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Formulation and Blood–brain Barrier Transport of Cannabidiol-loaded Nanovesicles

Frank Edet*

Department of Internal Medicine, University of the Witwatersrand, Johannesburg, South Africa

Introduction

Nanovesicles have emerged as a promising drug delivery system for enhancing the bioavailability and therapeutic potential of various pharmacological agents, particularly those targeting the central nervous system. Cannabidiol, a non-psychoactive cannabinoid, has demonstrated neuroprotective, anti-inflammatory, and anticonvulsant properties, making it a promising candidate for treating neurological disorders such as epilepsy, multiple sclerosis, and neurodegenerative diseases. However, its therapeutic efficacy is often limited by poor solubility, rapid metabolism, and difficulty in crossing the blood-brain barrier. The development of cannabidiol-loaded nanovesicles aims to overcome these limitations by improving drug stability, enhancing transport across biological barriers, and providing sustained release within the central nervous system. Nanovesicles are lipid-based or polymer-based carriers that encapsulate therapeutic molecules, protecting them from enzymatic degradation and facilitating controlled drug release. Liposomes, exosomes, and polymeric nanoparticles are among the most commonly explored nanocarriers for brain-targeted drug delivery. The choice of nanovesicle composition is crucial in determining drug loading capacity, stability, and biocompatibility. Lipid-based nanovesicles, such as liposomes and solid lipid nanoparticles, have been widely used due to their ability to mimic biological membranes, enabling efficient interaction with cellular surfaces and enhancing endocytic uptake. Exosomes, naturally derived extracellular vesicles, offer an additional advantage by leveraging endogenous signaling mechanisms to facilitate targeted delivery. Polymeric nanoparticles, composed of biodegradable materials such as poly(lactic-co-glycolic acid) (PLGA) and chitosan, provide tunable drug release profiles and improved circulation time.

Description

Encapsulation of cannabidiol within nanovesicles involves various techniques such as solvent evaporation, thin-film hydration, and microfluidic-based synthesis. The choice of method depends on factors such as drug solubility, encapsulation efficiency, and particle size control. Thin-film hydration, one of the most commonly used techniques for liposome preparation, involves dissolving lipid components in an organic solvent, followed by solvent removal and hydration in an aqueous medium containing cannabidiol. This process results in the formation of bilayer vesicles encapsulating the drug, which can be further refined using sonication or extrusion methods to achieve uniform particle size distribution. Microfluidic-based synthesis offers a more precise approach, enabling controlled mixing of lipid and aqueous phases to generate monodisperse vesicles with optimized drug loading. The physicochemical properties of cannabidiol-loaded nanovesicles play a critical role in determining their ability to penetrate the blood-brain barrier. Key parameters include particle size, surface charge, hydrophobicity, and ligand functionalization. Nanoparticles within the size range of 50 to 200 nanometers exhibit enhanced permeability due to their ability to evade rapid clearance while maintaining efficient cellular uptake. Surface charge influences vesicle stability and interaction with the negatively charged endothelial cells of the blood-brain barrier; neutral or slightly positive charges have been found to enhance penetration while minimizing nonspecific protein adsorption. Modifying nanovesicle surfaces with targeting ligands such as transferrin, lactoferrin, or cell-penetrating peptides further enhances receptor-mediated transport across the blood-brain barrier, facilitating precise drug delivery to neuronal tissues [1,2].

The mechanisms by which cannabidiol-loaded nanovesicles cross the blood-brain barrier include passive diffusion, transcytosis, and receptor-mediated transport. The lipid composition of nanovesicles allows for partial integration with endothelial membranes, facilitating passive diffusion of cannabidiol into the brain parenchyma. However, this process is often inefficient, necessitating the utilization of active transport mechanisms. Receptor-mediated transcytosis, facilitated by ligands that bind to specific transporters expressed on the blood-brain barrier, enhances targeted delivery. For example, functionalizing nanovesicles with apolipoprotein E can exploit low-density lipoprotein receptors, which are highly expressed in brain endothelial cells, promoting vesicular transport across the barrier. Additionally, nanoparticle-mediated disruption of tight junctions using transient permeability enhancers can further improve brain penetration without causing irreversible damage. Preclinical studies have demonstrated the potential of cannabidiol-loaded nanovesicles in enhancing drug accumulation in the brain and improving therapeutic outcomes in neurological disorders. Animal models of epilepsy and neurodegeneration have shown that nanovesicle-encapsulated cannabidiol exhibits prolonged circulation time, higher brain concentrations, and enhanced neuroprotective effects compared to free cannabidiol. Pharmacokinetic studies indicate that nanovesicle formulations increase the half-life of cannabidiol by reducing hepatic metabolism and renal clearance, thereby enabling sustained drug release and reducing the need for frequent dosing. Functional outcomes such as reduced seizure frequency, attenuation of neuroinflammation, and improved cognitive function further support the efficacy of these formulations [3].

Despite promising results, challenges remain in optimizing the formulation and delivery of cannabidiol-loaded nanovesicles for clinical applications. Stability issues, potential immunogenicity, and large-scale production constraints must be addressed to ensure reproducibility and safety. The development of scalable manufacturing processes, such as high-pressure homogenization and microfluidic-based synthesis, is crucial for translating these nanovesicle formulations from laboratory research to clinical use. Additionally, regulatory considerations surrounding the use of cannabinoids in medicine necessitate thorough evaluation of pharmacokinetics, toxicity, and long-term effects before approval for therapeutic use. Future directions in the development of cannabidiol-loaded nanovesicles include the incorporation of stimuli-responsive materials, personalized drug delivery approaches, and combination therapies. Stimuli-responsive nanovesicles can be engineered to release cannabidiol in response to physiological triggers such as pH changes, temperature fluctuations, or enzymatic activity within the brain microenvironment. This approach enables precise control over drug release kinetics, minimizing off-target effects and maximizing therapeutic benefits. Personalized medicine strategies, leveraging patient-specific biomarkers and genetic profiling, can further refine nanovesicle formulations to optimize drug efficacy based on individual patient needs. Additionally, combining cannabidiol with other neuroprotective agents within multi-drug-loaded nanovesicles presents an opportunity to enhance therapeutic synergy and address multiple pathological pathways in complex neurological disorders [4,5].

***Address for Correspondence:** Frank Edet, Department of Internal Medicine, University of the Witwatersrand, Johannesburg, South Africa, E-mail: edetfrank@gmail.com*

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Conclusion

In conclusion, the formulation and blood-brain barrier transport of cannabidiol-loaded nanovesicles represent a promising advancement in drug delivery for neurological disorders. Nanovesicles enhance the bioavailability, stability, and targeted delivery of cannabidiol, overcoming key challenges associated with its clinical use. Advances in formulation techniques, surface functionalization, and transport mechanisms continue to drive the development of optimized nanocarrier systems for brain-targeted therapy. While further research is needed to address scalability and regulatory considerations, the potential of cannabidiol-loaded nanovesicles in improving treatment outcomes for neurological diseases underscores their significance in the evolving landscape of cannabinoid-based therapeutics.

Acknowledgement

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Conflict of Interest

None.

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