GINKGOLIDE-LOADED NANOEMULSION FOR INTRANASAL BRAIN DELIVERY: A REVIEW

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Abstract

Neurological disorders such as Parkinson's disease, Alzheimer's disease, stroke, epilepsy, and dementia continue to represent a major global healthcare burden. The effective treatment of these disorders is significantly limited by the presence of the blood–brain barrier (BBB), which restricts the entry of most therapeutic agents into the central nervous system (CNS). Intranasal drug delivery has emerged as a promising non-invasive approach for direct brain targeting through the olfactory and trigeminal pathways, thereby bypassing the BBB. Nanoemulsions have attracted considerable attention as brain-targeting carriers due to their small droplet size, enhanced drug solubilization capacity, improved mucosal permeation, and ability to increase drug bioavailability. Ginkgolide, a diterpene lactone isolated from Ginkgo biloba, exhibits potent neuroprotective, antioxidant, anti-inflammatory, and anti-apoptotic activities. However, its therapeutic application is limited by poor aqueous solubility, low oral bioavailability, and restricted BBB penetration. The incorporation of Ginkgolide into intranasal nanoemulsion systems offers a promising strategy to improve brain targeting and therapeutic efficacy. This review discusses the pharmacological properties of Ginkgolide, the principles of nose-to-brain delivery, nanoemulsion technology, formulation considerations, recent advancements, challenges, and future prospects of Ginkgolide-loaded nanoemulsions for the management of neurological disorders.

Keyword: Ginkgolide, Nanoemulsion, Intranasal Delivery, Brain Targeting, Blood-Brain Barrier, Parkinson's Disease, Neuroprotection

1.INTRODUCTION

Brain disorders remain among the most challenging diseases to treat because of the highly selective blood–brain barrier (BBB). The BBB protects the brain from toxins and pathogens but simultaneously restricts the transport of therapeutic agents. Approximately 98% of small-molecule drugs and nearly all macromolecules fail to reach the brain in therapeutically effective concentrations.

Intranasal drug delivery has emerged as a promising alternative for direct brain targeting. Through the olfactory and trigeminal neural pathways, drugs can bypass the BBB and rapidly reach the CNS. Nanoemulsion-based delivery systems have demonstrated substantial potential for improving drug transport, stability, and bioavailability while reducing systemic side effects.

Ginkgolide, a bioactive constituent of Ginkgo biloba, has attracted considerable interest because of its neuroprotective and anti-inflammatory properties. However, poor solubility and low bioavailability limit its clinical utility. Nanoemulsion-mediated intranasal delivery offers a potential solution to these challenges.

1.1 Anatomy and Physiology of the Nose

The nasal cavity is a highly specialized anatomical structure that plays a crucial role in both respiration and drug delivery. Due to its rich vascularization, large surface area, and direct connection with the central nervous system (CNS), the nasal route has emerged as a promising pathway for systemic and brain-targeted drug delivery. Anatomically, the nasal cavity occupies the space between the base of the skull and the roof of the mouth. Superiorly, it is supported by the ethmoid bone, while laterally it is bounded by the ethmoid, maxillary, and inferior conchae bones. The nasal cavity is

divided into two symmetrical halves by the nasal septum. Each half has an approximate volume of 7.5 mL and a surface area of nearly 75 cm^2, providing a favorable environment for drug absorption.

The nasal cavity extends from the external nares (nostrils) to the nasopharynx and is divided into four distinct functional regions based on anatomical and histological characteristics: the nasal vestibule, atrium, respiratory region, and olfactory region. Each region contributes differently to the absorption and transport of therapeutic agents.

1.1.1 Nasal Vestibule

The nasal vestibule represents the anterior-most portion of the nasal cavity and covers an area of approximately 0.6 cm^2. Histologically, it is lined with stratified squamous keratinized epithelium containing sebaceous glands and nasal hairs. The primary function of this region is to filter inhaled particles and protect the respiratory tract from foreign materials.

From a drug delivery perspective, the vestibular region has limited significance because of its relatively small surface area, low vascularity, and low permeability. Consequently, only minimal drug absorption occurs through this region.

1.1.2 Atrium

The atrium serves as a transitional zone between the nasal vestibule and the respiratory region. The anterior portion is lined with stratified squamous epithelium, while the posterior portion contains pseudostratified columnar epithelial cells with microvilli.

Similar to the vestibule, the atrium exhibits limited vascularization and permeability. Therefore, its contribution to drug absorption is relatively minor. However, it acts as an important transitional region facilitating the movement of inhaled air and administered formulations toward the deeper nasal cavity.

1.1.3 Respiratory Region

The respiratory region constitutes the largest and most important area of the nasal cavity for systemic drug delivery. It is divided into three turbinate structures: superior, middle, and inferior conchae. This region accounts for approximately 160 cm^2 of the nasal surface area and possesses an extensive blood supply, making it highly favorable for drug absorption.

The respiratory epithelium is composed of pseudostratified columnar epithelial cells, goblet cells, basal cells, and serous glands. The presence of approximately 300 microvilli per cell significantly increases the absorptive surface area. Beneath the epithelium lies the lamina propria, which contains an extensive network of blood vessels, nerves, serous glands, and mucous glands.

A mucus layer approximately 5 µm thick covers the respiratory epithelium and serves as a protective barrier. This mucus layer consists of two phases: an outer viscous gel layer and an inner aqueous sol layer. The mucus is continuously renewed every 10–15 minutes through mucociliary clearance mechanisms. The pH of nasal secretions typically ranges from 5.5 to 6.5 in adults and from 5.0 to 6.5 in children.

The combination of high vascularity, large surface area, and permeable epithelium makes the respiratory region the principal site for rapid systemic absorption of drugs administered intranasally.

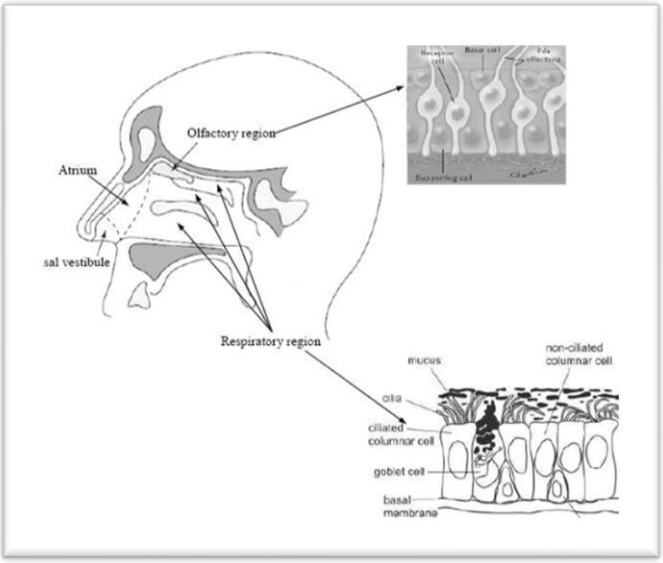

Figure 1. Anatomical and Physiological Considerations in Human Nasal Cavity

1.1.4 Olfactory Region

The olfactory region is located in the upper part of the nasal cavity, extending along the roof of the nasal cavity, the superior nasal septum, and the superior turbinate. Although it constitutes only about 8% of the total nasal

surface area in humans, it plays a pivotal role in direct nose-to-brain drug delivery.

The olfactory epithelium is composed of specialized olfactory receptor neurons (ORNs), supporting cells, and basal cells. Unlike other regions of the nasal cavity, the olfactory epithelium is directly connected to the central nervous system through the olfactory bulb. This unique anatomical feature provides a direct pathway for therapeutic agents to bypass the blood-brain barrier (BBB) and reach the brain.

The olfactory region also contains Bowman's glands, which secrete serous fluid that helps dissolve odorant molecules and maintain olfactory function. Despite its relatively small surface area, the olfactory region is of immense pharmaceutical importance because it enables rapid and direct transport of drugs to the CNS through olfactory neuronal pathways.

For brain-targeted drug delivery systems such as nanoemulsions, nanoparticles, and nanostructured lipid carriers, the olfactory region serves as a key gateway for delivering therapeutic agents directly to the brain while minimizing systemic exposure and bypassing BBB-associated limitations.

Significance of Nasal Anatomy in Brain Drug Delivery

The unique anatomical and physiological characteristics of the nasal cavity make it an attractive route for brain targeting. The extensive vascular network of the respiratory region facilitates systemic absorption, while the olfactory region provides a direct connection to the CNS. These features have led to increasing interest in intranasal delivery systems, particularly nanoemulsion-based formulations, for the treatment of neurological disorders such as Parkinson's disease, Alzheimer's disease, epilepsy, and brain tumors.

1.2. Ginkgolide: Chemistry and Pharmacological Significance

Ginkgolides are diterpene trilactones naturally present in Ginkgo biloba leaves. The major forms include Ginkgolide A, B, C, J, and M. Among them, Ginkgolide B is considered the most pharmacologically active.

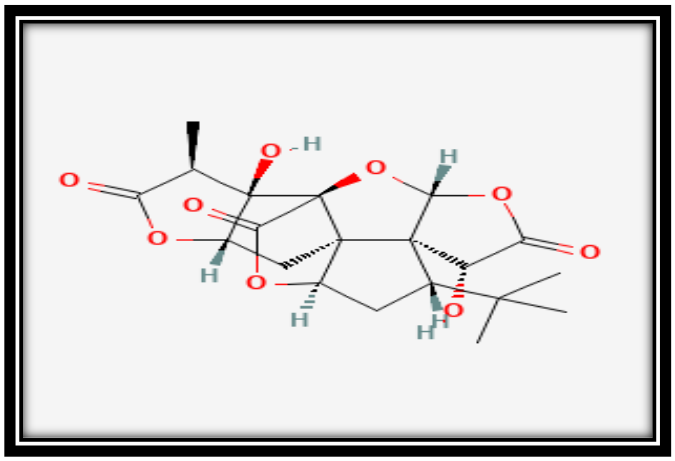

Figure 2: Stucture of Ginkgolide

Physicochemical Properties

- Molecular Formula: C20H24O9
- Molecular Weight: 408.40 g/mol
- Class: Diterpene Trilactone
- Melting Point: 245–247°C

Pharmacological Activities

Neuroprotective Activity

Ginkgolide protects neurons against oxidative stress and excitotoxicity, thereby reducing neuronal damage associated with neurodegenerative disorders.

**Antioxidant Activity **

It scavenges reactive oxygen species (ROS) and reduces oxidative stress-induced neuronal injury.

Anti-inflammatory Activity

Ginkgolide inhibits inflammatory mediators and suppresses neuroinflammation.

Platelet Activating Factor (PAF) Antagonism

Ginkgolide acts as a potent antagonist of platelet activating factor, improving cerebral blood flow and reducing ischemic injury.

Therapeutic Applications

- Parkinson’s disease
- Alzheimer’s disease
- Dementia
- Stroke
- Cerebral ischemia
- Cognitive impairment

1.3. Challenges in Brain Drug Delivery

The BBB consists of tightly connected endothelial cells that regulate molecular transport into the CNS. Major obstacles include:

- Restricted permeability
- Efflux transporter activity
- Enzymatic degradation
- First-pass metabolism
- Poor drug solubility
- Low bioavailability

These limitations necessitate alternative approaches such as nose-to-brain drug delivery.

1.4. Intranasal Route for Brain Targeting

The nasal cavity provides direct access to the brain through neural pathways.

Olfactory Pathway

The olfactory epithelium is directly connected to the olfactory bulb, allowing drugs to enter the brain without crossing the BBB.

Trigeminal Pathway

The trigeminal nerve provides an additional route connecting the nasal cavity to different regions of the CNS.

Advantages

- Direct brain targeting
- Avoidance of BBB
- Rapid onset of action
- Reduced systemic exposure
- Avoidance of hepatic first-pass metabolism
- Improved patient compliance

Limitations

- Mucociliary clearance
- Limited administration volume
- Nasal irritation
- Variable absorption

1.5. Nanoemulsion Technology

Nanoemulsions are isotropic colloidal dispersions consisting of oil, surfactant, co-surfactant, and water with droplet sizes generally ranging from 10–200 nm.

Advantages

- Enhanced drug solubility
- Improved bioavailability
- Increased permeation
- Better stability
- Controlled drug release
- Protection from degradation

Components
Oils

- Oleic acid
- Capmul MCM
- Coconut oil
- Castor oil
- Olive oil

Surfactants

- Tween 80
- Tween 20
- Cremophor EL
- Labrasol

Co-surfactants

- Transcutol P
- PEG 400
- Propylene glycol
- Ethanol

1.6. Nanoemulsion-Based Nose-to-Brain Delivery

Nanoemulsions improve brain delivery through:

1. Enhanced permeation across nasal mucosa.
2. Increased drug dissolution.
3. Prolonged nasal residence time.
4. Improved uptake through olfactory neurons.
5. Direct transport to the CNS.

The nanosized droplets provide a large surface area that facilitates absorption and drug transport into brain tissues.

1.7. Ginkgolide-Loaded Nanoemulsion Rationale

Despite its therapeutic potential, Ginkgolide suffers from:

- Poor water solubility
- Low oral bioavailability
- Limited BBB penetration
- Variable gastrointestinal absorption

Nanoemulsion systems can overcome these limitations by enhancing solubility, stability, and brain targeting efficiency.

Expected Benefits

- Improved brain uptake
- Enhanced therapeutic efficacy
- Reduced dose requirement
- Faster onset of action
- Better patient compliance
- Reduced systemic toxicity

1.8. Recent Advances

Recent studies have highlighted the growing importance of nanoemulsion-based nose-to-brain delivery systems for neurological disorders. Research demonstrates that intranasal nanoemulsions can improve CNS drug distribution, enhance bioavailability, and bypass BBB limitations. Mucoadhesive nanoemulsions and nanoemulgels have further improved nasal residence time and drug absorption. The integration of lipid-based nanocarriers with intranasal delivery is increasingly recognized as a promising strategy for Parkinson's disease, Alzheimer's disease, epilepsy, and cerebral ischemia.

1.9. Challenges and Future Perspectives

Despite promising results, several challenges remain:

- Long-term safety evaluation
- Scale-up and manufacturing issues
- Regulatory approval
- Stability concerns
- Limited clinical studies

Future research should focus on optimized formulations, targeted nanocarriers, in vivo biodistribution studies, and clinical translation.

2. CONCLUSION

Ginkgolide is a promising neuroprotective agent with significant therapeutic potential in neurological disorders. However, poor solubility and limited brain penetration restrict its clinical utility. Intranasal nanoemulsion-based delivery systems offer an effective strategy for direct nose-to-brain transport, enhanced bioavailability, and improved therapeutic outcomes. Continued research in this field may facilitate the development of clinically successful Ginkgolide-loaded nanoemulsion formulations for the treatment of Parkinson's disease and other neurodegenerative disorders.

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