of diseases like diabetes is one of the major uses of nanoparticles in the field of medical science. To enable the administration of insulin through the best pathways possible without the need for injection, such as via oral or nasal routes, nanoparticles have been proposed as insulin carriers. Nanoparticles are defined as particles in the nanometer range that can be made from a variety of substances (such as polysaccharides, synthetic polymers, and lipids) and are frequently used to increase the loaded drug's bioavailability and physicochemical stability. This review discusses the use of various nanoparticle types, such as metallic, synthetic, polymeric, and lipid nanoparticles, to enhance the loaded drug's physicochemical stability and increase its bioavailability in comparison to conventional treatments. In this review article, we highlight recent developments in nanoparticle therapy and their therapeutic applications in the treatment of diabetes. This review's objective is to shed more light on recent developments and the influence of nanoparticles on biomedical sciences in the fight against diabetes.

Key Words: Anti-diabetic, Nanoparticles, Insulin, Bioavailability, Drug delivery systems

1. INTRODUCTION

In recent years, diabetes mellitus (DM) has become a global epidemic and has been identified as the fifth leading cause of death in the majority of developed and developing nations.[1] Its chronic hyperglycemia will harm the body's tissues and organs and could result in complications.[2] Recently, diabetes mellitus has become a common metabolic disorder. Diabetes has become a serious medical problem that affects people of all ages, genders, cultures, and races, and its prevalence has been rising at a startling rate.[3] The pancreatic beta cells are primarily responsible for diabetes. As a result, the amount of insulin produced declines, and/or the peripheral tissues become more resistant to the effects of insulin.[4]

There are various varieties of diabetes, each with its cause. Types of diabetes are:

1. TYPE 1 DIABETES MELLITUS- Type 1 diabetes is an autoimmune disease in which insulin deficiency usually occurs due to the destruction of pancreatic beta cells.[5] Insulin-dependent diabetic Mellitus (IDDM) is another name for it. Degeneration of beta cells, viral infection, congenital abnormality of beta cells, and autoimmune disorders are all causes of type 1 diabetes mellitus.[6]

2. TYPE 2 DIABETES MELLITUS- Type 2 DM is characterised by insulin resistance, insulin deficiency, or both.[7] It is a more typical form of diabetes mellitus. Non-insulin-dependent Diabetes Mellitus is referred to as NIDDM. Type 2 diabetes mellitus is caused by a combination of genetic abnormalities, stress, and lifestyle modifications like poor eating patterns and inactivity.[3] Both oral and injectable medications are available to treat patients with type 2 diabetes.[5]

3. GESTATIONAL DM- This condition affects pregnant people who have never had diabetes before. Later, it might cause T2DM. This type of DM affects approximately 2-5% of all pregnancies but may get better after delivery.[8] By way of its complications, the foetus may develop macrosomia, or high birth weight, as well as cardiac and central nervous system abnormalities.[1]

Research on nanoparticles has recently attracted a lot of attention in the field of nanotechnology.[9]Nanoparticles have a very small volume, can cross a tissue barrier to enter cells and be absorbed, can travel through the body's tiniest capillaries, and can cross the blood-brain barrier. To deliver active ingredients to the target site, controlled release nanocarriers can first encapsulate or adsorb them using nanoparticles, and then the release rate can be regulated to produce a therapeutic effect.[2] Nanoparticles are used in the research of contemporary drugs because of their small molecular size and variety of functions, which is helpful in resolving the barrier issue with conventional treatment. Drugs can be transported using nanoparticles, and their side effects can be lessened or eliminated. They also possess the property of sustained release, which can increase the stability of drug action, lengthen the duration of drug action, make drug storage simpler, and create

some new drug delivery methods.[10] Drug delivery and the reduction or avoidance of side effects are both possible using nanoparticles.[11]

Since nanoparticles have a larger surface area than microparticles, they are more soluble, bioavailable, and have better controlled release, making it possible to deliver natural bioactive substances to the site of action in an efficient manner. Bioactive substances can attach to nanoparticle surfaces or become trapped in the nanoparticle matrix. Entrapping in nanoparticles can mask an unpleasant taste.[7] These outcomes encourage the development of medications with low doses, minimal side effects, and ease of use.[2] By lengthening the time of retention and the extent of interaction with the mucus layer of the intestine, these systems have improved oral delivery of drugs and proteins that are poorly adsorbed.[1] The targeted drug delivery method using nanoparticles has enormous advantages, such as improving drug bioavailability by focusing on particular tissues, organs, and tumors and delivering the highest dose of the drug right where it is needed.[12]

Excellent uses for nanotechnology exist in the creation of drug delivery systems (DDS). The direct interaction of nanoparticles (NPs) with subcellular components can trigger intracellular processes.[13] The most popular nano-based drug delivery methods in the treatment of DM are liposome, polymer-based NPs, and inorganic NPs.[14] Diverse polymer-based NPs, such as nanocapsules, dendrimers, micelles, and nanospheres, are among them and have been proven to be effective drug carriers. These nanocarriers have many potential benefits, including the ability to increase bioavailability, shield drugs from enzymatic degradation, and improve stability by overcoming various biological barriers in vivo.[15] They can also act as a non-linear response to an external signal and an adaptive automated system to simulate endogenous insulin supply, reducing the risk of hypoglycemia and boosting patient compliance.[16]

Insulin administered orally to diabetic patients may be helpful not only to lessen the discomfort and trauma associated with injections but also to mimic the physiological fate of insulin.[16] A major obstacle to the absorption of high molecular weight hydrophilic macromolecules (such as proteins, polysaccharides, and nucleic acids) before they reach the target cell for their specific action is the low pH of the gastric medium in the stomach and its digestive enzymes as well as the intestinal epithelium.[17] Prodrugs (insulin-polymer conjugated drugs), micelles, liposomes, solid lipid nanoparticles, and biodegradable polymer nanoparticles are some examples of the nanomedicine technologies that could be used for oral insulin delivery.[18]The most practical way to manage diabetes mellitus is through oral insulin administration. Since lipid-bilayer cell membranes prevent the diffusion of hydrophilic medications like insulin into the bloodstream, the intestinal epithelium is thought to be a significant barrier to their absorption.[19] Gastric enzyme-based drug delivery systems guarantee the transfer and breakdown of the insulin in the stomach. The active ingredient must be embedded in a protective matrix to shield it from the hostile environment of the stomach. As a result, they can effectively carry insulin, offering a promising method for administering insulin orally.[20]

2. USE OF NANOPARTICLES IN ANTI-DIABETIC THERAPY

Recent years have seen a rise in popularity of nanoparticles due to their advantages in terms of decreased dosing frequency, increased bioavailability, prevention from degradation specifically in the harsh gastric environment, site specificity, and decreased side effects. However, conventional dosage forms have a number of drawbacks, including insolubility in water, gastric irritation, diarrhoea, appetite loss, lactic acidosis in people with abnormal kidney or liver function, and they do not adhere to the patients' safety and efficacy. Nanoparticles were created in order to get around these limitations in conventional dosage forms. They used to offer sustained effective concentration for a longer period of time as well as effective optimal concentration at the desired site of action.[1]

Another type of nanodrug delivery system being investigated for the delivery of insulin is nanoparticles. Researchers have created insulin-loaded nanoparticles using a variety of polymers, including dextran, polylactide-co-glycolic acid, and chitosan. Insulin delivery through solid lipid nanoparticles has also been developed. The lymphatic system in the small intestine, which has a mucus layer covering the enterocytes, is known to absorb other types of nanoparticles, mucus-penetrating nanoparticles. These nanoparticles are specifically made to pass through this thick mucus layer before reaching the blood stream.[21] Without using invasive methods, nanoparticles enable the controlled release of the medication into intraocular tissues. The amount of drug being absorbed and its bioavailability both rise as the retention time is extended. Site-specific targeting with nanoparticles can reduce the possibility of negative side effects.[22]

3. NANOPARTICLES-BASED INSULIN DELIVERY

Currently, when oral hypoglycemic medications have failed to control type 2 diabetes, insulin replacement therapy is advised for both type 1 and type 2 diabetics. Only 20% of the insulin administered subcutaneously is said to make it to the liver. Multiple insulin injections administered to a patient are linked to low patient compliance. A major obstacle to the absorption of high molecular weight hydrophilic macromolecules (such as proteins, polysaccharides, and nucleic acids) before they reach the target cell for their specific action is the low pH of the gastric medium in the stomach and its digestive enzymes as well as the intestinal epithelium.[8]

Several types of nanoparticles, including polymeric biodegradable nanoparticles, ceramic nanoparticles, dendrimers, etc., are currently being researched for the delivery of insulin in the treatment of diabetes. Since multiple injections are believed to be uncomfortable for patients, the slow release of insulin provided by the nanoparticles will extend the action of insulin

and thus replace the need for multiple injections, improving patient compliance. Chitosan-insulin nanoparticles for effective oral delivery of insulin.[23]

4. NANOPARTICLES-BASED HYPOGLYCEMIC DRUGS DELIVERY

The majority of oral hypoglycemic medications can be found as tablets or capsules. The limited accessibility of conventional dosage forms at the desired site of action, higher systemic toxicity, constrained therapeutic window, and complex dosing regimen for long-term treatment were all revealed by these adverse effects. Because oral hypoglycemics have certain drawbacks, researchers have been able to create new delivery systems with higher therapeutic efficacy. Nanoparticles have received a lot of attention recently as drug delivery systems based on nanotechnology. Many research projects exploring the potential use of these nanostructures in drug delivery have been sparked by their potential benefits, such as the possibility of controlled drug release, targeting, proper incorporation of lipophilic as well as hydrophilic drugs, remarkable biocompatibility, low biotoxicity, and the capability of avoiding organic solvents in the production cycle and ease of scale up.[23]

Due to their distinctive in vivo characteristics and high design flexibility, nanoparticle (NP)-based drug delivery systems are regarded as a promising platform to enhance the oral absorption of peptide drugs. These can load peptide medications and improve their intestinal stability. Furthermore, nanoparticles can help peptide medications pass through mucus and intestinal epithelial cells, improving their oral absorption into blood circulation. The use of different nanoparticles in oral formulations to treat diabetes mellitus has been investigated. In this review, we'll go over in detail the unfavourable GI tract conditions that arise after oral administration and offer solutions for how to deal with them. Additionally, we will try to give a thorough overview of the nanoparticles that have been developed for oral peptide drug delivery. We will emphasise the special qualities of each type of oral peptide drug nanoparticle for the treatment of diabetes mellitus.[24]

The stability of the former can be increased by loading drugs into nanoparticles, preventing chemical and/or enzymatic degradation in the GIT. Additionally, nanoparticles increase contact with the GI epithelium, lengthening the time that a drug remains in the body and increasing its bioavailability. Drugs must be released close to the absorption site, either by being entrapped within the nanoparticle matrix or attached to their surface. The nature of the chosen polymer, the mean particle size and polydispersity, the surface electrical charge, hydrophilicity, and particle morphology are important factors for the uptake of nanoparticles in the GIT. The ideal nanoparticle should enter through the GI membrane. Additionally, nanoparticles need to exhibit longer circulation times, longer mean residence times (MRT), and lower clearance.[22]

5. RECENT ADVANCEMENT OF NANOPARTICLES IN ANTI-DIABETIC THERAPY

Inadequate insulin administration is a major challenge in controlling diabetes, and nanotechnology in medicine has made insulin delivery more effective. Drug delivery has been a key component of medical advancement for the past 20 years, according to researchers who study the improvement of the medical factor. In this regard, a wide variety of drug delivery methods were acknowledged. In addition to long-term redistribution and drug-assisted release at the target site, these systems will enhance stability and drug therapy concentration in objective tissue. Drug administration occurs less frequently, which improves patient comfort.[25] There are different types of nanoparticles used in treatment of diabetic therapy which is categorized below:-

5.1 Metallic Based Nanoparticles

Metallic nanoparticles have made significant strides in the biomedical sciences and can inhibit antibacterial, anti-diabetic, and anticancer effects. Since it has produced impressive results, a decade of research on entrapping plant extracts in metallic nanoparticles has attracted the attention of numerous scientists. Metallic nanoparticles have special qualities that make them advantageous for biotechnology, targeted drug delivery, and potential in vivo imaging, such as large surface areas, specialised functional groups, effective quantum self-assembly, and the capacity to conjugate with the drug of interest. Metallic nanoparticles have also demonstrated a number of benefits, including ease of manufacturing, repeatability, economy, stability, environmental friendliness, and high entrapment efficiency, which makes them a good candidate for a variety of applications. Gold, silver, copper, and titanium-cerium-zinc oxide are among the metals and metal oxides most commonly used in the synthesis and production of metallic nanoparticles.[26]

5.1.1 Zinc Oxide

ZnO NPs are frequently used for a variety of biomedical purposes, such as anti-inflammatory, anti-cancer, anti-cancer, antifungal, anti-diabetic, and antibacterial activities. In addition to being essential for insulin biosynthesis, secretion, and storage, zinc is also responsible for maintaining insulin structure. Numerous zinc transporters, including zinc transporter-8, have been found to be essential for the pancreatic beta cell to secrete insulin, according to research. Zinc may also improve insulin signaling through a number of different pathways, such as elevated phosphoinositide 3-kinase activity, decreased glycogen synthase kinase-3 activity, and increased insulin receptor phosphorylation. Additionally, ZnO NPs can reverse changes in pancreatic tissue brought on by diabetes.[26]

According to structural and ultrastructural changes as well as mean biochemical stability around blood sugar and serum insulin, ZnO NPs reversed pancreatic damage brought on by diabetes. ZnO nanoparticles, alone or in combination with thiamine, have shown to be more effective in the treatment of diabetes. This may signify high levels of antidiabetic activity

in both lipid and blood glucose parameters.[27] ZnO NPs were discovered in the study to be a promising antidiabetic agent. Also in 2020, a study used a sonochemical technique to create ZnO nanoparticles. According to this study, ZnONPs is a promising antidiabetic activity that can be used to create antidiabetic medications. All earlier studies showed that ZnO NPs are effective in treating diabetes and lowering its complications.[26]
Numerous studies have shown that ZnO NPs can lower blood sugar levels in diabetics when given orally to animals along with the DPP-4 inhibitor vildagliptin and ZnO NPs (1–10 mg/kg/day). The outcomes showed that administering ZnO NPs to diabetic rats caused their blood glucose levels to drop. Blood glucose homeostasis is regulated by two key pancreatic hormones: glucagon and insulin. They are crucial to the growth of DM. When given orally for a month, either alone or in conjunction with vildagliptin, ZnO NPs reduced the diabetic rat's pancreatic histological changes.[17]

5.1.2 Cerium oxide Nanoparticles

Calcium phosphate, silica, alumina, or titanium is the materials used to make ceramic nanoparticles. These ceramic nanoparticles are advantageous due to their low size (less than 50 nm), high biocompatibility, and simple preparation methods.[28] They also have good dimensional stability. The insulin was carried by calcium phosphate nanoparticles, which were characterised and studied in vivo. Comparing the effectiveness of this drug delivery systems in vivo performance to that of conventional porcine insulin solution yielded better results. Tricalcium phosphate nanoparticles can be used to deliver insulin orally, according to a recent study.[26]

5.1.3 Copper Nanoparticles

One of the most significant transitional elements in many biochemical pathways is copper. Cu NPs have superior antioxidant properties, inhibit alpha-amylase and alpha-glycosidase, and are effective trace metal NPs for the treatment of Type 2 diabetes in animals. Cu NPs demonstrated a significant reduction in diabetic cardiovascular defects. These NPs may lessen oxidative stress and improve the vascular endothelium's bioavailability of nitric oxide. A number of earlier studies have demonstrated the value of using copper nanoparticles in the diagnosis of diabetic wounds in mice, not only in controlling the disease but also in promoting faster wound healing. In conclusion, there may be a connection between diabetes patients and Cu NPs.[26]

5.2 Natural Polymeric Nanoparticles

Natural resources are abundant and processing costs for inartificial polymers are low. The two main benefits of natural polymers over synthetic polymers are that they are non-toxic and biocompatible.[29] A variety of gums, mucilages, and polysaccharides are natural polymers that are used to deliver anti-diabetic medications. They are biocompatible and non-toxic, which gives them a significant advantage over synthetic polymers. Natural polymers are also widely accessible and reasonably priced. Their properties, however, may vary because they are frequently extracted from various regions, species, and climatic conditions, making it impossible to control them.[30]

5.2.1 Chitosan Based Nanoparticles

Chitosan is one of many intestinal permeation boosters that have been used to aid in the absorption of hydrophilic macromolecules. Therefore, if protein drugs are administered orally, a carrier system is required to shield them from the hostile environment in the stomach and small intestine. Furthermore, chitosan nanoparticles (NPs) improved intestinal protein absorption more than chitosan aqueous solutions did in vivo. Due to their pH sensitivity or degradability, the insulin-loaded nanoparticles coated with mucoadhesive Chitosan may prolong their stay in the small intestine, infiltrate into the mucus layer, and subsequently mediate transiently opening the tight junctions between epithelial cells.[31]

Chitosan and its derivatives have been used in numerous studies as a coating material to shield insulin-loaded nanoparticles from release in the gastric environment and to lengthen the time that the particles spend at the intestinal mucosa before entering the small intestine.[32] An easy and frequently mentioned method to coat nanoparticles is to add chitosan solution to previously prepared nanoparticle formulations. Chitosan solution can also be added during the nanoparticle formation process. In order to help peptide drugs effectively penetrate the intestinal epithelial cell layer, CS can act as an intestinal permeation enhancer. In order to improve the encapsulation efficiency of peptide drugs, extend the time that NPs spend in the small intestine, and increase their cellular permeability, CS has also been used in combination with other biodegradable and biocompatible nature polymers, such as alginate and dextran.[33]

It has been discovered that chitosan can shield insulin from stomach acids and improve the absorption of insulin into the bloodstream. The transport potential of the chitosan-coated NPs is also higher than that of free drug and unaltered particles. Such polymeric NPs have advanced in recent years to a greater extent in the delivery of oral insulin. When SLN were coated with chitosan, the hypoglycemic effect was seen to last longer, once again highlighting the crucial contribution of chitosan to the improvement of insulin absorption. While the uncoated SLN caused the maximum drop in glucose levels to occur after 8 hours of administration, the coated SLN's relative pharmacological bioavailability increased by two times.[34]

The studies mentioned here show that chitosan and its derivatives are useful for enhancing the drug stability and bioavailability of anti-diabetic medications. Due to its low immunogenic risks and good biodegradability, chitosan is a potential delivery system for new anti-diabetic drugs, especially when taken orally.[35]

5.2.2 Alginate-Based Nanoparticles

Alginate nanoparticles were also researched as a means of delivering diabetic medications. In order to successfully lower the serum glucose level and raise the serum insulin level in diabetic rats, a study was done to develop alginic acid nanoparticles along with nicotinamide as a permeation enhancer for sublingual delivery of insulin. To prevent any negative effects on insulin stability, these nanoparticles were made using a gentle, aqueous procedure. In comparison to insulin solution, alginic acid nanoparticles demonstrated strong bioadhesion with 95% entrapment efficiency. Alginic acid nanoparticles released insulin using first-order kinetics. Examining the insulin release profile of these nanoparticles over a 12-hour period revealed a very quick initial burst (65%) in just 2 h, followed by a slow release. In STZ-induced diabetic wistar rats, hypoglycemic effects and serum insulin levels were assessed. These sublingual insulin nanoparticles' pharmacological availability and relative bioavailability were compared to insulin SC injections. It was discovered that alginic acid nanoparticles had a high pharmacological availability of 100.2% to 125.1% at doses of 5 IU/kg. In a similar vein, the dose-corrected bioavailability in comparison to SC injection (1 IU/kg) was also markedly higher (20%–25%).[35]

5.2.3 Dextran-Based Nanoparticles

Dextran is a negatively charged, hydrophilic, biodegradable, and biocompatible polysaccharide that can link with positively charged chitosan and proteins. It has been suggested that alginate-dextran nanoparticles made using the nanoemulsion dispersion method and in situ gelation could be loaded with insulin. Alginate limits insulin release by forming a tight matrix at pH 1.2, but at pH 7.4, the matrix opens up and releases the peptide. Insulin-containing dextran sulfate-chitosan nanoparticles were administered orally to reduce the BSL. Alginate, dextran sulphate, chitosan, and albumin multilayered nanoparticles based on the LBL technique were also reported to be resistant to acidic pH, lowering the basal blood sugar level and increasing insulin bioavailability. Dextran nanoparticles with vitamin B12 coating that were loaded with insulin decreased BSL and the hypoglycemic effect in diabetic rats. A ternary inter-polyelectrolyte complex of insulin, dextran sulphate, and poly (methylaminophosphazene) (PMAP) has been proposed to improve the insulin encapsulation effciency of these particles. When released under a simulated intestinal environment (SIF), the gastric proteolytic enzyme could no longer damage the loaded insulin due to the enhancement provided by this complex.[22]

5.3 Lipid Based Nanoparticles

Biocompatible/biodegradable lipid ingredients are used in lipid-based nano delivery systems, which are generally regarded as safe. Lipids can increase the oral bioavailability of medications that are poorly water soluble, making them absorption enhancers.[29] Drugs that are both hydrophilic and hydrophobic can be successfully encapsulated by lipid NPs, which are lipid-based delivery systems. A lot of research has been done on liposome as drug delivery systems because of how well they can load drugs and are biocompatible.[24] Drugs are wrapped or embedded in a lipid core in lipid-based NPs, which are made up of an inner solid lipid phase and an outer aqueous phase. According to the internal structure of lipid materials, it can be broadly divided into solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). Both SLNs and NLCs demonstrated the following benefits: improved solubility, particularly for hydrophobic drugs; avoidance of organic solvents; easily scaled-up synthesis processes; and decreased toxicity through the use of biocompatible and physiologically tolerated lipids components.[36]

5.3.1 Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLN) were created for drug delivery nanoparticulate systems as an alternative to polymeric nanoparticles.[37] Drug bioavailability and solubility can be increased by using solid lipid nanoparticles (SLNs), which are nanosize (50-1000 nm) colloidal carriers made of solid lipids (high melting fat matrix).[16] Solid lipid matrices with single layers of phospholipids make up solid lipid nanoparticles (SLNs). When combined with different surfactants, a variety of solid lipids, including triglycerides, fatty acids, and steroids, can produce steric stabilisation in the creation of SLN. The encapsulated active agents are protected from chemical deterioration in biological environments by the solid lipid matrices, which are identical to those in polymeric nanoparticles. They also offer high flexibility in terms of the release properties of the drugs. Drugs that are hydrophobic and lipophilic can both be enclosed by SLNs. These nanoparticles can contain hydrophobic drugs thanks to the solid lipid matrices' lipophilic nature. Because hydrophilic drugs have a low affinity for these lipid matrices, it is expected that they will not be well-encapsulated. The targeted and controlled releases of the encapsulated drug as well as the increased bioavailability of the drug are additional benefits of SLNs.[5]

Chitosan-coated, insulin-loaded SLN for oral administration were developed by Anchan et al., and their potential as potent substitutes for subcutaneous injection was examined. Compared to groups receiving uncoated insulin-loaded SLN or the oral insulin solution, which was equivalent to subcutaneous insulin, the oral administration of chitosan-coated insulin SLN to STZ-induced diabetic rats resulted in a significant hypoglycemic impact (p 0.05) after an 8-hour trial. An effective oral insulin formulation may include SLN coated with chitosan.[16] After overnight fasting, diabetic rats received oral administration of insulin-loaded SLN. The decline in initial glucose levels with passage of time following intragastric insulin-loaded SLN. The median plasma glucose baseline value was used as the reference point. In comparison to rats given an oral insulin solution, insulin-loaded SLN reduced blood sugar levels. This hypoglycemic effect was found to be biphasic, with an initial peak between 4 and 8 hours with a decrease of 25% of the initial glucose level and a later peak after 12 hours of assay lasting up to 24 hours.[38]

The attempts to create an oral formulation of insulin-loaded SLN led to the production of spherical nanoparticles with a slight negative zeta potential and good association efficiency. When rats were given oral insulin-loaded SLN, their plasma

glucose levels were lower than when they were given oral insulin solution or empty SLN for up to 24 hours. Insulin was able to be partially protected from intestinal chemical deterioration by the solid matrix of SLN, which also helped to increase intestinal absorption. In conclusion, it was discovered that SLN were suitable carrier systems for the oral administration of insulin. This research could aid in the creation of an improved oral insulin formulation.[39]

5.3.2 Niosomes

Niosomes are bilayered nanostructures that self-assemble and are made of cholesterol and non-ionic surfactants. A hydrophilic head that faces the aqueous solvent and a hydrophobic tail make up the bilayered framework (oriented far from the solvent). Their distinctive structure aids in trapping hydrophilic and hydrophobic drugs in the aqueous core and lipid bilayer, respectively.[11] Niosomes' bilayer membranes and enclosed aqueous cores allow them to encapsulate both hydrophilic and lipophilic substances. As an alternative to liposomes for drug delivery systems, niosomes have been developed.[5]

Niosomes have been used as a system to increase the bioavailability of medications with extremely low aqueous solubility and to extend the time that the active medication is available for action at the desired site. When sodium deoxycholate was used as a surfactant, insulin-loaded niosomes were also discovered to have good stability in the presence of digestive tract proteolytic enzymes. Niosome-encapsulated active ingredients may prove to be an effective way to increase drug action, stability, and absorption while reducing the toxicity of anti-diabetic medications.[1]

Niosomes are thought to be potential drug delivery system carriers because they have the ability to act as drug reservoirs, maximising drug entrapment in sustained and prolonged drug release. Niosomes can accommodate drugs with varying solubilities in addition to having hydrophilic, amphiphilic, and lipophilic moieties in their structure. The potential of niosomes as a drug delivery system for diabetic therapy was examined in a few studies. By using the lipid phase evaporation technique and sonication, Span 40 and Span 60 composing niosomes loaded with insulin were created and given to Wistar rats with ovariectomies who had been made diabetic by alloxan. Both niosome types were found to lower blood sugar levels while improving insulin bioavailability when compared to subcutaneous administration. Long-lasting insulin release was followed by a hypoglycemic effect in niosomes.[22]

A niosomal formulation for the simultaneous encapsulation and release of hydrophobic and hydrophilic anti-diabetic medications was reported by Samed et al. Glipizide and metformin hydrochloride were found to have encapsulation efficiencies of 67.64% and 58.72%, respectively. The drug release followed a linear profile up to 8–10 h, slowed down, and lasted for 12–14 h, according to experiments performed in buffers with various pH values (simulating the blood plasma pH, cellular endosomal, and gastric environments). As a result, this formulation provides a promising DDS for the simultaneous sustained release of antidiabetic medications.[16]

5.3.3 Liposomes

Liposomes are vesicular systems that have been synthesised and are primarily made of a lipid bilayer.[1] An aqueous core and lipid bilayer structure make up liposomes. A liposome is created by the aqueous core and lipid bilayer, and it can carry both hydrophobic and hydrophilic drugs into the body. Drug solubility is improved by liposomes, which also prevent biological and chemical deterioration when the drugs are stored.[16] The physicochemical characteristics, onset time, and toxicity of the incorporated compounds can all be enhanced by liposomes.[5] Multinational corporations are currently developing many of the formulations for anti-diabetic drugs, and liposomal technologies have been extensively researched.[1] A drug is incorporated into liposomes through the encapsulation process, and the composition, pH, osmotic gradient, and environment all affect how quickly the drug is released from the liposomes.[40] The particle size and entrapment efficiency (EEf) of insulin-loaded liposomes have an impact on their physiochemical characteristics.[41]

It has also been suggested that coating liposomes with chitosan will decrease the absorption of insulin in the gut due to the particles' increased mucoadhesiveness and higher zeta potential, which is facilitated by the positively charged polysaccharide. When these liposomes were given orally to Kunming mice, they showed to be just as effective at enhancing the hypoglycemic effect as parenteral insulin. These liposomes were trypsin and pepsin resistant to prolong the formulation's gastric residence time. Compared to conventional liposomes, bile salt-based liposomes improve the peptide's oral bioavailability while promoting gut insulin absorption. By using liposomes to deliver peptides (such as insulin and GLP-1) and other medications that lower blood sugar, the hyperglycemic stage can be better controlled through alternative administration routes.[22]

5.3.4 Dendrimers

Dendrimers are uniform, clearly defined, three-dimensional (3D) structures with branches that resemble trees. In order to achieve controlled drug delivery, dendrimers have attracted a lot of attention. In comparison to poly (ether hydroxylamine), poly (propylene imine), poly (amidoamine), poly (L-lysine), and polyester dendrimers, dendrimers exhibit a greater diversity of chemical structure. Surface groups enable a tunable toxicity profile and dendrimer targeting, so it is anticipated that soon researchers will succeed in creating dendrimer-based novel antidiabetic therapeutics to effectively control high BGL and the complications linked to diabetes.[16]

5.4 Polymeric Nanoparticles

The FDA has given the biodegradability and biocompatibility of synthetic polymer NPs made of poly (vinyl alcohol) (PVA), poly (-caprolactone) (PCL), poly (lactic acid) (PLA), and poly (lactic-co-glycolic acid) (PLGA).[29] Insulin is carried by polymeric biodegradable nanoparticles. Biodegradable polymers with a grafted glucose oxidase membrane enclosing an insulin-polymer matrix. When blood glucose levels rose, the nano-porous membrane underwent modification, which in turn caused biodegradation and insulin delivery. The glucose/glucose oxidase reaction lowers pH. It increases the polymer system's swelling, which enhances the release of insulin.[30]

The polymeric NP used in reservoir systems where the drug is contained in a cavity and contained by a polymer film is referred to as a nanocapsule or matrix system, whereas the term "nanosphere" is used when the drug is dispersed across all of the particles. Drugs' enhanced bioavailability and avoidance of first-pass metabolism are the main benefits of enclosing them within nanoarchitectured DDS. As a result, the drug's toxic effects on cells other than those it is intended to treat are lessened.[42] For the treatment of diabetes complications, the NPs made of poly(lactic acid), a biodegradable and biocompatible polymer, are frequently used for oral drug delivery.[16]

To achieve the ideal therapeutic drug concentration while minimising the exposure of the drug to undesirable locations, polymeric nanoparticles can be designed to deliver drugs at specific sites and then release them at specific rates. In gastrointestinal fluid, polymeric nanoparticles are more stable than other nanocarriers like liposomes and micelles.[21] In terms of effectiveness and efficiency, polymeric nanoparticles outperform conventional oral and intravenous methods of administration. A higher concentration of a pharmaceutical agent can be delivered to a targeted location with the help of polymeric nanoparticles because they can have engineered specificity. Polymeric nanoparticles are the best possible candidates for diabetes treatment and insulin delivery because of this characteristic.[43]

In a different study, pellets containing polymeric nanoparticles loaded with insulin were used to administer the hormone orally to diabetic rats. As a result of the administration of insulin via the buccal route, the results revealed a significant drop in blood sugar levels. It has been demonstrated that encapsulating insulin in mucoadhesive alginate/chitosan nanoparticles significantly improved oral absorption and oral bioactivity in diabetic rats.[38] These methods support the potential use of polymeric nanoparticles in oral insulin administration, avoiding the stomach's enzymatic breakdown.[43]

5.4.1 Poly (lactic-co-glycolic acid)

A synthetic polymer called PLGA is one of the most widely used for creating nanoparticles for drug delivery because of its biodegradability and biocompatibility. Because PLGA nanoparticles are typically negatively charged, they have a difficult time penetrating the mucus layer because it also has a negative charge.[44] Cui et al. suggested the formation of an insulin-phospholipid complex followed by the production of PLGA nanoparticles by reverse micelle-solvent evaporation in order to increase the loading capacity of insulin in PLGA nanoparticles. The obtained nanoparticles were subjected to digestive enzymes and an acidic stomach. In vivo, no burst release of insulin was observed. It has been suggested to modify the nanoparticle surface, use enzyme inhibitors, or coat the insulin with an enteric coating to stabilise it at low pH levels. The hydrophobic ion pairing method has been used to increase the hydrophobicity of insulin in order to improve absorption in the epithelial membrane. By using the emulsion solvent diffusion method, a complex of insulin and sodium deoxycholate was loaded into PLGA nanoparticles to increase the peptide's encapsulation effectiveness and be administered to diabetic rats with a lower BSL.[22]
By using the multiple emulsions solvent evaporation method, insulin loaded PLGA-Eudragit®RS nanoparticles (particle size: 374-1426 nm) were created and administered orally to diabetic rats. The two-stage system's hypoglycemic effects were investigated in diabetic rats using oral administration (50 IU/kg), and they were contrasted with positive controls of insulin solution administered by SC injection (5 IU/kg) and negative controls of insulin administered orally (50 IU/kg) in the absence of nanoparticles. According to the findings, positive control of insulin solution by SC injection and negative control of insulin in the absence of nanoparticles had a significant hypoglycemic effect in diabetic rats. Within 2 hours of SC administration of the insulin solution, a significant reduction in plasma glucose levels (to 90% of initial levels) was seen. However, after oral administration of insulin-loaded PLGA/Eudragit®RS nanoparticles in the enteric-coated capsule, blood glucose levels slowly decreased and demonstrated a prolonged hypoglycemic effect.[35]

Utilizing Concanavalin A to improve lymphatic uptake, biodegradable PLGA nanoparticles are used for oral insulin delivery. These nanoparticles reduce blood glucose levels in diabetic rats 4 hours after oral administration. They offer improved stability and absorption along with sustained release. Concanavalin A nanoparticles have the potential to be an effective treatment for type-I diabetes when used for oral insulin delivery. As a sustained release carrier, glipizide-loaded biodegradable nanoparticles were created using biodegradable polymer. Glipizide-encapsulated PLGA nanoparticles offer sustained release for type-II diabetes mellitus management that is effective with fewer side effects, fewer doses, and better patient compliance.[30]

5.4.2 Poly (Lactic Acid) (PLA)-Based Nanoparticles

For oral drug delivery, PLA, a biodegradable and biocompatible polymer, is typically used. A vesicle made of polymeric PLA-b-pluronic-b-PLA (PLAF127-PLA) was used to deliver insulin orally. Zwitterion-coated PLA nanoparticles

produced the highest hypoglycemic effect with a decreased BSL in a short period of time after oral administration compared to other insulin-containing PLA nanoparticles, highlighting the advantages of this coating on GI uptake.[22]
A separate investigation, Malathi et al. created insulin PLGA nanoparticles for oral administration that also contained D-tocopherol poly(ethylene glycol) 1000 succinate (TPGS, an emulsifier). The water-oil-water emulsion solvent evaporation method was used to create the insulin-loaded PLGA-TPGS nanoparticles, which were then given orally to diabetic rats (20 IU/kg). The in vivo research revealed that insulin-loaded PLGA-TPGS nanoparticles reduced blood sugar levels while being administered and displayed a sustained hypoglycemic effect for up to 24 hours. After oral administration of insulin-loaded PLGA-TPGS nanoparticles, the serum insulin concentration level gradually increased and reached its peak (6 IU/dL) at 12 hours, whereas the control group treated with insulin in the absence of PLGA nanoparticles reached its peak serum insulin level (roughly 3 IU/dL) at 3 hours. According to this study's findings, encapsulating insulin in PLGA-based nanoparticles prevented it from being enzymatically broken down in the GI tract, producing an effective and long-lasting hypoglycemic effect.[35]

As a result, biodegradable polymer-based formulations can provide a reduction in the daily dosage of antidiabetic medications. The frequency of injections can be reduced while maintaining or improving the bioavailability and therapeutic efficacy of the drugs, which is advantageous in particular for patients receiving injection-based treatments.[35]

5.4.3 Poly (alkyl cyanoacrylate) (PACA)

The properties of PACA depend on the type of PACA side chain and can be made by the quick anionic polymerization of alkylcyanoacrylates when they come into contact with water. It is a biocompatible and biodegradable polymer. In vitro release and bioactivity of insulin entrapped in PACA nanoparticles made from microemulsions with various microstructures and containing isopropyl myristate, caprylocaproyl macro golglycerides, polyglyceryl oleate, and insulin solution were studied. Additionally, oral administration of insulin-loaded polybutylcyanoacrylate nanoparticles (IPN) to streptozotocin (STZ)-induced diabetic rats in an oily medium (soybean oil containing 0.5% (v/v) Tween-20 and 5% (v/v) Vitamin E) was also tested for the hypoglycemic effect. It was determined that IPN can act as an efficient and reliable method of delivering oral insulin.[37]

In a study involving the oral delivery of insulin, Graf, Rades, and Hook used microemulsion -based PACA poly (ethyl cyanoacrylate)-based nanoparticles as templates. Fasted induced diabetic rats were given intragastrically by gavage the insulin loaded PACA nanoparticles dispersed in microemulsion tem-plates (insulin loaded nanoparticle sizes: 200-400 nm) for in vivo studies (insulin dose: 100 IU/kg). According to the findings, the insulin-loaded PACA nanoparticles-based formulation consistently reduced blood sugar levels for up to 36 hours after intragastric administration (reduction to 68% of the initial blood glucose level achieved at 9 h).Contrarily, there was no discernible drop in blood glucose level in insulin solution devoid of nanoparticles and micro-emulsion templates.[31] In spite of the formulation's ability to sustain a glucose reduction for up to 36 hours, according to this study, the glucose reduction started rather slowly (for example, starting nine hours after intragastric administration), delaying the release of insulin.[35]

5.4.4 Poly-γ-glutamic acid

A water soluble, biodegradable polymer called poly-glutamic acid (PGA) has been used to create nanoparticles for the delivery of insulin orally.[45] The oral delivery of insulin-loaded -PGA-based nanoparticles was investigated by Sonaje et al. Ionic-gelation was used to prepare the insulin-loaded -PGA nanoparticles, which were then freeze dried. For in vivo studies, the freeze dried insulin -PGA nanoparticles (nanoparticle size: 240–260 nm) were then put into hard gelatine capsules and given orally to diabetic rats. The in vivo study was carried out by contrasting the plasma insulin and blood glucose levels between the formulations: SC injection of an insulin solution (5 IU/kg of insulin) additionally, oral administration of the freeze-dried, insulin-loaded -PGA nanoparticles (insulin dose: 30 IU/kg) in diabetic rats that have been induced to develop diabetes. The outcomes showed that insulin solution (5 IU/kg) caused a significant reduction in glucose level at 2 h (75%) and reached maximum plasma insulin level (Cmax) within an hour after administration (Cmax: 119.67.4 IUmL-1, AUC: 196.234.5 IUmL-1). The freeze dried insulin loaded -PGA oral formulations, on the other hand, showed a gradual and continuous reduction in glucose level for up to 10 hours (roughly 50%) and reached maximum plasma insulin level at 5 hours after administration (Cmax: 49.92.4 IUmL-1, AUC: 235.830.2 IUmL-1).[35]

5.4.5 Polyallylamine (PAA) Based Nanoparticles

By grafting insulin and palmitoyl pendant groups onto PAA and quaternizing it with methyl iodide, comb-shaped amphiphilic nanoparticles were created. The nanoparticles had a high encapsulation efficiency and protected the insulin from trypsin and pepsin. Cetyl- and cholesteryl-grafted nanoparticles were given quaternary ammonium moieties, which further improved the formulation's resistance to chymotrypsin. Reversible tight junction opening occurred in Caco-2 cells, and paracellular and transcellular transports were used to take up nanoparticles in the GIT. However, due to incomplete GIT transport and tight junction opening limitations, only a small amount of insulin was detected in the basal chamber.[22]

5.5 Future Prospective

The development of new delivery systems for anti-diabetic medications, including pills, nano- and microstructures, and NDDS-based systems, is being pursued by businesses and numerous top research institutions.[47] The solution provided by nano-delivery systems, which translates into improved control of T2DM, is, in short, the safe and controlled delivery of

anti-diabetic medications to the targeted site. This does not, however, negate the fact that nanodrugs have drawbacks, chief among them the reproducibility of their properties and the stability of the carriers.[46] By offering a variety of administration routes, hiding unpleasant tastes, enhancing the controlled release of medications, enhancing the stability of active ingredients, and enhancing target specificity, nanocarriers have been found to improve patient compliance and therapeutic efficacy. As a result, research into nanocarriers as antidiabetic agents has grown recently.[48]

In contrast to oral delivery of anti-diabetic peptides (such as insulin) to improve oral bioavailability, nanoparticle studies have generally focused on controlled drug release to reduce the frequency of injection, limit the initial burst release, and sustain hypoglycaemic/hypoglycemic effect. In light of these, it is anticipated that the nanoformulations of naturally occurring hypoglycaemic agents will present enormous opportunities by enhancing patient compliance, ensuring cost effectiveness, and lowering toxicity in the treatment of diabetes in the future. The frequency of injections can be reduced while maintaining or improving the bioavailability and therapeutic efficacy of the drugs, which is advantageous in particular for patients receiving injection-based treatments.[49] The prospect of an effective therapeutic modality for lowering blood sugar in the near future is compelling given the nanotechnology industry's ongoing technological advancements.[50]

5.6 Discussion

The use of nanoparticle drug delivery systems has many advantages for the biopharmaceutical industry. Nanoparticles are better than conventional drug delivery strategies. They are widely used for the diagnosis, imaging, and treatment of many diseases. They can deliver a variety of therapeutic agents using sustained and targeted delivery. Increasing the effectiveness of the treatment and patient adherence as a result. Because of the size restriction imposed on them at the nanoscale, nanoparticles can be used successfully as carriers of powerful therapeutic agents. To overcome the limitations of conventional dosage forms, researchers have long been investigating drug delivery systems based on nanoparticles. The traditional subcutaneous insulin injection may soon be replaced by this nanoparticle-based insulin delivery system. Additionally, nanoparticulate drug delivery systems will decrease the frequency of drug dosages and will increase the patient compliance.

Systems for controlled or prolonged drug delivery as well as improved stability and bioavailability are goals of nanoparticle drug delivery systems. Nanoparticles can encourage the development of platforms that boost the bioavailability of peptide drugs by removing barriers to oral delivery. The majority of research on nanoparticles has focused on the oral delivery of anti-diabetic peptides (like insulin) to increase oral bioavailability. Studies on nanoparticles have demonstrated that insulin is protected from enzymatic degradations and that intestinal absorption is improved by encasing the medication in biodegradable synthetic polymers. Nanoparticles can lessen some of these drugs' unique issues by ensuring stability and maintaining their structure. Additionally, controlled release and targeted delivery are made possible by nanoparticles, allowing for innovative treatment.

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