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Review Paper

Review paper on nanomedicine: advancements in drug delivery systems

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Abstract

Nanomaterial-based drug delivery systems (NBDDS) enhance the safety and therapeutic efficacy of drugs due to their unique properties. By combining therapeutic drugs with nanoparticles, these systems address the limitations of conventional treatments, such as poor stability, solubility, transmembrane transport, short circulation time, and toxicity. This review covers recent advancements in targeting design strategies and therapeutic approaches using various nanomaterial-based systems. It also discusses the challenges and future perspectives of smart systems in targeting both intravascular and extravascular diseases. Nanomedicine has revolutionized drug delivery, offering precise control over drug release and targeting. Key developments in nanoparticle formulations, targeting mechanisms, and clinical applications are highlighted, along with the challenges and future prospects of nanomedicine in improving therapeutic efficacy and reducing side effects.

Keywords: Nanotechnology. Liposomes, nanocarrier, conventional drugs, Bioavailability, Pharmacokinetics.

Introduction

Nanotechnology offers innovative solutions to overcome limitations of conventional drug delivery systems, such as poor bioavailability, limited targeting capabilities, and side effects. This review focuses on recent advancements in nanocarrier design and their applications in targeted and stimuli-responsive drug delivery. Nanomedicine, the application of nanotechnology in medicine, has emerged as a transformative approach to drug delivery. By leveraging the unique properties of nanoparticles, researchers have developed sophisticated delivery systems that enhance the efficacy and safety of therapeutic agents. This paper aims to review recent advancements in nano drug delivery systems, examining their potential to address existing challenges in drug delivery and exploring future research directions. Nanomedicine encompasses a wide range of technologies designed to deliver drugs at the nanoscale. Recent studies have demonstrated significant improvements in drug solubility, stability, and targeting capabilities through the use of nanocarriers such as liposomes, polymeric nanoparticles, and dendrimers recent advancements in nanomedicine have focused on developing multifunctional nanoparticles capable of simultaneous drug delivery, imaging, and therapy. Nanotechnology is shown to bridge the barrier of biological and physical sciences by applying nanostructures and nanophases at various fields of science; specially in nanomedicine and nano based drug delivery systems, where such particles are of major interest[1].

Nanomaterials can be well-defined as a material with sizes ranged between 1 and 100 nm, which influences the frontiers of nanomedicine starting from biosensors, microfluidics, drug delivery, and microarray tests to tissue engineering. Nanotechnology employs curative agents at the nanoscale level to develop nanomedicines. The field of biomedicine comprising nanobiotechnology, drug delivery, biosensors, and tissue engineering has been powered by nanoparticles. As nanoparticles comprise materials designed at the atomic or molecular level, they are usually small sized nanospheres. Hence, they can move more freely in the human body as compared to bigger materials. Nanoscale sized particles exhibit unique structural, chemical, mechanical, magnetic, electrical, and biological properties. Nanomedicines have become well appreciated in recent times due to the fact that nanostructures could be utilized as delivery agents by encapsulating drugs or attaching therapeutic drugs and deliver them to target tissues more precisely with a controlled release. It implicates the utilization of nanodimensional materials including nanorobots, nanosensors for diagnosis, delivery, and sensory purposes, and actuate materials in live cells[2].

Types of Nanocarriers

Liposomes: Liposomes are spherical vesicles with a phospholipid bilayer, offering advantages like biocompatibility and the ability to encapsulate both hydrophilic and hydrophobic drugs. Recent advancements include PE Gylation to enhance circulation time and targeted liposome's for cancer therapy.

Polymeric Nanoparticles: Polymeric nanoparticles, including PLGA and PLA, provide controlled drug release and protection of drugs from degradation. Innovations involve surface modifications for targeted delivery and stimuli-responsive release.

Dendrimers: Dendrimers are highly branched, tree-like structures with multiple functional groups for drug attachment. Recent research focuses on enhancing drug loading efficiency and reducing toxicity.

Inorganic Nanoparticles: Inorganic nanoparticles like gold, silica, and iron oxide offer unique properties for imaging and therapy. Functionalization with targeting ligands has improved specificity and therapeutic efficacy.

Lipid-based Nanocarriers: SLNs and NLCs combine the benefits of liposomes and polymeric nanoparticles, providing stability and controlled release. Recent developments include the use of natural lipids to reduce toxicity and enhance biocompatibility[2].

Table-1: Mechanism of Nanomedicine and Nanomedicine Drug Delivery System Vs. Traditional Drug Delivery System.

Comparison Aspect	Nanomedicine Drug Delivery Systems (NDDS)	Traditional Drug Delivery Systems (TDDS)
Bioavailability	Enhanced bioavailability. Example: Liposomal formulations improve drug solubility and stability.	Lower bioavailability. Example: Conventional oral tablets may degrade in the digestive tract.
Drug Degradation	Reduced drug degradation. Example: Polymeric nanoparticles protect drugs from enzymatic degradation.	Higher drug degradation. Example: Peptide drugs degraded by proteases in the stomach.
Patient Compliance	Improved patient compliance. Example: Nanoparticles allow for less frequent dosing.	Lower patient compliance. Example: Multiple daily doses required for conventional drugs.
Required Dose	Lower required doses. Example: Doxil (liposomal doxorubicin) achieves therapeutic effects at lower doses.	Higher required doses. Example: Standard chemotherapy requires higher doses with more side effects.
Site Specificity	Increased site specificity. Example: Targeted nanoparticles deliver drugs directly to tumor cells.	Less site specificity. Example: Systemic drug distribution affects both diseased and healthy tissues.
Uptake by Diseased Cells	Higher uptake by diseased cells. Example: Gold nanoparticles are preferentially taken up by cancer cells.	Lower uptake by diseased cells. Example: Traditional drugs often affect both diseased and healthy cells equally.
Side Effects	Minimized side effects. Example: Liposomal drugs reduce cardiotoxicity in cancer treatment.	Increased side effects. Example: Chemotherapy causes hair loss and immune suppression.
Control Over Drug Release	Superior control over drug release. Example: Polymeric micelles provide controlled and sustained drug release.	Poor control over drug release. Example: Immediate-release tablets release drugs all at once.
Targeting Capabilities	Advanced targeting capabilities. Example: Antibody-drug conjugates target specific cell surface markers.	Limited targeting capabilities. Example: Non-specific drug distribution.
Effectiveness in Disease Management	More effective disease management, especially for cancer and chronic diseases. Example: Nanoparticles improve drug delivery in chronic illnesses like diabetes.	Less effective disease management. Example: Traditional drugs may require combination therapies to achieve similar outcomes.

Table-2: Marketed dosage form comparison.

Nanodrug delivery system	Traditional Drug Delivery Systems (TDDS)
Doxil: A liposomal formulation of doxorubicin used to treat various cancers. The liposomal encapsulation reduces toxicity and enhances drug accumulation in tumor tissues through the EPR effect	Conventional Doxorubicin: Has a higher risk of cardiotoxicity and non-specific distribution, leading to greater side effects.
Onpattro (Patisiran): A lipid nanoparticle formulation of siRNA used to treat hereditary transthyretin-mediated amyloidosis. It provides targeted delivery to the liver, improving RNA interference efficacy and reducing off-target effects.	Traditional RNA Interference Therapies: Often face challenges with stability, delivery, and off-target effects.
Abraxane (Nab-Paclitaxel): An albumin-bound nanoparticle formulation of paclitaxel used in breast cancer, non-small cell lung cancer, and pancreatic cancer. It improves solubility and reduces hypersensitivity reactions compared to conventional paclitaxel.	Conventional Paclitaxel: Requires solvents like Cremophor EL, which can cause severe allergic reactions and require premedication with steroids and antihistamines.
Vyxeos (CPX-351): A liposomal formulation of cytarabine and daunorubicin used for acute myeloid leukemia (AML). It delivers a fixed molar ratio of the drugs directly to the cancer cells, enhancing efficacy and reducing toxicity.	Conventional Chemotherapy: Often results in non-specific distribution and higher toxicity, affecting healthy cells.

Mechanisms of drug release control

Targeted Drug Delivery: Targeted drug delivery systems use specific ligands or antibodies to direct nanocarriers to particular cells or tissues, enhancing therapeutic outcomes and minimizing side effects. Advances in molecular targeting and bioengineering have significantly improved targeting efficiency. i. Passive Targeting: Utilizes the enhanced permeability and retention (EPR) effect, where nanocarriers accumulate in tumor tissues due to leaky vasculature. Control is enhanced by adjusting the size and surface properties of the nanocarriers. ii. Active Targeting: Functionalizes nanocarriers with ligands such as antibodies or peptides that specifically bind to receptors on target cells, enhancing specificity and efficacy.

Stimuli-Responsive Release: i. pH-Responsive: Uses materials that change solubility or degradation rate in acidic environments. ii. Temperature-Responsive: Involves polymers that undergo phase transitions at specific temperatures. iii. Redox-Responsive: Leverages higher intracellular levels of reducing agents to trigger drug release. iv. Enzyme-Responsive: Targets enzymes over expressed in diseased tissues to degrade the carrier and release the drug[4].

Recent advancements and data

Multiple Mechanisms: Drug release from nanocarriers often involves several mechanisms. For example, drug-loaded nanogels with a polymer membrane control release through both swelling and diffusion.

Improved Pharmacokinetics: Nanoparticles, due to their size and physical properties, can target specific cells and accumulate in subcellular structures, modifying cellular processes. Common therapeutic nanoparticles include encapsulated mRNA (siRNA) or DNA (gene therapy), inorganic metal complexes, and chemotherapeutic agents.

Liposomes: Effective for encapsulating both hydrophobic and hydrophilic drugs, enhancing therapeutic effects, and reducing toxicity. Modified liposomes allow for passive or active tumor targeting, delivering drug payloads to malignant cells while sparing non-malignant cells. Encapsulation of doxorubicin within DPPC-based liposomes, for example, enhances drug cytotoxicity and reduces side effects compared to conventional doxorubicin.

AI Tools in Nanotechnology: i. DeepChem: An open-source AI tool that aids in drug discovery by predicting molecular properties and interactions. ii. NanoNet: AI-based platforms for analyzing nanoparticle characteristics and optimizing their design. iii. Chemoinformatics Tools: AI-driven tools for predicting the behavior of nanomaterials based on chemical and biological data[3].

Clinical applications and case studies

Nanotechnology-based drug delivery systems have shown promise in various clinical applications, particularly in oncology, neurology, and infectious diseases. Recent clinical trials demonstrate the potential of these systems to improve patient outcomes and reduce side effects. Traditional chemotherapy drugs often cause severe side effects due to lack of specificity. Nanotechnology-based drug delivery systems can target cancer cells specifically, reducing side effects and improving therapeutic outcomes.

Liposomes: Example: Doxil, a liposomal formulation of doxorubicin, is used to treat ovarian cancer and Kaposi's sarcoma. The liposome encapsulates the drug, reducing cardiotoxicity and improving drug accumulation in tumors.

Polymeric Nanoparticles: Case Study: A study demonstrated that PLGA nanoparticles loaded with paclitaxel effectively inhibited tumor growth in a mouse model of lung cancer, showing higher efficacy and lower toxicity compared to free paclitaxel.

Inorganic Nanoparticles: Case Study: Gold nanoparticles conjugated with the anti-cancer drug cisplatin have shown improved targeting and reduced toxicity in preclinical models of prostate cancer.

Lipid-based Nanocarriers: Example: Solid lipid nanoparticles (SLNs) encapsulating curcumin have demonstrated enhanced bioavailability and anti-inflammatory effects in a study on inflammatory bowel disease (IBD)[6].

Nanotechnology has significant therapeutic applications across various fields, including:

Cancer Treatment: Nanoparticles can be engineered to target cancer cells specifically, delivering drugs directly to tumors while minimizing damage to healthy tissue. This approach improves the efficacy of the treatment and reduces side effects.

Drug Delivery: Nanocarriers, such as liposomes, dendrimers, and polymeric nanoparticles, can encapsulate drugs and release them in a controlled manner. This targeted delivery system enhances the bioavailability of drugs and improves therapeutic outcomes.

Gene Therapy: Nanoparticles can be used to deliver genetic material, such as DNA or RNA, into cells. This method can correct genetic defects, modify gene expression, or introduce new genes to treat various genetic disorders.

Imaging and Diagnostics: Nanotechnology enables the development of advanced imaging techniques. For instance, quantum dots and magnetic nanoparticles can enhance the contrast in imaging studies, allowing for better diagnosis and monitoring of diseases.

Regenerative Medicine: Nanomaterials can be used to create scaffolds that support tissue regeneration. They can also deliver growth factors or other therapeutic agents to promote the healing of damaged tissues and organs.

Vaccines: Nanoparticles can be used as vaccine adjuvants or delivery systems. They can enhance the immune response by presenting antigens in a way that stimulates a stronger and more targeted immune reaction.

Antibacterial and Antiviral Agents: Nanoparticles, such as silver and copper nanoparticles, have antimicrobial properties and can be used in coatings, wound dressings, and other applications to prevent or treat infections.

Neurological Disorders: Nanotechnology holds promise for treating neurological diseases by delivering drugs across the blood-brain barrier, targeting specific brain cells, or providing neuroprotective effects.

Cardiovascular Diseases: Nanoparticles can be used to deliver drugs to specific sites within the cardiovascular system, such as plaques in arteries, or to provide imaging and diagnostic tools for better management of cardiovascular conditions[5].

Recent innovations and recent developments

Smart Nanoparticles: Recent developments include stimuli-responsive nanoparticles that release drugs in response to specific triggers, such as changes in pH, temperature, or magnetic fields. These smart NPs offer enhanced precision and control over drug release.

Combination Therapy NPs: New formulations combine multiple drugs or therapeutic agents within a single nanoparticle system, optimizing treatment regimens and improving therapeutic outcomes.

Biofunctionalization: Advanced biofunctionalization techniques are being used to enhance targeting capabilities by attaching specific ligands or antibodies to the surface of nanoparticles, enabling them to bind selectively to disease-specific markers.

Nanoparticle-Loaded Imaging Agents: Integration of imaging agents with therapeutic nanoparticles allows for real-time monitoring of drug delivery and efficacy, providing valuable insights into treatment progress. These advancements are significantly improving the efficacy, stability, and targeting of drug delivery systems, paving the way for more effective and personalized medical treatments.

Advanced Green Synthesis: New techniques are emerging to reduce the environmental impact and toxicity of nanoparticle synthesis, such as using biological methods and less toxic reagents.

Enhanced Risk Assessment Frameworks: Regulatory agencies are developing more comprehensive frameworks to assess the safety of nanomedicines, including better tools for risk evaluation and management.

Innovative Safety Testing: New in vitro and in vivo models are being developed to better predict the safety and biological interactions of nanoparticles[7].

Potential side effects and safety concerns of nanomedicine

Nanomedicine offers numerous benefits, but it also presents potential adverse effects and safety concerns. Due to their small size, nanoparticles (NPs) can penetrate the human body more easily, which may lead to unforeseen risks.

Toxicity: Nanoparticles can induce cytotoxicity through the generation of reactive oxygen species (ROS), which damage cellular components such as mitochondria, nuclei, and plasma membranes. For example: i. **Quantum dots**: containing cadmium (Cd), they release Cd^{2+} ions, which are toxic. ii. **Silica Nanoparticles**: At concentrations above 0.1mg/ml, they can be toxic, reducing cell viability and proliferation. iii. **TiO and Silver Nanoparticles**: Amorphous TiO_2 nanoparticles (30nm) and silver nanoparticles (15nm) are associated with high ROS production. They can also trigger inflammatory responses, increasing levels of inflammatory mediators like TNF-α, MIP-2, and IL-1β.

Macrophage Interaction: Silver nanoparticles and quantum dots can be absorbed by macrophages, enhancing the production of inflammatory mediators regardless of particle size.

Regulatory and Safety Challenges: i. Green Synthesis: There is a need for environmentally friendly synthesis methods and standardized reference materials to ensure safety. ii. Risk-Benefit Analysis: Regulators must balance the unique therapeutic benefits of nanomedicine against potential risks. This requires robust scientific evidence from preclinical and clinical studies. iii. Clinical Trials: Designing and conducting trials for nanomedicines involves challenges such as patient recruitment, sample size, and endpoint selection[8].

Challenges and future directions

Despite the promising advancements, challenges such as biocompatibility, scalability, and regulatory hurdles remain. Future research should focus on addressing these issues and exploring new materials and methods to further enhance the effectiveness and safety of nanotechnology-based drug delivery systems[9].

Conclusion

Nanotechnology-based drug delivery systems have the potential to revolutionize medicine by enabling targeted, controlled, and efficient delivery of therapeutic agents. Recent advancements in nanomedicine have facilitated the design and engineering of nanoparticles with specific properties, presenting new opportunities for treating complex diseases. To fully harness the

potential of nanomedicine, continued interdisciplinary research and collaboration are essential to address existing challenges. Ensuring safety remains a priority, requiring ongoing studies, the adoption of green synthesis practices, and the refinement of regulatory frameworks. The integration of advanced tools and technologies, such as AI-driven drug design and sophisticated imaging techniques, can further enhance the precision and efficacy of nanomedicine. Collaborative efforts among regulators, industry stakeholders, and researchers are crucial to safely integrate nanomedicine into healthcare, thereby maximizing its benefits and minimizing associated risks.

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