Available online on 15.09.2023 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Review Article

Nanotechnology and Nanocapsule-Based Approaches for the Diagnosis and Therapeutics of Diabetes Mellitus: A Concise Survey

Pratik P. Terse*[1], Pranav Pawaskar[1], Pranita K. Pawar[2], Sheetal S. Samant[2], Aishwarya Teli [3]

[1] *Shree Pushpasen Sawant College of Pharmacy, Digas, Sindhudurg, Rumadgaon, Maharashtra 416521*

[2] *Yashawantrao Bhosale College of Pharmacy, Charatha, Vazarwadi, Maharashtra 416510*

[3] *VP College of Pharmacy, Madkhol, Sawantwadi, Maharashtra*

Article Info:

Article History:

Received 02 July 2023
Reviewed 10 Aug 2023
Accepted 21 Aug 2023
Published 15 Sep 2023

Cite this article as:

Terse PP, Pawaskar P, Pawar PK, Samant SS, Teli A, Nanotechnology and Nanocapsule-Based Approaches for the Diagnosis and Therapeutics of Diabetes Mellitus: A Concise Surve, Journal of Drug Delivery and Therapeutics. 2023; 13(9):151-159

DOI: http://dx.doi.org/10.22270/jddt.v13i9.6197

*Address for Correspondence:

Mr. Pratik P. Terse, 3565, Hindu Colony, Near Akerkar Hospital, Kudal. Dist: Sindhudurg. Maharashtra Pin: 416520

Abstract

A serious health concern of frightening proportions is diabetes mellitus, a common metabolic illness marked by increased blood sugar levels as a result of insufficient insulin production or response. Nanosensors and nanomaterials have recently shown tremendous promise for enhancing glucose detection for the treatment of diabetes. Significant improvements in glucose sensor sensitivity, specificity, and reversibility have been achieved through the incorporation of nanoscale carbon structures, nanocomposites, and other nanomaterials. The use of these tailored nanocarriers offers a viable technique to enhance patient compliance and diabetes management by addressing the difficulties associated with oral peptide medication delivery for the treatment of diabetes caused by adverse circumstances in the gastrointestinal system. Nanocapsules are a promising approach for effective medication transportation via biological barriers by protecting drug molecules from the biological environment. A workable solution to problems with oral peptide medicine distribution for treating diabetes, particularly when it comes to unfavorable gastrointestinal conditions, is the use of customized nanocarriers. These nanocarriers have a flexible design and special in vivo characteristics that make it possible to go beyond cellular and tissue absorption barriers while improving the stability and effectiveness of therapeutic peptides. The management of diabetes mellitus has a great deal of potential for targeted lipid-based nanoparticles, which operate as an efficient drug delivery technique for oral administration of therapeutic peptides. With these developments in nanotechnology and nanocapsule-based techniques, diabetes treatment might be improved, patient compliance could be increased, and drug administration frequency could be decreased, potentially changing the field. This article presents a comprehensive review of recent advances in nanotechnology for diabetes mellitus diagnosis and the utilization of nanocapsules in diabetes treatment

Keywords: Nanotechnology, Nanocapsules, Diabetes Mellitus, Nanocarriers, Nanomaterial, Nanotube

Introduction:

Diabetes is form of metabolic disorder in which patient suffers from high blood sugar level because their bodies do not respond to or don't produce enough amount of insulin (A hormone that helps to maintain the blood sugar level by directing the cells to use glucose and stops hepatic glucose production). Diabetes is biggest health problem which have banged alarming level. In 2019 about half a billion people (9.3 % of adults 20-79 years) were sufferings from diabetes in the whole world. The approximate count of people (20-79 years) having diabetes has raised by 62% since past 10 years; from 285 million in 2009 to 463 million [1, 2,10]

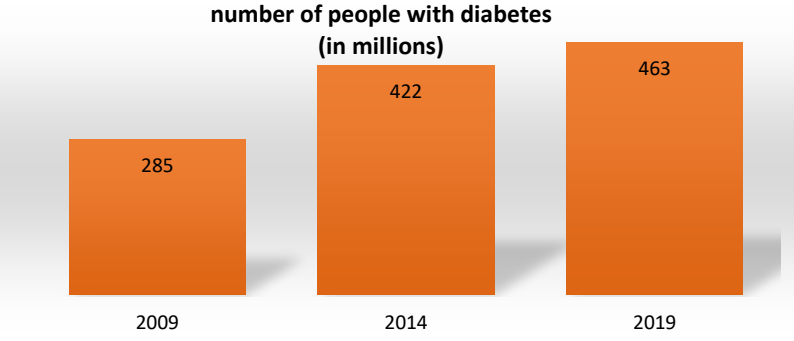

Figure 1: This graph will show the trend of diabetes prevalence over the 10-year period.

Types of Diabetes mellitus:

1) Type 1:

It results from destruction of autoimmune beta cell in pancreas and is categorised by a complete absence of production of insulin. In these the insulin productive cells are destroyed by its own immune system. [1]

Classified into two types

1. Immune mediated: This is form of diabetes which associated with only 5-10% of those with diabetes, previously encompassed by the term insulin-dependent or juvenile-onset diabetes. It results from cellular mediated autoimmune destruction of beta cells of pancreas. In this type of diabetes rate of destruction of beta cell is little bit variable.
2. Idiopathic diabetes: less part of patients with type 1 diabetes comes under this category, of those most of patient are of African or Asian ancestry. One with this form of diabetes experiences episodic ketoacidosis and exhibit changing degrees of insulin deficiency between episodes. This form of diabetes is majorly inherited, don't have immunological affirmation for beta cell autoimmunity and it is not HLA associated. [3]

2) Type 2:

It is identified by impairment of carbohydrate, lipid and protein metabolism and results from dysregulation of insulin secretion, insulin resistance or both. [4]

3) Gestational diabetes mellitus:

It is defined as diabetes diagnosed during pregnancy that is not clearly overt diabetes, is becoming more common as the epidemic of obesity and type 2 diabetes mellitus continues.[5]

It is glucose intolerance type of diabetes which occurs in second and third trimester of pregnancy, resulting in hyperglycaemia of variable severity. [6]

4) Other specific types:

i. Genetic defects of beta cell function
ii. Genetic defects in insulin action
iii. Diseases of the exocrine pancreas
iv. Endocrinopathies
v. Drug or chemical induced components
vi. Infections
vii. Uncommon forms of immune mediated diabetes
viii. Other genetic syndromes sometimes associated with diabetes

Causes:

Development of diabetes comprises of so many pathogenic processes. The impaired action of insulin on target tissues is basis of the irregularities in metabolism of carbohydrate, fat and protein in diabetes.

Impaired insulin action results from abnormal insulin secretion and decreased tissue response to insulin at one or more points in the system pathways of hormone action [3]

It has been evidenced that obesity is major cause of diabetes. Obesity and weight gain both are related with high risk of diabetes. Also aging, obesity, insufficient energy consumption, alcohol drinking, smoking etc. are independent risk factor of causes of diabetes. [2]

Over eating, nervous and endocrine system disorder, raised level, impairment in sex hormone secretion, decreased energy consumption because of not doing exercise and genetic factors can cause diabetes mellitus. [7]

Symptoms:

- ADA symptoms [8]
  i. Frequent urination
  ii. Increased fatigue
  iii. Irritability
  iv. Excessive thirst
  v. Blurry vision
  vi. Extreme hunger
  vii. Unusual weight loss
- Other symptoms [8]
  i. Erectile / sexual dysfunction
  ii. Shortness of breath
  iii. Chest pressure, discomfort or pain
  iv. Temporary disability
  v. Recovering from surgery
  vi. Severe illness

Treatment:

- There are some mainly used treatment –

A. Lifestyle intervention

B. Pharmacological intervention

a. Metformin

b. Thiazolidinedione

c. Alpha-Glucosidase inhibitor

d. Incretins

e. sodium-glucose co-transporters 2 inhibitor

f. Anti-obesity drugs

C. Bariatric surgery [2]

Treatment of diabetes involves several standard therapeutics like sulphonylureas and repalglinide which elevates insulin secretion, troglitazone enhances insulin action in fat and muscle, metformin stimulates insulin mechanism in liver tissue, miglitol and acarbose act out for delayed carbohydrates absorption.

The main and important medication ideas constitute of combinational therapy of insulin with drugs like sulphonylureas, metformin and troglitazone which gives out different action and results

i. Insulin-sulfonylureas = Lowers daily requirement of insulin
ii. Insulin-metformin = reduces weight gain
iii. Insulin-troglitazone = minimize insulin requirement and enhance glycaemic control

Eventually, secondary forms of disease may occur due to deficiency/ mutation in genome of organism [9]

Limitations/ disadvantages of current treatment

The disease with its several complications brig ups the immediate need to act with a comprehensible strategy. The primary platform is aimed at receiving complete glycemic regulations, possible through estimation of present glycemic status and Study of associated disorder would aim at issuing the healthcare facilities to the patient.

i. The new generation of drugs like sulphonylureas or insulin results in hypoglycaemia and weight gain as well.

ii. Biguanide like metformin can show gastrointestinal effects like diarrhoea, nausea and sometimes lactic acidosis.

iii. Thiazolidinedione used is also results in weight gain, which is an issue of concern as type 2 diabetes patients are already obese

iv. Drug like incretins mimetic may Show nausea, vomiting and diarrhoea.

v. Drugs showing ability to cure diabetes have been used individually and in combination With Different oral agents and also with insulin but obtaining total glycemic control is tough. [9]

Nanocapsule

In last 50 year, nanocapsules are found to be as drug carriers. It is a type of nanoparticles. It is vesicular system, where the drug is placed in a cavity which is made up of inner liquid core and Outer polymeric membrane. Nanoparticles is a ball shaped, void structure. They are consisting of one or more than one functioning material i.e., core and it also made up of preventive matrix i.e., shell. Nanocapsules are comprises of protective coating which is pyrophoric and easily get oxidized. Nanocapsules have been developed as dosage form for various routes of administration like oral and parental. Nanocapsules prevents molecules of drug from biological environment and transportation of drug becomes easy through biological barrier. The drug is placed into a cavity which is enclosed by particular polymer membrane which is consist of synthetic polymer. Nanocapsules have submicron size when they take intravenously, they travel towards the target and releases the enclosed drug. It has microscopic size; therefore, they have more capability to take up a considerable range of applications. They are found in the range of 10nm to 1000nm. Nano materials are used in various biomedical, pharmaceutical, electronic and molecular diagnostic fields [11, 12, 13, 14]

Types of Polymers used

1) Natural Polymer

Proteins, enzymes, muscle fibres, polysaccharides and gummy exudates are the natural polymer used in formulation of different pharmaceutical products. Pharmacy and various other fields commonly utilize natural polymers such as chitosan, carrageenan, ispaghula, acacia, agar, gelatin, shellac, guar gum, and gum karaya.[14]

2) Synthetic Polymer

Synthetic polymers are the polymers which are human-made. A various Kinds of synthetic polymers are available which shows variations in main chain and side chains. The main part of common synthetic polymers like polythene, polystyrene and poly acrylates are consist of carbon-carbon bonds, whereas hetero chain polymers like polyamides, polyesters, polyurethanes, polysulphides and polycarbonates are made up of other elements such as oxygen, sulphur, nitrogen and inserted along the backbone. Also, without the need of carbon atoms silicon formulates identical materials, for example silicones through siloxane linkages; that's why these compounds can be called as an inorganic polymer [14]

Methods of Preparation?

1) Polymerization method

2) Interfacial polymerization

3) Arc-discharge method

4) Emulsion polymerization

1) Polymerization method

The monomers are polymerized in an aqueous solution to develop nanoparticles subsequently placing the drug either by dissolving in the medium of polymerization or by the adsorption of nanoparticles. Ultracentrifugation method, which is used for purification of the nanoparticle suspension, separates various stabilizers and surfactants which were previously utilized for polymerization. Then the nanoparticles are resuspended in an isotonic surfactant free medium. It has been recommended for preparing polybutylcyanoacrylate or polyalkylcyanoacrylate nanoparticles. The preparation of nanocapsules and their particle size depends on the consumption concentration stages of the surfactants, physical and chemical stabilizers.

2) Interfacial polymerization

For bulk polymerization of condensation polymers substitute is interfacial polymerization. which would necessitate high temperatures. It includes two non-miscible solvents, in which monomer present in one solvent spontaneously reacts with monomer present in another solvent or it may depend on the time scale. Attaining higher molecular weights of monomers is facilitated by the increased likelihood of encountering a growing chain, as opposed to encountering an opposing monomer. For example, the nanocapsules can be prepared by making use of the aqueous core having oligonucleotides of isobutyl cyanoacrylate present in a W/O emulsion. The final nanocapsules are then decontaminates by ultracentrifugation which is then followed by resuspending in water to obtain a dispersion of aqueous core nanocapsules.

3) Arc-discharge method

Arc-discharge has been hardly ever applied in producing aggregates of self-assembled nanocapsules. The method improved with modified plan in a another new way of producing the aggregates, for instance, by including changes in the hydrogen pressure, bringing up a gadolinium–aluminium alloy (GdAl2) ingot as an anode and maintaining the proportions of elements in the anode as per their evaporation pressures, to synthesize a another type of nanocapsule, with the intermetallic compound GdAl2 which will function as core and amorphous Al2O3 function as shell, that increase the group of magnetic nanocapsules.

4) Other preparation methods involve electron irradiation deposition, Emulsion polymerization, chemical vapour deposition, laser vaporization-condensation, charge transferring, organic reagent assisted method, solution-liquid-solid method and catalytic vapour-liquid-solid growth [11]

Evaluation Parameters [14]

1) X-Ray Diffraction (XRD) studies

Phase analysis of the products is performed by powder XRD on a Rigaku D/max-2000 diffractometer along with graphite monochromatized CuKα (λ = 0.154 056 nm) at a voltage of 50

kV and a current of 250 mA [14]. The XRD pattern shows the phase composition of prepared products.

2) Scanning Electron Microscopy (SEM)

The architecture of the hierarchical branching aggregates, categorised from nano capsules, may be of flocculent structure, small clusters, big clusters and big branches one by one at different scales, which finalize the self-similar characteristics of the structure. It is identified by a Philips XL-30 scanning electron microscope (SEM). It shows the clear morphology of small clusters at a high magnification.

3) Differential Scanning Calorimetry (DSC)

DSC analysis is carried on in both open samples i.e., no lid and closed samples that is pan capped possessing a small hole in the centre.

Both methods have identical thermal behaviour according the observations reported.

4) Transmission Electron Microscopy (TEM)

The carry away of specifically insulin-loaded nanocapsules through the epithelium can be determined by transmission electron microscopy after its oral administration in experimental rats when they are placed for in vitro and in vivo studies. TEM observations shows the intestinal absorption of biodegradable nanocapsules resulting transport of insulin through the epithelium mucosa.

5) High-Resolution Transmission Electron Microscopy (HRTEM)

The detailed morphology of the corresponding nanocapsules tested by use of high-resolution transmission electron microscopy clearly indicates the shell/core arrangement of the nanocapsules. The overall structure of nanocapsules constructing the aggregates is examined using the low-magnification TEM images.

6) X-Ray Photoelectron Spectroscopy (XPS)

X-ray photoelectron spectroscopy measurements are carried out on an ESCALAB-250 with a monochromatic x-ray source (an aluminium Kα line of 1486.6 eV energy and 150 W) to show the valency of surface aluminium atoms present on the nanocapsules at a depth of 1.6 nm. The XPS technique is more specific for the solid surface because of the small range of photoelectrons that are excited. The binding energies of the peaks are had particular characters to each element. The peak areas are used (with equivalent sensitivity factors) to signify the configuration of the surface materials. The appearance of each peak and binding energy slightly varies by the emitting atom of chemical state. XPS technique also gives the chemical bonding information.

7) Superconducting Quantum Interference Device (SQUID)

The magnetic properties of nanocapsules are characterized by use of Quantum Design MPMS-7s or MPMS-5s superconducting quantum interference device. SQUIDs are the most fragile detectors in indicating the little changes in magnetic flux, these take an account to the wide spectrum of application potential of SQUID devices.

8) Multi Angle Laser Light Scattering (MALLS)

Vaults are having capsule-like structure which has very thin shell, size approximately 2 nanometres and it is surrounded by a large internal cavity. The vault particle present in a nanocapsule has an huge potential for compound encapsulation, protection, and delivery. Vault conformation in solution is investigated by using the multi angle laser light scattering to find out the conditions that can stimulate the interconversion of opened and closed conformers. Due to these studies the control of entrapment and release of encapsulated materials is carried out. The vaults which contains binding site for the toxic metals has importance in environment and medical detoxification.

9) FT-IR analysis

The presence of characteristics peaks is confirmed by using the FTIR analysis. The peaks indicate the characteristic functional group of compound.

Advantages of Nanocapsules?

1. Higher dose loading with smaller dose volumes

2. Longer site-specific dose retention

3. More rapid absorption of active drug substances

4. Increased bioavailability of the drug

5. Higher safety and efficacy

6. Improved patient compliance

Uses of Nanocapsules? [15]

1) Nanocapsules as Drug Delivery Systems

Dispersed polymer Nanocapsule can function as Nano-sized drug carriers to obtain controlled release and efficient drug targeting also.

2) Nanocapsules for Targeted Drug Delivery

Scientists in Australia have developed minute Nanocapsules which can be used to target anti-cancer drugs to tumours, sparing other healthy tissue from side effects.

The capsules, which measure about 1 micron across - or 1 thousandth of a millimetre - can be coated with an antibody which directs them from the bloodstream to a tumour.

Once they are in the tumour, a quick blast with a harmless skin-penetrating laser producing near infrared light causes the capsules to open up, discharging their contents.

To make them, a polymer which when added to a suspension of drug particles forms a sphere enclosing the drug, several layers thick.

3) Future Nanocapsule Bandages to fight infection

Nanocapsules bandage might also be used for other types of wounds, such as ulcer and even by the military on the battlefield.

The medical dressing will release antibiotics from Nanocapsules, activated by the presence of disease-causing pathogenic bacteria, targeting treatment before the infection aggravates.

4) Liposomal Nanocapsules in Food Science and Agriculture

Liposomes, spherical bilayer vesicles from dispersion of polar lipids in aqueous solvents, have been widely studied for their ability to act as drug delivery vehicles by shielding reactive or sensitive compounds prior to release.

Liposome entrapment has been shown to stabilize encapsulated, bioactive materials against a range of environmental and chemical changes, including enzymatic and chemical modification, as well as buffering against extreme pH, temperature, and ionic strength changes.

5) Magnetic Nanocapsules for Smart Drug Delivery

By combining peptide-based polymers with modified iron oxide Nanoparticles, researchers have developed

Nanoparticles that can be manipulated in a magnetic field and that can respond to changes in pH and other physiologic stimuli.

These Nanoparticles, which can be modified to include targeting molecules, could serve as a versatile, smart platform for delivering drugs and imaging agents to tumours.

6) Nanocapsules Delivers Radiotherapy

Using this method, the team was able to create Nanocapsules that could deliver a highly concentrated dose of radiation (800% ionizing dose per gram) of the kind needed for radiotherapy.

Even after a week in the body the Nanocapsules remained stable without any significant leaking of radiation beyond the lung.

7) Nanocapsules with Functionalized Surfaces and Walls

With the possibility of creating and handling nanometre-sized objects, it became popular to dream of future miniaturized tools allowing completely new applications in medicine and technology.

8) New Cancer Weapon-Nuclear Nanocapsules

Chemists have found a way to package some of nature's most powerful radioactive particles inside DNA-sized tubes of pure carbon -- a method they hope to use to target tiny tumours and even lone leukaemia cells.

9) Nanocapsules for Self-Healing Materials

Damage in polymeric coatings, adhesives, microelectronic components, and structural composites can span many length scales.

Repair of large-scale damage (e.g., a projectile or blast is difficult and, when possible, requires use of bonded composite patches over the effective area.

For smaller scale crack damage, however, a novel method of autonomic repair has been achieved through the use of self-healing polymers Microcapsules that contain the healing agent must possess adequate strength, long shelf-life, and excellent bonding to the host material.

10) Polymer-based Nanocapsules for Drug Delivery

A review of the state of knowledge on Nanocapsules prepared from preformed polymers as active substances carriers is presented.

This entails a general review of the different preparation methods: Nano precipitation, emulsion-diffusion, double emulsification, emulsion-coacervation, polymer-coating and layer-by-layer, from the point of view of the methodological and mechanistic aspects involved, encapsulation of the active substance and the raw materials used.

11) Preparation of Biodegradable Insulin Nanocapsules from Biocompatible Micro emulsions

Interfacial polymerization of spontaneously forming water-in-oil micro emulsions represents a convenient method for the preparation of poly (alkylcyanoacrylate) Nanocapsules suitable for the entrapment of bioactive peptides.

Recent Advancement by Nano technology in the Glucose Sensing:

It is clear that efficient diabetes care depends on the creation of reliable and frequent glucose sensors. Although current clinical glucose measurement techniques are accurate, numerous needle sticks and intermittent testing, which may miss dangerous variations in blood glucose levels, can be uncomfortable and painful for patients. The development of glucose sensors that can do precise, continuous, and painless glucose measurements is thus the biggest issue in diabetes research. In the past two decades, researchers have investigated a variety of glucose sensing techniques, frequently using Concanavalin A (Con A), phenylboronic acid (PBA), or Glucose Oxidase (GOx) as sensors to detect glucose in solution. However, it might be difficult to measure solely glucose in solution due to typical interfering species found in human fluids such uric and acetic acids, as well as other carbohydrates like fructose, lactose, and sucrose. There are two types of glucose measurement systems: electrical and optical. [16, 17, 18, 19]

Using hydrogen peroxide (H2O2) or other reduced species as a chemical bridge to induce the reduction of another species and produce a detectable signal is one popular technique for detecting glucose. While very simple sensor operation and characterization are advantages of hydrogen peroxide-based detection, negatives include the degenerative effects of hydrogen peroxide on the sensor and the potential for sensor interference. As nanoscale carbon structures exhibit good conductivity and catalytic capabilities, numerous electrical-based H2O2 sensors have been created or modified for glucose monitoring. Researchers have immobilized GOx in carbon nanoscale structures, particularly carbon nanotubes, and altered the electrical resistance of the structures dependent on how active the immobilized GOx was in response to the injection of glucose. Accurate glucose readings have been made possible by the coupling of nanoparticles like graphene and gold nanoparticles with GOx in nanocomposite materials. These materials have demonstrated synergistic interactions and better electrocatalyzation of hydrogen peroxide and oxygen. [20, 21, 22, 23]

To protect glucose sensors from interfering chemical species, many tactics have been used. To avoid interference and contamination of the glucose signal, some groups have utilized thin Nafion films or nanoporous membranes with selected pore sizes. Furthermore, enzyme-free techniques have been created, such as the direct detection of glucose using cobalt nanowires or silicon nanoparticles. Moreover, continuous glucose monitoring has proven to be a useful strategy since it makes it possible to detect both rising and falling glucose levels, improving the sensor's reversibility. By boosting catalytic activity, reducing detection limits, and increasing sensitivity, nanotechnology significantly contributes to the improvement of glucose sensors. [24, 25, 26, 27, 28, 29]

Finally, nanosensors and nanomaterials have showed great promise in improving glucose detection for the treatment of diabetes. The sensitivity, specificity, and reversibility of glucose sensors have all increased thanks to the use of nanoscale carbon structures, nanocomposites, and other nanomaterials. This has helped to overcome some of the issues in modern diabetes management. Nanosensor-based continuous glucose monitoring has the potential to change diabetes care by delivering precise and painless glucose readings for better disease management and patient outcomes. [31, 32]

Table 1: List of systems reported for measuring glucose:

Type	Detection Principle	Response Time	Detection Limit	Reference
Optical	Nanotube Near-IR emission	~1 min	34.7 μM	23
Optical	Nanotube Fluorescence Enhancement	~1 min	2.5 mM	28
Optical	Fluorescence Enhancement and AuNP Growth	30–60 min	0.01 mM (QDs); 0.1 mM (AuNPs)	8
Optical	Graphene Catalytic Activity	1h	1 μM	37
Optical	Nanotube Fluorescence Enhancement	~1 min	5 mM	29
Optical	Raman spectroscopy	~10 min	0.5 μM	6
Optical	Hydrogel Mediated Bragg Diffraction	5 min	90 μM	11
Optical	Protein FRET signal	~1 min	25 μM	9
Electrical	Nanotube conductance modulation	~20 s	0.1 mM	24
Electrical	Hydrogen Peroxide catalysis via Nanotubes	<20 s	0.08 mM	25
Electrical	Hydrogen Peroxide catalysis	<5 s	1.5 μM	18
Electrical	Hydrogen Peroxide catalysis via AuNPs	<30 s	180 μM	17
Electrical	Nanomaterial enhanced conductance modulation	<20 s	0.5 μM; 5 μM	27
Electrical	Nanomaterial enhanced conductance modulation	<20 s	0.56 mM; 0.26 mM	30
Electrical	Enzyme-free glucose catalysis	<20 s	<25 nm	22
Electrical	Nanoparticle catalysis of Hydrogen Peroxide	3 s	0.7 μM	32
Electrical	Enzyme-free glucose catalysis	<20 s	1 mM	21
Magnetic	Shift in magnetic resonance of a membrane	<1 min	--	34

Recent Advancement in the treatment of Diabetes Mellitus:

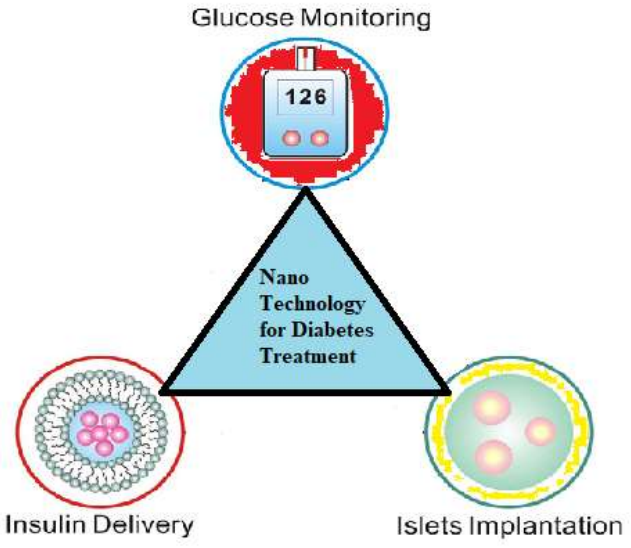

Figure 2: Research themes employing nanotechnology to cure diabetes are depicted schematically.

In the study conducted by Yue Cheng and his colleagues, novel cryopreservation technology was used to prepare colon responsive nanocapsules. Islet transplantation has been one encouraging strategy in diabetes treatment, which can sustain patient's insulin level long-term and avoid periodical insulin injections but shortage of donor temporal mismatch between donors and recipients has limited its use. Which leads to this research for islet substitutes and developing efficient cryopreservation technology. In this search a novel cryopreservation method was developed for islet β cells by combining microfluidic encapsulation and cold-responsive nanocapsules. Unlike from traditional cryopreservation methods, this method combining the cold-responsive nanocapsules and hydrogel encapsulation replaces the toxic cryoprotectants with natural trehalose. The preservation outcomes are impressive, and subsequent transplantation trials on diabetic rats further validate the remarkable glucose regulation capability of these hydrogels containing β cells after cryopreservation. This novel cryopreservation method aids to establish a reliable and ready-to-use bank of biological samples for transplantation therapy and other biomedical applications and also provides an alternative strategy for islet transplantation and has great potential in other cell-based applications [33]

The study named "Size Effect on Lipid Nanocapsule-Mediated GLP-1 Secretion from Enteroendocrine L Cells" looks into how nanoparticle size affects the secretion of glucagon-like peptide-1 (GLP-1) by enteroendocrine L cells. GLP-1 is a peptide with major physiological significance that is released by L cells, enteroendocrine cells found throughout the gastrointestinal system. GLP-1 is immediately released into the bloodstream after dietary treatment and is essential for controlling hyperglycemia

Lipid nanocapsules (LNCs) of five different sizes were tested on murine L cells in vitro to test this theory. The sizes that were put to the test were 25, 50, 100, 150, and 200 nm. The outcomes demonstrated that only the 200 nm size LNCs were able to trigger GLP-1 secretion. The significance of the relationship between LNC particle size and GLP-1 production from L cells is highlighted by this research.

The study also showed how 200 nm LNCs affected normoglycemic mice in vivo. as given to mice, the 200 nm LNCs significantly raised GLP-1 levels by four times and three times, respectively, after 60 and 180 minutes after delivery as compared to untreated control mice. It's interesting to note that the various LNC formulations had no effect on the expression of proglucagon mRNA, proving that the observed increase in GLP-1 secretion was not the result of improved GLP-1 synthesis.

The results imply that GLP-1 secretion from enteroendocrine L cells is significantly stimulated by the size of lipid nanocapsules. Particularly, the 200 nm LNCs shown great potential as therapeutic candidate nanocarriers by inducing endogenous GLP-1 secretion. In type 2 diabetes mellitus, where GLP-1-based medications are essential for treating the illness, this approach shows potential.

The research advances knowledge of nanoparticle-based drug delivery systems and offers insightful advice on how to create efficient carriers for incretin-based diabetes treatment. The development of oral peptide delivery methods that are more effective and focused could lead to better patient outcomes and treatment choices for type 2 diabetes mellitus with further research into lipid-based nanoparticles with optimal sizes. [34]

Fatemeh Shamekhi and his colleagues developed chitosan coated calcium-alginate nanocapsules for oral delivery of liraglutide to diabetic patients. The result of coating components including sodium alginate, calcium chloride, and chitosan concentrations on the particle size was studied based on response surface methodology. Dynamic light scattering, scanning and transmission electron microscopy was used to characterize the beads and it showed that the diameter of the beads depends on the encapsulation technique and alginate concentration. SEM showed spherical and smooth particles of up to 100 nm diameter and optimum composition of alginate 0.5%, chitosan 0.5% and calcium chloride 0.5% in the volume ratio of 3:1:1 was found by all the characterization. The prepared bead formulation had a loading efficiency of 92.5% and loading capacity of 54.16 %. Prepared nanocapsules showed stability of 92.4% and 72.3% over freeze drying and subsequent 60 days storage at 4°C, respectively. In-vitro release studies in simulated gastrointestinal conditions showed drug release of 59.1% after 6 hours. This study demonstrated that chitosan coated calcium-alginate nanocapsules hold promise as a prospective natural biodegradable polymerbased oral carrier of liraglutide for better management of diabetes. [35]

The investigational study was done to prepare Nanoencapsulation of Insulin into Zirconium Phosphate by Agustın Dıaz and is colleagues. This study shows a new approach for protein nanoencapsulation using layered zirconium phosphate (ZrP) nanoparticles produced without any preintercalator present. The use of ZrP without preintercalators gives a highly pure material, without any kinds of contaminants, such as the preintercalator, which can be noxious. The in vitro release profile of the hormone later the intercalation was resolute and circular dichroism was used to study the hormone stability upon intercalation and release. The insulin remains stable in the layered material, at room temperature, for a significant amount of time, improving the shell life of the peptidic hormone. The hormone remains stable during the whole process and does not appear to have any significant chemical or structural changes over a period of time (up to six months). This kind of material characterizes a strong candidate to developing a noninvasive insulin carrier for the treatment of diabetes mellitus [36]

The work described in the article "Metformin-loaded alginate nanoparticles as an effective antidiabetic agent for controlled drug release" focuses on creating a novel drug delivery method to overcome the drawbacks of existing diabetes treatment modalities. Through the use of metformin-loaded alginate nanoparticles (MLANs), the research intends to better patient outcomes, decrease resistance, and improve drug absorption.

Hydrophilic medication metformin has a high solubility but has subpar absorption properties. To help metformin's intestinal permeability and gastrointestinal absorption, the researchers employed alginate nanocapsules made using an emulsion cross-linking technique. Transmission electron microscopy (TEM), Fourier transform infrared (FTIR) spectroscopy, and photon correlation spectroscopy (PCS)-based particle size analysis were all used to characterize the MLANs.

The amount of metformin added to 100 mg of nanoparticles (i.e., the drug loading and encapsulation efficiency in MLANs) were 3.12 mg and 78%, respectively, according to key findings. Studies on the sustained drug release from MLANs in vitro showed that this occurs over time. Furthermore, compared to pure metformin, MLANs demonstrated improved efficiency and responsiveness in in-vivo efficacy studies utilizing animal models. At the same dosage, it was discovered that MLANs had around three times the efficacy of pure metformin.

The study demonstrates the potential of metformin-loaded alginate nanoparticles as an efficient antidiabetic agent with controlled drug release, which could address the drawbacks of existing diabetes treatments, such as erratic absorption, high dosage requirements, and patient-to-patient variability. [37]

In a study Lungile Nomcebo Thwala, designed a polymer nanocapsules (NCs) intended for the oral delivery of insulin glulisine. Peptides represent an encouraging therapeutic class with the potential to alleviate many severe diseases. A key restraint of these active molecules relies on the difficulties for their efficient oral administration. The polymer shell of the NCs was made of a single layer of protamine, a cationic polypeptide selected for its cell penetration properties, otherwise a double protamine/polysialic acid (PSA) layer. The solvent displacement method was used for the preparation of these nanocapsules. Showed a size that varied in the range of 200-400 nm and a neutral surface charge (from +8 mV to -6 mV), depending on the formulation. Colloidal stability studies were also did in simulated intestinal media containing enzymes and the results showed that protamine NCs were stable and able to protect insulin from the harsh intestinal environment, and that this property could be further improved with a double PSA-Protamine layer. These nanocapsules were freeze-dried and stored at room temperature without changing of the physicochemical properties. When the insulin-loaded protamine NCs were administered intra-intestinally to diabetic rats (12 h fasting) it resulted in a extended glucose reduction (60%) as compared to the control insulin solution. This work raises scenarios that protamine nanocapsules may have a potential as oral peptide delivery nanocarriers [38]

The article "Insulin-Delivery from Glucose-Responsive Self-Assembled Polyamine Nanoparticles: Smart 'Sense-and-Treat' Nanocarriers Made Easy" introduces a unique method for creating smart nanocarriers for the delivery of insulin in the management of diabetes mellitus. The work focuses on polyamine-salt aggregates (PSA), bioinspired soft materials renowned for their excellent drug-loading efficiencies and pH-triggered release characteristics.

Cross-linked poly(allylamine hydrochloride)/phosphate PSAs (GI-PSA) with a hydrodynamic diameter of 360 nm were made by the researchers using a quick and easy multicomponent self-assembly procedure. The human recombinant insulin was used as the therapeutic drug, and the glucose oxidase enzyme served as a glucose-responsive element in these nanocarriers.

These clever nanocarriers' capacity to adapt to shifting glucose concentrations is a key innovation. The catalytic production of gluconic acid by glucose oxidase causes the disassembly of the GI-PSAs in response to rising glucose levels. As a result, this disassembly encourages the release of insulin and makes it possible for a "sense-and-treat" mechanism to distribute insulin.

The integrity of the GI-PSAs lasts for at least 24 hours in normoglycemia, the presence of normal blood glucose levels. But after 4 hours of glucose administration, there is a quick and full release of insulin under hyperglycemic circumstances.

The development of glucose-responsive delivery nanocarriers shows tremendous potential when using the completely supramolecular approach used in this study. With a focused and adjustable insulin release mechanism that reacts to the patient's blood glucose levels, this strategy offers a potential breakthrough in the treatment of diabetes.

This article's research offers insightful information on the creation of nanocarriers with "sense-and-treat" characteristics, which have the potential to transform insulin therapy for people with diabetes. [39]

The article "Targeted nanoparticles towards increased L cell stimulation as a strategy to improve oral peptide delivery in incretin-based diabetes treatment" examines a novel way to improve oral peptide administration for the treatment of diabetes while concentrating on the incretin system. It has been extremely difficult for the pharmaceutical industry to administer therapeutic peptides orally. The researchers want to address this issue by creating a drug delivery system based on lipidic nanocapsules.

The efficacy of various fatty acid-targeted lipid and polymeric nanoparticles to stimulate L cells, which are involved in the release of glucagon-like peptide-1 (GLP-1), a crucial hormone for glucose management, was studied in the study. Due to its ability to improve insulin secretion and lower blood glucose levels, GLP-1 is a crucial component of incretin-based diabetes treatment.

The most encouraging outcomes were shown using lipid-based nanocarriers that had been surface-modified with DSPE-PEG2000. The biological impact of these targeted nanocarriers was greatly enhanced, resulting in an up to 8-fold increase in endogenous GLP-1 levels in normoglycemic mice. Additionally, after a month of treatment, they successfully extended the antidiabetic benefit in obese/diabetic mice.

The research shows the promise of these focused nanocarriers in enhancing the oral transport of therapeutic peptides, particularly GLP-1 analogues, for the treatment of diabetes. This nanocarrier-based approach to treating incretin-based diabetes shows promise due to the increased GLP-1 secretion and increased bioavailability of the encapsulated peptide. The targeted nanocarriers were also efficient even when administered less often, suggesting potential advantages for patient compliance. The results of this study offer important new perspectives on the creation of nanocarriers for precise and effective oral peptide administration in the treatment of diabetes. Through the provision of a more practical and efficient substitute for existing treatments, the technique has the potential to improve patient outcomes. The study promotes additional research into the creation of novel nanomaterials for the diagnosis and treatment of diabetes and offers up new avenues for therapies in the field of diabetes. [40]

Conclusion:

The stability, secretion, and therapeutic efficacy of therapeutic peptides, such as GLP-1 analogues, for the treatment of diabetic mellitus, can all be improved with the use of lipid-based targeted nanoparticles for oral peptide delivery. In preclinical investigations using normoglycemic and obese/diabetic mice, these targeted nanocarriers exhibit enhanced endogenous GLP-1 levels and extended antidiabetic effects when the surface is changed with particular substances, such as DSPE-PEG2000. The study also emphasizes the significance of nanoparticle size in affecting GLP-1 production from enteroendocrine L cells, offering prospective applications in the management of type 2 diabetes mellitus. The use of these tailored nanocarriers offers a viable technique to enhance patient compliance and diabetes management by addressing the difficulties associated with oral peptide medication delivery for the treatment of diabetes caused by adverse circumstances in the gastrointestinal system. In addition to improving the stability and effectiveness of therapeutic peptides like GLP-1, these nanocarriers offer design freedom and special in vivo features to get around obstacles to cellular and tissue absorption.

These nanocarriers provide design flexibility and unique in vivo properties to get around barriers to cellular and tissue absorption, in addition to enhancing the stability and efficiency of therapeutic peptides like GLP-1. As a viable drug delivery technology for the oral administration of therapeutic peptides, notably in the treatment of diabetic mellitus, targeted lipid-based nanoparticles show tremendous potential. These developments could result in better diabetes management, greater patient compliance, and less frequent delivery, providing a fresh way to boost the effectiveness of diabetic treatment. However, more investigation and clinical studies are required to confirm and use these findings in real-world clinical settings.

Conflicts of Interest: Nil

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