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Nanocarriers in Targeted Drug Delivery: Design Strategies to Overcome Biological Barriers

Tiba Al Temimi [1, *], Huda Mohammed Reda [1], Reda Elfeshawy [2, 3], Amal Talib Al Sa'ady [4], Shatha Khazal K. Hindi [5]

[1] *Pharmacy College, Al-Mustaqbal University, Hillah, Iraq*

[2] *Faculty of Nursing, Menofia University, Menofia, Egypt*

[3] *Nursing College., Al-Mustaqbal University, Hillah, Iraq*

[4] *College of Pharmacy, University of Babylon, Hillah, Iraq*

[5] *Immunodeficiency Center in Al-Mu'allimin in the Rusafa Health Department, Baghdad, Iraq*

[*] *Corresponding Email:* teba.jasim.mohmed@uomus.edu.iq

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ABSTRACT

Efficient drug delivery faces critical challenges such as enzymatic degradation, rapid immune clearance, and limited tissue penetration. This review highlights recent advancements in nanocarrier systems — including polymeric nanoparticles, PEGylated liposomes, dendrimers, and exosome-mimetic vesicles — that overcome these biological barriers through smart design strategies. Surface functionalization with targeting ligands, pH- or enzyme-responsive release mechanisms, and stealth coatings have significantly improved drug bioavailability and site-specific delivery. Notably, nanocarriers have shown marked success in enhancing therapeutic outcomes in oncology, antibiotic-resistant infections, and neurodegenerative diseases. Comparative insights into design efficiency, drug loading capacity, and clinical translation potential are also discussed.

Keywords: Biological Barriers, Cancer Therapy, Controlled Release, Dendrimers, Exosomes, Liposomes, Nanocarriers, Neurodegeneration, Polymeric Nanoparticles, Targeted Drug Delivery

1 Introduction

THE effective delivery of therapeutic agents, including small molecules and nucleic acids, remains a critical challenge in modern medicine due to the presence of complex biological barriers. These barriers — such as the blood-brain barrier, placental barrier, ocular epithelium, and intestinal lining — restrict the distribution and cellular uptake of drugs, limiting their therapeutic potential [1, 2]. Nanocarriers have emerged as promising platforms to address these limitations by enhancing drug stability, targeting specificity, and intracellular delivery [3, 4].

Nanocarriers can be engineered from lipid-based, polymeric, or metallic components, and designed to be either water- or oil-soluble depending on the therapeutic context. Their surface properties, size, charge, and rigidity significantly influence their circulation time, tissue distribution, and ability to cross physiological barriers [5]. For instance, smaller and more flexible particles tend to accumulate more efficiently in tissues, while larger and more rigid carriers offer enhanced stability and controlled release, often achieved by coating them with secondary nanoscale components [6].

Targeting specific tissues — especially tumors — has led to several commercially successful nanomedicines [7, 8]. However, achieving precise delivery in more restrictive environments, such as the brain, placenta, or conjunctival

lacrimal duct, remains a formidable obstacle [9, 10]. To overcome these challenges, researchers have developed nanocarriers incorporating pH-sensitive components, enzyme-cleavable linkers, and stimuli-responsive release mechanisms to ensure drug activation occurs only at the intended site [11-13].

Additionally, rational design strategies — including the selection of optimal targeting ligands, carrier composition, backbone charge, and surface features — can enhance the specificity and efficacy of bioactive compound delivery [14, 15]. Advances in computational modeling and artificial intelligence (AI) now support the prediction of nanocarrier behavior and improve design precision for efficient cellular uptake and functional outcomes [16].

2 Overview of Drug Delivery System

This review explores the recent developments in nanocarrier design aimed at overcoming biological barriers. We focus on surface modification techniques, stimuli-responsive delivery systems, and targeting strategies, with applications spanning oncology, antibiotic-resistant infections, and neurodegenerative disorders. By integrating emerging design principles with clinical perspectives, we aim to provide a comprehensive overview of the current landscape and future directions in nanocarrier-based drug delivery [17-20].

Nanocarrier-based drug delivery systems have transformed the therapeutic landscape by enhancing the precision, stability, and bioavailability of various pharmaceuticals. These carriers — typically composed of lipids, polymers, or inorganic materials — are engineered to encapsulate and transport therapeutic molecules such as small drugs, peptides, or nucleic acids to specific tissues or cells [3, 4].

However, in vivo drug delivery remains limited by biological barriers, including the blood-brain barrier, placental interface, ocular surfaces, and intestinal mucosa, all of which restrict the passive diffusion and accumulation of therapeutic agents [1, 2]. Although some commercial products have overcome these obstacles in systemic therapy (e.g., Doxil® for cancer), challenges persist for targeted delivery to complex compartments like the brain or placenta [7, 17, 18].

Two primary strategies govern drug delivery: passive targeting and active targeting. Passive targeting relies on the enhanced permeability and retention (EPR) effect, especially effective in tumors due to leaky vasculature and poor lymphatic drainage [18]. In contrast, active targeting utilizes ligands such as antibodies, peptides, or aptamers that bind to specific receptors on target cells, improving selectivity and cellular uptake [8, 9]. For example, trastuzumab-modified nanoparticles have shown enhanced delivery to HER2-positive breast cancer cells, while transferrin-coated carriers aim to cross the blood-brain barrier by receptor-mediated transcytosis [10, 14].

Nanocarrier performance is governed by size, surface charge, rigidity, and composition. Smaller and flexible particles (under 100 nm) often exhibit deeper tissue penetration, while rigid, larger particles offer prolonged circulation [5, 16]. A hybrid approach combines both: for instance, rigid core nanoparticles coated with flexible shells to enhance tissue accumulation and stability [6, 11].

Furthermore, smart delivery systems can be engineered to respond to physiological triggers, such as acidic pH in tumor microenvironments or overexpressed enzymes in inflamed tissues. These stimuli-responsive systems enable on-demand release, reducing systemic toxicity and enhancing efficacy [12, 13, 19]. Controlled biodegradation and tunable release kinetics — achieved through materials sensitive to pH or enzymatic cleavage — allow precise spatial and temporal control of drug release [20, 21].

With advances in computational modeling and AI-assisted design tools, the next generation of nanocarriers is expected to become even more sophisticated, with tailored surface modifications and optimized internalization profiles to overcome multi-layered biological barriers efficiently [15].

3 Nanocarriers: Definition and Types

Nanocarriers are nanoscale delivery systems (5–1000 nm) engineered to transport drugs—including small molecules, proteins, and nucleic acids—to target tissues, enhancing bioavailability and reducing systemic toxicity [3, 4]. They are typically composed of polymers, lipids, surfactants, or metals and can be tailored in size, structure, and surface properties. The core contains the active drug, while a hydrophilic shell provides stability [4].

These carriers protect drugs from degradation, ensure sustained release, improve tissue accumulation, and enable passive or active targeting [1]. Major types included in Table 1.

4 Mechanisms of Targeted Drug Delivery

Active targeting strategies in nanocarriers include:

- Ligand–Receptor Targeting (e.g., folate-liposomes for ovarian cancer) [2].
- Antibody-based Targeting (e.g., trastuzumab-coated nanoparticles for HER2) [17].
- Peptide-based Targeting (e.g., RGD peptides for integrins) [18].
- Endosomal Escape Strategies using pH-sensitive materials and proton sponge effects.

Challenges include receptor heterogeneity, immune clearance, and tumor microenvironment barriers [7].

Table 1. Major types

Nanocarrier	Size Range	Drug Types	Advantages	Limitations	Example
Liposomes	50–200 nm	Hydrophilic & hydrophobic	Biocompatible; clinically used	Stability, cost	Doxil®
PNPs	10–500 nm	Hydrophobic & nucleic acids	Controlled release	Polymer toxicity	Abraxane®
Dendrimers	~5–20 nm	Small molecules, siRNA	High loading capacity	Complex synthesis	VivaGel®
SLNs	50–1000 nm	Lipophilic & hydrophilic	Biodegradable	Low hydrophilic loading	Curcumin SLNs (clinical trial)

5 Biological Barriers

Nanocarriers must overcome:

- **Cell Membrane Permeability**: Enhanced via receptor-mediated uptake and endosomal escape [8].
- **Blood–Brain Barrier (BBB)**: Strategies involve transferrin-mediated transcytosis [9].
- **Tumor Microenvironment (TME)**: Addressing hypoxia, ECM density, and leveraging EPR effect [10, 14].

6 Design Strategies for Nanocarriers

Strategic design of nanocarriers is critical to overcoming biological barriers in drug delivery. An effective nanocarrier must achieve three essential objectives: target recognition, barrier penetration, and controlled payload release [3, 4]. Key design features include surface modifications, size and shape tuning, and efficient drug loading methods.

6.1 Surface Modification

Surface engineering enhances biological stability and targeting.

- **PEGylation**: Attaching polyethylene glycol (PEG) chains reduces immune recognition, prolongs circulation time, and enhances tumor accumulation via the Enhanced Permeability and Retention (EPR) effect [1, 2].
- **Ligand conjugation**: Linking antibodies, peptides, or sugars to nanocarriers enables active targeting of overexpressed receptors, such as folate or transferrin receptors [17].
- Surface modifiers like chitosan and poloxamers can also enable stimuli-responsive release.

6.2 Size and Shape Optimization

Nanocarrier size and geometry influence circulation, distribution, and uptake.

- **Size range**: 10–200 nm avoids renal clearance and favors tumor accumulation [18].
- **Shape effects**: Rod-like or discoidal particles enhance vascular margination and tissue penetration compared to spherical forms [7].

6.3 Drug Loading Techniques

Drug encapsulation affects therapeutic efficacy and release kinetics:

- **Passive loading**: Simple co-incubation suitable for hydrophobic drugs, but with limited control [4].
- **Pre-formulation**: Drug incorporation during nanocarrier synthesis ensures uniformity and controlled release [8].
- **Post-insertion**: Post-synthesis drug loading via covalent or non-covalent interactions (e.g., hydrogen bonding) is ideal for site-specific delivery [9].

7 Targeting Strategies for Nanocarriers

Nanocarriers can be engineered to enhance drug selectivity and efficacy while minimizing systemic toxicity. Targeting strategies are classified into passive, active, and stimuli-responsive approaches.

7.1 Passive Targeting

Passive targeting relies on the EPR effect, where leaky vasculature in tumors allows nanoparticle accumulation [10]. While effective in preclinical models, limitations include immune clearance, serum protein adsorption, and variability in tumor vasculature.

7.2 Active Targeting

Active targeting involves ligand-mediated recognition of specific receptors:

- Examples include antibodies, aptamers, or peptides that trigger receptor-mediated endocytosis [14].
- Challenges include high production costs, ligand instability in vivo, and potential immunogenicity.

7.3 Stimuli-Responsive Targeting

Stimuli-responsive nanocarriers release drugs in response to biological or external signals:

- **Internal stimuli**: pH, redox potential, and enzyme levels in tumor tissues.
- **External stimuli**: Light, ultrasound, or magnetic fields to trigger drug release [15]. This strategy allows precise temporal and spatial control but requires careful design and validation.

8 Characterization of Nanocarriers

Accurate characterization is crucial for ensuring nanocarriers meet pharmacological and safety requirements [13, 19, 20]. Three major evaluation domains are:

8.1 Physical Characterization

Key Parameters: Size, shape, surface charge, stability, drug release kinetics [21, as shown in Tabel 2.

- **DLS**: Measures hydrodynamic size distribution; can overestimate due to hydration [21].
- **TEM**: High-resolution imaging of morphology, though sample prep may introduce artifacts.
- **Zeta potential**: Indicates colloidal stability; values >|30 mV| suggest good suspension properties.
- **SAXS/SANS**: Reveal internal structures (e.g., bilayers) without disrupting integrity [20].

Table 2. Physical characterization tools.

Method	Precision	Limitation	Output
DLS	High for size	Overestimates due to hydration shell	Size distribution
TEM	High morphology	Sample drying may distort structure	2D images
Zeta potential	Moderate	Sensitive to ionic environment	Charge vs. pH
SAXS/SANS	High structure	Requires expertise	Bilayer profiles

8.2 Chemical Characterization

Essential for verifying synthesis, drug conjugation, and payload quantification.

- **H NMR and UV–Vis**: Confirm conjugation; UV–Vis may saturate with intense dyes [1, 20].
- **Fluorescent dyes**: Use of calibrated dyes (e.g., naphthalimide at 370 nm) improves loading quantification [22].
- **Post-conjugation DLS and zeta analysis**: Confirm structural integrity after surface modifications [1].

8.3 Biological Characterization

Assesses behavior within biological systems — circulation, immune interaction, and cellular uptake [4, 20]:

- **In vitro**: Transwell and 3D spheroids simulate barriers and tissue architecture [22].
- **Advanced models**: Organ-on-chip systems for dynamic, physiologically relevant insights (e.g., BBB transport) [22].
- **Immune assays**: Evaluate protein corona formation, macrophage uptake, complement activation.
- **In vivo studies**: Must extend beyond survival to include pharmacokinetics, biodistribution, and targeted tissue accumulation.

9 In Vitro & In Vivo Studies

Thorough evaluation using both models is essential to predict clinical success [1, 4]:

9.1 In Vitro Models

- **2D monolayers**: High-throughput but oversimplified; e.g., PLGA–doxorubicin in breast cancer lines showed uptake and cytotoxicity [20].
- **3D spheroids/co-cultures**: Better emulate tissue gradients; HER2-targeted liposomes penetrated 3D spheroids more effectively than in 2D [21].
- **Organs-on-chip**: Recreate dynamic tissue flow; transferrin-modified nanoparticles crossed BBB under flow—later validated in animal models [22].

9.2 In Vivo Studies

Animal models reveal systemic dynamics not captured in vitro:

- **Mouse xenograft studies**: e.g., siRNA PLGA nanoparticles reduced lung tumor volume with minimal toxicity [1].
- **PET-tracked lipid carriers**: Fluorodeoxyglucose-labeled NLC-FA-SN38 showed 85.9% inhibition of metastatic tumors, aligning with in vitro efficacy [20-24].

9.3 Correlations

- **Uptake & toxicity**: 2D often overestimates, while 3D more closely mimics in vivo behavior.
- **Biodistribution**: Animal imaging (PET/IVIS) is necessary — data not deducible from static in vitro systems.
- **Endosomal escape/gene silencing**: Validated in vitro but subject to immune clearance in vivo.

10 Conclusions from Current Research

Nanocarriers offer substantial promise in improving drug solubility, stability, penetration of biological barriers, and targeted delivery, yet challenges remain due to the intricate structure and function of biological barriers. Extensive multidisciplinary efforts are required for the design, evaluation, and clinical translation of nanocarrier-based drug delivery systems. Enhancing education on potential safety concerns and expanding preclinical testing are critical steps. Although in early stages, the field holds great potential for addressing unmet medical needs globally through continued scientific, technological, and policy advances [4, 9].

11 Conclusion

The progress of nanocarriers in targeted drug delivery has significantly advanced the goal of safe and efficacious therapies. These developments enable a more personalized approach to treating human diseases by allowing drugs to be delivered more effectively to specific organs, tissues, or cellular sites, thereby optimizing therapeutic efficacy while minimizing harmful side effects. Nanocarriers also potentiate diagnostic imaging and combination therapies by synergistically co-delivering drugs and imaging agents within the same platform. While many applications of nanocarrier-based drug delivery and imaging are still in preclinical stages, some have progressed into early-phase clinical trials. Significant advances over recent decades have demonstrated that rational nanocarrier design—incorporating targeted surface modifications, core engineering, and responsive elements—is feasible and effective for enhancing delivery to desired tissues and cells.

Targeted delivery vehicles utilizing surface engineering, small molecule ligands, or monoclonal antibodies as targeting moieties are well-established and are currently undergoing clinical translation. Meanwhile, bulk modifications with mechanisms still under investigation continue to show promise in preclinical research. To overcome persistent challenges, interdisciplinary collaboration among scientists is essential, particularly to address the complexity of systematically targeting heterogeneous diseases such as cancer. Designing nanocarriers that are biocompatible, non-immunogenic, versatile, and effective remains a high-risk yet high-reward endeavor. Although many nanocarrier platforms targeting specific diseases are promising candidates for market entry, the first to achieve clinical approval and commercialization remains uncertain. Regulatory agencies will rigorously assess safety and efficacy before approval. Nonetheless, decades of dedicated research have produced valuable insights and expertise, laying a solid foundation for future breakthroughs in nanocarrier-based drug delivery systems.

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