Non-Invasive Drug Delivery through Respiratory Routes

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With rapid and non-invasive characteristics, the respiratory route of administration has drawn significant attention compared with the limitations of conventional routes. Respiratory delivery can bypass the physiological barrier to achieve local and systemic disease treatment.

nasal drug delivery | pulmonary drug delivery | nanoparticles | COVID-19

1. Introduction

Non-invasive drug delivery generally refers to painless drug delivery methods that provide alternative routes for the delivery of therapeutics via oral, nasal, pulmonary, ocular, or rectal [1]. Oral administration has been the most widely used way to treat diseases. However, some barriers affect the delivery of drugs to target sites, such as the blood-brain barrier (BBB) and pulmonary barriers [2]. As a complex anatomical and physiological barrier, BBB selectively restricts the entry of substances into the brain; thus, effectively transporting drugs to the brain is a great challenge. Similarly, there are three significant barriers during pulmonary drug delivery. Mucociliary clearance is a mechanical barrier, mainly in the upper respiratory tract. Enzyme chemical barriers, such as peptidases and proteases, are responsible for protein and peptide degradation, and alveolar macrophage immunological barriers restrict the penetration of substances into the alveoli or further absorption into the systemic blood circulation [3].

Advances in anatomy and physiology provide advantageous features that make respiratory delivery an excellent route in drug delivery therapies. Novel drug formulations and devices are simultaneously developed to achieve more efficient drug delivery through the respiratory route. Nanoformulation is a particularly promising formulation for overcoming drug delivery barriers. Nanocarriers improve the efficiency of the drug and are promising viable formulations, making them important targets for research in preclinical and clinical practice [4]. In recent years, the study of respiratory delivery has increased markedly; however, theoretical reviews in respiratory delivery have rarely been summarized.

2. Non-Invasive Drug Delivery

A significant challenge in achieving therapeutic success is the efficient delivery of drugs. Due to pain, infection risk, high cost, and low patient compliance, parenteral injections are not the preferred method of administration. Furthermore, concerns about needle disposal hinder parenteral administration [5]. There are significant advantages

to non-invasive drug delivery over injection, including a decreased risk of needle sticks, a low risk of infection, and an increased level of patient compliance with treatment [6][7].

However, molecular size, hydrophilicity, low permeability, chemical or enzymatic instability, and low permeability of therapeutics pose formidable obstacles to developing non-invasive drug delivery systems [8]. Many small molecules and almost all biologics do not possess the ideal physicochemical properties for good absorption from mucosal surfaces or the skin. Various formulation strategies have been proposed to overcome these problems. Innovative nanoformulations with controllable particle sizes and surface modifications have been developed to improve target selectivity, systems half-life, and bioavailability of drugs. Nanotechnology plays a vital role in developing non-invasive drug delivery systems to improve drug clinical outcomes [9].

Non-invasive drug delivery mainly includes oral, nasal, pulmonary, rectal, and transdermal routes. Oral administration is the most used drug delivery strategy due to its convenience. Still, it faces the absorption and degradation of drugs in the gastrointestinal tract due to the acidic environment and microorganisms [10]. Transdermal administration can eliminate first-pass metabolism and maintain sustained drug release, thereby reducing dosing frequency. The stratum corneum, the outermost part of the skin that contains dead keratinocytes and lipids [11], acts as a drug barrier because it limits the absorption of large molecular weight and hydrophilic molecules. Intestinal irritation and poor patient compliance are some of the problems associated with rectal administration.

Respiratory delivery (e.g., nasal and pulmonary drug delivery) has unique advantages compared to other non-invasive drug delivery routes. Nasal drug delivery can bypass hepatic first-pass metabolism, is effective, and patient-friendly regarding self-medication. Moreover, it allows drugs to bypass the BBB and be directly delivered to brain tissue or cerebrospinal fluid via olfactory neurons [12]. In the lungs, the size of the surface area (about 80–140 m^2), thin alveolar epithelium (0.1–0.5 mm), and ample blood supply contribute to rapid and high drug absorption [13]. All these advantages make nasal and pulmonary routes suitable for local and systemic drug delivery.

3. Therapy for Central Nervous System Disorders

Despite an increase in the prevalence of neurological and psychiatric disorders such as Parkinson's disease, Alzheimer's disease, brain tumors, and depression at the global level, drug molecules are still not effectively delivered to the central nervous system (CNS) [14]. It is possible to directly administer drugs into parenchyma or cerebrospinal fluid via intraparenchymal or intrathecal infusions, respectively, but these routes of administration are invasive and unsuitable for chronic treatment [2]. Furthermore, delivering diagnostic agents or therapeutic drugs with non-targeted may also severely damage neurons and glial cells. Therefore, there is an urgent need for new avenues to deliver therapeutic drugs for neurological diseases [15]. More and more researchers have paid attention to treating CNS diseases by nasal drug delivery. However, the precise drug delivery mechanism of the nasal cavity to the CNS is not fully understood. Several reports demonstrate that nose-to-brain drug delivery is mainly mediated by olfactory and trigeminal nerve pathways located at the roof of the nasal cavity [16]. The functional pathway through which drugs pass into the CNS from structures deep in the nose innervated by the cranial nerve is called

“nose-to-brain” transport [17]. In addition, the treatments of Parkinson's disease [18], anxiety [19], and migraines [20] have reported promising results for delivering CNS therapeutics through different inhaler techniques.

3.1. Bypass the Blood-Brain Barrier

The CNS is protected by a highly regulated complex structure called the BBB [21]. The BBB is composed of the capillary endothelium, pericytes, and the astrocyte foot processes [22]. Specifically designed endothelial cells of the BBB do not have fenestrations, and they possess extensive tight junctions that prevent hydrophilic and polar compounds as well as molecules with high molecular weight from entering the CNS from the bloodstream [23]. Astrocytes, which surround cerebral capillaries, also prevent passive diffusion through the cell membrane to minimize the uptake of extracellular substances [24]. Although the structure of the BBB is vital to keep harmful substances out, it is also a significant obstacle to the pharmacological treatment of CNS and mental diseases [25].

The nose-to-brain route provides a practical, non-invasive way to bypass the BBB and delivers therapeutic agents to the brain. A variety of drug delivery systems, such as nanogels [26], nanoparticles [27], and solid lipid nanoparticles [28], have been studied to deliver drugs to the CNS through intravenous administration, which can cross BBB [29]. However, intravenous administration is not suitable for major depressive disorder, Parkinson's disease, and other diseases that need daily administration. Nasal drug delivery has the following advantages: (1) about 98% of small molecules and almost all large proteins and genes cannot pass through the BBB [30], but intranasal administration can bypass the BBB and deliver drugs directly to the brain; (2) the nasal cavity has a lot of strengths such as high surface area, high permeability, high vascularization, and the nose-to-brain pathway; and (3) the nose-to-brain route avoids first-pass metabolism in the gastrointestinal tract and liver, thereby avoiding most drug inactivation.

Many pharmaceutical preparations have been used to improve penetration through the physiological barrier of the nasal cavity. As a drug preparation method, nanotechnology combined with the nasal drug delivery route is expected to provide an effective drug delivery system [31][32]. Currently, by loading a drug that is poorly distributed in the brain into the nanocarrier system, good interactions with the nasal mucosa can be achieved to prolong the residence time and ultimately produce higher drug concentration in the brain parenchyma. Such a nanocarrier can be modified with targeting ligands to preferentially bind to receptors or transporters expressed at the BBB to enhance brain selectivity and permeability [33]. In addition, by crossing the barrier through the process of cell transcytosis, this system can be further used for effective drug delivery [34]. Among them, nanoparticles are one of the most researched drug delivery systems, ranking as the third most frequent keyword. Since nanoparticles can protect encapsulated drugs from degradation, chemicals, and P-gp efflux, proteins are extracellularly delivered, thus improving the nose-to-brain drug delivery [7].

3.2. Treatment of Parkinson's Disease

Parkinson's disease (PD), a neurodegenerative disorder, affects approximately 1–2% of the population over the age of 65 [35]. It is characterized by the loss of dopaminergic receptors in the nigrostriatal and mesolimbic systems

in the brain [36]. As α-synuclein accumulates and dopamine levels are depleted, it develops into the dysfunction of daily tasks. Symptoms of the disease include movement disorders, tremors, and difficulty walking due to a loss of balance and coordination. Treatment for PD involves increasing dopamine levels in the brain or reducing the concentration of dopamine inhibitors. Drugs such as levodopa and carbidopa are converted into dopamine when delivered to the brain.

Combining nanotherapeutics with nasal drug delivery promises to bypass the BBB for targeted therapy to the brain. This approach has been effective in treating a variety of neurodegenerative diseases in previous studies. Monoamine oxidase B (MAO-B) inhibitors are an established therapy for PD and work in part by blocking the MAO-catalyzed metabolism of dopamine in the brain [37]. Selegiline and rasagiline are two MAO-B inhibitors commonly used in the clinic. Sridhar et al. synthesized selegiline-loaded chitosan nanoparticles by ionic gelation [38]. Compared to oral administration, selegiline concentrations in the brain and plasma were 20- and 12-fold higher, respectively, after intranasal administration, greatly reducing the dose and the side effects of selegiline. Furthermore, C_{max} in the brain after intranasal nanoparticle administration was significantly higher than that after intranasal thermosensitive gel and plain solution administration. This suggested that chitosan was a biodegradable permeation enhancer that increases the nasal mucosal penetration of selegiline nanoparticles. Rasagiline has advantages over selegiline because its metabolites do not include potentially toxic amphetamines [39]. Mittal et al. used the ionic gelation technique to prepare rasagiline-loaded chitosan glutamate nanoparticles (RAS-loaded CG-NPs) [40]. After intranasal and intravenous administration, the biodistribution of RAS formulations in mice brains and blood was performed using the HPLC. Intracerebral drug concentrations were significantly always elevated in nasally administered CG-NPs. The results showed that the brain bioavailability was significantly improved following intranasal administration of RAS-loaded CG-NPs, which may represent an achievement of direct nose-to-brain targeting in PD treatment.

3.3. Treatment of Alzheimer's Disease

Alzheimer's disease (AD) is a degenerative brain disease characterized by memory loss and associated cognitive impairments, including poor judgment and decision-making, language impairment, loss of temper control, and emotional disturbances [41]. AD initially occurs with the loss or destruction of neurons involved in the brain's cognitive function. Neurons in other brain parts are gradually destroyed, making it difficult to perform essential body functions, such as walking and swallowing. Eventually, the brain will lose its function completely. Although genetics, age, and environmental factors influence this disease, the etiology of AD is not fully understood. Drugs that FDA has approved for AD treatment act as cholinesterase inhibitors and include donepezil, rivastigmine, galantamine, and tacrine [42]. Currently, most approved drugs are orally administered in tablet form. Still, they suffer from poor absorption from the digestive tract, difficulty reaching the brain, and a lack of effectiveness at recommended doses. There are several ways to deliver specific drugs to the brain, one of which is the nasal route [43].

Tacrine hydrochloride (THA) is an FDA-approved drug for AD treatment with a short half-life. It is a reversible acetylcholinesterase inhibitor that enhances the deficiency of brain cholinergic neurotransmission and prevents the degradation of neurotransmitters by increasing the level of acetylcholine in the brain [44]. Jogani et al. investigated

a microemulsion delivery system to enhance nasal-brain transport of THA. Additionally, a mucoadhesive agent (Carbopol 934P) was added to prolong the contact time of the formulation in the nasal cavity and enhance THA absorption in the brain, reducing systemic distribution and side effects. The prepared formulation exhibited the mean globule size < 27 nm and zeta potential <−20 mV, and the addition of a mucoadhesive agent further negatively contributed to the system. The biodistribution of the THA solution and its formulation after intravenous and intranasal administration was assessed using 99mTc as a marker. Results showed that nasal drug delivery enhanced brain selectivity and accumulation of THA over intravenous administration [45]. In another study, Qian et al. conducted a pharmacokinetic and pharmacodynamic study of HLS-3, a tacrine dimer with high anti-acetylcholinesterase activity, for the treatment of AD. The results showed that intranasal administration of HLS-3 had similar central effects and fewer peripheral adverse effects at a much lower dose than oral tacrine, suggesting that intranasal administration of HLS-3 might be a potential therapy for AD treatment [46].

3.4. Treatment of Depression

Depression is a common mental illness that affects a person's thoughts, behaviors, feelings, and circadian rhythms. Pathological causes of depression include chemical imbalances in the brain, decreased energy metabolism, and altered hormone levels [47]. According to the serotonin hypothesis, depression results from dysfunctional serotonergic activity leading to reducing serotonin levels in the brain. Selective serotonin reuptake inhibitors (SSRIs) such as paroxetine, vilazodone, and fluvoxamine are first-line medications for patients with depression [48]. However, the approved oral antidepressants have reduced bioavailability due to first-pass metabolism. The time it takes for a drug to reach its saturation point is often prolonged, resulting in delayed and reduced efficacy. In addition, due to low bioavailability, higher doses need to be ingested, leading to an increased incidence of side effects [49]. Furthermore, the therapeutic effect is also limited due to the presence of the BBB.

Nasal drug delivery is an attractive therapeutic strategy and has been used to treat depression. Ketamine, an intranasal antidepressant, has been studied in multiple clinical trials. As an antidepressant, there are several hypotheses for the mechanism of action of ketamine, including synaptic or GluN2B-selective extra-synaptic N-methyl-D-aspartate receptor (NMDAR) inhibition, inhibition of NMDARs localized on GABAergic interneurons, inhibition of NMDAR-dependent burst firing of lateral habenula neurons, and the role of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor activation. These preclinically proven ketamine mechanisms of action are not mutually exclusive and may act synergistically to exert the drug's antidepressant effects [50][51]. In March 2019, FDA approved intranasal esketamine (the S (+) enantiomer of ketamine) for the treatment of treatment-resistant depression [52]. It was the first antidepressant in the form of a nasal spray, and the therapeutic effects of intranasal esketamine were observed after 4 h from application [53]. The rapid onset of action is a considerable advantage of esketamine compared with conventional antidepressants.

Intranasal administration is one of the easier options for delivering molecules to the brain region. Antidepressants like venlafaxine increase synaptic neurotransmitter levels that are diminished due to depression [54]. Due to its short elimination half-life and inherent hydrophilicity, it requires frequent administration to maintain its therapeutic concentration and its penetration into the brain needs to be improved. Using venlafaxine-loaded alginate nanogels,

Hague et al. showed increased drug permeation through the isolated porcine nasal mucosa. This was attributed to the positively charged amino groups on alginate and the negatively charged sialic acid on the cell membranes. In vivo studies of rats showed that the drug had a higher brain to blood ratio after intranasal administration, revealing that the drug bypassed the BBB and was transported directly to the brain via the nose. Intranasal administration produced a significantly higher brain concentration of the drug (743 ng/mL; t_{max} = 60 min) than intravenous administration (383 ng/mL; t_{max} = 30 min). In another study, Haque et al. designed antidepressant nanoparticles containing venlafaxine-loaded alginate chitosan (VLF AG-NPs) for the nose-to-brain treatment of depression. The antidepressant activity of VLF AG-NPs was evaluated by the forced swim test. It showed a significant improvement in behavioral analysis parameters, including swimming, climbing, and immobility, which was observed after intranasal administration of VLF AG-NPs [55].

3.5. Treatment of Glioblastoma

In adults, malignant brain tumors are devastating diseases with high morbidity and mortality. Among children, they are the second leading cause of cancer-related death [56]. Currently, there are no effective therapies, mainly due to high tumor heterogeneity, chemoresistance, and difficulties imposed by BBB. It is urgently needed to develop new treatment options for glioblastoma, which currently undergoes surgery, radiation therapy, and chemotherapy concurrently [57].

Various types of biodegradable and biocompatible polymers have been widely studied, which can prevent toxic and side effects and simultaneously achieve the goal of sustained and controlled release. Chitosan, the 10th highest frequency keyword in the keyword frequency analysis, is the only polycationic polysaccharide extracted from biological sources and is widely used in nano drug delivery systems. Chitosan can increase the residence time of drugs in the olfactory area, reduce mucus clearance, and open the tight junctions between epithelial cells, thereby enhancing the penetration of drugs through mucosal membranes. Galectin-1 (Gal-1), a natural galactose-binding lectin, is overexpressed in glioblastoma multiforme (GBM). To inhibit Gal-1 in GBM, Woensel et al. prepared a highly concentrated suspension of small interfering RNA (siRNA)-loaded chitosan nanoparticles to deliver siRNA to the CNS via nasal drug delivery. The chitosan nanoparticles did not affect the effectiveness of siRNA molecules and rapidly delivered siRNA to murine and human GBM cells, thereby reducing tumor cell migration. Following intranasal administration in healthy mice, it was observed to rapidly spread into the nasal mucosa and further into the olfactory bulbus and the hindbrain [58]. Cetuximab (CET) is an anti-epidermal growth factor receptor (EGFR) monoclonal antibody developed for brain tumor targeting because CET specifically binds with high affinity to EGFR. EGFR is simultaneously overexpressed in most brain tumors but not expressed in normal tissues [59]. Ferreira et al. [60] prepared poly (lactic-co-glycolic acid) (PLGA) and oligomeric chitosan (OCS)-based mucoadhesive nanoparticles to co-deliver α-cyano-4-hydroxycinnamic acid (CHC) and CTX into the brain by nasal drug delivery. Stable nano sized particles (213–875 nm) with high positive surface charge (+33.2 to +58.9 mV) and entrapment efficiency (75.69 to 93.23%) were produced by emulsification/evaporation technique and further combined with the CTX. The CHC-loaded NPs exhibited high cytotoxicity against different glioma cell lines (U251 and SW1088). Analysis of chicken chorioallantoic membranes demonstrated the anti-angiogenic activity of CHC-

loaded NPs. In conclusion, this nano drug delivery system can potentially be a new therapeutic alternative for glioblastoma therapy.

3.6. Treatment of Epilepsy

Epilepsy is a neurological disorder characterized by recurrent seizures that affect people of all ages, genders, races, and geographic locations [61]. Nearly 50 million people are infected worldwide, with a prevalence rate of 5–10 per 1000 people and more than 0.5% of the global disease burden [62].

Antiepileptic drugs, including phenobarbital, phenytoin, felbamate, topiramate, vigabatrin, and gabapentin, are usually taken orally in the form of tablets, capsules, solutions, and suspensions [63]. Commercial antiepileptic doses are ineffective for about one-third of epileptic patients [64]. Drug resistance may result from a drug not reaching its target area or from a lower concentration of the drug in the brain. Researchers have used nanoformulations to deliver antiepileptic drugs to receptor sites via intravenous, oral, nasal, and transdermal routes [65]. Jain et al. formulated amiloride-loaded mucoadhesive nanoemulsions for nose-brain administration. The mucoadhesive nanoemulsions had no toxicity to the sheep nasal mucosa and were determined to be safe after intranasal administration of antiepileptic drugs. The developed formulation also needs to be pharmacokinetically and pharmacodynamically evaluated [66]. Gonçalves et al. studied a thermoreversible gel loaded with levetiracetam and administered it to mice in an aerosolized form. Pluronic F-127 and Carbopol® in the formulation helped form a thermosensitive gel with adequate structural characteristics so that it can act as a liquid aerosol gel in the nasal mucosa. The absolute intranasal bioavailability was 107.44%, indicating a high proportion of the drug systemically absorbed. Histopathological examination of lung tissue after repeated administration by intranasal route showed that the preparation caused no toxicity or structural damage. Although further exploration is required, these nonclinical studies offer new hope for epilepsy treatment [67].

4. Therapy for Tracheal/Bronchial and Lung Diseases

Tracheal or bronchial and lung diseases are important causes of death globally, including cough, common cold, and more severe diseases like pulmonary hypertension, lung cancer, and COPD [68]. Due to the limitations of conventional administration routes and existing treatment methods, the pulmonary administration route has attracted widespread attention. It has become an important research area for effective therapeutic interventions for respiratory diseases [69]. Due to the large surface area of the respiratory endothelium, the elimination of the first-pass metabolism, and small dosages, pulmonary drug delivery has shown enormous potential and has attracted significant attention in pulmonary disease treatment [70]. Compared to oral or parenteral routes, even if the dose is reduced, it can take effect quickly and help to minimize adverse reactions. Pulmonary drug delivery can also deliver high concentration biologics to the lungs, and can be effectively used for respiratory infections, lung cancer, and asthma [71]. Some of the FDA-approved inhalation products have been summarized in **Table 1**.

Table 1. Some of the FDA-approved inhalation products [72].

Brand Name	Drug	Indication	Manufacturer	Approval Year
Qvar Redihaler®	Beclomethasone dipropionate	Asthma	Norton Waterford	2017
Bevespi Aerosphere®	Glycopyrronium, Formoterol fumarate	COPD	Astrazeneca Pharms	2016
Asmanex® HFA	Mometasone furoate	Asthma	Merck Sharp Dohme	2014
Duaklir Pressair®	Aclidinium bromide, Formoterol fumarate	COPD	Circassia	2019
Trelegy Ellipta®	Fluticasone furoate, Umeclidinium, Vilanterol	Asthma, COPD	Glaxosmithkline	2017
Airduo Respiclick®	Fluticasone propionate, Salmeterol xinafoate	Asthma	Teva Pharm	2017
Utibron®	Glycopyrrolate, Indacaterol maleate	COPD	Sunovion Pharms Inc	2015
Stiolto Respimat®	Tiotropium bromide, Olodaterol	COPD	Boehringer Ingelheim	2015
Spiriva Respimat®	Tiotropium	COPD	Boehringer Ingelheim	2014
Striverdi Respimat®	Olodaterol hydrochloride	COPD	Boehringer Ingelheim	2014

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5. Therapy for Systemic Diseases

The nasal mucosa has rapid blood flow, a highly vascularized epithelial layer, and a significant absorption area. These characteristics offer many advantages for introducing drugs into systemic circulation. The nasal route has been widely studied for the systemic administration of therapeutic agents and has been clinically used, for example with hormones and vaccines. Moreover, research on the lungs as an entrance for systemic drug delivery has been conducted for decades. Due to its large surface area of about 70–100 m^2, permeable epithelium, and high perfusion properties, the respiratory mucosa is one of the best targets for biopharmaceutical uptake [73].

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