RESEARCH ARTICLE

Utilizing Intranasal Drug Delivery Systems for Novel Antipsychotics Drug Development

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ABSTRACT

Psychotic illnesses are significant symptoms of various mental disorders, including psychotic depression, bipolar disorder and schizophrenia. The high incidence of psychotic illness can be attributed to several factors, including low patient compliance stemming from limitations in antipsychotic treatments. Antipsychotics are pharmacological therapies used to manage psychotic disorders, addressing acute episodes and preventing relapses. However, these drugs often exhibit limited physicochemical properties, suboptimal pharmacokinetic profiles, low bioavailability, and insufficient solubility, which hinder their ability go through the blood-brain barrier (BBB). The traditional dosage forms and routes of administration, primarily oral and injectable also pose further challenges. The intranasal delivery system offers a promising alternative to overcome these limitations by facilitating drug administration through the nasal cavity, allowing for quick uptake into the bloodstream while circumventing enzymatic degradation and first-pass metabolism associated with oral routes. The intranasal route can achieve significant drug concentrations in the brain without interference from the BBB, increasing bioavailability and enabling a rapid onset of pharmacological effects at lower doses and frequencies than oral medications. Nonetheless, anatomical, physiological, histological challenges as well as the fundamental processes involved in drug uptake via the nasal epithelium complicate systemic and brain distribution. The effectiveness of intranasal antipsychotic formulations can be improved through different drug delivery systems (DDS) such as nanoparticles, liposomes, nanogels, and other nanocarriers that help transport the drugs from the nasal cavity to the brain.

Keywords: antipsychotics, formulation development, intranasal, drug delivery system

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INTRODUCTION

Psychotic illness is a severe mental disorder that significantly alters an individual's perception of reality.[1] It can manifest through hallucinations, delusions, and profound confusion that can severely disrupt social and personal functioning. Psychosis may serve as a primary symptom across various mental disorders, including psychotic depression, bipolar disorder, and schizophrenia. Current epidemiological data indicate that disorders closely associated with psychotic illnesses exhibit a high prevalence. The incidence of first-time episodes of psychosis has been reported at 50 per 100,000 individuals, while the incidence of schizophrenia stands at 15 per 100,000 globally.[2] This elevated incidence may be attributed to several factors, including inadequate patient compliance arising from limited access to effective antipsychotic treatments.[3]

Antipsychotics are the pharmacological agents predominantly employed in the management of psychotic illnesses. They are utilized to address acute psychotic episodes and to mitigate the risk of relapse.[3] However, first-generation antipsychotics (FGAs), commonly prescribed for typical psychotic symptoms, are associated with significant extrapyramidal adverse effects.[4] These adverse effects can include dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia. Additional adverse effects may encompass anticholinergic symptoms, orthostatic hypotension, weight gain, and sedation.[5] Furthermore, adjunctive treatments for co-occurring disorders, like selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines, may induce their own adverse effects, including sexual dysfunction and withdrawal syndromes. The pharmacological profiles of antipsychotic medications are further complicated by limitations related to their physicochemical properties and pharmacokinetic behaviors, which can lead to a variety of adverse drug reactions.[6] Oral antipsychotic medications typically demonstrate low bioavailability, mainly because of initial metabolic processes and the transport function of P-glycoprotein, alongside challenges associated with low solubility and short half-lives.[3] The profiles of adverse effects and pharmacokinetics for several antipsychotics are summarized in Tables 1 and 2. The ability of most antipsychotic drugs to effectively penetrate the blood-brain barrier (BBB) presents a significant challenge in the development of therapeutics targeting central nervous system (CNS) disorders.[3] The unique physiological and anatomical characteristics of the blood vessels supplying the brain, such as the enzymatic surveillance mechanisms, limited presence of pinocytic vesicles, efflux transporters

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within endothelial cells, tight junctions that restrict intercellular space, and the surrounding pericytes and astrocytes, contribute to this challenge. Consequently, only compounds with molecular weights less than 400–500 Da and possessing lipophilic characteristics can effectively traverse the BBB.[7,8] Moreover, the limitations associated with the dosage forms and routes of administration for antipsychotic drugs further complicate their clinical efficacy and safety.

Currently, antipsychotic medications are typically administered via oral and injectable routes. The oral route, while common, is associated with frequent administration requirements and is often unsuitable for emergency situations. In contrast, injectable formulations are invasive, potentially leading to reduced patient compliance, and may only be administered by qualified healthcare professionals. Therefore, there is a pressing need for alternative delivery routes that minimize adverse effects, enhance the pharmacokinetic profiles of antipsychotic drugs, improve drug penetration through the BBB, and ultimately increase patient compliance and tolerance. The intranasal delivery system presents a promising solution to the limitations associated with both oral and injectable antipsychotic formulations. This system facilitates drug administration through the nasal cavity, allowing for rapid absorption into systemic circulation without the first-pass metabolism and enzymatic degradation that characterize oral medications. One of the principal advantages of intranasal administration is its ability to deliver significant drug concentrations directly to the cerebrospinal fluid (CSF) and olfactory bulb, bypassing the BBB. The region in the nasal cavity that is associated with the trigeminal nerves and olfactory terminate can grant drugs direct access to the brain, effectively facilitating their passage across the BBB. As a result, intranasal delivery systems can enhance the bioavailability of antipsychotic medications and provide a rapid onset of pharmacological effects at lower doses and frequencies compared to oral formulations, thereby reducing the risk of adverse drug reactions (ADRs). Furthermore, the intranasal route can enable high molecular weight drugs to reach their targets in the brain through various transport mechanisms, including transcellular, paracellular and neuronal transport pathways. This route is particularly efficient for drug delivery that is minimally invasive, as the respiratory mucosa exhibits favorable permeability and substantial absorption capabilities. However, significant challenges remain in the creation of efficient intranasal drug delivery systems (DDS). The systemic and brain distribution of drugs administered via the nasal route is complex, influenced by the anatomical, physiological, and histological properties of the nasal cavity as well as by the fundamental processes involved in the absorption and transport of drugs via the nasal epithelium. To enhance the transport of intranasally administered drugs from the nasal cavity to the brain, advanced DDS, such as liposomes, nanoparticles, and nanoemulsions may be employed. These innovative formulations can potentially improve the efficiency of intranasal drug delivery, thus facilitating better therapeutic outcomes for patients requiring antipsychotic treatment.

Psychotic Disorders

Psychotic disorders are clinical conditions marked by significant alterations in cognition and judgment, which profoundly impact interpersonal relationships and disrupt overall functioning and quality of life.[26] Psychosis, a prevalent symptom across various psychiatric conditions, manifests as an inability to comprehend reality and is often characterized by the presence of hallucinations, delusions, or both.[2,27,28] Among these disorders, schizophrenia stands out as one of the primary psychotic conditions, exhibiting both positive symptoms—such as hallucinations, delusions, behavioral changes, and hyperactivity—and negative symptoms, including alogia, avolition, and anhedonia.[29,30,31] Several theories elucidate the pathophysiology of schizophrenia, notably focusing on

Table 1. Adverse effect profile of antipsychotic drugs

Drugs	Category	Adverse Drug Reactions	Reference
Clozapine	SGAs	Anticholinergic effects, diabetes, weight gain, increased lipids, neutropenia, sedation	5
Chlorpromazine	FGAs	Diabetes, weight gain, increased lipids, tardive dyskinesia, akathisia.	5
Olanzapine	SGAs	Anticholinergic effects, diabetes, weight gain, increased lipids	5
Haloperidole	FGAs	Acute parkinsonism, akathisia, hyperprolactinemia	5
Quetiapine	SGAs	Diebetes, weight gain, increased lipids, orthostatic hypotension	5
Risperidone	SGAs	Acute parkinsonism, weight gain, hyperprolactinemia	5
Paroxetine	SSRIs	Drowsiness, dry mouth, sweating, sexual dysfunction, withdrawal syndrome from discontinuation	17
Citalopram	SSRIs	Drowsiness, insomnia, dizziness, headache, gastrointestinal disorder, sexual dysfunction	18
Lorazepam	Benzodiazepine	Apnoea, asthenia, disinhibition, extrapyramidal syndrome, sexual dysfunction	19
Diazepam	Benzodiazepine	Respiratory depression, bradycardia, hypotension sedation, fatigue, depression, ataxia, irritability, withdrawal symptoms	20

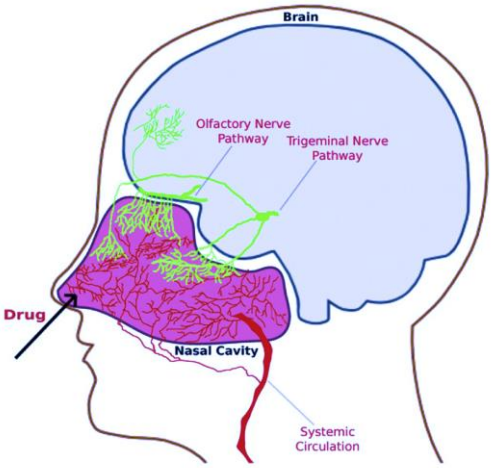

Figure 1: Drug delivery route from the nasal cavity to the bloodstream in the brain. Nerves endings are illustrated in green, whereas blood vessels are depicted in red.

abnormalities in the regulation of key neurotransmitters, including dopamine, serotonin, and glutamate.[29,32] The dopamine hypothesis posits that dysregulation occurs at the D_2 receptor sites across four distinct dopaminergic pathways: the mesolimbic-mesocortical route, the nigrostriatal route, the tuberoinfundibular route, and the medullary periventricular route. Elevated dopamine levels in the mesolimbic pathway are linked to the development of positive symptoms, while diminished dopamine levels in the mesocortical pathway are associated with the onset of negative symptoms.[29]

Mental Illness Associated with Psychosis

Several psychiatric conditions beyond schizophrenia are associated with psychosis, including psychotic depression and bipolar disorder. These mental disorders typically employ treatments that include antipsychotic medications to address the symptoms of psychosis, often in conjunction with other drug classes such as antidepressants and anxiolytics. Bipolar disorder (BD) is an important mental health condition marked by shifts between depressive episodes and periods of significantly elevated mood, which can last from days to weeks.[34] Bipolar disorder can manifest psychosis, characterized by the occurrence of delusions, hallucinations, or a combination of both, with more than half of BD patients experiencing psychotic symptoms at some point in their lives.[35] Conversely, psychotic depression, also referred to as depressive psychosis, manifests as a major depressive episode accompanied by psychotic symptoms.[36] In major depressive disorder characterized by psychotic features, the symptoms are episodic and happen solely during a particular episode of major depression. On the other hand, people with schizophrenia display psychotic symptoms consistently that arise independently of any identifiable mood disorder.[34]

Antipsychotic

Antipsychotics are pharmacological agents that act on the central nervous system to alleviate psychotic symptoms across a spectrum of conditions, including schizophrenia, bipolar disorder, psychotic depression, dementia-related psychoses, and drug-induced psychoses. Generally, antipsychotic are divided into two categories: typical antipsychotics (first-generation) and atypical antipsychotics (second-generation).[33] Both classes share the common mechanism of action by blocking dopamine D2 receptors; however, they differ significantly in their receptor profiles and adverse effect profiles. First-generation antipsychotics primarily exert their effects by blocking D2 receptors in the mesolimbic and striatal-frontal systems, thereby reducing excessive dopaminergic activity in line with the dopamine hypothesis.[37] Nonetheless, their less selective receptor affinity often leads to the blockade of D2 receptors in the nigrostriatal pathway, resulting in extrapyramidal adverse effects such as tremors, akathisia, and dystonia. While

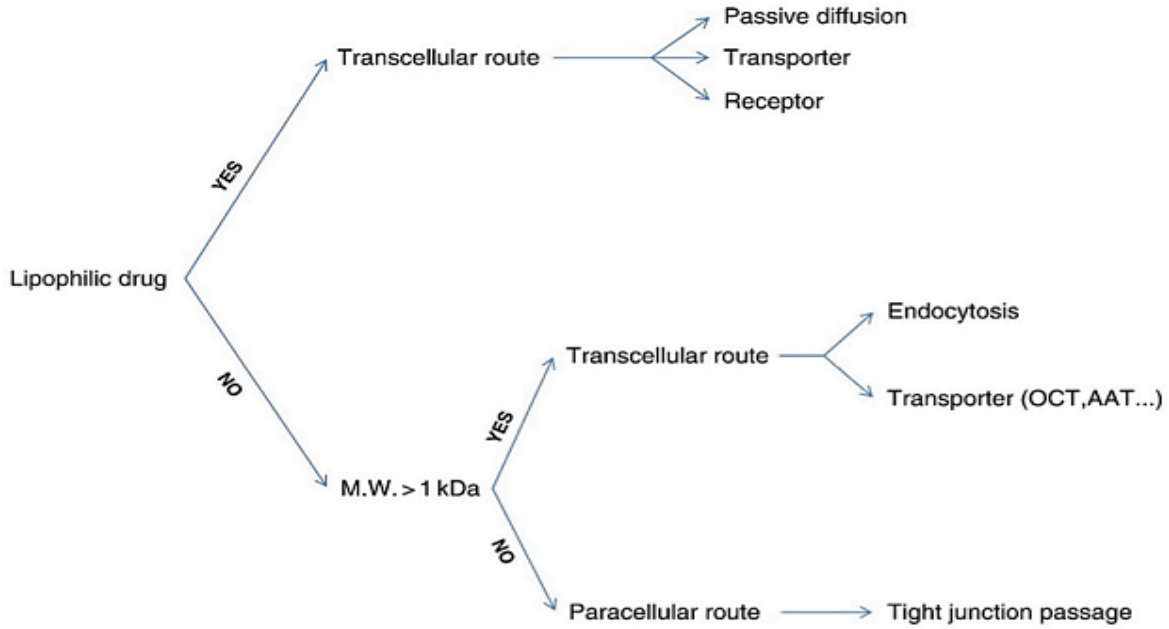

Figure 2: The crossing of respiratory epithelium by drugs through various pathways

effective in managing the positive symptoms of schizophrenia, these agents are generally ineffective against negative symptoms.[38]

In contrast, second-generation antipsychotics block D2 receptors and interact with serotonin receptors, particularly 5-HT2A receptors, that influence the regulation of neurotransmitters like dopamine, norepinephrine, glutamate, GABA, and acetylcholine.[39] This multifaceted action allows second-generation antipsychotics to address both positive and negative symptoms of psychosis while typically resulting in fewer extrapyramidal adverse effects compared to their first-generation counterparts. These advantages make second-generation antipsychotics the preferred choice in the primary treatment for psychotic disorders, including schizophrenia.[40] However, second-generation antipsychotics may be associated with adverse effects including sedation, hypotension, sexual dysfunction, and weight gain.[5] From a chemical perspective, first-generation antipsychotics can be subdivided into several classes, including phenothiazines, thioxanthenes, and butyrophenones, while second-generation antipsychotics comprise dibenzodiazepines, benzisoxazoles, thienobenzodiazepines, dibenzothiazepines, dihydroindolones, and dihydrocarbostyrils.[33] Antipsychotic medications are frequently prescribed in conjunction with antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) like paroxetine and citalopram, serotonin-norepinephrine reuptake inhibitors (SNRIs) like duloxetine and escitalopram, and anxiolytics, particularly benzodiazepines, for the treatment of conditions such as bipolar disorder. SSRIs and SNRIs function primarily by increasing the extracellular concentration of serotonin through the inhibition of its reuptake into presynaptic neurons. SNRIs also have the added capability of inhibiting norepinephrine reuptake, thereby elevating extracellular norepinephrine levels. Benzodiazepines, on the other hand, enhance the effects of gamma-aminobutyric acid (GABA) at the GABAA receptor, producing sedative, hypnotic, anxiolytic, anticonvulsant, and muscle relaxant effects.[41,42,43]In clinical practice, it is generally advised to avoid the use of antidepressants as a first-line treatment for bipolar disorder due to their potentially detrimental adverse effects. Nevertheless, antidepressants are widely prescribed to tackle the depressive episodes associated with bipolar disorder, whether mood stabilizers are concurrently administered.[44,45] Antipsychotic medications are typically administered orally but may also be given parenterally under certain circumstances. Oral administration presents limitations, including rapid drug elimination, hepatic metabolism, plasma protein binding, potential drug-drug and drug-food interactions, and extensive extravascular distribution, which may result in insufficient drug delivery to the CNS and necessitate repeated doses.[46] These factors contribute to a significant challenge, as patients often experience pronounced adverse effects—such as metabolic changes, weight gain, sexual dysfunction, and exacerbated extrapyramidal symptoms—that can lead to non-compliance with treatment regimens, ultimately worsening their condition. Given these challenges, the exploration of alternative routes of administration, such as intranasal delivery, is warranted. Intranasal administration offers a potentially more comfortable and safer alternative for the therapeutic management of psychotic disorders, addressing the high incidence of symptoms and adverse effects associated with traditional routes. Consequently, intranasal delivery emerges as a viable non-invasive alternative in the development of antipsychotic therapies.[47] The inherent characteristics of conventional antipsychotic drugs present limitations concerning their solubility, particularly their difficulty in dissolving in non-acidic aqueous solutions. This challenge complicates the safe intranasal administration of these medications.[14] Consequently, the development of controlled-release DDS for the prolonged release of antipsychotic agents via intranasal routes has emerged as a promising area of research. Various formulations for intranasal delivery have been extensively investigated, including nasal drops, sprays, emulsions, suspensions, liposomal, and powders.

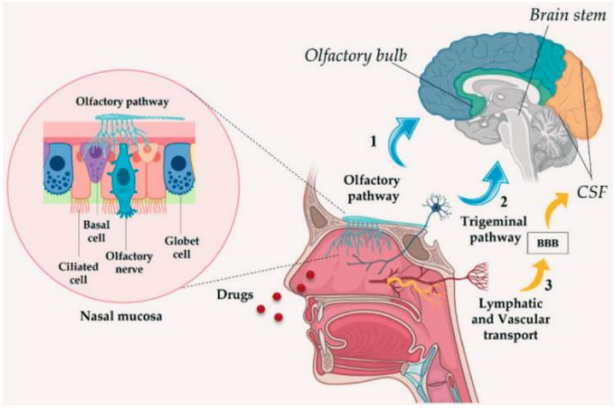

Figure 3: Drug delivery route from the nasal cavity to the brain: (1) through the intracellular route of the olfactory nerve leading to the olfactory bulb, (2) via the intracellular pathway of the trigeminal nerve to the brainstem, (3) through the lymphatic and vascular systems to reach the cerebrospinal fluid across the BBB.

Intranasal

Intranasal administration refers to the delivery of drugs through the nasal passages or cavity, facilitating direct absorption through the nasal mucosal membrane into the bloodstream. This route effectively bypasses the gastrointestinal tract and first-pass metabolism in the liver, allowing for a more efficient delivery of therapeutic agents. The advantages of intranasal drug administration include enhanced patient compliance, convenience of use, security, quick action commencement, and minimized systemic exposure.[48] Drugs delivered via the intranasal route are typically cleared more quickly compared to those administered orally or via intraperitoneal (IP) routes. Various dosage forms for intranasal delivery have been developed, including nasal sprays, emulsions, liposomal, suspensions, and dry powders that may incorporate peptides or polymers. The nasal passages represent the only olfactory areas in direct contact with the external environment, providing a direct and non-invasive access point to the CNS. This route of administration effectively supports systemic drug delivery while circumventing

gastrointestinal degradation and hepatic effects commonly associated with oral administration.[47] The drug delivery pathway through the nasal cavity involves several steps: first, the drug is carried to the vestibular area, where it is retained in the nasal mucosa. From there, the drug molecules can reach the brain via multiple pathways: (1) trigeminal nerve-mediated transport, (2) olfactory nerve-mediated transport, and (3) vesicular and lymphatic transport pathways.[49] The nasal route of administration provides a unique opportunity for direct interaction between the olfactory epithelium, the external environment, and the CNS, allowing for targeted delivery of therapeutic agents to the brain while circumventing the BBB.[50] This targeted intranasal delivery minimizes adverse effects associated with systemic drug administration and enhances the efficacy of neurotherapeutics. However, intranasal drug delivery is not without its limitations. One significant disadvantage is the restricted volume of drug that can be safely administered due to the relatively small size of the nasal cavity, the surface area is roughly 150 cm^2, and the total volume is about 20 mL. Furthermore, both pathological and physiological conditions affecting the nasal mucosa can hinder drug absorption. Liquid formulations may also face challenges related to microbiological and chemicals stability. The typical volume for liquid dosage forms is around 100 to 150 µL, while powder formulations are limited to approximately 10 to 25 mg. Consequently, it is crucial to consider the physical characteristics of active pharmaceutical ingredients (APIs) and their biopharmaceutical profiles, including permeation, mucoadhesiveness, and drug release, to evaluate their potential for absorption via the nasal route. Intranasal dosing remains a complex challenge and is generally not recommended for drug candidates with low bioavailability or those requiring higher therapeutic doses.[51] Moreover, the hydrophilicity of certain molecules can significantly reduce their absorption, permeation, and bioavailability through the nasal mucosa.

Intranasal Administration of Olanzapine

Intranasal administration of olanzapine has been shown to be more acceptable than oral administration, particularly in clinical settings. A phase one clinical trial demonstrated that the intranasal formulation of olanzapine resulted in rapid absorption and pharmacodynamic effect, effectively penetrating the blood-brain barrier.[52] In this study, intranasal olanzapine was prepared by dissolving the drug in 5% polypropylene glycol and 100% glyceryl guaiacol ether (GGA) at a pH of 5, adjusted using 5 M sodium hydroxide. In rat clinical trials investigating anorexia therapy, olanzapine was administered intranasally at a dose of 10 µL per 100 grams of body weight. The results indicated a significant impact on maintaining fat mass at an appropriate dose. Low-dose intranasal olanzapine effectively reduced anticipatory food-seeking behavior in the activity-based anorexia (ABA) model. Furthermore, adjusting the dosage of olanzapine for intranasal administration provides advantages in managing sedation. High doses can induce a dose-dependent sedative effect, leading to increased immobility, while lower doses administered systemically may suppress locomotor activity and enhance hunger and eating behaviors in the test subjects.[53]

Intranasal In Situ Gel of Paroxetine

An in situ gel is an innovative DDS that is originally prepared as a solution and transforms into a gel upon administration due to particular physiological factors like pH, temperature, and ion presence.[54] In its solution phase, this system offers several advantages, including ease of drug administration and precise dosing accuracy. Upon transitioning to the gel phase, the system adheres well to the epithelial layer, extending its retention time and thereby enhancing the bioavailability of the drug.[55] This delivery system is typically composed of biodegradable polymers such as poly(DL-lactide-co-glycolide), gellan gum, poly(DL-lactic acid), alginic acid, pectin, chitosan, polycaprolactone, and xyloglucan. In situ gels provide numerous benefits, including simplified drug administration, reduced dosing frequency, improved patient compliance, and greater comfort during use.[55] Furthermore, they offer sustained and prolonged drug release compared to conventional delivery systems, with the added advantage of being relatively simple to manufacture, which results in lower investment and production costs. Extensive research has demonstrated their potential in improving drug delivery and bioavailability. These gels are adaptable to various administration routes, including ophthalmic, nasal, rectal, vaginal, and injectable systems.[56] Nasal in situ gels, for example, overcome the challenges associated with administering drugs orally, such as low bioavailability, poor permeability, and degradation by digestive enzymes.[57] Several polymer systems are employed in the gelation process, including thermo-sensitive polymers and ion-responsive polymers. Thermo-responsive polymers undergo gelation through polymer desolvation triggered by temperature increases, leading to conformational changes in the polymer's side chains, dehydration of water molecules, and reorganization of micelles to form a gel. These polymers may include synthetic types like poloxamers, naturally occurring thermo-responsive polymers like xyloglucans, or synthetic derivatives of natural polymers such as chitosan.[58] In contrast, ion-responsive systems utilize polymers that react to the presence of ions. For example, gellan gum an anionic polysaccharide, undergoes cation-induced gelation in response to physiological ion concentrations. This process involves the formation of double-helix junction zones and helix interactions, forming a three-dimensional structure by means of cation complexation. Ion-responsive systems have employed hydroxypropyl methylcellulose (HPMC) to formulate a intranasal brain-targeted in situ gelling spray for paroxetine.[54] This gel formulation was designed to enhance both the bioavailability and targeted delivery of paroxetine to the brain. Upon interacting with simulated nasal fluid, the formulation exhibited immediate gelation and demonstrated adequate mucoadhesive strength, which is crucial for prolonged nasal retention. In vitro studies confirmed that the gel had sufficient drug loading capacity and provided controlled drug release. Nasal toxicity studies

indicated the formulation's safety for intranasal use. In vivo pharmacokinetics and pharmacodynamics studies conducted on rats revealed that intranasal administration of the paroxetine gel spray led to higher drug concentrations in the brain compared to oral administration. The gel also showed a faster onset of action and enhanced drug delivery to the brain, highlighting its potential as a promising alternative for targeted paroxetine delivery. The results suggest that the gel spray can effectively transport paroxetine to the brain via the olfactory region, enabling it to cross the BBB more efficiently than oral administration.

Intranasal In Situ Nanoemulgel Formulations for Quetiapine

Intranasal in situ nanoemulgel formulations for Quetiapine Fumarate offer a promising approach for targeting the CNS by partially bypassing the BBB. The intranasal route has demonstrated the potential to effectively deliver antipsychotic compounds directly to the brain through the olfactory region, enhancing therapeutic efficacy. Quetiapine Fumarate, known for its effectiveness in treating schizophrenia, typically exhibits limited bioavailability (9%) when administered orally.[59] Excessive dosing of Quetiapine Fumarate can lead to significant adverse effects,

Table 2. Pharmacokinetic profile and limitations of antipsychotic drugs

Drug	Pharmacokinetic Profile		Limitations	Reference
	Bioavailability (%)	Half Time (Hour)		
Clozapine	12 - 81	11 - 105	Clozapine falls into the BCS Class II category, which is defined by its poor solubility in water and high permeability. While it has good absorption properties, clozapine needs to be taken regularly in divided doses throughout the day, which can negatively impact patient compliance. To address this issue, a DDS can be developed to provide effective long-term controlled release therapy.	[21]
Risperidone	68	3 - 24	Risperidone is associated with significant adverse effects that may outweigh those experienced during manic episodes, necessitating a careful evaluation of the drug's side effects in relation to its therapeutic benefits in psychiatric treatment. Pharmacokinetic data indicate that, in adult psychiatric patients, risperidone reaches a maximum concentration (Cmax) within 1 hour and exhibits a half-life (T1/2) of 3.2 hours per 1 mg dose. The typical daily dosage ranges from 4 to 6 mg. The implementation of a DDS for risperidone, as demonstrated in studies utilizing microplates, may effectively mitigate cognitive deficits associated with dysbindin by reducing the adverse properties of the drug within the brain.	[13]
Quetiapine	9	6,88	Quetiapine fumarate exhibits relatively low bioavailability (approximately 9%) primarily due to first-pass metabolism, necessitating the utilization of DDS to enhance its therapeutic efficacy. Currently, quetiapine is only available in oral form, which presents limitations for patients with dementia or delirium who may have difficulty with oral administration. Furthermore, the absorption of oral quetiapine directly from the gastrointestinal epithelium into the bloodstream can result in undesirable hematological toxicity.	[22,23]
Haloperidol	40 - 70	12 - 36	Haloperidol is categorized as a BCS category class II drug, noted for its low solubility and high permeability. It exhibits low bioavailability (60-70%) due to extensive hepatic metabolism, resulting in only 1% of the given dose being eliminated unaltered.	[24]
Chlorpromazine	10 - 30	8 - 35	Chlorpromazine is categorized as a BCS Class IV drug, while its salt form, chlorpromazine HCl, falls under BCS Class III. Chlorpromazine has a plasma half-life that ranges between 6 and 24 hours and displays an oral bioavailability of 4-38%, largely because of considerable first-pass metabolism in the liver and a high protein binding rate of 90-99%.	[25]

thus necessitating careful management to maintain therapeutic drug concentrations. The DDS for Quetiapine Fumarate in this intranasal nanoemulgel formulation has proven to be highly effective in providing sustained therapeutic effects for psychotic patients. In vitro studies have shown that the nanoemulgel system ensures sustained drug release while maintaining safety by minimizing toxicity through dose adjustments, biodegradation of the nanoemulgel, and reducing the frequency of administration.[60,61] The development of this formulation involved a combination of polymers, including chitosan and Poloxamer 407, along with oil phase components such as Capmul MCM, surfactants (Tween 20), co-surfactants (Transcutol HP), and other excipients like solvents, emulsifiers, and preservatives. The use of a cationic nanoemulgel formulation, incorporating chitosan and poloxamer, has shown potential for crossing the BBB. Furthermore, the study of biodegradable Quetiapine Fumarate nanoemulgel revealed its capacity to avoid mucus clearance in the nasal reflux mechanism while facilitating drug permeation across the BBB and enhancing CNS delivery.[62]

Intranasal Polymeric Nanoparticles for Clozapine

The intranasal route presents a promising alternative for clozapine administration due to its non-invasive nature and potential to enhance patient compliance by allowing for self-administration. This route also offers the advantage of bypassing first-pass metabolism, resulting in a faster onset of action. In this formulation, nanoparticles are prepared using eudragit RS100 and eudragit RL100 copolymers, which differ in their quaternary ammonium salt content. The quaternary ammonium groups facilitate the penetration of water molecules into the polymer matrix, leading to the formation of a swollen matrix that can modulate and extend the drug release. The release rate can be further controlled by adjusting the ratio of the two copolymers. The ammonium groups contribute a positive charge plays a critical role in electrostatic interactions with the negatively charged mucin present in the nasal cavity. The nanoparticle suspension is lyophilized, as studies suggest that drugs encapsulated in nanoparticles in powder form exhibit superior diffusion and absorption through the nasal mucosa, resulting in better bioavailability compared to liquid formulations. Moreover, the powder form offers improved storage stability and allows for the administration of larger doses.[63] Absorption primarily occurs through the nasal epithelium, where the drug is released from the solid nanoparticles and diffuses into the bloodstream via the highly vascular nasal mucosa. To reach the brain, the drug must cross the BBB, which can be achieved by nanoparticles smaller than 300 nm. These nanoparticles can be absorbed through the olfactory nerve, bypassing the BBB and delivering the drug directly to the brain.[64] The clozapine-eudragit nanoparticle formulation demonstrated nearly complete release (99.85%) within eight hours. In the initial hour, the drug close to the particle surface is released quickly, whereas eudragit RS creates a thicker barrier that delays the penetration of the surrounding medium, resulting in a controlled release over the remaining time. In contrast, the presence of eudragit RL, which contains more quaternary ammonium groups, increases erosion and permeability of the polymer matrix, facilitating complete drug release within eight hours.[65]

Intranasal Nanocarrier for Haloperidol

Haloperidol administered via the intranasal route has been formulated with dendrimer-based delivery systems. Dendrimers are monodisperse macrostructures characterized by uniform, highly branched architectures, with a branching degree (DB) of 100%. Two principal methods of dendrimer synthesis are employed: the convergent and divergent approaches. The convergent method involves the covalent bonding of two or more monomers. Dendrimers offer a suitable DDS for targeting drugs to the brain, particularly for drugs with poor water solubility. Notably, higher concentrations of haloperidol were detected in the brain following intranasal administration.[66] An intranasal nanoemulsion formulation of haloperidol combined with selegiline demonstrated significantly enhanced therapeutic efficacy in a Parkinson's disease mouse model compared to oral administration. Nanoemulsions, with their increased retention time in the nasal mucosa, facilitate targeted drug delivery to the brain via the BBB. However, the safety and toxicity of nanoemulsions remain critical challenges, particularly for the long-term use of haloperidol in therapeutic settings.[67] One study involving human subjects analyzed the administration of intranasal aqueous antipsychotics.[68] The bioavailability of haloperidol following intranasal administration was 63.8%, compared to 48.6% after intramuscular (IM) administration. The maximum concentration (Cmax) after intranasal administration was higher than that achieved through IM administration, with a median Tmax of 15 minutes. However, the direct transport of the drug to the brain could not be assessed as cerebrospinal fluid (CSF) concentrations were not measured. Furthermore, limitations in the study arose from the acidic nature of the formulation, which caused nasal irritation in two of the four subjects.

Intranasal Administration of Risperidone

Intranasal administration of risperidone has been explored through the formulation of solid lipid nanoparticles (SLNs) containing risperidone (RSLN), offering advantages over intravenous (IV) administration. Risperidone, classified under the BCS as a class II drug, exhibits high permeability but low solubility. Studies have shown that the ratio of brain to blood radioactivity is significantly higher for RSLN (1.5-2 times) and risperidone solution (6-10 times) when administered intranasally compared to other methods.[14] Notably, the highest brain radioactivity was observed in the intranasal RSLN group. In another study comparing risperidone intranasal nanoemulsion formulations, it was found that brain radioactivity after the administration of a mucoadhesive nanoemulsion labeled with 99mTc was 3-4 times higher than that of a risperidone solution, and 1.5-3 times higher than a non-mucoadhesive emulsion. Similarly, mucoadhesive and non-mucoadhesive nanoemulsions containing 99mTc-labeled paliperidone produced

comparable results. The mucoadhesive emulsion group demonstrated the highest brain distribution and drug transfer potential (DTP), indicating superior transnasal penetration and brain radioactivity distribution of risperidone when formulated in cubosome gel. Pharmacokinetic data for risperidone in adult psychiatric patients show a peak plasma concentration (Cmax) reached within 1 hour and a half-life (T1/2) of 3.2 hours per 1 mg dose. The typical daily dose of risperidone ranges from 4-6 mg. The use of advanced DDS, such as microplate technology, has been shown to reduce the dysbindin properties of risperidone in the brain, thereby improving cognitive deficits associated with dysbindin dysfunction.[13]

Intranasal Administration of Chlorpromazine

Chlorpromazine (CPZ) is under the BCS class IV compound, while CPZ hydrochloride (CPZ HCl) falls under BCS class III. Although oral CPZ HCl demonstrates better solubility, it has low permeability, a half-life of 6-24 hours, and bioavailability ranging from 4-38%, necessitating continuous administration, which is often impractical. Intranasal administration presents a viable alternative, particularly with the use of mucoadhesive formulations designed to prevent drug drainage into the pharynx post-administration. The intranasal formulation of CPZ employs neuronanoemulsions (NNEs), which are modified with stearylamine cationic lipids and loaded into a *Eulophia herbacea* mucoadhesive hydrogel.[25] In this formulation, CPZ is dissolved in flaxseed oil, while the aqueous phase consists of D-alpha-Tocopherol polyethylene glycol 1000 succinate (TPGS) and Lipoid S100 dissolved in aquabides, with stearylamine added to create cationic NNEs. This intranasal system demonstrates a bioadhesive capacity of 18.622 mN, a drug release rate of 71.9%, and a permeation rate of 70.36% over 24 hours, indicating a sustained release profile. Histopathological testing on sheep nasal mucosa revealed no significant changes in cellular integrity, suggesting that the formulation is safe for use without causing damage to the nasal tissue.

Intranasal Administration of Lorazepam

Lorazepam is classified as a BCS class II drug that has extensive first-pass metabolism. Oral administration is limited by its low half-life of approximately 2 hours, while parenteral administration can result in precipitation and discomfort at the injection site. Therefore, formulating intranasal microemulsions presents a promising alternative for enhancing drug delivery.[69] Microemulsions are beneficial for improving the solubilization of lorazepam. However, the low viscosity of microemulsions may lead to rapid clearance through mucociliary movement, resulting in suboptimal in vivo absorption. To address this issue, an innovative formulation approach incorporating in situ gelling techniques is employed to increase viscosity and prolong retention time in the nasal cavity. The intranasal formulation of lorazepam combines gellan gum, PBC 34, oil, a surfactant mixture (Smix), Transcutol P, and carbopol 934 to create a stable preparation. In vitro studies indicate that this formulation achieves a drug release of 97.32% within 6 hours, highlighting its potential for effective intranasal administration and improved therapeutic outcomes.

Intranasal Transmucosal of Diazepam

Transmucosal intranasal administration presents a viable alternative to the rapid parenteral route, utilizing the nasal cavity to achieve effective absorption that can provide therapeutic effects nearly comparable to intravenous (IV) administration. This route also minimizes drug loss by circumventing first-pass metabolism. The physicochemical characteristics of diazepam are critical for achieving the desired therapeutic outcomes. An illustrative example of transmucosal intranasal diazepam is VALTOCO® (Neurelis), which demonstrates a Cmax and area under the curve (AUCt) variability that is 2 to 4 times lower than that of rectal gel formulations.[16] The formulation of diazepam for intranasal delivery consists of a non-aqueous solution combined with non-ionic surfactants and n-Dodecyl beta-D-maltoside, significantly enhancing diazepam's bioavailability to achieve an absolute bioavailability of 97%, with a Tmax of 1.5 hours. As a BCS class I drug, diazepam exhibits excellent permeability and high solubility, further supporting its efficacy in this delivery system. Moreover, the formulation of diazepam in an intranasal transmucosal dosage form combined with zolmitriptan in a nanoemulsion demonstrates rapid onset of action and increased drug concentration in the brain. This is attributed to enhanced permeation coefficients resulting from the incorporation of chitosan at a concentration of 0.3% in the zolmitriptan nano suspension.[70] Pharmacokinetic parameters for this zolmitriptan nanoemulsion formulation indicate higher AUC0-8 and shorter Tmax values in the brain compared to IV solutions or standard intranasal formulations. The intranasal delivery of SLNs containing naloxone has been investigated for reversing opioid overdose toxicity, leveraging its non-invasive nature. These SLNs, composed of glyceryl monostearate, Tween 80, and Pluronic F127, demonstrated superior brain disposition compared to naloxone solutions. In vivo pharmacokinetic studies revealed a Cmax of 163.95 ± 2.64 ng/mL, a Tmax of 240 ± 2.1 minutes, and AUC(0-t) and AUC(0-∞) values of 17.75 ± 1.08 ng·h/mL and 18.82 ± 2.51 ng·h/mL, respectively, indicating a strong capacity for sustained drug release and prolonged brain deposition time. Therefore, intranasal administration of this nanoparticle system represents a promising alternative to parenteral routes, offering ease of use in emergency situations.

Prospects for Development

The development of intranasal DDS for new antipsychotic medications holds considerable promise. This delivery method has demonstrated effectiveness in achieving systemic drug delivery, particularly for small molecular weight compounds, small proteins, and peptides. Utilizing the intranasal route addresses local issues, such as nasal or sinus disorders and presents a unique opportunity to target mental health conditions by facilitating direct delivery to the brain via the trigeminal nerve, which connects the nasal cavity to the CNS. The primary advantages of intranasal drug delivery include ease of administration, high safety

profiles, increased patient compliance, and rapid onset of therapeutic effects. Specifically, in the context of developing new antipsychotics, this route can facilitate the use of lower doses compared to traditional methods, such as oral or intravenous administration. This reduction in dosage does not only minimize the systemic exposure but also enhances the efficiency and effectiveness of treatment. However, the intranasal administration route still requires further refinement due to certain limitations. These include restrictions on the types of drugs that can be effectively absorbed, challenges related to penetration into the brain after nasal absorption, and the variability in individual nasal cavity conditions. To address these challenges, modifications to the drug formulation or the delivery compounds can be explored. For instance, employing slow-release formulations for various types of antipsychotic medications may ensure safer and more controlled therapeutic effects. The intranasal dose required for effective absorption into the brain's olfactory region can be as little as approximately 1% of the equivalent oral dose.[51] This highlights the potential for significant dose optimization. This study underscores the promising avenues for advancing antipsychotic drug development via the intranasal route, emphasizing the need for formulation and delivery compound innovations to achieve safe and effective therapeutic outcomes. In situ gels and nanoemulgels present exciting opportunities for improving bioavailability and targeting drug delivery to the brain. References from this study provide a foundational basis for further research aimed at developing efficient and innovative intranasal DDS, as well as exploring in situ gel and nanoemulgel formulations specifically tailored for antipsychotic drug delivery.

CONCLUSION

The formulation of antipsychotic drugs for intranasal delivery holds significant potential for enhancing pharmacokinetic profiles and improving the pharmacological efficacy of these medications, ultimately leading to increased patient compliance. By utilizing the intranasal route, antipsychotic formulations can leverage various advanced DDS, including liposomes, nanoparticles, nanogels, and other nanocarriers. These innovative approaches can facilitate more effective drug transport through the nasal cavity.

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