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Nanotechnology-Based Drug Delivery Systems for Glioblastoma: Overcoming the Blood-Brain Barrier Through Advanced Nanoparticle Platforms

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202650112

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 May 2026 and was last updated on 19 May 2026.

INTRODUCTION

Review question / Objective What is the efficacy and safety of nanoparticle-based drug delivery systems for overcoming the blood-brain barrier (BBB) in glioblastoma (GBM) treatment, with emphasis on translational evidence from clinical trials, and what are the critical barriers to clinical translation?

Rationale Glioblastoma multiforme (GBM) remains the most lethal primary brain malignancy, with median overall survival of 12-15 months despite maximal treatment. The blood-brain barrier (BBB) restricts approximately 98% of therapeutic agents. Nanotechnology-based drug delivery systems offer engineered platforms capable of crossing the BBB through multiple mechanisms. Despite promising preclinical results, clinical translation remains limited, and a systematic evaluation of available evidence from clinical trials is needed to identify translational barriers and guide future research.

Condition being studied Glioblastoma multiforme (GBM) — WHO Grade IV primary brain malignancy. The review also addresses the blood-brain barrier (BBB) as the primary pharmacological obstacle in GBM treatment, and the blood-tumor barrier (BTB) with its heterogeneous permeability characteristics.

METHODS

Search strategy Systematic literature search in PubMed, PubMed Central (PMC), Scopus, and Ovid MEDLINE. Date range: January 2010 to December 2025. MeSH descriptors: "glioblastoma" OR "glioma" AND "nanoparticles" OR "nanotechnology" AND "drug delivery" OR "blood-brain barrier" AND "clinical trial" OR "in vivo". Total records: 347; studies meeting full inclusion criteria: 25 (PRISMA 2020 guidelines followed).

Participant or population Patients with glioblastoma multiforme (GBM), including newly diagnosed and recurrent disease. In vivo animal

models of GBM were included for studies providing translational data. No geographic restriction. English-language publications only.

Intervention Nanoparticle-based drug delivery systems for GBM: (1) lipid-based nanoparticles (liposomes, solid lipid nanoparticles); (2) polymeric nanoparticles (PLGA, dendrimers); (3) metallic nanoparticles (gold, iron oxide); (4) spherical nucleic acids (SNAs). Surface modification strategies (PEGylation, active targeting with angiopep-2, transferrin, RGD peptides) and combination approaches with focused ultrasound and immunotherapy.

Comparator Comparison between nanoparticle platform types (lipid-based vs. polymeric vs. metallic vs. SNAs); passive EPR-dependent vs. active ligand-mediated targeting strategies; nanoparticle-based delivery vs. standard chemotherapy (temozolomide); monotherapy vs. combination approaches.

Study designs to be included Original research articles, systematic reviews, and clinical trials (phases 0-II) with in vivo or clinical data. English-language publications from January 2010 to December 2025.

Eligibility criteria Inclusion: (1) original research articles, systematic reviews, or clinical trials; (2) nanoparticle-based drug delivery systems specifically targeting GBM; (3) in vivo or clinical data; (4) English-language publications. Exclusion: (1) purely in vitro studies without translational data; (2) non-GBM brain tumors; (3) conference abstracts.

Information sources PubMed, PubMed Central (PMC), Scopus, and Ovid MEDLINE. No grey literature, trial registries, or author contact was used. Date restriction: January 2010 to December 2025.

Main outcome(s) Overall survival (OS) and progression-free survival (PFS) in clinical trials; disease control rate; blood-brain barrier penetration and tumor accumulation; safety profile (adverse events, dose-limiting toxicities); Bcl2L12 knockdown for SNA studies.

Additional outcome(s) Pharmacokinetic parameters (circulation half-life, clearance); nanoparticle physicochemical properties (size, surface charge, encapsulation efficiency); BBB penetration mechanisms; barriers to clinical translation; comparative efficacy between passive vs. active targeting strategies.

Data management Data were extracted independently by both review authors into a standardized extraction form. Variables included: study design, nanoparticle type/platform, drug payload, surface modification, BBB penetration mechanism, primary outcomes, and key findings. Discrepancies resolved by consensus.

Quality assessment / Risk of bias analysis Study quality assessed using PRISMA 2020 guidelines. Clinical trials evaluated for bias using standard oncology trial criteria: sample size, randomization, blinding, and follow-up. Preclinical studies assessed for translational relevance and methodological rigor.

Strategy of data synthesis Narrative synthesis due to heterogeneity of study designs, nanoparticle platforms, and outcome measures, which precluded meta-analysis. Results synthesized qualitatively by nanoparticle platform category. Clinical trial data tabulated and compared systematically. PRISMA 2020 reporting guidelines followed throughout.

Subgroup analysis Subgroup analyses planned by: (1) nanoparticle platform type (lipid-based, polymeric, metallic, carbon-based); (2) targeting strategy (passive vs. active targeting); (3) therapeutic approach (drug delivery, gene therapy, immunotherapy, combination); (4) clinical stage (preclinical animal models vs. human clinical trials); (5) cancer type (glioblastoma, meningioma, metastatic brain tumors, other).

Sensitivity analysis Sensitivity analyses to be conducted by: (1) excluding studies with high risk of bias; (2) restricting to studies with in vivo models or human trials; (3) excluding studies published before 2015; (4) excluding studies with sample sizes below threshold; (5) comparing results across databases to assess search strategy robustness.

Language restriction English only.

Country(ies) involved Brazil.

Other relevant information This systematic review was completed prior to registration due to unawareness of journal registration requirements. The review follows PRISMA 2020 reporting guidelines throughout. Retrospective registration is being submitted to fulfill the requirements of the Journal of Neurosurgery Publishing Group for manuscript resubmission.

Keywords nanoparticles; brain tumors; glioblastoma; systematic review; drug delivery;

blood-brain barrier; nanotechnology; neurosurgery; targeted therapy; cancer treatment.

Dissemination plans Submission to the Journal of Neurosurgery. Results will be disseminated through peer-reviewed publication and academic conference presentations.

Contributions of each author

Author 1 - Wuilker K. Campos - Conceived the study, designed the search strategy, performed literature search and screening, extracted and synthesized data, interpreted results, drafted and revised the manuscript.
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Author 2 - Edmundo L. R. Pereira - Provided clinical expertise in neuro-oncological surgery, contributed to study design, reviewed and critically revised the manuscript for intellectual content.
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