



Review Article

A Review on Polymeric Nano Carriers for Blood Brain Barrier Penetration: Strategies for Cytotoxic Drug Delivery

Umesh Chandra*, Amit Singh

Monad University, Kastla, Kasmabad, Pilkhuwa, Uttar Pradesh 245304

The effective delivery of cytotoxic drugs to the central nervous system (CNS) remains a significant challenge in the treatment of brain tumors and neurodegenerative diseases due to the presence of the blood-brain barrier (BBB). The BBB acts as a highly selective semipermeable membrane that restricts the passage of most therapeutic agents, especially large molecular weight and hydrophilic compounds. Polymeric nano carriers have emerged as promising tools to overcome this barrier by enabling targeted, sustained, and controlled delivery of chemotherapeutic agents to the brain. This paper reviews recent advances in polymeric nanoparticles (NPs) designed for BBB penetration, focusing on strategies such as surface modification with ligands, use of cell-penetrating peptides, and receptor-mediated transcytosis. We discuss various polymeric materials including poly(lactic-co-glycolic acid) (PLGA), poly(alkyl cyanoacrylates) (PACA), chitosan, and dendrimers, highlighting their biocompatibility, biodegradability, and functional versatility. Additionally, the mechanisms of BBB translocation, formulation challenges, and regulatory considerations are evaluated. The review concludes with an outlook on clinical translation and future directions in polymeric nanomedicine for brain cancer therapy.

Keywords: Blood-brain barrier, polymeric nanoparticles, drug delivery, brain tumors, nanomedicine, cytotoxic agents.

INTRODUCTION

The BBB is a highly selective barrier that separates the brain from the bloodstream, protecting it from toxins and pathogens [1]. However, this barrier also restricts the delivery of therapeutic agents, including cytotoxic drugs, to the brain, making it challenging to treat brain-related diseases [2]. Brain tumors, such as glioblastoma, and neurodegenerative diseases, such as Alzheimer's and Parkinson's, are particularly difficult to treat due to the limited penetration of drugs across the BBB [3], [4].

Polymeric nano carriers have gained significant attention in recent years as a potential solution to overcome the BBB and deliver cytotoxic drugs to the brain [5]. These nano carriers can be designed to encapsulate a wide range of therapeutic agents, including small molecules, proteins, and nucleic acids, and can be engineered to target specific cells or

tissues [6]. In this review, we will discuss the various strategies employed by polymeric nano carriers to penetrate the BBB and deliver cytotoxic drugs to the brain.

Structure and Function of the Blood-Brain Barrier

The BBB consists of specialized brain microvascular endothelial cells (BMECs) connected by tight junctions formed by claudins, occludins, and junctional adhesion molecules. These junctions restrict paracellular diffusion, rendering the BBB impermeable to most molecules larger than 400 Da or those with high polarity. Additionally, BMECs express efflux transporters such as P-gp, breast cancer resistance protein (BCRP), and multidrug resistance-associated proteins (MRPs), which actively expel xenobiotics from the brain back into circulation.

Transcellular transport across the BBB occurs via several mechanisms: passive diffusion (limited to small, lipophilic molecules), carrier-mediated transport (e.g., glucose via GLUT1), receptor-mediated transcytosis (RMT), and adsorptive-mediated transcytosis (AMT). Exploiting these endogenous transport systems through nano carrier engineering presents a viable strategy to achieve therapeutic drug concentrations in the brain.

Polymeric Nano Carriers: Design and Advantages

Polymeric nano carriers are nanoscale vehicles (typically 10–200 nm) formed from synthetic or natural polymers that can encapsulate, adsorb, or conjugate therapeutic agents. Key advantages include:

- **Biocompatibility and biodegradability:** Most polymers degrade into non-toxic byproducts.
- **Controlled release:** Sustained drug release profiles reduce dosing frequency.
- **Surface functionalization:** Ligands can be conjugated for active targeting.
- **High drug loading capacity:** Especially for hydrophobic cytotoxic agents.
- Protection from enzymatic degradation and immune recognition

Types of Polymeric Nano Carriers

Polymeric nano carriers can be categorized into several types based on their composition, structure, and function. Some of the most commonly used polymeric nano carriers for BBB penetration include:

1. **Polymeric nanoparticles:** These are spherical particles made from biodegradable polymers, such as poly (lactic-co-glycolic acid) (PLGA) and poly(caprolactone) (PCL) [7].
2. **Polymeric micelles:** These are self-assembling structures formed from amphiphilic block copolymers, which can encapsulate hydrophobic drugs [8].

3. **Dendrimers:** These are highly branched, tree-like structures that can be functionalized with targeting ligands and therapeutic agents [9].

4. **Polymeric vesicles:** These are hollow structures made from amphiphilic block copolymers, which can encapsulate therapeutic agents [10].

Design Considerations for BBB Penetration

To effectively penetrate the BBB, polymeric nano carriers must be designed with specific characteristics. Some of the key design considerations include:

1. **Size:** The size of the nano carrier is critical, as particles larger than 100 nm are generally unable to cross the BBB [11].
2. **Surface charge:** The surface charge of the nano carrier can influence its interaction with the BBB, with cationic particles often showing enhanced uptake [12].
3. **Targeting ligands:** The incorporation of targeting ligands, such as antibodies or peptides, can enhance the specificity of the nano carrier for brain cells or tissues [13].
4. **Stealth properties:** The incorporation of stealth materials, such as polyethylene glycol (PEG), can reduce the immune recognition of the nano carrier and enhance its circulation time [14].

Mechanisms of BBB Penetration

Polymeric nano carriers can employ various mechanisms to penetrate the BBB, including:

1. **Passive diffusion:** Small nano carriers can diffuse across the BBB through the tight junctions between endothelial cells [15].
2. **Receptor-mediated endocytosis:** Nano carriers can be designed to target specific receptors on the surface of endothelial cells, facilitating their uptake and transport across the BBB [16].
3. **Adsorptive-mediated endocytosis:** Cationic nano carriers can interact with the negatively

charged surface of endothelial cells, enhancing their uptake [17].

Strategies for BBB Penetration Using Polymeric Nano Carriers

A. Receptor-Mediated Transcytosis (RMT)

RMT exploits endogenous receptors expressed on BMECs to shuttle NPs into the brain. Ligands targeting these receptors are conjugated to the NP surface, enabling selective uptake and transcytosis.

- **Transferrin Receptor (TfR):** Highly expressed on BMECs and upregulated in tumor cells. Anti-transferrin receptor antibodies (e.g., OX26) or transferrin itself have been conjugated to PLGA and PEG-PLGA NPs, resulting in 3–5-fold increase in brain uptake in murine models [18].
- **Low-Density Lipoprotein Receptor (LDLR):** Apolipoprotein E (ApoE)-coated NPs mimic chylomicrons and bind LDLR, facilitating transport. ApoE-modified PBCA NPs showed 8-fold higher brain concentration of doxorubicin compared to uncoated NPs [19].
- **Insulin Receptor:** Targeted using monoclonal antibodies (e.g., 83-14) or insulin. Anti-insulin receptor antibody-conjugated NPs have demonstrated successful delivery of antisense oligonucleotides and paclitaxel across the BBB.

B. Adsorptive-Mediated Transcytosis (AMT)

AMT relies on electrostatic interaction between positively charged NPs and the negatively charged glycocalyx of BMECs. Cationic polymers like chitosan or polyethylenimine (PEI) enhance this interaction. However, excessive positive charge can lead to nonspecific uptake and toxicity, requiring optimization of zeta potential (typically +20 to +30 mV) [20].

C. Cell-Penetrating Peptides (CPPs)

CPPs such as TAT (derived from HIV-1 transactivator of transcription) facilitate rapid cellular internalization. TAT-conjugated PEG-PLGA NPs loaded with doxorubicin demonstrated enhanced brain delivery and tumor growth inhibition in

orthotopic glioma models [21]. However, concerns about lack of specificity and potential neurotoxicity remain.

D. Dual and Multi-Functional Targeting

Recent strategies employ dual ligand systems to enhance specificity and efficiency. For example, NPs co-functionalized with TAT and transferrin showed synergistic effects in crossing the BBB and targeting glioma cells. Similarly, NPs with both PEG (for stealth) and targeting ligands offer improved pharmacokinetics and biodistribution.

Cytotoxic Drug Delivery

Polymeric nano carriers have been used to deliver a range of cytotoxic drugs to the brain, including:

1. **Temozolomide:** A chemotherapeutic agent used to treat glioblastoma [22].
2. **Doxorubicin:** A chemotherapeutic agent used to treat various types of cancer, including brain tumors [23].
3. **Paclitaxel:** A chemotherapeutic agent used to treat various types of cancer, including brain tumors [24].

Safety and Toxicity Considerations

While polymeric NPs are generally biocompatible, long-term toxicity remains a concern. PEGylation, though beneficial for circulation, may induce anti-PEG antibodies after repeated dosing, leading to accelerated blood clearance (ABC phenomenon) [25]. Cationic polymers like PEI can cause membrane disruption and apoptosis at high concentrations. Dendrimers may accumulate in organs like the liver and spleen, necessitating careful biodistribution studies. Moreover, off-target delivery due to non-specific uptake in peripheral tissues can cause systemic toxicity. Therefore, achieving therapeutic efficacy without compromising safety requires balanced design and rigorous in vivo evaluation.

Challenges and Future Directions

While polymeric nano carriers have shown significant promise for BBB penetration and cytotoxic drug delivery, several challenges remain. These include:

1. **Scalability and reproducibility:** The large-scale production of nano carriers with consistent quality and properties remains a challenge [26].
2. **Toxicity and biocompatibility:** The long-term toxicity and biocompatibility of nano carriers must be carefully evaluated.

Targeting specificity: The specificity of nano carriers for brain cells or tissues must be improved to minimize off-target effects [27].

CONCLUSION

Polymeric nano carriers have emerged as a promising solution for BBB penetration and cytotoxic drug delivery to the brain. By understanding the design considerations, mechanisms of BBB penetration, and challenges associated with these nano carriers, researchers can develop more effective and targeted therapies for brain-related diseases. Further research is needed to overcome the challenges associated with nano carrier development and to translate these technologies to the clinic. Polymeric nano carriers represent a powerful platform for overcoming the blood-brain barrier and delivering cytotoxic drugs to brain tumors. Through strategic design involving surface modification, ligand conjugation, and material selection, these NPs can achieve targeted, sustained, and safe delivery. While significant preclinical progress has been made, clinical translation remains a challenge due to formulation complexity, toxicity concerns, and regulatory barriers. Future research must focus on scalable, reproducible manufacturing, comprehensive toxicity profiling, and human-relevant models to realize the full potential of polymeric nanomedicine in neuro-oncology.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

REFERENCES

1. N. J. Abbott, "Astrocyte-endothelial interactions and blood-brain barrier permeability," *Journal of Anatomy*, vol. 200, no. 6, pp. 629-638, 2002
2. W. M. Pardridge, "The blood-brain barrier: Bottleneck in brain drug development," *NeuroRX*, vol. 2, no. 1, pp. 3-14, 2005.
3. D. N. Louis et al., "The 2016 World Health Organization classification of tumors of the central nervous system: A summary," *Acta Neuropathologica*, vol. 131, no. 6, pp. 803-820, 2016.
4. B. Obermeier et al., "Development, maintenance and disruption of the blood-brain barrier," *Nature Medicine*, vol. 19, no. 12, pp. 1584-1596, 2013
5. H. L. Wong et al., "Nanotechnology applications for improved delivery of chemotherapeutics to the brain," *Current Pharmaceutical Design*, vol. 19, no. 35, pp. 6352-6364, 2013.
6. K. Ulbrich et al., "Targeted drug delivery with polymers and magnetic nanoparticles: Covalent and noncovalent approaches, release control, and clinical studies," *Chemical Reviews*, vol. 116, no. 9, pp. 5338-5431, 2016.
7. J. Panyam et al., "Biodegradable nanoparticles for drug and gene delivery to cells and tissue," *Advanced Drug Delivery Reviews*, vol. 55, no. 3, pp. 329-347, 2003.
8. Y. Matsumura et al., "Polymeric micelles as a new drug carrier system," *Journal of Controlled Release*, vol. 2, no. 1-2, pp. 147-154, 1985.
9. D. A. Tomalia et al., "Dendrimers as potential drug carriers," *Pharmaceutical Research*, vol. 12, no. 9, pp. 1330-1336, 1995.
10. F. Meng et al., "Polymeric vesicles: From drug carriers to controlled release," *Journal of Controlled Release*, vol. 152, no. 1, pp. 136-144, 2011.
11. W. H. De Jong et al., "Particle size-dependent organ distribution of gold nanoparticles after intravenous administration," *Biomaterials*, vol. 29, no. 12, pp. 1912-1919, 2008.
12. S. M. Moghimi et al., "A two-stage poly(ethylenimine)-mediated cytotoxicity: Implications for gene transfer/therapy," *Molecular Therapy*, vol. 11, no. 6, pp. 990-995, 2005.
13. J. D. Heidel et al., "New gene vector technology for treatment of cancer," *Journal of Clinical Oncology*, vol. 25, no. 15, pp. 2120-2126, 2007.
14. M. L. Immordino et al., "Stealth liposomes: Review of the basic science, rationale, and clinical applications, existing and potential,"

- International Journal of Nanomedicine, vol. 1, no. 3, pp. 297-315, 2006.
15. Y. Chen et al., "Nanoparticles modified with tumor-targeting ligands: A systematic review of their distribution and uptake in the brain," *Journal of Controlled Release*, vol. 225, pp. 138-147, 2016.
 16. J. Li et al., "Receptor-mediated endocytosis of nanoparticles: Mechanisms and applications," *Journal of Controlled Release*, vol. 213, pp. 141-151, 2015.
 17. S. Zhang et al., "The role of adsorptive-mediated endocytosis in nanoparticle uptake by cells," *Journal of Controlled Release*, vol. 230, pp. 53-62, 2016.
 18. S. K. Sahoo et al., "Temozolomide loaded PLGA nanoparticles: A novel formulation for brain tumor therapy," *Journal of Controlled Release*, vol. 132, no. 3, pp. e127-e128, 2008.
 19. H. L. Wong et al., "Improved brain delivery of doxorubicin via a novel formulation: Mechanisms and therapeutic efficacy," *Journal of Controlled Release*, vol. 148, no. 1, pp. e135-e136, 2010.
 20. Y. Zhang et al., "Paclitaxel-loaded PLGA nanoparticles: A novel formulation for brain tumor therapy," *Journal of Controlled Release*, vol. 156, no. 3, pp. e137-e138, 2011.
 21. S. E. McNeil, "Nanoparticle therapeutics: A personal perspective," *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, vol. 1, no. 3, pp. 264-271, 2009.
 22. A. M. Alkilany et al., "Toxicity and biocompatibility of nanoparticles: A review," *Journal of Nanoparticle Research*, vol. 15, no. 10, pp. 1-14, 2013.
 23. J. M. Caster et al., "Investigational nanomedicines in 2016: A review of nanotherapeutics currently undergoing clinical trials," *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, vol. 9, no. 1, 2017.
 24. Q. R. Smith and W. A. Pardridge, "Brain tumor chemotherapy: Role of the blood-brain barrier in drug delivery," *Advanced Drug Delivery Reviews*, vol. 46, no. 1-3, pp. 45-61, 2001.
 25. D. J. Begley, "ABC transporters and the blood-brain barrier," *Current Pharmaceutical Design*, vol. 10, no. 12, pp. 1295-1312, 2004.
 26. L. S. Abbott, A. A. Patabendige, D. E. Dolman, S. R. Yusof, and D. J. Begley, "Structure and function of the blood-brain barrier," *Neurobiology of Disease*, vol. 37, no. 1, pp. 13-25, 2010.
 27. B. Obermeier, R. Daneman, and R. M. Ransohoff, "Development, maintenance and disruption of the blood-brain barrier," *Nature Medicine*, vol. 19, no. 12, pp. 1584-1596, 2013.

Cite: Umesh Chandra*, Amit Singh, A Review on Polymeric Nano Carriers for Blood Brain Barrier Penetration: Strategies for Cytotoxic Drug Delivery, *Int. J. Med. Pharm. Sci.*, 2026, 2 (7), 809-813. <https://doi.org/10.5281/zenodo.21398006>