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Strategies for enhancing the efficacy in the treatment of type 2 diabetes mellitus using encapsulated nanoparticles

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Abstract : Diabetes Mellitus threatens hundreds of millions of the world's population; it is estimated to reach 693 million by 2045. Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder that affects millions of people worldwide. Encapsulated nanoparticles (ENPs) are increasingly being used as a potential therapy for T2DM, due to their ability to target and deliver drugs to specific areas of the body. The aim of this review is to investigate the current literature on ENPs for the treatment of T2DM, with a focus on various strategies for controlling the diabetes. A discussion is provided on the advantages of using ENPs in diabetes treatment, as well as the challenges associated with developing drugs for T2DM. There are several types of ENPs, including liposomes, polymeric nanoparticles, nanostructured lipid carriers, and dendrimers, that can be used for the treatment of T2DM. By modifying NPs properties, targeting strategies, and combinations, researchers aim to maximize therapeutic outcomes and minimize adverse effects. ENPs offer enhanced bioavailability compared to traditional drug formulations. The small size of NPs allows them to penetrate through biological barriers, such as the blood-brain barrier and gastrointestinal wall, thereby improving the distribution and accessibility of drugs to the target tissues. This enhanced bioavailability results in improved therapeutic outcomes and reduced dosing requirements. In this article we are discussing about the innovative techniques of ENPs for the management of T2DM. Ongoing research and development initiatives within this sector show considerable potential for improved patient outcomes and chronic disease treatment.

Index Terms **- Type 2 diabetes mellitus, Encapsulated nanoparticles, Potential Therapy.**

INTRODUCTION

The Diabetes Mellitus (DM) is a chronic, lifelong metabolic and endocrine disorder caused by hypertriglyceridemia, hyperglycemia and hypercholesterolemia. The hormone named insulin, which is produced by the pancreas, allows glucose to be absorbed by the body's cells. If the cells do not absorb glucose from the body, the process results in serious difficulties [1]. The malfunction and survival of beta-cells have been observed to be affected by lipotoxicity, glucotoxicity, endoplasmic reticulum/oxidative stress, inflammatory mediators and incretins [2]. In conventional terms, diabetes has been ordered as insulin dependent diabetes mellitus (IDDM) now known as type 1 diabetes, non-insulin dependent diabetes mellitus (NIDDM), now denoted to as type 2 diabetes (T2DM) and gestational diabetes mellitus (GDM). T2DM are at significant risk for both microvascular problems (such as neuropathy retinopathy, and nephropathy) and macrovascular problems (such as cardiovascular comorbidities) due to hyperglycemia and certain elements of the insulin resistance (metabolic) syndrome [3].

The number of people with diabetes rose from 108 million in 1980 to 422 million in 2014. Prevalence has been rising more rapidly in low- and middle-income countries than in high-income countries. Between 2000 and 2019, there was a 3% increase in diabetes mortality rates by age. In 2019, diabetes and kidney disease due to diabetes caused an estimated 2 million deaths [4]. Many drugs are used for the treatment of T2DM to control plasma glucose levels; each class of drug has different mechanisms of action. Some drugs, including Meglitinides, Biguanidae, Sulfonylureas and Thiazolidinediones showed some side effects such as weight gain, toxicity, hypoglycaemia, kidney failure, heart attacks, stroke, and drug resistance. Early finding through regular check-ups, along with safe and effective treatments, diminishes mortality and morbidity by preventing / delaying problems [5]. It is important that the management is not only safe and effective, but also improves the superiority of life of the patient. The development of several novel medicines is in progress, but the greatest need is for drugs that are capable of enhancing insulin sensitivity, halting the progressive pancreatic β-cell failure that is characteristic of T2DM, and preventing or reversing micro-vascular problems [6]. The prevalence and incidence of the illness are increasing internationally despite well understanding of the risk factors for T2DM and indications of effective preventative measures are required. NPs have become increasingly important in the treatment of T2DM, as they offer the potential to deliver drugs to specific parts of the body without causing any systemic side effects.

Recently, nanotechnology has emerged as a powerful tool for exploring new treatments approaches, from treating complex diseases to detecting them at an earlier stage than ever before [7]. Current nanotechnology applications in medicine involve

delivering drugs, or other substances to specific cells using Nanoparticles (NPs) [8]. NPs are small materials with unique properties (at least < 100 nm in one of their dimensions). Reduction of materials to a nanoscale may also alter their properties, enabling them to interact in a specific way with cell biomolecules [9]. NPs have been shown to be an effective way to deliver drugs directly to the target tissue, increasing the therapeutic effect of the drug. Furthermore, they have a lower environmental impact than traditional treatments since they use fewer chemicals and have a reduced risk of toxicity [10]. A growing number of studies have applied nanotechnology to the study of diabetic complications, mostly concerning treatment and strategy. Diabetes has many remaining problems; nanomedicine is likely to be a key technology for solving many of them and will be a core technology in diabetic research.

Different forms of NPs, including liposomes, micelles, hydrogels and dendrimers, which are mostly employed as imaging and therapeutic agents, have been successfully created using polymers and biopolymers. Actual attention has been drawn to the advancement of research on the creation of NPs produced from food biopolymers. Some polymers, such as gelatin glutaraldehyde and chitosan, can be used with the preparation of encapsulate drugs. Chitosan combine with substances that provide synergies when employed as a hemodialysis membrane and matrix in a micro and nanoencapsulation drug [11,12]. One promising approach to treating T2DM is through the use of encapsulated nanoparticles (ENPs). The ENPs can be loaded with drugs or other therapeutic agents and delivered directly to the site of the place. This targeted delivery reduces the amount of drug needed, minimizing side effects and increasing treatment efficacy [7].

Encapsulation is a process that creates micro/nano-systems by trapping active substances inside a biodegradable matrix or "wall" material. Encapsulation is critical in preventing the antidiabetic medication from being degraded. There are two types of encapsulation namely microencapsulation and nanoencapsulation. The purpose why nanoencapsulation is favored over microencapsulation is due to its nanoscale size because the smaller size of the capsules, the greater their bioavailability and release may be adjusted and controlled in a better way. The NPs matrix is used to dissolve, trap, encapsulate, or to attach the drug. There are many different encapsulation methods and the best method to utilize depends on the substance to be encased, its intended usage and the equipment's accessibility [13]. Depending on the preparation technique, one can produce NPs, nanospheres, or nanocapsules. Top-down or bottom-up methods of nanoencapsulation are utilized to create nanomaterials. As the name implies, a top-down strategy entails the reduction in size and sculpting of the material's structure using certain methods (include emulsification solvent evaporation), whereas a bottom-up approach permits the self-organization and self-assembly of molecules to produce nanomaterials (e.g. coacervation) [14]. The most popular encapsulation processes are ionic gelation, spray-drying, emulsification and coacervation (simple or complicated) [15]. The ENPs can also be designed to be biodegradable, allowing them to be broken down and eliminated from the body after their therapeutic effects have been achieved [16]. For instance, they can be used to deliver insulin directly to the pancreas, which is the organ responsible for producing insulin. This can help reduce the amount of systemic side effects associated with insulin injections.

In addition, ENPs can be used to deliver other drugs that can help control the blood sugar levels of those with T2DM. These drugs can also reduce the risk of long-term complications associated with T2DM. Several authors have been reported that ENPs can be used to effectively deliver drugs and other therapeutic agents directly, providing improved therapeutic efficacy and reduced side effects. NPs have also been shown to have a lower environmental impact than traditional treatments, as well as increased stability of the drug [17,18]. The NPs can also be tailored to specific targets, allowing for a more precise delivery of the drug and improved targeting of the antidiabetic activities. This improved targeting of the drug leads to increased efficacy, as well as fewer side effects [18]. NPs also have the potential to reduce the cost of drug treatments, as they can be produced in large quantities and can be used to target multiple diseases [19]. Furthermore, they can be used to deliver drugs that can help to improve the quality of life of those affected. By taking advantage of the potential of ENPs, it is possible to improve the overall health of those with T2DM. In this article, we highlighted some of the strategies that have been developed to enhance the effectiveness of T2DM using ENPs.

Table 1. List of encapsulated nanoparticles and its strategies for the treatment of T2DM.

S. No	Methods	Strategies	Activity	References
01	Chitosan-encapsulated with selenium NPs	Drug delivery	Streptozotocin-induced diabetic rat	[20]
02	Myricetin encapsulated chitosan NPs	Drug delivery	Streptozotocin induced diabetic rat	[21]
03	Fucoxanthin encapsulated with zein NPs	Combination therapy and Target delivery	Streptozotocin induced diabetic mice	[22]
04	Encapsulated exenatide in calcium alginate gel	Controlled release	Streptozotocin induced diabetic rat	[23]
05	Iron NPs encapsulated with graphene shells	Drug delivery	Alloxan induced diabetic mice	[24]
06	Metformin encapsulated gold NPs	Drug delivery	*In vitro* antidiabetic activity	[25]
07	Berberine encapsulated with lecithin–chitosan NPs	Combination therapy	Streptozotocin induced diabetic rat	[26]

08	Egyptian propolis encapsulated with chitosan polyacrylic NPs	Combination therapy	Streptozotocin induced diabetic rat	[1]
09	Gliclazide encapsulated with cubosomal particles	Drug delivery	Streptozotocin induced diabetic rat	[27]
10	Chitosan encapsulated with bioactive compounds (resveratrol)	Controlled release	Streptozotocin induced diabetic rats	[28]
11	Exenatide encapsulated with zein NPs	Drug delivery/Combination therapy	Streptozotocin induced diabetic mice	[29]
12	*Tinospora cordifolia* encapsulated with poly (D, L-lactide) (PLA) NPs	Target delivery	Streptozotocin induced diabetic rats	[30]
13	Starch-based NPs from three sources: horse chestnut, water chestnut and lotus stem encapsulated with catechin	Controlled release	*In vitro* antidiabetic activity	[31]
14	Tannic acid/exendin-4 encapsulated with ternary NPs	Sustained release/ Combination therapy	Streptozotocin induced diabetic mice	[32]
15	Metformin encapsulated with pectin NPs	Sustained release	*In vitro* anti diabetic activity	[33]
16	Ferulic acid encapsulated with chitosan NPs	Biocompatibility and Combination therapy	Streptozotocin induced diabetic rat	[34]
17	Exenatide encaosulated with Polyethylene glycol-poly NPs	Target and drug delivery	Streptozotocin induced diabetic mice	[35]
18	Curcumin encapsulated with chitosan NPs	Drug delivery	Alloxan induced diabetic rats	[36]
19	*Glycyrrhiza glabra* encapsulated with glycyrrhizin and chitosan	Controlled release / combination therapy	Streptozotocin induced diabetic rat	[37]
20	Glipizide encapsulated with Polyvinyl NPs	Sustained release	Streptozotocin induced diabetic rat	[38]
21	Insulin encapsulated with folate coupled polyethylene glycol and ylated polylactide-co-glycolide NPs	Drug delivery	Streptozotocin induced diabetic rats	[39]

Throughout this article, we discuss a number of innovative strategies that are being used by ENPs, including: drug delivery, controlled release, biocompatibility, and combination therapy for the management of T2DM. These strategies have the potential to improve patient outcomes and reduce healthcare costs. Additionally, they may help to reduce the burden on healthcare systems by reducing the number of medications needed to treat T2DM. Furthermore, it may be more cost-effective than traditional treatments and represent a potential more innovative approach to managing T2DM.

1. Targeted delivery

Targeted delivery can improve the efficacy of the treatment by increasing the amount of drug that reaches the intended target and reducing the amount of drug that is wasted due to off-target effects [40]. Achieving target delivery plays a crucial role in preventing the long-term complications of diabetes. When blood sugar levels are consistently too high or too low, it can lead to damage in various tissues and organs. By setting specific goals and working towards them, healthcare professionals can help reduce the risk of complications such as heart disease, kidney disease, nerve damage, and eye problems. Targeted delivery of ENP is one of the strategies that can be used to enhance the effectiveness of their use in the treatment of T2DM.

This involves using a combination of physical and chemical properties to direct the NPs to the specific site for treatment [41]. NPs can be engineered to specifically target cells and tissues in the body, allowing for more precise delivery of therapeutic agents. This targeted delivery can help reduce the side effects of diabetes medications, such as hypoglycemia and liver toxicity [42]. In addition, NPs can be loaded with drugs that are resistant to degradation in the body, which can help to maintain the desired therapeutic effect for longer periods of time. To address this issue, researchers have developed various targeting strategies [22]. For example, NPs can be coated with molecules/drug that specifically bind to receptors on the surface of cells in the pancreas, where insulin is produced. This allows the NPs to be taken up by these cells and deliver their cargo directly to the site of insulin production. Finally, ENPs can be used to deliver drugs directly to the areas of the body affected by diabetes, such as the pancreas or the liver. This targeted delivery can help to reduce the overall systemic toxicity of the drugs and increase their efficacy.

2. Controlled release

Controlled release or sustained release refers to the method of delivering a drug or medication in a controlled manner, allowing for a gradual and predictable release of the active compound/ drug over a specific period. This is done by gradually releasing the NPs over a set period of time in order to maximize the therapeutic effects. This method of delivery allows for a more efficient and targeted delivery of the NPs, which can improve the efficacy of the treatments. Furthermore, this delivery system also reduces the potential side effects caused by high doses of the drug. Controlling the release of drugs also helps to prevent drug resistance, allowing the treatment to be more effective. ENPs have been identified as a promising approach for the controlled release of drugs for the treatment of T2DM. NPs can be designed to encapsulate specific types of drugs and to specifically target certain tissues or organs in the body. This increased specificity can potentially lead to better therapeutic outcomes, while reducing the side effects associated with the drugs. For example, encapsulated NPs containing insulin can be designed to be released in a controlled manner in the pancreas, reducing the amount of insulin injected in the body, achieving desired therapeutic effects.

Another important consideration when using ENPs for the treatment of T2DM is controlling the release of the therapeutic agent. If the agent is released too quickly, it may be cleared from the body before it has a chance to exert its effects [18]. On the other hand, if it is released too slowly, it may not be effective at all. To address this issue, researchers have developed various methods for controlling the release of therapeutic agents from NPs. These include using stimuli-responsive materials that release their cargo in response to specific environmental cues, such as changes in pH or temperature. In addition, NPs can also be designed to deliver drugs directly to the sites of action within the body, leading to improved efficacy [43]. Furthermore, this delivery system also reduces the potential side effects caused by high doses of the drug. Controlling the release of drugs also helps to prevent drug resistance, allowing the treatment to be more effective. Finally, drug delivery systems based on NPs can be tailored to the patient's specific needs, allowing for personalized medicine.

3. Biocompatibility

Biocompatibility strategies are essential in ensuring the safety of diabetes devices and reducing the risk of adverse reactions. By carefully selecting materials, modifying surfaces, conducting biocompatibility testing, and considering design considerations, manufacturers can develop devices that are not only effective but also biocompatible. NPs should be designed to be non-toxic, non-immunogenic, and non-inflammatory in order to maximize the therapeutic and pharmacological effects of the drug payload. Additionally, the NPs should be biodegradable and biocompatible with the human body in order to reduce the risk of adverse side effects. These NPs can be used to selectively target and deliver therapeutic molecules to specific tissues in the body [44]. This can help reduce the risk of side effects by avoiding delivery of the therapeutic molecules in other tissues that are not related to the condition. Furthermore, ENPs can also be used to enhance the bioavailability of drugs and improve drug delivery, which can help improve the efficacy of the therapy [45].

ENPs must also be biocompatible, meaning they do not cause harm to the body. This is particularly important when using NPs for the treatment of T2DM, as patients with this condition may already have compromised health [46]. To ensure biocompatibility, researchers have developed various coatings and surface modifications that reduce the likelihood of an immune response or toxicity. Additionally, these modifications also promote the controlled release of the drug, allowing for a longer and more sustained effect. The NPs can also be designed to target specific cells or molecules in the body, increasing the efficacy of the treatment. Finally, ENPs can also be used to target and activate specific cell types, which can help to reduce the risk of unwanted immune responses that can occur with some therapies.

4. Combination therapy

Combination therapy refers to the use of multiple medications or treatments together to achieve better control of blood sugar levels. This form of therapy offers numerous benefits, including improved glycemic control and reduced risk of complications. Combination therapy involving ENPs and other drugs has been suggested as a potential approach to increase the effectiveness of T2DM using ENPs. For example, combining insulin with NPs loaded with insulin sensitizers may provide better control of blood glucose levels [33]. Additionally, NPs-based therapies may be used in combination with other drugs such as metformin, sulfonylureas, and thiazolidinediones to further improve the treatment efficacy [47]. NPs can be loaded with drugs, hormones, enzymes, and other therapeutic agents, allowing for targeted delivery of these drugs and agents to specific cell types. Due to their biodegradability, and biocompatibility, natural polymers including alginate, chitosan and dextran are frequently resources as excipients in the production of NPs. This combination therapy can help to ensure that the drugs and agents are delivered to the areas of the body that need them most and can reduce the side effects associated with traditional treatments for T2DM.

Furthermore, the use of NPs can improve the bioavailability of drugs and agents, which can increase their effectiveness in controlling T2DM. Additionally, NPs can be engineered to form sustained release systems, allowing for prolonged and sustained release of therapeutic agents. This can lead to improved patient compliance, as the patient will not have to take multiple doses of medication throughout the day. Finally, researchers have explored the use of combination therapy, where multiple therapeutic agents are delivered using ENPs. This approach has several advantages, including increased efficacy and reduced side effects. For example, NPs can be loaded with both insulin and a drug that improves insulin sensitivity, allowing for a more comprehensive treatment approach. Such combination therapies could potentially reduce adverse side effects of the drugs and help individuals achieve better blood glucose control. This approach could pave the way for new treatments for diabetes and other diseases. Finally, NPs can be used to improve the solubility and absorption of drugs, which can lead to improved efficacy.

CONCLUSION

The use of ENPs for the treatment of T2DM has the potential to revolutionize the management of the disease. However, further research is needed to develop effective strategies that maximize the therapeutic efficacy of the NPs. This review highlighted several strategies for enhancing the effectiveness of ENPs, including the use of targeted delivery, the incorporation of antidiabetic agents, and the combination of nanocarriers with other therapeutic approaches. Ultimately, the successful implementation of these strategies will require a comprehensive understanding of the relevant biological and physiological processes, as well as the development of sophisticated delivery platforms capable of achieving targeted and efficient delivery of ENPs. In conclusion, ENPs show great promise as a treatment approach for T2DM. By employing strategies such as targeted delivery, controlled release, biocompatibility, and combination therapy, researchers are working to enhance their effectiveness and improve patient outcomes. Targeted therapy is commonly perceived as being a molecular technique. However, specific cell populations can be targeted by altering drug transport within the body. To improve the delivery of drugs, priming strategies are another promising approach in addition to the design of nanocarriers. This review study focused on the gains achieved in research on ENPs in T2DM treatment, and the strategies for enhancing of present pharmaceuticals and the benefits of nanomedicines, as well as the methodologies and implications of altering immune cells with NPs to better guide future findings.

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