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A COMPREHENSIVE REVIEW OF ADVANCES IN NANOPARTICLE BASED FORMUATION FOR CONTROLLED AND SUSTAINED DRUG DELIVERY IN SYSTEMIC THERAPY

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Abstract:
Nanoparticles have revolutionized modern medicine by significantly improving drug bioavailability, targeted delivery, and controlled release mechanisms. Traditional drug delivery systems often suffer from rapid clearance, poor solubility, and systemic toxicity, leading to limited therapeutic efficacy. In contrast, nanoparticles possess unique physicochemical properties that enable precise drug targeting, thereby minimizing off-target effects and enhancing treatment outcomes.Various types of nanoparticles—such as polymeric nanoparticles, liposomes, solid lipid nanoparticles , dendrimers, and metallic nanoparticles—have been extensively investigated for drug delivery applications. These nanocarriers utilize both passive and active targeting strategies, including ligand-based functionalization, to improve therapeutic precision.A major application of nanoparticles is in oncology, where traditional chemotherapy often causes severe side effects and insufficient drug accumulation at tumor sites. Nanocarrier systems address these issues by enabling controlled drug release, improved stability, and tumor-specific delivery, thereby reducing toxicity. Moreover, photosensitizer-loaded nanoparticles have shown great promise in photodynamic therapy, offering enhanced retention and selectivity in tumor tissues. Nanoparticles are also being developed for the delivery of nucleic acids and proteins, overcoming biological barriers to improve gene therapy, RNA interference, and protein-based treatments. Biological barriers like the blood-brain barrier and mucosal layers further complicate efficient delivery.To address these limitations, current research focuses on designing biodegradable, biocompatible, and stimulus-responsive nanoparticles. Future developments are expected to integrate personalized nanomedicine, artificial intelligence, and real-time imaging technologies to further refine drug formulations and treatment strategies.This review explores emerging trends, medical applications, and the ongoing evolution of nanoparticle-based drug delivery systems. It highlights the growing importance of nanotechnology in creating precision, multifunctional, and patient-centered therapeutic solutions.
KEYWORDS: Nanotechnology, Nanoparticles, solid lipid, targeted delivery

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INTRODUCTION:

The therapeutic efficacy, bioavailability, and targeted distribution of pharmacological agents have significantly improved due to advancements in drug delivery systems. Among these breakthroughs, nanoparticles have emerged as one of the most promising vectors, enabling precise delivery of drugs to specific sites within the body.Typically ranging in size from 1 to 100 nanometers, nanoparticles exhibit several unique physicochemical properties, including a high surface area-to-volume ratio, tunable surface characteristics, and controlled drug release mechanisms. These features make them highly attractive candidates for drug delivery applications.Traditional drug delivery methods often face challenges such as poor biodistribution, rapid drug clearance, and systemic toxicity. Nanoparticle-based approaches help to overcome these limitations by enhancing drug stability, prolonging circulation time, enabling targeted delivery, reducing side effects, and improving overall therapeutic outcomes[1].

Substantial research has explored the use of nanoparticles in treating a wide array of diseases, including cancer, infectious diseases, neurological disorders, and cardiovascular conditions. Through both passive and active targeting mechanisms, nanoparticles offer improved localization at disease sites. The enhanced permeability and retention (EPR) effect facilitates passive accumulation in tumor tissues. Meanwhile, surface functionalization with ligands or antibodies enables active targeting of specific cells, minimizing damage to healthy tissue.An emerging innovation in this field is the development of stimuli-responsive nanocarriers—nanoparticles that respond to specific physiological triggers such as pH, temperature, or enzymes. These systems release their therapeutic payload in response to changes in the tumor microenvironment, thereby increasing the precision and effectiveness of treatment.

Nanoparticles are particularly beneficial in photodynamic therapy (PDT), where they serve as carriers for photosensitizers. Upon activation by light, photosensitizers generate reactive oxygen species that induce localized cell death. However, their clinical application is often hindered by poor solubility, rapid clearance, and off-target effects. Nanoparticle carriers address these limitations by enhancing the solubility, bioavailability, and selective accumulation of photosensitizers at disease sites[2].

Hybrid nanocarriers—such as liposomes, micelles, and polymeric nanoparticles—have shown promise in enhancing the efficacy of PDT while reducing systemic toxicity. Furthermore, the integration of imaging agents into nanoparticles enables real-time tracking of drug distribution, enhancing treatment precision.Nanoparticle systems have also shown potential in the delivery of proteins and nucleic acids, which face challenges such as low serum stability and inefficient intracellular delivery. Nanoparticles can shield these biomolecules from enzymatic degradation and facilitate controlled release, thereby increasing therapeutic viability [3].
Effective delivery systems are essential for the success of nucleic acid-based therapeutics, such as gene therapy and RNA interference (RNAi), to ensure cellular uptake and therapeutic efficacy. Non-viral nanoparticle carriers, including polymeric systems and lipid nanoparticles, have emerged as promising alternatives to viral vectors. These carriers can efficiently deliver nucleic acids to target cells, helping to overcome biological barriers and improving treatment outcomes.

Despite significant advancements, the clinical translation of nanoparticle-based drug delivery systems continues to face major challenges. These include issues of reproducibility, large-scale manufacturing, regulatory approval, and concerns over long-term toxicity. Addressing these barriers requires further research into the interactions between nanoparticles and biological systems, especially in relation to immune responses, biodistribution, and clearance mechanisms.

Personalized nanomedicine also demands consideration of patient-specific factors such as genetic variability and disease heterogeneity. Developing safe, effective, and tailored nanoparticle-based therapeutics requires interdisciplinary approaches that integrate advances in materials science, pharmacology, and genomics.
This review provides a comprehensive analysis of the latest developments in nanoparticle-mediated drug delivery, emphasizing key breakthroughs, mechanisms of action, and therapeutic applications. It also highlights emerging trends in nanotechnology, including targeted delivery, enhanced biocompatibility, and multifunctional nanoparticles designed to address current limitations. By evaluating both the potential and challenges of these systems, this work aims to support the advancement of nanomedicine and guide future innovations in precision drug delivery [4].

2. Drug delivery system

Nanoparticles have emerged as a crucial tool in drug delivery due to their distinctive features and potential advantages. Typically ranging from 1 to 100 nanometers in size, these microscopic entities can be precisely engineered to deliver medications to specific target sites within the body. Their ability to enhance therapeutic efficacy makes them a promising solution for the future of drug delivery.

One of the major challenges in treating many diseases is delivering therapeutic agents directly to the affected area. Traditional pharmaceuticals often suffer from poor biodistribution, limited effectiveness, and low selectivity. Depending on their surface properties, nanoparticles are commonly absorbed by organs such as the liver, spleen, and other components of the reticuloendothelial system. Controlled drug delivery systems using nanoparticles enable targeted transport of drugs, increasing their effectiveness at the site of action while minimizing side effects. Nanoparticle-based delivery methods are generally classified into five categories: diagnostic, anticancer, photosensitizer, nucleic acid, and protein delivery. Each approach utilizes nanotechnology to improve precision, reduce side effects, and enhance treatment outcomes. These strategies play a vital role in advancing modern medicine, particularly in disease diagnosis and targeted therapy[5].

3.Applications of nanoparticles in drug delivery :

Over the past few decades, nanoparticles have emerged as one of the most advanced drug delivery systems, owing to their unique advantages and characteristics. In the United States, the Food and Drug Administration (FDA) has approved several nanoparticle-based chemotherapy formulations for the treatment of breast cancer, with many more currently undergoing clinical trials. These formulations include polymeric nanoparticles, liposomes, and paclitaxel-bound nanoparticles.Polymer-based nanoparticles offer a high degree of functionality: their outermost layers can be engineered to be permeable, biocompatible, and biodegradable. These nanoparticles are commonly fabricated using synthetic polymers such as poly(lactic-co-glycolic acid) (PLGA), polyvinyl alcohol, and polyethylene glycol, or natural polymers like chitosan and cellulose. They are characterized by high drug-loading capacity, scalable production processes, and the ability to control drug release kinetics. Notably, PLGA has been shown to suppress P-glycoprotein (P-gp) activity, a mechanism that contributes to the reversal of multidrug resistance (MDR).Nanoparticles are also employed in combinatorial drug delivery for breast cancer, where multiple therapeutic agents are delivered simultaneously. This synergistic approach enhances therapeutic efficacy, reduces the likelihood of drug resistance, and improves patient survival rates. However, the in vivo efficacy of such systems is influenced by tumor heterogeneity and the vascularization of the tumor microenvironment. Effective inhibition typically occurs only in regions where the nanoparticle construct is successfully delivered intracellularly and sustains drug release over time[6].

Small interfering RNA (siRNA) delivery via nanoparticles also shows promise, but its effectiveness is subject to similar in vivo limitations. To accurately assess the efficacy of novel therapies, patient-derived xenograft (PDX) mouse models are considered superior to traditional human mammary carcinoma cell lines. These models retain the molecular, cellular, genomic, and epigenomic characteristics of original tumors, providing a more realistic platform for clinical translation. In particular, freshly isolated breast cancer xenografts preserve the complexity and heterogeneity of the tumor microenvironment. Nanoparticle-based drug delivery systems are currently categorized into six primary medical application areas: cancer, mucosal, skin, lung, brain diseases, and clinical drug delivery. The metaphor of a prism aptly illustrates the versatility of nanoparticles, reflecting their ability to be tailored for specific therapeutic contexts. These advancements enhance drug bioavailability, minimize systemic side effects, and improve the overall effectiveness of treatment.

4. **Advanced nanoparticle-enabled drug delivery systems**

Nanoparticle-based drug delivery systems represent a cutting-edge advancement in modern medicine, enabling the precise and effective administration of therapeutically active compounds. These systems enhance the solubility, stability, and targeted distribution of drugs by leveraging the unique properties of nanoparticles, such as their high surface area, functional versatility, and nanoscale dimensions. Recent research has focused on the development of biodegradable and biocompatible nanocarriers, including liposomes, polymeric nanoparticles, and metal-based nanoparticles.Innovations in surface modification techniques and stimulus-responsive release mechanisms have further expanded the applicability of these systems, particularly in cancer therapy, immunotherapy, and regenerative medicine. Despite their potential, challenges remain—most notably, large-scale manufacturing limitations, toxicity concerns, and regulatory complexities. Nevertheless, ongoing advancements continue to address these issues.The technology holds significant promise for the advancement of personalized medicine by improving treatment outcomes. Enhanced targeting efficiency, controlled drug release, and improved solubility and stability collectively contribute to increased bioavailability of therapeutic agents. Furthermore, the ability of nanoparticles to carry a wide range of drug molecules while overcoming biological barriers opens new avenues for more effective and precise medical interventions[7].

5. Nanoparticles-based drug delivery system:

Nanoparticles are defined as structures with at least one dimension in the nanometer range. Although the term typically refers to particles between 1 and 100 nm, particles up to several hundred nanometers are also frequently categorized as nanoparticles. Due to their small size, nanocarriers exhibit enhanced physicochemical and biological properties, allowing for more efficient delivery of bioactive compounds. These carriers are more readily taken up by cells compared to larger particles.

While smaller nanoparticles can penetrate tissues and are prone to rapid renal clearance, larger ones are often quickly opsonized and eliminated from circulation by macrophages in the reticuloendothelial system .Each type offers unique advantages such as targeted delivery**,** controlled drug release**,** biocompatibility**,** and surface modification capabilities. A schematic classification of these nanoparticles helps illustrate their roles in enhancing therapeutic efficacy and minimizing side effects.Pharmaceutical nanotechnology has emerged as a powerful discipline with vast potential for the precise spatial and temporal delivery of bioactive agents and diagnostics. It also offers innovative smart materials for tissue engineering. This field introduces new tools and opportunities that are expected to significantly impact disease diagnosis, prognosis, and treatment through advanced nano-engineered technologies.It enables the improvement of materials and medical devices, fostering the development of novel technologies where traditional methods may have reached their limits. Pharmaceutical nanotechnology also presents new prospects for the industry by creating patented technologies, which can help counteract revenue losses caused by the expiration of drug patents[8].

Furthermore, pharmaceutical nanotechnology plays a crucial role in disease prevention by providing innovative tools to better understand cellular processes and the distinctions between healthy and abnormal cells. It offers valuable insights into the molecular mechanisms underlying diseases, thereby advancing research and therapeutic approaches.Overall, the systematic development and classification of nanoparticles support the expanding role of nanotechnology in personalized medicine**,** offering improved therapeutic strategies and more precise drug delivery solutions.

6. Current challenges for the drug delivery system

Drug delivery systems (DDS) play a crucial role in modern medicine by enhancing the effectiveness and safety of therapeutic drugs. However, several challenges limit their full potential. One of the major issues is poor bioavailability, especially for drugs with low solubility or instability in biological environments. Many promising drug candidates fail because they are not adequately absorbed, are rapidly metabolized, or degrade before reaching their target site. To overcome these obstacles, innovative formulation strategies such as nanocarriers, liposomes, and polymeric systems have been developed.

Targeted drug delivery remains another significant challenge. It involves directing drugs to specific tissues or cells to minimize systemic side effects. Despite advances in ligand-based targeting, nanoparticle design, and stimuli-responsive carriers, achieving precise and controlled drug release continues to be difficult. The complexity of biological barriers, like the blood-brain barrier (BBB), further restricts treatment options for neurological disorders[9].

The immune system also poses a barrier to DDS, particularly nanomedicine-based therapies. The mononuclear phagocyte system (MPS) rapidly clears many drug carriers from circulation, reducing their therapeutic effectiveness. Stealth technologies such as polyethylene glycol (PEG) coatings help evade immune detection, although issues like PEG immunogenicity remain unresolved.Patient compliance is a persistent concern, especially for chronic diseases requiring long-term medication adherence. Factors such as frequent dosing, invasive delivery methods, and adverse effects contribute to poor compliance. Innovations like long-acting injectables, transdermal patches, and controlled-release oral formulations aim to improve adherence.

Manufacturing challenges also exist, as producing sophisticated DDS in a cost-effective and scalable manner is difficult. Additionally, rigorous safety and efficacy testing prolong regulatory approval processes, creating further hurdles.Environmental and ethical concerns regarding the disposal of DDS materials, especially nanoparticles and synthetic polymers, are growing. Research into biodegradable and biocompatible alternatives seeks to reduce long-term environmental impact.Although DDS have revolutionized drug administration, challenges remain in bioavailability, targeting, immune evasion, patient compliance, manufacturing, regulatory approval, and environmental safety. Continued multidisciplinary research integrating nanotechnology, biomaterials science, and pharmaceutical engineering holds promise for overcoming these obstacles and advancing drug delivery technologies[10].

7. Future prospects of drug delivery systems

Nanomedicine is one of the most promising and rapidly evolving fields of study today. Over the past two decades, significant research efforts have resulted in the filing of approximately 1,500 patents and numerous clinical studies. Cancer serves as a prime example of a disease where nanotechnology has enhanced both diagnosis and treatment. Nanomedicine and nano-drug delivery systems are poised to dominate future research and development by enabling the precise delivery of medication directly to affected cells, such as cancer or tumor cells, while sparing healthy tissue .

The nanoparticles discussed herein vary in size, ranging from nanometers to sub-micrometers. Future research will focus on developing materials with greater uniformity and improved drug loading and release capabilities. Among the most critical advances are those involving metal-based nanoparticles, particularly gold nanoparticles, which have shown promise in both diagnostics and therapy. Gold nanoparticles are well-absorbed by soft tumor tissues and can sensitize tumors for selective thermal ablation treatments.The emergence of drug resistance and severe side effects associated with conventional therapies for diseases such as leishmaniasis has intensified the need for alternative treatments. However, limited commercial incentives for neglected diseases have constrained financial support for drug research and development, thus impeding progress in nanoparticle-based solutions.

While nanotechnology offers excellent biocompatibility, its targeting efficiency requires further improvement. Quantum dots (QDs), widely studied in bio-imaging, contain heavy metals that reduce toxicity while retaining targeting and imaging capabilities. A deeper understanding of inflammatory diseases and tailored nanoparticle applications will enhance therapeutic efficacy and reduce adverse effects[11].

Numerous nanomaterials have gained attention for cancer therapy, although these applications are still emerging. Despite progress in developing drug delivery systems, challenges remain. Molecularly targeted drugs alter specific protein functions to treat aberrant conditions, but more fundamental molecular research is needed to fully understand drug permeation and cellular barriers. Enhancing drug retention and delivery effectiveness, alongside comprehensive safety assessments, is critical to accelerating clinical translation.

Future developments in buccal mucoadhesive drug delivery systems could focus on biologics such as vaccines, peptides, and proteins. Additionally, innovative strategies—like enzyme-directed self-assembly that forms intracellular supramolecular nanofibers—offer new mechanisms to control nanocarrier aggregation and drug release within tumor tissues.Ocular diseases pose a significant challenge due to the eye’s unique anatomy, which limits drug bioavailability. Conventional therapies often require frequent dosing and have limited efficacy. Polymeric nanocarriers (PNCs) and lipid nanocarriers (LNCs), with enhanced permeability, retention, solubility, reduced toxicity, and targeted, sustained release, represent promising advances for effective ocular drug delivery.

Physical drug delivery methods hold great potential compared to viral or chemical approaches, and hybrid techniques combining multiple physical strategies show promise for efficient distribution and high cell viability. However, these novel systems require further research before clinical trials can commence.Overall, future nanomedicine research will emphasize understanding transport mechanisms, endocytosis, biological barriers, degradation pathways, and minimizing adverse effects to fully realize nanotechnology-based therapies[12].

8. CONCLUSION:

Nanoparticle-based drug delivery systems represent a novel approach in modern medicine, addressing many limitations of traditional drug administration methods. These nanomaterial carriers, due to their nanoscale size, enhance drug solubility, stability, targeted delivery, and controlled release, thereby improving therapeutic outcomes while minimizing systemic toxicity.Various nanoparticle platforms—such as polymeric nanoparticles, liposomes, solid lipid nanoparticles (SLNs), dendrimers, and metallic nanoparticles—have shown promising applications across multiple medical fields. In cancer treatment, nanoparticles facilitate precise drug distribution via passive and active targeting, reducing off-target effects and enhancing efficacy. Additionally, they play vital roles in gene therapy, protein delivery, and photodynamic therapy, contributing to innovative treatment strategies for complex diseases.Despite these advances, several challenges hinder the widespread clinical adoption of nanoparticle-based therapeutics. Key issues include biocompatibility, scalable manufacturing, regulatory approval, immune system interactions, and potential long-term toxicity. Biological barriers like the blood-brain barrier (BBB) and mucosal layers further complicate effective drug delivery. Consequently, there is a growing demand for stimuli-responsive, biodegradable, and multifunctional nanocarriers.The heterogeneity of diseases and patient-specific characteristics also highlight the need for personalized drug delivery approaches. Future research aims to integrate nanomedicine with cutting-edge technologies such as artificial intelligence (AI), real-time imaging, and precision medicine to optimize nanoparticle design and application. Moreover, innovative drug formulations and hybrid nanocarrier systems combining multiple delivery strategies hold great promise for enhancing targeting and therapeutic outcomes.

Ongoing development of safety assessments and regulatory frameworks will be essential to translate these technologies into clinical practice. In summary, nanoparticle-based drug delivery systems offer tremendous potential to revolutionize treatment by providing safer, more effective, and personalized therapies. Continued advancements in nanotechnology, biomaterials, and pharmaceutical engineering are expected to drive the evolution of next-generation drug delivery platforms, overcoming existing limitations and unlocking new possibilities in healthcare.

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