



Advances In Nanoglobule Formulations For The Treatment Of Major Depressive Disorder

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Abstract: Depression is a major psychiatric disorder affecting millions globally, often associated with treatment resistance and delayed therapeutic onset. Esketamine, the S-enantiomer of ketamine, has emerged as a promising rapid-acting antidepressant targeting the NMDA receptor pathway. However, its therapeutic utility is limited by poor bioavailability, rapid metabolism, and potential systemic side effects. Nanotechnology-based drug delivery systems, particularly nanoglobules, offer a novel approach for improving the delivery of lipophilic drugs like esketamine by enhancing brain targeting and bioavailability while reducing systemic exposure. This review highlights current advances in the formulation and characterization of esketamine-loaded nanoglobules, emphasizing their potential role in improving nanotherapeutic delivery for effective management of depression.

Keywords: Nanoglobules, Depression, Brain targeting, Nanotechnology, Antidepressant therapy.

I. INTRODUCTION

Depression is a serious ,chronic psychiatric disorder characterized by persistent low mood ,loss of interest ,fatigue ,and impaired cognitive function .it is one of the leading causes of disability worldwide ,conventional antidepressant such as selective serotonin reuptake inhibitors [SSRIs],serotonin-norepinephrine reuptake inhibitors [SNRIs],and tricyclic antidepressants [TCAs] often required several weeks to exert clinical benefits and are ineffective in a significant proportion of patient ,particularly those with treatment -resistant depression [TRD]. 1

Esketamine the S-enantiomer of ketamine, is a novel NMDA receptor antagonist that produces rapid antidepressant effects, often within hours .it modulates glutamatergic neurotransmission and promotes synaptic plasticity, which distinguishes it from traditional monoaminergic antidepressants. However, its clinical utility is limited by systemic side effects, variable bioavailability, and the need for specialized administration routes. Nanoglobules oil in water nanometre range represent an advanced nanotherapeutic platform that can enhance solubility, improve mucosal permeation, and protect labile drugs from degradation. When optimized for physicochemical stability, mucoadhesion, and droplet size, Nanoglobules can significantly improve the rate and extent of Esketamine delivery to the central nervous system while reducing systemic exposure. Esketamine (S-enantiomer of ketamine) is a novel, fast-acting antidepressant primarily used for the management of treatment-resistant depression (TRD) and major depressive disorder (MDD) with acute suicidal ideation or

behaviour. It is available in the form of Esketamine hydrochloride and is marketed under the brand name Spravato® by Janssen Pharmaceuticals. 2.

Unlike traditional antidepressants that act on monoaminergic systems, Esketamine works through a unique mechanism involving N-methyl-D-aspartate (NMDA) receptor antagonism, making it an important advancement in the treatment of resistant depression. 3.

Nanoglobules are lipid-based nanocarrier systems designed for the delivery of poorly soluble drugs, especially those targeting the central nervous system (CNS), cancer therapy, and other challenging therapeutic areas. They are typically composed of lipidic globules dispersed in an aqueous phase, stabilized by surfactants, and usually have a size range of 20–200 nm. Due to their small size and high surface area, Nanoglobules exhibit enhanced drug solubility, bioavailability, and targeted delivery properties 4.

Nanoglobules have gained significant attention in pharmaceutical nanotechnology because they can cross biological barriers such as the blood-brain barrier (BBB), making them ideal for delivering neuroactive drugs like Esketamine, etc and other CNS agent 5

Depression is a complex neuropsychiatric disorder affecting millions worldwide and is characterized by persistent low mood, anhedonia, fatigue, and cognitive dysfunction. Conventional antidepressants, such as SSRIs, SNRIs, and tricyclics, often require weeks to months to produce therapeutic effects, and a significant proportion of patients experience treatment-resistant depression (TRD), where symptoms fail to improve even after multiple therapeutic attempts. In this context, Esketamine-loaded Nanoglobules have emerged as a novel nanomedicine-based therapeutic strategy to enhance drug delivery and improve clinical outcomes 6

Depression is a mood disorder characterized by persistent low mood, lack of motivation, feelings of worthlessness, and loss of interest in pleasurable activities, lasting at least two weeks or longer. It is different from normal sadness, as it involves significant functional impairment in everyday life. 8

Nanoglobules have gained immense attention in pharmaceutical nanotechnology, particularly for central nervous system (CNS) drug delivery, where crossing the blood-brain barrier (BBB) is a major challenge. Due to their nano-size, lipidic nature, and biocompatibility, they are an excellent choice for delivering drugs like Esketamine effectively to the brain and other target sites. 9

Depression is a leading cause of disability worldwide, characterized by persistent sadness, anhedonia, and cognitive impairment. Conventional antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), exhibit delayed onset of action and limited efficacy in treatment-resistant depression (TRD). Recent research has identified esketamine, the S-enantiomer of ketamine, as a rapid-acting antidepressant offering new hope for patients unresponsive to traditional therapies.

Despite its promising pharmacological profile, esketamine faces significant delivery challenges due to its poor solubility, extensive first-pass metabolism, and limited brain bioavailability when administered via conventional routes. These drawbacks necessitate innovative nanocarrier-based approaches to ensure efficient brain targeting and sustained therapeutic action.

Nanoglobules, lipid-based nanosystems, have gained attention for their capacity to encapsulate lipophilic drugs and enhance their stability, solubility, and permeability across the blood-brain barrier (BBB). This review explores the formulation aspects, physicochemical characteristics, and therapeutic potential of esketamine-loaded nanoglobules for improved antidepressant delivery.

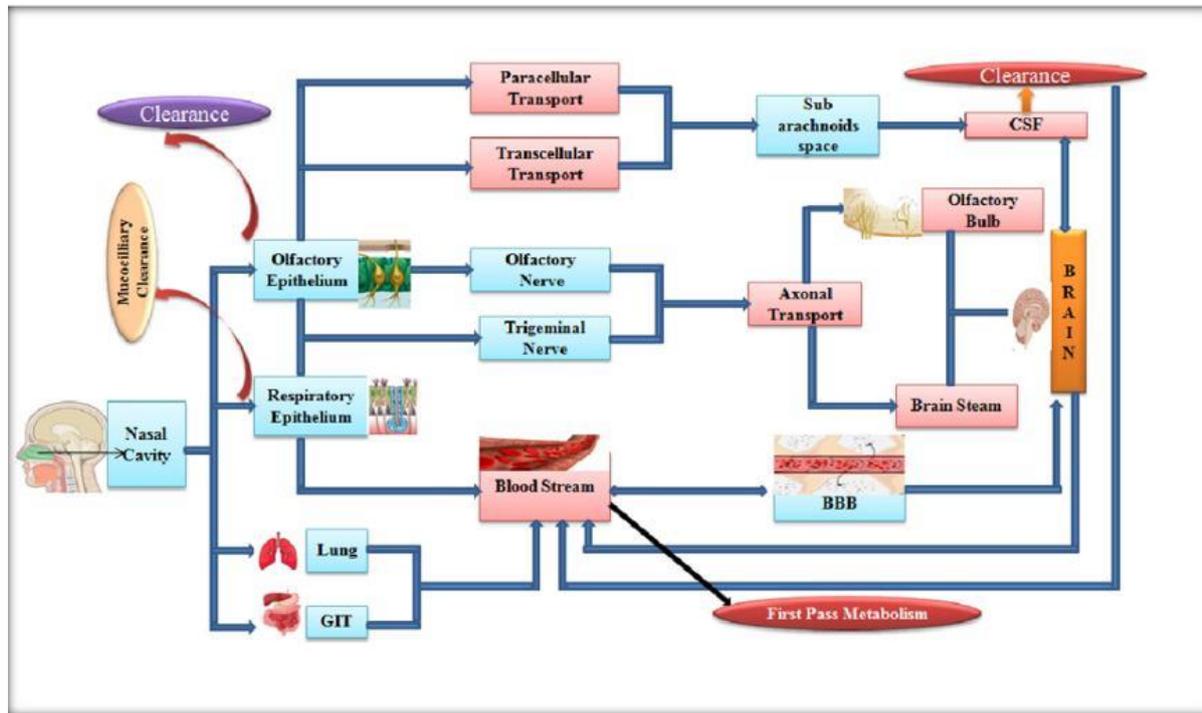
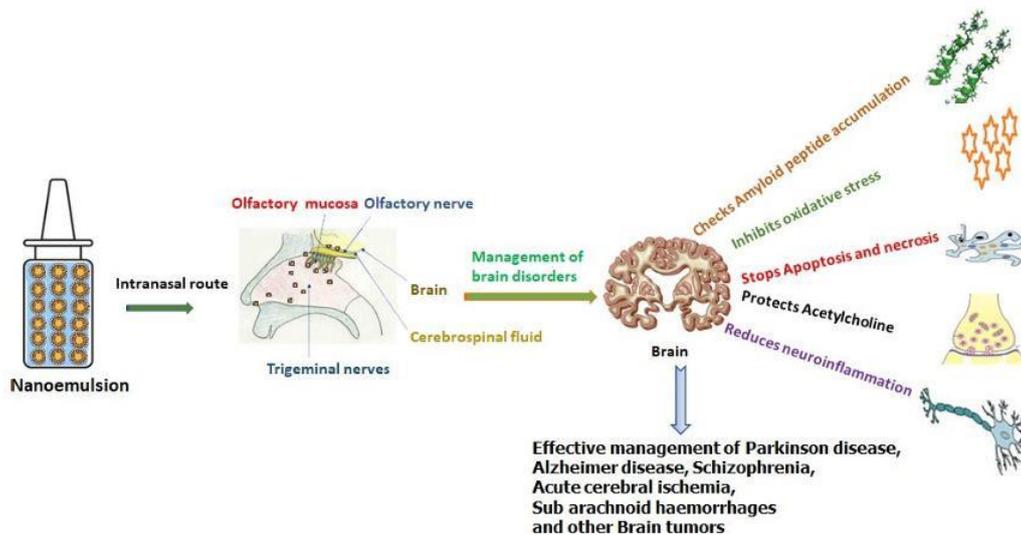


Figure 1. Complex pathway involved in the transport of therapeutics through nose-to-brainroute.

2. Nanoemulsions

Researchers are consistently engaged in the development of promising and potential non-invasive brain drug delivery systems. To achieve the targeted CNS response, various scientific investigations have been reported that define the olfactory and trigeminal are colloidal systems orconventional and controlled effects as well.



Intranasal drug delivery occurs when particles are inhaled into the nasal cavity and transported directly into the nervous system. Though pharmaceuticals can be injected into the nose, some concerns include injuries, infection, and safe disposal. Studies demonstrate improved patient compliance with inhalation. Treating brain diseases has been a challenge due to the blood brain barrier. Previous studies evaluated the efficacy of delivery therapeutics through intranasal route for brain diseases and mental health conditions. Intranasal administration is a potential route associated with high drug transfer from nose to brain and drug bioavailability

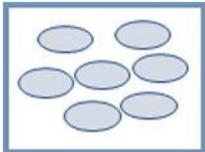
Advanced Emulsion	Structure	Salient Features	Applications	Ref.
Nanoemulsion		Nanoscaled droplets provide thermodynamically (kinetically stable) colloidal dispersions. Controlled and effective lipophilic bioactive agents can be transported.	Widely explored in food industry for its superb stability and shelf life of encapsulated colouring/flavouring components/nutraceutical and bioactive agents	[16]

Figure 2. Intra nasal delivered nanoemulsion and management of brain disorders.

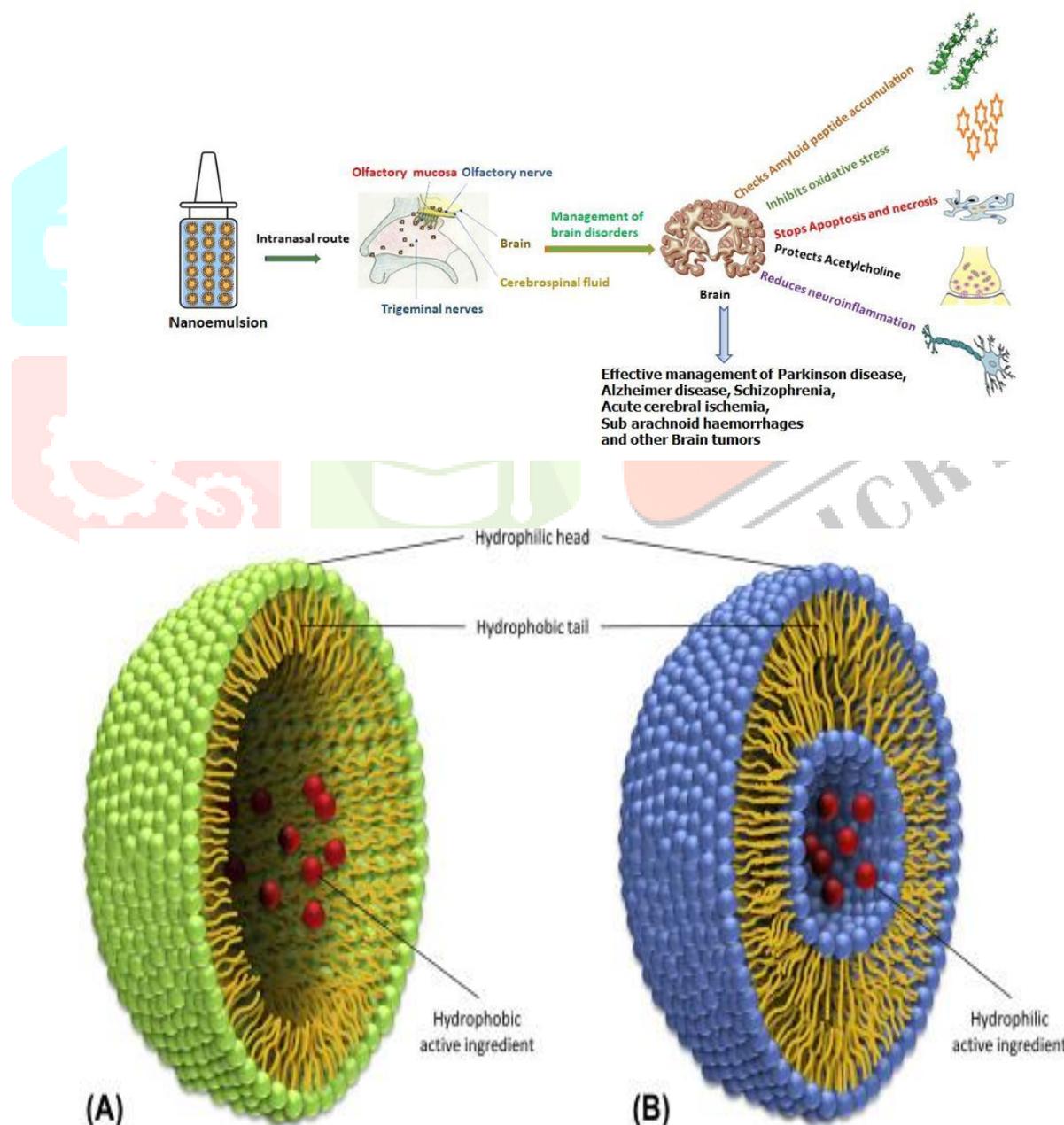


Figure 3. Nanoemulsion

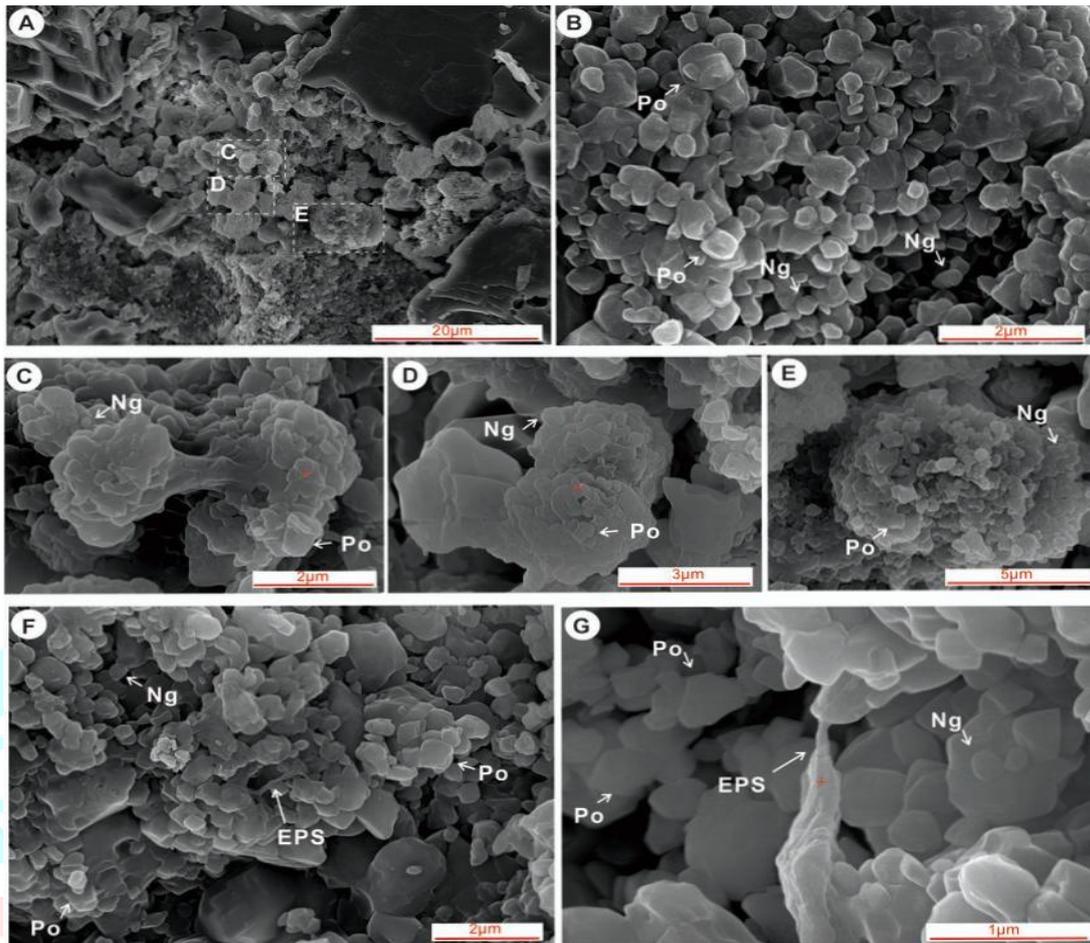


Figure. 4. Nanoemulsion

Pharmacology and Mechanism of Action

Esketamine is a non-competitive NMDA receptor antagonist that enhances glutamatergic neurotransmission, leading to increased synaptogenesis and neuroplasticity. This mechanism contrasts with traditional antidepressants that modulate monoamine levels. The rapid antidepressant effect of esketamine has been linked to activation of AMPA receptors and downstream mTOR signaling pathways, promoting neuronal growth and connectivity.

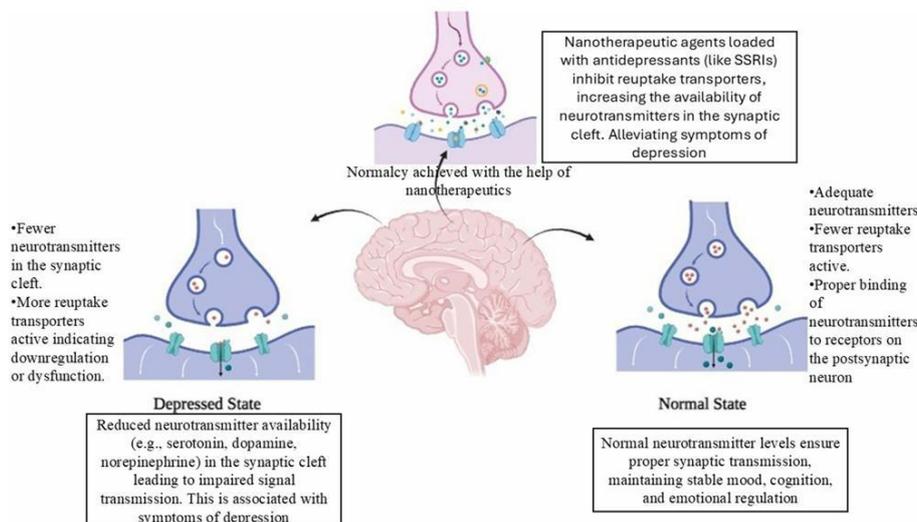


Figure.5 Restoration of neurotransmitter levels through nanotherapeutic delivery.

Limitations of Conventional Therapy

Poor oral bioavailability (<20%) due to extensive hepatic metabolism

Short half-life and rapid systemic clearance

Potential psychotomimetic effects with intravenous or intranasal administration

Nanoglobules as a Drug Delivery System

Nanoglobules are submicron-sized lipid-based globular carriers (typically 50–300 nm) composed of oil, surfactant, and co-surfactant dispersed in an aqueous phase. They are thermodynamically stable, transparent, and suitable for encapsulating hydrophobic drugs like esketamine.

Advantages include enhanced drug solubility, bioavailability, improved BBB penetration, controlled drug release, reduced systemic toxicity, and suitability for multiple routes of administration (nasal).

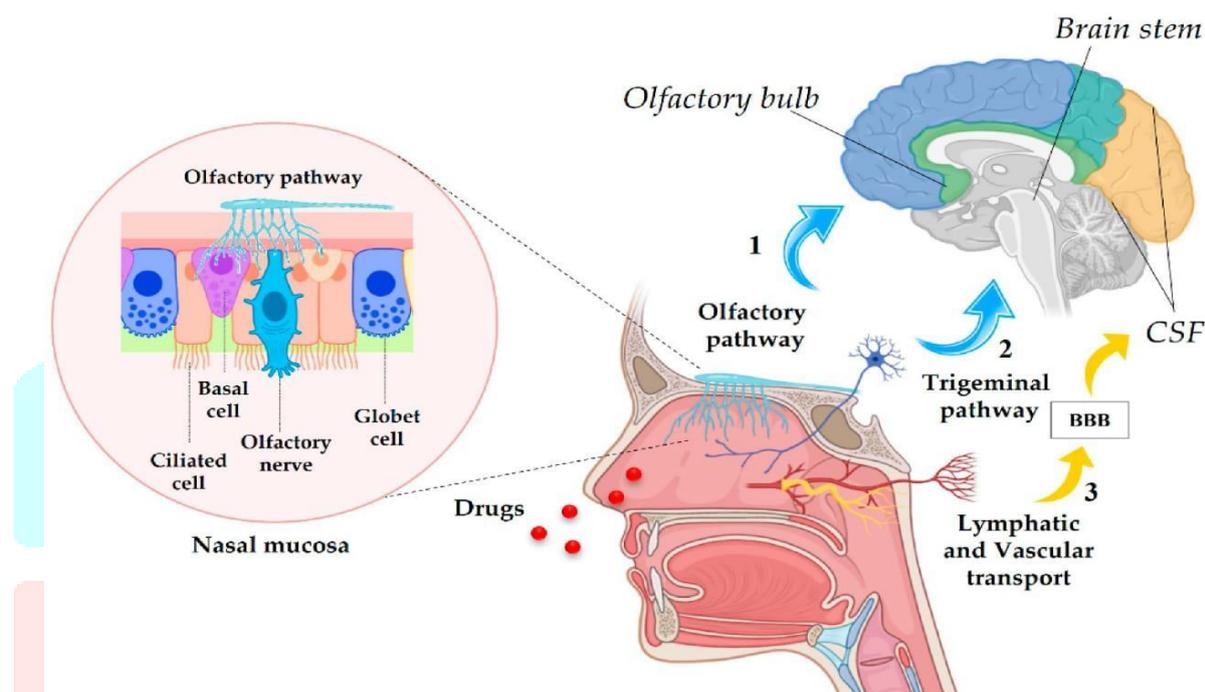


Figure 6 .Nanoglobules as a Drug Delivery System

Characterization of Nanoglobules

Characterization involves determining particle size, zeta potential, morphology (TEM/SEM), drug loading, entrapment efficiency, in vitro release, and stability studies as per ICH guidelines. In vitro cytotoxicity using neuronal cell lines and pharmacokinetic evaluations demonstrate enhanced brain delivery.

Pharmacological Evaluation and Brain Targeting

Animal models of depression such as forced swim and tail suspension tests are used to assess antidepressant efficacy. Fluorescent or radiolabeled nanoglobules confirm brain localization.

Pharmacokinetic studies show improved C_{max} , AUC, and brain-to-plasma ratios compared to conventional formulations.

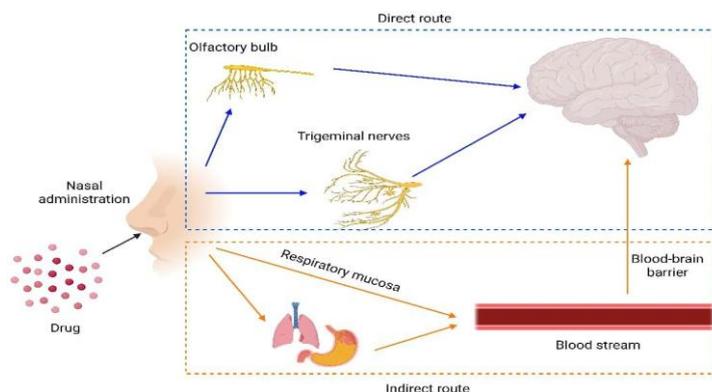


Figure 7. Pharmacological Evaluation and Brain Targeting nasal administration

Recent Research and Developments

Recent studies show lipid-based nanocarriers improve CNS delivery by increasing lipophilicity and reducing systemic clearance. Esketamine-loaded nanoglobules combine rapid onset with sustained delivery, reducing dosage frequency and abuse risk.

Challenges and Future Perspectives

Challenges include large-scale manufacturing, stability, regulatory concerns, and need for long-term toxicity studies. Future research should focus on targeted nanoglobules using surface ligands (transferrin, lactoferrin) for receptor-mediated BBB transport.

Conclusion

Esketamine-loaded nanoglobules offer a promising platform for improving the nanotherapeutic management of depression. By enhancing brain targeting, bioavailability, and controlled release, they can overcome the pharmacokinetic limitations of conventional formulations. Continued advances could establish nanoglobule-based esketamine delivery as a breakthrough in depression treatment.

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