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Insight into central nervous system targeted nanostructured lipid carriers *via* the nose to brain pathway

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In nanomedicine, targeting the central nervous system (CNS) is one of the biggest challenges. The presence of the blood–brain barrier (BBB) leads to the failure of drugs to reach the brain; hence, CNS-related diseases are challenging to treat. Various invasive and noninvasive methods have been established to overcome the difficulty of passing through the BBB. Delivery of drugs by using nanoparticles through the nasal route is one of the noninvasive methods developed to treat CNS disorders. The nose to brain pathway allows direct transport to the brain without crossing the BBB. Among the nanocarriers designed to target the CNS, nanostructured lipid carriers (NLC) are the focus of this review. NLCs appeared as a newer generation of solid lipid nanoparticles (SLN) developed to get over SLN's limitations. They are novel pharmaceutical preparations made of lipids, surfactants and co-surfactants that are physiologic and biocompatible. Liquid lipids (oil) are added to the solid lipid to create a matrix which results in structural flaws in the solid lipids and creates a less ordered crystalline framework that prevents leakage of the drug and provides high drug loading. The imperfection in the internal arrangement of NLCs aids more drug accommodation. A systematic search was performed across the main databases like PubMed, Springer, Scopus, Taylor and Francis, Google Scholar and Wiley. The search applied terms and keywords related to nose to brain delivery, nanostructured lipid carriers and neurodegenerative diseases. This review discusses the anatomy of the nose, associated pathways, advantages and limitations of NLCs, and preparation techniques and recent developments of NLCs delivered *via* the nose to brain route. The reported records demonstrated the feasibility and potential of NLCs for innovative uses for treatment in the future *via* the nose to brain route.

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1. Introduction

Drug buildout for central nervous system (CNS) diseases and psychiatric conditions is arduous due to the possible side effects caused by the drug, the complexity of the brain and especially the lack of systematic strategies for delivering drugs across the blood–brain barrier (BBB).[1] A relevant obstacle in the entry of active molecules into the CNS is the BBB. More than 98% of CNS-active medications are unable to penetrate the barrier because their physiochemical characteristics do not fit the entrance requirements for molecules entering the CNS.[2] The CNS is made up of the brain and spinal cord, which are the body's processing center. Any abnormality of these neurons causes various neurological dysfunctions. The term neurodegenerative disease refers to a group of deteriorating, incurable conditions that affect neurons and are characterized by a progressive, slow decline in the structure and performance of the central or peripheral nervous system. These neurons are nonreproducible and nonrenewable, so they cannot be replaced if the body loses them. These disorders are one of the most important medical and socioeconomic issues of our time, impacting a wide variety of elderly people and having a substantial impact on patients' professional, social and family lives, ultimately rendering them completely incapable of performing any daily activity. These are a few examples: Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), prion disease and amyotrophic lateral sclerosis (ALS).[3] The BBB provides a great obstacle to deliver drugs into the CNS. Routes such as parenteral and transdermal have been known to provide insufficient results that favor the nasal route as being superior when confirmed by a comparative study.[4] Thus, recent research focuses on searching for alternative routes for improving drugs that treat CNS conditions.[5] Comparing intranasal delivery, a noninvasive drug delivery approach to traditional drug delivery methods which are unable to cross the BBB provides a remarkable possibility to deliver drugs to the CNS in a focused and noninvasive way to provide direct nose-to-brain transport.[6] Intranasal

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administration can give direct access to drugs in the CNS through the different pathways present in the nose to brain route.[7] This route offers various advantages over other routes of administration: the convenience of administration, patient acceptance, non-invasiveness, a quick beginning of action, decreased enzymatic activity, a comparatively broad and permeable absorption surface and minimization of hepatic first-pass metabolism. As a result, there are more products on the market that use the nose to deliver small and large molecules (peptides, proteins and vaccinations) systemically. Therefore, nasal administration has been suggested as a treatment for several CNS illnesses including migraine, sleep difficulties, viral infections, brain tumors and conditions like multiple sclerosis (MS), schizophrenia, Parkinson's disease (PD), Alzheimer's disease (AD), and even obesity. Although the nasal route provides a large number of advantages, the lack of established translational animal models, inadequate olfactory area deposition from typical nasal devices, limited residence time, insufficient bioavailability of hydrophilic or big compounds, mucosal irritation and tiny nasal cavity spaces are some examples of potential constraints.[8]

Nanotechnology-based approaches to conquer the limitations of nasal drug delivery have attained the attention of researchers. Due to the unique properties of nanoparticles, they can circumvent the BBB, but the adverse effects of nanoparticles in the CNS is unknown. The nasal route is one way for nanoparticles to enter the brain. However, once inside the brain, they may concentrate and not be removed by the systemic circulation, leading to neurotoxicity.[9] To overcome these restrictions, researchers focus on creating advanced drug delivery systems. Nanostructured lipid carriers (NLCs) are advanced lipid-based nanoparticle carriers in drug delivery systems. They are composed of a binary mixture of solid and liquid lipids, strengthened with surfactants. The ratio of solid to liquid lipids ranges from 70 : 30 to 99.9 : 0.1, while surfactant concentrations vary from 1.5% to 5% (w/v). NLCs are spherical, with oil droplets embedded in the solid lipid matrix. Deficiencies in the lipid matrix create amorphous regions that enhance drug encapsulation and payload. The average size of NLCs is 10–500 nm. NLCs offer significant advantages over other lipid nanocarriers. They exhibit excellent biocompatibility, avoid organic solvents, and are easier to sterilize and scale up. As the second generation of solid lipid nanoparticles (SLNs), NLCs improve drug loading and storage time, addressing issues like drug expulsion. They are more stable, have a lower water content, and are cost-effective, providing better pharmaceutical stability and higher drug content. NLCs can encapsulate both lipophilic and hydrophilic drugs, are simple to manufacture and have improved aqueous dispersibility and excellent drug entrapment. They offer extended drug release, and their solid lipid matrices are widely acknowledged as safe.[10] In recent years, NLCs have gained more interest as potential drug carrier systems as they have a vast capacity to deliver therapeutic agents such as those that act specially on treating and managing neurological disorders.[11]

The main focus of this systematic review is the exploration of aspects of CNS-targeted nanostructured lipid carriers for nose-to-brain delivery. The literature search was conducted through various databases such as PubMed, Scopus, Science Direct, Taylor and Francis, Google Scholar, Web of Science, RSC, Springer and Wiley, using the keywords nose to brain delivery, nanostructured lipid carriers and neurodegenerative diseases. In this article different obstacles in CNS drug delivery and the potential of nose to brain drug delivery were discussed, including the anatomy of the nose, the pathways available for drug delivery through the intranasal route and the difficulties faced in delivering drugs intranasally and how to overcome them. The various advantages and disadvantages of NLCs, the different types of excipient used, NLC types, manufacturing and evaluation methods, as well as recent developments of NLCs for effective nose-to-brain delivery, pharmacokinetic considerations, stability, patents, and regulatory aspects of NLCs were summarized. Additionally, future prospects in the field of nose-to-brain delivery of NLCs were discussed.

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2. Obstacles in drug delivery to the CNS

The brain and CNS are incredibly intricate systems that naturally protect the body against potentially damaging or contagious bloodborne pathogens.[12] The human brain's molecular and cellular biochemical structure is continually changing due to developmental processes and life experiences, which affect how information is processed and flows through the brain.[13] Its regular operation depends on the CNS's ability to maintain homeostasis.[9] The drug delivery system towards the brain is challenging since the blood capillary endothelial cells of the brain have a strong defense mechanism against xenobiotics. The same defense systems that keep the brain safe from outside influences also prevent the admission of potentially useful drug molecules.[14] Drug movement to the brain parenchyma is impeded by three causes. The blood–brain barrier (BBB) is found in vessels in the brain, the blood–cerebrospinal fluid barrier (BCSFB) is displayed by ventricles having a choroid plexus epithelium, and the cerebrospinal fluid–brain barrier is where ependymal cells cover the brain tissue inside the ventricles by an epithelial layer of cells and restrict the passage of substances to the brain tissue *via* the CSF (Fig. 1).[15,16]

2.1. Blood–brain barrier

Drug development for brain diseases is difficult and more complex than for other therapeutic areas. Many drugs cannot enter the brain, complicating brain targeting.[17] The blood–brain barrier is a natural semipermeable edge between the brain and the rest of the body. This barrier is shaped by astrocytes, tight-jointed endothelial cells, pericytes, neurons and basal membrane.[18] Endothelial cells linked by tight junctions separate the brain parenchyma and blood. The tight junctions are the reason for the strict permeability, as they enclose the intercellular spaces between endothelial cells. Pericytes cover the endothelial cells by supplying a type of additional layer or second layer to the BBB.[19] Astrocytes contribute by secreting chemical reagents modifying the permeability through the BBB in response to neuronal signals, providing a cellular linkage between the neuronal circuitry and blood vessels, and stabilizing the BBB.[20] The existence of efflux transporters in the BBB is the cause of the poor penetrating ability of drugs.[26] The primary function of the BBB is to protect the brain tissue and maintain the exchanges within the brain and blood circulation.[21] The BBB confines the passageway of large hydrophilic molecules but then consents to the passage of small lipophilic molecules of molecular weight <400 Da to the brain[22,23] To prevent the influx of random complexes into the brain, the BBB acts as a barrier and allows selective passage to the brain. Several transport processes ensure the particular entry of molecules, such as diffusion, carrier-mediated transport, paracellular transport, adsorptive transcytosis, receptor-mediated transport and proton pump efflux transporters.[23]

2.2. Blood–cerebrospinal fluid barrier

When delivering a drug to CNS, the blood–cerebrospinal fluid barrier (BCSFB) prevents drugs from being administered. This barrier is formed by the discordance between the CSF and interstitial fluid.[24] It is located in the choroid plexus epithelium, the modified ependymal lining of the ventricles in the brain secreting cerebrospinal fluid.[25] The transporters in the BCSFB are recognized for maintaining the permeation of various molecules between the systemic circulation, CSF and brain interstitial space. Like the BBB, this barrier also comprises tight junctions restraining molecules' paracellular diffusion. Even though, when compared with the BBB, the BCSFB is much leakier, it is exceedingly capable of monitoring the CSF's molecular composition by selective transport mechanisms.[22] CSF serves as the foundation of the extracellular fluid surrounding neurons, playing a crucial role in supporting and sustaining their synapses. The BCSFB also significantly provides ions, micronutrients, and growth factors to the CNS. It also serves as a potential entry point for pathogens because of the secretion of CSF, causing the BCSFB to be more permeable, resulting in a lower electric resistance between the epithelial cells making it more vulnerable to diffusion from the blood.[27]

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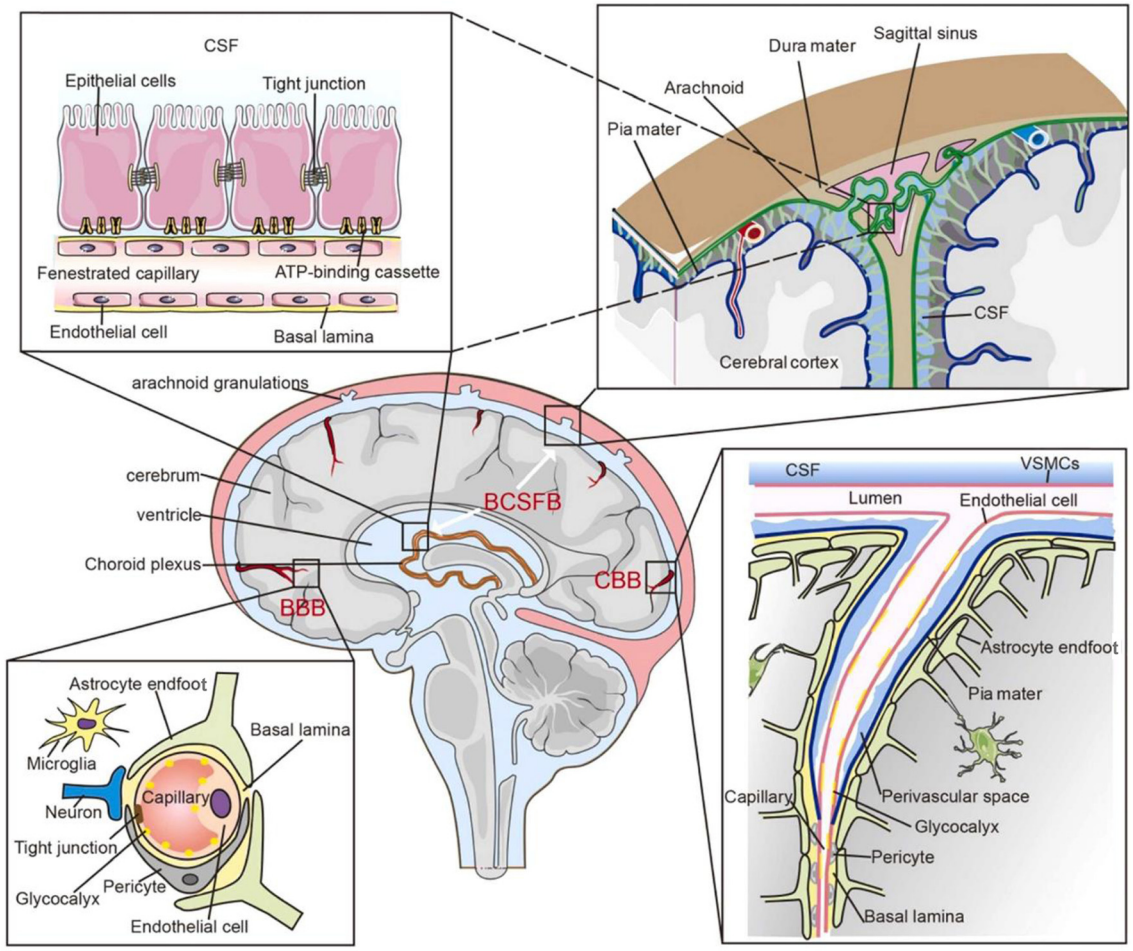

Fig. 1 Obstacles in drug delivery to the central nervous system (CNS). The CNS barrier system includes the blood–brain barrier (BBB), the blood–cerebrospinal fluid barrier (BCSFB), and the cerebrospinal fluid–brain barrier (CBB). The BBB is composed of pericytes, a basement membrane (BM), and astrocyte endfeet encircling tightly connected capillary endothelial cells, all surrounded by neurons, microglia, and other cells. The BCSFB exists in arachnoid granulations protruding into veins and the choroid plexus (CP), and is made up of a BM and tightly connected epithelial cells. The CBB consists of the pia mater and a glial boundary membrane composed of astrocytes. Additionally, a perivascular (PV) space is formed between the blood vessels extending into the brain parenchyma and the pia mater. As arterioles penetrate deep into the brain parenchyma and become capillaries, the surrounding pia mater gradually transforms into a BM. This figure has been adapted from the open access article from ref. 29. The figure is licensed under https://creativecommons.org/licenses/by-nc-nd/4.0/.

2.3. Cerebrospinal fluid–brain barrier

The cerebrospinal fluid–brain barrier (CBB) outlines the spinal canal and cerebral ventricles by an ependymal cell monolayer. The CBB is formed by these ependymal cells linked together with cell junctional proteins adjacent to the apical surface. They enable debris movement and CSF bulk flow by acting as a barrier that is protective by defending the periventricular white matter tissues and juxtaposed basal subependymal gray from CSF-laden toxins.[28] This barrier promotes water, exogenous tracer and CSF protein entry from the CSF by selective permeation due to the presence of gap junctions. Drugs can enter brain parenchyma through the CSF by two routes, diffusion and convection. Diffusion takes place by the drug diffusing from the CSF to the brain by the ependymal cells, and convection involves penetration of the drug in the CSF to the brain by the perivascular surfaces originating at the CSF exterior. Drugs injected into the CSF distribute to the blood and brain surface but do not diffuse into the brain parenchyma beyond a distance of 1–2 mm from the CSF compartment, according to studies, and the distribution of drugs in the CSF does not reflect the number of drugs permeating the brain parenchyma.[29]

3. Potential of nose to brain delivery

The BBB prevents chemicals from entering the brain or CNS, making direct administration of therapeutics to the brain extremely difficult. Many researchers developed substitute routes and methodologies to subdue this hurdle, but nose to brain routes emerged as an excellent help for CNS targeting.[30] Comparing the nose to brain route with the conventional route, it is a noninvasive method that provides access to the

CNS with the olfactory pathway or trigeminal pathway. Another potential of nose to brain delivery is through the systemic pathway which is undesired while delivering the drug through the nose to the brain. The systemic pathway is an indirect pathway that reaches the systemic circulation by nasal blood vessels to arteries and from arteries to the brain and spinal cord but the chances of reaching the brain by crossing the BBB is very low. Even though small-sized molecules can eventually enter, the dose reaching the brain will be too low for any therapeutic efficacy.[31] The nasal route prevents encounters with the BBB, which eventually does not lead to any obstacle related to crossing the BBB.[32] Due to its proximity to the CSF, the olfactory area has a direct connection to the CNS.[33] The nasal cavity has benefits that offer effective absorption and better permeability of small molecules and biopharmaceuticals. In order to safeguard the nerves that extend to the brain, the nasal cavity's roof has been built nearby. Nasal delivery would be able to supply a direct and less invasive strategy for treating CNS diseases including neurological disorders like Alzheimer's disease or Parkinson's disease and others by targeting the site of action.[34]

4. Anatomy of nose

The nose is considered to be a complicated creation and before studying drug absorption and penetration of the nose, it is necessary to understand the structure of the nasal cavity and its functions. The cavity is divided to three parts: the first is the vestibule region (with a surface area of ~0.6 cm^2), the second being olfactory region (with a reported surface area of 2–12.5 cm^2) and lastly the respiratory region (Fig. 2).[5] It has various functions, which include respiration and olfaction.[35] It also involves functions such as maintenance of the humidity and temperature of the inhaled air in addition to exclusion of external pathogens.[6,36]

The vestibule region of the nasal cavity prevents the entry of pathogens and has no absorption activity in its anterior part. It includes mucus and nasal hair that filter air particles entering the nose. Also, it is less porous owing to minimal vasculature and a reduced surface area.[36]

The olfactory region comprises basal cells, olfactory receptor cells and sustentacular cells.[9] The olfactory receptor neurons that are bipolar neurons transmit data through the epithelium to the olfactory bulb.[37]

The third part of the nasal cavity, *i.e.*, the respiratory region, surrounds the lateral walls of the nasal cavity and is considered to be the most vascular region. It has an area of ~130 cm^2.[35] The respiratory epithelium of the respiratory region is comprised of ciliated columnar cells and non-ciliated columnar cells, goblet cells that secrete mucus and basal cells. This area plays a major role in the absorption of drugs.[9]

5. Pathways of nose to brain delivery

The features of the nasal cavity, including its highly vascularized and permeable mucosal lining, facilitate the rapid and efficient absorption of drugs. Additionally, the availability of the olfactory and trigeminal nerve pathways is crucial in this context. The olfactory region is directly connected to the brain, particularly the olfactory bulb, *via* the olfactory nerves. The respiratory region, on the other hand, is supplied with trigeminal sensory neurons and blood vessels. Drugs can potentially reach different brain regions through a direct neuronal pathway, offering a strategy to bypass the blood–brain barrier (BBB) (Fig. 2).[38] Although the exact mechanism of drug transport from the nasal cavity to the brain remains a topic of ongoing research, some authors suggest that transporters present in both the olfactory bulb and the respiratory mucosa of the nasal cavity may play a significant role.[39,40] The pharmacokinetics of nose to brain targeted drugs through various pathways has been illustrated in Fig. 3.

5.1. Olfactory pathway

For a drug to be delivered to the brain from the nasal cavity it must pass through the olfactory epithelium through the olfactory nerve pathway.[41] This pathway is separated into various parts: olfactory tract, olfactory epithelium, piriform cortex, anterior olfactory nucleus, amygdala and hypothalamus. It is considered a significant route for brain delivery *via* intranasal administration.[42] This pathway is further subdivided into two categories. They are the intracellular or intraneuronal and extracellular or extraneuronal pathways.[43] In the intraneuronal pathway, through mechanisms like endocytosis, olfactory neurons ingest the molecules or drugs in the olfactory epithelium, after which they enter the olfactory bulb.[44] In the extraneuronal pathway, the drugs delivered intranasally cross the olfactory nerves and reach the olfactory bulb. For targeting various CNS disorders, the olfactory area allows a transparent connection between the nose and the brain.[45]

5.2. Trigeminal pathway

The second pathway of the nasal route is the trigeminal pathway, the most significant nerve pathway joining the CNS by innervating the respiratory epithelium and olfactory epithelium of the nasal passage.[46] The dorsum of the head, a portion of the eye, a large portion of the nasal mucosa, cerebral blood vessels, and the meninges are all innervated by means of the ophthalmic division of the trigeminal nerve.[47] The trigeminal nerve transfers sensory information through the nasal cavity, oral cavity, eyelids and cornea to the CNS.[48] The trigeminal nerve pathway comprises three branches: the ophthalmic nerve, the maxillary nerve and the mandibular nerve.[49] This pathway is important for the nose to brain delivery of drugs because the ophthalmic branches and maxillary branches of the trigeminal nerve pass directly through the nasal mucosa.[50,51] The drug targeted to the brain administered from the nose uses this pathway to channel drugs from the pons of the brainstem and to the hindbrain.[46] The transfer of many agents has been the subject of numerous research studies, for instance, insulin-like growth factor 1 (IGF-1) and interferon-β-1b (IFNβ-1b) through the trigeminal route.[52,53]

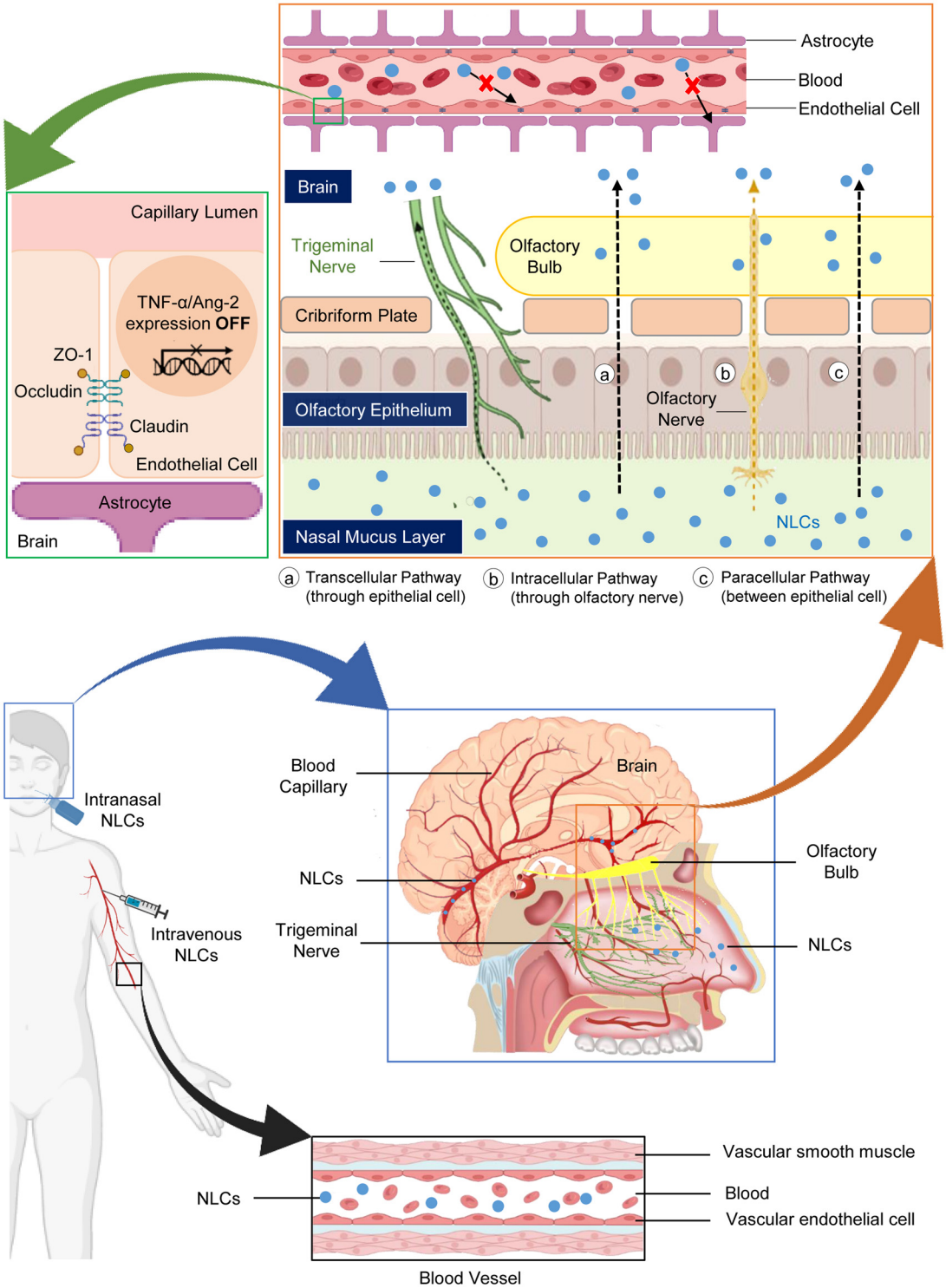

Fig. 2 Anatomy and *in vivo* fate of NLCs administered through intranasal and intravenous routes.

5.3. Systemic pathway

The systemic pathway is an indirect route for drug delivery to the brain that reaches the brain from the lungs and blood circulation. Being an indirect pathway it requires the drug to transport from the BBB to reach the brain.[31] Crossing the BBB is a rate-limiting stage because it requires more time to acquire the desired beneficial outcome and limits the quantity of drug entering the brain.[54] Hence, this pathway is suitable for small and lipophilic molecules as they can cross the BBB

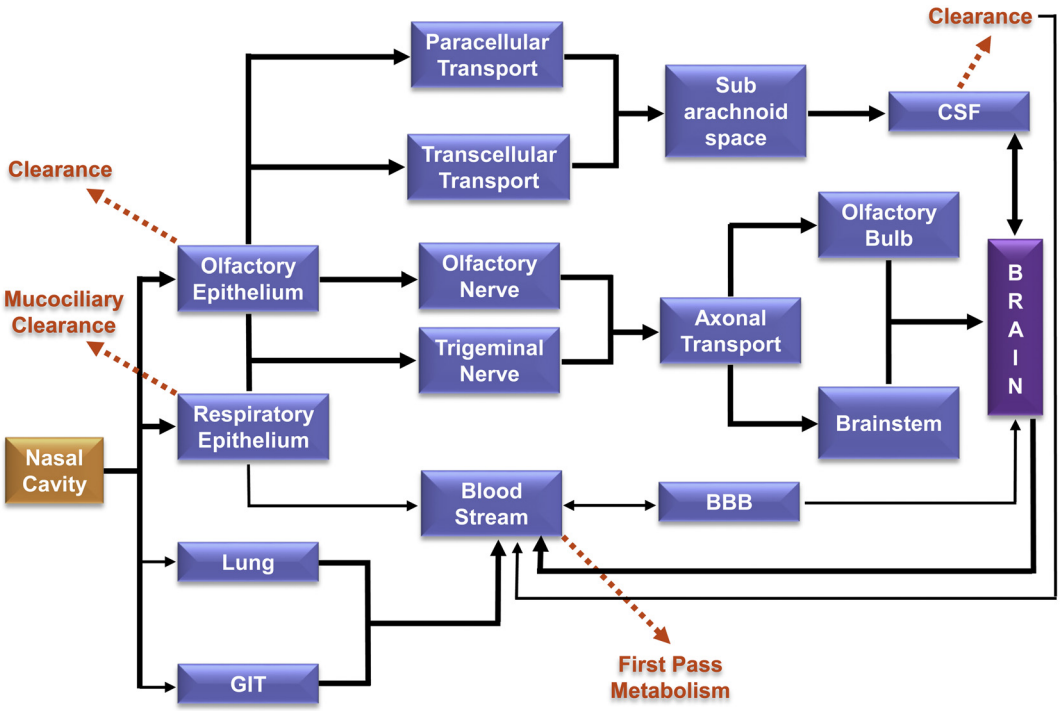

Fig. 3 Pathways of nose to brain drug delivery and pharmacokinetics. This figure has been adapted from the open access article from ref. 64. The figure is licensed under https://creativecommons.org/licenses/by/4.0/.

transcellularly.[55] Through the nasal blood vessels, the drug enters and reaches the carotid artery, after which the drug reaches the brain and, finally, the spinal cord. This pathway is least ideal because of various peripheral effects that can be caused.[56] A few observations on animals have claimed that medications can penetrate the brain *via* a local balance pathway from the venous to the carotid artery.

5.4. Lymphatic pathway

For drug transport at the submucosal level, several extracellular pathways exist in the olfactory nerve, spreading to the bulb of the olfactory region to the brain, consisting of perivascular, perineural or lymphatic channels.[57] The lymphatic pathway connects the subarachnoid space to the nasal lymphatic network.[58] Some drugs administered through the nasal route permeate the nasal mucosa and can get circulated through lymph nodes of the well-developed lymphatic network situated beneath the nasal mucosa.[59] This route finally ends in the neck's cervical lymph nodes, maintains water balance in the brain, and exports antigens to the cervical lymph nodes *via* the cerebrospinal fluid (CSF). Through this lymphatic pathway, drugs can be transported to the CSF which will successfully reach the brain tissue. It can also be said that this pathway may potentially overcome BBB limitations by maintaining the concentration in the brain and reducing possible peripheral side effects.[60] Although these connections among the subarachnoid space, nasal mucosa, and deep cervical lymph nodes are not entirely understood, a study describing them has been published that reports CSF clearance occurring through the lymphatic system, and evidence showing a relationship to the lymphatic vessels after intranasal administration for transporting substances to the CNS is deficient.[61–63]

6. Challenges in formulating nose to brain delivery

Although the nose to brain route offers many rewards, some limitations limit the delivery of drugs to the brain.

6.1. Mucociliary clearance

An essential mechanism of cleaning the nasal cavity during inhalation to eliminate foreign particles, likely dust, allergens and bacteria trapped in the nasal cavity's mucosa, is the activity of nasal mucociliary clearance.[65] When the nasal preparation does not match the physiological conditions of the nasal cavity, the residence time in the cavity shortens, leading to decreased drug bioavailability. This limitation can be overcome by reducing mucociliary clearance (Cecilia de Barros *et al.*, 2022).[66]

6.2. Permeation

The nasal route befits the passage of small molecules; hence, comparatively larger molecules, like proteins and peptides, need the advantages of absorption enhancers.[67] These absorption enhancers upgrade the permeability leading to a rise in the bioavailability.[68] Excipients used as mucoadhesives greatly

increase the time of interaction through the nasal mucosa for better permeation of the formulation.[69]

6.3. Enzymatic degradation

The presence of certain enzymes such as exopeptidases (monoaminopeptidase and diaminopeptidase) and endopeptidases (cysteine, serine) in the lumen and epithelial barrier of the nasal cavity debases various proteins and peptides.[70] Also, the presence of the peptidase enzyme restricts the bioavailability of the proteins and peptides as the enzyme cleaves these large molecules.[71] To protect the bioactive substance from enzymatic degradation, enzyme inhibitors or novel drug carriers are used to improve bioavailability in the nasal cavity.[72]

6.4. pH and nasomucosal toxicity

A significant concern for CNS disorders is toxicity. A certain bacterium available in the nasal secretions is known to be killed in acidic pH by lysozyme, which in alkaline pH seems to be inactive and the tissue of the nasal mucosa is liable to microbial infection.[73] For successful drug delivery, the pH of the formulations should be around 5.5–6.5 to avoid nasal irritation and tissue damage that renders the formulation toxic.[74] The application of mucoadhesive agents that increase the interaction period with the nasal epithelium produces toxicity. Modifying the absorption enhancers used in the formulation can help diminish toxicity.[75]

7. Nanostructured lipid carriers

Nanostructured lipid carriers (NLCs) fall under the lipidic drug delivery system category and have gained awareness in the area of nanoparticulate delivery of drugs (Fig. 4). The primary factor, as compared with alternative nanoparticulate delivery techniques, is the recognized biocompatibility.[76] NLCs are a new delivery system that proved to be more stable and capable of forming concentrated dispersions.[77] Among the point mentioned above, NLCs exhibit several other advantages over other drug delivery systems.

7.1. Advantages and disadvantages of NLCs over other nanoparticles

NLCs are known to have excellent advantages over other lipid nanocarriers. Some of them show excellent biocompatibility. Organic solvents can be avoided, and they are easier to sterilize and scale up. NLCs are the second generation of SLNs, which were discovered as an alternative for liposomes and other nanoparticles. Due to the distinct structure of NLCs, they cover up the disadvantages of other nanoparticles available like drug expulsion and are seen to improve the drug loading along with storage time.[78] Also, NLCs can be more stable and have a lower water content as compared with others.[79] When compared with polymeric or surfactant-based carriers, NLCs are inexpensive, provide better pharmaceutical stability, and deliver a higher content of drug as related to different carriers available in the market. NLCs have the opportunity to transport both lipophilic drugs and hydrophilic drugs at the same time.[77] Additionally, NLCs are simple to make, and have improved aqueous dispersibility, excellent drug entrapment for hydrophilic and lipophilic substances and a controllable particle size. They are a cutting-edge and effective drug delivery method, particularly for lipophilic drugs, and show extended drug release. Due to their solid lipid matrices, which are also widely acknowledged as safe or have regulatory acceptance, these carriers are extremely effective systems (Jaiswal *et al.*, 2016).[80] Also, surface modifications are possible to accomplish easily.[81] Looking over the advantages of NLCs over other nanoparticles, it can be justified that they are a suitable nanocarrier for the nose to brain delivery of therapeutics. Apart from the several advantages of NLCs, there are also certain limitations. Some limitations or demerits embrace a lower loading capacity for hydrophilic drugs and the combination of two or more therapeutic agents can cause a decrease in the encapsulation efficiency.[82] Also, the type and number of surfactants used can sometimes lead to irritation, sensitivity or cytotoxicity.[83]

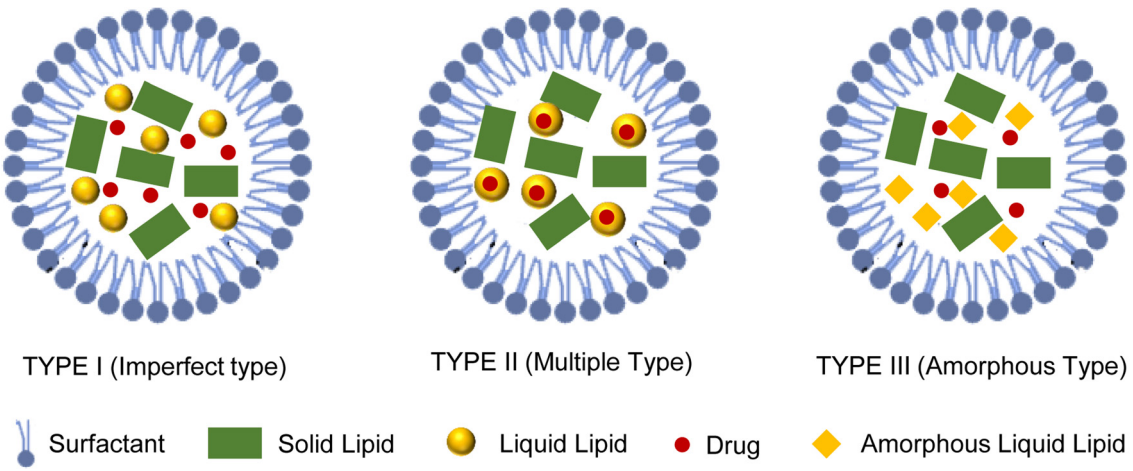

Fig. 4 Different types of NLC.

7.2. Composition of NLCs

Lipids, surfactants, organic solvents and other agents are the main components in formulating NLCs (Table 1).[84]

7.2.1. Lipids. The main elements are lipids that influence various factors while formulating an NLC, such as drug loading capacity along with stability.[85] It contains two lipids, solid and liquid lipids, for its preparation. For preparing NLCs, the solid lipid and liquid lipid are usually assorted in a ratio of 70 : 30 up to 99.9 : 0.1.[86] The kind and structure of lipids influence the different properties of the nanocarriers. It has been claimed that the most appropriate parameters for selecting a suitable lipid are the solubility or the lipid's apparent partition coefficient of bioactives in it. The solubility of drug molecule in lipids determines the drug loading and encapsulation efficiency. The evaluation parameters of NLC formulations, such as drug entrapment, drug loading, size of NLC and charge of NLC, are affected by the degree of crystallization of the different lipids used. The particle size of nanodispersion increases due to the increased viscosity in the dispersed phase and high melting point lipids. Other lipid-related characteristics that could affect the standard of the NLC include lipid hydrophilicity, lipid crystal shape, and composition fluctuation.[87]

The lipid at room temperature is solid but it melts at temperatures above 80 °C. It should be biodegradable, stable chemically without any toxic or hazardous effects, physiologically acceptable and a generally-recognized-as-safe (GRAS) status lipid. The lipids used include triglycerides, fatty acids, waxes and partial glycerides. Some commonly used solid lipids are Compritol 888 ATO, Precirol ATO5, *etc*.[88]

The solubility of drugs in liquid lipids is typically greater than in solid lipids.[89] Liquid lipids are selected or obtained from natural sources, which should be cost effective and non-irritating. Some liquid lipids used are sunflower oil, oleic acid *etc*. Oil-based liquid lipid assimilation leads to flaws in a solid lipid's structural integrity. These structural imperfections help in more drug loading as they cause the crystalline arrangement of solid lipid to be less ordered, leading to minimized drug leakage.[90]

7.2.2. Surfactants. Surfactants are required to improve the NLCs' interface quality to produce nanoparticles with stable characteristics.[91] They stabilize the formulation by coating the surface and minimizing the interfacial tension in between the organic and aqueous phases.[92] Emulsifiers (surface-acting agents) are adsorbed on the interface as a result of their amphipathic character within which they reduce the tension seen between the aqueous and the lipid phases. Surfactants are selected based on the delivery method, impact on particle size, hydrophilic–lipophilic balance (HLB) value, and lipid modification.[93] Several studies have proposed that the toxicity of NLCs, their physical stability and the crystallinity of NLCs have been largely impacted by the content and concentration of the surfactant.[94] Colloid particle crystallization occurs concurrently with solidification during the formulation of an NLC, but the particle's surface area increases noticeably during crystallization, making the entire system unstable. Therefore, a surfactant is necessary to enhance the nanoparticle interface quality stability.[95] NLCs to be prepared may also be subjected to aggregation and to protect the formulation from such, a combination of emulsifiers is used. Various surfactants include hydrophilic, lipophilic, and amphiphilic surfactants.[96] Examples of surfactants used include Tween 80 and Span 40.[97] Since the role of emulsifiers or surfactants used in the fabrication of NLC is to provide stability, preservation is another requirement for the stability of the formulation. Hence, using preservatives during the preparation of NLCs can maintain the physical stability of these formulations.[98]

7.2.3. Other agents. NLC formulations can include other components besides lipids and surfactants, such as counter-ions and surface enhancers. Cationic and water-soluble drugs may be enclosed in lipid nanoparticles with counter-ions including organic anions or anionic polymers.[99] Surface properties of colloidal drug carriers can be altered utilizing various methods to prevent phagocytic absorption and modify the biodistribution parameters of medications for their prolonged blood circulation. Surface coating with polyethylene glycol (PEG) polymers is one of the many methods employed to lengthen the blood circulation time of particles, and it has been reported to be effective.[100] Some counter-ions used include mono-octyl phosphate, mono-hexadecyl phosphate, mono-decyl phosphate and sodium hexadecyl phosphate. An example of an ionic polymer is dextran sulphate sodium salt and a few of the surface modifiers are DPPE-PEG_{2000}, DSPE-PEG_{2000} and $mPEG_{2000}$-C-LAA18.[99]

Table 1 Formulation ingredients of nanostructured lipid carriers (NLCs)

Components	Examples	Ref.
Solid lipid	Stearic acid, Dynasan 116, Dynasan 118, lauric acid, glyceryl monostearate, cetyl palmitate, Compritol 888 ATO, tristearin, Tefose 63	101–104
Natural liquid lipid	Sunflower oil, castor oil, lavender oil, cinnamon oil, clove oil, jojoba oil, soyabean oil, sesame oil, olive oil, garlic oil, almond oil, shark liver oil (squalene)	105–108
Synthetic liquid lipid	Vitamin E, isopropyl myristate, Capmul MCM, liquid paraffin, Lauroglycol 90, isopropyl palmitate, Miglyol 829, Miglyol 840, Captex 300, Miglyol 812	109–112
Hydrophilic surfactants	Tween 60, Tween 80, sodium oleate, polyvinyl alcohol, Pluronic F-68, Poloxamer 407, Poloxamine 908, sodium cholate, tyloxapol	113–115
Lipophilic surfactants	Span 20, Span 40, Span 60, Span 80, Myverol 18-04K	116 and 117
Amphiphilic surfactants	Egg lecithin, soy lecithin, phosphatidylcholine, Gelucire 50/13, phosphatidylethanolamines	118–120

7.3. Types of NLC

From studies on suppositories, it is well recognized that well-ordered crystalline lipid matrices will cause pharmacological ejection. This can occur with solid lipid nano- and microparti-

cle mixes particularly when nanoparticles are ordered from very pure lipids such as tristearin.[121] The NLC matrix is a disorganized structure where the various lipid molecules are combined to produce a matrix with as many flaws as possible. The combination of both the lipids results in a core that is solid at body and room temperature. Different forms of NLC are produced, each with a unique morphology depending on the varied production methods and the makeup of the lipid mixes (Fig. 4). The primary idea is to give the lipid matrix a specific nanostructure to maximize the payload for active chemicals and decrease compound ejection during storage.[122]

7.3.1. Type I (highly imperfect matrix). The crystal order is hampered by mixing spatially dissimilar lipids, including various oils and solid lipids.[123–125] We use these flaws to accommodate drugs with large payloads.[114] Examples of spatially diverse lipids that allow for comparatively large chain lengths within fatty acid chains are glycerides made up of several fatty lipids.[126] This type of NLC provides extra space to fit the drug molecules because of the development of small voids and has a low oil content.[115] The small voids present in the structure are because of the disordered shape of the solid matrix.[116]

7.3.2. Type II (multiple types). Within a solid lipid matrix, this kind of NLC has distinct liquid lipid compartments. Throughout the crystallization process, phase separation of the solid and liquid lipid takes place. When lipids reach a specific temperature, oil residues form tiny droplets.[127] Oily nanocompartments are arranged as a result of the solidification of the lipid that originally encased these droplets in solid form.[128] When the solid lipid lacks drug solubility, a larger amount of liquid lipid is added to gain an advantage of the solid matrix that averts leakage of the drug. The liquid lipid reveals high solubility for the lipophilic drug.[129] These have the dual benefits of increased loading capacity of the drug and extended release of the drug because drugs are more soluble in oily compartments.[130] This type is known as type II NLC.[119]

7.3.3. Type III (amorphous types). The third form of NLC inhibits the process of crystallization brought on by the fusion of solid and liquid lipids.[131] Crystallization is inhibited because it causes drug expulsion and to limit the drug expulsion, the polymorphic nature of the lipid matrix of NLC is sustained.[99] The lipid matrix is amorphous and solid and produces a lipid–drug conjugate.[132] In this type, specific lipids like hydroxyoctacosanyl hydroxystearate or isopropyl myristate that do not crystallize after homogenization and cooling are combined with the solid lipid to create an amorphous matrix that lacks any structure.[128] The NLC thus takes on an amorphous structure as opposed to an organized state, preventing drug expulsion brought on by modification during storage.[133]

7.4. Surface modification

Surface modification is coating the NLCs with hydrophilic polymers, ensuring the ease of transport across the epithelium, and its stability and targeting ability.[134] During the transport of drug-loaded NLC *via* the nose to brain route, the surface of the NLC is modified to improve the limitations of the nasal cavity, mainly mucociliary clearance and penetration. To increase the adhesion property of the NLC to the nasal mucosa, the NLCs are coated with chitosan,[135] *Delonix regia* gum[136] and gelatin.[137] Cell-penetrating peptides (CPP), for example, can be added to the surfaces of NPs to make them more capable of travelling from the nose to the brain.[138] The penetration of chitosan-coated NLCs, PLGA NPs and NLCs in a study utilizing an *in vitro* model of olfactory cell monolayers is 0.7%, 8% and 22%, respectively. After surface modification with CPPs, Tat or penetratin, Tat-chitosan-NLCs and penetratin-PLGA-NPs displayed 46% and 7% penetration, respectively.[139] As a result, ligand conjugation affects the rate at which molecules pass over the epithelium of the nose. Lectins, including wheat germ agglutinin, are a relevant targeting ligand for NP delivery from the nose to the brain.[140] For nasal administration applications, lactoferrin is potentially a target ligand.[141]

7.5. Fabrication techniques

There are numerous protocols available for formulating NLCs. The methods for creating SLNs can also be used to create NLCs. The process that makes use of both high pressure and high temperature is known as the high-pressure homogenization method. It is further subclassified as hot homogenization and cold homogenization.[142] Hot homogenization involves drug and lipid melting which then at the same temperature is joined with an aqueous surfactant.[143] The cold homogenization technique is applied to or developed to solve the limitations observed by the hot homogenization technique (Jaiswal *et al.*, 2016).[80,144] Other techniques include the microemulsion technique which involves keeping the temperature equivalent while melting and heating the lipid in an aqueous phase.[145] The double emulsion method helps prepare NLCs that will be loaded with hydrophilic drugs. The process involves dissolving the drug in the aqueous solvent, further dispersion in the lipid phase forming a primary emulsion where both phases are maintained under the same temperature,[146] and emulsification by the solvent evaporation method, where an aqueous phase dissolves and emulsifies the lipid in a water-insoluble organic solvent.[34] Low-pressure evaporation of the solvent allows for lipid precipitation and dispersion in the aqueous solution.[147] The membrane contactor method includes the usage of a specific membrane contactor to produce NLC. The process involves pressing the lipids above their melting point temperature, permitting the development of tiny droplets over the membrane.[148] The aqueous phase flows inside the membrane and eradicates droplets that are formed in the outlets of the pores. After this step, by cooling the preparation at room temperature NLCs are formed.[149] The melt extrusion method involves using an extruder self-possessed of three parts: the feeding zone, barrel and screw assembly.[150] The feeding zone is the entry point of materials into the extruder and the barrel is the main body of the extruder, passing material from the feeder to the discharge unit.[151] The screw assembly is comprised of three different screws, which are conveying screws that help in pushing the material

in the forward direction, mixing screws for mixing the materials to form a homogeneous mixture that is arranged at different angles (0 and 90°) and a discharge screw that extrudes out the final product which is the NLC. This technique comprises two stages.[152] In the first step, the amalgamation of both solid and liquid lipids, an aqueous phase and the drug causes the development of a pre-emulsion by extrusion. The second step follows the reduction in the size of the formed pre-emulsion with the help of a probe sonicator.[153] The microfluidization method involved in formulating NLCs requires a microfluidizer device and is a mixing technique.[154] The process involves applying a very high pressure in the range of 500 up to 20 000 psi to force out the liquid over the interaction chamber, and the interaction chamber contains microchannels that are small channels of a special configuration.[155]

7.6. Evaluation of nose to brain targeted NLCs

The prepared NLC formulations can be evaluated by a variety of characterization techniques like particle size, for which two methods can be used, photon correlation spectroscopy (PCS) or laser diffractometry (LD).[156] A typical NLC particle diameter lies between 10 and 1000 nm. The particle size of NLCs must be lower than 200 nm for easy permeation through the nasal mucosa.[157] Photon correlation spectroscopy uses the dynamic light scattering (DLS) technique.[158] The polydispersity index determines whether the particles are monodispersed or polydispersed, and is a measurement of the dispersion quality of the particles.[159] The size distribution measurement of NLCs ranges from 0.0000 to 1.0000, with the recommended PDI value below 0.5 for the uniform drug distribution through the nasal mucosa.[157,160] A greater value could result in pharmacokinetic irregularity and unpredictability in the therapeutic outcome. In contrast, a lower value suggests an increased likelihood of an additional undeviating absorption *via* the nasal mucosa.[161] The zeta potential relates to the evaluation of non-aggregation and physical stability and is crucial for determining how NLC particles repel one another. The zeta potential is estimated using Zetasizer and is based on electrophoretic mobility under an electric field.[162] A higher zeta potential represents values greater than +30 mV and less than −30 mV. These values represent increased stability upon storage.[162,163] The zeta potential is preferred to be positively charged as the particles can form electrostatic bonds along with the negatively charged nasal mucosa membrane leading to increased accumulation of drug in the brain.[157] Morphology is a characterization method to determine the form of the particles and to see the potential aggregation.[164] It can be determined using two approaches, scanning electron microscopy (SEM) and transmission electron microscopy (TEM), providing precise details on particle shape.[165] SEM makes use of electron transmission from the sample surface while TEM makes use of electron transmission through the sample. Another approach for determining the morphology of the NLC is atomic force microscopy (AFM).[166] AFM gives a three-dimensional surface profile of a sample, in contrast to electron microscopy, which only generates a two-dimensional image of a material.[167] It can resolve surface features as small as 0.01 nm.[164] The molecules' ability to exist in different crystalline forms due to diverse lattice arrangements is known as polymorphism. Some lipids with low melting points used in NLC preparation might exist in their different polymorphic forms.[168] For evaluating the crystallinity of NLCs, two useful tools applied are differential scanning calorimetry (DSC) and X-ray diffraction (XRD).[169] The DSC method can assess physical and chemical changes, such as the degree of crystallinity and melting behavior. It is the quantity of thermally-induced physical and chemical alterations to solid nanoparticles within a sample. The ratio of the enthalpy of the NLCs to the bulk enthalpy is used to determine the NLCs' degree of crystallinity calculated based on the total weight of the preparation.[170] XRD uses the spacings between various polymorphic forms to identify them. The length of the lipid lattice's long and short spacings can be measured. DSC may be used to distinguish between amorphous solids and liquids. Still, X-ray diffraction distinguishes between crystalline and amorphous materials and evaluates the oily ingredient's impact on the sub-cell parameters and long spacings of the solid lipid nanocrystals,[171] drug loading efficiency is defined as the ratio between drugs and lipids in NLCs. It depends on the drug's ability to dissolve in melted lipid, the lipid's and the drug's miscibility, the physical and chemical makeup of the matrix of solid lipid (partition coefficient, water solubility), the polymorphic state of the lipid material,[172] and the entrapment efficiency (EE) which is defined as the number of active components integrated into the particles over the overall amount present in the dispersion, also called the encapsulation efficiency.[173] The process of centrifugation determines the drug entrapment efficiency. The entrapment efficiency should be more than 80% for the intranasal delivery of lipid-based nanocarriers.[157] The supernatant obtained by centrifugation of the formulation is evaluated for drug concentration. During centrifugation, the free drug will stay in the supernatant after the centrifugation forms an NLC sediment.[145] The entrapment efficiency can be measured by the equation given below:[174]

$$\%\mathrm{EE} = \frac{\text{total added amount of drug} - \text{amount of drug in supernatant}}{\text{total added amount of drug}} \times 100$$

8. Recent developments in nose to brain targeted NLCs

Alzheimer's disease is a progressive neurological condition that affects older people resulting in a person losing their memory and thinking capability. It makes it difficult for the person to fulfil their daily tasks. Dementia is caused by AD, and is the cause of the deprivation of thoughts, identification, and cognitive developments and the behavioral changes that hamper a person's everyday life. A carbamate anticholinesterase inhibitor active only in the brain is rivastigmine hydrogen tartrate, which effectively manages AD. Anand *et al.* designed

NLCs loaded with rivastigmine hydrogen tartrate by employing Compritol 888 ATO, Ryoto Sugar Ester and triacetin as its components for treating dementia caused by Alzheimer's disease. By modifying the preparation technique of the solvent emulsification–diffusion method, RHT-NLCs were formulated. For optimization a Box–Behnken design was applied. The values obtained for particle size, polydispersity index, zeta potential and percent entrapment efficiency were observed to be 266 ± 0.94 nm, 0.233, −16.58 mV and 61.82 ± 2.52%, respectively. For drug diffusion through goat nasal mucosa, RHT-NLC showed 81.23 ± 2.14% in 12 h. Noteworthy development was observed afterwards in the treatment with the formulated NLC in escape and transfer latency in a rat model.[175]

Similarly, Cunha *et al.* optimized two NLC formulations targeting rivastigmine from nose to brain. For optimizing the formulations in two steps, the QbD approach was used because of QTPP and CQAs for intranasal delivery. Optimization designs used were the Box–Behnken and central composite designs. The parameters permitting the most significant values of CQAs were designated. Rivastigmine-loaded NLCs were formulated by the method of ultrasound and high-pressure homogenization and showed particle size values of 114.0 ± 1.9 nm and 109.0 ± 0.9 nm; the polydispersity index showed values of 0.221 ± 0.003 and 0.196 ± 0.007, the zeta potential −30.6 ± 0.3 mV and −30.5 ± 0.3 mV and the entrapment efficiency 97.0 ± 0.5% and 97.2 ± 0.3%. *In vitro* drug release specified sustained release, and stability studies directed rivastigmine-loaded NLCs to be stable after storage of 90 days.[176]

Again, for treating AD, Wavikar *et al.* developed *in situ* gelling rivastigmine-loaded NLC for nose to brain delivery prepared by an ethanol injection method with the components glyceryl monostearate, Capmul MCM C8, lecithin and Tween 80. They displayed a particle size and entrapment efficiency of 123.2 ± 2.3 nm and 68.34 ± 3.4%, respectively.[177]

Another research study on Alzheimer's was performed by Cunha *et al.*, who developed *in situ* thermosensitive gels with NLC and nanoemulsion loaded with an acetylcholine inhibitor (rivastigmine-RVG). The evaluated values for rivastigmine-loaded NLC for particle size, PDI, zeta potential and EE were seen to be 114.00 ± 1.91 nm, 0.45 ± 0.00, −3.58 ± 1.62 mV and 95.13 ± 0.34% respectively. The stability study showed long-term stability, good nasal mucoadhesion, and prolonged drug release.[178]

Pioglitazone is a diabetic drug found to improve brain insulin signaling and can directly control multiple targets that are included in AD. It falls under the PPARγ agonist insulin sensitizer class. Jojo *et al.* prepared NLCs loaded with pioglitazone intranasally for targeting the brain and optimized *via* a Box–Behnken design. The formulation showed values of particle size, zeta potential, polydispersity index and entrapment efficiency of 211.4 ± 3.54 nm, 14.9 ± 1.09 mV, 0.257 ± 0.108 and 70.18 ± 4.5%, respectively. Stability of the formulation upon storage was seen to be at 4 °C and 25 °C. It showed sustained release in an *in vitro* drug release study. An *ex vivo* permeability study showed an improvement in nasal permeability. Toxicity and *in vivo* biodistribution studies ensured the formulation's safety and direct transport from nose to brain in rats.[179]

Resveratrol is a compound found naturally that shows many anti-inflammatory, antioxidant, and neuroprotective effects. It is found that resveratrol can be used in preventing and treating AD because a neuroprotective effect can be seen due to the ability of the drug to remove Aβ peptide and the breaking down of APP. Rajput *et al.* prepared an *in situ* hydrogel of NLCs loaded with resveratrol for its administration intranasally by the melt emulsification–probe sonication method optimized by the Plackett–Burman design. They characterized the hydrogel after loading the NLC into the *in situ* gel. Evaluating the formulation showed a particle size of 132 ± 12 30 nm, a polydispersity index of 0.165 ± 0.002, a zeta potential of −23 ± 4 mV, drug loading of 10 ± 3% and an entrapment efficiency of 74 ± 6%. A high amount of drug distribution in the brain was confirmed by a pharmacokinetic study showing the safety along with the efficacy of the formulation over the nose to brain route, indicating a hopeful method to treat Alzheimer's disease (AD).[180]

Lamotrigine shows efficacy and tolerability in patients experiencing epilepsy. It offers fewer complications like dizziness, asthenia and somnolence than phenytoin and carbamazepine. Alam *et al.* prepared and investigated lamotrigine-loaded NLC for brain targeting following intranasal administration. A Box–Behnken design optimization method was used to optimize the formulation and estimates made for particle size, PDI, zeta potential and EE; the observed values were 151.6 ± 7.6 nm, 0.249 ± 0.035, 11.75 ± 2.96 mV, 96.64 ± 4.27% respectively. After 24 h of treatment, a study of drug release *in vitro* revealed sustained release.[181]

Similarly, Nair *et al.* prepared phenytoin-loaded NLCs by the nose-to-brain route to experiment with the release of phenytoin sodium in the brain for treating acute epileptic seizures. Three phenytoin sodium-loaded NLCs were prepared of size of <50, size ranging in between 50–100 nm and size of >100 nm by the method of melt emulsification. *In vitro* drug release, *in vivo* pharmacokinetic studies and *ex vivo* permeation studies of three NLCs showed that NLC of particle size <50 nm offered immediate drug release, a higher concentration of drug in the brain and CSF, with greater permeation within 5 min of administration intranasally. The results ensured that phenytoin sodium NLCs could treat acute epileptic seizures.[182]

Also, Khan *et al.* fabricated carbamazepine-loaded NLCs for better brain delivery to treat epilepsy. CBZ-NLC were prepared using trilaurin and oleic acid stabilized with usage of Poloxamer 188, Tween 80 and Span 80 and optimized. CBZ-NLCs showed a particle size, zeta potential and % drug incorporation of 97.7 nm, −22 mV and 85%, respectively. A biphasic release pattern with an initial fast release followed by a prolonged release was demonstrated by an *in vitro* release study.[183]

Depression is a health issue affecting individuals of all age groups worldwide and is caused by the disproportion in neuro-

transmitter levels that transfer information from the presynaptic to the postsynaptic neuron. Thymoquinone, obtained from *Nigella sativa* seeds, shows various pharmacological activities. It provides peroxidation to lipid membranes, delaying neuroinflammation by obstructing the inflammatory mediators' development known to be causing depression. Qizilbash *et al.* prepared NLCs loaded with thymoquinone-enriched naringenin for the treatment of depression by the nasal pathway. For preparing naringenin-loaded NLCs, thymoquinone was used as the liquid lipid established by the method of ultrasonication and optimized by a central composite rotatable design. The formulation exhibited particle size: 84.17 to 86.71 nm, PDI: 0.258 to 0.271, zeta potential: −8.15 to −8.21 mV and %EE: 87.58 to 88.21%. Comparing the *in vitro* drug release profile of TQ-NGN-NLC with NGN suspension, it was found that the NLC had a cumulative drug release of 82.42 ± 1.88% while the drug suspension had a release of 38.20 ± 0.82%.[184]

Flibanserin was primarily established as an antidepressant, but it was found to show increased libido in females and was adapted for treating female sexual interest/arousal disorder. Ahmed *et al.* fabricated flibanserin-loaded NLC *in situ* gel to enhance the delivery of flibanserin in the brain by a hot emulsification method, and optimization was done by the Box–Behnken method. After being prepared, FLB-NLC was fused into gellan gum *in situ* gel and subjected to rat histological evaluation, *in vitro* drug release and *in vivo* pharmacokinetic performance. The vesicular size was determined to be 114.63 nm, with a spherical shape. When compared with raw FLB control gel, *in vitro* release demonstrated improved release. *In vivo* studies improved the drug concentration in the plasma and brain compared with control gel. Lastly, the histological analysis confirmed that there were no abnormal indications. These outcomes confirmed that the FLB-NLC *in situ* gel could be administered nasally.[185] Besides these, several other nose-to-brain targeted NLCs have been summarized in Table 2.

9. Pharmacokinetic considerations of NLCs

Pharmacokinetics plays a significant role in the delivery of NLC inside the body. It tackles the delivery of drugs inside the body and is subject to the drug's physicochemical properties, like molecular weight, size, shape, charge and aqueous solubility. The development of the carrier system, which in this case is NLC, also plays an important part in pharmacokinetic considerations (release and absorption of drug) that determine the drug's bioavailability. The therapeutic effect is mainly expressed by the pharmacokinetics and tissue distribution of NLC.[191] Different *in vivo* models are used to determine the PK profile. Choosing an appropriate *in vivo* model is crucial for studying the anatomy of the nasal cavity. Directing the intrana-

Table 2 NLCs developed for neurological diseases

Formulation	Solid lipid	Liquid lipid	Disease	Characteristics	Ref.
Zopiclone-loaded NLC	Palmitic acid	Cod liver oil	Insomnia	Particle size was found to be 71.27 ± 13.57 nm with PDI of 0.097 ± 0.15, ZP ranging from −24.75 ± 3.04 to −34.1 ± 4.86 mV along with %EE showing 94.31 ± 2.44%. Results showed superior delivery of zopiclone intranasally with faster and higher brain uptake of 6.9 ± 1.02% ID g^{-1} at 5 min post-administration.	186
Chitosan-coated buspirone-loaded NLC	Glyceryl monostearate	Oleic acid	—	Particle size was found to be 190.98 ± 4.72 nm along with ZP of 17.47 mV and %EE of 80.53 ± 1.26%. TEM showed incorporation of drug into the NLC adequately and DSC studies proved the presence of drug in an amorphous state. Results showed shelf life of 27.61 months with high DTP value of 1462.49%.	187
Agomelatine-loaded NLC	Stearyl alcohol	Oleic acid	Depression	Particle size was shown to be 99.8 ± 2.6 nm with PDI of 0.142 ± 0.017, ZP of −23.2 ± 1.2 mV and %EE of 97.1 ± 2.1%. TEM showed a spherical shape of the particle and DSC showed an amorphous state of the drug within the NLC matrix. DTE value was reported to be 321.21% and DTP value to be 74.55% showing an effective strategy for brain targeting.	188
Chitosan-coated donepezil-loaded NLC	Compritol	Capryol 90	Alzheimer's disease	Particle size was found to be 192.5 ± 7.3 nm along with PDI of 0.298 ± 0.021, ZP of 38.9 mV and %EE of 89.85 ± 2.17%. Spherical shape was observed by TEM and DSC showed an amorphous state of the drug in the NLC matrix. DTE value of 321.21% and DTP value of 74.55% showed efficient brain targeting by intranasal administration.	189
Chitosan-coated rotigotine-loaded NLC	Compritol 888 ATO	Caproyl 90	Parkinson disease	Particle size was found to be 170.48 ± 8.37 nm, PDI of 0.19 ± 0.03, ZP of 26.73 mV and %EE of 82.37 ± 2.48%. *In vitro* studies showed a sustained release pattern with DTE value of 422.03% and DTP value of 76.03% after intranasal administration. Results of confocal laser scanning microscopy proved better targeting of brain by the prepared formulation.	190

sal study, the first model used was the rat, and later on other animal models of sheep, monkeys, mice and dogs were used for advancement of the absorption data. For the initial absorption studies, mouse and rat models are used.[192] Different nose to brain delivery strategies' efficiency is expressed using specific metrics. Drug targeting efficiency % (DTE%) and drug transport percentage (DTP%) are the parameters used. DTE% signifies the competence of drug to reach the brain when compared with blood, following intranasal administration *vs.* parenteral administration. DTP% denotes the drug percentage entering the brain by the nasal route directly in relation to the complete quantity of the drug found in the brain.[193]

$$\mathrm{DTE}\% = \frac{(\mathrm{AUC_{brain}}/\mathrm{AUC_{blood}})\mathrm{intranasal}}{(\mathrm{AUC_{brain}}/\mathrm{AUC_{blood}})\mathrm{parenteral}} \times 100\%$$

$$\mathrm{DTP}\% = \frac{(B_{\mathrm{in}} - B_x)}{B_{\mathrm{in}}} \times 100\%$$

10. Stability of NLCs

NLCs are the second generation of solid lipid nanoparticles (SLNs) developed to solve problems related to the delivery of therapeutics with the help of SLNs. Though NLCs provide many advantages, they are somewhat limited by the stability problem. The issue of stability arises because of less water.[194] Other reasons for the instability of NLCs include increased particle size, the expulsion of drugs from the matrix, and aggregation alongside long-term storage. Upon storage, highly concentrated NLCs link with each other, forming a pearl-like structure, causing movement restriction within the dispersion. Low-concentration NLCs, when stored, show the collision of particles with each other, resulting in aggregation.[195] To overcome the instability of NLC, three methods are usually employed. One approach is the application of the freeze drying method. The others are the addition of preservatives or stabilizers in the formulation and spray drying.[196] Freeze drying or lyophilization is the water removal process to improve stability. It involves the sublimation of ice followed by desorption in a vacuum. This process ensures storage for an extended period without the risk of damage to the original properties of the formulation.[197] The second approach of stabilizers/preservatives involves the addition of primary surfactants into the formulation. Surfactants can lower the interfacial tension between two phases of NLC by gathering in the interface of the binding surface, producing a layer around the particles, thus improving the physical stability of the prepared formulation upon storage.[198] Preservatives are categorized into four kinds based on their capacity of maintaining NLC stability: (a) propylene glycol is a preservative that has no stabilizing effects, (b) caprylyl glycol is a preservative that has minor stabilizing effects, (c) Euxyl K700 is a preservative having major stabilizing effects and (d) pentylene glycol is a preservative showing a stability effect.[133] For spray drying the formulated NLC, it is required that the lipid matrix should have a melting point above 70 °C.[144]

11. Regulatory and toxicity aspects of nose to brain targeted NLCs

For the widespread acceptability of NLCs, one of the accepted modest regulatory hurdles by the regulatory authorities is using GRAS (generally regarded as safe) excipients.[199] These systems enlist excipients with physiological, non-toxic, biodegradable and compatible profiles.[200] In addition to having the GRAS designation, excipients must be used following the regulatory authorities' frequently acceptable concentrations. A toxicity study must prove an excipient's safety at a given concentration when used in more significant quantities.[201] It has been found that the minimization of toxicity and possible side effects is effective because of nanocarriers achieved by reducing the dose required. When the molecules are transformed from natural to nanoscale, they may change completely or notably in both physicochemical and biological properties and may show toxicity.[202] It is essential to thoroughly investigate the toxicity of the bioactive molecules and excipients used in the formulation before targeting it to the desired site of action. NLCs are a blend of hydrophilic and lipophilic bioactive compounds stabilized by surfactants. These excipients may have some responsibility in causing toxicity to the brain. Surfactants can trigger the immune system; thus, *in vitro* toxicity studies may be performed to deliver favorable safety data.[203] Testing the toxicity of NLC administered through the nose to brain route can be done by conducting a nasal tissue toxicity test. A nasal tissue toxicity study inspects the probable toxic properties to be shown on the nasal mucosa by the formulated preparation. It can be performed on the nasal mucosa of sheep, pigs, or other suitable animals obtained freshly. This study showed the pathological changes in the nasal mucosa after administering the formulation intranasally and is compared with untreated nasal mucosa. The treated mucosa (mucosa with the formulation) is examined under a microscope to determine whether the formulation is showing safe or toxic effects.[204]

12. Patents on NLCs

So far numerous studies have been conducted on NLCs for drug delivery applications. Many of them are patented. This section summarized a few important patents for various drug delivery approaches (Table 3).

Shandong University developed a silybin nanostructured lipid carrier using improved microemulsion technology-emulsification and evaporation-low-temperature curing methods. This invention establishes and relates to the silybin NLC preparation method. The invention claims to provide good compatibility and stability and release controllable biological silybin NLC.[205]

Nelson Eduardo Duran Caballero *et al.* developed NLC on triblock copolymers by the preparation technique of hot homogenization under high pressure. The invention includes cosmetic usage precisely for hair that contributes moisture retention on the hair fibres for a prolonged time, reducing the frizz in the hair strands and boosting the shine.[206]

Table 3 Patents registered on NLCs

Patent number	Title of patent	Inventors/assignee	Claims	Ref.
CN101632638B	Silybin nanostructured lipid carrier and preparation method thereof	Shandong University	Silybin NLC comprises silibinin 0.05–0.5 wt%, solid lipid material 0.1–5 wt%, liquid lipid 0.02–2 wt%, fat-soluble emulsifier 0.2–5 wt%, water-soluble emulsifier 0.2–5 wt%, surplus is water. The described organic solvent is selected from one of the following: chloroform, acetone, ethanol, ethyl acetate.	205
WO2016065444A1	Method for producing nanostructured lipid carriers on triblock copolymers, nanostructured lipid carriers thereby produced and uses thereof.	Nelson Eduardo Duran Caballero, Alzira Xavier Pinto DINI	NLC in a block copolymer comprises two solid fused lipids selected from cupuassu butter and lanolin, a photoprotective property liquid lipid and a triblock copolymer. The photoprotective liquid lipid is selected from the group of buriti oil, coconut oil, passion fruit oil, chamomile oil, sunflower oil, avocado oil or any photoprotective liquid lipid	206
CN101658493B	Azithromycin nanostructured lipid carrier and preparation method thereof	Suzhou Nanohealth Biotech Co Ltd.	Azithromycin NLC has the composition of: azithromycin 0.1–1%, emulsifying agent 20–40%, complex lipid material 3–8%, all the remainder is water. The particle size range is found 40–100 nm.	207
CN101658468B	Coenzyme Q nanostructured lipid carrier and preparation method thereof	Suzhou Nanohealth Biotech Co Ltd.	Coenzyme Q nanostructured lipid carrier has the composition of: ubiquinone 1–5%, emulsifying agent 0.5–25%, tristerin and suffering/caprin 0.5–25%. Particle size range of described compositions is at 40–120 nm.	208
BR1020190138 56A2	Solid lipid composition for production of nanostructured lipid carrier	Nágila Maria Pontes Silva Ricardo, Tamara Gonçalves De Araújo, Bianca Oliveira Louchard	Production of NLC contained at least one oil, a wax, a butter and a surfactant that are fused and recrystallized. NLC characterized obtained from 2 to 20% of solid lipid composition through an emulsification method followed by sonication.	210
CN115054578A	Tumor-targeting norcantharidin nanostructured lipid carrier and preparation method thereof	Panzhihua central hospital	The tumor-targeting norcantharidin nanostructured lipid carrier is characterized by comprising the following raw materials in parts by weight: 0.1–6 parts of norcantharidin, 5–15 parts of polyethylene glycol-400, 8–16 parts of polyoxyethylene castor oil, 20–50 parts of ethyl oleate, 0.4–2 parts of tripalmitin, 1–5 parts of phospholipid, 2–5 parts of glyceryl monostearate, 801-5 parts of Tween-801 and 72–308 parts of a water phase. The tumor-targeted norcantharidin NLC is round and oval, and has an average particle diameter less than 100 nm and encapsulation efficiency of 87.41 ± 0.16%.	209

A simple and controllable preparation method and good repeatability can be applied to preparing azithromycin antibacterials for eye doses. Suzhou Nanohealth Biotech Co. Ltd developed azithromycin NLC providing good stability and higher bioavailability. The components involve 0.1–1% of azithromycin, 20–40% of emulsifier, 3–8% of lipid materials and the balance as water.

Suzhou Nanohealth Biotech Co. Ltd developed coenzyme Q NLC to provide high stability and good compatibility and has been able to solve problems like the stability of ubiquinone medicine, whose bioavailability is low.[207]

Nágila Maria Pontes Silva Ricardo developed NLC. The invention aimed to acquire a mixture of lipid components comprising wax, butter and oil that is melted and recrystallized to form a single lipid element entitled solid lipid. This invention ideally has the lipid balance required to produce NLC effectively in one step.[208]

Panzhihua Central Hospital invented a tumor-targeting norcantharidin NLC to overcome the problems associated with the low bioavailability and poor tumour targeting of the current delivery carrier of norcantharidin.[209]

13. Conclusion and future prospects

In the field of research, nanotechnology has emerged as a promising area for scientists to target and treat specific areas and diseases. The presence of the BBB limits brain targeting, for which the nose to brain pathway has arisen as the substitute route to target the brain. Advancement in medicine and nanotechnology has led to the development of many nanoplatforms, NLC being one of them. This review delivers information about nose to brain targeted NLCs, including different formulations of NLC prepared over a period administered *via* the nose to brain route. NLCs are becoming of interest because of their superiority above other lipid nanoparticles, such as their extended release of drug, enhanced bio-

availability in the CNS and increased therapeutic efficacy. Also, the involvement of both solid and liquid lipids provides an advantage in high drug loading capacity, inhibiting drug expulsion. Despite the availability of several benefits, there is still a requirement to achieve appropriate, affordable, cost-effective dosage forms. All the latest works have been done in recent years; it can be resolved that nanotechnology will be achieving intense attention in the future. Because of the several advantages of NLC, it will have the upper hand compared with SLN, liposomes and other lipid nanoparticles.

Further research is needed since it is unclear exactly how nanosystems go from the nasal mucosa to the olfactory and trigeminal nerves, and then to the central nervous system (CNS), as well as how they are distributed and interact with receptors in various sections of the brain. Before moving to clinical trials, it will also be crucial to conduct additional research on the toxicological effects of nanosystems administered by IN, including the brain as well as neural pathways in addition to the nasal mucosa. In conclusion, nanosystems administered intranasally have the potential to enhance patient quality of life and advance our understanding of the pathophysiology behind neurological diseases; however, additional research must be done before these technologies may be commercialized as drugs. We can also say that nasal formulations may be available to treat CNS disorders.

Author contributions

Mridusmita Das: writing – original draft, writing – review & editing. Anupam Sarma: conceptualization, writing – original draft, writing – review & editing, supervision. Debojeet Basak: writing – original draft. Himakshi Baruah: writing – original draft.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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