Dean&Francis
ISSN 2959-409X

From Nanotechnology to Targeted Therapy: Advances in Drug Delivery Systems

Xinlei Tian

China Medical University,
Shenyang, Liaoning, 110000, China
Email:xtian04@qub.ac.uk

Abstract:

Advanced drug delivery systems (ADDS) have transformed modern therapeutics by improving drug pharmacokinetics, biodistribution, and safety profiles. Nanotechnology — including liposomes, polymeric nanoparticles, lipid nanoparticles (LNPs), metallic nanoparticles, and nanoemulsions — enables controlled release, enhanced solubility, image-guided delivery, and active targeting[1][2]. Clinical successes such as liposomal doxorubicin, albumin-bound paclitaxel, siRNA LNP therapeutics, and mRNA vaccines illustrate both the promise and translational challenges of nanomedicine[3][4][5][8]. This review outlines historical development, compares major nanocarriers and targeting strategies, highlights clinical case studies, addresses biological and regulatory barriers, and emphasizes emerging directions including stimuli-responsive systems, personalized nanomedicine, and computational design[6][7][9]. Opportunities and limitations for converting laboratory concepts into clinically relevant therapies are discussed.

Keywords: Nanotechnology, Liposomes, Lipid nanoparticles, Targeted therapy, Controlled release, Clinical translation

1. Introduction

Achieving effective drug delivery at the correct dose, timing, and location is essential for therapeutic efficacy and patient safety. Conventional routes — oral, intravenous, intramuscular, and subcutaneous — are indispensable but frequently face challenges such as low solubility, rapid clearance, off-target toxicity, and narrow therapeutic windows. Over recent decades, controlled-release formulations and novel carriers have emerged to overcome these limitations. Nanotechnology has further advanced this field, enabling systems that actively target tissues, cross biological barriers, and respond to internal or external stimuli. The field's growth has been fueled by materials science, molecular biology, and translational medicine, yet clinical translation remains complex, demanding careful assessment of safety, manufacturability, and therapeutic benefit.This review aims to provide a comprehensive overview of this evolution, from fundamental nanocarrier designs to cutting-edge clinical applications, while critically examining the hurdles that remain on the path to clinical translation.

ISSN 2959-409X

2. Historical development and classification of drug delivery platforms

2.1 From conventional formulations to nanocarriers

Pharmaceutical formulations evolved from immediate-release tablets and injections to controlled-release implants and depot systems, which improved dosing frequency but minimally affected biodistribution. Nanoscale carriers (<200 nm) introduced new parameters — particle size, surface chemistry, shape, and flexibility — influencing circulation time, cellular uptake, and tissue penetration[1]. Lipid-based carriers (liposomes, LNPs), polymeric systems (PLGA nanoparticles, micelles), metallic nanoparticles (gold, iron oxide), and hybrid platforms offer distinct advantages and limitations in drug loading, release, and targeting[2].The selection of a specific nanocarrier is dictated by the physicochemical properties of the drug (e.g., hydrophilicity/hydrophobicity), the intended route of administration, and the therapeutic objective.

2.2 Major nanocarrier families

Liposomes: Bilayer vesicles encapsulating hydrophilic drugs in the core and hydrophobic drugs in the membrane. PEGylation extends circulation, and ligands enable targeting.

Lipid nanoparticles (LNPs): Ionizable lipid carriers optimized for nucleic acid delivery (siRNA, mRNA). They protect oligonucleotides from degradation and facilitate endosomal escape. Clinical approval of siRNA therapeutics and mRNA vaccines demonstrates their translational potential[5].

Polymeric nanoparticles and micelles: Biodegradable polymers (PLGA, PEG-PLA) allow tunable release and stability; micelles improve solubility of hydrophobic drugs.

Protein- or albumin-bound carriers: Utilize endogenous transport proteins to enhance delivery, exemplified by nab-paclitaxel.

Metal/metal-oxide nanoparticles: Employed for imaging and photothermal therapy; clearance and biocompatibility remain critical considerations.

Nanoemulsions and dendrimers: Support solubility enhancement and multivalent functionalization.

3. Principles and strategies of targeting

3.1 Passive targeting: Enhanced permeability and retention (EPR)

The Enhanced Permeability and Retention (EPR) effect has long been a cornerstone of oncology nanomedicine, driving strategies aimed at tumor-specific drug delivery. The leaky vasculature and impaired lymphatic drainage in tumors promote nanoparticle accumulation and retention. However, the EPR effect exhibits substantial heterogeneity across different tumor types and individual patients, undermining its consistency. This variability limits the reliability of EPR as a standalone targeting mechanism and highlights the need for complementary approaches in nanomedicine design.

3.2 Active targeting: Ligands, antibodies, and ADCs

Active targeting attaches recognition motifs — small molecules, peptides, aptamers, or antibodies — to carriers to bind overexpressed receptors. ADCs, such as ado-trastuzumab emtansine (T-DM1), couple cytotoxins to monoclonal antibodies, improving uptake. Performance depends on receptor levels, internalization kinetics, and tumor microenvironment.

3.3 Triggered release: Stimuli-responsive systems

Carriers responsive to internal (pH, enzymes, redox) or external (heat, light, ultrasound, magnetic) triggers allow spatiotemporal control, minimizing systemic exposure. Preclinical studies are promising, yet consistent, predictable release in humans remains challenging.

4. Representative clinical successes

4.1 Liposomal doxorubicin (Doxil)

Doxil® was shown to exhibit favorable pharmacokinetics and a reduced risk of cardiotoxicity. Furthermore, its clinical development demonstrated the critical importance of reproducible manufacturing processes, product stability, and controlled release profiles for achieving regulatory approval and successful clinical adoption.

4.2 Albumin-bound paclitaxel (Abraxane)

By employing albumin, paclitaxel delivery improved without Cremophor, lowering hypersensitivity risks and enabling higher tolerated doses. This illustrates leveraging endogenous transport for clinical advantage.

4.3 Nucleic acid therapeutics: Onpattro (patisiran)

Patisiran LNPs for hereditary transthyretin-mediated amyloidosis highlight that engineered LNPs can deliver oligonucleotides systemically with meaningful endpoints.

Regulatory approval required clear demonstration of safety, consistent manufacturing, and clinical benefit.

4.4 mRNA vaccines: LNP translation

SARS-CoV-2 mRNA vaccines (BNT162b2, mRNA-1273) used ionizable LNPs for mRNA protection and uptake. They validated safety and efficacy at scale, accelerated formulation know-how, cold-chain logistics, and manufacturing. Key lessons: reproducible manufacturing, clear clinical benefit, manageable safety, and scalable supply chains.

5. Biological, technical, and regulatory challenges

5.1 Biological barriers

Protein corona formation affects immune recognition and biodistribution. The mononuclear phagocyte system sequesters nanoparticles, reducing delivery. Tumor heterogeneity, interstitial pressure, and poor vascularization hinder penetration.Upon intravenous administration, nanoparticles are rapidly coated by plasma proteins, forming a 'protein corona' that masks engineered surface ligands and dictates subsequent immune recognition and biodistribution, often diverting carriers to the mononuclear phagocyte system.

5.2 Safety and immunogenicity

Inorganic nanoparticles may trigger oxidative stress or inflammation. Biodegradable carriers can still provoke immune reactions (CARPA). Surface engineering (PEGylation) mitigates but does not eliminate risks.

5.3 Manufacturing and quality

Scale-up requires precise particle size, encapsulation efficiency, and stability control. Process variation can alter pharmacology, necessitating robust analytics and in-process controls.

5.4 Translational gaps

Murine models exaggerate EPR and do not fully replicate human clearance or immunity. Patient stratification, adaptive designs, and organoid models can improve prediction. To bridge this gap, more physiologically relevant models such as patient-derived organoids and complex in vitro microfluidic systems ('organs-on-chips') are being increasingly adopted."

5.5 Regulatory considerations

Nanomedicines follow core safety, efficacy, and quality principles. Characterization of nanomaterials, stability, and biological interactions is crucial. Early regulatory engagement aids alignment on comparability and CMC expectations.

6. Emerging research directions

1. Multi-Stimuli Responsive Carriers: Developing carriers that respond to multiple specific triggers in the disease microenvironment for precision targeting.
2. Combination and Multimodal Therapies: Integrating therapeutics with complementary mechanisms of action to overcome resistance and enhance efficacy.
3. Personalized Nanomedicine: Engineering nanocarriers tailored to individual patient's disease profiles and genetic makeup.
4. Computational and AI-Guided Design: Utilizing in-silico models and artificial intelligence to accelerate the rational design of nanomedicines.
5. Expansion to Non-Oncology Indications: Applying advanced nanoplatforms to treat infectious, inflammatory, and degenerative diseases.

7. Practical recommendations

1. Integrate Manufacturing Considerations Early: Incorporate scalability and robust production processes during initial design phases.
2. Employ Clinically Relevant Models: Utilize disease models that accurately recapitulate human pathology for predictive efficacy and safety assessment.
3. Pursue Early Regulatory Dialogue: Engage with regulatory agencies (pre-IND) to align on critical development pathways and requirements.
4. Implement Biomarker-Driven Patient Stratification: Identify and utilize biomarkers to select patient populations most likely to respond to therapy.
5. Prioritize Comprehensive Toxicology: Conduct thorough safety, biodistribution, and long-term toxicity studies to de-risk clinical translation.

8. Conclusion

The clinical translation of nanotechnology, exemplified by liposomal, albumin-bound, and lipid nanoparticle (LNP) platforms, has yielded drugs with demonstrably improved therapeutic profiles. These pioneering achievements, while confirming the potential of nanomedicine, have concurrently delineated significant biological, industrial, and regulatory complexities. Future progress is directed towards stimuli-responsive and combinatorial platforms, refined patient selection via biomarkers, and AI-driven de-

ISSN 2959-409X

sign—all critical for advancing laboratory innovations to the clinic. Ensuring this transition will require a steadfast focus on resolving safety, manufacturing reproducibility, and cost-effectiveness to fulfill the overarching clinical promise of these sophisticated therapeutics.

References

[1] Allen, T. M., & Cullis, P. R. (2013). Liposomal drug delivery systems: From concept to clinical applications. Advanced Drug Delivery Reviews, 65(1), 36–48.

[2] Shi, J., Kantoff, P. W., Wooster, R., & Farokhzad, O. C. (2017). Cancer nanomedicine: Progress, challenges and opportunities. Nature Reviews Cancer, 17(1), 20–37.

[3] Adams, D., Gonzalez-Duarte, A., O'Riordan, W. D., et al. (2018). Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin-Mediated Amyloidosis. NEJM, 379, 11–21.

[4] Polack, F. P., Thomas, S. J., Kitchin, N., et al. (2020). Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. NEJM, 383, 2603–2615.

[5] Schoenmaker, L., Witzigmann, D., Kulkarni, J. A., et al. (2021). mRNA-lipid nanoparticle COVID-19 vaccines: Structure and stability. Int. J. Pharmaceutics.

[6] van der Meel, R., Vehmeijer, L. J., Kok, R. J., et al. (2019). Smart cancer nanomedicine. Nature Nanotechnology.

[7] Tran, S., DeGiovanni, P.-J., Piel, B., & Rai, P. (2017). Cancer nanomedicine: A review of recent success in drug delivery. Clin. Transl. Med.

[8] Suzuki, Y., Ishii, T., & et al. (2021). Difference in the lipid nanoparticle technology employed for Patisiran and COVID-19 mRNA vaccines. Pharmaceutics/Review.

[9] Giri, P. M., et al. (2023). A recent review on cancer nanomedicine. Cancers (MDPI).