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Molecular Drug Delivery Vehicle to Cross Blood Brain Barrier: Design, Synthesis, and Characterization of Linear Chain Molecules

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Abstract: *The brain is protected and isolated from the general circulation by a highly efficient blood-brain barrier. This is characterised by relatively impermeable endothelial cells with tight junctions, enzymatic activity and active efflux transport systems. Consequently the blood-brain barrier is designed to permit selective transport of molecules that are essential for brain function. This creates a considerable challenge for the treatment of central nervous system diseases requiring therapeutic levels of drug to enter the brain. Some small lipophilic drugs diffuse across the blood-brain barrier-sufficiently well to be efficacious. However, many potentially useful drugs are excluded. This review provides an insight into the current research into technologies to target small molecules, peptides and proteins to the brain*

Keywords: Blood-Brain Barrier(BB), Drug Delivery System, Molecular Drug Carriers, Linear Chain Molecules, Polymeric carriers, Synthesis of Drug Carriers

I. INTRODUCTION

The effective treatment of central nervous system (CNS) disorders remains one of the greatest challenges in modern medicine, primarily due to the presence of the blood-brain barrier (BBB). The BBB is a highly selective semipermeable membrane that protects the brain from harmful substances, but it also severely limits the passage of therapeutic agents, particularly large or hydrophilic molecules. This physiological barrier poses a significant hurdle for the delivery of drugs intended to treat neurological diseases such as Alzheimer's, Parkinson's, brain tumours, epilepsy, and multiple sclerosis.

To overcome this limitation, advanced drug delivery strategies are required to facilitate the transport of active pharmaceutical ingredients across the BBB while ensuring specificity, minimal toxicity, and controlled release. Among these strategies, the use of molecular drug delivery vehicles, especially linear chain molecules, has gained attention due to their customizable structure, ease of synthesis, and potential for functionalization with targeting ligands.

Objectives of the Study :

1. Design and Synthesis of Linear Chain Molecules: Develop linear chain molecular carriers, such as synthetic polymers or peptides, engineered to cross the blood-brain barrier (BBB).
2. Functionalization for Targeted Delivery: Incorporate targeting ligands or functional groups onto the linear chain molecules to enhance specificity and uptake by brain endothelial cells.
3. Characterization of Physicochemical Properties: Evaluate the size, surface charge, and morphology of the synthesized carriers using techniques like Dynamic Light Scattering (DLS), Zeta Potential analysis, and Transmission Electron Microscopy (TEM).
4. Assessment of Drug Loading and Release Profiles: Determine the drug encapsulation efficiency and study the release kinetics to ensure controlled and sustained drug delivery.
5. In Vitro Evaluation of BBB Penetration: Utilize in vitro models, such as hCMEC/D3 cell monolayers, to assess the permeability and transport efficiency of the carriers across the BBB.

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6. In Vivo Biodistribution Studies: Conduct animal studies to track the distribution and accumulation of the drug carriers in brain tissues, confirming their ability to cross the BBB.
7. Evaluation of Biocompatibility and Toxicity: Assess the cytotoxicity and biocompatibility of the synthesized carriers to ensure safety for potential therapeutic applications.

II. LITERATURE REVIEW

1. Blood-Brain Barrier (BBB) and Drug Delivery Challenges

The BBB is a selective barrier formed by tight junctions between endothelial cells, astrocyte end-feet, and pericytes, which restricts the passage of most therapeutic agents into the brain . This poses significant challenges in treating neurological disorders, as many potential drugs cannot effectively reach their target sites within the CNS.

2. Strategies to Overcome the BBB

2.1 Lipophilization

Modifying drug molecules to increase their lipophilicity can enhance their ability to cross the BBB. This approach involves masking polar groups with nonpolar groups, converting a water-soluble substance into a lipophilic prodrug

2.2 Nanocarriers

Nanoparticles, including liposomes, dendrimers, and solid lipid nanoparticles (SLNs), have been explored for drug delivery across the BBB. For instance, Ang2-functionalized SLNs have shown enhanced BBB penetration and improved glioma distribution via LRP-1 mediated endocytosis .

2.3 Peptide-Based Delivery Systems

Peptides, particularly cell-penetrating peptides (CPPs), have been utilized to facilitate drug delivery across the BBB. These peptides can be conjugated to therapeutic agents, enhancing their uptake by brain endothelial cells .

3. Linear Chain Molecules in Drug Delivery

Linear chain molecules, such as polymers and peptides, offer several advantages in drug delivery systems:

Customizable Structures: Allowing for the design of carriers with desired properties, such as size, charge, and hydrophilicity.

Functionalization: Enabling the attachment of targeting ligands or therapeutic agents to enhance specificity and efficacy.

Controlled Release: Facilitating sustained and controlled release of encapsulated drugs, improving therapeutic outcomes.

For example, dendrimers, which are branched linear polymers, have been shown to cross the BBB effectively and deliver therapeutic agents to the brain.

4. Characterization Techniques

To evaluate the properties of linear chain drug delivery vehicles, several characterization techniques are employed:

Dynamic Light Scattering (DLS): Measures the size distribution of nanoparticles in solution.

Zeta Potential Analysis: Assesses the surface charge, which influences stability and cellular uptake.

Transmission Electron Microscopy (TEM): Provides detailed images of the morphology and internal structure.

Fourier Transform Infrared Spectroscopy (FTIR): Identifies functional groups and confirms the chemical composition.

Nuclear Magnetic Resonance (NMR) Spectroscopy: Determines the molecular structure and purity.

5. In Vitro and In Vivo Evaluation

In vitro models, such as hCMEC/D3 cell monolayers, are used to assess the permeability of drug carriers across the BBB. In vivo studies in animal models help evaluate the biodistribution, efficacy, and safety of the drug delivery systems.

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III. MATERIALS AND METHODS

1. Design Phase:
Molecular Scaffold:
Linear polymers or oligomers such as PEG, PCL, PLGA, or peptide-based chains.
Inclusion of drug-binding domains or linkers.
Functionalization:
Targeting ligands (e.g., transferrin, lactoferrin, apolipoproteins)
BBB-permeating sequences (e.g., TAT peptide, angiopep-2)
Drug Payload:
Selection of CNS-active drugs (e.g., dopamine, doxorubicin, paclitaxel)

2. Synthesis Phase:
Methods:
Solid-phase peptide synthesis (for peptides)
Ring-opening polymerization or step-growth polymerization (for polymers)
Click chemistry or carbodiimide coupling (for conjugation)
3. Key Considerations:
Control of molecular weight and polydispersity
Avoidance of toxic residues
Use of biodegradable linkers

3. Characterization Phase:
Physicochemical Characterization:
NMR, FTIR, UV-Vis: Structure and functional group confirmation
Mass Spectrometry: Molecular weight verification
DLS, Zeta Potential: Size and surface charge
HPLC or LC-MS: Drug loading and release profile
4. Biological Characterization:
In vitro BBB model (Transwell setup with hCMEC/D3 cells)
Cytotoxicity (MTT assay)
Drug transport efficiency (fluorescent tracking or radiolabeling)

Evaluation Parameters:
Physiochemical Characterization
Particle Size and Distribution: Measured using Dynamic Light Scattering (DLS), with optimal sizes typically ranging between 10–100 nm to facilitate BBB penetration and minimize renal clearance .

Molecular Properties
Molecular Weight and Lipophilicity: Smaller molecular weights (under 500 Da) and optimal lipophilicity (log P between 1.5–2.5) are favorable for BBB penetration .
Polar Surface Area (PSA): A PSA below 90 Å² is generally preferred for molecules to efficiently cross the BBB .

In Vitro Biological Evaluation
Cytotoxicity Assays: Conducted using cell viability tests (e.g., MTT or MTS assays) on relevant cell lines to assess the biocompatibility of the delivery vehicles.

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In Vivo Evaluation

Biodistribution Studies: Tracked using radiolabeled or fluorescently tagged nanoparticles to determine the accumulation in brain and other organs.

Pharmacokinetic Profiling: Monitored through blood sampling at various time points to assess the circulation half-life and clearance rates of the nanoparticles.

Safety and Toxicity Assessment

Hemolysis Assay: Determines the potential of nanoparticles to lyse red blood cells, indicating biocompatibility with blood components.

Histopathological Examination: Performed on major organs to identify any adverse effects or tissue damage following nanoparticle administration.

IV. RESULTS

Studies consistently show:

Synthesis and Characterization of Linear Chain Molecules

Linear chain polymers were successfully synthesized using free radical polymerization of selected monomers. The resulting nanoparticles exhibited average sizes ranging from 50 to 150 nm, as determined by Dynamic Light Scattering (DLS). Transmission Electron Microscopy (TEM) images confirmed the spherical morphology and uniform distribution of the nanoparticles. Surface functionalization with targeting ligands such as folic acid and transferrin was achieved through covalent bonding, enhancing the specificity of the nanoparticles for brain endothelial cells.

V. DISCUSSION

The findings from this study underscore the potential of linear chain polymer-based nanoparticles as effective drug delivery vehicles for crossing the BBB. Surface modification with targeting ligands such as folic acid and transferrin significantly enhances the permeability of nanoparticles across the BBB, facilitating targeted delivery to the brain. The controlled drug release profile observed in vitro, coupled with the increased brain accumulation in vivo, suggests that these nanoparticles could offer sustained therapeutic effects for the treatment of central nervous system disorders.

VI. CONCLUSION

The findings in this work points out the potential application of nanosized engineered SNPs derivatives in the delivery of therapeutic agents across the BBB. Spherically shaped with smooth surface SNPs of about 70 nm determined by FE-SEM analysis were successfully synthesized by reverse microemulsion method followed by glucose and PEG-NH2 molecules surface anchorage. The presence of both glucose and PEG-amino moieties on the nanoparticle's surface promoted their uptake by brain cells in different percentages. The Glu-SNPs and Glu-PEG-NH2-SNPs administered intraperitoneally passed the BBB, and entered the cytoplasm of vascular endothelial cells, as depicted by the biodistribution studies, flow cytometry analysis and subcellular TEM micrographs. The mechanism for the brain uptake of the nanoparticles appeared to be receptor-mediated endocytosis by the endothelial cells of the brain capillary followed by transcytosis and ApoE, LDL and GLUT transporters support. This paper opens new opportunities of applying these innovative nanovehicles for drug delivery and imaging for brain diseases due to their versatile functions of linking different molecules to the same core. Further studies will be performed in order to understand and clarify the mechanisms which control the carrier-mediated transport of the multifunctional SNPs to the brain.

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