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CHITOSAN-COATED SOLID LIPID NANOPARTICLES FOR NOSE-TO-BRAIN DRUG DELIVERY: A COMPREHENSIVE REVIEW

Samruddhi Rakshe[1], Manisha Lalan[1]*, Pranav Shah[2], Dikshitkumar Modi[3], Vrutti Parmar[3]

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ABSTRACT
Background: The blood-brain barrier (BBB) limits the effectiveness of treatment of several central nervous system (CNS) diseases, including Alzheimer's disease, Parkinson's disease, schizophrenia, and bipolar disorder. Because of this limitation, intranasal drug delivery is an effective, non-invasive way to bypass the BBB via the olfactory and trigeminal pathways. **Methodology:** In this review, we critically evaluate the design, characterization, mechanism of action, and potential therapeutic use of Chitosan-coated Solid Lipid Nanoparticles (SLNs) as a delivery system for drugs from the nasal cavity to the brain. A structured literature search was conducted in PubMed, Scopus, and Web of Science for studies published between 2019 and 2025 using keywords related to chitosan-coated solid lipid nanoparticles and nose-to-brain delivery. Studies reporting pharmacokinetic parameters, such as brain AUC, brain-targeting efficiency (BTE%), and drug-targeting index (DTI), were included. **Results and Discussion:** Preclinical studies show that some chitosan-coated SLN formulations significantly improve drug pharmacokinetics, increasing the brain area under the curve (AUC) compared with conventional formulations. Reported brain targeting efficiency (BTE%) with drug targeting index (DTI) values confirmed preferential nose-to-brain transport and improved CNS exposure. The improved targeting efficiency is attributed to the mucoadhesive nature of chitosan, enhanced permeability, and prolonged nasal residence time of SLNs. **Conclusion:** Chitosan-coated Solid Lipid Nanoparticles (SLNs) are an interesting candidate for a nanocarrier system to deliver drugs through the intranasal route into the CNS (Central Nervous System). Future research should emphasize Quality by Design (QbD)-based optimization, advanced surface modifications for targeted delivery, and comprehensive safety and clinical validation to support successful translation into clinical practice.

INTRODUCTION

Conditions of the CNS affect more than 1.5 billion people worldwide, accounting for approximately 1/3 of the global disease burden. This poses tremendous challenges to healthcare systems, and it is projected that the burden of CNS conditions

[1]*Department of Pharmaceutics, Parul Institute of Pharmacy and Research, Parul University, Vadodara-391760, Gujarat, India.*
[2]*Department of Pharmaceutics, Maliba Pharmacy College, Uka Tarsadia University, Tarsadi-394350, Bardoli, Gujarat, India.*
[3]*S. S. Agrawal Institute of Pharmacy, Navsari Veeranjali marg, near Devina park Society, gandevi road, Navsari- 396445, Gujarat, India.*

For Correspondence:** **Manisha_lalan79@yahoo.co.in

will significantly increase over the next several decades. The World Health Organization believes that CNS disease will become the key medical challenge of the 21st century [1]. The human body's most complex organ is the CNS, whose functions depend on intrinsic factors such as cell–cell interactions and gene expression, as well as extrinsic factors such as nutrition, trauma, and potentially behavioural experience [2]. Disorders of the CNS encompass a wide range of neurodegenerative and mental health conditions, including Bipolar disorder, schizophrenia, Alzheimer's disease (AD), and Parkinson's disease (PD) [3]. The most prevalent neurodegenerative condition affecting the elderly is PD [4]. Due to the large number of people who suffer from AD, the disease's economic burden, and the lack of a known cure, the global health crisis continues [5]. Schizophrenia is a severe, weakening mental illness that affects about 1% people in every culture in the world. Schizophrenia occurs in men and women equally, though it tends to occur later in women [6]. More than 1% of the total population worldwide experiences episodic, recurrent, chronic mood disorder known as bipolar disorder, regardless of nationality or ethnicity [7].

The BBB, which restricts drug delivery to the brain, is a major obstacle in the diagnosis of CNS disorders [8]. Nanocarrier systems and modified surfaces are two advanced strategies that aim to reduce side effects and improve therapeutic efficacy [9]. Recently, intranasal drug delivery has been identified as a useful approach for targeting CNS disorders, as it is an effective means of rapidly and accurately delivering drugs to the CNS [10,11]. New strategies have emerged because conventional administration methods often fail to deliver the pharmaceutical agent to the CNS. The nasal cavity is uniquely situated such that it has direct links to the CNS via the olfactory pathway and peripheral circulation [12]. Nose-to-brain emergence is a new, painless drug-delivery strategy that offers several benefits over systemic administration, including reduced systemic toxicity and side effects, faster onset, greater CNS bioavailability, and delivery not hindered by the BBB [13, 14].

Nanoparticles (NPs), which are colloidal carriers made of synthetic or natural polymers and have a submicron size of 100-200 nm, have further potential to boost delivery from the nose to the brain. The nose-to-brain route more effectively delivers smaller particles, down to 100nm, via the olfactory nerve. In comparison, particles in the 100–200 nm range are more likely to be transported via the trigeminal nerve, are better functionally on the surface, and are more stable in the formulation [15]. Chitosan is a natural polysaccharide that is safe, biodegradable, non-toxic, and hypoallergenic [16]. Chitosan is derived from chitin. Nanoparticles can prevent pharmaceuticals from degrading, thereby enhancing CNS availability of therapeutics [17].

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are lipid-based nanoparticles that enable drug targeting. When SLNs and NLCs are delivered directly to the brain via nasal administration, they are effective in treating CNS diseases such as neurodegenerative disorders [18, 19]. The extent of deacetylation and the molecular weight of chitosan affect how well it facilitates drug uptake through the nasal passages. In conclusion, while chitosan is potentially an excellent way to increase the efficiencies of drug delivery systems from the nose to the brain, the methods used to manufacture (deacetylate) chitosan and its molecular weight will be among the most determining factors when designing effective nose-to-brain drug delivery systems [20, 21].

NOSE TO BRAIN PATHWAYS AND BARRIERS

When delivering drugs through the nose, in the context of various drug delivery systems, an understanding of the anatomical and physiological characteristics of the nose is necessary to develop efficient methods for transporting drugs from the nose to the CNS. The various anatomical and physiological barriers that prevent drugs from entering the nasal mucosa include blood flow (perfusion), lymphatic drainage, the nasal valve, and the characteristics of the nasal airflow and mucociliary clearance [22,23].

Anatomy and Physiology of the Nasal Cavity

Approximately 10,000 litres of air, differing in temperature and humidity and containing dust, microorganisms, and other particulates, is inhaled by humans at a rate of 12–24 times per minute [24]. The outer nose surrounds the lumen of the nasal cavities, which are small and measure about 5cm high and 10cm long, consisting of two separate cavitary spaces. Each of these cavities is bounded medially by a septal wall and laterally by a lateral wall, with three (seldom four) turbinates—inferior, middle, and superior—extending into the cavity [22]. The turbinates are lined with thick respiratory mucosa, especially on their medial surfaces. There are specialized cell types that are

all anchored to the basal membrane that contribute to the function of the respiratory mucosa, such as basal cells, columnar cells & goblet cells [25,26]. The nasal cavity serves the purpose of all of the above-mentioned functions—respiration, olfaction, conditioning inspired air, and immune defence. Mucus in the nose also protects the epithelium from external particles, which is significant during inflammation [27]. The nasal cavity exists as two distinct cavities, divided by a septum, which has bony and cartilaginous support. Each cavity has a 3 regions: the respiratory region, the olfactory region, and the nasal vestibule. [28]. Anatomy and physiology characteristics affect the paths of airflow within the nasal passages. Turbulence can result from even the smallest disruption of normal laminar airflow, thereby disrupting the nose's functions, such as humidifying inspired air and transferring it to the olfactory epithelium [29]. A mucous membrane lines each nasal passage within the larger chamber, is innervated, and covered by an ongoing layer of mucus. The layer of mucus is transported posteriorly to the oropharynx, where it can be delivered to the oesophagus [30].

Drug transport pathway in the nose to the brain for delivery

Drugs are delivered through the olfactory and trigeminal nerve pathways, which bypass the blood-brain barrier, using intranasal drug delivery, which is painless and non-invasive [31]. Free-nerve endings associated with the ophthalmic (V1) and trigeminal (V) nerves, which are distributed along the nasal mucosa and olfactory epithelium, initiate activity in the majority of odorants. Olfactory receptors (cranial nerve I) are located in the upper portion of the nasal mucosa [32]. Drugs may access target cells through passive diffusion, paracellular transport, or the trigeminal nerve pathways (as shown in fig 1). The trigeminal nerve allows drugs to enter the brain either slowly through intracellular axonal transport or quickly through extracellular bulk flow. Rapid nose-to-brain delivery is primarily through the extracellular bulk flow pathway [10]. The trigeminal system, long recognized as a primary system for facial and dural sensitivity, has only recently been considered a relevant system of brain nociceptive innervation [33]. The chemosensory and motor functions of the face are controlled by the trigeminal nerve, the fifth and largest cranial nerve [34]. The nasal cavity contains olfactory neurons that can number in the millions to tens of millions in mammals, and they play an important role in delivering medication through the nose [32]. Additionally, there are potential connections along the trigeminal pathway between the nasal lamina propria and the brainstem, as the V1 (ophthalmic) and V2 (maxillary) branches innervate the respiratory regions of the nasal mucosa [35]. Lipid-based nanocarriers like SLNs enable effective nose-to-brain delivery of hydrophobic drugs, as previously stated. Hydrophilic drugs can readily traverse extracellular pathways [36]. Thus, intranasal drug administration to the CNS is mediated by several pathways, including the trigeminal and olfactory nerves and nasal lymphatic vessels. Among these, the trigeminal nerve is a major pathway because it shares structural similarities with the olfactory nerve [37]. The trigeminal nerve projects directly into the CNS at the level of the pons, thus representing an important connection between the nasal cavity and brain [36].

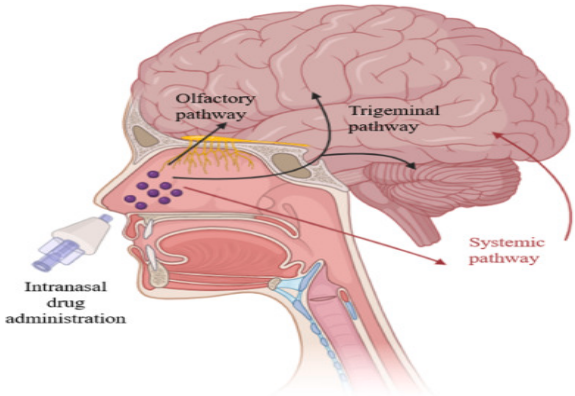

Figure 1: The drug movement from the brain to the nasal cavity is characterized in a general schematic format. By administration via the nostrils, the agent crosses the blood-brain barrier, then enters either the systemic circulation or is translocated directly through the olfactory and/or trigeminal neural pathways. As indicated in the schematic representation of multiple transport routes above, the use of intranasal nanocarriers for targeted delivery to the brain is supported by the data shown in the figure [38]: copyright 2023, permission from Elsevier.

Factors affecting nose-to-brain delivery

When designing an intranasal drug delivery system, it is important to consider multiple physicochemical, formulation, and physiological factors, including but not limited to particle size, molecular weight cutoff, and mucociliary clearance [39]. The primary drawback of nasal absorption is the low permeability of the nasal membrane barrier, especially for drugs that dissolve in water and for high-molecular-weight molecules, such as proteins. Additionally, mucociliary clearance significantly restricts drug transport across the membrane barrier [40]. The nasal mucosa contains a mucin layer that provides a physical barrier and can also inhibit drug dissolution & accelerate mucociliary clearance, limiting the effectiveness of drug delivery intranasally [10].

Table 1: Quantitative comparison of nasal and systemic pharmacokinetic outcomes [41,42,43].

PK Parameter	Nasal Delivery	Systemic (e.g., Oral/IV)	Typical Difference
Bioavailability (F)	Zolmitriptan intranasal has a relative AUC similar to the oral tablet (intranasal: oral AUC ratio ~0.92–0.96 for 2.5 and 5 mg doses).	Oral zolmitriptan absolute bioavailability ~40% (bioavailability limited by first-pass).	Nasal can have a similar or slightly lower total systemic AUC but a faster onset.
Cmax (peak conc.)	Sumatriptan intranasal (Breath Powered 22 mg) Cmax ~20.8 ng/mL; nasal spray 16.4 ng/mL	Oral sumatriptan (100 mg) Cmax ~70.2 ng/mL.	Nasal Cmax is often lower than high-dose oral, but may occur earlier.
Tmax (time to peak)	Sumatriptan intranasal Tmax ~0.33 h (20 min)	Oral sumatriptan Tmax ~1.5–3 h (median ~2 h).	Nasal Tmax is substantially faster (minutes vs hours).
AUC (total exposure)	Sumatriptan intranasal AUC0-∞ ~64.9 ng·h/mL (22 mg nasal powder) vs ~61.1 ng·h/mL (20 mg liquid nasal spray)	Oral sumatriptan 100 mg AUC0-∞ ~308.8 ng·h/mL	Lower total systemic exposure after nasal vs. high-dose oral sumatriptan
Absorption onset	Zolmitriptan detected in plasma as early as ~2 min intranasally vs ~10 min oral.	Oral zolmitriptan has a slower onset (~10 min).	Nasal provides earlier detection/absorption.

ROLE OF CHITOSAN COATING IN INTRANASAL DRUG DELIVERY

Chitosan is a natural polysaccharide derived from chitin and possesses a variety of beneficial characteristics, making it an ideal agent for coating nanoparticles. Chitosan is expected to have uses in the pharmaceutical and medical fields because it exhibits biocompatibility, biodegradability, and non-toxicity; it helps modify the tight junction and facilitate easy drug penetration (as shown in Fig. 2) [44, 45]. Furthermore, the positively charged surface of chitosan nanoparticles enables attraction to negatively charged cell membranes, thereby increasing residence time on the nasal mucosa [46]. The tight-junction opening, paracellular transport, and nasal permeability of chitosan are influenced by its degree of Deacetylation (DA) and molecular weight (MW).

Chitosan coatings on NPs increase permeability compared to non-coated NPs when tested against goat nasal mucosa (ex vivo). NPs coated with Chitosan reduce mucociliary clearance (MCC) and increase interaction with epithelial cells [47]. Chitosan can also bind with mucin and proteins to form complexes that may alter the stability, solubility, or bioactivity of the compounds. Moreover, chitosan and its derivatives exhibit additional biological activities, including antibacterial, antifungal, immunostimulant, and antioxidant effects [48]. Research has shown that SLNs coated with chitosan can open tight junctions in the nasal mucosa, thereby increasing drug permeation. Chitosan has two types of electrostatic interactions with negatively charged mucins: stronger electrostatic interactions occur when chitosans are deacetylated to a higher degree; thus, an increase in deacetylation increases the positive charge density of chitosan and results in a better ability to form mucoadhesion. Due to its increased biocompatibility and ability to penetrate nasal membranes, low-molecular-weight, highly deacetylated chitosan is an excellent choice for systems that deliver medicines to the brain via the nasal cavity. However, the formulation stability remains a significant challenge [49].

Under physiological conditions, the positive charge of chitosan-coated nanoparticles interacts strongly with negatively charged mucin proteins, thereby reducing ciliary clearance and prolonging nanoparticle retention in the nasal cavity [50]. Chitosan's percentage of DA, which determines how many free amine groups (-NH2) are present on the polymer backbone, is directly related to its ability to interact with the nasal mucosa and alter epithelial barrier function. In solution at or slightly below physiological pH, chitosan (a cationic polysaccharide) becomes positively charged (enhanced zeta potential, in this case, protonation of the amine making –NH2 to –NH3+) due to protonation of its amine groups on the polymer backbone, at acidic to neutral conditions typical of the nasal cavity. Therefore, coatings or other forms of chitosan will exhibit higher zeta potential as the density of protonatable amines is increased [51]. Increased electrostatic attraction due to an increase in zeta potential creates stronger interactions between the positively charged polymer and the negatively charged sialic acid residues on mucin glycoproteins (major components of nasal mucus), thereby increasing mucoadhesive interactions & residence time on the epithelial surface. There are also secondary forces, such as hydrophobic interactions and hydrogen bonding, that

contribute to adhesion and the formation of chitosan-mucin (polymer-mucin) complexes [52]. A greater number of mucoadhesive contacts may transiently modulate tight junctions and increase interaction between chitosan and the epithelial surface, thereby aiding the paracellular transport of drug molecules [51].

The enhanced nasal permeation, sustained drug release, and increased mucoadhesion of chitosan-coated nanostructured lipid carriers (NLCs) compared to uncoated NLCs [53]. Hybrid films and capsules may be produced using chitosan in combination with other materials. Chitosan-coated SLNs can deliver drugs to the brain via the bloodstream [54]. Comparative data with other nanoparticle systems, such as polymer micelles, dendrimers, and lip-polymer hybrids, are limited regarding their relative advantages for loading, remnant kinetic, and targeting efficiencies compared with SLNs [55]. In addition, several critical issues must be addressed, including conflicting preclinical results, clinical trial failures, and regulatory concerns related to excipient approval and reproducibility. These data will assist us in further developing our understanding of this field and in future design applications of nasal nanocarrier systems [56].

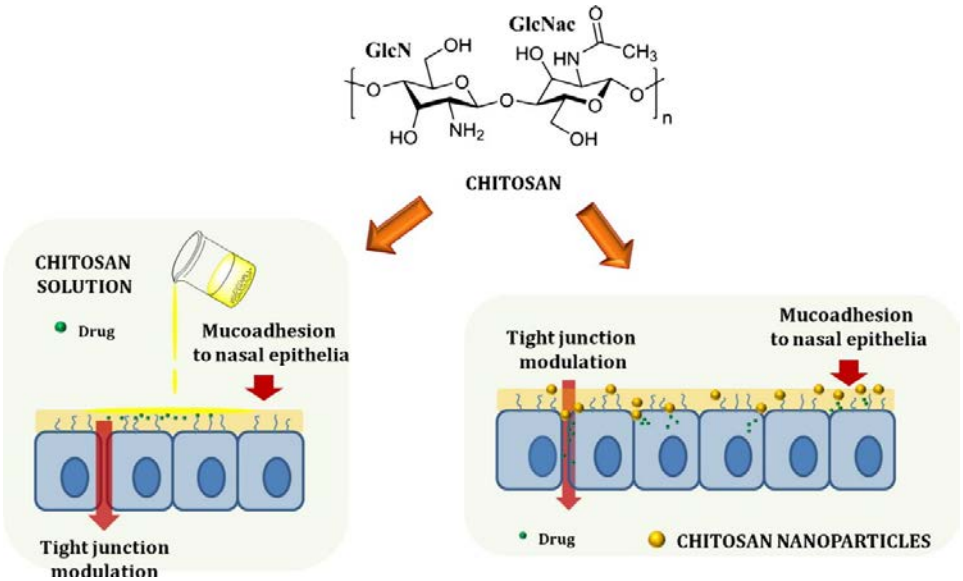

Figure 2: A diagrammatic illustration that represents the mechanism of chitosan in delivering medicine via the nasal route. This illustration not only presents the structural and functional properties of chitosan including the ability to adhere to the nasal epithelium and open tight junctions to facilitate improved paracellular transport, but also demonstrates evidence for the use of chitosan as a permeation enhancer in intranasal formulations, with the superior permeability of chitosan nano- particles as compared to chitosan solutions through epithelium, in addition to their increased residence time at the mucosal surface, further supporting the use of these compounds in this manner [57]. Copyright 2014, permission from Elsevier.

NANOPARTICULATE SYSTEM FOR BRAIN TARGETING

Nanoparticles are broadly defined within the range of 50–500 nm. The characteristics and properties of these tiny materials vary immensely, and in most cases, they are too small to see with the unaided human eye. Within the field of nanomedicine, engineered and optimized devices and products have emerged.

One can use a variety of nanoparticle types to deliver drugs (e.g., solid lipid nanoparticles, polymeric nanoparticles & liposomes) or drug coatings. SLNs stand out because they possess a unique blend of advantages: controlled drug release, enhanced drug stability & enhanced biocompatibility (as compared to polymeric devices) without the potential toxicity or the complexity associated with the manufacture of polymeric systems. SLNs are a promising research area for developing a safe, effective, and efficient drug delivery system; in addition to SLNs, many other nanoparticle types are available [58]. Delivery of drugs to patients with CNS disorders is particularly difficult as a result of the blood-brain barrier. It is therefore very important to find new ways of providing APIs directly into the CNS [59]. The unique structural and functional characteristics of the BBB make it exceedingly difficult to deliver compounds directly to the CNS. To effectively deliver therapeutics to the brain, we must develop new methods to deliver APIs to specific brain regions (as shown in Fig. 3) [60].

SLNs are a highly viable option for delivering drugs to treat brain-related ailments, which are restricted by tight junctions that inhibit the transfer of most drugs into the CNS [61].

SLNs are a particularly promising option for drug delivery rather than other nanoparticles, such as dendrimers, liposomes, and polymeric nanoparticles. Several research studies have shown that particles with sizes less than 200 nm penetrate nasal mucus more effectively and result in enhanced absorption, prolonged residence time, and reduced adverse reactions than larger-size particles, which tend to be deposited and absorbed differently than smaller-size particles [62].

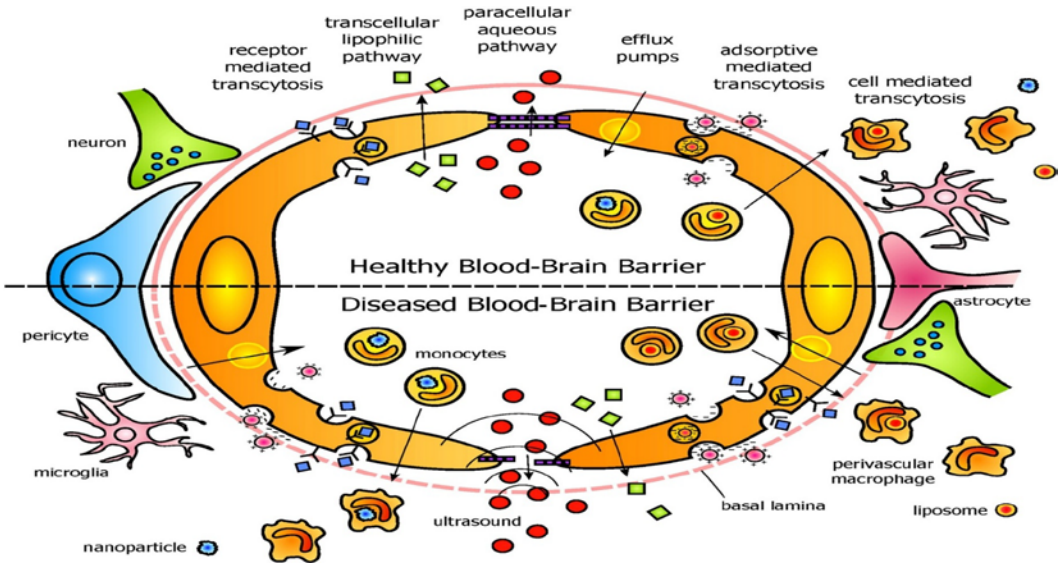

Figure 3: The picture above depicts mechanisms that allow substances to cross the BBB to the CNS and how those mechanisms work in both healthy and unhealthy individuals. In the image, you can see the following processes: transcellular lipophilic diffusion, paracellular aqueous transport, receptor-mediated and adsorptive-mediated transcytosis, and the role of efflux pumps in preventing drugs from entering the CNS. In addition, the image illustrates that, with disease, the BBB can undergo both structural and functional changes (e.g., breakdown of tight junctions, increased permeability), which would allow drugs/nanoparticles easier access to the CNS. Lastly, the presence of pericytes, astrocytes, immune cells, and microglia underscores the complexity and importance of using nanocarrier-based strategies to improve CNS drug delivery and to regulate the BBB [63]. Copyright 2012, permission from Elsevier.

Advantages of Nanoparticles

Nanoparticles can be employed as carriers for drugs because of the difference in their physical and chemical characteristics. With the unique properties of nanoparticles, the way drugs are delivered and remain active in the body for extended periods will be enhanced compared to direct administration. As a result, the drug's efficacy may increase significantly. Nanoparticles can be employed to create a Sustained Release Delivery System that enables a single administration of a therapeutic drug to patients for extended periods (days–months) rather than multiple administrations over shorter time frames. This will reduce the frequency of administration, stabilize the drug's plasma concentrations, and improve patient compliance [64]. Nanoparticles modified on the surface have attracted significant interest for drug delivery. As a consequence of their interactions with physiological fluids and tissues, the characteristics of the surface, or shell, are more relevant than the core. For targeted drug release, the surface of nanoparticles can be functionalized with binding molecules having a high affinity for the site of action. For optimal nanoparticle design, the surface should be hydrophilic [65,66].

Nanoparticles can stabilize drugs without a chemical reaction by encapsulating them. This system can accurately control the drug release and degradation, minimize drug waste, and maximize bioavailability at the targeted site. Furthermore, they can solubilize drugs with low aqueous solubility, reduce their immunogenic potential, extend their circulation time in the bloodstream, and deliver drugs via sustained-release, thereby reducing the need for frequent dosing [67,68].

Types of Nanoparticles

Using a variety of newly developed nanomaterials, numerous nanoparticle (NP)- based drug delivery systems have been developed. These include liposomes, dendrimers, polymeric micelles, and polymer nanoparticles, which can enable drug delivery to a target site.

- ***Liposomes***

Liposomes are the subject of extensive research for the potential treatment of neurological diseases and drug delivery due to their unique properties. Liposome-encapsulated drugs have higher cellular uptake, which partially overcomes the BBB's low permeability [69, 70].

- ***Dendrimers***

Dendrimers are macromolecules that possess nanosized, hyper-branched, globular structures. Due to their monodispersity and well-defined chemical structure, dendrimers are utilized in drug delivery applications. A typical dendrimer consists of a central core, which can be a single atom or a multi-atom group; generations of recurring building blocks; and surface functional groups for drug formation on the dendrimer surface [71,72].

- ***Polymeric micelles***

Polymeric micelles are a specific type of self-assembling nanostructure composed of amphiphilic copolymers, have a size of 300 nm or less, and offer superior drug-delivery properties for hydrophobic drugs [73, 74].

- ***Lipid-based nanoparticles***

These nanoparticles were developed to address the shortcomings of conventional formulations. The NLCs are made up of a core matrix of both liquid and solid lipids. Increased solubility, enhanced storage stability, improved permeability and bioavailability, reduced adverse effects, a longer half-life, and tissue-targeted delivery were all demonstrated to be advantages of NLCs over conventional carriers for drug therapy. In recent years, more and more attention has been paid to NLCs [75, 76].

- ***Solid lipid nanoparticles (SLNs)***

SLNs are particularly effective for brain targeting. They possess greater drug-carrying capacity and decreased toxicity than polymeric nanoparticles. When delivered via intravenous administration, SLNs enhance both drug delivery and therapeutic benefit to the CNS [77,78]. SLN systems are an excellent candidate for multi-use drug delivery systems, as they are both biocompatible and biodegradable. In addition, SLNs can carry both water-soluble (hydrophilic) and fat-soluble (lipophilic) drugs and exhibit different drug-release characteristics depending on their structure [79]. Furthermore, SLNs have many advantages, such as controlling the rate and site of drug release, increasing drug availability & providing chemical stability for drugs. One way to increase the degree of interaction between an SLN and mucus in vivo is to enhance mucoadhesion or to apply techniques for transporting SLNs across biological barriers, e.g., the blood-brain barrier, by modifying the SLN surface with coatings such as chitosan.

Compared with traditional formulations, chitosan-coated SLNs had a dramatically improved capacity to absorb drugs and thus provided greater therapeutic benefit when delivering medications to the brain. SLNs are an appealing platform for the development of targeted drug delivery systems due to these properties [80]. Techniques related to the creation of novel systems for targeted delivery, surface modifications, and the use of multifunctional formulations are increasingly being utilized in the evolution of SLNs. Targeted delivery enhancements, improved bioavailability, sustained release profiles & targeted applications in brain and cancer therapies represent some of the areas being developed with respect to SLNs. In particular, chitosan-coated SLNs, ligand-functionalized SLNs, and stimuli-responsive SLNs have been developed. These newer methodologies have demonstrated improved stability, cellular uptake & therapeutic effectiveness compared with traditional SLNs. Critically comparing the methods revealed considerable variation in surface modification approaches, with at times modifications to targeted deliverables surpassing those of traditional lipid-based SLNs [81, 82]. Different structural classifications of SLNs, such as homogeneous matrix systems, drug-enriched cores, or drug-enriched shells, affect the methods used to load and release drugs from these nanoparticles. Thus, SLNs provide a useful foundation for the creation of targeted drug delivery techniques [83].

- ***Chitosan-based nanoparticles***

Chitosan is utilised as a carrier for these nanoparticles, enabling controlled drug release, protection against enzymatic degradation, and enhanced drug delivery to the site of action. Additionally, chitosan can increase the drug's movement across the BBB through modulation of tight junctions [45].

Comparison of SLNs and NLCs for Chitosan-Coated Nose-to-Brain Delivery

Due to their biocompatibility, ability to increase drug solubility and permeability, and ability to facilitate drug targeting to the brain, SLNs and NLCs have been used as lipid-based nano-

carrier systems for drug delivery from the nose to the brain. The solid lipid core of SLNs remains solid at both body and room temperatures. As a result, the rigid structure not only ensures stability but also permits controlled drug release from the carrier. However, because of their highly ordered crystalline structure, SLNs may have limited drug loading, as drug molecules may be pushed out of the lipid matrix during long-term storage due to lipid polymorphic transitions [84]. NLCs, on the other hand, are a second-generation lipid nanocarrier system that uses a combination of liquid and solid lipids to form a crystalline matrix that is less ordered or not perfectly ordered. The SLNs' closely arranged crystalline structure is disrupted when a liquid lipid is added, creating additional space to accommodate additional drug molecules. This often allows for a greater drug-loading capacity, as well as a reduced likelihood that drugs will be expelled from SLNs upon storage. In general, these flexible structures allow these systems to deliver greater encapsulation efficiency and to produce more regulated release rates. In general, SLNs can be expected to demonstrate superior physical stability and ease of use for formulations compared with non-crystalline lipid nanoparticles (NLC); however, NLC may offer advantages in drug loading capacity and stability when developing formulations with large drug loads or long release times. Both SLN and NLC-based carriers should be coated with chitosan to enhance their drug-carrier performance through surface modification. Overall, due to their natural structural flexibility, NLCs are more likely than SLN to be employed in the formulation of higher drug-loaded and longer-lasting systems [85].

Safety and Immunogenicity Considerations

Although lipid nanoparticles and chitosan carriers are generally considered "biocompatible" or "non-toxic", recent findings suggest that chronic use via the nasal route warrants a more rigorous safety assessment than short-term toxicity testing. Particulates, excipients, and mucoadhesive polymers in the nanocarrier systems could negatively affect the nasal mucosa, compromise the structural integrity of the epithelial layer and the mucociliary system, and mechanically promote localized inflammation. Furthermore, the intranasal route provides a pathway for transporting substances via the nose-finger tract to the brain via the olfactory and trigeminal pathways. Theoretically, lipid matrices that are long-acting or slowly biodegradable could accumulate in the CNS and have potential neurotoxic effects. To date, no studies have examined these potential neurotoxic effects or the biodistribution of these delivery systems within the CNS over time. Additionally, the surface modification of nanocarriers and their components may be recognised by the innate and adaptive immune systems, leading to either a pro-inflammatory response or activation of local immunity with repeated dosing of lipid nanoparticles and chitosan nanocarriers, and it is critical to evaluate immunogenicity and inflammatory biomarkers in safety assessment studies [86].

QUALITY BY DESIGN (QBD) CONSIDERATIONS FOR CHITOSAN-COATED SLNS: CRITICAL QUALITY ATTRIBUTES AND CRITICAL PROCESS PARAMETERS

Critical Quality Attributes (CQAs)

CQAs for chitosan-coated solid lipid nanoparticles (SLNs) include their physical, chemical, and functional properties, all of which must be controlled to ensure product quality and performance. The physical CQAs include Particle size and polydispersity can affect how well a particle will deposit in the nasal cavity, how well it can be taken up by cells, and how well it can transport to the brain; The zeta potential reflects the surface charge of the particle and reflects successful chitosan coating of the SLN for mucoadhesion; The drug entrapment efficiency controls how long the drug can be delivered using sustained or controlled release; The in vitro drug release profile; and the physical stability of the formulation during storage, as aggregation or expulsion of drug affects the efficacy of an SLN. Chitosan-coated systems must have a positive surface charge to interact more effectively with the negatively charged nasal mucosa. This allows the particulate system to remain in this area for longer and enhances absorption into the nasal mucosa, enabling systemic delivery of the drug or other active pharmaceutical ingredient (API). Thus, the aforementioned characteristics sum up the reproducibility, efficacy, and safety of any SLN coated with chitosan [87].

Critical Process Parameters (CPPs)

The formulation and processing variables, known as CPPs, directly affect the CQAs of chitosan-coated solid lipid nanoparticles (SLNs). Surfactant type and concentration directly affect particle stabilization and size reduction; the drug-to-lipid ratio affects entrapment efficiency; and homogenization or ultrasonication speed and time affect particle shape and distribution, all of which are critical CPPs during SLN

manufacturing. The processing temperature is also very important because it affects the crystallinity and stability of emulsified and melted lipids. Because these variables control coating thickness, surface charge, and mucoadhesion, chitosan concentration, chitosan molecular weight, coating medium pH, and stirring time all contribute to the total critical CPPs. You will achieve reproducible particle characteristics, efficient surface functionalization, and consistent therapeutic performance by carefully optimizing and controlling the CPPs [88].

Characterization Parameters of Nanoparticles

- ***Particle Size and Polydispersity Index (PDI)***

Dynamic light scattering (DLS) was used to measure the polydispersity index and mean particle size of chitosan-coated SLNs using a Zetasizer. Nanoparticles delivered intranasally to the CNS are usually in the 100-300nm range. Because of their small size, they are less likely to be cleared quickly by mucociliary clearance and therefore provide greater ability to improve retention time and penetration through the olfactory and trigeminal pathways via direct nose-to-brain transport. PDI measures the uniformity of particle sizes in your nanoparticle suspension. PDI < 0.3 indicates narrow dispersion of particle size (particles are uniform in size, good quality) [89]. Because light scattering intensity is strongly correlated with particle size, larger particles or aggregates dominate the outcome. The core of the particle, any surface modifications (such as the hydrated chitosan coating), and the solvent used to collect the data are all included in this [90].

- ***Zeta Potential Measurement***

The zeta potential measures the surface charge of nanoparticles and is measured using the zeta sizer, which combines Phase Analysis Light Scattering (PALS) and Laser Doppler Velocimetry (DLV) principles. Particles within this range have a significantly higher positive zeta potential (+20 to +40 mV) than larger particle sizes; therefore, they may contribute to greater mucoadhesion due to their interaction with negatively charged nasal mucosa. This increases the residence time of the particles in the nasal cavity, thereby enhancing cellular uptake. High and positive (+30 mV) generally indicate stable dispersions (electrostatic repulsion prevents aggregation) [91]. pH and ionic strength have a significant impact on the zeta potential, which is actually a measurement of the electrokinetic potential at the slipping plane. Protonation and ion adsorption of amine groups (with pKa values between approximately 6.3 and 6.5) on protonated chitosan NPs have a dramatic effect on the measurement of the zeta potential (the particle's surface charge), as well as on the pH-dependent zeta potential. Thus, straightforward media-based measurements of zeta potential may not reflect the true in vivo stability of chitosan-based NPs [92].

- ***Transmission Electron Microscopy (TEM) Analysis***

From TEM micrographs, the morphology of these nanoparticles and the size of SLNs can be established. Typically, SLN dispersions are dried onto carbon-coated copper grids before microscopic examination [93]. Due to the combined effects of hydrodynamic contributions to scattering and intensity bias in light-scattering measurements, DLS commonly overestimates particle size relative to TEM. The use of polymer coatings provides a true measurement of the core size for polydisperse materials using TEM analysis, whereas the DLS method does not [94].

- ***Powder X-ray Diffraction (PXRD)***

The sample's crystallinity is being evaluated using XRD. PXRD spectra of the drug and drug-loaded SLNs are being obtained to assess changes in crystallinity upon encapsulation in the nanoparticles, as reflected by a reduction in peak number and intensity [89].

- ***Fourier Transform Infrared Spectroscopy (FTIR)***

Using a Fourier Transform Infrared Spectrophotometer (FTIR), the FTIR spectra of the API, API-loaded chitosan-SLNs, blank chitosan-SLNs & the suspensions of the physical mixtures were recorded. The lyophilized samples were prepared as KBr discs and scanned at wavelengths measured between 400–4,000 cm^{-1} [93].

- ***Differential Scanning Calorimetry (DSC)***

Measures lipid thermal transitions, providing information about crystallinity. It reveals SLN crystallinity through lipid melting peaks. Slightly lower or broader peaks indicate less-ordered structures, which can improve drug loading and influence release. Nanoparticles containing amorphous or partially crystalline drugs provide better solubility and controlled release. The physical state of the drug within the lipid matrix can be confirmed by using differential scanning calorimetry (DSC). Crystalline forms of the drug can decrease the rate at which it is released from the nanoparticles, which may also affect stability. We demonstrate DSC to evaluate dry blends of excipients, lyophilized preparations, and thermal behaviour. Samples were

introduced into flat-bottomed aluminium pans and heated at 10 °C/min under a nitrogen atmosphere from 20 to 500 °C [91].

- ***Entrapment Efficiency Determination***

It was detected by ultracentrifugation. HPLC analysis was performed after centrifugation of the samples at 13,000 rpm for 1 h to quantify the free drug content in the supernatant. Drug entrapment was calculated from the free drug concentration using the appropriate equation [89].

DRUGS USED TO TREAT VARIOUS CNS DISORDERS

Multiple CNS agents have been evaluated for use in conjunction with chitosan-coated SLNs or other forms of lipid-based nanoparticles. Studies using chitosan-coated SLNs containing ferulic acid have reported cognitive improvement in animal models of Alzheimer's disease [95]. Chitosan-coated carriers were also tested in AD models using Aβ1-42, exhibiting sustained release and enhanced nasal absorption properties [53] and in research on Parkinson's disease that used Tan-ShiNo delivered intranasally. Using chitosan-coated nanostructured lipid carriers for IIA and GDNF, significant increases in behaviour and histological response were observed [96]. Chitosan-coated SLNs containing dopamine were also found to have the potential to cross the BBB and increase the availability of CNS drugs [97]. Chitosan-coated solid lipid nanoparticles have demonstrated that ferulic acid, a compound with moderate lipophilicity, can be incorporated into the lipid core of the SLNs at a high level of entrapment efficiency (about 51% EE). By contrast, dopamine, a highly hydrophilic and ionizable compound, has been incorporated into SLNs with a lower entrapment efficiency (approximately 36% EE). The findings underscore the influence of drug physicochemical properties—particularly lipophilicity and ionization behaviour—on drug partitioning and entrapment within chitosan-coated SLN systems [95,97].

PHARMACOKINETICS AND BIODISTRIBUTION

A double-emulsion technique has enhanced the ability to load hydrophilic drugs into nanoparticles. Several investigations reported that hydrophilic drugs can effectively enter the brain via intranasal drug delivery. Intranasal drug delivery has clinical benefits, including noninvasiveness, ease of dosing, rapid CNS drug delivery, and multiple administrations. Intranasal delivery of therapeutics has been shown to increase brain uptake by more than 5-fold compared with intraperitoneal administration [98,99]. Pharmacokinetic studies in animals have shown that the use of chitosan-coated SLNs for intranasal drug delivery has advantages over the other usual methods of delivering drugs via the mouth and the rectum; for example, sinapic acid that has been delivered intranasally as chitosan-coated SLNs had a significantly greater area under the concentration-time curve ($AUC_{0-\infty}$) in the brain than did the same compound when delivered intravenously in solution form (table 2). This is evidenced by a 3.7-fold increase in the AUC of the brain tissue with chitosan-coated SLNs compared with the intravenous delivery method, indicating that these formulations have a greater ability to reach the brain [80]. The quantitative information (i.e., the area under the curve [AUC] and fold differences) provides solid data supporting that the use of chitosan-coated SLNs for nasal administration can improve delivery to the central nervous system when compared to traditional systemic routes of administration. The data also support the feasibility of using chitosan-coated SLNs as a direct route (nose-to-brain) to achieve enhanced delivery and greater availability in the cerebral circulation compared with other drug-delivery methods [100]. Chitosan-coated nanoparticles have shown even greater nose-to-brain transport efficacy than simpler chitosan, primarily because a chitosan coating increases mucoadhesion, minimizes enzymatic degradation, and prolongs nasal residence time, all of which improve a drug's likelihood of achieving bioavailability through the central nervous system [44]. Pharmacokinetic and regional distribution studies are necessary to quantitatively compare the kinetic profiles of intranasal administration with those of systemic administration. The results indicate that, when intranasally delivered, chitosan-coated SLNs produce a greater AUC and maximum plasma concentration (Cmax) in the brain, as well as a higher brain-to-plasma ratio, than when administered via the systemic route. However, the final results will depend on the formulation of the SLNs; their particle size and zeta potential will influence the availability of SLNs in the nose and on the brain. In addition, the literature shows significant variability in both the regional distribution of the drug within the brain and overall systemic exposure, due to inconsistencies in the models and analytical methods employed by researchers. Therefore, the precise relationship between formulation features and the reproducibility of directed brain drug delivery requires further study [101]. Comparative studies of plain drug solutions and intravenous drug formulations confirm that chitosan-coated SLNs provide better brain bioavailability than other forms of caregiver-oriented delivery. First, techniques used to identify

drug distribution in specific brain regions (e.g., radiolabeling or fluorescence) have limitations. Specifically, radiolabeled drugs may dissociate from their labeled component and lead investigators to overestimate drug accumulation in the brain. Second, fluorescent dye-based approaches allow for drug molecules to diffuse away or degrade, ultimately leading to inaccurate measurements for the target area [102]. The increased area-under-the-curve values for brain-drug targeting indicate that chitosan-coated nanoparticles delivered via the intranasal route represent a viable strategy for achieving successful drug transport via the nose-to-brain pathway, despite the drawbacks of some methods [103].

Table 2: Pharmacokinetic studies on chitosan-coated SLN

Drug/formulation	Model	Route of administration	Target tissue	Pharmacokinetic changes	Relevance
99mTc Radiolabeled SLNs & Chitosan-Coated SLNs [102]	Mice	IV	Plasma/ organ	Blood radioactivity of chitosan-coated SLNs was 7.5×, 3.17× & 3.5× higher at 1, 4, and 8 h, respectively, compared to uncoated SLNs.	Chitosan coating altered biodistribution by reducing liver uptake and improving systemic circulation
Griseofulvin Loaded Chitosan-Coated SLNs [104]	Rat	oral	Plasma	1.7–2.0 fold increase in bioavailability compared to conventional formulation.	Demonstrates enhancement of systemic PK via chitosan coating
Insulin-Loaded Chitosan-Coated SLNs with Piperine [105]	Rat	oral	Plasma	Sustained insulin release with significant blood glucose reduction; improved PK/PD correlation (quantitative PK not explicitly reported).	Included for formulation-dependent PK improvement, though non-CNS
Artemether-Loaded Chitosan-Coated SLNs [106]	Rat	oral	Plasma	Improved bioavailability and controlled drug release compared to artemether suspension.	Non-CNS study included to highlight PK enhancement by chitosan-coated SLNs

PRECLINICAL STUDIES

Table 3: Preclinical Studies on Intranasal Chitosan-Coated SLNs/NLCs.

Drug	Formulation	Animal model	Pharmacokinetic effect	Behavioural / Biochemical Endpoints	Therapeutic Implication
Buspirone (Brain Targeting) [107]	Chitosan-coated NLCs	Rat	Enhanced brain uptake, prolonged half-life, sustained release, improved AUC, and higher C max.	Elevated brain drug levels; reduced systemic clearance	Potentially better efficacy for anxiety and depression
Sinapic Acid (Cognitive Enhancement) [53]	Chitosan-coated SLNs	Mice (Alzheimer's model)	Increased brain bioavailability, higher brain C max, sustained release, and reduced systemic clearance.	Improved memory performance; ↓ oxidative stress markers (e.g., MDA)	Improved cognitive function & reduced oxidative stress.
Ferulic Acid (Alzheimer's Disease) [9]	Chitosan-coated SLNs	Preclinical Alzheimer's models	Enhanced brain targeting, higher AUC in the brain, extended half-life, and improved nasal mucosa permeation.	↓ Amyloid burden; ↓ oxidative stress biomarkers	Effective neuroprotective therapy.
Dihydroergotamine (Migraine Treatment) [108]	Chitosan nanoparticles	Preclinical systemic studies	Improved bioavailability, faster onset of action, higher systemic and brain conc.	Rapid onset of pharmacological effect	Enhanced efficacy for migraine relief

CHALLENGES AND LIMITATIONS OF PRECLINICAL STUDIES

Using the nasal route for drug administration does have some disadvantages**.** The main limitation to the diffusion of water-soluble, high-molecular-weight drugs (such as proteins) is their low membrane permeability. Additionally, mucociliary clearance limits absorption, as the nasal cavity's drug-excretion

rate is high [109,110]. The nasal cavity's absorption surface area is also much smaller than that of the gastrointestinal tract. Other concerns include nasal irritation (which could contribute to patient non-compliance) and susceptibility to enzymatic degradation [111,112]. The clinical translation of intranasal chitosan-coated solid lipid nanoparticles (SLN) to Humans has several limitations that will impede their use, despite pre-clinical data supporting these formulations. The lack of reproducibility of SLNs in Humans is primarily due to variability in Mucus composition, clearance, and physiology, resulting in wide variability in SLN drug absorption and delivery [113].

Anatomical and physiological differences between animal models and humans—such as a proportionally larger olfactory region in rodents (~50% of the nasal cavity) compared to humans (~3–10%)— can underestimate direct transport from the nose to the brain in preclinical studies, complicating direct translation to clinical outcomes [114]. Also, given the limitations of dose volume for intranasal SLNs in Humans (typically ≤100-150 µL per nostril in adults), only very potent and concentrated SLN formulations can be administered to patients in a single dose [115]. These factors contribute to clinical trial design barriers, including dose selection, variability in patient responses, and delivery device optimization for consistent deposition, which must be considered in early clinical development to ensure reproducible and effective nose-to-brain delivery [116]. While it is possible to deliver drugs using this method (chitosan-coated nanoparticles), which are absorbed into the brain after intranasal administration, several limitations must be considered. One such limitation is the potential for nasal toxicity arising from the chronic nature of the intranasal route of administration, which can lead to mucosal irritation or injury over time [117]. Another factor that must be taken into account is the anatomical and physiological differences in the nasal cavity among individuals; hence, the way a drug is delivered and absorbed will vary from one patient to another, potentially affecting the efficacy of a given drug in each patient [118].

During preclinical studies, the use of three-dimensional (3D) printed nasal casts derived from human anatomy will enable a more accurate representation of human nasal anatomy and will increase translational relevance for nose-to-brain delivery studies. The intricate geometry of the human nasal cavity, including the olfactory region, turbinates, and nasal valve structures, is represented in these nasal casts reconstructed from CT or MRI images. Quantification of drug deposition by region can also be conducted in vitro using these devices, overcoming some anatomical differences observed in rodents (such as the relative size of the olfactory region) that can limit translation to clinical practice. The evaluation of powder and spray deposition patterns, as well as further analysis of administration parameters (such as head position or nozzle angle) to optimize olfactory targeting, has been extensively analyzed using 3D-printed nasal casts. The design of customized devices and formulations has also taken into account individual nasal geometries. The nasal anatomical models also use multiple CT-derived models with different nasal geometries to represent intersubject variability. These models have been shown to yield details that animal testing alone cannot, thereby enhancing the prediction of human nasal deposition profiles and directing optimal delivery strategies for nose-to-brain applications [119]. Also, for a chitosan-coated formulation to be transferred from the laboratory to commercial scale, it is essential to produce uniformly sized, coated particles, which is extremely difficult to achieve. Moreover, the regulatory aspect of developing chitosan-coated formulations is also an important consideration [120]. To receive regulatory approval for any chitosan-coated formulation, every batch must be identical; therefore, companies will find it challenging to demonstrate that their excipients (such as chitosan) are acceptable for use in humans. For these reasons, all of these aspects must be addressed by anyone who wishes to develop a chitosan-coated formulation for use intranasally to the CNS before commencing clinical development [121]. Studies on ex vivo nasal mucosa are conducted in an ex vivo environment that preserves the natural tissue structure and enables direct assessment of drug deposition and safety, thereby increasing clinical relevance. E.g., in the study of the cytotoxicity of mucoadhesive nasal gel and its dexamethasone release profiles, human nasal mucosa was explanted from the nasal cavity while maintaining its structural integrity (ex vivo) and allowing for the direct measurement of drug deposition, data indicating the drug's distributions were consistent across both ex vivo and in vivo conditions. Given that human-tissue-based models provide human-translational attributes, they can inform regulatory bodies of their human relevance and provide guidance for subsequent in vivo animal studies. Initial human safety trials would be required to assess tolerability in nasal tissue [122]. To proceed with the clinical development of intranasal carriers, the product development plan must align with current Agency guidelines for nanocarriers, as set out in FDA (Food & Drug

Administration) and EMA (European Medicines Agency) regulations. These guidelines require the complete characterization of all aspects of the nanocarrier, including size/shape distribution, surface charge, drug load, stability, and reproducibility across batches [123]. Until 2026, neither the European Medicines Agency (EMA) nor the United States FDA maintains databases that include chitosan as an excipient for intranasal medication products. In addition, chitosan is not listed in the FDA's Inactive Ingredient Database (IID) for medications intended for nasal use. The IID is a crucial list of excipients used in the formulations of approved drugs. An excipient's inclusion in the IID for a specific route of administration indicates that regulatory agencies have accepted it in previously approved products. Since the IID contains no chitosan, there is no indication that chitosan has been established as a novel excipient for the currently available intranasal pharmaceuticals [124].

Each submitted dossier must provide quality and safety information for excipients and support for their use in development based on the assessment of empirically supported safety and efficacy, as the EMA is responsible for assessing the described level of safety of an excipient's use in all medicinal products for human use marketed in the EU. In addition, none of the various marketing authorizations issued by the EMA for any intranasal drug product has included chitosan as an excipient [125]. Therefore, a developer must demonstrate that chitosan qualifies as a novel excipient for use in intranasal formulations and must also provide all required regulatory documentation and scientific support for its use when submitting to the FDA and EMA [124]. In addition to these requirements, the Agency has indicated that manufacturers of nasal nanocarrier products will need to conduct local nasal toxicity assessments; therefore, these assessments must be included in the clinical development information package submitted for approval. Lastly, because of the need to produce products on a large scale, scalable and robust manufacturing processes are imperative for maintaining product quality throughout [126]. The clinical translation of chitosan-coated SLNs faces several challenges, including nasal irritation, variability in batch-to-batch reproducibility, and patient compliance with therapy, which depends on dosing frequency and formulation comfort. To be successful using intranasal nanoparticles, these challenges need to be addressed [127].

FUTURE PROSPECTS

The advancement of new nasal drug delivery systems will likely increase tremendously in the upcoming years. Most initial uses will focus on acute diagnosis, such as acute pain, panic episodes, sleep disorders, erectile dysfunction, myocardial infarction, and Parkinson's disease [128]. Nasal formulations may be advanced for longer-term conditions such as diabetes, growth hormone deficiency, and osteoporosis. For neurological disease states, the intranasal delivery approach is the most promising, as drugs can be targeted to the brain via the olfactory mucosa, which offers a route to bypass the BBB. However, the therapeutic benefit could be affected by the small volume that can be administered via the nose. As such, there is a need to explore adjunctive and/or parametric administration routes to increase transportation to the CNS [129]. The development of tomorrow's SLN will likely place increasing emphasis on using a QbD approach to systematically determine and control the primary variables that affect the quality attributes of these products (for example, particle size, drug loading, and stability) [87]. Also, AI optimization enables automated prediction of the optimal formulation conditions, reducing development time and resources. Collectively, many believe that both innovative approaches will greatly improve the reproducibility, efficiency, and success of developing the next generation of SLN formulations compared to traditional methods [131].

Table 4: Comparative analysis of the brain targeting performance of intranasal drug delivery systems reported in the literature

Drug/Formulation	Brain AUC Increase	DTE% / DTI / DTP%	Results
Clonazepam nanocarriers [132]	Brain AUC increased 3.6–7.2 fold compared to IV	DTE and DTP confirmed direct nose-to-brain transport	Intranasal nanocarriers showed 3.6–7.2× higher brain AUC than IV solution, confirming direct brain uptake
Piribedil lecithin-CS NPs [31]	Brain AUC 6.4× vs free drug	DTP 56%	Nanoparticle gel delivered via intranasal route had much higher brain AUC & DTP1
Rivastigmine-DHA PLNs [133]	Brain AUC increased ~5.18× to 7.67× (compared to free drug)	DTE up to 792.5%, DTP up to 87.4%	Cationic PLNs produced strong brain targeting metrics
Rotigotine NLC [134]	Relative brain bioavailability ~3.2× compared to drug dispersion	DTE 422.03, DTP 76.03%	Rotigotine NLCs enhanced brain targeting metrics

CONCLUSION

Many reports on chitosan-coated SLN formulations using both olfactory and trigeminal routes of administration, as well as direct transport from the nose to the brain, have suggested that these systems may provide new opportunities for developing intranasal delivery systems to the central nervous system. It has been suggested that the properties of chitosan for its mucoadhesive properties combined with the lipid matrix of solid lipid nanoparticles will improve the length of time for the drug remains retained in the nasal cavity before being absorbed and transported into the brain, as well as improve the penetrability of the formulation through the nasal mucosa (nose) and enable better targeting of the brain. Based on the preclinical study, intranasal nanocarrier-based formulations markedly improve brain-targeting efficiency compared with conventional formulations (Table 4). These systems enhance brain bioavailability and demonstrate effective direct nose-to-brain transport, highlighting their strong potential for improved CNS drug delivery. For chitosan-coated SLNs to translate successfully into clinical outcomes, however, it will be important to develop effective formulations (optimization of the formulation) that are stable for long-term storage, are scalable, and to conduct further research on the pharmacodynamics and pharmacokinetics of these formulations to ensure adequate preclinical and clinical validation of the technology. In the light of the current situation regarding a growing demand for non-invasive, patient-friendly drug delivery systems targeting the CNS, this review has highlighted the opportunity for chitosan-coated SLNs to be further explored and potentially developed into commercially viable drug delivery formulations, providing the basis for further research on the rational design, mechanistic understanding, and clinical use of these nanoparticle formulations for drug delivery to the CNS. Despite significant progress made in demonstrating the efficacy of chitosan-coated SLNs both in vitro and in preclinical animal studies, it has been very difficult to fully realize their ultimate clinical potential due to the numerous challenges encountered when attempting to translate from bench to bedside; the primary challenge being the transition from manufacturing at a smaller-scale laboratory level to a larger-scale industrial level.

In general, maintaining the same size, shape, charge (i.e., Zeta Potential), and drug loading of nanoparticles from one batch (or lot) to the next is more difficult in subsequent large-scale production runs. To satisfy FDA requirements for the manufacture of any new drug product, state-of-the-art technology and stringent operational controls must be employed throughout all stages of manufacturing [131]. Another hurdle related to the eventual clinical use of products derived from chitosan-coated SLNs will be the need to consider any stability issues associated with the final chitosan-coated SLNs formulation before clinical use (e.g., much time/effort may need to be expended to find appropriate methods for mitigating issues related to lipid polymorphic transitions and drug leakage during storage). Finally, the manufacture and consistency of drug products will be subject to intense regulatory scrutiny [8]. Technical and Regulatory considerations regarding chitosan-coated SLNs will need to be carefully evaluated before clinical translation occurs.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Samruddhi Rakshe was responsible for the original draft preparation of the manuscript. Manisha Lalan contributed to the study's conceptualization and design. Pranav Shah, Vrutti Parmar, and Dikshitkumar Modi were involved in reviewing and editing the manuscript for important intellectual content.

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