An analysis of recent nanotechnology-based treatments for diabetes mellitus and their management

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Abstract- The Egyptians are credited with originally describing diabetes, which is defined by polyuria and weight loss. However, the term diabetes mellitus (DM) was first used by the Greek doctor Aertaeus. Diabetes means "to pass through" in Greek, while the Latin term for honey (which denotes sweetness) is mellitus. The World Health Organisation (WHO) estimates that DM affects more than 346 million people worldwide. By 2030, if nothing is done, this number will likely have more than doubled. In low- and middle-income countries, diabetes fatalities account for about 80% of all deaths. According to a WHO study, India, which currently has more than 32 million diabetic patients worldwide, will have 79.4 million by the year 2030. In India and Sri Lanka, diabetes now affects a surprising 10-16% of the urban population and 5-8% of the rural population, according to recent assessments.

Nanotechnology is a recent and important technology in the twenty-first century. In this branch of science and technology, materials are made from lone atoms and molecules. It examines the properties and applications of substances with structures varying in size from 0.1 to 100 nm. The arrangement and fusion of various particles results in the creation of a new configuration of matter. Today, a wide range of sectors and professions, including those in the fields of health, materials science, electrical engineering, and the energy sector, among others, use nanotechnology significantly.

Keyword: Diabetes Mellitus (DM), Managing, Nanotechnology, Quality of Life (QoL)

INTRODUCTION

Around the world, approximately 171 million people have diabetes mellitus (DM), and by 2030, that figure is expected to increase to 366 million. Deficiencies in insulin secretion or poor insulin action result in a group of chronic metabolic diseases known as diabetes. (1). The metabolic illnesses known as diabetes mellitus affect the metabolism of proteins, lipids, and carbohydrates. It is characterized by persistent hyperglycemia, which can be brought on by errors in insulin secretion, insulin action, or a combination of both errors in insulin secretion and actions. Diabetes mellitus comes in two basic varieties: type 1 (insulin-dependent) and type 2 (non-insulin-dependent). Type 1 diabetes is brought on by the autoimmune destruction of the pancreatic islet -cells, while type 2 diabetes is brought on by decreased insulin secretion and resistance to the effects of insulin. According to recent epidemiological data, 9% of adults who are 18 years of age and older have diabetes mellitus, and the disease is thought to have killed 1.5 million people in 2012 (2). Diabetes mellitus is highly prevalent in India, and the rate of growth is concerning. By 2030, there will be 79.4 million people living with diabetes worldwide, up from 40.6 million in India alone in 2006. According to studies, Type 2 diabetes is four to six times more common in urban than in rural areas, and it affects roughly 12.1% of adult Indians living in cities. This is a decade earlier than it does in western countries. High family aggregation, central obesity, insulin resistance, and lifestyle changes brought on by urbanization are among the risk factors particular to developing diabetes among Indians. Pregnant women should be screened for gestational diabetes and impaired glucose tolerance since this opens the door to primary prevention of the illness in both mothers and babies (3). Men are slightly more likely than women to have diabetes mellitus, and the prevalence is rising across all age categories. The likelihood of being diagnosed with depression among type 2 diabetes patients is one in four, which is five times more likely than it is in the general population. Chronic, non-communicable type 2 diabetes mellitus can cause major long-term consequences, including abnormalities of the heart, blood vessels in the legs, eyes, brain, kidneys, and reproductive system. Depression worsens the prognosis for diabetic patients by raising the frequency of diabetic complications and the danger of cardiac death (4). At the moment, type II can be prevented by maintaining excellent health, exercising, and eating a nutritious diet, whereas type I cannot. Management of diabetes requires early diagnosis. However, type II affects a large portion of the population and can cause difficulties with the heart, nerves, eyes, kidneys, and other body organs (5). As of 2015, India had the second-highest number of people living with diabetes mellitus (69 million), making it one of the centres of the global pandemic. A significant portion of the population in other South Asian nations like Bangladesh, Pakistan, Sri Lanka, and Nepal also has diabetes mellitus(1). Additionally, there is a sizable diaspora of Asian Indian people living in countries like the UK, the USA, Mauritius, Fiji, Malaysia, Singapore, South Africa, and those in the Gulf region of the...
Middle East. These people have been found to have a much higher prevalence of diabetes mellitus than the native populations of the countries mentioned earlier. People who identify as Asian Indians—generally speaking, those who are from the nations of India, Pakistan, Bangladesh, Sri Lanka, Afghanistan, Nepal, Bhutan, and the Maldives come from the Indian subcontinent (6). Researchers have been attempting to treat diabetes with nanotechnology for the past few decades. For delivering hypoglycemic medications, a variety of nanocarriers including liposomes, polymer nanoparticles, micelles, emulsions, and hydrogels have been produced. Low side effects, targeted, long sustained release, higher drug permeability, and improved efficacy are all benefits of nanocarriers. Natural nanocarriers are more biocompatible and biodegradable, safer, and have better storage and physiological stability when compared to synthetic nanocarriers (7).

ETIOLOGY
Environmental and genetic factors can both contribute to diabetes mellitus. Physical inactivity, medicines and hazardous substances, obesity, viral infection, and geography are some environmental factors that may contribute to the development of diabetes mellitus. There is still much to learn about the causes of diabetes mellitus. Nowadays, it is commonly acknowledged that both genetic and environmental factors contribute to the multifactorial origin of diabetes mellitus (8).

EPIDEMIOLOGY
A major public health concern is the increased prevalence of diabetes mellitus, which places unmanageable demands on patients, those who care for them, healthcare institutions, and society as a whole. According to the most recent projections, there were 425 million cases of diabetes worldwide in 2017; by 2045, that number is predicted to reach 629 million. This is fueled by the rise in obesity rates and other harmful behaviours, such as poor diets and physical inactivity, which are in turn encouraged by broader socioeconomic drivers, such as global shifts in nutrition (the so-called "nutrition transition") (9). Diabetes is classified in several different ways, and these classifications and diagnoses have undergone much review, discussion, and revision throughout the years. In terms of the diagnostic criteria for diabetes, based on the measurement of fasting or 2-hour post-load glucose, expert committees from the World Health Organization and American Diabetes Association have developed, converged, and diverged in their positions. However, most recently, there has been an on-going discussion about whether glycated haemoglobin (HbA1c) should be used for diagnosis. Type 1 and type 2 diabetes are the two main kinds of the disease, and type 2 diabetes makes up the majority (>85%) of all cases of diabetes. The aetiological classification of diabetes is now widely accepted (10). Over the past 40 years, diagnosed diabetes has become far more common both in the United States and around the world. Around 30 million people worldwide have diabetes as of today; by 1995, this number had increased to 135 million (4% of the world's population); and by 2025, it is predicted that this number will rise by 42% to 300 million (5.4% of the world's population) (11).
PATHOPHYSIOLOGY

Absolute insulin insufficiency results from the death of pancreatic beta cells caused by type 1 diabetes mellitus (T1D), a heterogeneous illness. T1D is typically diagnosed in children and adolescents, often manifests as symptomatic hyperglycemia, and necessitates the rapid replacement of exogenous insulin. However, a quarter of T1D patients are diagnosed as adults and frequently given the diagnosis of latent adult autoimmune illness. Between 5% and 10% of persons with type 2 diabetes may actually have T1D. Juvenile diabetes and insulin-dependent diabetes have been replaced because they no longer accurately reflect our knowledge of the pathophysiology and natural history of T1D (12). The pathogenesis of the disease is characterized by unusually high blood glucose levels as a result of dysfunctional feedback loops between insulin action and insulin production. The body’s ability to maintain physiological glucose levels is constrained when -cell dysfunction occurs because insulin production is decreased. However, IR also has a role in decreased glucose uptake in adipose tissue, muscle, and the liver, as well as increased glucose synthesis in the liver. Even though both of these events occur early in the pathophysiology and help to cause the disease, -cell dysfunction typically manifests as a more severe condition than IR. The development of T2DM, however, is accelerated by hyperglycemia when both IR and -cell dysfunction are present (13). Multiple factors, including genetic and environmental factors that influence beta-cell function and tissue (muscle, liver, adipose tissue, pancreas) insulin sensitivity, contribute to type 2 diabetes development. Although the relative contributions of beta-cell dysfunction and decreased insulin sensitivity to the development of diabetes are hotly contested, it is generally accepted that both of these variables are significant. Uncertainty exists regarding the processes governing how these two deficits interact. In the pathophysiology of type 2 diabetes, a variety of factors have been put out as potentially connecting insulin resistance and beta-cell malfunction. The majority of type 2 diabetics have central visceral adiposity and are obese. As a result, the pathophysiology of type 2 diabetes should include adipose tissue significantly (14).

MANAGING OF DIABETES MELLITUS

According to the World Health Organization (WHO), DM affects more than 346 million people globally. Without any action, this number is probably going to more than double by 2030. Nearly 80% of diabetes fatalities take place in low- and middle-income nations. Currently leading the globe in the number of diabetic patients with over 32 million, India is expected to have 79.4 million by the year 2030, according to a WHO research. According to recent assessments, diabetes currently affects a startling 10-16% of the urban population in India and Sri Lanka and 5-8% of the rural population (16). Although randomized trials are needed to conclusively demonstrate benefit, early management with a
potential reduction in future complication rates is made possible by the identification of people with diabetes or pre-diabetes by screening. Obesity, high blood pressure, and a history of diabetes in the patient's family are risk factors that call for screening. At the time of diagnosis, 25% of type 2 DM patients already have microvascular problems, indicating that they have had the condition for more than 5 years. As a result, multiple methods are used to diagnose diabetes depending on the person.

**BOTH KINDS OF DIABETES ARE DIAGNOSED**

- **Unplanned plasma test**
The simplest test, which doesn't call for fasting beforehand. If blood glucose levels are 200 mg/dl or more, it is likely a sign of diabetes but needs to be validated.

- **Test for fasting plasma glucose**
Before taking the test, you should have fasted for eight hours. Diagnosis of diabetes is confirmed by blood glucose readings of more than 126 mg/dl on two or more tests performed on different days (17).

A thoughtful mix of nutrition, exercise, and insulin administration is used to manage diabetes during pregnancy. In patients carrying a singleton fetus, caloric needs rise by about 300 kcal over baseline during pregnancy. To promote dietary flexibility, new recommendations encourage the use of carbohydrate counting. When considering overall daily caloric intake to prevent excessive weight gain, carbohydrate counting is highly helpful during pregnancy. Typically, the diet for women with normal body weight is 30-35 kcal/kg of actual weight, increasing to 30-40 kcal/kg in the case of women who are under 90% of their ideal body weight and to 24 kcal/kg in the case of women who are above 120% of their ideal body weight. Complex, high-fiber carbs make up 40–50% of total calories, followed by protein (20%), unsaturated fats (30–40%), and protein (40–50%). The calories might be divided as follows: 10%–20% at breakfast, 20%–30% at lunch, 30%–40% at supper, and 30% with snacks, particularly a snack before bed to prevent nocturnal hypoglycemia (18). It is anticipated that the maintenance of long-term, near-normoglycemia will be simpler with insulin analogues, provided that they are used appropriately and implemented in the overall strategy of diabetes care for Type I diabetes, even though both CSII and multiple daily insulin injections already enable the achievement of fair to good glycaemic control. In contrast to s. c. injection of human insulin, insulin analogues will provide an insulin profile that is more in line with normal physiology. This is because of their pharmacokinetic properties. Thus, both Type I and Type II diabetes patients may benefit from better metabolic management and lifestyle through the proper administration of the analogues (19).

![Diagram of diabetes management](image)

**Fig. 2 General diabetes mellitus management (20).**
TREATMENT APPROACHES FOR DIABETES MELLITUS

➢ Mediations for type 1 diabetes

1. Oral Insulin Capsule
The drug ORMD-0801 is produced by Oramed Pharmaceuticals (Jerusalem, Israel), and its technology consists of two parts: (1) a chemical composition that safeguards insulin throughout passage through the GI system, and (2) absorption enhancers that enable insulin to be absorbed by the intestine. Insulin is mixed with certain adjuvants in this to prevent it from being destroyed by pepsin and gastrin (21).

2. Oral Insulin Tablets
A conjugated insulin molecule called IN-105, produced by Biocon Ltd. (Bangalore, India), imitates the manner that insulin is delivered into the portal vein circulation (hepatic route delivery). Contrast this with all other known delivery techniques, such as inhaling insulin, which moves insulin from the periphery into the bloodstream. To stop insulin from being degraded in the stomach, polymers have been added to the B chain of the insulin in this oral insulin pill at specified sites (22).

3. Oral Spray Insulin
Generex Biotechnology Corporation (Toronto, Ontario, Canada), the company that makes Oral-Lyn, is now conducting a phase 3 clinical research. It is a liquid formulation that is sprayed into the mouth; the insulin is then absorbed through the buccal mucosa, an area with a dense network of blood vessels. Oral-Lyn is a supplement to current long-acting insulin therapy as well as a replacement for injectable short-acting insulin. A coadministration of bile salts as absorption promoters can increase the systemic bioavailability, which was only 0.5% when no absorption promoter was utilized (22).

4. Rectal Insulin Suppository
The company that makes ORMD-0802 is Oramed Pharmaceuticals. This substance exhibits quick insulin absorption as well as a quick glucose-lowering action. During the experiment, the suppositories were well tolerated; they are comparatively painless, and no adverse events were noticed. These are being developed as a therapy alternative to insulin injection (23).

5. Oral Glucagon-Like Peptide
Currently in phase 2b of its clinical studies, ORMD-0901 was created by Oramed Pharmaceuticals. It is an oral glucagon-like peptide-1 (GLP-1) analogue that contains oris as an active component. Oris is an incretin hormone, a class of gastrointestinal hormone that stimulates the pancreatic release of insulin. It is a member of the incretin class of medications, which are used to treat diabetes and have actions include lowering blood sugar and glucagon secretion suppression. In preclinical studies is ORMD-0901 (22).

➢ Type 2 Diabetes Mellitus
A diverse condition called type 2 diabetes mellitus is characterized by chronic hyperglycemia. The genetic inheritance and its interaction with environmental circumstances imply the aetiological heterogeneity. The two main pathophysiological characteristics of type 2 diabetes that lead to the development of hyperglycemia are impaired insulin secretion and decreased insulin sensitivity. Only a small subset of individuals have had these disorders' genetic causes proven, though. Although it is generally accepted that abnormal insulin release is a necessity for the condition to develop, it is unknown whether reduced insulin secretion or action is the underlying issue in the majority of patients (24). Type 2 diabetes is characterized by absolute or relative insulin insufficiency, which leads to hyperglycemia. The inability to sufficiently correct for insulin resistance is the main cause of relative insulin insufficiency. Numerous genetic or metabolic variables can contribute to insulin resistance. Central adiposity is the most frequent etiological cause for insulin resistance. A number of metabolic problems, including glucose intolerance, hypertension, a particular dyslipidemia, a procoagulant condition, and an increase in macrovascular disease are linked to insulin resistance. Clinical intervention studies have shown that treating hyperglycemia to attain haemoglobin A1c 7.0%, blood pressure 130/80 mmHg, and plasma LDL-cholesterol 2.6 mmol/L (100 mg/dL) is necessary for reducing the chronic microvascular and macrovascular consequences of type 2 diabetes. By delaying the absorption of complex carbohydrates, oral antihyperglycemic medications can boost endogenous insulin production, reduce insulin resistance, or reduce the rise in postprandial plasma glucose levels. For type 2 diabetes, long-term glycemic management involves a progressive, stepwise combination of oral medications, and eventually a combination of oral medications plus insulin (25). Several causes, including impaired insulin production, the insulin resistance of insulin-sensitive tissues, ageing, and environmental variables, such stress and obesity, can cause type 2 diabetes, a common metabolic condition (26). Patients with persistent hyperglycemia typically experience development impairment and are more susceptible to certain illnesses. After a considerable amount of time, DM affects many body systems in patients with elevated blood glucose levels. Blindness, neuropathy, exocrine gland insufficiency, renal failure, and foot amputation are long-term consequences (27). There are both oral and injectable medications available to treat patients with type 2 diabetes.
Medications for type 2 diabetes

1. Gastric Inhibitory Peptides
The FDA has not approved any of the gastric inhibitory peptides (GIPs). GIP was found to be a factor in intestinal extracts. K cells in the duodenum and jejunum elaborate GIP. GIP's main effect is to increase the insulin secretion in response to glucose infusions by stimulating glucose-dependent insulin secretion. GIP lowers stomach motility, which reduces hunger and blood sugar levels (28).

2. Incretin Mimetics
Drugs known as incretin mimetics imitate the glucose-lowering effects of incretins, which are naturally occurring human hormones. Incretins have been linked to the regeneration of insulin-secreting cells in the pancreas and are thought to have tissue-protective qualities, including heart protection. Gastric inhibitory peptides (GIP) and glucagon-like peptide-1 (GLP-1) are incretin mimics, however only GLP-1-class medications have received FDA approval since April 2005 (29).

3. Glucagon-Like Peptide-1
A hormone called glucagon-like peptide-1 is released by the neuroendocrine L cells of the colon and ileum, and it triggers the pancreas to generate glucose-dependent insulin (28). It causes the production of the hormone glucagon after meals to be inhibited, which slows the rate at which nutrients are taken into the bloodstream and decreases food intake. It also causes the insulin response to high blood sugar levels. It contains medications like lixisenatide, exenatide, liraglutide, and tasapoglutide. Eli Lilly (Indianapolis, Indiana) and Amylin Pharmaceuticals (San Diego, California) are the companies that produce exenatide. It is made from the Gila monster's saliva. The kidneys remove exenatide. It is given subcutaneously in the thigh, belly, or upper arm in doses of 5 or 10 µg, 60 minutes before breakfast and dinner (30). One study found that combining Byetta (exenatide) and sulfonylurea enhanced the risk of hypoglycemia (31). Exenatide produces mild nausea, a decrease in appetite, and a loss in body weight; it should not be used in people with type 1 diabetes as it can lead to severe pancreatitis, ketoacidosis, and renal impairment. It is connected to the advancement of markers for improved cell function. It enhances blood sugar regulation, promotes insulin production only when blood sugar levels are elevated, and restores the first-phase insulin response (an action of the pancreatic insulin-producing cells that is lost in type 2 diabetes patients). Patients who have not experienced appropriate control
when using metformin or sulfonylureas are prescribed exenatide injection. In order to release insulin, GLP-1 is required (32).

Phase 3 clinical studies for the Novo Nordisk (Bagsvaerd, Denmark) drug liraglutide were carried out in 2007. On July 3, 2009, the European Medicines Agency (EMEA) granted its approval. It is made to withstand degradation by the enzyme dipeptidyl peptidase-4 (DPP-4). It binds to serum albumin after injection; its half-life is between 11 and 15 hours; and it has a sustained effect for over 24 hours (33). Liraglutide, which is given subcutaneously at a dose of 10 mg/kg, is removed via the kidneys. Comparing the incidence of nausea to exenatide, it was minimal. Common adverse effects include weight loss, wooziness, vomiting, and diarrhoea (34).

The first once-weekly human GLP-1 analogue, taspoglutide, is undergoing phase 3 clinical studies with Hoffmann-La Roche in Basel, Switzerland. It resembles the naturally occurring hormone GLP-1, which plays a significant part in controlling blood sugar. Taspoglutide's kinetics are not understood. Its negative effects include nausea, loss of weight, and a reduction in stomach motility. One weekly dose of taspoglutide is given, which aids in maintaining compliance. After eight weeks of treatment, there are appreciable improvements in glucose management and weight loss. For obese patients with type 2 DM, once-weekly therapy with taspoglutide is a promising and very effective option. Jin claims that (35).

The most recent GLP-1 medication, lixisenatide (ZP10A), was created by SanofiAventis in Paris, France; it lowers fasting blood glucose levels and raises HbA1c. There is a phase 3 clinical trial for lixisenatide. Studies using receptor agonists showed that ZP 10 A had a 4-fold higher affinity for the human GLP receptor than GLP-1 amide. Clinical trials of lixisenatide have demonstrated reductions in fasting blood glucose and enhanced HbA1c levels (36).

4. Incretin Enhancers
The effects of incretins, which are organic hormones that reduce blood sugar, are enhanced by incretin enhancers. Incretin enhancers are DPP-4 inhibitors. DPP-4 inhibitors lower blood glucose levels by blocking the DPP-4 enzyme, which also stimulates insulin release and activates GLP-1 (37).

Vildagliptin is made by Novartis in Basel, Switzerland, and has a half-life of 12 hours and an 85% bioavailability. It is given daily in dosages of 50 or 100 mg, with the kidneys being the principal organ via which it is primarily excreted. Vildagliptin has a half-life of 12 hours between doses, with a 50-mg dose inhibiting 70% of DPP-4 enzyme activity and a 100-mg dose inhibiting 90%. Merck and Company, located in Whitehouse Station, New Jersey, is the producer of sitagliptin. 100 mg once daily is the usual dosage. Its half-life varies with dose and has an 87% bioavailability. 80% of the DPP-4 enzyme's activity is inhibited by sitagliptin at doses of 50 mg and 100 mg for 12 and 24 hours, respectively. The kidneys rid the body of it (38).

The FDA authorized saxagliptin, which is produced by Bristol-Myers Squibb (New York, New York), in July 2009. To lower HbA1c values, it is provided at doses of 2.5 to 5 mg once daily, either alone or in conjunction with oral antidiabetics (39).

5. Gastric Inhibitory Peptides
The FDA has not given its approval to any gastric inhibitory peptides (GIPs). Intestinal extracts were found to include GIP as a factor. The duodenum and jejunum's K cells elaborate GIP. GIP's main effect is to stimulate insulin secretion that is dependent on glucose, which means it increases insulin production in response to glucose infusions (28).

6. Sodium-Dependent Glucose Transporter Inhibitors
Inhibitors of the sodium-dependent glucose transporter (SGLT)-1 work by reducing the amount of glucose that is absorbed from the gastrointestinal tract; however, because they can only reduce glucose absorption by 2%, they are not very effective in treating type 2 diabetes. By interfering with glucose metabolism, SGLT-2 inhibitors prevent 98% of glucose from the renal filtrate from being reabsorption (40). Recent research indicate that a novel strategy for treating type 2 diabetes called increasing glucose excretion in urine may be more beneficial than lifestyle changes. Dapagliflozin, remogliflozin, and sergliflozin are SGLT-2 inhibitors (41). Koury (2009) found that when dapagliflozin was combined with metformin and insulin in type 2 DM patients, it decreased renal glucose absorption and enhanced glycemic control (42). Remogliflozin has been shown to be a strong and highly selective SGLT-2 inhibitor that enhances urinary glucose excretion in a dose-dependent way. Remogliflozin reduces HbA1c levels at higher doses (43).

7. Amylin Analogs
The FDA authorised the amylin analogue pramlintide in March 2005. Amylin, a naturally occurring human hormone, is replaced by symlin. In response to meals, the pancreatic beta cells co-secrete amylin, a 37-amino acid peptide neurohormone, together with insulin. By slowing stomach emptying, lowering food intake, and reducing glucagon release, it reduces blood glucose. Blood glucose levels measured before meals are unaffected. Subcutaneous injections of pramlintide are given just before meals. The medicine's bioavailability is between 30% and 40%, and the kidneys are responsible for its metabolism. About 60% of the drug is bound to proteins. The negative side effects include swelling of the lips, tongue, and throat as well as severe hypoglycemia, nausea, itching, and tightness in the chest. Patients with diabetes, both type 1 and type 2, who take insulin, can utilize it (44). Any decrease in HbA1c is linked to a decrease in diabetes complications in patients with type 1 and type 2 DM, according to research from the Diabetes Control and Complications Trial (DCCT) Research Group and the UK Prospective Diabetes Study (UKPDS) (45).
8. Fructose 1,6-Bisphosphatase Inhibitors
As adenosine monophosphate (AMP) mimics, fructose 1,6-bisphosphatase inhibitors block the enzyme. A fructose 1,6-bisphosphatase inhibitor, MBO6322 (CS-917), is a prodrug of MBO5032. It is made by Metabasis Therapeutics in La Jolla, California, and is now undergoing a phase 2b clinical trial. Through the combined efforts of an esterase and a phosphoramidase, MBO6322 is transformed into MBO5032 in two steps. Through the gluconeogenesis (GNG) pathway, the liver overproduces glucose in type 2 DM. The GNG route is blocked by MBO6322, which lowers glucose synthesis. Fructose 1,6-bisphosphatase's AMP binding site is the mechanism by which AMP mimetics block the GNG pathway. Without any indication of hypoglycemia, glucose levels fall. The human liver FBPase is substantially more potently inhibited by MBO5032 than by naturally occurring AMP inhibitors. Indirectly, metformin blocks GNG. More significant glucose reduction is seen with direct GNG inhibitors (46).

9. Peroxisome Proliferator-Activated Receptor (PPAR)-α/γ Ligands
These medications work by activating PPAR-α/γ receptors. Thiazolidinediones activate PPAR- receptors and enhance glycemic management primarily by raising peripheral insulin sensitivity and decreasing hepatic glucose output, aiding in the maintenance of β-cell function. Fibrates, which stimulate PPAR-γ, enhance dyslipidemia, reduce atherosclerotic lesions, and may have an impact on cardiovascular events but have no effect on glycemia. In addition to protecting β-cell function, PPAR-α agonists also help to reduce atherosclerotic plaques and therefore severe cardiovascular events. These medications include muraglitazar, tesaglitazar, and aleglitazar. Phase 3 clinical studies for the drug Muraglitazar, which was created by Bristol-Myers Squibb, were finished in 2006. Edema, heart failure, transient ischemia attacks, and congestive heart failure are all results of it. The effectiveness of muraglitazar for type 2 DM and related lipid abnormalities was evaluated in a Horizon scanning evaluation in 2005. In comparison to placebo, the results showed a drop in triglycerides and a rise in high-density lipoprotein (47).

In May 2006, AstraZeneca (London, UK) began phase 3 clinical studies for tesaglitazar. It results in hemodilution, weight gain, and edema. Tesaglitazar was found to cause subcutaneous fibrosarcomas in a 2-year carcinogenicity investigation in rats (48). Hoffmann-La Roche created aleglitazar, which is presently undergoing phase 2 clinical studies. Edema and weight gain are two possible side effects. The SYNCHRONY trial was carried out to determine the safety profile of aleglitazar as well as its effects on decreasing glucose and altering lipids. The findings revealed no congestive heart failure occurrences in any of the patients, but aleglitazar had side effects such edema and weight increase in a dose-dependent manner, however the weight gain was smaller than that linked to pioglitazone (49).
TREATMENT OF DIABETES MELLITUS (DM) WITH NANOTECHNOLOGY

The first line of treatment for diabetes mellitus, an incurable metabolic condition, is the subcutaneous injection of insulin. Diabetes mellitus is characterized by alterations in the homeostasis of blood sugar levels. Due to the possibility of pain, discomfort, and local infection, this administration route is however associated with low patient compliance. To enable the administration of the peptide through safer methods without the need for injection, such as by oral or nasal routes, nanoparticles have been proposed as insulin carriers.

In the twenty-first century, nanotechnology is a brand-new and crucial technology. Single atoms and molecules are used in this field of science and technology to create materials. It investigates the characteristics and uses of materials with structures ranging in size from 0.1 to 100 nm. A new configuration of matter is produced by the arrangement and fusion of different particles. Nanotechnology has rapidly advanced and is now employed extensively in a variety of industries and professions, including health, materials science, the electrical industry, the energy business, and others (50,51).

Nanoparticles are defined as particles in the nanometer range that can be made from a variety of substances (such as polysaccharides, synthetic polymers, and lipids) and are frequently utilised to increase the loaded drug's bioavailability and physicochemical stability. The utilisation of various nanoparticles (such as lipid and polymeric nanoparticles, liposomes, dendrimers, niosomes, micelles, nanoemulsions, and drug nanosuspensions) for enhanced administration of various oral hypoglycemic medications in comparison to conventional therapy is covered in this study (52). To improve the paracellular absorption of medications, nanoparticles may be utilized. For epithelial endocytosis, nanoparticles having hydrophobic surfaces are favourable. However, cationic nanoparticles interact with the mucus layer, which is negatively charged, restricting their absorption (53). Drug metabolism and a lack of target specificity in conventional drug delivery methods are frequently linked to low efficacy (caused by inappropriate or inadequate dosage), low potency, and changed consequences (54). The development of more physiologically friendly insulin formulations to be administered by less invasive routes (such as oral, transdermal, inhaled and nasal, buccal, ocular and rectal) is still needed because current insulin formulations do not mimic the physiology of human insulin, which is endogenously secreted. While stability and therapeutic efficacy of these new formulations have been considered in their development, the results on the bioavailability are still falling short of expectations. Various forms of nanocarriers have been tested to transport anti-diabetic medications (55,56).

Nanomaterials are highly active, and various interactions exist between various nano units. This property gives nanomaterials their distinctive characteristics, including the quantum impact of growing surface energy, the size effect resulting from a large specific surface area, the interface effect resulting from a rapid increase in surface atomic ratio, and the quantum properties of various atoms, which can be converted into various forms of energy (57-60).
and others (57). Because of the in-depth research into the characteristics of nanomaterials, ongoing advancements in the fields of molecular biology, new materials, and other disciplines and technologies, as well as the organic fusion of modern medical research and nanotechnology, the latter has advanced to a new level, particularly in the diagnosis and treatment of diseases (58). Nanotechnology is used in medication research nowadays because of its small molecular size and variety of functionalities, which makes it possible to overcome a barrier that is present in conventional medicine (59).

In contrast to the conventional medication delivery method, nanotechnology has been extensively utilized in the creation of novel pharmaceuticals (60,61). By producing mucins and antimicrobial peptides, the secretory goblet and Paneth cells simultaneously guard and repair the intestine. Nanoparticles created for oral insulin administration must get beyond epithelial and mucous barriers. When removing mucus, neutral and hydrophilic nanoparticles are preferred, however their ability to interact with epithelial cells may be hampered (62). Pre-systemic chemical breakdown in the stomach is also blamed for the low oral bioavailability that was discovered to be caused by insufficient penetration into the intestinal epithelium. The intestine's pH ranges between the neutral/alkaline range (pH 6.5-8) and the stomach's very acidic (pH 1-3.7) lumen, which might trigger pH-induced oxidation and deamination (63). Other insulin delivery methods, such as pulmonary and nasal delivery, have also been researched and are currently available on the market under the brand names Exubera® and Afrezza®. These methods of delivery also have several downsides, including poor patient compliance, variations in alveolar surface absorption, and the need for the proper handling inhaling technique (63).

ANTI-DIABETIC DRUGS DELIVERED ORALLY BY NANOPARTICLES

The stability of the former can be increased by putting medicines onto nanoparticles, preventing chemical and/or enzymatic breakdown in the GIT. Additionally, nanoparticles increase interaction with the GI epithelium, lengthening the period that a medicine remains in the body and boosting its bioavailability. Drugs must be delivered close to the absorption site, either by being entrapped within the nanoparticle matrix or linked to their surface (64). The nature of the chosen polymer, the mean particle size and polydispersity, the surface electrical charge, hydrosolubility, and the morphology of the particles are important for the uptake of nanoparticles in the GIT. An ideal nanoparticle should penetrate via the GI membrane (65). Drugs can also be absorbed through the lymphatic system as an alternative to first pass metabolism. Although the lymphatic system contains a network of channels running throughout the body, it is a one-way passage and is thought to be an effective approach to transfer oral medications through the intestinal wall. M cells help nanoparticles enter the lymph and travel to the lymphatic system (66,67).
Fig. 5 Oral Insulin Delivery Route Using Nanocarrier (68).
ANALYSES OF NANOCARRIERS PROPERTIES

It is well recognized that the physicochemical characteristics of nanocarriers, such as their size and polydispersity index, morphology, surface charge, zeta potential, entrapment effectiveness, drug release evaluation, compatibility, and stability, are related to their effectiveness and applications (24,69). In nanocarriers, size and polydispersity play crucial roles in determining the drug release properties as well as biodistribution and bio-elimination of nanocarriers. The size and polydispersity of nanocarriers can be determined using a variety of techniques, including atomic force microscopy (AFM), centrifugal liquid sedimentation (CLS), dynamic light scattering (DLS), and microscopic approaches. The approach chosen will depend on the anticipated population and size of the nanocarriers (24,70,71). Nanoparticles' morphology or shape may have an impact on their biodistribution, targeting effectiveness, and level of cytotoxicity. Transmission electron microscopy (TEM) or scanning electron microscopy (SEM) can be used to analyse this property (24).
Fig. 7 Many kinds of nanocarriers for antidiabetic drugs (24).

1. **Liposomes**

Small vesicles called liposomes are made from naturally occurring, non-toxic phospholipid bilayers and cholesterol (72). Because of their biodegradability, biocompatibility, low toxicity, ability to entrap both lipophilic and hydrophilic medicines, and usefulness for site-specific/targeted distribution, they are utilised in drug delivery. Liposomes have been used in a variety of ways to target particular cells and reduce the toxicity of loaded medications, improving efficacy and safety (73). For oral delivery, Zhang et al. created inulin-loaded liposomes that were altered with the specific ligand biotin. Biotin-1,2-distearoyl-sn-glycero-3-phosphatidylethanolamine (DSPE) was added to the lipid bilayer of liposomes to create them (74). A 3:1 lipid:cholesterol ratio decreased the likelihood that internal aqueous compartments would leak insulin. The biotin-DSPE ratio and mean size of the carriers were found to be important determinants of the hypoglycemic effect of insulin-loaded liposomes. Liposomes' smaller size did in fact encourage a greater uptake through intestinal epithelia via receptor-mediated endocytosis. Insulin bioavailability was increased by biotin-DSPE liposomes in contrast to normal liposomes (74). When these liposomes were given orally to Kunming mice, they showed to be just as effective at enhancing the hypoglycemic impact as parenteral insulin. These liposomes were trypsin and pepsin resistant to prolong the formulation's stomach residence period. Chitosan molecules have a coiled conformation at neutral pH, adhering to the surface of liposomes, and therefore forming a layer of protection. Because of the particles' increased mucoadhesiveness and higher zeta potential caused by the positively charged polysaccharide, it has also been suggested that covering liposomes with chitosan will decrease the uptake of insulin in the stomach (75). When compared to normal liposomes, those made of bile salts improve the peptide's oral bioavailability while promoting gut insulin absorption (76). As a result, liposomes can be an effective choice for the transport of peptides (insulin, GLP-1), as well as other medications that lower blood sugar, enabling better control of the hyperglycemic stage through alternate administration methods (77,78).

2. **Niosomes**

Niosomes are artificial nanometric-sized vesicles made from non-ionic surfactants (such as alkyl-ether, esters, and amides) that are rearranged in concentric bilayers and stabilized by cholesterol (77). They are categorised as small unilamellar vesicles (SUV; 10-100 nm), large unilamellar vesicles (LUV; 100-3000 nm), or multilamellar vesicles (MLV) based on their sizes and bilayers (79). Wistar rats that had undergone ovariectomies and been infected with
alloxan-induced diabetes were given niosomes made of the span 40 and span 60 proteins and loaded with insulin. Both types of niosomes resulted in a drop in blood sugar levels and a higher insulin bioavailability than subcutaneous delivery. Insulin release from niosomes was extended and then had a hypoglycemic impact (80). By using the thin film hydration approach, niosomes containing cholesterol, dicetyl phosphate, and a non-ionic surfactant (Span 60 or 40) were created to load metformin (81). To make the vesicles more stiff and prevent medication leakage, cholesterol is employed in the construction of niosomes. These vesicles were reported as having a protracted release profile with a Fickian diffusion pattern. Another study measured the serum levels of the medication and glucose in Wistar rats to investigate the bioavailability of metformin-loaded niosomes (82). Male Wistar rats were used in the in vivo pharmacodynamic investigation, which showed that RPG-loaded niosomes reduced blood glucose levels more than the standard dose form. Additionally, it maintained RPG at a therapeutic level for a longer duration. These findings demonstrated that niosomes also served as drug-carriers in deeper mucosal layers of the epithelium, where the drug is slowly released from its encapsulation, creating a prolonged release effect. Niosomes were thereby demonstrated to be effective delivery agents, increasing bioavailability and decreasing dose frequency while maintaining sustained control of hyperglycemic state over an extended period of time (52).

3. Nanoemulsions

Additionally, nanoemulsions have been shown to improve the distribution of substances with anti-diabetic effects that are lipophilic (83). An oral administration of bitter gourd seed oil nanoemulsions containing α-oleostearic acid to a diabetic rat model resulted in increased antidiabetic effects (84), antioxidant actions and increased cellular absorption (85). Alpha-tocopherol-loaded nanoemulsions were administered to diabetic rats caused by streptozotocin, and they showed protective effects in a number of organs (86). Li et al. created insulin-loaded nanoemulsions that were polyelectrolyte cross-linked and coated with chitosan/alginate. While nanoemulsions maintained their integrity during the in vitro leakage testing in simulated gastric media, the conformational stability of insulin during cross-linking was demonstrated. In both healthy and diabetic rats, hypoglycemic effects were seen. The coated nanoemulsions oral delivery resulted in a substantially longer hypoglycemic effect than subcutaneous insulin, as was previously shown (87).

4. Drug Nanosuspensions

Another delivery method that can be utilized for oral administration is the use of drug nanosuspensions (also known as drug nanocrystals), which include active ingredients in the solid state and have particles up to 1 μm in size surrounded by a hydrophilic surfactant in an aqueous dispersion (88). Another BCS class II medication with improved solubility is glimepiride, which was created as nanoemulsions (89). To increase the solubility of Biopharmaceutical Classification System (BCS) II and IV medications, drug nanosuspensions have been proposed. Vaculíková et al. produced nanosuspensions by the emulsion solvent evaporation method using dichloromethane as the solvent and carbosymethyl dextran sodium salt as the stabiliser in order to increase the solubility of the poorly water soluble glibenclamide, an oral hypoglycemic BCS class II drug that stimulates pancreatic beta cells to secrete insulin (90). A nanosuspension approach was used to make gymnemic acids, which also showed enhanced bioavailability (91). With a lower dosage level, berberine nanosuspensions—an anti-diabetic compound—have demonstrated an increased anti-diabetic activity in T2DM animal models (92).

5. Metallic Nanoparticles

Metallic nanoparticles have made significant strides in the health sciences and can inhibit antibacterial, anti-diabetic, and anticancer effects. Since it has produced impressive results, a decade of study on entrapping plant extracts in metallic nanoparticles has attracted the attention of numerous scientists. Metallic nanoparticles have distinctive qualities that make them advantageous for biotechnology, targeted drug delivery, and possible in vivo imaging, such as large surface areas, specialized functional groups, effective quantum self-assembly, and the capacity to conjugate with the drug of interest. Metallic nanoparticles have also demonstrated a number of benefits, including ease of manufacturing, repeatability, economy, stability, environmental friendliness, and high entrapment efficiency, which makes them a good choice for a variety of applications. Gold, silver, copper, titanium-cerium-zinc oxide, and other metals and metal oxides are frequently used in the synthesis and production of metallic nanoparticles. Plant extracts function as stabilizing and lowering agents in nano-formulations (93). Gold nanoparticles (Au NPs) and silver nanoparticles (Ag NPs) are the most prevalent metallic nanoparticles that need to be investigated. Silver nanoparticles are often made using the bio-reduction process, while gold nanoparticles are typically made using the Turkevich method (94). Due to their high binding energy, zinc oxide nanoparticles (ZnO) are highly prevalent metallic particles (95).

6. Polymeric Nanoparticles

Solid colloidal particles known as polymeric nanoparticles range in size from 1 nm to 1000 nm and are composed of biocompatible polymers (96). Large molecules known as polymers are created by chemically joining one or more different types of tiny units, or monomers, to form a straight or branching chain (97). As long as they have at least two functional groups to interact with another monomer, monomers can have any structure. Block copolymers, which comprise at least two polymer chains with distinct hydrophobicities and spontaneously assemble into a core-shell structure in an aqueous solution, can be used to create polymeric nanoparticles. While the hydrophilic blocks construct the outer shell to stabilise the core, the hydrophobic blocks construct the core to lessen their exposure to the aquatic
To reach the ideal therapeutic drug concentration while minimizing the exposure of the medication to undesirable regions, polymeric nanoparticles can be made to deliver pharmaceuticals at specified places and subsequently release them at specific rates. In gastrointestinal fluid, polymeric nanoparticles are more stable than other nanocarriers like liposomes and micelles. Strong chemical bonds are formed, giving polymeric nanoparticles more stiff and stable structures.

7. Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

Single layers of phospholipids are present in solid lipid matrices that make up solid lipid nanoparticles (SLNs). Combining a variety of surfactants with a wide range of solid lipids, such as triglycerides, fatty acids, and steroids, can result in steric stabilization and the creation of SLNs. While avoiding their drawbacks, SLNs combine the advantages of polymeric nanoparticles, emulsions, and liposomes. The lipids utilized to create SLNs are less hazardous than particular polymeric nanoparticles and similar to liposomes and nano-emulsions in that they are biocompatible. In place of conventional nanocarrier drug delivery systems such emulsions, liposomes, and polymeric micelles, SLNs, which were created in the 1990s, are used. The encapsulated active agents are protected against chemical deterioration in biological environments by the solid lipid matrices, which are identical to those in polymeric nanoparticles. They also offer significant flexibility in terms of the release qualities of the medications. Drugs that are both lipophilic and hydrophobic can be encapsulated by SLNs. These nanoparticles can contain hydrophobic medicines thanks to the solid lipid matrices' lipophilic nature. Because hydrophilic medicines have a low affinity for these lipid matrices, it is anticipated that they will not be well-encapsulated. However, for hydrophilic medicines, the double emulsion/solvent evaporation approach can provide satisfactory loading efficiencies. The potential drawbacks of SLNs were then addressed by the development of nanostructured lipid carriers (NLCs).

8. Alginate-Based Nanoparticles

An anionic polysaccharide called alginate is made up of blocks of (1-4)-linked d-mannuronic acid and l-guluronic acid residues that alternate. It is a mucoadhesive, pH-sensitive, hydrophilic, biodegradable, and biocompatible polymer. Due to the polymer's guluronic acid residues, which can interact with divalent ions to produce a gel matrix by exchanging sodium ions, insulin can be retained in the nanoparticles. When the peptide was loaded into alginate-chitosan nanoparticles created by ionotropic pre-gelation, the structure of the insulin α-helix and β-sheet was preserved. These particles can then be strengthened using glutaraldehyde and divalent ions (Ca2+). Prior to being encapsulated in alginate-chitosan nanoparticles, insulin can be electrostatically coupled with cationic -cyclodextrin polymer (CPCDs) to further boost its stability. Prior to being enclosed in alginate-chitosan nanoparticles, insulin can be electrostatically coupled with cationic -cyclodextrin polymer (CPCDs) to further boost its stability. These particles, however, weren't suitable for the protein's modified release since more than 40% of it leaked into simulated gastric fluid (SGF).
QUALITY OF LIFE IN DIABETES MELLITUS

According to the WHO, "Quality of life is defined as individuals' perceptions of their position in life in relation to their goals, expectations, standards, and concerns, as well as the culture and value systems in which they live." Evaluation of "quality of life" has become a crucial indicator of how well chronic disease care is working. In this context, a wide range of general and disease-specific measures for assessing quality of life have been validated and assessed in a range of demographic contexts (122–124). Chronic, non-communicable diabetes mellitus has long-term complications that have a major negative influence on the quality of life of those who have it. In order to maintain appropriate blood sugar levels, diabetic patients must adhere strictly to prescribed dietary guidelines as well as take hypoglycemic drugs for extended periods of time. In order to maintain stable blood sugar levels and prevent potential problems, they must follow the recommendations for exercise and weight loss (125). 425 million individuals were predicted to have diabetes mellitus (DM) in the world in 2017, and 79% of them lived in developing nations (126). The quality of life (QoL) construct will be emphasised in the current study due to its significance in providing care for a person with diabetes mellitus (DM), as quality of life can aggravate the condition or make it challenging to treat. QoL is described as a perspective of the person and their place in relation to their objectives, aspirations, and concerns as well as the culture and value systems in which they live (127). Studies in this field can help with planning the treatment and care of this group and provide information for caring for people with diabetes since QoL relates to the perception of wellbeing (128,129). It is becoming more widely accepted that in people with diabetes, psychosocial factors play a significant role in self-care, acceptance of therapeutic regimens, and the success of treatment, and that metabolic metrics like glycemic control are poorly linked with quality of life, needing separate assessment (130–133). In turn, diabetes treatment plans including methods to pinpoint and improve patients' health-related quality of life issues have the potential to boost adherence and, in turn, their metabolic state. Each specific subset of patients has a different perspective of quality of life, which is influenced by factors such as their ethnicity, culture, level of education, money, and so on. Quality of life is an individual perception (134).

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CONCLUSION AND FUTURE DIRECTION

When your blood sugar (glucose) level is too high, you develop diabetes. It happens when your body doesn't process insulin effectively or when your pancreas doesn't produce any insulin at all. All ages are impacted by diabetes. Diabetes comes in a variety of forms, the majority of which are chronic (lifelong) and treatable with medication and/or dietary modifications. Carbohydrates in your meals and beverages are the main source of glucose (sugar). It is the primary energy source for your body. All of the cells in your body receive glucose from your blood to be used as fuel. While type 2 diabetes is caused by decreased insulin secretion and resistance to the effects of insulin, type 1 diabetes is caused by the autoimmune destruction of the pancreatic islet cells. Recent epidemiological data show that diabetes mellitus affects 9% of those who are 18 years of age or older, and that it claimed 1.5 million lives in 2012. India has a high prevalence of diabetes mellitus, and the increasing rate is alarming. Diabetes will affect 79.4 million people worldwide by 2030, up from 40.6 million in India alone in 2006. The frequency of type 2 diabetes mellitus (DM), a chronic metabolic condition, has been continuously rising worldwide. Due to this pattern, it is quickly turning into an epidemic in some countries around the world, with the number of those affected predicted to double in the following ten years due to an ageing population, adding to the burden already placed on healthcare providers, particularly in less developed nations. In order to boost the bioavailability and physicochemical stability of the loaded medicine, nanoparticles are widely used. Nanoparticles are described as particles in the nanometer range that can be created from a number of substances (such as polysaccharides, synthetic polymers, and lipids). This study focuses on the use of various nanoparticles (such as lipid and polymeric nanoparticles, liposomes, dendrimers, niosomes, micelles, nanoemulsions, and drug nanosuspensions) to improve the delivery of different oral hypoglycemic drugs compared to conventional therapy. The nanocarriers-based treatment is good but does not provide a permanent cure for diabetes mellitus (type 2), according to our conclusion. Diabetes has no known cure, although therapy can help you feel better. Additional randomised controlled trials on the treatment of diabetes are required. We are attempting a ground-level study for diabetes mellitus in the future.
Table: Current status of clinical trials on diabetes mellitus.

<table>
<thead>
<tr>
<th>S. no.</th>
<th>Drug</th>
<th>Mode of administration</th>
<th>Disease</th>
<th>Enrollment</th>
<th>Allocation/Intervention model/Masking</th>
<th>Official Title of the study</th>
<th>status</th>
<th>Clinical trial #</th>
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<td>Characterization of the Kinetics of Renal Glucose Reabsorption in Response to Dapagliflozin in Healthy Subjects and in Subjects With Type 2 Diabetes Mellitus</td>
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<td>Muraglitazar</td>
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<td>A Phase 3, Randomized, Double-blind, Placebo Controlled, Multicenter Trial to Evaluate the Safety and Efficacy of BMS-298585 in Combination With Glyburide Therapy in Subjects With Type 2 Diabetes Who Have Inadequate Glycemic Control on Sulfonylurea Therapy Alone</td>
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<td>A Randomized, Double-blind, Placebo-controlled, Sequential Single and Multiple Ascending Doses (SAD/MAD) Study Following Oral Administration in Healthy Subjects to Evaluate the Safety, Tolerability, and Pharmacokinetics of YG1699</td>
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<td>Effectiveness and Safety Study of the FreeStyle Libre Flash Glucose</td>
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