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Emerging Trends of Nanotechnology in Type 2 Diabetes Mellitus Treatment

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Diabetes mellitus (DM) also know as Type 2 diabetes is widely escalating chronic disease in developed countries. DM is most common in elder person and it is characterized by altered blood sugar homeostasis. Once diabetes related problems marked, they tend to be permanent and challenging to treat effectively. At present, no effective treatment are available in market for diabetes. The conventional treatments are expensive and pose several shortcomings. Therefore the treatment and prevention of DM and its complications have become major health concerns now days. Admit this health crisis, nano-based antidiabetic therapeutics has emerged as a promising path for address various issues associated with diabetes. Over the past few years, scientists have increasingly used nanotechnology for development of effective antidiabetic therapeutics. Various nanocarriers such as nanoparticles (NPs), liposomes, carbon nanotubes, nanoemulsions, and micelles are the potent transporter of hypoglycemic drug which paved the way for effective diabetes management. These nano-transporters are more effectively control the blood sugar level and enhance bioavailability, specificity, absorption, and biocompatibility compared to traditional therapeutics approaches. This work mainly focuses on nanomaterials, nanocarriers, synthesis of nanoparticles, and therapeutic application of nanotechnology for the management of diabetes. Future trends are also emphasized for effective nano formulation of antidiabetic drugs as an ultimate therapy.
Keywords: Diabetes Mellitus, Nanoparticles, Nanocarriers, Glucose.

1. Introduction

Diabetes is a metabolic disorders and it is a critical challenge to global health [1]. Diabetes is not only originator to kidney and heart problems but also significantly increase susceptibility to various infections. Literature review revealed that persons suffering from diabetes face larger mortality threats from COVID-19. Accordingly, the COVID-19 pandemic has highlighted the significance of addressing impacts on individuals with diabetes, demanding a deeper discovery of advanced science and technology, such as nano-drug and nanotechnology.

Diabetes mellitus (T2DM) is a widespread chronic metabolic illnesses marked by insulin resistance and impaired insulin secretion or both leading to hyperglycaemia [2]. The lifestyles, unhealthy diets, obesity and many others factor are the reasons for fundamental rising mortality of T2DM. The International Diabetes Federation (IDF) predicts that occurrence of diabetes is projected to increase extensively over the years. It is expected to affect about 693 million persons by 2023 and 783 million persons by 2045 [3]. WHO predict that the diabetes mortality rate is approximate to 1.5 million worldwide in every year [4]. WHO practiced that if the occurrence of diabetes is increasing at the current rate it becoming the 7th leading cause of death by 2030 [5]. The long-term consequences of T2DM's drastically impact the patients' quality of life and increased healthcare expenses. The treatment and management of diabetes involves the conventional pathways through modulation of diet, physical workout, and suitable medicine (Fig. 1) [6]. Sodium-dependent glucose transporters (SGLT-2) and a-glucosidase inhibitors, biguanides, thiazolidinediones, sulfonylureas, and insulin preparation are commercially available for diabetes treatment [7].

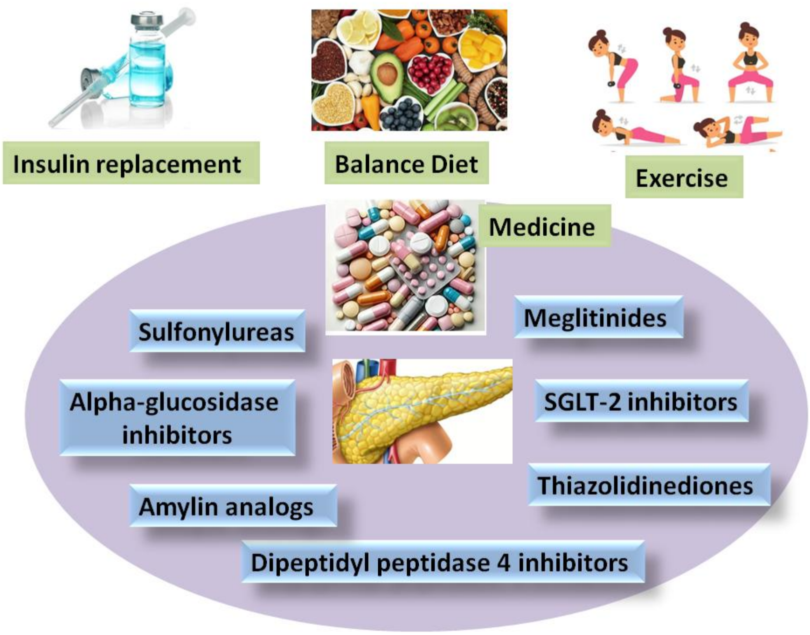

Fig. 1 Different approaches for management of diabetes

While these categories of medicines have shown some efficacy, but they also have some limitations like poor patient compliance, suboptimal drug delivery, and potential adverse effects [8]. Subsequently, scientist and researchers have been working on innovative and targeted strategies to address the challenges in T2DM treatment. Nanotechnology has emerged as a promising field that holds great potential in management of T2DM [9]. Scientists have begun to develop novel nanocarriers for diabetes management by developing the nanoscale materials with unique properties. These advancements in nanotechnology field offer thrilling opportunities to enhance drug delivery, improve glucose monitoring, and provide innovative solutions for T2DM complications [10].

Nanomaterials/nanoparticles in diabetes therapeutics

Nanoparticles are smaller circular biologically compatible and biodegradable particles of 100–300 nm size containing drugs. Nanoparticles act as drug carriers that deliver the drug at site of action by protecting from environmental condition. It can be administered by oral or parenteral routes. Polymeric nanoparticles, polymeric nanocapsules, liposomes, and lipid nanoparticles are generally used for diabetes treatment [11] (Figure 2).

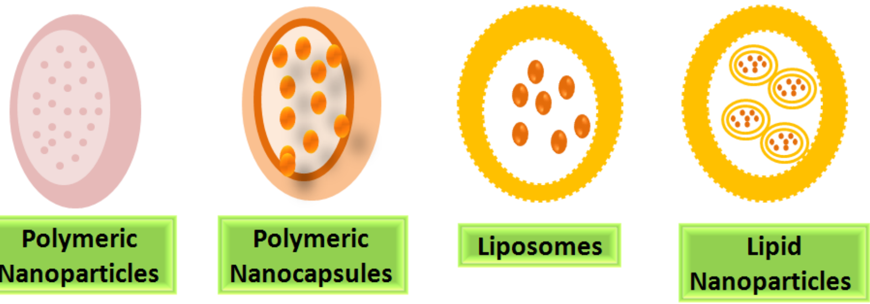

Fig. 2 Schematic representation of the main types of nanoparticles used in the management of diabetes

Nanocarriers for Drug Delivery for Type 2 DiabetesNanotechnology has shown great promise in improving the delivery of oral hypoglycemic drugs, which are commonly used to manage Type 2 Diabetes (T2DM) [12, 13]. Nanocarriers are nano-sized delivery systems that can encapsulate and protect drugs, enhancing their efficacy, bioavailability, and targeted delivery. In the context of T2DM, nanocarriers offer several advantages for drug delivery, making them a promising approach in diabetes management [12]

There are several advantages of nanocarrier-based drug delivery:

a) Improved Bioavailability

Nanocarriers can protect drugs from degradation in the gastrointestinal tract and improve their absorption, resulting in higher drug bioavailability [14].

b) Enhanced Targeting

Nanocarriers can be designed to target specific tissues or cells, such as pancreatic beta cells or insulin-resistant tissues, thereby increasing drug delivery to the desired sites of action [15].

c) Reduced Side Effects

By targeting drug delivery to specific tissues, nanocarriers can minimize off-target effects, reducing side effects and improving patient tolerability [16].

d) Sustained Release: Nanocarriers can provide controlled and sustained drug release, leading to more stable and prolonged therapeutic effects, reducing the frequency of drug administration [7].

Lipid-Based Nanocarriers

a) Solid lipid nanoparticles (SLNs)

Solid lipid nanoparticles have emerged as a promising nanotechnology-based approach for diabetes management. These nanoparticles are composed of biocompatible lipids and offer several advantages, including improved drug delivery, enhanced stability of encapsulated drugs, and reduced toxicity compared to traditional drug delivery systems [18]. For, e.g., Ansari et al., have formulated insulin-loaded solid lipid nanoparticles to enhance the bioavailability of insulin [19].

b) Lipid-based nanocapsules

Lipid-based nanocapsules have shown promise as a delivery system for various therapeutic applications, including diabetes treatment. These nanocapsules are typically composed of a lipid bilayer that encapsulates the therapeutic agent, such as insulin or other antidiabetic drugs. Such nanocapsule had been made by Xu et al., for the oral delivery of peptides [20].

c) Liposomes

Liposome is phospholipids bilayers vesicles contain aqueous phase. Liposomes are use for administration of both hydrophilic and hydrophobic drug [21].

Polymeric Nanocarriers

a) Polymer based nanoparticles (NPs)

Polymeric nanoparticles are solid polymer matrices made up of biodegradable plymer in which drug particles are spread uniformly. Polymeric NPs protect the drug from enzymatic degradation. Polymeric nanoparticles improved the solubility and bioavailability of oral hypoglycemic agent [22]. Damge et al., have formulated polymeric NPs for the oral delivery of insulin [23].

b) Polymer based nanocapsules

Polymeric nanocapsules shell contains made up of serum albumin protein which are cross-linked together and contain liquid phases. Cross linking of protein avoid solubilisation at the site of administration body fluids. For lipophillic drug nanocapsules contain hydrophobic liquid vegetable oils, while for hydrophilic drug nanocapsules shell made of PLA and PLGA and contains aqueous liquid phase. Aqueous liquid phase are use for insulin and other hydrophilic biological preparation [24].

c) Micelles

Micelles are colloidal structures formed by self-assembly of amphiphilic molecules in aqueous solutions. They have a hydrophilic shell and a hydrophobic core, making them suitable for encapsulating poorly water-soluble drugs [25]. Micellar nanocarriers have shown promise in enhancing the oral delivery of antidiabetic drugs, optimizing drug absorption, and reducing dosing frequency. Singh et al., have designed Quercetin enveloped Soluplus®/P407 micelles in diabetes treatment [26].

1.1. Others

Gold, silver, and zinc nanoparticles are being investigated for their potential in diabetes treatment. These nanoparticles can be functionalized with insulin and other diabetes-related drugs for improved delivery. Some formulations are enlisted in Table 1.

Table 1. Different types of nano-formulations for type II diabetes care.

Formulation Type	Objective	Mechanism/Evaluation	Outcome	Ref.
Solid lipid NPs (SLNs)	Development and assessment of an effective oral insulin administration SLN carrier	Particle size, polydispersity index (PDI) and drug entrapment	❖ Insulin-loaded SLNs had five times the bioavailability of insulin solution, indicating improved gastrointestinal protection. ❖ Loaded in SLN, insulin bioavailability was five times that of pure insulin solution.	[27]
	To manufacture and characterize cetyl palmitate-based SLN encapsulating insulin and assess their oral administration capability	Unloaded and insulin-loaded SLN particle size, zeta potential, and association efficiency	In diabetic rats, oral insulin-loaded SLN caused significant hypoglycemia for 24 h. SLN improved oral insulin absorption	[28]
	To investigate the inclusion of the weakly water-soluble medication glibenclamide (GLB) into SLNs, which gives longer drug release and enhanced oral bioavailability	Pharmacokinetic, pharmacodynamic, histological studies of optimized SLNs	❖ Optimized SLNs reduced blood glucose levels in rats with a rapid onset time (0.5 h) and long duration (24 h). ❖ SLNs of GLB had beneficial effects in controlling diabetes in diabetic rats.	[29]
Nanocapsules	To create a novel medication delivery nanosystem to increase GLP-1 production and peptide absorption to treat type 2 diabetes.	In vitro in testing in human L-cells (NCl-H716) and murine L-cells. In vivo tested in high-fat diet-induced diabetic mice following acute or chronic treatment (5 weeks) in obese and diabetic mice.	This nanosystem secretes GLP-1 in human and murine cells and animals in vivo. This method improves endogenous GLP-1 secretion and oral bioavailability of the GLP-1 analogue exenatide.	[30]
	An enhanced oral peptide delivery technique using a lipidic nanocapsule.	Compared fatty acid-targeted lipid and polymeric NPs and assessed L cell activation in murine L cells in vitro. Oral administration frequency and antidiabetic efficacy in vivo.	❖ Increased endogenous GLP-1 levels in vivo. ❖ Normalizing plasma glucose levels prolonged the in vivo anti-diabetic impact. ❖ When administered every other day, tailored nanocarriers were equally effective.	[31]
Polymeric NPs Natural: polysaccharides (chitosan, sodium alginate, hyaluronic acid) and proteins (serum albumin, gelatin, keratin). Synthetic:	For oral insulin delivery, poly(-ε-caprolactone) and Eudragit® RS NPS have been utilized	Oral insulin nanoparticles (25, 50, and 100 IU/kg) were tested in diabetic rats for therapeutic efficacy	❖ Polymeric NPs preserve insulin's biological action. ❖ Insulin NPs raised serum insulin levels and delayed the glycemic response to an oral glucose challenge.	[32]
	Development of dual-responsive (glucose and pH) oral insulin delivery nanocarrier	NPs of modified guar gum those are sensitive in two ways (esterification and amidation)	Dual-responsive NPs protect insulin from digestive tract pH changes and	[33]

polylactic acid, poly lactic-co-glycolic acid, polyethyleneimine			transport insulin to the body for hypoglycemic effects	
Micelles	Formulation of Quercetin-loaded Soluplus® micelles (SMs) for diabetes control to improve bioavailability and release.	Box–Behnken response surface approach optimized cosolvent evaporation formulation.	Enveloping the medication in SMs increased bioavailability in the in vivo pharmacokinetic study.	[26]
	Creation of Polysaccharide-based micelle-hydrogel	Single electron transfer living radical polymerization produced micelles.	The micelle-hydrogel synergistic therapy method treats diabetes and vascular diabetes complications.	[34]
Gold NPs	Evaluation of the anti-diabetic characteristics of Datura stramonium seed-derived gold nanoparticles	Evaluation of in vivo study.	Gold nanoparticles (AuNPs) reduce blood sugar levels.	[35]
	Evaluation of Gymnema sylvestre gold nanoparticles (AuNPs) in diabetes	AuNPs synthesized from Gymnema sylvestre R. Br have anti-diabetic action in wistar albino rats.	Significant reduction in blood glucose level on diabetic rats.	[36]
Silver NPs	Evaluation of Solanum nigrum leaf extract loaded in silver nanoparticles against diabetes	Alloxan-induced diabetic rats tested photosynthesized AgNPs for anti-diabetic efficacy.	❖ Improved dyslipidemic condition. ❖ Reduced the blood glucose level.	[37]
Zinc NPs	Evaluation of biological efficacy of zinc oxide nanoparticles against diabetes	Evaluation of in vivo study with streptozotocin (STZ) mice.	Reduction in blood glucose levels (approximately 25.13 and 29.15%)	[38]

2. Conclusion and future perspective

A. Personalized Nanomedicine:

Tailoring nanotherapeutics: Nanotechnology enables customized diabetes treatments based on individual characteristics, optimizing drug delivery and minimizing side effects.

Nanoparticle-based insulin delivery: Innovative insulin delivery systems using nanoparticles offer precise glucose control, potentially replacing conventional injections.

B. Nanotechnology and Artificial Pancreas Development:

Continuous glucose monitoring: Nanosensors integrated with monitoring technology enable real-time and minimally invasive glucose level tracking.

Closed-loop insulin delivery: Nanotechnology-driven closed-loop systems mimic a healthy pancreas, autonomously adjusting insulin delivery for better glucose management.

Nanotechnology offers transformative possibilities in Type 2 diabetes management, enabling personalized nanomedicine for improved drug delivery and precise glucose control. The integration of nanosensors and nanocarriers in artificial pancreas systems holds the potential to revolutionize diabetes care, enhancing patients' well being and treatment outcomes. Nanotechnology holds immense promise in revolutionizing Type 2 diabetes management through personalized medicine, improved drug delivery, and advanced glucose monitoring. While various nanocarriers and nanosensors offer potential benefits, addressing safety concerns and regulatory challenges will be crucial for successful clinical translation. Embracing these advancements will propel diabetes care towards a more effective, patient-centric future, enhancing overall well being and reducing the burden of the disease.

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