Review Article

Nose-to-Brain Drug Delivery for Depression Therapy: Current Perspectives on Bilosomal in Situ Nasal Gel Systems

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Abstract
Depression is the multifactorial neuropsychiatric and chronic disorder that continues to the pose significant in the therapeutic challenges due to their limited brain bioavailability, and delayed onset of action. blood–brain barrier remains the major by obstacle in achieving the effective in drug concentrations within their central nervous system. nose-to-brain drug delivery has occurred the promising for the non-invasive strategy that for enables the direct transport of the therapeutic agents to their brain via the olfactory and trigeminal pathways, thereby the bypassing blood–brain barrier. Recent advances in this nanotechnology have further strengthened this approach by through the development of the novel carrier-based systems. Among these, the bilosomal in situ nasal gels have gained the considerable attention due to their enhanced stability, and permeation efficiency, and the prolonged nasal residence time. Bilosomes, stabilized with the bile salts, offer improved vesicular the flexibility which high drug encapsulation efficiency, and for enhanced brain targeting, while in situ nasal gels provide controlled release and resistance to mucociliary clearance. In this review comprehensively discusses about the nasal cavity anatomy and physiology of the relevant brain targeting and pathophysiological mechanisms and advantages of their nose-to-brain delivery for role of the novel drug delivery systems, and also their potential of bilosomal for in situ nasal gels for the depression therapy.

Keywords: Nose-to-brain, Bilosomes, Depression therapy, In situ nasal gels, Antidepressant drugs, Brain targeting.

Introduction

A person's ideas, behavior, emotions, physical health, and circadian rhythm can all be impacted by depression, which is characterized by a poor mood and an aversion to exercise [1]. Depression is a major contributor to the global health burden and the primary cause of disability globally [2]. The number of young individuals who may experience depression has increased by as much as 8%. These figures are made even more concerning by the fact that over 50% of depressed patients do not respond to their first-line pharmacological activity and 30% do not achieve remission after multiple pharmacological interventions, despite the numerous medications with demonstrated antidepressant efficacy that are available in clinical practice.[3]. Despite that the availability of numerous pharmacological therapies which effective management of the depression remains that challenging due to their delayed onset of action and the systemic side effects, and the limited brain bioavailability of the antidepressant drugs [4]. The blood–brain barrier acts according the physiological obstacle and restricting the transport the therapeutics for central nervous system (CNS). A possible non-invasive method for getting beyond the blood-brain barrier and improving direct drug administration to the brain is nose-to-brain drug delivery [5]. By combining the nanocarrier-mediated brain targeting with the extended nasal residence in time, advanced drug delivery methods, including bilosomal in situ nasal gels, offer a novel platform for increasing therapeutic outcomes in depression therapy. [6].

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1.1 Pathophysiology of Depression

The pathophysiology of the depression is multifactorial which involving the dysregulation of monoaminergic neurotransmitters such as norepinephrine, serotonin, and the dopamine. In the addition of neurotransmitter imbalance, as well as emerging evidence highlights the involvement of the neuroinflammation, and oxidative stress, hypothalamic–pituitary–adrenal (HPA) axis dysfunction, and impaired neuroplasticity, and the reduced brain-derived neurotrophic factor (BDNF) levels [7]. The progression of the disease is further influenced by structural and functional abnormalities in brain regions such the hippocampus, prefrontal cortex, and amygdala. shown in figure 1 [8].

1.2. Anatomy and Physiology about Nasal Cavity Relevant the Brain Targeting

The nasal cavity is a unique and highly specialized portal for the drug delivery direct from brain due to it's their anatomical proximity and the physiological connections by central nervous system [9].

1.2.1 Nasal Mucosa and Epithelial Barriers

The nasal epithelium acts like the protective barrier against for foreign particles, comprising tightly joined and epithelial cells interconnected the tight by junctions that are restrict paracellular transport. A mucus layer in rich mucins covers that the epithelial surface, trapping particulate matter and the facilitating mucociliary clearance [10]. While this are the barrier protects the nasal cavity, it also the limits drug permeation. Enzymes such as the cytochrome P450, esterases, and to the peptidases present in the nasal in mucosa can be further degrade susceptible in drugs before absorption. Advanced the formulation strategies, including the nanocarriers and to mucoadhesive in situ gels, are the designed to overcome these epithelial barriers by the enhancing residence time, protecting drugs from the enzymatic degradation, and to the facilitating transcellular or paracellular transport [11]

1.2.2. Olfactory and Trigeminal Pathways

The trigeminal is a nerve pathway which are serves as a complementary route, in innervating both the respiratory and the olfactory regions of the nasal cavity [12]. It connects that the nasal mucosa to the brainstem and as well as spinal cord, allowing drugs to the access deeper and the broader areas of the central nervous system. Transport by trigeminal pathway is the particularly relevant for the achieving widespread in brain distribution [13].

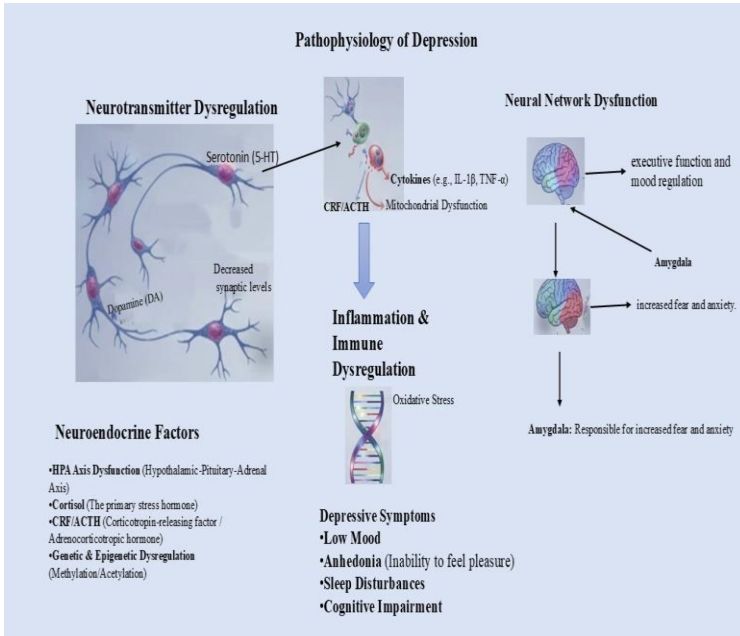

Figure 1. Pathophysiology of Depression

1.2.3 Nasal Drug Absorption Factors Affecting

drug Physicochemical properties are including lipophilicity, molecular weight, solubility, and the ionization state, which play a critical role in the determining permeation across in the nasal epithelium [14]. Small, and lipophilic molecules generally the exhibit better nasal absorption [15]. Inter-individual the variability in nasal anatomy and the breathing patterns also to contributes to inconsistent drug absorption. Formulation-related factors such as viscosity, pH, osmolarity, and to use of permeation enhancers directly the impact drug stability and absorption. In situ nasal gels with the optimal rheological properties can be resist mucociliary clearance and to the provide prolonged contact with the absorption site [16]. Incorporation of the nanocarriers like bilosomes further for the enhances of drug permeation, stability, and the brain-targeting efficiency by their facilitating sustained release and the neuronal transport.

2. Mechanisms and Advantages of Nose-to-Brain Drug Delivery

drug delivery Nose-to-brain this are represents a promising the non-invasive approach their direct targeting about central nervous system by their exploiting the unique anatomical and the physiological connections between their nasal cavity and brain [17]. Unlike to conventional systemic routes, this was strategy enables to therapeutic agents to the bypass the blood–brain barrier (BBB), thereby it enhancing brain bioavailability and the therapeutic efficacy. That are approach for gained considerable the attention in treatment of neurological and the psychiatric disorders, including depression, where its rapid and efficient in drug delivery to brain is essential [18].

2.1 Transport Mechanisms to the Brain

In brain nasal cavity the Drug transport occurs through their multiple interconnected pathways. The olfactory pathway is their primary route, wherein the drugs traverse by olfactory epithelium located in upper nasal cavity and to reach the olfactory bulb through by the intracellular (axonal transport) and about extracellular (paracellular diffusion) mechanisms [19]. This was the pathway which provides to direct access central nervous system and to enables rapid drug distribution of various brain regions. The nerve trigeminal pathway which serves as the additional route for the drug transport, connecting to the epithelium nasal respiratory to their brainstem and involve spinal cord [20]. Drugs absorbed via this pathway can be reach deeper brain structures, which complementing olfactory transport. [21].

2.2 Nose-to-Brain Drug Delivery Over Oral and Parenteral Routes Advantages

Table 1. Advantages of Nose-to-Brain Drug Delivery Over Oral and Parenteral Routes [22,23]

Parameter	Oral Route	Parenteral Route	Nose-to-Brain Route
Blood–brain barrier	BBB severely the limited drug entry into brain	BBB limits the brain penetration	Bypasses BBB by the olfactory and also with trigeminal pathways
First-pass metabolism	Extensive the hepatic first-pass metabolism	Avoided	Completely that avoided
Brain bioavailability	Low and the variable	Moderate but the limited	High and to direct brain targeting
Dose requirement	High the doses required	Moderate the doses	Lower the doses sufficient
Onset of action	Delayed	Faster than the oral	Rapid onset due to direct transport
Systemic side effects	High risk due to systemic exposure	Moderate risk	Minimal systemic exposure
Patient compliance	Moderate; affected by GI side effects	Poor due to invasiveness	High; non-invasive and to painless
Drug–drug interactions	Common	Possible	Reduced
Suitability for long-term	Limited by the side effects	Poor	Highly they suitable

therapy			
Effect of in situ gel systems	Not applicable	Not applicable	Prolonged nasal residence and enhanced efficacy

3. Novel Drug Delivery Systems of Depression Therapy and its Role

The complex pathophysiology of the depression and limited the effectiveness of conventional antidepressant therapies to have the driven by development of novel drug delivery systems which aimed to improving in the brain targeting and the therapeutic outcomes [24]. Advanced delivery approaches are the designed to overcome by physiological barriers like blood–brain barrier, enhance the drug bioavailability, reduce systemic side effects, and to provide sustained and to controlled drug release. In the context of the depression therapy the nanotechnology-based delivery systems offer the promising solutions for achieving efficient and the site-specific drug delivery to the central nervous system [25].

3.1. **Need for Advanced Delivery Approaches**

Conventional the antidepressant delivery is too often associated with the poor brain penetration, delayed onset of action, and the significant inter-individual the variability in therapeutic response. Oral administration leads to the extensive first-pass metabolism and the systemic distribution, resulting in low drug concentrations at target sites in the brain [26]. In Parenteral routes, that although capable of the delivering drugs systemically, remain to invasive and unsuitable for the long-term management of the chronic conditions as the depression. In the Advanced drug delivery approaches are required to the bypass in blood–brain barrier, enhance drug stability, and the provide controlled release directly to the brain [27]. Nanocarrier-based systems can be encapsulate both of the hydrophilic and lipophilic drugs, protect them from the degradation, and to improve their pharmacokinetic and the pharmacodynamic profiles.

3.2 **Lipid-Based Nanocarriers for Brain Targeting**

Lipid-based nanocarriers occurs highly effective platforms for the brain-targeted drug delivery by to their biocompatibility which ability to the encapsulate lipophilic drugs to enhanced interaction with the biological membranes [28]. These carriers can be the improve drug solubility, stability, and the permeability across biological barriers, including their blood–brain barrier. Additionally, the surface modification of the lipid-based carriers with mucoadhesive polymers or the targeting ligands can further to enhance the nasal retention and neuronal uptake. For the antidepressant therapy, lipid-based in nanocarriers enable the efficient nose-to-brain transport, rapid the onset of action, and the sustained drug release by the central nervous system [29].

3.3 **Vesicular in Drug Delivery Systems**

Vesicular in drug delivery systems are the nano- or microscale carriers composed of the lipid bilayers enclosing an aqueous core, capable of the encapsulating drugs with diverse the physicochemical properties. These systems offer to protection against enzymatic degradation, improved the drug stability, and to controlled release characteristics [30]. Vesicular systems have to gained significant attention for the brain-targeted delivery due to their ability to the cross biological barriers and the enhance intracellular drug transport [31]. Various vesicular systems, including liposomes, niosomes, and transferosomes, as well as ethosomes, and bilosomes, have been explored for the central nervous system delivery. Each system exhibits the distinct structural and to functional attributes influencing the drug loading, permeability, and the stability [32]. Among these are bilosomes—vesicles stabilized with the bile salts and demonstrate the superior membrane flexibility, enhanced stability, and to improved permeation characteristics. These are properties make vesicular systems, particularly the bilosomes, highly suitable for the incorporation into nasal in situ gel formulations aimed at the effective nose-to-brain delivery of depression therapy [33].

4. Nose-to-Brain Delivery by Bilosomes as Emerging Carriers

Bilosomes are the novel vesicular drug delivery systems composed of the lipid bilayers stabilized by bile salts, which the impart enhanced membrane flexibility and the stability compared to conventional vesicles. The Originally developed to improve oral delivery of the labile drugs, bilosomes have to recently gained significant attention for those the nose-to-brain to drug delivery occurs the superior the permeation, stability in biological environments, and the enhanced interaction with the mucosal membranes [34].

4.1 Composition and Structural Characteristics of Bilosomes

Bilosomes are the typically composed of phospholipids, and cholesterol, also bile salts like sodium deoxycholate, sodium cholate, or sodium taurocholate. The incorporation of bile salts into lipid bilayer alters the membrane fluidity, conferring that greater deformability and to resistance the enzymatic degradation. Structurally, the bilosomes consist of one or the more concentric lipid bilayers surrounding the aqueous core, allowing encapsulation of the hydrophilic and lipophilic drugs both [35]. In presence of bile salts enhances to vesicular stability and the prevents aggregation or fusion, resulting in nanosized, uniformly distributed vesicles. bilosomes physicochemical properties of the, including zeta potential, particle size, and also encapsulation efficiency, can be the tailored by optimizing the formulation variables such as the lipid composition, bile salt concentration, and the preparation method [36]. These are customizable characteristics are the essential for achieving efficient for nasal permeation and the neuronal transport.

4.2 Stability and Brain Targeting Potential

Stability is the critical parameter by success for nasal drug delivery systems, as formulations must withstand the mucosal enzymes, mechanical stress, and the clearance mechanisms. Bilosomes exhibit enhanced physical and the chemical stability due to the bile salt–mediated membrane reinforcement, making them the less susceptible to aggregation and for degradation [37]. Their nanoscale size and the flexible structure facilitate uptake through with olfactory as well as trigeminal nerve pathways which enabling the direct transport for brain while they are bypassing in blood–brain barrier. When they incorporated into mucoadhesive in situ nasal gel systems, bilosomes was demonstrate prolonged the nasal residence time, controlled drug release, and to enhanced brain targeting efficiency [38]. This synergistic approach significantly improves the therapeutic efficacy and to reduces systemic exposure, highlighting the strong potential of bilosomes carriers of the nose-to-brain delivery for depression therapy [39].

5. In Situ Nasal Gel Systems

The system of in situ nasal gel are advanced drug delivery platforms for the designed by undergo a reversible sol–gel transition in nasal cavity administration, thereby the improving drug retention and absorption. These systems are the typically administered as the low-viscosity liquids that transform into gels in the response to physiological stimuli such as the temperature, pH, or ionic strength, and are they classified accordingly into the thermosensitive, pH-sensitive, and ion-activated in situ gels [40]. Commonly used the polymers in nasal in situ formulations include the poloxamers, chitosan, carbopol, gellan gum, and sodium alginate, and the hydroxypropyl methylcellulose, and selected for their biocompatibility, mucoadhesive properties, and they ability to form gels under nasal conditions. The sol–gel transition mechanism is the governed by polymer–polymer and polymer–mucosal interactions, leading to the increased viscosity and the gel formation or temperature [41]. Advantages of their in situ nasal gels include prolonged nasal residence time, reduced mucociliary clearance, and enhanced drug stability, also controlled drug release, and improved patient compliance. When the combined with nanocarrier systems such as the bilosomes, in situ nasal gels further enhance in the nose-to-brain delivery by promoting in release sustained drug, improved the mucosal adhesion, and the efficient transport through olfactory and to trigeminal pathways, making them highly suitable for the brain-targeted depression therapy [42].

6. Bilosomal In Situ Nasal Gels for Depression Therapy

Bilosomal in situ nasal gels represent the synergistic drug delivery approach that the integrates the advantages of bile salt–stabilized which vesicular carriers with the mucoadhesive in situ gel systems to the achieve efficient nose-to-brain delivery in the depression therapy.

6.1 Formulation considerations

Formulation considerations involve in the careful selection and to optimization of lipids, bile salts, polymer type, gelation temperature or the pH, viscosity, and to nasal compatibility to the ensure stability, patient comfort, and the effective brain targeting [43].

6.2 encapsulation efficiency and drug loading

encapsulation efficiency and High drug loading both are achieved through the bilosomal vesicle optimization, enabling to protection of the antidepressant drugs from the degradation and providing for sustained release profiles.

6.3 mucoadhesive polymers

The incorporation of the mucoadhesive polymers enhances to interaction with nasal mucosa, prolongs residence the time, and minimizes rapid mucociliary the clearance, thereby they improving drug availability at absorption site [44]. Additionally, the bile salts act as the natural permeation enhancers by the modulating epithelial tight junctions and to facilitating transcellular transport, while the nanoscale size of the bilosomes promotes uptake the through olfactory and the trigeminal pathways.

7. Antidepressant Drugs Delivered via Nose-to-Brain Route

The extensively explored nose-to-brain route has been delivery of the various antidepressant drugs to the overcome the limitations associated with the conventional systemic administration. Conventional in antidepressants, including the serotonin–norepinephrine reuptake inhibitors selective serotonin reuptake inhibitors and, tricyclic antidepressants, the atypical agents, have demonstrated to improve the brain bioavailability and faster the onset of action when they administered intranasally [45]. Recent advances have been focused on the newer multimodal antidepressants such as the vortioxetine, which exhibits the combined serotonin transporter inhibition and the receptor modulation. vortioxetine Intranasal delivery and similar agents has to show the enhanced brain uptake, reduced the systemic exposure, and the improved therapeutic response due to the direct transport via olfactory and trigeminal pathways [46]. Comparative in the evaluations other than nanocarrier systems it including like niosomes, liposomes, solid lipid nanoparticles, and polymeric nanoparticles, as well as indicate that vesicular systems and particularly bilosomes and offer superior stability, the higher encapsulation efficiency, enhanced permeation, and the prolonged nasal residence time [47].

8. Evaluation Parameters for Bilosomal In Situ Nasal Gels

8.1 Physicochemical Characterization

Physicochemical characterization is the essential to ensure the stability, reproducibility, and to performance of the bilosomal in situ nasal gel formulations. Key parameters include the polydispersity index, particle size, and the zeta potential, which is influence vesicle stability, nasal permeation, and the brain uptake. Encapsulation efficiency and to drug loading are evaluated to assess the ability of bilosomes to the effectively entrap in antidepressant drugs [48]. Additional characterization includes such as pH, viscosity, gelation temperature or pH, rheological behavior, and as well as in vitro drug release profiles to the confirm nasal compatibility, and sol–gel transition behavior, and the controlled release performance [49].

8.2 In Vitro and Ex Vivo

studies of In vitro and ex vivo provided the preliminary insights into the drug release, permeation, and mucoadhesive properties of the bilosomal in In situ nasal gels. The In studies about vitro drug to release are commonly conducted the using dialysis membrane or the diffusion cell methods to the evaluate release kinetics [50]. Ex vivo permeation studies using of the excised nasal mucosa, typically from the sheep or goat, help assess drug transport across their nasal epithelium. Mucoadhesion strength and the residence time studies further the demonstrate the ability of in situ gels to the resist mucociliary clearance and maintain to the prolonged contact with nasal mucosa [51].

8.3 In Vivo Pharmacokinetic and Pharmacodynamic Studies

In vivo studies are the critical for evaluating the brain-targeting efficiency and the therapeutic potential of bilosomal in situ nasal gels. Pharmacokinetic studies assess the drug concentration in the plasma and brain tissues following their intranasal administration, enabling calculation of the parameters such as brain-to-plasma ratio, with drug targeting efficiency, and to direct transport percentage [52]. Pharmacodynamic evaluations the involve behavioral and biochemical assessments in the animal models of perform in depression to determine the antidepressant efficacy. These studies help to establish the correlation between to enhanced brain delivery and the improved therapeutic outcomes [53].

8.4 Safety, Toxicity, and Nasal Irritation Studies

Development of the nasal drug delivery systems the safety evaluation is the crucial component. Nasal irritation and the toxicity studies are performed to the assess biocompatibility of bilosomal formulations and polymers used in situ gels. Histopathological examination of the nasal mucosa is commonly employed to detect the epithelial damage, inflammation, or the structural alterations following repeated administration [54]. Acute and the sub-chronic toxicity studies further for ensure systemic safety. These evaluations are too essential the confirm that the bilosomal in situ nasal gels are safe for long-term administration in the depression therapy.[54,55]

9. Regulatory Considerations and Translational Challenges

9.1 Regulatory Requirements for Nasal Nanoformulations

Regulatory approval of the nasal nano formulations requires rigorous in evaluation of quality, safety, and efficacy in accordance with the guidelines established by regulatory authorities such as the Drug Administration and US Food also the European Medicines Agency. Nasal drug products they must demonstrate the acceptable physicochemical characteristics, stability, and reproducibility, and the batch-to-batch consistency [55]. Scaling up the bilosomal in situ nasal gels from the laboratory to industrial production presents several their manufacturing challenges. Maintaining consistent to the vesicle size, encapsulation efficiency, and stability during the large-scale production is critical. Variations in the raw material quality, processing conditions, and sterilization methods can significantly impact product performance

9.2 Clinical Translation Barriers

Despite promising in the preclinical outcomes, that occurs clinical translation in bilosomal In situ nasal gels remains challenging. Differences in the nasal anatomy, mucociliary the clearance rates, and disease conditions between the animal models and humans can lead to the variable clinical responses. Limited the clinical data, uncertainty regarding their long-term safety, and to patient-related factors such as nasal pathology and the adherence further for complicate translation. Additionally, lack of the standardized regulatory frameworks specifically they tailored for nose-to-brain with Nano formulations delay clinical development

10. Recent Advances, Patents, Ongoing Research, and Future Perspectives

Recent research trends in the delivery by nose-to-brain in drug depression therapy have focused on the development of the advanced nanocarrier-based systems, particularly the lipid-based vesicles and to stimuli-responsive in situ nasal gels, to the enhance brain targeting, stability, and therapeutic efficacy. Bilosomal of formulations have to gained increasing attention due to the bile salt–mediated stability, and improved permeation, and for compatibility with the nasal administration. Several intranasal formulations that for targeting in central nervous system disorders have been progressed to clinical evaluation, and to limited number of nasal products for the neurological indications are already available in the market, demonstrating the feasibility of this route However, the most nose-to-brain nano formulations for the depression remain at the preclinical or the early clinical stage. Future research opportunities the lie in optimizing formulation scalability, and to establishing long-term safety profiles, and which conducting well-designed clinical trials, and the developing standardized to regulatory guidelines specific to nose-to-brain delivery systems. Integration of the advanced nanocarriers such as the bilosomes with patient-friendly in nasal delivery platforms to holds significant the promise for achieving effective, safe, and also personalized depression therapy in future.

Conclusion

Nose-to-brain drug delivery is promising the innovative strategy for improving therapeutic management in depression by the overcoming limitations of their conventional antidepressant in administration routes. in anatomical connection direct in between the nasal cavity and brain both allows is efficient bypassing of blood–brain barrier, and resulting in enhanced to brain bioavailability, rapid onset of action and reduced the systemic side effects. the bilosomal in situ nasal gel systems represent the advanced and the synergistic delivery platform that to combines the stability and permeation-enhancing their properties of the bile salt–stabilized vesicles with their prolonged nasal residence and to controlled release offered by the in-situ gels. In this reviewed evidence highlights that the bilosomal in situ nasal gels can be the significantly improve drug loading, and mucoadhesion, permeation, and the brain uptake of antidepressant agents, particularly they newer multimodal drugs such as vortioxetine. These systems are demonstrated to superior physicochemical stability, and enhanced in nose-to-brain transport by olfactory and the trigeminal pathways, and to improved pharmacokinetic and the pharmacodynamic performance compared to the conventional and the other then nano-based delivery approaches. Overall, this delivery strategy holds in substantial promise as a next-generation with patient-friendly approach for the effective and targeted depression therapy.

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