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DIABETES COMPLICATION MANAGEMENT THROUGH NANOPARTICLE-BASED THERAPEUTIC APPROACHES

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ABSTRACT

Diabetes mellitus is a global epidemic associated with numerous complications that affect multiple organ systems. The conventional approaches to managing these complications often have limitations in terms of efficacy and safety. Nanoparticle-based drug delivery systems have emerged as a promising avenue to address diabetes-related complications more effectively. This review explores the recent developments in nanoparticle delivery systems for treating complications such as diabetic retinopathy, neuropathy, nephropathy, and cardiovascular diseases. We discuss the advantages, challenges, and potential future directions of utilizing nanoparticles to improve the therapeutic outcomes of patients with diabetes.

Keywords: diabetes complications, nanoparticle delivery systems, diabetic retinopathy, neuropathy, drug delivery, nanomedicine, clinical translation

1. INTRODUCTION

The term "diabetes" has its origins in the Greek word "diabetes," meaning "siphon," which conveys the excessive passing of fluids, and the Latin word "mellitus," signifying "sweet." The first recorded use of the term "diabetes" can be traced back to Apollonius of Memphis, dating around 250 to 300 BC. Ancient Greek, Indian, and Egyptian civilizations independently noticed the sweet taste of urine in individuals with this condition, ultimately leading to the coining of the term "Diabetes Mellitus" **[1, 2]**.

In 1889, Mering and Minkowski made a groundbreaking discovery by linking the pancreas to the development of diabetes. However, it wasn't until 1922, at the University of Toronto, that Banting, Best, and Collip successfully isolated and purified insulin from the pancreas of cows. This landmark achievement marked the availability of an effective treatment for diabetes **[1]**.

Over the years, substantial progress has been made, with numerous discoveries and advancements in the management of diabetes. Despite these achievements, diabetes remains one of the most prevalent chronic diseases, both in the United States and globally. In the US, it stands as the seventh leading cause of death.

Diabetes mellitus (DM) is a metabolic disorder characterized by inappropriately high levels of blood glucose. DM encompasses several categories, including Type 1 diabetes mellitus (T1DM), Type 2 diabetes mellitus (T2DM), maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and secondary forms stemming from endocrinopathies, steroid usage, among other factors. The primary subtypes, T1DM and T2DM, result from defects in insulin secretion (T1DM) and/or insulin action (T2DM). T1DM typically manifests in children or adolescents, while T2DM is commonly associated with middle-aged and older adults who have prolonged hyperglycemia due to lifestyle and dietary factors. The pathogenesis of T1DM and T2DM is markedly distinct, leading to varying etiologies, clinical presentations, and treatment approaches. Despite significant advancements, diabetes remains a pressing global health concern **[1, 3]**.

2. Nanoparticle Types and Properties

Nanoparticles come in various forms, including liposomes, polymeric nanoparticles, dendrimers, and metallic nanoparticles. These nanoscale carriers offer unique advantages, such as controlled drug release, improved bioavailability, and enhanced tissue targeting. The choice of nanoparticle type depends on the specific characteristics of the therapeutic agent and the targeted complication. Nanoparticles (NPs) are typically categorized into three main classes based on their composition: organic, carbon-based, and inorganic.

2.1. Classification of NPs

2.1.1 Organic NPs

This category encompasses nanoparticles (NPs) composed of organic compounds, including proteins, carbohydrates, lipids, polymers, and various organic substances. Prominent examples within this class include dendrimers, liposomes, micelles, and protein complexes such as ferritin (illustrated in **Figure 1**). Typically, these NPs exhibit qualities of non-toxicity, biodegradability, and, in some instances, possess a hollow core, as seen in liposomes. Organic NPs are susceptible to thermal and electromagnetic radiation, such as heat and light. Moreover, they often form through non-covalent intermolecular interactions, rendering them relatively unstable and facilitating their elimination from the body. Several factors, including composition, surface morphology, stability, and carrying capacity, influence the potential applications of organic NPs. Presently, organic NPs find extensive use in the biomedical field, particularly in targeted drug delivery and cancer therapy **[4, 5]**.

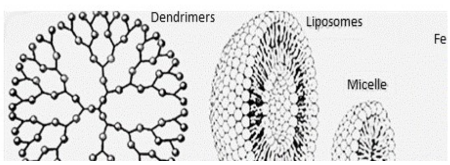

Figure 1: Types of organic NPS: A-Dendrimers, B-Liposomes, C-Micelles and D-Ferritin

2.1.2. Carbon-based NPs

This category encompasses nanoparticles (NPs) composed exclusively of carbon atoms **[5]**. Notable examples within this class include fullerenes, carbon black NPs, and carbon quantum dots (depicted in **Figure 2**). Fullerenes are distinctive carbon molecules with symmetrical closed-cage structures. The renowned C60 fullerene, for instance, consists of 60 carbon atoms arranged in the shape of a soccer ball, while other fullerene variants like C70 and C540 have also been documented. Carbon black NPs are clusters resembling grapes, composed of tightly fused spherical particles. In contrast, carbon quantum dots consist of discrete, quasi-spherical carbon NPs with sizes smaller than 10 nm **[6, 7]**.

Carbon-based NPs harness the unique properties stemming from sp2-hybridized carbon bonds and exhibit extraordinary physicochemical characteristics at the nanoscale. Their exceptional electrical conductivity, high strength, electron affinity, optical properties, thermal properties, and sorption capabilities make carbon-based NPs valuable in various applications. These applications span drug delivery, energy storage, bioimaging, photovoltaic devices, and environmental sensing for monitoring microbial ecosystems or detecting microbial pathogens **[8]**.

Additionally, more intricate carbon-based NPs like nanodiamonds and carbon nano-onions are notable for their low toxicity and biocompatibility, making them suitable for applications in drug delivery and tissue engineering **[9]**.

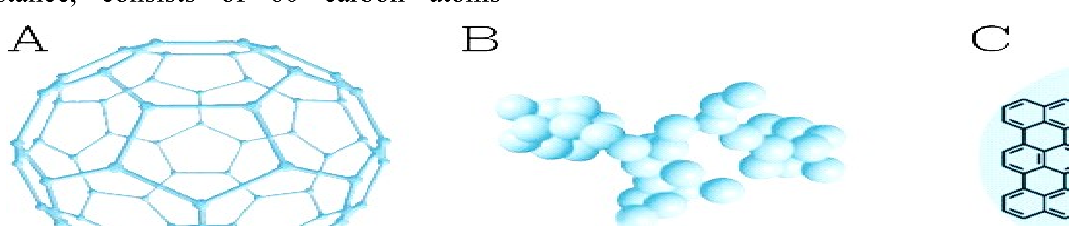

Figure 2: Different types of carbon-based NPs. A C60 fullerene; B carbon black NPs; and C carbon quantum dots

2.1.3. Inorganic NPs

This category encompasses nanoparticles (NPs) that do not consist of carbon or organic materials. Typical examples within this class include metal, ceramic, and semiconductor NPs.

Metal NPs are composed solely of metal precursors and can be monometallic, bimetallic **[4]**, or polymetallic. Bimetallic NPs can be created through alloying or by forming distinct layers (core-shell). These NPs exhibit unique optical and electrical properties due to their localized surface plasmon resonance characteristics **[7]**. Some metal NPs also possess distinctive thermal, magnetic, and biological propertie, making them increasingly vital materials in the development of nanodevices applicable in various physical, chemical, biological, biomedical, and pharmaceutical contexts **[10]** (these applications will be discussed in detail in the applications section of this review). Presently, the controlled synthesis of metal NPs with specific sizes, shapes, and facets is pivotal in the creation of cutting-edge materials **[11]**.

Semiconductor NPs are crafted from semiconductor materials, which display properties that bridge the gap between metals and non-metals. These NPs possess wide bandgaps and exhibit significant alterations in their properties when their bandgap is tuned, in contrast to bulk semiconductor materials **[7]**. Consequently, semiconductor NPs play a crucial role in applications such as photocatalysis, optics, and electronic devices **[10]**.

Ceramic NPs, on the other hand, are inorganic solids composed of carbonates, carbides, phosphates, and oxides of metals and metalloids, such as titanium and calcium **[11]**. They are typically synthesized through heat treatment and subsequent cooling processes, and they can take on various forms, including amorphous, polycrystalline, dense, porous, or hollow structures **[7]**. These NPs are primarily employed in biomedical applications due to their high stability and impressive load-carrying capacity **[10]**. However, they also find use in other fields, including catalysis, dye degradation, photonics, and optoelectronics **[4, 11]**.

2.2. Properties of NPs

Nanomaterials exhibit significant deviations from their bulk counterparts across various aspects, including chemical, physical, electrical, optical, thermal, mechanical, and biological characteristics. These disparities mainly arise from their minute sizes, diverse structural forms, and extensive specific surface areas. For instance, copper nanoparticles (NPs) measuring less than 50 nm exhibit ultra-hard properties, lacking the ductility and malleability typically associated with bulk copper.

The unique attributes of nanomaterials have opened up a broad spectrum of potential applications at the nanoscale, spanning fields such as optoelectronics, catalysis, electronics, water treatment, and beyond. Metal, semiconductor, and oxide-based NPs have found utility as quantum dots, catalysts in chemical reactions, effective adsorbents, drug delivery systems, and versatile biosensors, among other diverse applications.

Nanoparticles have become a focal point of scientific exploration due to their unique ability to bridge the gap between the characteristics exhibited by bulk materials and the atomic/molecular structural features. In the case of gold and silver nanoparticles (AuNPs and AgNPs, respectively), they manifest size-dependent properties like surface plasmon resonance and superparamagnetism, enabling them to confine electrons and induce quantum effects, also referred to as quantum confinement, in semiconducting NPs **[12, 13]**.

3. Nanoparticle Applications in Diabetes Complications

3.1. Diabetic Retinopathy

Diabetic retinopathy (DR) has emerged as the leading cause of blindness among individuals aged 16 to 64 years, a trend exacerbated by the increasing prevalence of diabetes. The factors contributing to DR are multifaceted and include hypertension, genetic predisposition, and the duration of diabetes onset. The pathological changes often involve retinal edema resulting from damage to retinal capillary endothelial cells, thickening of the basement membrane, microvascular blockages, and impairment of the blood-retinal barrier function. These changes lead to retinal edema and the development of abnormal blood vessels (neovascularization) **[15]**.

Nanotechnology has revolutionized the treatment of DR and has reached a new stage of practical application in clinical settings. Some researchers have developed silicate (Si) nanoparticles and examined their antiangiogenic effects on retinal neovascularization. Histological analyses have demonstrated that silicon nanoparticles have no toxic impact on retinal tissue and can effectively inhibit the formation of retinal neovascularization induced by vascular endothelial growth factor (VEGF). Consequently, silicon nanoparticles show promise as an effective treatment for VEGF-induced retinal neovascularization **[15]**.

In a separate study, Kim and colleagues reported their research involving gold nanoparticles, which exhibited the ability to inhibit retinal neovascularization. The results indicated that gold nanoparticles effectively suppressed the proliferation and migration of retinal microvascular endothelial cells and the formation of capillary-like networks induced by VEGF. Furthermore, gold nanoparticles were found to be safe and did not disrupt the activity of microvascular endothelial cells or induce retinal toxicity **[16]**.

Another category of nanoparticles, namely titanium dioxide (TiO_2) nanoparticles, was investigated by Jo *et al*. These nanoparticles were shown to effectively inhibit angiogenesis in vitro without causing any toxic effects on the retina. Intravitreal injection of these nanoparticles also resulted in the inhibition of neovascularization, suggesting their potential usefulness in treating retinopathy mouse models when used at specific concentrations **[17]**.

A study conducted by Gurunathan *et al*. demonstrated that silver nanoparticles could effectively inhibit VEGF-induced angiogenesis in mice, further highlighting the potential of nanoparticles in combating angiogenesis associated with DR **[15, 18]**.

3.2. Diabetic Neuropathy

Diabetic peripheral neuropathy (DNP) is a chronic condition that significantly contributes to the incidence of complications in diabetic patients, often leading to foot ulceration and the risk of amputation. Relevant data and statistics **[19]** reveal that DNP frequently co-occurs with other diabetic complications. Current clinical investigations have identified several factors that can induce DNP, including microvascular damage, disruptions in glucose metabolism, immune system weakening, deficiencies in vitamins and nerve growth factors, as well as theories involving Schwann cells.

Within the dorsal root ganglion (DRG), satellite glial cells (SGCs) envelop the neuronal bodies and express the purinergic 2 (P2) Y12 receptor. The activation of SGCs plays a pivotal role in the pathogenesis of DNP. Curcumin, known for its anti-inflammatory and antioxidant properties, has been employed to target and enhance its bioavailability through encapsulation in nanoparticles. Researchers have explored this avenue and found that curcumin-coated nanoparticles can reduce the upregulation of the P2Y12 receptor on SGCs in the DRG, subsequently diminishing the mechanical and thermal hyperalgesia observed in diabetic rats **[20]**.

Moreover, studies have examined the impact of nanocurcumin on sensorimotor polyneuropathy (DSPN) severity in type 2 diabetes mellitus (T2DM) patients. The findings indicate that short-term nanocurcumin supplementation can improve DSPN and reduce its severity in T2DM patients. Notably, serum fasting blood sugar (FBS) and HbA1c levels significantly decreased, suggesting that controlling hyperglycemia in T2DM patients presents an opportunity to ameliorate DSPN **[21]**.

Nano-mir-146a-5p, on the other hand, has demonstrated the ability to enhance nerve conduction velocity and mitigate morphological damage and demyelination in the sciatic nerve of DPN rats. These nanoparticles have also been found to suppress the expression of inflammatory cytokines, caspase-3, and cleaved caspase-3 in the sciatic nerve. Additionally, nano-mir-146a-5p promotes the expression of myelin basic protein, indicating its protective effect on peripheral nerves in the DPN rat model. This protective effect is likely achieved through the regulation of inflammatory responses and apoptosis **[22]**.

3.3. Diabetic Nephropathy

Diabetic nephropathy (DN) stands as a major contributor to kidney disease, and currently, effective prevention and treatment methods for DN remain elusive, resulting in less than satisfactory outcomes. In recent years, the integration of nanotechnology into DN treatment has shown promise in enhancing drug effectiveness and improving the prognosis for diabetic patients. This approach offers the potential to alleviate patient suffering and reduce the economic burden associated with the disease. The pathogenesis of DN is multifaceted, involving genetic factors, disturbances in glucose metabolism activating multiple endocrine pathways, the production of endothelial nitric oxide synthase, advanced glycation end products (AGEs), and the inhibition of nitric oxide formation. Contributing factors also encompass insulin resistance, inflammatory responses, and alterations in renal hemodynamics, collectively fostering the onset and progression of DN. Research has identified advanced glycation end products (RAGE) and their various ligands as pivotal molecules in the development of DN **[23]**.

Poly(lactic-co-glycolic acid) (PLGA) is a synthetic polymer material. Yang **[46]** devised and optimized a nanoscale formulation of crocin (CT-PLGA-NP), a therapeutic agent for DN induced by streptozotocin (STZ). In experiments, CT-PLGA-NPs exhibited drug accumulation in the kidneys and livers of diabetic rats, delivering renal antifibrotic and anti-inflammatory effects. Treatment with CT-PLGA-NPs significantly reduced the production and expression of renal fibrosis factors (TGF-β1 and fibronectin) and inflammatory cytokines, including MCP-1 and TNF-α. This treatment also notably decreased the activation of NF-κB expression and PKC activity. Existing research suggests that CT-PLGA-NPs can mitigate diabetic nephropathy by virtue of their antifibrotic and anti-inflammatory effects.

Ahangarpour *et al*. **[24]** conducted an assessment of myricetin solid lipid nanoparticles (SLN) in a murine model of streptozotocin nicotinamide (STZ-NA)-induced DN. Myricetin and its administration as SLN were found to ameliorate DN-related changes by reducing oxidative stress and elevating antioxidant enzyme levels. These effects were more pronounced in mice treated with SLN.

In another study by Ahad *et al*. **[25]**, nanoliposomes containing Eprosartan mesylate were prepared and evaluated in STZ-induced diabetic nephropathy in Wistar rats. The results indicated significant reductions in serum creatinine, urea, lactate dehydrogenase, total albumin, and malondialdehyde levels, signifying the renal protective properties of Eprosartan mesylate-loaded nanoliposomes.

3.4. Cardiovascular Complications

Diabetic cardiomyopathy (DCM) is a myocardial condition occurring in diabetic patients and cannot be attributed to other cardiac diseases. Research indicates that oxidative stress-induced damage to myocardial cells due to diabetes mellitus is a significant factor leading to complications like DCM, ultimately resulting in impaired myocardial contractility and diastolic function **[26]**. Common pathological features of DCM include myocardial fibrosis and apoptosis, which play crucial roles in subsequent cardiac functional impairment **[27]**. Another primary characteristic of DCM is microvascular disease within the myocardium, closely associated with the decline in left ventricular function **[28]**.

Nanotechnology has found application in addressing DCM, with studies focusing on poly(lactic-co-glycolic acid) (PLGA) as a drug carrier to prepare PSS-loaded nanoparticles. Yu *et al*. investigated the impact of PSS-NP on vascular endothelial function in DCM rats. Their findings demonstrated that PSS-NP significantly improved ventricular wall motion and cardiac systolic and diastolic functions in DCM rats. Importantly, it played a role in regulating the ultrastructure of myocardial microvascular endothelial cells in the DCM rat heart, thus retarding the progression of vascular endothelial dysfunction. This treatment led to a notable increase in the concentration of nitric oxide synthase (eNOS) and vascular endothelial growth factor A (VEGFA) in serum, further mitigating vascular endothelial injury in DCM rats **[29]**.

Studies have also explored the therapeutic potential of acidic fibroblast growth factor-l (FGFl) nanoliposomes combined with ultrasound targeted microbubble blasting (UTMD) for DCM. The evaluation of cardiac function indexes revealed significant improvements in left ventricular systolic pressure (LVESP), left ventricular end diastolic pressure (LVEDP), and maximum rate of left ventricular development pressure (LV ± DP/dtmax) in the FGFl-combined treatment group compared to other treatment and DCM groups. This suggests that FGFl can enhance myocardial systolic and diastolic function in DCM rats. Additional assessments involving collagen volume fraction (CVF) and the apoptotic index of cardiomyocytes showed significant reductions in the FGFl-combined treatment group, indicating an improvement in cardiac function. Furthermore, the study observed an increase in myocardial microvascular density (MVD) in the FGFl-combined treatment group, indicating a potential enhancement in myocardial blood flow and a reduction in oxidative stress injury in DCM rats. As such, FGFl nanoliposomes combined with UTMD exhibit the potential to ameliorate both pathological and functional changes in DCM induced by diabetes **[30]**.

While nanotechnology has shown promise in animal experiments for DCM treatment, translating these results to clinical settings requires careful consideration. Questions regarding the clinical effectiveness of nanodrugs, as seen in animal experiments, as well as concerns about biocompatibility, biodegradability, and drug release kinetics, need to be addressed to ensure their successful clinical application.

4. Challenges and Future Directions

While nanoparticle-based drug delivery systems hold great promise for diabetes complications, several challenges remain. These include scaling up production, ensuring safety, and navigating regulatory hurdles. Furthermore, long-term clinical data on the efficacy and safety of these therapies are needed.

Nanomedicines are intricate, three-dimensional structures composed of multiple components meticulously arranged for optimal functionality. Consequently, even slight alterations in their composition or manufacturing processes can have adverse effects, disrupting the delicate balance of these components and yielding undesirable outcomes. Achieving a comprehensive understanding of these components, facilitated by thorough physicochemical characterization and functional assessments, becomes imperative to ensure the consistent and reproducible production of nanomedicines.

The journey of a nanomedicine from development to clinical application presents several challenges, commencing with the need for meticulous characterization and the successful fabrication of these intricate constructs. In addition to adhering to standard criteria for safety, efficacy, and desirable pharmaceutical attributes, such as stability and ease of administration, which apply to most drugs, the ideal nanoparticle system or nanomedicine designed for therapeutic purposes should encompass the following attributes:

- In-Depth Component Understanding: A profound comprehension of the critical components and their intricate interactions is essential.

- Key Characteristic Identification: The identification of pivotal characteristics and their correlation with performance is crucial.
- Replicability under Manufacturing Conditions: The capacity to replicate these key characteristics consistently during manufacturing processes is vital.
- Sterile Form Production: The ability to produce the nanomedicine in a sterile form is imperative.
- Targeting or Accumulation Capability: The capability to target or accumulate at the intended site of action, surmounting biological barriers, is advantageous.
- In-Use Stability: The nanomedicine should exhibit stability during use, be easy to store, and straightforward to administer.

These attributes collectively define an ideal nanomedicine system tailored for therapeutic applications **[31]**.

Future research should focus on optimizing nanoparticle formulations, exploring combination therapies, and tailoring treatments to individual patient profiles. Collaborative efforts between academia, industry, and regulatory bodies are crucial for advancing these innovative strategies from the laboratory to clinical practice. Here are some key aspects of the future of nanoparticles:

1. Advanced Drug Delivery: Nanoparticles will continue to revolutionize drug delivery systems. They can be designed to carry drugs directly to target cells or tissues, increasing drug efficacy and reducing side effects. This is especially promising in cancer treatment, where nanoparticles can selectively target tumor cells.

2. Personalized Medicine: Nanoparticles will play a pivotal role in personalized medicine, allowing for tailored treatments based on an individual's genetic makeup and specific health needs. This could lead to more effective and safer treatments.

3. Vaccines: Nanoparticles are being explored as a platform for vaccine delivery. They can enhance the immune response, increase vaccine stability, and enable the development of novel vaccines for various diseases.

4. Diagnostic Tools: Nanoparticles are used in diagnostic tools for detecting diseases at an early stage. They can improve the sensitivity and accuracy of diagnostic tests, leading to earlier interventions and better patient outcomes.

5. Regenerative Medicines: Nanoparticles can be employed in regenerative medicine to stimulate tissue repair and regeneration. They may be used to deliver growth factors or stem cells to damaged tissues, promoting healing.

6. Electronics: Nanoparticles are essential in the development of smaller and more efficient electronic components. They enable the creation of nanoscale transistors, memory devices, and sensors, driving advancements in electronics.

7. Energy Storage: Nanoparticles are being utilized to improve energy storage technologies, such as batteries and supercapacitors. They can enhance energy density, charge-discharge rates, and overall performance.

8. Environmental Remediation: Nanoparticles are used in environmental science to remove pollutants from water and air. They can adsorb or break down contaminants, contributing to cleaner environments.

9. Materials Science: Nanoparticles are employed to develop novel materials with unique properties. This includes super-strong and lightweight materials, as well as materials with advanced thermal, electrical, or optical properties.

10. Nanotechnology Safety: As the use of nanoparticles becomes more widespread, there will be a growing emphasis on understanding their potential health and environmental impacts. Research into the safety of nanomaterials will be crucial.

11. Nanofabrication: Advances in nanofabrication techniques will enable the precise and scalable production of nanoparticles and nanostructures, expanding their practical applications.

12. Space Exploration: Nanoparticles could have applications in space exploration, from advanced materials for spacecraft to drug delivery systems for astronauts during long missions.

In summary, the future of nanoparticles is incredibly promising, with potential breakthroughs in medicine, electronics, energy, and environmental science. Continued research and innovation in nanotechnology will drive these advancements and shape the future of various industries.

5. CONCLUSION

Nanoparticle-based drug delivery systems have the potential to revolutionize the treatment of diabetes-related complications by improving drug targeting, bioavailability, and safety profiles. The versatility of nanoparticles allows for tailored approaches to address specific complications affecting different organ systems. While challenges in clinical translation exist, the continued development and refinement of nanoparticle-based therapies offer hope for enhanced outcomes and a better quality of life for individuals living with diabetes and its complications.

Nanotechnology stands out as one of the most promising scientific frontiers in the 21st century. Its continuous development holds immense potential for advancing modern medicine, sparking fresh insights, and making significant contributions to disease prevention and treatment.

Despite advancements in modern medical practices, the incidence of diabetes continues to rise, accompanied by increasingly severe complications. In this context, effective treatment measures are urgently needed. Nanotechnology has opened doors to a plethora of new nanomaterials applicable to biomedical purposes and disease management. While finding suitable carriers and methodologies remains a challenge, it's worth noting that traditional Chinese medicine ingredients can also be harnessed through nanotechnology, offering promising avenues for further research.

Nanotechnology's pivotal role in the realm of nanomedicine, especially in drug delivery systems, cannot be overstated. Among various drug delivery methods, oral administration is the most convenient. However, physiological obstacles within the body, such as pH fluctuations in the digestive tract and enzymatic degradation processes, limit its full potential. Nanostructures present several advantages over traditional drug delivery, overcoming pharmacokinetic and pharmacodynamic limitations and facilitating advanced drug delivery approaches, including targeted delivery, controlled release, and leveraging the enhanced permeability and retention (EPR) effect.

Challenges in nanotechnology's medical applications primarily revolve around the instability of the preparation process and the absence of a comprehensive biosafety evaluation system. Given the size constraints inherent to nanoparticles at the nanoscale, they serve as effective carriers for crucial therapeutic agents. Research focused on structural enhancements of these nanocarriers holds the potential to address these issues. Various nanopreparations for oral administration have shown promise in reducing adverse reactions associated with diverse diseases. These oral nanostructures extend beyond drug delivery and find applications in gene therapy and vaccination. Comprehensive research efforts are essential to enhance and refine oral nanopreparations for optimal effectiveness.

While nanotechnology has made initial strides in various disease trials, several challenges, including biodegradability, biocompatibility, drug release kinetics, stability of biomacromolecules, and nanoparticle targeting, require further refinement. Moreover, ensuring nanotechnology's safety for clinical disease treatment demands extensive molecular studies. These steps are essential to better serve the clinical community in advancing disease treatment.

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Conflict of interest

Authors has no conflict of interest.

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