REVIEW ARTICLE

A review on trends in nano technology – new era in diabetes treatment

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Abstract

Diabetes mellitus is a prevalent metabolic syndrome that is associated with high blood glucose levels. When diet and exercise fail to control hyperglycemia, patients are forced to start therapy with antidiabetic agents. These drugs cause several drawbacks that can affect the course of treatment; however, due to the side effects of these drugs, plant extract and bioactive compounds with antidiabetic properties are gaining as alternative treatment for diabetes. Natural products are biocompatible, cheaper, and expected to cause few side effects and patient compliance to therapy is reduced. Over the past few years', nanotechnology has found in the development of novel delivery modalities that effectively enhance antidiabetic regimen efficacy. Efforts have been targeted toward the protection of the drug by encapsulating it into a nanocarrier system and efficiently release the drug in a gradual as well as controllable manner. These systems have been applied to overcome the limitations and improve the efficacy of plant-based antidiabetic drugs. The main challenges in the formulations of plant-based nanocarriers are the loading capacity of the plant extract and the stability of the carriers. A special emphasis is placed on metallic nanoparticles with their advantages and associated complications being reported to high light their effectiveness for treating hyperglycemia. The additional inputs of nanotechnological approaches regarding exploration of herbal potential may lead to certain novel drug molecules and act as an advantage in management of diabetes for betterment of mankind.

Key words: Antidiabetic, metallic nanoparticles, nanocarriers, nanotechnology, plant extract

INTRODUCTION

Nanotechnology is a leading scientific technique that offers sensing technologies and miniature devices to diagnose disease accurately and within time. There are a wide range of applications of nanotechnology in the field of drug delivery and to simplify the oral absorption of proteins and peptide nanocarriers modified with specific ligands.[1] Over the past few years, several methods have been proposed for non-invasive monitoring of blood glucose and this can be made possible by nanotechnology. Various types of nanoparticles (NPs) are studied for insulin delivery in diabetes treatment such as,

1. Polymeric biodegradable NPs
2. Polymeric micelles
3. Ceramic NPs
4. Liposomes
5. Dendrimer.

Polymeric NPs are found to be effective and efficient over traditional oral and intravenous administration methods. They are biodegradable polymers surrounded by nanoporous membrane and are used as carriers of insulin. pH change swells the polymer system resulting in release of insulin. Copolymers such as N, N-dimethyl aminoethylmethacrylate, polyanhydrides, polyurethanes, polyacrylic acids, and polyacrylamide are used for these applications.[2] Different plasticizers and nanomaterial's with potential applications in everyday life for diabetic patients were introduced particularly at the level of glucose metabolism impairment as in diabetes mellitus (DM).

Nanotechnology has been linked to diabetes, with side effects of nano molecules that cause glucose profile damage, or as applications. Transdisciplinary nanotechnology involving diabetes is developing due to the major epidemiological effect in the general population and it can be applied through the use of traditional protocols of diagnosis and therapy and using

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advanced computer-assisted drug design chemoinformatic instruments.

DM is a common metabolic disease and non-infectious endocrine disorder that is associated with hyperglycemia or high blood glucose levels, which are caused by the body's impaired ability to metabolize glucose.[3,4] According to the survey in low-and middle-income countries, there are 366 million people living with diabetes and the count is expected to rise to 552 million by 2030.[5] Diabetes has been categorized as Type 1 and Type 2. Type 1 diabetes is insulin dependent condition, characterized by deficiency of insulin due to destruction of insulin-producing beta cells of islets of Langerhans by autoimmune system in pancreas, while type 2 diabetes is distinguished as disorders of both insulin resistance and secretion due to defects in insulin receptor on cell membranes. Besides these types of diabetes, gestational diabetes has also been reported in pregnant women. During pregnancy, abnormal hormonal production leads to woman's sensitivity to insulin resulting in high blood sugar levels.[6] The increasing incidence of DM over the past decades is highly underestimated in the general population, generated increased economic and social burden, rendering it important to study the potential molecules involved in its pathogeny and new efficient treatment options. Multiple factors play a role in the pathophysiological mechanisms of DM including lifestyle choices (sedentary habits and junk food consumption), genetic susceptibility (such as genes involved in glucose metabolism, insulin control, and secretion), chronic inflammation, oxidative stress, growth hormone, and cortisol axis anomalies which contribute to insulin resistance and are a necessary step in type 2 diabetes mellitus (T2DM) development.[7-9]

AIMS OF NANOTECHNOLOGY IN PREDIABETES/T2DM TREATMENT

Nanotechnology is applied to resolve major drawbacks of the modern marketed drugs that hinder therapy such as the limited bioavailability and the quick drug release into blood stream that consequently cause unwanted side effects [Figure 1]. For this reason, nanostructured-biomolecules and nanomaterials are synthesized to (1) increase bioavailability by protecting oral drugs and ensuring safe reach to blood circulation from initial absorption in the gastrointestinal tract, for example, protection of GLP1 from enzymatic digestion (DPP4 enzymes), (2) prolong drug release: (a) maintain constant drug concentration; (b) reduce frequency of dosing; and (c) improve patient compliance, and (3) reduce drug's potential side effects such as hyperglycemia, weight gain, increase in insulin resistance, β-cells destruction, and renal and cardiovascular complications. The interplay of nanotechnology with pharmacology and pathophysiology for the development of high efficiency innovative drugs for cancer treatment[10] was well appreciated. The in-depth understanding of the pharmacological mechanisms in conjunction with the physiological characteristics of normal and disease states should also guide the design for nanodrugs in diabetes treatment. This conjunction (pharmacology, pathophysiology, and nanotechnology) potentially produces nanotechnology-based drug formulations with the desired functionalities for precision treatment in T2DM.

NANOTECNOLOGY IN MEDICINE

NPs possess a series of excellent properties compared to their bulk structures as nano-materials become more dependent on its shape and size and interfaces are easier to be accessed[11] The use of nanomaterials and nanodevices in the field of health and medicine, has established of a new nanoscience area, of nanomedicine. The advancements of nanotechnology in medicine can be summarized into three categories:

Drug Delivery/Therapeutics

The development of novel nanomaterial-based carrier systems aims to the controllable and targeted release and biodistribution of a pharmaceutical compound.[12] It is also applied in drug design to increase absorbability. Some NPs have unique properties which enable them to be directly used in therapy; magnetic NPs can induce malignant cells without affecting the surrounding normal tissue and silver and zinc-oxide NPs show effective antimicrobial activity and potentially become alternatives to antibiotics.[13]

Diagnosis/Imaging

Through nanomedicine, early detection, diagnosis, and prevention of diseases can be improved using certain NPs as labels for diagnostic tools and high-resolution imaging or substrates for the development of biosensors.[14] The application of nanosensors will lead to the production of highly sensitive biomedical devices for the fast and high throughput detection of disease biomarkers. Nanotechnology offers advantages in the area of diagnosis considering that the unique properties of some nanomaterial (biological, physical, optical, magnetic, chemical, and structural properties) render them suitable for diagnostic imaging (tumor detection, atherosclerotic plaque imaging, etc.).[15] Advances in nanotechnology, molecular imaging, and biomedical imaging tools are creating new opportunities for the early diagnosis, staging and monitoring of disease progression for patients with type 1 or type 2 diabetes.[16]

Tissue Repairing/Biomaterials

Nanomaterials are used for the design of artificial cell and implants for the repair or reproduction of damaged tissues. Nanotechnology allows the development of biocompatible scaffolds, mimicking extracellular matrix complexity and

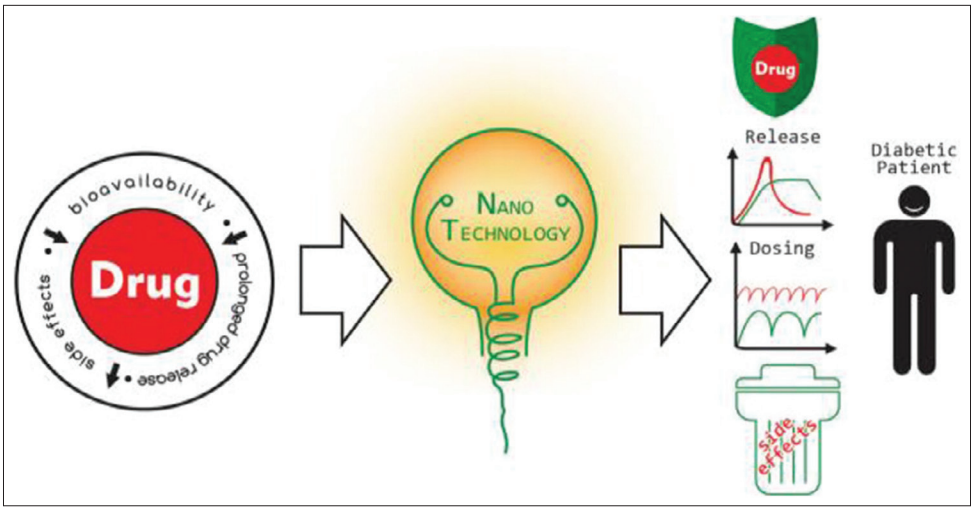

Figure 1: Nanotechnology approach in T2DM treatment

functionality, which are used for tissue regeneration.[17] Moreover, nanofeatured scaffolds are designed to encapsulate and control the spatiotemporal release of drugs (e.g., growth factors). Nanotechnology-based biomaterials (nanocoatings or nanostructured surfaces) are also used to overcome several issues of implant materials, such as bacterial adhesion or corrosion resistance.[18]

Nano medicine, in the form of nanotherapeutics, is defined as an application of nanotechnology where the NPs are loaded with the drug improving its therapeutic properties and reducing morbidity, where the drug can be delivered to targeted tissue with high efficacy. Nanotechnology has been applied to a wide range of medical pathological conditions, such as cancer, Parkinson's disease, Alzheimer's disease, tuberculosis, and DM. Nanotechnology has enabled the design of robust insulin delivery vehicles which facilitate the direct transfer of insulin molecules into the bloodstream, bypassing the gastric acidic environment and thus offering an alternative for daily subcutaneous injections.[19]

Nanomedicine can be applied for the management of T2DM subgroups. Specifically:

Drug delivery

The nanotechnology has developed in the novel delivery modalities that can potentially enhance antidiabetic regimes efficacy.[20,21] Various smart material formulations are targeted toward two main vital steps which are to protect the drug by encapsulating it into a nanocarrier system and to efficiently release the drug in a gradual as well controllable manner.

Diagnosis (detection and drug delivery)

Today therapy of diabetes is relying on "open-loop" delivery methods, where the patient administers the drug to himself at different times in a day. A most advanced approach is the "closed-loop" therapy, where the involvement of the patient in maintaining glucose control is minimal. A "closed-loop" system determines insulin or drug requirement at proper time and delivers the required dosage (for example the development of "synthetic pancreas" an external device that uses glucose sensors and pumps).[22] The development of highly sensitive nano-sensors as well as nanomaterials improves glucose sensor function eventually and improves the lives of patients living with diabetes (T1 and T2DM).

HERBAL DRUG TREATMENT

The antidiabetic drugs in each class can be used as monotherapy or in combination with drugs from other classes. All of the side effects and long-term treatments that are associated with the drugs have led to an increasing demand for efficacious, safe (few side effects), and affordable agents for the treatment of diabetes. Herbal medicines have been traditionally used to treat many diseases, including diabetes.[23] To ensure the efficacious drug delivery of phytochemicals that are present in plant extracts for the treatment of type 2 diabetes, various strategies have been employed, including nanocarrier-based therapy models, such as liposomes, niosomes, solid lipid nanoparticles (SLNs), and nano emulsions. Hydrogels are also known for delivering bioactive agents in chronic conditions, such as diabetic wounds. They possess high water contents and are developed using state-of-art designs that change according to temperature and pH.[24] Many plant-derived secondary metabolites were reported to possess significant antidiabetic activities. Plant secondary metabolites have revealed to exhibit antidiabetic effect through multiple mechanisms, which include suppression of glucose absorption, restoration of the functional mass of β-cells, improvement of insulin expression, reversal of insulin resistance, promotion of glucose utilization, and regulation of carbohydrate and lipid metabolism [Figure 2].

Several phytochemicals have been found to suppress postprandial hyperglycemia by interrupting carbohydrate digestion and retarding glucose absorption through inhibition

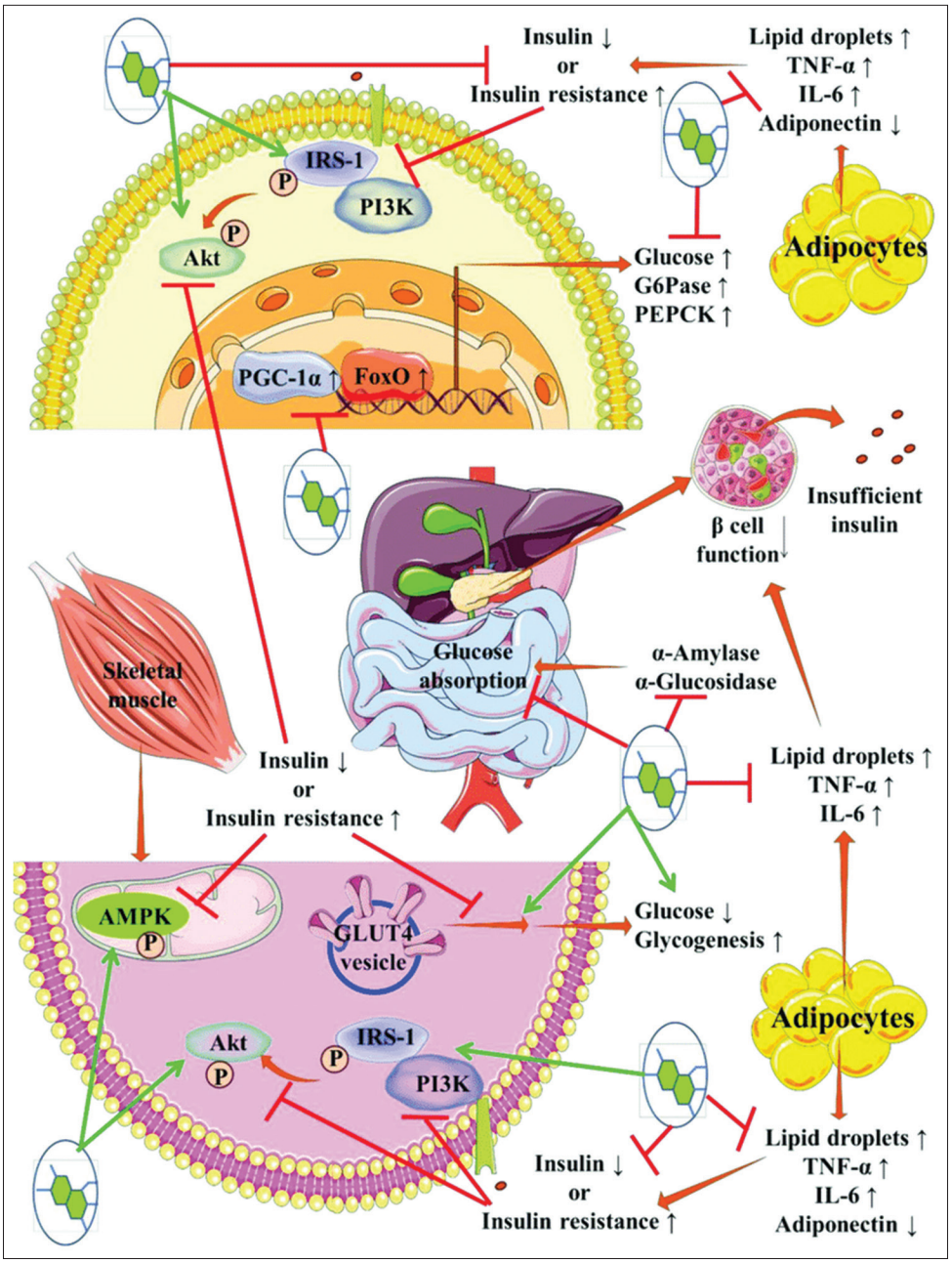

Figure 2: Multiple therapeutic targets of plant secondary metabolites in diabetes management

of intestinal carbohydrate digesting enzymes, such as α-amylase, α-glucosidase, and β-glucosidase.

Encapsulation of drugs into NPs aims to prolong drug release and presence of drug into systemic circulation releases gradually and improve drug uptake from targeted tissues and thereby reduce the toxicity. Many plant-based extracts and isolated bioactive compounds have been used across the world as therapeutic agents for the prevention and treatment of diseases and ailments.[25] Any plant-based products that are used to preserve or recover health are classified as herbal medicines. Herbal medicines have been gaining public interest and are more popular regarding their effectiveness, changes in consumer preferences for natural medicines, the high costs, and adverse effects of modern medicines and improvements in herbal medicines with the development of science and technology.[26] Research of identifying the chemical compounds from medicinal plants and their common uses lead to new innovative drugs with fewer adverse effects than existing drugs.[27] The development of new antidiabetic drugs from plants has more attention as plants contain bioactive constituents that have positive effects in the treatment of DM. The application of herbal bioactive constituents and extracts in phytopharmaceuticals is still limited due to certain factors, such as unfavorable taste (e.g., bitterness), low solubility, poor permeability, physiological instability, and low bioavailability.[28,29] To overcome these limitations, nanotechnological approaches have been explored as drug

delivery mechanisms. Nanostructured drug delivery systems exhibit better physicochemical and biological properties than microscale drug delivery systems. The former systems have better optical properties, higher surface areas, better conductivity, and improved interactions with biological molecules.[30]

Most of the bioactive compounds in plant extracts, such as flavonoids, tannins, and terpenoid, are highly water-soluble. These compounds exhibit poor absorption as they cannot move across the lipid membrane which results in decreased bioavailability and efficacy. By loading herbal medicines into nanocarriers, the absorption of the compounds can be improved, allowing for cellular uptake across the gastrointestinal wall of the bioactive compounds through passive transport. Encapsulating these compounds into nanocarriers can increase their surface areas, thereby improving their water solubility. Nanocarriers also allow for the controlled and sustained release of the natural compounds at the target site, which reduces the clearance, improves the therapeutic efficacy, and reduces the adverse effects of the bioactive compounds. Natural compounds are better preserved when encapsulation occurs without any chemical reactions and nanocarriers can protect the compounds from gastric degradation.[31]

TYPES OF NANOCARRIERS FOR PLANT-BASED ANTIDIABETIC EXTRACTS/ ACTIVE AGENTS

Nanocarriers have sizes of between 1 and 100 nm and have been used as transporters to deliver active agents to target sites.[32] Nanocarriers are becoming more popular than conventional drug delivery systems due to their effectiveness, stability, and improved drug bioavailability; target specificity and ability for the sustained release of the drug nanocarriers can carry various drugs with various biological properties.

Liposomes

Phospholipid molecules were found to assemble by forming closed bilayer vesicles in water and termed as liposomes.[33] These drug carriers were used for various administrative routes, such as parenteral, oral, pulmonary, nasal, and transdermal routes.[34] Liposomes have one or more cell-like lipid bilayers, which are suitable for cellular investigations. They also have functions, as motility and shape changes and the ability to impersonate biophysical properties of living cells.[35-37] Phospholipids are amphipathic molecules with water-loving (hydrophilic) and fat-loving (hydrophobic) parts. The hydrophobic parts, are the tails of the phospholipids, results in the self-assembly of liposomes through hydrophilic interactions, van der Waals interactions, and hydrogen bonding interactions.[38]

Liposomes improve the physicochemical properties and onset time of the incorporated compounds and decrease their toxicity.[39] Liposomes fulfill the requirements of suitable drug carriers as they are biodegradable, biocompatible, and stable in colloidal solutions. When determining the final liposome structures, several crucial factors need to be considered: Type and amount of phospholipid; the charge properties of the aqueous solution; hydration time; and the use of mechanical procedures and organic solvents.[40] Liposomes also have poor permeability to pass through the intestinal epithelia due to the relatively large size of their particles and the various epithelial barriers. Furthermore, it is difficult to mass-produce liposomes due to inconsistencies between batches. The most important limitation of the use of liposomes as nanocarriers is their inability to retain active agents for prolonged periods compared to polymeric system nanocarriers.[41] Combined herbal extracts can also be used within a single nanoliposomal formulation to improve its therapeutic efficacy.

Niosomes

Niosomes are prepared using non-ionic surfactants instead of phospholipids. Niosomes were first developed for cosmetic purposes by a cosmetic company. Niosomes have the same advantages as liposomes for use as drug delivery systems. Niosomes can encapsulate both hydrophilic and lipophilic compounds due to their bilayer membranes and their enclosed aqueous cores.[42] The drug encapsulation efficiency of niosomes is better due to their lower concentrations of cholesterol. Niosomes are also less expensive for mass production and do not require special storage conditions, such as inert atmospheres, freezing temperatures (א20_C), and darkness, which are essential for the manufacture of liposomes. The non-ionic surfactants that are used in the preparation of niosomes are much more stable than the lipids that are used for liposome production in terms of physical and chemical stability.[43] Liposome preparation is expensive and unique handling methods are essential. On the other hand, niosomes can extend the circulation of the incorporated drugs due to their longer shelf life. Liposomes have shorter shelf lives than niosomes due to their lipid components, which rapidly undergo rancidification.[44] Niosomes have been applied as drug vehicles to reduce crucial biopharmaceutical problems, such as drug insolubility, adverse effects, target specificity, drug bioavailability, and poor chemical stability.[45] Some negatively charged molecules, such as diacetyl phosphate, and phosphatidic acid, and positively charged molecules, such as stearyl amine, can be added to the formulation of niosomes to improve their drug loading, increase their efficacy, and improve their stability.[46] Compared to liposomes, niosomes have better stability and they are processed under less stressful conditions.

Polymeric NPs

Polymeric NPs are solid colloidal particles that range from 1 nm to 1000 nm and are made up of biocompatible polymers.[47] Polymers are large molecules that are made by chemically linking one or more different types of small units, which are known as monomers, to form a linear or branched chain.[48] Monomers can have any structure, as long as they have at least two functional groups to form an interaction with another monomer. Polymeric NPs can be prepared using block copolymers that have at least two polymer chains with different hydrophobicity that spontaneously assemble into a core-shell structure in an aqueous solution. The hydrophobic blocks create the core to reduce their exposure to the aqueous environment, while the hydrophilic blocks from the outer shell to stabilize the core. As delivery systems, polymeric NPs can transport various molecules, including drugs, proteins, plasmids, DNA, and small interfering RNA.[49]

Nanoemulsions

Nanoemulsions are thermodynamically stable dispersion systems that are made up of two immiscible liquids, such as water and oil, which are mixed with suitable surfactants and cosurfactants to form an interfacial film. The selected surfactants can be non-ionic or ionic surfactants.[50] Based on the composition of the oil and water portions, nanoemulsions can be classified into three types: oil in water (O/W), water in oil (W/O), and bicontinuous. For oil-in-water (O/W) nanoemulsions, oil droplets are dispersed in the aqueous phase. Meanwhile, for water-in-oil (W/O) nanoemulsions, water droplets are dispersed in the oil phase. As for bicontinuous nanoemulsions, microdomains of oil and water are inter-dispersed within the system. As drug delivery systems, nanoemulsions have similar advantages to other nanocarriers; for example, nanoemulsions can deliver drugs to specific sites, protect drugs against degradation, and increase their bioavailability.[51] Furthermore, nanoemulsions can dissolve a large number of lipophilic drugs.

SLNs and Nanostructured Lipid Carriers (NLCs)

SLNs consist of solid lipid matrices with single layers of phospholipids. Many solid lipids, such as triglycerides, fatty acids, and steroids, can be used in combination with various surfactants, which can produce steric stabilization in the formation of SLNs.[52] It is a substitute to other nanocarrier drug delivery systems, such as emulsions, liposomes, and polymeric micelles. SLNs combine the benefits of polymeric NPs, emulsions, and liposomes while averting their disadvantages. The lipids that are used in the preparation of SLNs are biocompatible and less toxic than specific polymeric NPs.[53,54] The solid lipid matrices, which are identical to those in polymeric NPs, protect the encapsulated active agents against chemical degradation in biological environments and provide high flexibility in terms of the release properties of the drugs. SLNs are capable of encapsulating both lipophilic and hydrophobic drugs.[55] The lipophilic property of the solid lipid matrices enables these NPs to incorporate hydrophobic drugs. It is expected that hydrophilic drugs would be poorly encapsulated due to their low affinity to these lipid matrices. However, the double emulsion/solvent evaporation method can achieve satisfactory loading efficiencies for hydrophilic drugs.[56] Other advantages of SLNs include the targeted and controlled release of the encapsulated drug and the improved bioavailability of the drug.[57] NLCs were then developed to overcome the potential limitations of SLNs. The potential limitations of SLNs include low drug loading capacity, drug expulsion after polymeric transitions and the relatively high-water volumes of the dispersions. NLCs are synthesized using spatially different lipids that are composed of different fatty acids, which lead to bigger spaces between the fatty acid chains and imperfect crystallization. These also improve the drug loading.

CHARACTERISATION OF NANOCARRIERS

The physicochemical characterization of nanocarriers has been known to be related to their efficacy and applications, including their size and its polydispersity index, morphology, surface charge, zeta potential, entrapment efficiency, drug release evaluation, compatibility, and stability.[58-60] Size and polydispersity are important parameters in nanocarriers as they determine the drug release characteristics and the biodistribution and bioelimination of nanocarriers. There are various methods to determine the size and polydispersity of nanocarriers, such as dynamic light scattering (DLS) and microscopic techniques, including atomic force microscopy and centrifugal liquid sedimentation. The selection of the method is dependent on the expected size and population of the nanocarriers. The morphology or shape of NPs may affect their biodistribution, targeting efficacy, and degree of cytotoxicity. This characteristic can be determined using scanning electron microscopy (SEM) or transmission electron microscopy.[61] For metallic NPs, compositional analysis is performed using energy-dispersive X-ray spectroscopy (EDX) with a scanning electron microscope (SEM-EDX). Surface charge and zeta potential affect the stability of dispersion nanocarriers. These two parameters govern the repulsion between the nanocarriers (electrophoretic mobility distribution) and stability is achieved when the value of the zeta potential is at or above_30 mV. DLS instruments, such as Brookhaven (NanoDLS® series), Microtrac (Wave II® series), and Malvern (Zetasizer® series), are used to determine the particle size and surface charge of nanocarriers.[62] Entrapment efficiency refers to the amount of drug that is encapsulated by nanocarrier and needs to be determined as it influences the release kinetics of the drug.

Drug Release Study

Evaluating the drug release characteristics of nanocarriers is very important as the results can be used to optimize the formulation and to predict the therapeutic efficiency and side effects. The most popular method that is adopted for this purpose is the dialysis method.

Compatibility and Stability Study

Nanocarriers are composed of various different chemicals and should be compatible and inert. Therefore, compatibility studies are required, which are commonly conducted using differential scanning colorimetry or X-ray diffraction. Nanocarriers need to be stable until the drug has reached the target site not to affect the efficacy of the drug. Therefore, predicting the stability of nanocarriers physically, chemically and in physiological environments is very important.

BIOLOGICAL APPLICATIONS OF NPs FOR DIABETES

Nanotechnology has emerged in the past few decades as a promising technique for many biomedical applications. NPs are small materials with unique properties (at least < 100 nm in one of their dimensions). Reduction of materials to a nanoscale may also alter their properties, enabling them to interact in a specific way with cell biomolecules. NPs for delivery to target cells are loaded with therapeutic agents. Furthermore, metal NPs seem to be less harmful compared to mineral salts and have a multifunctional effect on the organism.[63]

Metallic NPs

The use of metallic NPs has shown remarkable progress in biomedical sciences and can counter antibacterial, antidiabetic, and anticancer activities. A decade of research on using metallic NPs to entrap plant extracts has gained the interest of many researchers as it has presented remarkable results. Metallic NPs possess unique properties, such as large surface areas, functional groups, effective quantum self-assembly, and the ability to conjugate with the drug of interest, which make them favorable for biotechnology, targeted drug delivery, and potential *in vivo* imaging. Metallic NPs have many advantages, such as manufacturing simplicity, reproducibility, economy, stability, environmental friendliness, and high entrapment efficiency, which make them favorable candidates for various applications. The synthesis and fabrication of metallic NPs primarily use metal and metal oxides, such as gold, silver, copper, and titanium–cerium–zinc oxide (ZnO). In nanoformulations that involve plant extracts, they act as stabilizing and reducing agents.[64] The most common metallic NPs to be studied are gold (Au NPs) and silver nanoparticles (Ag NPs). Gold NPs are commonly synthesized using the Turkevich method, whereas silver NPs are synthesized using the bioreduction process.[65] ZnO NPs are very common metallic particles that are used due to their large binding energy.[66]

ZnO NPs

ZnO NPs are commonly used for a range of biomedical uses, including antidiabetic, antibacterial, anticancer, antifungal, drug delivery, and anti-inflammatory activities.[67] Zinc is responsible for maintaining insulin structure and plays a crucial role in insulin biosynthesis, secretion, and storage. Zinc transporters play a key role in insulin secretion from pancreatic beta-cells.[68] The synthesized NPs have been found to have strong biological activity with respect to antioxidants, anti-inflammatory, and anti-diabetes potentials that can be used in the cosmetics, food, and biomedical industries in various biological applications.[69] All studies demonstrated that ZnO NPs have a positive effect as a diabetes treatment and help reduce its complications.

Magnesium

Magnesium (Mg) is an important ion associated with the homeostasis of glucose. Mg plays a major role in both phosphorylation and glucose metabolism by involving many enzymes involved in these reactions and plays a prominent role in insulin secretion. Mg deficiency resulted in insulin resistance, carbohydrate dyslipidemia, and complications of the DM mice. MgO NPs decreased blood sugar levels by improving insulin sensitivity as well as eliminating changes in lipid level such as elevated LDL and triglyceride, and low HDL in diabetic mice.[70] Magnesium can have an effective role in treating diabetes, especially type II diabetes.

Cerium Oxide NPs

There are many rare earth elements including Ce which are in the lanthanide series in the periodic table. CeO2 NPs have shown a promising new treatment for oxidative disorders that overcome many previous brain injury therapies. A study suggested that CeO2 NPs could be used as an effective therapeutic regenerative agent that prevents diabetes-induced nerve damage. CeO2 NPs can be used as an antioxidant to treat diabetic neuropathy and also help in inhibiting gestational diabetes complications and used as an antioxidant for treating diabetic neuropathy.

Copper NPs

Copper is one of the most important transitional elements involved in many biochemical pathways. Cu NPs use trace metal NPs for the treatment of type 2 diabetes, along with superior antioxidant properties and radical scraping in animals by inhibiting alpha-amylase and alpha-glucosidase.

Cu NPs also showed substantial prevention of functional cardiovascular defects in diabetic. These NPs may increase nitric oxide bioavailability in the vascular endothelium and decrease oxidative stress.[71] Several previous studies have also shown that the use of copper NPs plays an important role in the diagnosis of wounds in mice with diabetes not only can the illness be controlled by a strain of bacteria but also can help in a faster healing.[72,73]

Selenium NPs

Selenium is a trace element found in most plants. The body deficiency of selenium has been shown to cause various illnesses including diabetes.[74] The antioxidant properties of Se NPs are also less toxic than selenium itself. Se NPs have antioxidant effects by scavenging various peroxide, protecting lipids, and cellular macromolecules from oxidative damage to membranes, and by increasing glutathione peroxidase, and thioredoxin reductase levels. T2DM showed that liposomal Se NPs have an antidiabetic capacity by maintaining beta-cell integrity, amplifying insulin secretion, reducing glucose levels, restoring the balance between oxidative and antioxidant production, and reducing pancreatic inflammation[75] effective doses, of selenium NPs have beneficial effects on liver function and the treat associated disorders in rats by lowering blood sugar and by reducing levels of gamma-glutamyl transferase. Se NPs is a promising treatment option that synergistically eliminates most complications of diabetes and insulin resistance.

Drug administration has been associated with various anatomical, physiological, and chemical barriers. These barriers can be overcome by NP-drug delivery systems that offer improved targeting of specific cells by utilizing different approaches: Active, passive, and stimuli-responsive targeting.[76] Drug molecules can be incorporated within specific NPs formulations (such as lipid bilayers and polymers) and released at a particular time and location after exposure to a specific external stimulus (pH changes, heat, magnetism, and ultrasound). Compared to the conventional formulations, the nanodrugs show reduced that toxicity NPs are increasingly tested in the clinical setting to improve the efficiency of the treatment. Current pharmacological nanoapproach on DM focuses mostly on the development of "carriers" that regulate insulin release according to glucose blood level.

FUTURE PERSPECTIVES

A drug's effects are evaluated in terms of potency, efficacy, and effectiveness. Effectiveness differs from efficacy since a drug might have high efficacy but low effectiveness because it causes many side effects. Considering these features, nanoformulations of antidiabetic drugs at similar doses have higher efficacy and effectiveness. The safe and controlled delivery of antidiabetic drugs to the specific site is the solution offered by the nanodelivery systems that translate into a better control of T2DM. This does not mean that nanodrugs lack of limitations which are mainly related with the stability of the carriers and the reproducibility of their characteristics.

Nanocarriers are gaining more attention within medicinal fields over recent years. In the treatment of diabetes, which requires continuous and prolonged treatment, patient compliance is crucial to achieve the treatment targets. Nanocarriers have been found to increase patient compliance and therapeutic efficacy by providing various routes for administration, concealing unfavorable tastes, improving the controlled release of drugs, increasing the stability of active agents, and improving target specificity. Hence, the study of nanocarriers as antidiabetic agents has increased over recent years. Due to the various side effects of modern antidiabetic drugs, plant-based active agents have also been gaining more attention. They could provide similar effects to the modern drugs but with fewer side effects. Most studies on plant-based antidiabetic active agent nanocarriers have focused on polymeric NPs which may be due to their more affordable nature and biocompatible components for developing polymeric NPs, such as chitosan and alginate. In addition, the up-scaling and mass production of polymeric nanocarriers are much easier than for liposomes or niosomes. Polymeric nanocarriers also exhibit better stability than other nanocarriers. Many plant-based antidiabetic active agents have other biological properties, such as antioxidant and antihyperlipidemic properties. Thus, there is the potential to use these nanocarriers in combination with treatments for other diseases.

CONCLUSIONS

At present, more than 400 plants have been clinically proven to have antidiabetic properties. Those plants have been slowly gaining attention as alternatives to allopathic medicines. The impact of nanotechnology on medicine is increasing rapidly with each passing day. It is useful in detection of insulin and blood sugar which are also useful in treatment of diabetes. Oral insulin seems to allow several types of encapsulations by bypassing the gastric acidic environment and thus dealing with the problem of daily subcutaneous injections. Nanotechnology has proven beneficial in treating DM by not only improving the catalytic properties of electrodes but also by increasing the available surface area of the sensor-receptor complex. This can revolutionize insulin delivery through enhanced oral formulations and islet encapsulation. Polyethylcyanoacrylate nanospheres have proven to be successful for insulin delivery in streptozotocin-induced diabetic rat model. At present, NPs-based drug delivery system are playing an essential role in the pharmaceutical industry. A new drug delivery system of an existing drug can provide a new marketability which is the important in the economic point of view. The next-generation NPs-based insulin may be the future medicine for T1DM.

Many studies have been conducted on nanocarriers formulations for antidiabetic bioactive compounds and extracts from plants to overcome the limitations of plant-based products, such as low solubility, poor permeability, and low bioavailability. The best properties for countering antidiabetic effects have been shown by metallic NPs and liposomes due to their versatile nature and their vast areas of application. The efficacy of these plant-based nano formulations against hyperglycemia-related conditions has been proven through both *in vitro* and *in vivo* assessments. Hence, nanocarriers for herbal antidiabetic medicines have a lot of potential as alternative treatments for DM. However, further research needs to be carried out to discover which nanocarriers could offer high therapeutic efficacy for managing diabetes and hyperglycemia complications.

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