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NOVEL INTRANASAL NANOCARRIERS FOR DIRECT BRAIN DELIVERY AND CNS DISEASE MANAGEMENT

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ABSTRACT

The blood-brain barrier (BBB) is a major obstacle to the treatment of central nervous system (CNS) illnesses because it limits the transport of most therapeutic medicines to the brain. Intranasal medication administration is a potential non-invasive approach that bypasses the BBB through olfactory and trigeminal pathways, allowing direct transfer of medicines into the brain. Recent breakthroughs in nanotechnology led to the creation of innovative intranasal nanocarriers which can increase nasal residence duration, enhance bioavailability, provide controlled drug release and targeted delivery of drugs to the brain and increase the stability of drugs. Several types of nanocarrier systems such as liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, polymeric micelles, dendrimers, mesoporous silica nanoparticles, nanogels, exosomes and hybrid nanocarriers have shown great promise for the effective delivery of drugs from the nose to the brain. These delivery platforms showed promising therapeutic effects in the treatment of Alzheimer's disease, Parkinson's disease, epilepsy, glioblastoma, stroke, multiple sclerosis, depression and other neurological diseases. Despite great advances in preclinical research, various hurdles such as mucociliary clearance, enzymatic degradation, formulation stability, nanoparticle toxicity, large-scale production, regulatory approval, and clinical translation still remain to hinder their extensive clinical application. Emerging techniques such surface-functionalized, ligand-targeted, stimuli-responsive and mucoadhesive nanocarriers are predicted to significantly improve the therapeutic effectiveness and patient compliance. This review summarises the anatomical basis and mechanisms of nose-to-brain transport, recent advances in intranasal nanocarriers, their uses in CNS disease management, current challenges and future perspectives. Intranasal nanomedicine holds promise as an effective platform for targeted brain drug delivery.

Keywords: nose to brain, nanocarriers, nanogels, formulation strategies, blood–brain barrier

1. Introduction

The nose-to-brain drug delivery system (DDS) is a novel concept in pharmaceutical research that offers a non-invasive and direct route for the transport of therapeutic agents from the nasal cavity to the brain, addressing many of the challenges associated with conventional drug delivery methods [1]. The intranasal route has been considered as an attractive alternative to oral and parenteral routes for systemic and central delivery of pharmacologically active compounds because it bypasses hepatic first-pass metabolism, is painless and convenient and may provide direct access to the central nervous system (CNS) bypassing the blood–brain barrier (BBB) [2–4]. The nasal cavity is uniquely connected anatomically to the brain, particularly through the olfactory and trigeminal nerves, which offer specialised routes that allow direct delivery of medicines into the CNS [5].

However, successful intranasal medication administration remains a challenge as drug absorption is dependent on the physicochemical qualities of the formulation and the complicated architecture and physiology of the nose cavity. Depending on the chemical features, formulation and nasal residence duration of a medication, the percentage of the supplied dose arriving to the systemic circulation or brain may vary widely [6,7]. Rapid mucociliary clearance, enzymatic degradation, restricted dosage volume and the restrictive epithelial barrier greatly diminish drug absorption and therapeutic effectiveness [5,8]. Hence, the development of sophisticated methods for drug administration which may enhance drug retention, penetration and brain targeting has become a vital topic of pharmaceutical research .

One of the most promising ways for improving intranasal brain delivery is the development of nanocarrier-based systems for medication administration. Nanoparticles provide a diverse platform for bypassing the physiological barriers of the nasal mucosa, while increasing medication stability, solubility, controlled release and bioavailability [9]. The physicochemical features such as particle size, surface charge and surface chemistry may be accurately designed to improve mucoadhesion, increase residence duration in the nose, promote epithelial transport and boost cellular absorption [10,11]. Additionally, functionalisation with polymers such as polyethylene glycol (PEG), chitosan, thiolated polymers or targeting ligands improves drug penetration through paracellular and transcellular routes and also facilitates receptor-mediated transport across the nasal epithelium [12,13]. Moreover, numerous nanocarrier systems employ olfactory and trigeminal neural routes for direct nose-to-brain delivery that decrease systemic exposure,

prevent hepatic first-pass metabolism, and provide quick therapeutic effect for CNS active medicines [14].

Recent advances in nanotech have also paved the way for the development of multifunctional nanocarriers with stimuli-responsive components such as pH-, redox-, enzyme- and temperature-sensitive materials that can facilitate site-specific and controlled drug release in the nasal cavity or target brain tissues [15,16]. These new nanosystems have shown great potential for delivering small molecules, peptides, proteins, nucleic acids, vaccines and biologics, while maintaining medication stability and enhancing therapeutic effects.

However, there are still several difficulties that limit successful clinical translation of intranasal nanomedicine. The small volume that can be administered through the nose, rapid mucociliary clearance, enzymatic degradation in the nasal cavity, patient variability in anatomy, and the presence of protective barriers due to the mucus layer, nasal epithelium, and lamina propria can greatly reduce the efficiency of drug transport [5,17–19]. Furthermore, long-term safety, such as local irritation, ciliotoxicity, inflammation, immunogenicity and inadvertent systemic exposure, must be carefully investigated before broad clinical application [2,20-23].

This review discusses anatomical basis and transport mechanisms involved in nose-to-brain drug delivery, recent advances in novel intranasal nanocarrier systems, their use in the treatment of CNS disorders, current formulation and translational challenges and future perspectives for clinical development. To summarise, intranasal nanomedicine is a very promising platform for safe, effective and targeted medication delivery to the brain for the treatment of many CNS illnesses.

2. Novel Intranasal Nanocarriers for Direct Brain Delivery

Intranasal medication administration has become a viable non-invasive approach for the direct delivery of therapeutic drugs to the brain circumventing the blood–brain barrier (BBB), one of the key challenges for the efficient treatment of central nervous system (CNS) diseases. Rapid mucociliary clearance, enzymatic degradation, low drug solubility and short nasal residence duration are challenges faced by conventional intranasal formulations, resulting in limited therapeutic effectiveness. Nanotechnology has improved intranasal drug delivery through increased drug stability, protection of therapeutic agents from degradation, improved mucoadhesion, controlled drug release and targeted brain transport via the olfactory and trigeminal pathways [24-28].

Nanocarriers are nanosized delivery devices, typically 10–500 nm in size, engineered to increase the transport of medications across biological barriers and reduce systemic toxicity.

Their tiny particle size, broad surface area and adjustable surface chemistry enable effective contact with the nasal epithelium and improve cellular absorption. Surface functionalisation with polyethylene glycol (PEG), chitosan, peptides, antibodies and receptor specific ligands further enhances mucoadhesion, prolongs the nasal residence time and improves receptor-mediated transport into the brain, thereby increasing drug bioavailability and therapeutic efficacy [26].

Various classes of novel nanocarriers have been studied for direct nose-to-brain drug delivery such as liposomes, polymeric nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), polymeric micelles, dendrimers, nanoemulsions, nanosuspensions, mesoporous silica nanoparticles (MSNs), nanogels, exosomes and hybrid nanocarriers. The physicochemical properties of the nanocarrier are distinct and impact drug loading, release kinetics, stability, as well as brain-targeting efficiency. Lipid based nanocarriers possess great biocompatibility and high encapsulation effectiveness whilst polymeric nanoparticles allow regulated drug release and increased durability. Emerging nanocarriers such as nanogels and exosomes provide prolonged release and increased penetration across biological barriers, achieving additional improvements in brain delivery [24–26].

Recent developments in nanotechnology have led to the creation of multifunctional, ligand-targeted, mucoadhesive and stimuli-responsive nanocarriers to overcome physiological hurdles associated with the nose-to-brain medication transport. Such sophisticated systems have demonstrated tremendous promise in enhancing therapy results in Alzheimer's disease, Parkinson's disease, epilepsy, glioblastoma, stroke, depression and multiple sclerosis. Preclinical data are promising but hurdles remain for large-scale production, long-term safety, regulatory approval and clinical translation. However, the new intranasal nanocarriers offer one of the most promising strategies for a safe, efficient and targeted delivery of drugs to the CNS [1–24–31].

3. Blood Brain Barrier

Blood-brain barrier is a barrier that prevents the entry of poisons and some other chemicals in the brain through blood and protects the neuronal tissues of the brain [32]. It is composed of two cell junctions, the paracellular tight junction and the intercellular adherents junction [33]. Paracellular tight junctions are critical for determining the permeability of the blood–brain barrier (BBB). In the adult, the BBB exists as a complicated cellular network. Its principal components are a highly specialised basal lamina, brain endothelial cells, many pericytes that are embedded in the basal lamina and astrocytic end-feet [32]. BBB provides

for the regulation of transport of ions and molecules by the vessels. CNS homeostasis is essential for neuronal function and preservation of brain tissues from toxins. To understand how our brain operates in a sick body it is vital to realise that all these cells interact with brain barrier features [34]. The blood-brain barrier is very important in the metabolism and function of the brain as it controls the inflow and outflow of biological molecules. The BBB is involved in the homeostasis of the brain [35]. The structure is incredibly complicated and dynamic. It is composed of endothelial cells, pericytes and astrocytes. It has two halves. One is cellular and the other non-cellular. The non-cellular component is less important than the cellular component [36].

The BBB is the main barrier for drug absorption through two different mechanisms: active and passive (Figure 1) [37,38]. Diffusion or passive diffusion is the transfer through non-energetic channels used by hydrophilic and lipophilic molecules, respectively, transcellular and paracellular diffusion [39]. Paracellular diffusion: Local inflammation can destroy the BBB thereby weakening tight junctions and allowing the passage of polar molecules across endothelial cells [40]. Transcellular diffusion: The BBB permits passive passage of some small lipophilic low molecular weight substances (400-600 Da) [44]. Conversely, active transport refers to the transfer of substances via energy-dependent mechanisms that allow the transit of biological gradients such as concentration or electrochemical gradients [41,42]. Carrier-mediated transport: Specific protein carriers transfer small molecules such as ions, amino acids, and glucose from the blood arteries to the extracellular environment of the brain [43].

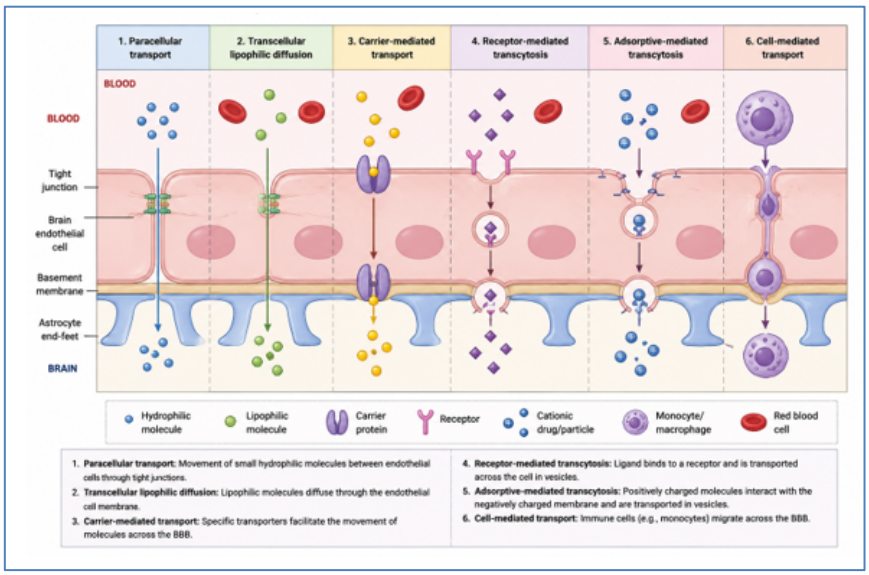

Figure 1. Transport routes across blood-brain barrier.

In instance, the glucose transporter 1 (GLUT-1) is important for glucose transport [45,46]. The L system is specific for the delivery of amino acids, such as valine, histidine, methionine, tyrosine, and phenylalanine, to the brain [47]. Neutral amino acids such as alanine, cysteine and serine can then use the alanine/serine/cysteine transporter (ASC). Receptor-mediated transcytosis (RMT) is the process in which specific receptors located on the inner aspect of the endothelial cells in the brain parenchyma allow the passage of big and hydrophilic molecules such as hormones and proteins. The ligand, after binding initially to its specific receptor, is easily absorbed [48]. Adsorption-mediated transcytosis (AMT): the most prevalent mechanism utilised by peptides or proteins with a positive charge, requiring the endocytosis of the vesicles of the charged molecule.

3.1 Blood-Cerebrospinal Fluid Barrier (BCSFB)

A further significant physiologic barrier is the blood-cerebrospinal fluid barrier (BCSFB), which controls the movement of chemicals from blood to the central nervous system (CNS). The endothelial cells that constitute the Blood-Brain Barrier (BBB) are found in the cerebral capillaries while the BCSFB is mostly situated in the choroid plexus in the brain ventricles. It is formed by specialised epithelial cells joined by tight junctions, separating circulating blood from cerebrospinal fluid (CSF). The major role of the BCSFB is to regulate the composition of the CSF, to control the movement of nutrients and ions, to eliminate the metabolic waste products and to protect the CNS from dangerous chemicals and infections. The BCSFB is selectively permeable, enabling only certain molecules to cross by passive diffusion, carrier-mediated transport, receptor-mediated endocytosis or active transport processes . Small lipophilic molecules are freely diffused over the barrier while the transport of hydrophilic chemicals, peptides, proteins and big therapeutic molecules is quite limited. Furthermore, medication entry into the CSF is limited by metabolic enzymes and efflux transporters, such P-glycoprotein and multidrug resistance related proteins, which reduce the efficacy of many traditional CNS therapeutics[49].

Intranasal medication delivery route can be an alternate technique to circumvent the limitations of BCSFB. The nasal route of drug administration can circumvent both the BBB and the BCSFB via the olfactory and trigeminal neural pathways, providing a direct access to the cerebrospinal fluid and brain tissues. Novel nanocarrier systems such as liposomes, polymeric nanoparticles, solid lipid nanoparticles, nano-emulsions and nanostructured lipid carriers enhance this transport by protecting drugs from enzymatic degradation, increasing the residence time in the nasal cavity, improving permeation through the epithelium and enabling targeted delivery to the CNS. Hence, BCSFB is a vital aspect in designing

intranasal nanocarrier-based drug delivery networks for the treatment of neurological diseases.

3.2 Anatomy of Nasal

The architectural and physiological properties of the nose cavity are intimately tied to medication absorption and brain targeting. These characteristics highlight the critical need for a detailed knowledge of nasal anatomy in the effective design of intranasal systems for drug delivery. The overall surface area of the human nasal cavity is roughly 150–200 cm^2, mostly due to the existence of the superior, middle and inferior turbinates that enhance the contact area accessible for drug deposition and absorption. The nasal cavity is the space between the nostrils (nares) and the nasopharynx, and is split into two symmetrical chambers by the nasal septum. The mucosa is highly vascularised, allowing for quick systemic absorption and access to the neurological connections connecting the nose and brain.

Anatomically the nasal cavity is separated into four functional parts known as the nasal vestibule, respiratory region, olfactory region and nasopharyngeal region. The nasal vestibule is the front region of the nasal cavity, coated with stratified squamous epithelium and coarse hairs (vibrissae). These hairs are the first line of defence, screening big airborne particles. This area, although contributing little to medication absorption, does affect initial deposition of intranasal formulations.

The respiratory portion of the nasal cavity represents around 90% of the entire nasal cavity and is lined with pseudostratified ciliated columnar epithelium including goblet cells. This area is highly vascularised and serves as the primary location for systemic absorption of drugs. However, constant ciliary and mucus activity, termed mucociliary clearance, rapidly clears foreign particles and drug formulations from the nasal cavity, hence limiting drug residence time and decreasing absorption efficiency[50].

The olfactory region, located in the upper posterior section of the nasal canal, is the most important location for direct nose-to-brain medication transport in humans, with an area of roughly 8–10 cm2. It comprises olfactory receptor neurones, sustentacular cells, basal cells and Bowman's glands The axons of olfactory receptor neurones pass through the cribriform plate to the olfactory bulb, forming a direct physical link between the nasal cavity and the brain. This unique property enables medicines and nanocarriers deposited in the olfactory area to circumvent BBB and BCSFB for fast and targeted delivery to CNS.

The nasopharynx connects the nasal cavity to the throat and is principally involved in the flow of air. Drugs designed to cross this area are commonly administered orally and absorbed via the gastrointestinal tract , which diminishes the efficacy of direct brain targeting .

Therefore, successful intranasal formulations need to maximise deposition within the olfactory area and minimise draining into the nasopharynx.

Intranasal medication absorption is greatly affected by several physiological parameters such as mucus composition, mucociliary clearance, enzyme activity, nasal pH, epithelial permeability and blood flow. Novel nanocarriers are designed to circumvent these restrictions by optimising particle size, surface charge and mucoadhesive characteristics to lengthen nasal residence duration, promote epithelial penetration and improve targeted transport to the brain. Hence, a detailed understanding of nasal cavity architecture and physiology is crucial to design efficient intranasal nanocarrier systems for direct brain administration and successful treatment of CNS illnesses.

4. Nose to Brain Delivery Mechanism

4.1 Permeation through nasal mucosa

Substances can also penetrate nasal mucosa to enter the human circulatory system and eventually reach the brain through bloodstream [76]. However, this route may include crossing the BBB that may limit the entry of some drugs to the brain.

4.2 Olfactory Transfer

The olfactory pathway is the most critical and direct route for transporting medicinal substances from the nasal cavity to the brain. The olfactory epithelium is found in the upper posterior part of the nasal cavity and occupies around 8–10 cm2 in people. It comprises of olfactory receptor neurones (ORNs), sustentacular (supporting) cells, basal cells, and Bowman's glands. The dendrites of the olfactory receptor neurones extend into the nasal mucus. Their axons pass through the cribriform plate of the ethmoid bone and finish in the olfactory bulb. This unique anatomical architecture allows a direct physical link between the nasal cavity and the CNS thereby circumventing the blood brain barrier (BBB)[52].

After intranasal delivery, molecules of medication deposited on the olfactory mucosa may reach the brain via intracellular and extracellular channels . Small lipophilic molecules diffuse across epithelial cell membranes, while hydrophilic molecules often depend on carrier-mediated or paracellular transport. The nanocarriers such as liposomes, polymeric nanoparticles, solid lipid nanoparticles and nanoemulsions improve drug transport by extending the duration the pharmaceuticals remain in the olfactory area, preserving encapsulated drugs from enzymatic destruction and promoting cellular absorption. Further, surface modification of nanoparticles with mucoadhesive polymers or targeting ligands boosts the adherence to the nasal mucosa and increases the transport efficiency. Drugs travelling in the olfactory pathway are mostly delivered to the olfactory bulb and then

distributed to other brain areas such the cerebral cortex, hippocampus and cerebellum. This route has thus been the focus of considerable investigation for the delivery of medicines for neurodegenerative illnesses, brain tumours, epilepsy and other CNS disorders [53].

4.3 Transport of the trigeminal nerve

Apart from the olfactory route, another major route for direct nose to brain delivery of drugs is through the trigeminal nerve . The respiratory and olfactory portions of the nose cavity are widely innervated by the trigeminal nerve, the fifth cranial nerve. It is broken up into three primary branches, the ophthalmic, maxillary and mandibular divisions, the ophthalmic and maxillary branches supplying the nose. These nerve fibres form a direct physical link between the nasal cavity and numerous parts of the brainstem, pons, and spinal cord[54].

After Intranasal delivery, drug molecules or nanocarriers may be taken up by trigeminal nerve terminals and delivered via axonal routes to the CNS. Whereas the olfactory pathway primarily targets the forebrain, drugs can be transported via the trigeminal pathway deep in brain areas such as the brain stem and cerebellum . Drug transportation along this route is believed to occur by both internal axonal transport and extracellular diffusion along perineural channels. Trigeminal transport is promoted by nanocarrier-based formulations because to improved medication stability, extended mucosal retention, and neuronal absorption. The trigeminal route is especially beneficial for treating neurological diseases of the brainstem and spinal cord, and for increasing olfactory transport for better brain medication delivery[55][75].

4.4 Intracellular and Extracellular Transport

Both intracellular and extracellular pathways are responsible for the transport of drugs from the nasal cavity to the brain . The proportional involvement of each route relies on the physicochemical properties of the medication, features of the delivery mechanism and the biological milieu of the nasal mucosa.

The intracellular route is characterised by the internalisation of drug molecules or nanocarriers into olfactory or trigeminal neurones by endocytosis or receptor-mediated internalisation. After internalisation, the drug-containing vesicles are carried by axonal transport mechanisms along the neuronal axons to other parts of the brain. Intracellular transport, however, is a very specific yet rather sluggish process, frequently taking many hours or days for full transit. The optimised particle size and surface properties of nanocarriers for neuronal uptake and intracellular trafficking might greatly affect the improved therapeutic efficiency of nanocarriers[56].

The extracellular route includes the passage of drug molecules through the intercellular spaces around the olfactory and trigeminal nerve fibres without penetrating the neuronal cells. Drugs diffuse through perineural channels and extracellular fluid, rapidly reaching cerebrospinal fluid (CSF) and surrounding brain regions. The process is far quicker than intracellular transport and is responsible for the rapid beginning of effect observed with many medicines given intranasally. Nanocarriers increase drug solubility, shield the active medicinal ingredient from enzymatic breakdown and allow extended interaction with the nasal mucosa, thereby facilitating its extracellular transport. Mucoadhesive and surface functionalised nanoparticles improve the efficacy of transport by decreasing mucociliary clearance and boosting penetration into the nasal epithelium[57].

Intracellular and extracellular transport systems act synergistically to promote effective nose-to-brain medication delivery. Understanding these pathways is critical for building innovative intranasal nanocarriers that can overcome biological barriers, optimise brain targeting and increase therapeutic efficiency for the management of CNS illnesses.

Nose-to-brain medication delivery involves a number of procedures that result in the administration of drugs from the nasal cavity to the brain (Table 1). The nasopharyngeal space-to-brain routes play a critical role in drug transport from the nasal cavity to the brain [51].

Table 1. Anatomical and physiological nasal cavity exploration: benefits, drawbacks, processes, and applications.

Category	Key Components	Significance	Ref.
Nasal Anatomy	Olfactory region	Primary site for direct transport of therapeutics into the brain	[52]
	Olfactory epithelium	Contains olfactory sensory neurons that facilitate neuronal drug transport	[52]
	Nasal mucosa	Highly vascularized tissue that supports rapid drug absorption	[53]
	Olfactory and trigeminal neural pathways	Establish direct communication between the nasal cavity and the CNS	[54]

Drug Transport Mechanisms	Transcellular and paracellular absorption	Enables drug permeation across the nasal epithelium	[54]
	Olfactory neuronal pathway	Direct delivery to the olfactory bulb and forebrain	[55]
	Trigeminal neuronal pathway	Facilitates transport to deeper brain regions and brainstem	[55]
	Lymphatic transport	Supports indirect movement of therapeutics into CNS tissues	[56]
Polymeric Drug Delivery Systems	Polymeric nanoparticles	Enhance drug stability, controlled release, and brain targeting	[58]
	Polymeric micelles	Improve solubility of poorly water-soluble drugs	[60]
	Polymeric hydrogels	Increase nasal residence time and sustained drug release	[61]
	Intranasal sprays containing nanocarriers	Convenient and non-invasive administration platform	[57]
Major Advantages	Rapid therapeutic onset	Faster drug absorption compared with oral administration	[62,63]
	Bypasses the blood–brain barrier	Delivers drugs directly to the CNS through neuronal pathways	[63,64]
	Reduced systemic exposure	Minimizes peripheral adverse effects and first-pass metabolism	[65]
	Improved brain bioavailability	Enhances therapeutic drug concentration in target brain regions	[58,63]
Therapeutic Applications	Alzheimer's disease and Parkinson's disease	Improves delivery of neuroprotective and symptomatic therapies	[66]

	Brain tumors (glioblastoma)	Enables targeted chemotherapy with reduced systemic toxicity	[67]
	Epilepsy, stroke, depression, and other CNS disorders	Improves therapeutic efficacy through direct brain targeting	[63,66]
Current Challenges	Interpatient variability in nasal physiology	Causes inconsistent drug absorption and therapeutic response	[63]
	Rapid mucociliary clearance	Reduces formulation residence time within the nasal cavity	[96]
	Dose limitation and formulation optimization	Restricts the amount of drug that can be administered intranasally	[17,18]
	Safety and long-term toxicity	Requires comprehensive evaluation before clinical translation	[86–90]

Four ways of nose-to-brain delivery are briefly described here (Figure 2). Olfactory pathway: One of the major channels is olfactory pathway. Medicines can bypass the BBB by directly entering the brain through the olfactory epithelium [73]. The medications are carried by the olfactory nerves (through axons and through nerve bundles that traverse the cribriform plate) to the olfactory bulb and then to the deeper areas of the brain [74].

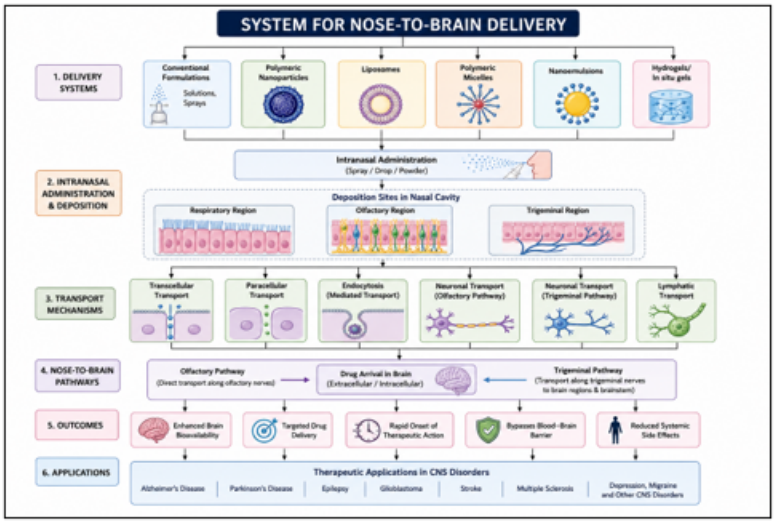

Figure 2. **System for nose-to-brain delivery.**

4.5 Lymphatic drainage: Several investigations have shown that nasal drug delivery may employ lymphatic drainage channels, potentially allowing medications to bypass the BBB and enter the brain interstitium via the glymphatic system [77].

4.6. Direct transport of drugs in solution from the nose to the brain.

The direct delivery of medications in solution from the nasal cavity to the brain involves transporting drug molecules via the nasal mucosa, enabling them to reach the brain without being absorbed into the circulation or crossing the BBB. This channel bypasses systemic circulation, allowing drugs to reach the brain directly via the nasal cavity [79]. Drugs administered as solutions or suspensions via the nasal route have a high likelihood of making contact with the nasal mucosa. The nasal epithelium, which is made up of a porous membrane, allows these medications to enter circulation while also providing a direct channel for certain pharmaceuticals to cross the BBB [78]. The drug's ability to permeate the nasal epithelium and enter the brain is determined by physicochemical properties such as molecular weight, lipophilicity, and solubility. Furthermore, the presence of transporters or receptors in the nasal mucosa may facilitate the direct delivery of some medications to the brain [78,79].

The drug's effectiveness is enhanced by its intranasal method of delivery, which makes it accessible exclusively to the brain, boosting site specificity and preventing systemic adverse effects. Nonetheless, certain medications may face challenges when trying to use this channel, whether due to the nasal epithelium or the necessity to circumvent the BBB. The goal of techniques that include formulation changes or specialised medication designs is to maximise the efficacy of this direct transport channel for drug delivery from the nose to the brain [78].

5. Advantages, Obstacles, and Limitations of Nose-to-Brain Drug Delivery

Nose-to-brain medication delivery has several benefits over traditional drug administration since it gives direct access to the central nervous system (CNS) via the olfactory and trigeminal pathways crossing the blood–brain barrier (BBB). Nanocarriers, such as liposomes, polymeric nanoparticles and lipid-based nanoparticles, promote targeted brain delivery by promoting drug transport across the nasal epithelium via receptor-mediated uptake and longer mucosal residence [34, 35]. They also boost medication bioavailability by preventing enzymatic degradation of therapeutic substances, promoting solubility, improving permeability and offering regulated or prolonged drug release. Surface

modifications, such as PEGylation and ligand conjugation, enhance stability, brain targeting and therapeutic effectiveness [2,9,22,36,45–49].

Lower therapeutic dosages may reach the effective drug concentration in the brain (50). Intranasal nanocarriers can limit the systemic drug exposure and minimise the unfavourable effects of drugs on the peripheral tissues (50). The direct link between the nasal cavity and the CNS allows a quick commencement of action, which makes this route especially advantageous for the treatment of acute neurological diseases [50,51]. In addition, intranasal delivery is a non-invasive, painless and patient-friendly method that avoids the need for injections, promotes patient compliance and facilitates long-term treatment of chronic CNS illnesses [52]. But obstacles such as mucociliary clearance, enzymatic degradation, short nasal residence time and formulation stability are still there, which need the development of sophisticated nanocarrier systems to improve the nose-to-brain drug delivery.

5.1 Barriers and Issues of Nose-to-Brain Drug Delivery and Its Solution

However, despite its great therapeutic promise, the practical use of nose-to-brain medication administration is limited by various biological and formulation-related obstacles. One of the major challenges is mucociliary clearance, a natural defence mechanism that quickly clears drug formulations from the nasal cavity, shortening their residence time and hence decreasing drug absorption. To address this difficulty, mucoadhesive polymers, PEGylated carriers, thiolated polymers, and mucopenetrating nanoparticles were engineered to increase nasal retention and boost drug delivery [53–55].

Drug-related parameters such as molecular size, lipophilicity, solubility, chemical stability and susceptibility to enzymatic degradation also impact nasal absorption and brain targeting. Large compounds or hydrophilic molecules frequently show poor penetration across the nasal epithelium. Efflux transporters and metabolic enzymes further decrease medication availability. Nanocarrier-based formulations may increase therapeutic effectiveness by protecting medicines from degradation, improving their solubility, enhancing permeability and allowing regulated release [56–58].

Differences in nasal architecture such as the thickness of mucosa, the pattern of airflow and structural deformities such as septal deviation or nasal polyps may alter the deposition and absorption of drugs. Delivery devices and formulation techniques for targeting olfactory area are optimised to maximise the deposition efficiency and minimise off-target medication loss [43,59-61].

Another key problem is to maintain formulation stability in a constantly changing nasal environment where enzyme activity, pH changes and fast mucosal turnover may lead to

compromised drug integrity. Encapsulation in liposomes, polymeric nanoparticles, solid lipid nanoparticles and other nanocarriers preserves the medicine, increases stability, prolongs residence duration and boosts brain delivery . Also particle size is important; nanoparticles typically < 200 nm have better penetration and transport via nasal epithelium [30,62–64].

Finally, the effective and site-specific medication transport to the brain is still a challenge due to the intricacy of the blood–brain barrier and the varied architecture of the CNS. Nanocarriers with surface functionalisation, ligand-mediated targeting and sophisticated nanosystems have demonstrated great potential in achieving brain-specific delivery, boosting drug accumulation at sick locations and maximising therapeutic effectiveness while minimising systemic exposure [1,45,65].

6. Nanoparticles for Nasal Drug Delivery to Brain

Nanoparticles are an innovative strategy for medication delivery from the nose to brain. They provide a versatile platform to tackle the numerous challenges for the delivery of medicinal chemicals to the brain. These tiny particles, generally in the size range of 1–100 nanometres, offer considerable potential to improve the stability of medications, control their release [79] and target them to particular areas of the brain [80]. Nanocarriers <100 nm in size often employ endocytic pathways to enable mucosal and transcellular transport. Nanoparticles can accurately control the rate of drug release, ensuring a steady and controlled delivery of medicine to the brain. The regulated release pattern of this carrier permits the steady maintenance of therapeutic concentrations, boosting the efficacy of the therapy and perhaps reducing the frequency of doses. Their excellent biocompatibility with live tissues and toxicity are absent make them safe, with no adverse effects on nasal tissue and brain. Figure 3 shows several formulations such as liposomes, polymeric nanoparticles, solid lipid nanoparticles (SLN) and dendrimers that are versatile platforms for drug encapsulation and provide tailored ways to drug delivery. Nose-to-brain medicine delivery has significant promise in general using nanoparticles. They are continuously being optimised and designed to overcome the barriers and increase the efficient and accurate delivery of medications to the brain for the treatment of neurological disorders [81]. Table 2 describes many nanoparticles with their properties for nose to brain delivery methods for drugs.

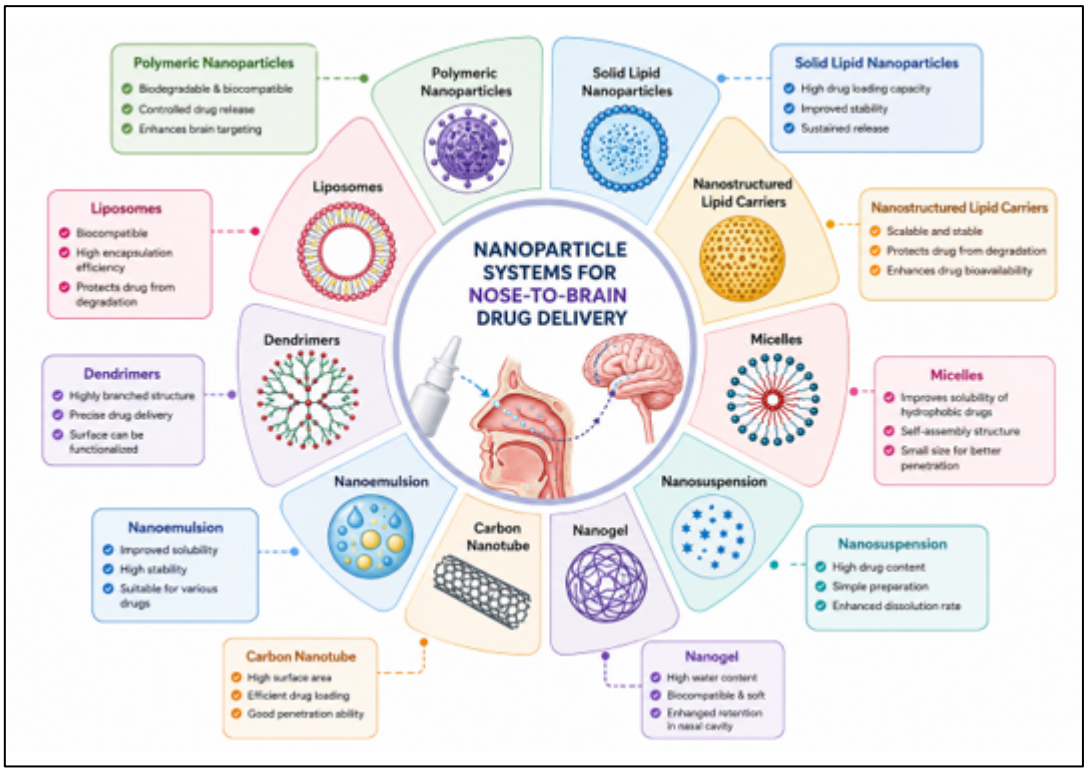

Figure 3. Different nanoparticles for nose-to-brain medication delivery.

Table 2. Different nanoparticles for nose-to-brain medication delivery.

Nanoparticle System	Representative Materials	Major Advantages	Representative Drugs	Key Limitations	Ref.
Polymeric nanoparticles	PLGA, PLA, Chitosan, PCL	Biodegradable, mucoadhesive, controlled drug release, improved brain targeting	Donepezil, Rotigotine, Temozolomide, Carbamazepine	Complex manufacturing and scale-up	[24–30]
Polymeric micelles	PEG–PLA, PEG–PCL block copolymers	High solubility for hydrophobic drugs, sustained release	Paclitaxel, Curcumin	Limited drug-loading capacity	[26,30]

Nanogels	Chitosan, Hyaluronic acid, PEG hydrogels	High water content, prolonged nasal residence, stimuli-responsive release	Peptides, Proteins, siRNA	Stability during storage	[29–30]
Dendrimers	PAMAM, PPI dendrimers	High surface functionality, efficient cellular uptake, ligand conjugation	DNA, siRNA, Anticancer drugs	Dose-dependent toxicity	[27,30]
Liposomes	Phospholipid vesicles	Excellent biocompatibility, suitable for hydrophilic and lipophilic drugs	Tacrine, Donepezil, Lamotrigine	Physical instability and drug leakage	[67–68]
Solid lipid nanoparticles (SLNs)	Glyceryl monostearate, Stearic acid	Controlled drug release, high stability, protection from enzymatic degradation	Sumatriptan, Haloperidol, Agomelatine	Limited drug-loading capacity	[63,73–74]
Nanostructured lipid carriers (NLCs)	Solid and liquid lipid mixtures	Higher drug loading, improved stability,	Rivastigmine, Quetiapine, Diazepam	Formulation complexity	[63,74]

		enhanced brain targeting			
Nanoemulsions	Oil–water emulsions	Rapid absorption, improved solubility, easy intranasal administration	Dolutegravir, Curcumin	Physical instability during long-term storage	[62,74]
Carbon nanotubes	Single- and multi-walled CNTs	High drug-loading efficiency and neuronal penetration	Neuroprotective agents	Safety and toxicity concerns	[89–90]
Hybrid polymer–lipid nanoparticles	PLGA–lipid hybrid systems	Combines polymer stability with lipid biocompatibility for enhanced brain delivery	Anticancer and neuroprotective drugs	Manufacturing complexity	[30,74]

New intranasal nanocarriers have developed as particularly efficient platforms to overcome the limitations of classical drug delivery to the central nervous system. These nanocarriers boost the drug bioavailability, enhance the brain targeting, increase the nasal residence time, and decrease the systemic toxicity by crossing the blood-brain barrier (BBB) via the olfactory and trigeminal pathways [31,42,73,74]. Liposomes are biocompatible vesicles that contain both hydrophilic and lipophilic drugs and so have improved nasal permeability and brain delivery of medicinal substances such as tacrine, lamotrigine, donepezil, olanzapine and growth factors [31,95-105]. Polymeric nanoparticles (PNs), especially those fabricated from PLGA, chitosan and other biodegradable polymers, have been successfully employed for the delivery of lamotrigine, temozolomide, clonidine, lurasidone, carboplatin, and astragaloside IV [42,73,74,106-119], offering controlled drug release, improved

mucoadhesion, and ligand-mediated targeting. Solid lipid nanoparticles (SLNs) have excellent physical stability, sustained drug release, protection from enzymatic degradation, and enhanced brain uptake of drugs like sumatriptan, asiatic acid, agomelatine, rosmarinic acid, haloperidol, piribedil, and BACE1 siRNA, thus improving therapeutic efficacy in several neurological diseases [120–129]. NLCs are the second generation of lipid nanoparticles, and contain a solid-liquid lipid matrix that provides them with a larger drug loading capacity and better stability than SLNs. They have demonstrated promising results for the intranasal delivery of quetiapine, diazepam, efavirenz, asenapine, rivastigmine, astaxanthin and other CNS drugs with enhanced pharmacokinetic performance and brain targeting [79, 130-139]. Dendrimers are highly branched polymeric architectures with modifiable surface functional groups, which enable targeted drug and gene delivery, whereas polymeric micelles improve the solubility, permeability and brain transport of poorly water-soluble drugs such as dexamethasone, lurasidone, clozapine, clonazepam and rotigotine [73,140-159]. Nanoemulsions have been shown to enhance the solubility, stability and nasal absorption of lipophilic drugs such as rivastigmine, curcumin, tacrine, levodopa, kaempferol, bromocriptine and resveratrol leading to better brain bioavailability and therapeutic outcomes [77, 84, 160-171]. Mesoporous silica nanoparticles (MSNs) have also been shown to be a good carrier owing to their large surface area, tunable pore size, high drug loading capacity, and controlled drug release features. These carriers allow for efficient targeting to the brain and have demonstrated promising outcomes for intranasal delivery of therapeutic agents for glioblastoma, multiple sclerosis, and other neuroinflammatory disorders but further studies are required to establish their long-term safety and clinical translation [91,92,186-190]. Biocompatible and mucoadhesive polymeric networks called nanogels provide prolonged drug release, resistance to enzymatic degradation, extended nasal residence time and enhanced direct brain delivery. Their usage has shown promise in treatment of Alzheimer's disease, schizophrenia, migraine, depression, hypertension and brain cancer via intranasal administration [33,93,94,191,192]. Nanosuspensions provide enhancement in solubility, dissolution rate and stability of poorly soluble drugs such as clozapine, efavirenz, breviscapine and resveratrol, which may improve nasal absorption and brain bioavailability [87,88,172-177]. Carbon nanotubes (CNTs) have unique structural and physicochemical properties that can facilitate the targeted delivery of neuroprotective agents across the BBB, but their toxicity and long-term safety remain concerns that limit their clinical use despite promising preclinical results [89,90,178-185]. Collectively, these nanocarrier technologies have shown great potential in enhancing the direct nose-to-brain

delivery of drugs and in the treatment of CNS diseases such as Alzheimer's, Parkinson's, epilepsy, glioblastoma, stroke, depression and multiple sclerosis. However, the use of such advanced intranasal nanocarriers for routine clinical practice requires further optimisation, large-scale production, thorough safety evaluation, and well-designed clinical research [73,74,79,95,120,130].

7. Nasal Mucosal Toxicity from Nanoparticles

The use of nanoparticles in medication delivery systems for nose-to-brain applications has immense promise, however there are worries regarding their toxicity to the delicate nasal mucosa. Their small size and diverse surface properties allow for more effective contact with biological tissues, raising the possibility of negative repercussions. The toxicological profile of nanoparticles is heavily impacted by their size, surface charge, and composition [193]. Submicron particles may infiltrate cellular structures, potentially interfering with cell function. Furthermore, changes to the surface characteristics and chemical content of these particles might trigger inflammatory responses or induce cellular stress. Non-biodegradable nanoparticles may accumulate in the mucosa, potentially causing prolonged exposure and harm [194]. Mitigation strategies include the creation of biocompatible materials, the optimisation of surface characteristics to prevent unfavourable interactions, and the study of biodegradable nanoparticles to reduce the possibility of accumulation. We may thoroughly analyse the possible negative effects of nanoparticles via extensive preclinical studies, which involve performing experiments in a controlled setting and employing animal subjects. The objective is to ensure that nasal medicine administration is safe and effective while also protecting the nasal mucosa. To guarantee the safe and effective delivery of medications from the nose to the brain via nanoparticles, it is critical to have a complete understanding of their potential side effects. Furthermore, it is critical to apply innovative design ideas to reduce any risks associated with their usage [195].

8. Challenges in Overcoming Nanoparticle-Derived Toxicity to Nasal Mucosa

To address concerns regarding the potential harmful effects of nanoparticles on the nasal mucosa in drug-delivery systems, a range of strategic techniques are being employed to mitigate unfavourable effects and increase safety. A critical approach requires thorough design and engineering of nanoparticle characteristics such as size, surface properties, and composition. Biocompatible materials and surface modifications, such as coatings or functional groups, aim to decrease interactions that may cause inflammation or cellular stress [90]. Nanoparticle safety and biocompatibility are carefully tested utilising in vitro and animal models. These tests are intended to better understand cellular reactions, inflammatory

responses, and potential ramifications for mucosal tissue integrity. The findings of this research are used to make appropriate adjustments in the design and composition of nanoparticles to guarantee safety while maintaining effectiveness [196]. To properly address the issue of nanoparticle toxicity to the nasal mucosa, a comprehensive strategy must involve meticulous modification of nanoparticle characteristics, the incorporation of biodegradable components, and thorough preclinical testing. By using these principles/alterations, researchers may be able to develop drug-delivery systems that specifically target the brain via the nasal route while minimising potential hazards to the delicate nasal mucosa [197].

9. Applications in CNS Disease Management

Central nervous system (CNS) diseases remain among the primary causes of disability and death globally. The blood–brain barrier (BBB) is a major obstacle to therapy because it limits the access of most therapeutic drugs to the brain. Intranasal medication administration has emerged as an attractive non-invasive approach since it bypasses the BBB via olfactory and trigeminal routes and so allows direct brain targeting with less systemic drug exposure [30–79]. The use of nanocarriers, including liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, dendrimers, nanogels, and exosomes, increases drug stability, nasal residence time, controlled release, and brain-specific delivery [199].

Intranasal nanocarriers have been widely researched for direct delivery of donepezil, rivastigmine, memantine, curcumin and other neuroprotective medicines to the brain in Alzheimer’s disease. They may boost drug accumulation in hippocampus and cerebral cortex, decrease amyloid-β deposition, relieve neuroinflammation and promote cognitive performance with less systemic toxicity [127,200].

In Parkinson's disease, intranasal nanocarriers are used for administration of levodopa, dopamine agonists, rotigotine, rasagiline and antioxidant chemicals directly to substantia nigra and striatum. This formulation increases the bioavailability in the brain, prolongs the therapeutic activity, decreases peripheral metabolism and boosts motor performance in comparison to standard formulations [197].

In epilepsy, the intranasal delivery of anticonvulsants such as diazepam, midazolam, lorazepam and carbamazepine with the use of nanocarrier systems allows for quick drug absorption and speedier management of seizures. Direct nose-to-brain transfer leads to a reduction in the latency of the therapeutic effect, which is especially important in the emergency treatment of seizures [201].

Brain tumours, especially glioblastoma, are challenging to treat due to low penetration of drugs across the BBB. Intranasal nanocarriers have shown promise in delivering chemotherapeutic drugs, genes and biological therapies directly to tumour tissues, improving therapeutic effectiveness and lowering systemic toxicity [202].

Intranasal nanocarriers have shown promise for delivering neuroprotective peptides, antioxidants, anti-inflammatory drugs and growth factors directly to the wounded brain in stroke. Fast targeting of brain may help to decrease neuronal damage, facilitate neuroregeneration and enhance functional recovery after ischaemic injury [200-202].

Intranasal nanocarriers are also being studied for multiple sclerosis, depression and anxiety disorders where localised medication delivery may increase therapeutic effectiveness, minimise systemic side effects and improve patient compliance. Despite the significant advances obtained in the preclinical investigations, clinical trials are necessary to determine the long-term safety, effectiveness and regulatory approval of these new delivery methods [200].

10. Nose-to-Brain Delivery in the Future

The future of nose-to-brain medication delivery will likely be geared towards the creation of intelligent, versatile and therapeutically translatable nanocarrier systems to overcome the existing biological and technical restrictions. Surface-functionalized nanoparticles containing receptor-targeting ligands, peptides, antibodies, and cell-penetrating compounds are projected to enhance selective uptake via the olfactory and trigeminal routes and increase drug accumulation in sick brain tissue [198]. Another intriguing method for site-specific and regulated drug administration is the use of stimuli-responsive nanocarriers that may release medications in reaction to pH, enzymes, temperature, oxidative stress or external magnetic fields. In addition, mucoadhesive and mucus-penetrating systems composed of chitosan, hyaluronic acid, polyethylene glycol, and other biodegradable polymers may significantly enhance nasal residence length, improve medication absorption, and minimise mucociliary clearance. Emerging biomimetic delivery technologies such as exosomes and extracellular vesicles offer advantages of great biocompatibility, low immunogenicity, and effective transport across biological barriers, making them potential candidates for next-generation brain-targeted therapies. Emerging developments in artificial intelligence, computational modelling, Quality-by-Design (QbD), personalised nanomedicine and scalable manufacturing technologies are also anticipated to facilitate formulation optimisation and clinical translation. Nevertheless, standardised regulatory criteria, long-term safety

assessments, pharmacokinetic investigations and well-designed clinical trials are still a need for successful commercialisation of intranasal nanomedicines[197].

11. Conclusions

The use of nanocarriers for intranasal drug delivery has evolved into a very promising technique for the treatment of CNS illnesses, because it allows the direct transfer of therapeutic molecules to the brain, bypassing the blood–brain barrier. Nanocarriers like liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, dendrimers, polymeric micelles, mesoporous silica nanoparticles, nanogels and exosome-based systems have shown significant improvements in drug stability, bioavailability, brain targeting and therapeutic efficacy. These delivery systems have great promise for neurological diseases including Alzheimer's disease, Parkinson's disease, epilepsy, glioblastoma, stroke, multiple sclerosis and depression. Despite important advances in preclinical studies, many issues such as mucociliary clearance, formulation stability, toxicity evaluation, manufacturing scalability and regulatory licensing still hamper their broad clinical use. Future research should focus on tailored and stimuli-responsive nanocarriers, biomimetic delivery systems, personalised healthcare, and comprehensive clinical assessment to enable effective translation into clinical practice. Overall, innovative intranasal nanocarriers constitute an emerging and revolutionary platform with great promise to revolutionise the treatment of CNS illnesses via safe, effective and patient-friendly brain-targeted medication delivery.

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