INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Stealth Liposomes for Targeted Drug Delivery: Recent Advances, Clinical Applications, and Future Perspectives

Aswathy Mohan*, Dr. Arun Raj R, Divyamol A.K, Gayathri P M, Krishna Haridas, Athmika Haika, Shabnam Shibu Sekumeeran, Praveena V A

Department of Pharmaceutical Sciences, RIMSR, Puthuppally, Kottayam, Kerala, India 686009.

ARTICLE INFO

Published: 05 Aug 2026
Keywords:
Stealth Liposomes, Targeted Drug Delivery, Polyethylene Glycol (PEG), Stimuli-Responsive Drug Delivery, Nanomedicine
DOI:
10.5281/zenodo.21808644

ABSTRACT

Liposomes have revolutionized the field of drug delivery, particularly through the development of "stealth" or sterically stabilized formulations. These second-generation nanocarriers, typically modified with polyethylene glycol (PEG), are designed to evade the mononuclear phagocyte system (MPS), thereby extending circulation half-lives and improving the therapeutic index of various drugs. While initially focused on passive targeting via the enhanced permeability and retention (EPR) effect in cancer, recent advances have transitioned toward active targeting strategies using bioaffinity ligands and stimuli-responsive mechanisms. This report provides a comprehensive overview of the current state of stealth liposome technology. It details recent breakthroughs in super-stealth designs, stimuli-sensitive release systems, and ligand-mediated targeting for diverse therapeutic areas including oncology, cardiovascular diseases, and neurological disorders. Furthermore, the report examines the clinical landscape, highlighting FDA-approved formulations and emerging candidates in clinical trials. Despite their success, challenges such as the accelerated blood clearance (ABC) effect, immunogenicity, and manufacturing scalability remain critical hurdles. The future of the field lies in biomimetic coatings, personalized nanomedicine, and multifunctional theranostic platforms that aim to provide safer and more effective targeted therapies.

INTRODUCTION

Liposomes are spherical vesicles composed of one or more lipid bilayers, capable of encapsulating both hydrophilic and hydrophobic therapeutic agents [1], [2]. Since their inception, they have been valued for their high degree of biocompatibility and ability to protect drug payloads from degradation [3], [4]. However, conventional liposomes are often limited by a short circulation half-life due to rapid recognition and uptake by the reticuloendothelial system (RES), primarily in the liver and spleen [5], [6].

***Corresponding Author:** Aswathy Mohan
Address: *Department of Pharmaceutical Sciences, RIMSR, Puthuppally, Kottayam, Kerala, India 686009.*
Email : aswathymohan4944@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

To overcome these pharmacokinetic barriers, "stealth" liposomes were developed. These formulations are surface-modified with hydrophilic polymers, most commonly polyethylene glycol (PEG), which creates a steric barrier—a hydrated "cloud"—that inhibits the adsorption of serum proteins (opsonins) and subsequent macrophage recognition [7], [6], [8]. This modification significantly prolongs circulation time, allowing for increased accumulation at disease sites, such as tumors, through the enhanced permeability and retention (EPR) effect [9], [10], [11].

2. Methods and Approaches in Stealth Liposome Design

2.1 Steric Stabilization Strategies

The primary method for achieving the stealth effect is PEGylation, where PEG chains are tethered to the liposome surface. Recent design improvements include "Super Stealth Immunoliposomes" (SSIL2), which utilize PEG-bi-phospholipid derivatives to stabilize the polymer shielding and provide more robust protection against immune clearance [12]. Beyond PEG, other materials like negatively charged glycolipids (e.g., GM1) and phosphatidylinositol have been explored for their ability to reduce RES uptake [13], [11].

2.2 Synthesis and Manufacturing

Traditional synthesis methods such as thin-film hydration are being supplemented by advanced techniques like microfluidic hydrodynamic flow focusing [14]. Microfluidic platforms allow for the one-step, continuous-flow synthesis of small, monodisperse PEG- and ligand-conjugated liposomes with precise control over size and encapsulation efficiency [14], [15]. Maintaining organic solvent-free synthesis remains a priority for ensuring clinical safety and regulatory compliance [16].

3. Recent Advances in Targeting Strategies

3.1 Active Targeting and Ligand Functionalization

Modern stealth liposomes are increasingly functionalized with site-specific ligands to enable active targeting. These ligands, often conjugated to the distal ends of PEG chains, facilitate selective binding to overexpressed receptors on target cells [5], [17].

- **Antibodies and Fragments**: Anti-HER2 antibodies and Fab' fragments have been successfully used to target breast cancer cells [12], [5], [18]. Anti-VCAM antibodies are being investigated for targeting inflamed endothelium in cardiovascular applications [19].
- **Peptides and Small Molecules**: RGD peptides are used to target integrins on tumor cells and active platelets [20], [21]. Other ligands include folate, transferrin, vitamins, and growth factors [22], [23], [19].
- **Phage Fusion Proteins**: Novel approaches involve inserting phage fusion proteins into the liposome bilayer to display tumor-binding peptides [18].

3.2 Stimuli-Responsive Systems

"Smart" stealth liposomes are designed to release their cargo in response to specific internal or external triggers, improving drug release kinetics at the target site [22], [17].

- **Internal Triggers**: pH-sensitive liposomes utilize the acidic microenvironment of tumors or endosomes to destabilize and release

drugs [7], [23], [16]. Redox-responsive and enzyme-sensitive (e.g., matrix metalloproteinase) systems are also under intensive study [22], [24], [25].

- **External Triggers**: Thermosensitive liposomes release payloads when exposed to localized hyperthermia [17], [26]. Other triggers include light, ultrasound, and magnetic fields [22], [27], [28].

3.3 Diversification of Applications

While oncology remains the primary focus, stealth liposomes are expanding into other therapeutic areas:

- **Cardiovascular Disease**: Targeting cRGD peptides to GPIIb/IIIa receptors on active platelets for myocardial infarction and atherosclerosis treatment [20].
- **Neurological Disorders**: Engineering liposomes to cross the blood-brain barrier for CNS drug delivery [16], [29].
- **Inflammatory Conditions**: Using PEGylated formulations for targeted delivery in arthritis (e.g., celecoxib) and colitis (e.g., folate-linked PEG liposomes) [19], [30].
- **Infectious Diseases**: Delivering antibiotics and antifungals (e.g., Amphotericin B) with reduced toxicity and improved site-specific action [31], [21].

4. Clinical Applications and Marketed Formulations

The clinical translation of stealth liposomes has seen several notable successes since the 1990s.

- **Doxil/Caelyx**: The first FDA-approved nano-drug (1995), a PEGylated liposomal doxorubicin formulation used for Kaposi's sarcoma, ovarian cancer, and breast cancer [23], [32], [16]. It exhibits a significantly prolonged plasma half-life compared to free doxorubicin [10], [33].
- **Other Approved Agents**: Myocet and DaunoXome are also established liposomal chemotherapeutics [23], [34].
- **Clinical Pipeline**: Several formulations are in various stages of clinical trials:
- **Phase III**: Lipoplatin, a cisplatin formulation [7], [23].
- **Phase I/II**: SPI-077, S-CKD602, Marqibo (vincristine), and LE-SN38 [7], [5], [23].
- **Emerging**: ThermaDox (thermosensitive) and Aroplatin [5].

5. Limitations and Challenges

Despite their therapeutic promise, stealth liposomes face significant biological and technical hurdles.

5.1 The Accelerated Blood Clearance (ABC) Effect

A major concern with PEGylated liposomes is the "ABC phenomenon," where repeated injections trigger the production of anti-PEG IgM antibodies. This leads to rapid clearance of subsequent doses by the liver, negating the stealth effect and reducing efficacy [7], [19], [26].

5.2 Immunogenicity and Hypersensitivity

Stealth liposomes can trigger complement activation-related pseudoallergy (CARPA), an acute hypersensitivity reaction [19], [26]. The potential for unexpected immune responses remains a barrier to widespread clinical use.

5.3 Technical and Regulatory Barriers

- **Manufacturing Complexity**: Large-scale production of complex, multi-component liposomes (e.g., those with multiple ligands or stimuli-responsive parts) is difficult and costly [35], [17], [31].
- **Stability and Release**: Problems with long-term stability and premature drug leakage can limit shelf life and therapeutic impact [20], [35], [31]. Steric hindrance from PEG can also interfere with cellular uptake or drug release at the target site [7], [5], [23].
- **Cost**: High excipient-to-drug ratios and expensive lipid constituents contribute to significant manufacturing costs [20], [34].

6. Future Directions and Research Gaps

The next generation of stealth liposomes aims to address current limitations through innovative engineering.

- **Biomimetic Camouflage**: Coating liposomes with cell membranes (e.g., red blood cells or platelets) to achieve "natural" stealth properties and better immune evasion [36], [37].
- **Personalized Nanomedicine**: Tailoring liposomal products to the unique physiological conditions and biomarkers of individual patients [36], [35], [29].
- **Multifunctional and Theranostic Platforms**: Integrating diagnostic imaging probes (e.g., PET, SPECT, MRI) with therapeutic agents to enable real-time monitoring of drug delivery and efficacy [38], [17], [3], [29].
- **Advanced Payloads**: Expanding beyond small molecules to deliver siRNA, mRNA, and CRISPR-Cas9 components for gene therapy [36], [18], [39].

CONCLUSION

Stealth liposomes have established themselves as a cornerstone of targeted drug delivery, particularly in oncology. The move from simple PEGylation to sophisticated, ligand-targeted, and stimuli-responsive systems represents a significant technological leap. While clinical successes like Doxil have paved the way, overcoming biological challenges like the ABC effect and technical hurdles in manufacturing remains essential for the future. With the integration of biomimetic strategies and personalized approaches, stealth liposomes are poised to continue transforming the landscape of precision medicine.

REFERENCES

1. Samad A, Sultana Y, Aqil M. Liposomal drug delivery systems: an update review. Current Drug Delivery. 2007;4(4):297–305.
2. Vishvakrama P, Sharma S. Liposomes: an overview. Journal of Drug Delivery and Therapeutics. 2014;4(1):47–55.
3. Urbinati G, Marsaud V, Renoir JM. Anticancer drugs in liposomal nanodevices: a target delivery for a targeted therapy. Current Topics in Medicinal Chemistry. 2012;12(15):1693–1712.
4. Rahman M, Beg S, Kumar V, Al-Kassas R, Al-Harbi MG, Ahmed A. Liposomes as anticancer therapeutic drug carrier's systems: more than a tour de force. Current Nanomedicine. 2020;10(2):178–185.
5. Bangale GS, Rajesh KS, Shinde G. Stealth liposomes: a novel approach of targeted drug delivery in cancer therapy. International Journal of Pharmaceutical Sciences and Research. 2014;5(2):330–338.
6. A AV, Padmini PJ. Stealth liposomes in human welfare: an overview. International

Journal of Pharmaceutical Sciences Review and Research. 2022;72(1):12–19.
7. Immordino ML, Dosio F, Cattel L. Stealth liposomes: review of the basic science, rationale, and clinical applications, existing and potential. International Journal of Nanomedicine. 2006;1(3):297–315.
8. Lasic DD, Martin FJ. Stealth Liposomes. Boca Raton (FL): CRC Press; 1995.
9. Liu Y, Castro Bravo KM, Liu J. Targeted liposomal drug delivery: a nanoscience and biophysical perspective. Nanoscale Horizons. 2021;6(2):78–94.
10. Federman N, Denny CT. Targeting liposomes toward novel pediatric anticancer therapeutics. Pediatric Research. 2010;67(5):514–519.
11. Huang SK, Mayhew E, Gilani S, Lasic DD, Martin FJ, Papahadjopoulos D. Pharmacokinetics and therapeutics of sterically stabilized liposomes in mice bearing C-26 colon carcinoma. Cancer Research. 1992;52(19):5135–5143.
12. Canato E, Grigoletto A, Zanotto I, Bellato F, Salmaso S, Caliceti P. Anti-HER2 super stealth immunoliposomes for targeted-chemotherapy. Advanced Healthcare Materials. 2023;12(28):e2301650.
13. Gabizon A, Uziely B, Kaufman B, Barenholz Y, Goren D. A new generation of doxorubicin-loaded liposomes with improved localization in tumors: preclinical and clinical studies. In: Liposomes in Biomedical Applications. Harwood Academic Publishers; 1994:174–182.
14. Hood RR, Shao C, Omiatek DM, Vreeland WN, DeVoe DL. Microfluidic synthesis of PEG- and folate-conjugated liposomes for one-step formation of targeted stealth nanocarriers. Pharmaceutical Research. 2013;30(6):1597–1607.
15. Chen X, Li Y, Wang Z, Zhang L, Liu M. High throughput microfluidics-based synthesis of PEGylated liposomes for precise size control and efficient drug encapsulation. Colloids and Surfaces B: Biointerfaces. 2024;236:113926.
16. Montesinos RN. Liposomal drug delivery to the central nervous system. In: Brain Targeted Drug Delivery System. InTechOpen; 2017:105–124.
17. Agrawal S, Baliga V, Londhe V. Liposomal formulations: a recent update. Pharmaceutics. 2025;17(1):36.
18. Bedi D, Musacchio T, Fagbohun OA, Gillespie JW, DeInnocentes P, Bird RC, Petrenko VA, Torchilin VP. Delivery of siRNA into breast cancer cells via phage fusion protein-targeted liposomes. Nanomedicine: Nanotechnology, Biology and Medicine. 2011;7(3):315–323.
19. Lenders V, Koutsoumpou X, Sargsian A, Scheeren FA, Cruz LJ. Biomedical nanomaterials for immunological applications: ongoing research and clinical trials. Nanoscale Advances. 2020;2(9):3771–3794.
20. Chandarana M, Curtis ADM, Hoskins C. The use of nanotechnology in cardiovascular disease. Applied Nanoscience. 2018;8(8):1807–1819.
21. Thomas S, Kumar R, Singh M. Development and evaluation of amphotericin B loaded iron oxide nanoparticles for targeted drug delivery to systemic fungal infections [master's thesis]. Memphis (TN): The University of Tennessee Health Science Center; 2015.
22. Jain A. Advances in tumor targeted liposomes. Current Molecular Medicine. 2018;18(3):148–157.
23. Lopes SCA, Giuberti CS, Rocha TGR, Oliveira MC. Liposomes as carriers of anticancer drugs. In: Cancer Treatment - Conventional and Innovative Approaches. InTechOpen; 2013:101–128.
24. Mustafa M, Lou J, Best MD. Development of ROS-responsive liposomes toward targeted drug delivery. Expert Opinion on Drug Delivery. 2025;22(2):185–198.
25. Johansen PT, Andresen TL, Jensen SS. Biological studies of matrix metalloproteinase sensitive drug delivery systems. Journal of Control Release. 2011;152(Suppl 1):e31–e33.
26. Agarwal K. Liposome assisted drug delivery-an updated review. Indian Journal of Pharmaceutical Sciences. 2022;84(4):812–820.

27. Awad N, Paul V, Mahmoud MS, Al-Sayegh M, Al-Sayah MH, Hussain A. Effect of pegylation and targeting moieties on the ultrasound-mediated drug release from liposomes. ACS Biomaterials Science & Engineering. 2020;6(1):315–326.
28. Aundhia C, Parmar G, Talele C, Shah S, Patel M. Light sensitive liposomes: a novel strategy for targeted drug delivery. Pharmaceutical Nanotechnology. 2024;12(3):210–222.
29. Mohammed V, Richard NS. Revolutionizing medicine: the promise of camouflage nanoparticles - a review. Current Nanomaterials. 2024;9(2):112–125.
30. Begum MY, Osmani RAM, Alqahtani A, Ghazwani M, Hani U, Rahamathulla M. Development of stealth liposomal formulation of celecoxib: in vitro and in vivo evaluation. PLoS ONE. 2022;17(3):e0264518.
31. Sengar A. Advancements in liposomal drug delivery systems and their therapeutic applications. Preprints. 2025:2025031540.
32. Gatto MS, Johnson MP, Najahi-Missaoui W. Targeted liposomal drug delivery: overview of the current applications and challenges. Life. 2024;14(6):672.
33. Drabu S, Khanna S, Bajaj R. Clinical pharmacokinetic aspects of stealth liposomes: a review. International Journal of Drug Development and Research. 2010;2(3):500–508.
34. Pinto AC, Moreira JN, Simões S. Combination chemotherapy in cancer: principles, evaluation and drug delivery strategies. In: Chemotherapy - Molecular Targets and Clinical Applications. InTechOpen; 2011:153–182.
35. Sharma R, Verma A. Liposomal drug delivery systems: a potential platform for anti-cancer therapies. Zenodo Repository. 2025. doi:10.5281/zenodo.14649450.
36. Saadh MJ, Mustafa MA, Kumar A, Singh S, Sharma P, Patel R. Stealth nanocarriers in cancer therapy: a comprehensive review of design, functionality, and clinical applications. AAPS PharmSciTech. 2024;25(5):118.
37. Li Z, Li M, Lu J. Biomimetic liposomes in drug delivery: from design mechanisms to applications. Chemical Society Reviews. 2025;54(2):620–648.
38. Powers D, Nosoudi N. Liposomes; from synthesis to targeting macrophages. Biomedical Research (Tokyo). 2019;30(3):412–418.
39. Rosenblum D, Joshi N, Tao W, Karp JM, Peer D. CRISPR-Cas9 genome editing using targeted lipid nanoparticles for cancer therapy. Science Advances. 2020;6(47):eabc9450.

HOW TO CITE: Aswathy Mohan, Dr. Arun Raj R, Divyamol A.K, Gayathri P M, Krishna Haridas, Athmika Haika, Shabnam Shibu Sekumeeran, Praveena V A, Stealth Liposomes for Targeted Drug Delivery: Recent Advances, Clinical Applications, and Future Perspectives, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 8, 775-780. https://doi.org/10.5281/zenodo.21808644