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A REVIEW ARTICLE ON NANOCARRIER-BASED DRUG DELIVERY SYSTEMS: ADVANCES AND CHALLENGES

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ABSTRACT

Nanocarrier-based drug delivery systems have revolutionized the field of targeted therapy by improving drug solubility, bioavailability, pharmacokinetics, and tissue specificity. This review explores various classes of nanocarriers, including lipid-based, polymeric, inorganic, and exosome-derived systems, and discusses key advances, such as stimuli-responsive drug release and active/passive targeting. Despite these advances, challenges remain in formulation stability, clinical translation, toxicity profiling, and large-scale manufacturing. Future perspectives, such as the incorporation of artificial intelligence (AI) and the design of smart programmable nanocarriers, hold promise for bridging the gap between research and clinical applications.

KEYWORDS: Targeted therapy, Nanocarriers, Clinical translation, Artificial intelligence, Clinical applications and Drug delivery systems.

1. INTRODUCTION

The field of drug delivery has undergone a revolutionary transformation in recent decades, driven by the increasing need to improve the efficacy and safety of therapeutic agents. Traditional drug administration methods such as oral tablets, injections and topical applications often suffer from critical limitations, including poor aqueous solubility, low bioavailability, rapid metabolism, non-specific biodistribution and systemic toxicity (Kaushik et al., 2022). These limitations can reduce therapeutic outcomes and result in unwanted side effects, which are particularly problematic in the treatment of complex diseases such as cancer, neurological disorders, and infectious diseases. Nanocarrier-based drug delivery systems have emerged as a promising strategy to overcome these challenges. Nanocarriers are nano-sized

vehicles typically ranging from 10 to 200 nanometers that encapsulate therapeutic molecules, thereby protecting them from premature degradation and facilitating targeted delivery to diseased tissues (Alshawwa et al., 2022). Due to their small size and modifiable surface properties, nanocarriers can improve the pharmacokinetics and pharmacodynamics of drugs, enabling controlled release, enhanced solubility and reduced immunogenicity.

A pivotal advantage of nanocarriers lies in their ability to exploit the Enhanced Permeability and Retention (EPR) effect, a phenomenon in which nanoparticles preferentially accumulate in tumour and inflamed tissues due to their leaky vasculature and impaired lymphatic drainage (Danhier et al., 2010). This passive targeting mechanism increases drug concentration at the disease site while minimizing systemic exposure and side effects. Furthermore, active targeting approaches can be employed by conjugating ligands such as antibodies, peptides or small molecules onto the surface of nanocarriers, enabling receptor-mediated endocytosis and improved cellular uptake (Hani et al., 2024).

This review aims to provide a comprehensive overview of the current landscape of nanocarrier-based drug delivery systems. It covers a range of nanocarrier platforms, including lipid-based, polymeric, inorganic, and exosome-based systems. Characterization methodologies essential for formulation optimization are examined. The review also highlights recent technological advancements such as stimuli-responsive carriers and artificial intelligence (AI)-assisted design strategies. Finally, it addresses critical challenges that limit the broader clinical adoption of nanocarriers and outlines future perspectives to accelerate translation from research to routine clinical use. Conventional drug delivery methods are often limited by issues such as poor aqueous solubility, rapid systemic clearance, low bioavailability and high off-target toxicity. Nanocarriers offer an innovative solution by encapsulating or conjugating drugs within particles in the nanometer range (typically <200 nm), thereby improving pharmacokinetics, biodistribution, and cellular uptake (Kaushik et al., 2022).

Nanocarriers enhance drug delivery by exploiting the enhanced permeability and retention (EPR) effect in tumor tissues for passive targeting or by using ligands (e.g., antibodies, peptides) for active targeting (Alshawwa et al., 2022). Various platforms like liposomes, polymeric nanoparticles, dendrimers, inorganic nanoparticles, and exosomes are under investigation or approved for clinical use. Despite the potential, nanocarrier-based therapeutics face hurdles including particle instability, aggregation, unpredictable in vivo behaviour and regulatory challenges.

2. METHODOLOGIES FOR NANOCARRIER CHARACTERIZATION

The successful development and clinical translation of nanocarrier-based drug delivery systems heavily depend on thorough characterization. Characterization techniques provide critical information about the physicochemical properties, drug loading, release behaviour, stability, and biological interactions of nanocarriers. These parameters directly influence their therapeutic efficacy, safety and regulatory approval.

2.1 Particle Size and Size Distribution

Particle size is one of the most important attributes of nanocarriers, typically ranging from 10 to 200 nm. It profoundly affects the pharmacokinetics, cellular uptake, biodistribution, and clearance pathways (Kaushik et al., 2022). Smaller nanoparticles (<100 nm) tend to exhibit longer circulation times and better tissue penetration. Size distribution, often reported as polydispersity index (PDI), indicates the homogeneity of the formulation.

Dynamic Light Scattering (DLS) is the most widely used technique for determining the hydrodynamic diameter and PDI of nanoparticles in suspension. It measures fluctuations in scattered light intensity caused by Brownian motion of particles. Complementary methods like Nanoparticle Tracking Analysis (NTA) provide size distribution profiles and particle concentration by tracking individual particles under microscopy.

2.2 Surface Charge (Zeta Potential)

The surface charge, commonly expressed as zeta potential, influences nanocarrier stability and interactions with biological membranes (Alshawwa et al., 2022). Charged particles repel each other, preventing aggregation and promoting colloidal stability. Typically, nanocarriers with zeta potentials greater than ±30 mV are considered stable.

Zeta potential is measured via electrophoretic light scattering, where the velocity of charged particles in an electric field is detected. Surface charge also affects cellular uptake and biodistribution; positively charged nanoparticles often exhibit higher internalization but may also induce toxicity.

2.3 Drug Loading and Encapsulation Efficiency

Quantifying the amount of drug encapsulated within nanocarriers and the efficiency of encapsulation is vital for dosage determination. Drug loading refers to the amount of drug per unit mass of the nanocarrier, while encapsulation efficiency indicates the percentage of the initial drug successfully entrapped.

High-Performance Liquid Chromatography (HPLC) and UV-Visible Spectrophotometry are standard analytical techniques used to measure free and encapsulated drug concentrations. Before analysis, the nanocarriers are usually separated from the free drug using centrifugation or dialysis. Optimization of drug loading minimizes wastage and controls release profiles.

2.4 In Vitro Drug Release Studies

One of nanocarriers' key advantages is controlled medication release. In vitro release studies simulate physiological conditions to predict how drugs will be released over time inside the body. Techniques include dialysis membrane diffusion, Franz diffusion cells, and sample-and-separate methods. Release profiles can be affected by nanocarrier composition, drug-nanocarrier interactions, and environmental factors such as pH and temperature. Mathematical models (e.g., zero-order, first-order, Higuchi, Korsmeyer-Peppas) are applied to understand release kinetics and mechanisms (Mahajan & Bhattacharya, 2024).

2.5 Morphological and Structural Analysis

Understanding the shape, surface morphology, and internal structure of nanocarriers is essential, as these features influence biological behavior and drug release. Transmission Electron Microscopy (TEM) offers high-resolution imaging to observe particle shape, size, and aggregation state. Scanning Electron Microscopy (SEM) provides detailed surface topography. Atomic Force Microscopy (AFM) is another valuable tool, providing three-dimensional surface profiles and mechanical properties at the nanoscale. X-ray diffraction (XRD) and Fourier-transform infrared spectroscopy (FTIR) can be used to confirm drug encapsulation and analyze crystalline vs. amorphous states.

2.6 Stability Studies

When stored and in physiological environments, nanocarriers must retain their structural integrity, drug content, and functionality. Stability studies evaluate the effects of temperature, light exposure, pH, ionic strength, and mechanical

stress on particle size, zeta potential, and drug leakage. Accelerated stability testing under stressed conditions predicts shelf-life. Lyophilization (freeze-drying) is often employed to enhance stability but requires optimization to prevent particle aggregation and preserve drug activity (Mahajan & Bhattacharya, 2024).

2.7 In Vitro Biological Evaluations

Assessment of nanocarrier interactions with cells is critical to predict in vivo behavior. Cellular uptake studies utilize fluorescent labeling and confocal microscopy or flow cytometry to quantify internalization. Cytotoxicity assays such as MTT, XTT, or live/dead staining evaluate the biocompatibility of nanocarriers. Additional studies include hemolysis assays, immunogenicity testing, and evaluation of reactive oxygen species (ROS) generation to ensure safety and efficacy (Palakurthi et al., 2024).

2.8 Emerging Methodologies: Artificial Intelligence and Modeling

Recent advances incorporate artificial intelligence (AI) and machine learning to simulate nanocarrier behavior, predict pharmacokinetics, optimize formulation parameters, and analyze large datasets rapidly (Wang et al., 2022). Computational models can reduce experimental costs and accelerate development by identifying critical formulation variables and predicting biological interactions.

3. REVIEW OF LITERATURE

3.1 Lipid-Based Nanocarriers

Liposomes are spherical vesicles with one or more phospholipid bilayers capable of carrying hydrophilic and lipophilic drugs. Liposomes and solid lipid nanoparticles (SLNs) are the most clinically advanced nanocarriers. FDA-approved liposomal formulations like **Doxil** (PEGylated liposomal doxorubicin) and **Vyxeos** (liposomal daunorubicin + cytarabine) illustrate their success in cancer therapy (Kaushik et al., 2022).

Despite their advantages—biocompatibility and scalable production—lipid nanocarriers often face **stability issues** such as leakage, fusion, and opsonization (Hani et al., 2024).

3.2 Polymeric Nanoparticles and Dendrimers

Polymeric nanoparticles offer controlled release through hydrolysis or enzymatic degradation. Dendrimers, like PAMAM, allow for multivalent drug conjugation and stimuli-triggered release mechanisms (Alshawwa et al., 2022).
For instance, **pH-sensitive dendrimers** release anticancer drugs preferentially in acidic tumor microenvironments, reducing off-target toxicity (Kaushik et al., 2022).

3.3 Inorganic and Hybrid Nanocarriers

Mesoporous silica nanoparticles (MSNs), gold nanoparticles, and magnetic iron oxide nanoparticles are gaining attention for their unique structural, magnetic, and optical properties (Mann et al., 2024).
MSNs functionalized with chitosan and folic acid have demonstrated enhanced uptake by colorectal cancer cells due to receptor-mediated endocytosis (Mann et al., 2024). However, issues such as **non-biodegradability and long-term accumulation** need thorough investigation.

3.4 Exosome-Based and Smart Nanocarriers

Exosomes, natural vesicles secreted by cells, have intrinsic targeting capabilities. Engineered exosomes and **hybrid exosome-liposome systems** are being developed for efficient delivery of siRNA and proteins (Palakurthi et al., 2024).

Programmable lipid nanoparticles (LNPs) with modular architectures allow precise control over payload release and have shown potential for intranasal, ocular, and pulmonary routes (Liu et al., 2024).

4. ADVANCES AND INNOVATIONS

4.1 Stimuli-Responsive Drug Release

Designing nanocarriers responsive to internal (e.g., pH, redox, enzymes) or external (e.g., heat, light, magnetic field) stimuli allows **site-specific release** of drugs. Redox-responsive disulfide bonds, for instance, cleave in the glutathione-rich tumor environment to trigger drug discharge (Kaushik et al., 2022).

4.2 Active Targeting

Functionalization with ligands like folic acid, transferrin, or monoclonal antibodies facilitates receptor-mediated uptake, particularly in cancer cells overexpressing specific markers (Hani et al., 2024).

4.3 AI-Assisted Nanocarrier Design

AI is increasingly employed to analyze formulation datasets, predict pharmacokinetics, and streamline optimization of particle size, ligand density, and drug ratios (Alshawwa et al., 2022).

4.4 Nanocarriers for Gene Therapy

Lipid-based and polymer-based carriers are being adapted to deliver siRNA, mRNA, and CRISPR/Cas systems. Lipid nanoparticles have recently facilitated mRNA vaccine success (Hou et al., 2021).

5. KEY CHALLENGES

5.1 Stability and Shelf-life

Nanocarriers often aggregate or degrade during storage. PEGylation, cross-linking, and lyophilization are some techniques that enhance shelf life but may have an impact on biological performance. (Mahajan & Bhattacharya, 2024).

5.2 Biocompatibility and Toxicity

Some inorganic nanocarriers (e.g., gold, silica) may induce ROS generation, genotoxicity, or organ accumulation. Long-term safety data are scarce, particularly for hybrid and smart carriers (Hani et al., 2024).

5.3 Scale-Up and Manufacturing

Reproducibility and cost-effectiveness remain major bottlenecks. Sterilization methods like gamma irradiation may alter nanoparticle structure. GMP-compliant scale-up requires significant investment (Kaushik et al., 2022).

5.4 Clinical Translation

Although hundreds of nanocarrier formulations are in preclinical or clinical trials, only a few have secured regulatory approval. Challenges include patient variability, complex pharmacokinetics, and lack of harmonized international guidelines (Hani et al., 2024).

6. FUTURE PERSPECTIVES

6.1 Personalized Nanomedicine

- **Trend**: Increasing integration of nanocarriers with precision medicine.
- **Future Direction**: Use of patient-specific biomarkers to design custom nanocarriers for optimal drug delivery.

- **Challenge**: Requires advanced diagnostic tools and regulatory frameworks for individualized therapy.

6.2. Smart and Stimuli-Responsive Systems

- **Trend**: Development of nanocarriers that respond to pH, temperature, enzymes, redox conditions, or light.
- **Future Direction**: Integration of sensors and responsive mechanisms for on-demand drug release.
- **Challenge**: Complexity in design and reproducibility for clinical translation.

6.3. Multifunctional Nanocarriers (Theranostics)

- **Trend**: Combining therapy and diagnostics (theranostics) in a single nanocarrier.
- **Future Direction**: Real-time monitoring of treatment response using imaging-enabled nanocarriers.
- **Challenge**: Balancing functionality with safety and scalability.

6.4. Overcoming Biological Barriers

- **Trend**: Enhanced delivery across physiological barriers (e.g., blood-brain barrier, tumor microenvironment).
- **Future Direction**: Use of biomimetic and surface-modified nanocarriers (e.g., using cell membranes, peptides).
- **Challenge**: Ensuring bioavailability and targeted accumulation without triggering immune clearance.

6.5. Green and Scalable Manufacturing

- **Trend**: Focus on eco-friendly, cost-effective, and scalable production methods.
- **Future Direction**: Use of biopolymers, green synthesis techniques, and 3D printing for nanocarrier fabrication.
- **Challenge**: Maintaining consistency, stability, and regulatory compliance.

6.6. Regulatory and Ethical Considerations

- **Trend**: Regulatory bodies lag behind rapid technological advances.
- **Future Direction**: Development of standardized testing protocols, safety assessments, and ethical guidelines.
- **Challenge**: Limited long-term toxicity data and the need for global harmonization of regulations.

6.7. Integration with AI and Machine Learning

- **Trend**: Using computational tools for nanocarrier design and optimization.
- **Future Direction**: Predicting drug–carrier interactions, optimizing formulations, and personalizing treatments via AI.
- **Challenge**: Need for large, high-quality datasets and model validation.

7. CONCLUSION

Nanocarrier-based drug delivery systems hold immense potential to transform therapeutic paradigms by improving drug targeting, reducing systemic toxicity, and overcoming multidrug resistance. Lipid-based systems dominate the approved formulations, but innovations in polymeric, inorganic, and biological carriers are accelerating. Nanocarriers must overcome several obstacles in order to reach greater clinical translation, including stability during storage, biosafety across a range of populations, scalable manufacturing, and regulatory clarity. Integration of smart design tools, especially AI and programmable platforms, may significantly shorten development timelines and improve precision targeting. Continued interdisciplinary collaboration among pharmaceutical scientists, materials engineers, and clinicians is essential to unlock the full therapeutic potential of nanocarrier systems.

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