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REVIEW

Multifaceted nanolipidic carriers: a modish stratagem accentuating nose-to-brain drug delivery

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Abstract The exponential growth of nanotechnology has focused on therapeutic pursuits, notably for brain disorders. Nanocarriers have submicron particle sizes, typically around 500 nm. Over the past few years, interest in nanostructured lipid carriers as alternative pharmaceutical delivery systems has increased on both the scientific and commercial fronts. It belongs to a more recent incarnation of lipid nanoparticulate systems with a solid matrix and superior room temperature stability. More recently, they have also been used in gene therapy, cancer treatment, and brain targeting. In this review, the uses and significance of nanostructured lipid carriers (NLC) in combating brain diseases have been thoroughly covered, with examples from several recent research papers. A summary of NLCs' present patent status has been provided to highlight their promising potential. Related patents and research reports associated with this topic are gathered and availed. The paper thoroughly summarizes NLCs and their application in different routes of administration. Drug administration directly to the brain via nose through NLCs is mainly focused. Nose-to-brain delivery has more benefits compared to the other routes. NLCs provide significant advantages such as targeted delivery, less toxicity, higher drug loading capacity due to imperfect structure, etc. However, the particle size of NLCs for intranasal drug delivery should be < 200 nm. Also, NLC is combined with a medical device to achieve the add-on benefits for delivering drugs effectively. According to the comprehensive review of literature and patents like CN110013471B, IN-MUM-2015-00667A, IN202021023420A, and AU2021104270A4, drug-loaded NLCs in nose-to-brain delivery show promising results. NLCs can increase bioavailability and reduce dosing frequency, indirectly reducing dose-related side effects. Intervening NLCs directly on the targeted site displays site specificity and many more benefits than conventional dosage forms. Thus, using NLCs in nose-to-brain drug delivery is invigorating.

Keywords Nose-to-brain drug delivery · Nanostructured lipid carriers · Intranasal administration · Brain targeted delivery · Medical device combination

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An overview of nanotechnology and nanocarriers

The still-evolving science of nanomedicine includes nanodelivery as a significant component. Nanomedicine is a multidisciplinary field incorporating elements of nanotechnology, chemistry, biochemistry, and pharmaceutical sciences [1]. The study of creating, characterizing, and using objects with at least one dimension on the "nano" scale is known as nanotechnology. In comparison to conventional medication delivery techniques, nanodistribution systems have some advantages. For example, they might be able to deliver medicines that target various body tissues with excellent specificity and treat various ailments. Since they should, in principle, prevent or significantly reduce drug interactions with non-target tissues, targeted therapy using nanodelivery systems could also reduce the side effects of many medications. As a direct result of fewer undesirable drug interactions, the amount of medication needed to treat the illness would need to be reduced, ultimately resulting in a cost reduction overall [2].

Nanocarriers are colloidal drug delivery devices with submicron particle sizes, typically around 500 nm. In the last few decades, nanocarriers have received much attention owing to their tremendous potential for drug delivery [3]. Since nanocarriers have a high surface-to-volume ratio, a medication's basic properties and bioactivity can be altered. The use of nanocarriers in drug delivery systems has been shown to improve pharmacokinetics and biodistribution, decrease toxicities, boost solubility, and stability, provide controlled release, and deliver therapeutic molecules to targeted sites [4]. Nanocarriers' physiochemical qualities (functional groups, PEGylation or other coatings, surface charge, inclusion of targeted molecules) as well as their sizes (large or small), shapes (spherical, rod, or cube), and surface features can also be altered. Nanocarriers are used in drug delivery to effectively cure a disease with little adverse effects, as shown in Fig. 1 [5].

Although not always, many different forms of nanoparticles (NPs) utilized as drug carriers typically comprised polymers or lipids. The lipid NPs outperform the polymeric NPs when the two are compared because polymeric NPs have several drawbacks, including cytotoxicity and the absence of effective mass production techniques. Solid lipid nanoparticles (SLNs), the first generation of lipid-based nanoparticles, were characterized in the early 1990s [6]. Due to polymorphism, drug-carrying SLNs were constrained by poor drug loading efficacy and a high probability of drug expulsion from the formulation during storage. As a next-generation SLN, nanostructured lipid carriers (NLCs) were developed in the late 1990s to overcome SLN formulation challenges [7]. Müller et al. created NLCs by combining solid lipids (SL) with liquid lipids (LL), which create an amorphous solid matrix at body and room temperatures. Since LL considerably improved the formulation's characteristics compared to SLNs, incorporating LL into the matrix was the first and most crucial step. LL aided

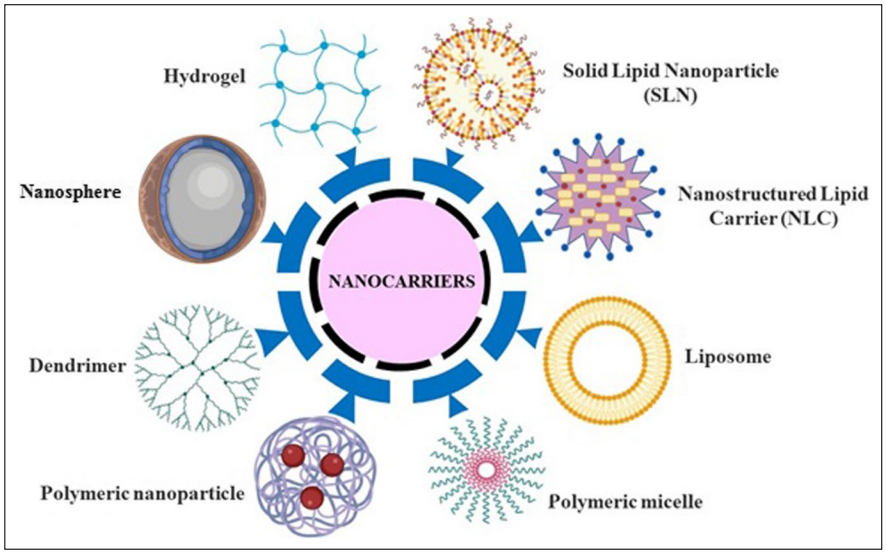

Fig. 1 Nanocarriers used in drug delivery

amorphous lattice formation with significant flaws in its solid crystalline matrix, enabling a higher drug load to be added, as opposed to SLNs, which form a solid crystalline matrix that restricts the quantity of drug loaded and causing its expulsion due to their spatial capacity [8]. According to numerous scientific studies, the NLC overcomes the SLN's drawbacks by preventing drug expulsion during storage and enhancing stability and loading efficiency [9] [10].

Types of NLCs

NLC can be divided into three types based on the variations in lipid and oil volume fractions and the diverse manufacturing techniques: the amorphous type, the imperfect type, and the multiple oil-in-solid-fat-in-water (O/F/W) types [7]. In comparison to SLN, Fig. 2 shows the many forms of NLC.

Improper-type NLC includes mixing spatially dissimilar lipids, such as glycerides, which are made up of many fatty acids and introduce flaws in the crystal order. By combining a combination of different glycerides with differing saturation and carbon chain length levels, the amount of drug load can be additionally enhanced by expanding defects.

Specific SL, such as isopropyl myristate or hydroxyoctacosanyl hydroxy stearate, create an amorphous matrix lacking structure. The NLC thus exists in an amorphous state as opposed to an organized state, preventing drug ejection brought on by modification during storage [11]. Numerous liquid oil compartments of various sizes spread that throughout the solid matrix are present in multiple O/F/W-type NLCs. Drug loading is augmented because these nanosized compartments have better drug solubility. The release is also prolonged because a solid lipid matrix surrounds the compartments.

Nanostructured lipid carriers (NLCs)

Due to the drug moieties' improved solubility in the solid lipid, the combination of liquid and solid lipids makes it simple to encapsulate a variety of hydrophobic medicines. However, hydrophilic drug loading into NLC can be tricky and best accomplished by conjugating the functional groups of a matrix of lipids and drugs. Notably, NLC retained a solid state throughout the body [11]. This happens because the mixture of LL and SL tends to lower the core substance's melting temperature without changing its physical attributes. NLCs are more stable than other nanocarriers and have lower toxicity while allowing for regulated or prolonged medication release [12]. They can also encapsulate both hydrophilic and lipophilic drug substances. Figure 3 shows a comparison between SLN and NLC.

Glycerol monostearate (GMS), Precirol® ATO5, stearic acid, mono-stearin, stearyl alcohol, cetyl palmitate, Witepsol®, and Gelucire® are examples of solid lipids that are frequently utilized in NLC formulation. Examples of liquid lipids include almond oil, oleic acid (OA), olive oil, sesame oil, soyabean oil, peanut oil, phosphatidylcholine, maize oil, soy lecithin, vitamin E, caprylic triglycerides, glyceryl caprylate/caprate, isopropyl myristate, etc. Poloxamer 188(P188), Polysorbate 80, Polysorbate 20, PVA21, Cremophor® RH, polyoxyethylene esters of 12-hydroxystearic acid, Cremophor® EL, Tego Care 450, Pluronic F68, Span® 85, and numerous other surfactants are also used to prepare NLC. Some of the LL, SL, and surfactants are shown in Figs. 4, 5, and 6, respectively.

Potentials of NLCs in drug delivery [13]

Figure 7 shows the potential of NLCs in drug delivery. Owing to the lipid matrix's constitution, the

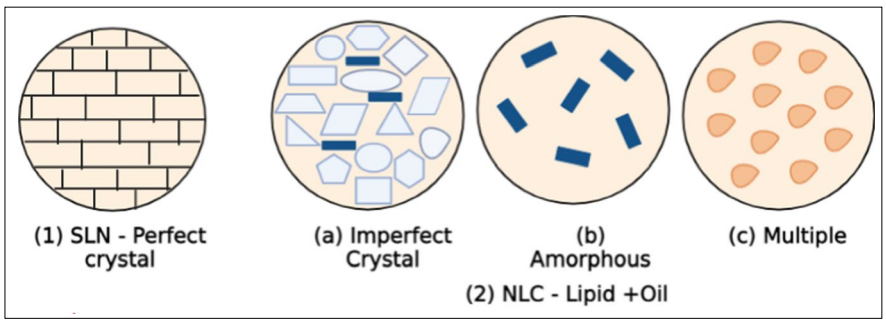

Fig. 2 Comparison of SLN (1) and NLC (2). The NLC categories are (**a**) imperfect crystal, (**b**) amorphous, and (**c**) multiple types

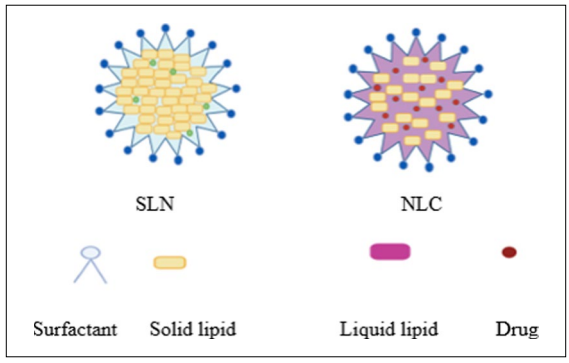

Fig. 3 Schematic comparisons of rigid SLNs with low drug loads and flexible NLCs with high drug loads

concentration, and the irritative and sensitizing actions of the surfactants, there might be some cytotoxic effects. Gene delivery technologies and applications for protein- and peptide-based medications still have untapped potential. One must look for scale-up strategies, improper methods, and lipid stability. In the end, most study researchers are unable to extensively replicate the results because they are entrenched at the laboratory scale or in the research evidence throughout the preclinical or clinical stages. The application of NLC for the delivery of bio-actives like peptides, genes, proteins, ribonucleic acid (RNA), and deoxyribonucleic acid (DNA) should also be given serious consideration [13].

An emphasis on fabrication techniques of NLC

Numerous methods can be employed to produce NLCs. The high-pressure homogenization technique is the most frequently employed that combines high temperature and high pressure. Other is the homogenization approach using low temperatures and high pressure. Table 1 shows the processes that include solvent dispersion, high-temperature emulsion evaporation–low-temperature curing, ultrasonic emulsion evaporation, microtube methods, film-ultrasonic method, microemulsion, supercritical fluid (SCF), emulsion, membrane contactor, and microchannel [14]. Some of the preparation methods are explained below.

Melt emulsification method

SL is melted at 10 °C above its melting point, followed by adding LL. Then drug is added to the molten lipid phase. At the same temperature, the aqueous surfactant solution is also heated. The aqueous phase is drop-wise added into the lipid phase with constant stirring on a magnetic stirrer at a specific rpm. Then the mixture is sonicated and allowed to cool down at room temperature.

High-pressure homogenization (HPH)

High pressure (100–2000 bar) is used, which causes shear stress and the breakup of micro- to

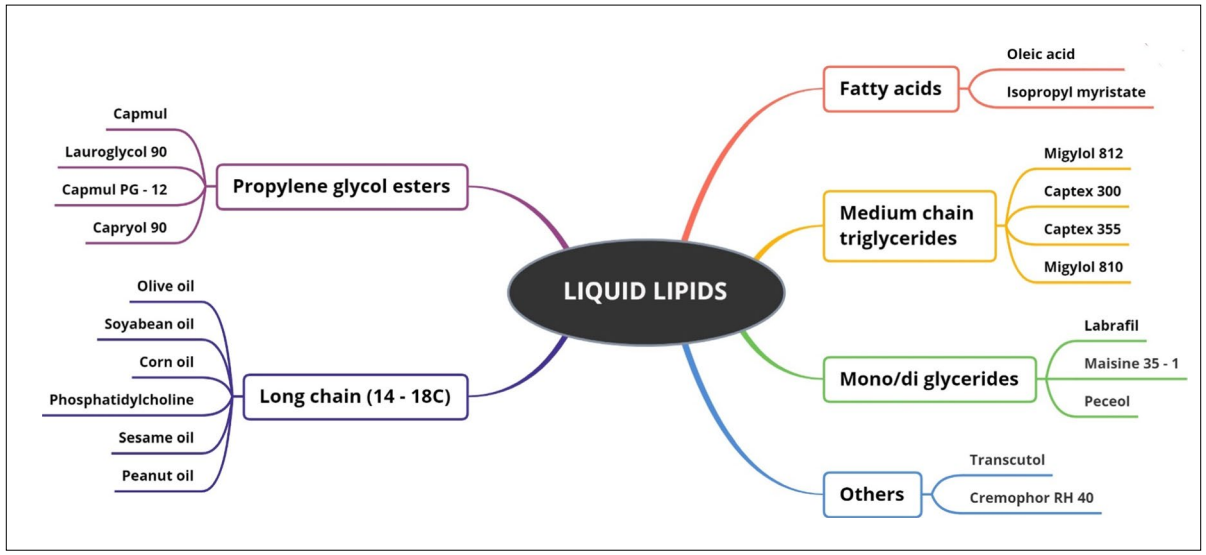

Fig. 4 Liquid lipids used in NLC

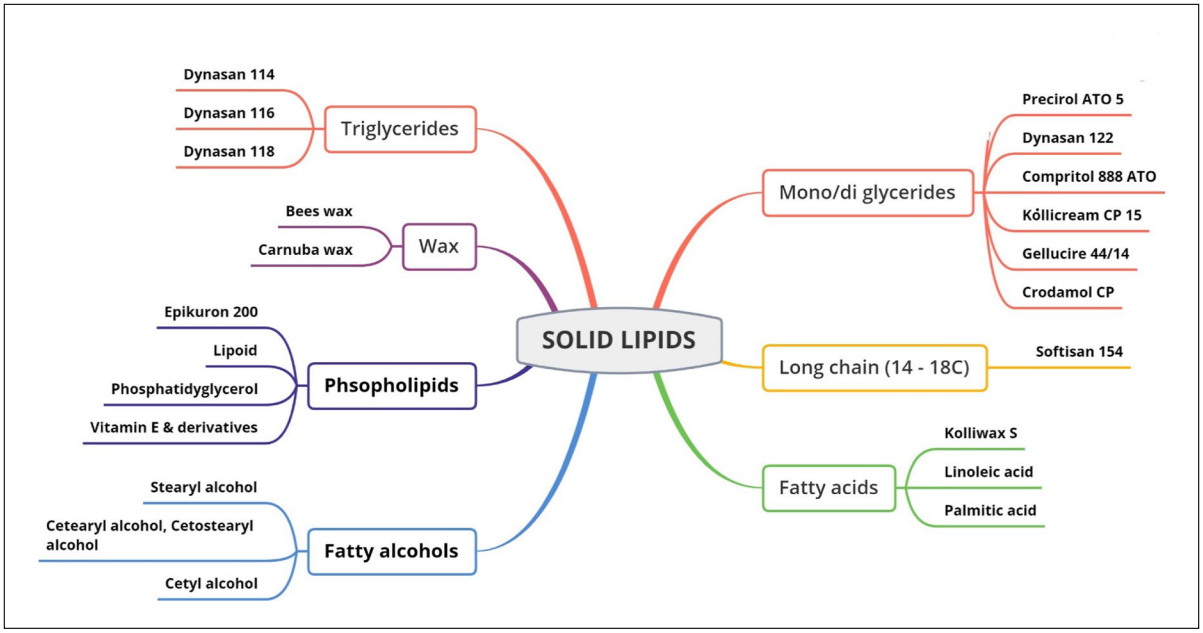

Fig. 5 Solid lipids used in NLC

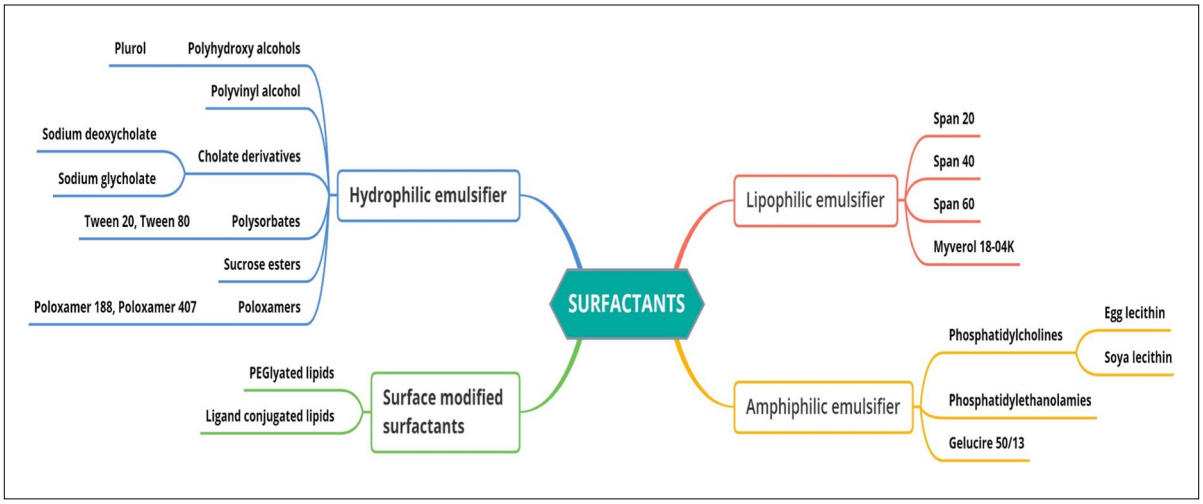

Fig. 6 Surfactants used in NLC

nanosized particles. Different cycles (10,000 rpm, 800 bar with 10–12 cycles) are carried out depending on the required particle size. Both the aqueous and lipid phases must homogenize at the same temperature to produce nanoparticles. NLC can be prepared using a hot and cold high-pressure homogenization process.

Solvent emulsification-evaporation technique

Using a high-speed homogenizer, a water-immiscible organic solvent dissolves hydrophobic drugs and lipophilic materials. Furthermore, an organic solvent is evaporated at room temperature by either gentle heating or mechanical stirring.

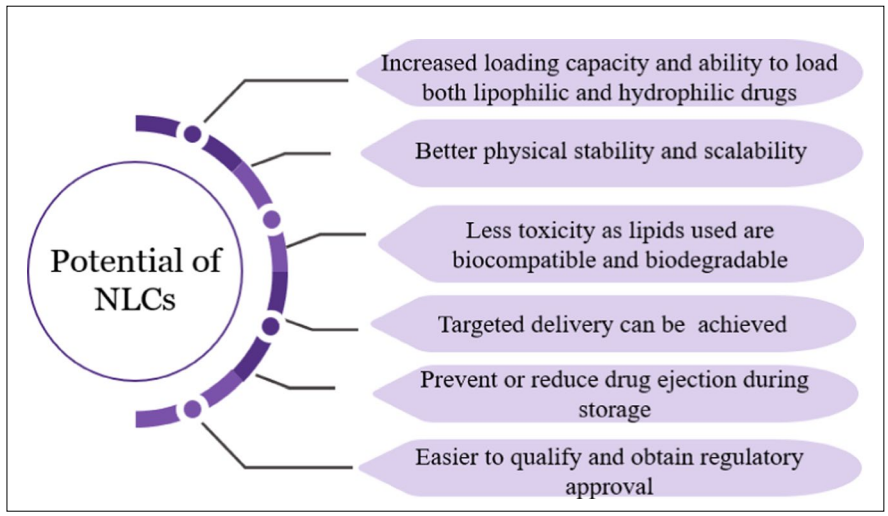

Fig. 7 Potential of NLCs

Table 1 Fabrication techniques of NLCs

Sr. no	Method	Pros	Cons
1	High-pressure homogenization method	• Useful insoluble and lipophilic drugs • Avoids organic solvents	• Not entirely appropriate for hydrophilic drugs
	Hot homogenization	• Heat-sensitive chemicals may degrade if high temperatures are used throughout the process	• Since surfactants have cloud points below 85 °C, their diminished ability to emulsify at high temperatures could cause nanocarrier instability
	Cold homogenization	• It reduces the drug's thermal exposure and is suitable for thermolabile drugs • More effective drug trapping and consistent drug distribution throughout the lipid	_____
2	Ultrasonic emulsion evaporation method	• Avoidance of heat	• Solvent residues could lead to toxicological issues
3	Solvent dispersion	• The bulk of the liquid generally causes the drug loading to rise • Quick, easy, and requires few tools	• Not entirely appropriate for industrial production • Organic solvent residue might be found
4	Film-ultrasonic method	• Used for its ease of use, convenience, and potential to create uniform, microscopic particles	• Solvent residues may cause toxicological issues
5	High-temperature emulsion evaporation—low-temperature curing	• Simplicity and speed	• Not appropriate for industrial production • The potential of leftover organic solvent
6	Microemulsion method	• Low drug content and simplicity • Ease of large-scale production	• An excessive number of supplementary emulsifiers and emulsifiers is needed • The industrial application of surfactant is occasionally constrained by the amount used
7	Melt emulsification method	• Absence of organic solvent traces • Initially, there was no burst release • Lipid-rich dispersion	• Unsuitable for industrial production • Possibilities of remaining organic solvent

Solvent diffusion

Using ethanol and methanol, two water-miscible solvents, to dissolve the medication and lipid in a single solvent or a solvent mixture. At the same temperature and with mechanical stirring, the organic phase is introduced to the aqueous phase that already has stabilizers, surfactants, and other excipients. The mixture is then cooled to room temperature to allow the organic phase to evaporate.

Solvent injection

Through fine needle injection, lipids are first dissolved in a water-miscible solvent and then introduced to the aqueous phase. Avoiding highly complex mixtures like high-pressure homogenizers and probe sonicators is the main benefit of adopting this mixture [15].

Landscaping of NLCs in drug delivery

We have presented the comprehensive work done with NLCs' drug delivery via different routes. Recently, NLCs have been used to deliver drugs to particular areas utilizing various administration methods. For instance, topical administration of NLCs is frequently used in dermatological and cosmetic treatments. Fungal infections are incredibly prevalent in the current situation [16] [17]. Over a billion people yearly receive diagnoses for severe systemic or localized fungal infections. Despite their effectiveness in treating fungal infections, antifungal medications are linked to severe side effects such as liver damage, estrogen levels, and allergic reactions [18]. In the skin, there will be effective drug targeting and increased skin absorption by the NLCs. Drug absorption in the human skin enhances by incorporating NLCs. NLCs can be prepared for major tropical diseases like gout, sunburn, rheumatoid arthritis, and inflammation-related skin diseases like atopic dermatitis and psoriasis. This gives rapid onset and intermediate action [19].

Tables 2 and 3 show the use of NLC in topical and oral drug delivery, respectively. Figures 8 and 9 show the graphical representation of Tables 2 and 3, respectively. Because of the poor water solubility and unfavorable physicochemical and pharmacokinetic characteristics of researchers' identified chemical entities, over 40% of them used in the pharmaceutical sector have limited oral bioavailability. Therefore, producing a conventional formulation that can reduce the threats bound with lipophilic medications is challenging [40]. Researchers have tried many strategies to increase bioavailability, including synthesis of the pro drug, formation of salt, drug nanosizing, and drug encapsulation in nanocarriers such as liposomes, polymeric micelles, NPs, emulsions, etc. Drug delivery techniques incorporating lipids have provided a glimmer of hope for their positive impacts on the absorption of encapsulated pharmaceuticals throughout the past few decades [41].

Further, owing to their extended absorption in the gastrointestinal tract, oral treatment of NLCs for inflammatory bowel illnesses is the subject of substantial research. Regarding chemotherapy, anti-cancer medications like paclitaxel and doxorubicin have been encapsulated in NLCs to be administered via the pulmonary route [42]. As discussed above, it offers significant advantages compared to the other conventional formulations.

Brain

Figure 10 illustrates the complex anatomy of the brain. About 2% of body weight belongs to the brain, which also needs 25% of the total glucose and oxygen supply and 20% of the overall cardiac blood supply [61]. The defensive system's three main layers are arachnoid, blood-cerebrospinal fluid, and blood–brain barriers (BBB). The brain is unique in that it has a highly complex network of neurons that communicate with each other via neurotransmitters and neuromodulators, as well as the presence of synaptic potential in such networks and a significant number of capillaries in the range of 100 billion. The intricate BBB effectively shields each of these components. The brain's ability to transmit signals to other body parts relies on the BBB's ongoing exchange of ions and other chemicals.

Brain and related disorders

The prevalence of neurodegenerative illnesses, defined by a continuous diminution in neuronal networks and functions, is highest in the age, although the actual reasons are unknown [62].

Table 2 NLCs for topical drug delivery

Sr. no	Drug	Disease/purpose	Ingredients	Method	Characterization	Outcomes	Year	Reference
1	Alpha-mangostin and resveratrol	To promote antioxidant activity	Palmitic acid, myristic acid, Imwitor 742, Span 80, Tween 80, Transcutol	High shear homogenization and ultrasonication	Particle size (PS): 103.3 to 116.8 nm Zeta potential (ZP): −40.0 to −35.2 mV Conductivity: 21.3 to 30.8 µS/cm	Enhanced antioxidant activity in combination, which provided improved antioxidant activity likened to that of the single drug Appropriate spreadability on the skin Low toxicity	2022	[20]
2	Luliconazole	Aiming to improve skin permeability and retention	-	Hot emulsification followed by ultrasonication	PS: 86.480 ± 0.799 nm Polydispersity index (PDI): 0.213 ± 0.004 ZP: ≥ −10 mV % entrapment efficiency (%EE): 85.770 ± 0.503	NLCs are released slowly for up to 42 h Favored occlusivity Spreading ability: 0.748 ± 0.160 Extrudability: 3.130 ± 1.570 Purity: 99.520 ± 0.890%	2022	[21]
3	Minoxidil and latanoprost	To treat alopecia with targeted topical therapy	Compritol, miglyol, Tween 80, and Span 80	Microemulsion technique	Hydrodynamic diameter: 393.3 ± 36.0 nm PDI: 393.5 ± 36.0 nm ZP: +22.5 ± 0.2 mV %EE: 86.9% of minoxidil and 99.9% of latanoprost	The toxicity of combined and formed substances was much lower at 24 h (84.9 ± 2.0%) than that of free individual compounds 50% of each medication was successfully deposited into hair follicles by NLC	2022	[22]
4	Resveratrol is loaded using chitosan hydrogel beads as a carrier system	For the efficient topical carrier	-	-	-	Enhanced physical stability A more pronounced sustained-release effect was demonstrated via an in vitro release experiment Transdermal investigations in culture revealed that resveratrol improved skin penetration Resveratrol-loaded NLC-Chitosan hydrogel beads may not pose a risk to L929 cells, owing to in vitro cytotoxicity results	2022	[23]

Table 2 (continued)

Sr. no	Drug	Disease/purpose	Ingredients	Method	Characterization	Outcomes	Year	Reference
5	Febuxostat	Treatment of gout and hyperuricemia	OA, P188, stearic acid, carbopol 938, and Tween 20	Hot, high-pressure homogenization	PS: less than 125 nm ZP: above 30 ± mV %EE: 90.32 ± 1.3% Drug content: 93.78 ± 0.04% Viscosity: 26,490 cp	Gel formulation showed good homogeneity, grittiness, and extrudability Spreadability: 25 ± 0.1 g.cm2 /s NLCs (1:3 drug: polymer) displayed significant drug entrapment 87% of the gel formulation of NLC was controlled-released in 6 h Enhances bioavailability and minimizes adverse effects	2022	[24]
6	Meropenem hydrochloride	Management of *Staphylococcus aureus* skin infection	Stearic acid, OA, and Tween 80	Solvent evaporation	PS: 126.5 ± 0.9 nm %EE: 79.1 ± 2.3% ZP: 0.967 mV	81.5% ± 3.1% of the medication was released in vitro after 48 h Improved occlusion, adhesion, and release properties	2022	[25]
7	Adapalene	Treatment of acne	Miglyol, tegocare 450, tween 80, Span 65, P188, poloxamer 407 (P407), sorbitan sesquioleate, glyceryl distearate, and GMS	Probe sonication	-	Exemplary %EE that illustrated a controlled drug release profile The frequency of inflammatory and noninflammatory lesions, as well as the severity index for acne, significantly decreased after 12 weeks of treatment	2021	[26]
8	Fluconazole	To increase permeability and, subsequently, efficient topical medication delivery	-	-	PS: 161.3 with a standard deviation of 1.385 nm PDI: 0.401 ZP: − 33 mV with a standard deviation of 0.46 %EE: 82.26 with 0.91% deviation	76.40 ± 0.21% in vitro drug release When compared to the commercial gel, the in vitro antifungal investigation indicated noticeably improved activity	2021	[27]
9	Clindamycin and rifampicin	To treat hidradenitis suppurativa	-	-	Diameter: 400 ± 14 nm PDI: 0.2 ZP: − 48.9 ± 0.7 mV %EE for clindamycin: 80.2 ± 0.4 %EE for rifampicin: 93.4 ± 0.7%	-	2021	[28]

Table 2 (continued)

Sr. no	Drug	Disease/purpose	Ingredients	Method	Characterization	Outcomes	Year	Reference
10	Apremilast	Better permeability and extended skin deposition	Glyceryl behenate, Dynasan 114, Precirol ATO 5, stearic acid, GMS, OA, Polysorbate 80	Hot emulsification	PS: 157.91 ± 1.267 nm PDI: 0.165 ± 0.017 %EE: 69.144 ± 0.278% ZP: − 16.75 ± 1.40 mV	NLCs showed controlled release for up to 24 h The NLC-loaded gel shows three times more skin retention compared to conventional gel preparation No toxicity or irritation	2021	[29]
11	Velutin	-	Cetyl palmitate and caprylic/capric triglyceride	Ultrasound dispersion	Average size: 250 nm PDI: 0.2	Sustained release at a steady pace over time of 36 h	2021	[30]
12	Methazolamide	For enhancement of ocular bioavailability	Cetostearyl alcohol, glyceryl behenate, medium chain triglycerides or isopropyl myristate, 2% polysorbate 80, and 0.15% stearyl amine	-	Smaller than 500 nm %EE: 30	Released within 8 h Shown a fivefold more significant intraocular pressure reduction than methazolamide solution	2021	[31]
13	Bergamot oil	Treatment of vitiligo	Precirol ATO 5, Plurol, Stearique WL1009, soyabean phosphatidylcholine 99%, acetone, tetrahydrofuran, sodium lauryl sulfate, potassium dihydrogen phosphate, disodium hydrogen phosphate, Tween 80, and phosphotungstic acid	High shear homogenization	-	Sustained release for 24 h NLCs enhanced the photostability and photodynamic characteristics	2021	[32]
14	Kojic acid	Treatment of cutaneous hyperpigmentation	OA, tween 20, cholesterol, GMS, Span 60	Probe sonication	PS: 172.9 ± 7.1 nm PDI: 0.3 ± 0.1 %EE: 76.4 ± 0.1% Drug loading: 17.6 ± 1.3% ZP: − 39.1 ± 2.7 mV	More excellent antioxidant activity compared to pure kojic acid and intense tyrosinase inhibitory action Enhanced percutaneous delivery	2021	[33]
15	Curcumin	For enhanced skin-retained topical delivery	Polysorbate 80, Precirol ATO 5, Carbopol 974P NF, Labrafac M 1944, P407, and Span 20	Hot emulsification	PS: 96.2 ± 0.9 nm %EE: 70.5 ± 1.65% ZP: − 15.2 ± 0.566 mV	Up to 48 h of in vitro drug release Curcumin-loaded NLC gel had 3.24 times better skin retention and permeability than free curcumin gel No toxicity toward keratinocyte cells	2020	[34]

Table 2 (continued)

Sr. no	Drug	Disease/purpose	Ingredients	Method	Characterization	Outcomes	Year	Reference
16	Apremilast	Management of psoriasis	Glyceryl behenate, Polysorbate 80, OA, Transcutol, Span 20, and Carbopol 940	Cold homogenization	PS: 758 nm %EE: 85.5% ZP: − 33.3 Mv PDI: 0.339	60.1% skin deposition Prolonged drug release and low drug diffusion	2020	[35]
17	Folic acid	Treatment of skin photo-aging conditions	Apifil, Plurol stearique WL 1009, Labrafil® M 2130 CS, CapryolTM 90, Tween 80, and propylene glycol	High-speed homog-enization followed by ultrasonication	%EE: 89.42–99.26% PS: 27.06 to 85.36 nm PDI: ranges from 0.137 to 0.442 ZP: >|27| mV	Pseudoplastic behavior of materials Significant spreadability (2.25–3.30 cm) 48-h promotion of occlusive characteristics After six hours, the skin layers have increased permeability and contain folic acid	2020	[36]
18	Astaxanthin	To enhance skin perme-ability, water solubility, stability, and retention while lowering drug-related adverse effects	DL-alpha tocopherol, glyceryl tribehenate, decanoyl/octanoyl-glyc-erides, and Pluronic F68	Hot homogenization and ultrasonication method	PS: 67.4 ± 2.1 nm %EE: 94.3 ± 0.5%	Nonirritating Excellent stability and water solubility At 48 h, drug release from NLC was 83 ± 3.4% Cumulative permeability: 174.10 ± 4.38 µg/cm^2 Retention: 8.00 ± 1.62 µg/cm^2	2020	[37]
19	Econazole	For enhanced antifungal activity against derma-tophytes	GMS, Capmul MCM, Eudragit RS PO, triethyl citrate, ethanol, and Natrosol 250H Pharm	Sonication	PS: 199 nm PDI: 0.2 %EE: 92.5%	No early burst release was seen, and a sustained release profile obtained for 72 h (88.2%) Over 90% of the medication is released within 24 h Long-term growth suppression of dermatophytes and greater skin adherence	2020	[38]
20	Curcumin	For topical application	Precirol ATO 5, Capmul MCM, Tween 80, Car-bopol 934	High-speed homogeniza-tion	PS: 189.4 ± 2.6 nm PDI: 0.262 ± 0.24 ZP: − 21.45 ± 1.3 mV %EE: 86.72 ± 09%	Sustain release of 60.2 ± 0.45% in 24 h Good permeation flux of 0.453 ± 0.76 µg/cm^2.h Retention obtained was 60.2 ± 0.45%	2020	[39]

Central nervous system (CNS) ailments, such as brain tumors and neurological disorders, continue to rank among the leading causes of disability and fatality around the globe. Treatments for CNS illnesses are lacking despite an alarming rise in occurrence over the past few years. Limited medication accessibility to the intended brain location is one of the factors contributing to the high failure rates in CNS drug development. A drug must cross the BBB in a sufficient concentration and interact with a target in the brain to have a pharmacological effect.

The burden of neurological illnesses has significantly expanded during the last 25 years on a global scale. The *Lancet Neurology* released the 2015 Global Burden of Disease (GBD) survey report, which states that neurological diseases are the second highest cause of mortality internationally and the primary cause of disability-adjusted life years (DALYs) worldwide.

Only the early phases of a disease's progression are shown to be responsive to currently available treatments. Most treatments only have symptomatic effects, meaning they treat the disease's symptoms and do not address its underlying causes. As a result, they are ineffective at curing the disease. The primary reasons for this are the brain's intricate structure and, more significantly, the BBB's protective barrier, which prevents most drugs from entering the brain [63]. Therefore, researchers are developing novel approaches, nanocarrier systems, and drug delivery systems that precisely deliver active substances to the brain by bridging the BBB or any alternate route, such as intranasal drug delivery systems [11].

Blood brain barrier (BBB)

Drug distribution to the brain is greatly aided by the BBB, which divides the blood from the brain interstitial fluid (extracellular fluid). The cause is a vast network of blood capillaries, which permit the movement of substances from the blood to the brain parenchyma with an average surface area of 100 to 200 cm^2 per gram of adult human brain. Although the BBB's selectivity is essential for preserving brain homeostasis, it presents a significant obstacle to the delivery of medicines into tumor areas. Passive diffusion via the extracellular matrix is significantly hampered by tight junctions that form between endothelial cells [64].

Active moiety/nanocarrier transportation from the nose to the brain

According to the current study, the nose-to-brain channel offers a viable method for the non-invasive delivery of therapeutic agents or nanocarriers into the brain without crossing the BBB. The olfactory pathway, trigeminal nerve pathway, and systemic pathway are three transport mechanisms involved, shown in Fig. 11.

Nose-to-brain drug delivery

An intriguing method for delivering medicine directly to the brain via the nose is the "nose-to-brain" drug delivery device. The olfactory area is directly connected to the CNS due to the olfactory receptors in neurons and their axons, which end in the olfactory bulb. The olfactory region is the sole area of the body where the CNS interacts with the surrounding environment. The active molecules can immediately enter the brain by the trigeminal and olfactory nerve pathways from the olfactory area, which is a crucial location. When medicine or formulation is delivered, it comes into contact with mucosa and travels straight to the brain, avoiding the BBB. This results in good bioavailability, a lower dose, and fewer side effects. Although nasal medication delivery generates research interest, it has certain drawbacks, such as a small dosage range (25–200 µL), mucociliary clearance, and nasal enzymatic barriers. These discourage scientists from creating cutting-edge drug delivery technology to overcome these constraints. The underlying benefit of the nose to brain medication delivery is that this is a quick, secure, non-invasive, and practical drug delivery approach [65]. It prevents the breakdown of medications in the digestive tract, especially peptide medicines [66].

Additionally, it prevents the gut wall and hepatic first-pass metabolism of medicines, resulting in increased bioavailability. Bypassing the BBB provides CNS-targeted drug delivery, lowering systemic exposure to treatments and their accompanying systemic adverse effects. No modifications are necessary for the therapeutic agent using a nose-to-brain medication delivery platform. Rapid drug absorption and speedy commencement of an action through the highly vascularized and permeable nasal mucosa are essential advantages of nose-to-brain

Table 3 NLCs for oral drug delivery

Sr. no	Drug	Disease/purpose	Ingredients	Method	Characterization	Outcomes	Year	Reference
1	Isradipine	Management of hypertension and isoproterenol-induced myocardial infarction	Emulcire 61, Capryol 90, P188	High-pressure homogenization	PS: 80.9 ± 1.7 nm %EE: 83.51 ± 2.15%	%Drug release: 83.3 ± 3.86% after 24 h Greater oral bioavailability by 4.207 and 1.907 times	2022	[43]
2	Lacidipine	For the improvement of oral bioavailability and antihypertensive activity	-	-	PS: 191.0 ± 5.89 nm PDI: 0.074 ± 0.013 ZP: − 28.9 ± 0.99 mV %EE: 90% ± 3.69%	%Drug loading: 9.26% ± 1.89% 3.45-fold higher relative oral bioavailability	2022	[44]
3	Hyaluronic acid-coated teriflunomide	Management of rheumatoid arthritis	-	-	PS: 284.9 ± 3.8 nm %EE: 96.89 ± 0.45%	Sustained release for 30 days Good stability	2022	[45]
4	Atazanavir	For lymph targeting	Capryol™ 90, Geleol, Tween 80, Span® 20, and D-mannitol	Emulsification-hot high-pressure homogenization	PS: 87.19 ± 1.09 nm PDI: 0.222 ZP: − 12 mV	92.37 ± 1.03% shows a sustained release pattern of the drug Complies to Korsmeyer-Peppas model (r^2 = 0.925, and n = 0.63) 2.54-fold relative bioavailability was determined	2022	[46]
5	Ribociclib and green tea extract	To treat breast cancer	-	-	PS: 1 75.80 ± 3.51 nm PDI: 0.571 ± 0.012 %EE for ribociclib: 80.91 ± 1.66% %EE for green tea extract: 75.98 ± 2.35%	72 h of controlled release Ribociclib and green tea extract bioavailability increased by 3.63 and 1.53 times, respectively, in female Wistar rats	2022	[47]
6	Ritonavir	Acquired immunodeficiency syndrome	Stearic acid, GMS, OA, alpha-tocopherol, Tween 20, and sodium lauryl sulfate	Simple hot-emulsion and ultrasonication	PS: 273.9 to 458.7 nm PDI: 0.314 to 0.480 ZP: − 52.2 to − 40.9 mV % EE: 47.37 to 74.51%	Comparing the improved formulation to a pure drug suspension in vivo, pharmacokinetic investigations showed a sevenfold increase in the area under the curve (AUC) and a more than tenfold increase in Cmax	2022	[48]
7	Chrysin	For improving biopharmaceutical performance	Capmul PG-12, GMS, stearyl amine, Phospholipid S-100, and P188	Hot-melt dispersion-high pressure homogenization	PS: 46.4 nm ZP: 11.4 mV	Continuous medication release from NLCs for over 48 h Stability studies indicated the robustness	2021	[49]
8	Bromelain	In rheumatoid arthritis management	Casein, tyrosine, Pluronic F-68, soya lecithin, stearic acid, polyvinyl alcohol, and trichloroacetic acid	Modified double emulsion solvent evaporation	PS: 298.23 nm %EE: 77%	Improved gastric stability and sustained release characteristics Improvement in the shelf life of 4.63 times over bromelain at room temperature	2021	[50]

Table 3 (continued)

Sr. no	Drug	Disease/purpose	Ingredients	Method	Characterization	Outcomes	Year	Reference
9	Perphenazine	For oral bioavailability improvement in schizophrenia	Amitriptyline, P188, GMS 900 K, dynasan 118, OA, ammonium acetate, Trichloroacetic acid, methanol, and acetonitrile	Emulsification-solvent evaporation	PS: less than 180 nm %EE: more than 95%	Extended-release properties of prepared formulation Good stability at 4 °C within 3 months Compared to a plain drug suspension, oral bioavailability was enhanced in NLC	2021	[51]
10	Fluconazole	Treatment of oral candidiasis	Stearic acid, OA, Pluronic F127, lecithin and chitosan	Emulsification/sonication	PS: 335 ± 13.5 nm %EE: 73.1 ± 4.9%	Sustained release characteristics Rabbit oral mucosal histopathological effects are minimal More effectiveness at inhibiting fungi than fluconazole solution over a more extended period Its anti-candidiasis effectiveness was increased by chitosan coating, which also reinforced its adhesion to rabbit oral, buccal mucosa	2021	[52]
11	Quetiapine Fumarate	To enhance oral bioavailability	P188, Phospholipon 90G, PrecirolATO5, and OA	Hot emulsification-ultrasonication	PS: 140.2 nm %EE: 77.21% ZP: − 19.9 mV	Follows Higuchi's kinetic model (AUC)0-∞ of prepared NLC is 3.93 times that of pure drug suspension	2021	[53]
12	Nintedanib esylate	To enhance oral bioavailability	GMS, Capmul MCM, P188, sodium deoxycholate, and tocopherol polyethylene glycol succinate	High-speed homogenization followed by probe sonication	PS: 125.7 ± 5.5 nm %EE: 88.5 ± 2.5% ZP: − 17.3 ± 3.5 mV	92.7 ± 23.40% in phosphate buffer pH 6.8 and 6.87 ± 2.72% in pH 1.2, respectively, were drug release rates Obeyed Higuchi model NLCs showed 26.31-fold improved oral bioavailability than pure drug suspension	2021	[54]

Table 3 (continued)

Sr. no	Drug	Disease/purpose	Ingredients	Method	Characterization	Outcomes	Year	Reference
13	Miltefosine	For treatment of cutaneous leishmaniasis	Tween 80, stearic acid, tricaprylin, beeswax, span 20, span 80, OA, glyceryl behenate, GMS, isopropyl palmitate, cremophore A6, Tween 65, and polyethylene glycol 400	Micro-emulsion technique	Narrow PDI and PS of 160.8 5.3 nm High incorporation efficiency of 96.17 ± 1.3%	Compared to the drug solution, NLC demonstrated a slower release of the incorporated drug 2.5-fold improvement in anti-leishmanial effectiveness Compared to the miltefosine solution, macrophage cytotoxicity was reduced by six times No gastric toxicity	2021	[55]
14	Nintedanib	To improve oral bioavailability and promote intestinal absorption	Glyceryl monooleate, Tricaprylin, Tween 80, and macorgolglycerides and labrasol	Melt-emulsification technique	PS of 142.70 ± 0.85 nm and 7.99 ± 0.06 nm in 2 batches Positive zeta potential	When compared to the solution, the oral bioavailability of two batches of NLCs was significantly increased by 3.13-fold and 2.39-fold, respectively Excellent tumor inhibition Fewer gastric irritations	2020	[56]
15	Raloxifene	For breast cancer treatment	-	Ultrasonication	PS: 121 nm % EE: 81%	An in vitro release research revealed an initial burst release for 4 h and a continuous release for up to 24 h An increase in intestinal permeability Oral bioavailability increased 4.79 times	2020	[57]
16	Fenofibrate	To enhance oral bioavailability and efficacy	Chitsosan, stearic acid, OA, and Tween 80	Ultrasonication	PS: 200 nm PDI: below 0.3 %EE: 85%	Drug bioavailability and stability are improved via a controlled release profile	2020	[58]
17	Ergosterol	Aiming to improve oral bioavailability and anti-diabetic nephropathy effects	GMS and decanoyl/octanoyl-glycerides	Hot emulsification-ultrasonication	PS: 81.39 nm ZP: 30.77 mV % EE: 92.95%	Drug loading capacity of 6.51% NLCs' relative oral bioavailability was 277.56% more than raw ergosterol	2020	[59]
18	Zotepine	For enhanced pharmacokinetic activity	-	Hot homogenization with probe sonication	PS: 145.8 ± 2.5 nm PDI: 0.18 ± 0.05 ZP: − 31.6 ± 1.8 mV	Sustained release profile by in vivo studies Oral bioavailability was improved 1.8-fold compared to the pure drug suspension	2020	[60]

This review article mainly focused on NLC-loaded nose-to-brain drug delivery

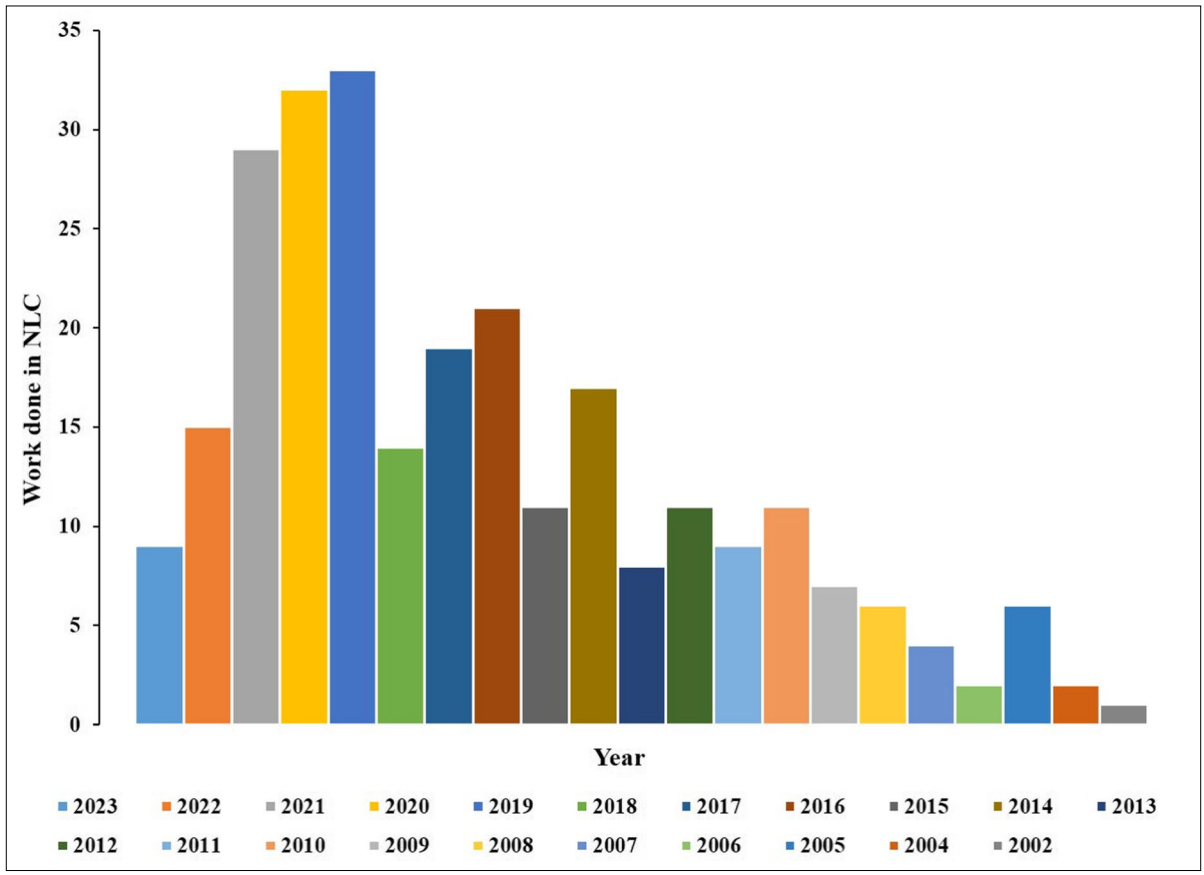

Fig. 8 NLCs prepared for topical drug delivery

transfer [67]. This improves patient compliance and provides a different method of parenteral delivery, particularly for medications containing proteins and peptides or even stem cells. It has good bioavailability for medicines with low molecular weight [68].

NLCs in nose-to-brain drug delivery

NLC is a combination of SL, LL, and surfactant. It can be prepared by the methods enlisted in Table 1. Some of the principles can be considered to develop NLCs for efficient brain drug delivery further, as shown in Fig. 12. Limiting the influences of protein corona/biological molecule corona/nutrient molecule corona is crucial for nose-to-brain drug delivery, as these coronas can alter the behavior and fate of nanocarriers and affect their therapeutic efficacy. It can be done through surface modification, shealth coatings, surface charge optimization, preconditioning strategies, engineered surface ligands, corona modulation agents, biological fluid mimicking media, in vitro and in vivo screenings, etc. By employing these strategies, it is possible to minimize the influences of the protein corona, biological molecule corona, or nutrient molecule corona and enhance the effectiveness of nose-to-brain drug delivery. Table 4 and Fig. 13 display the research done in NLCs for nose-to-brain drug delivery.

Modish stratagem of NLCs in drug delivery

Further, to develop better NLCs, we can also do PEGylation or surface modification on NLCs to enhance the drug-loaded carrier's effectiveness [92] [93]. Combination devices, or those that include both functional prosthetic implants and drug-releasing components, are versatile, developing clinical technology that has the potential to enhance the functionality of implant devices across a

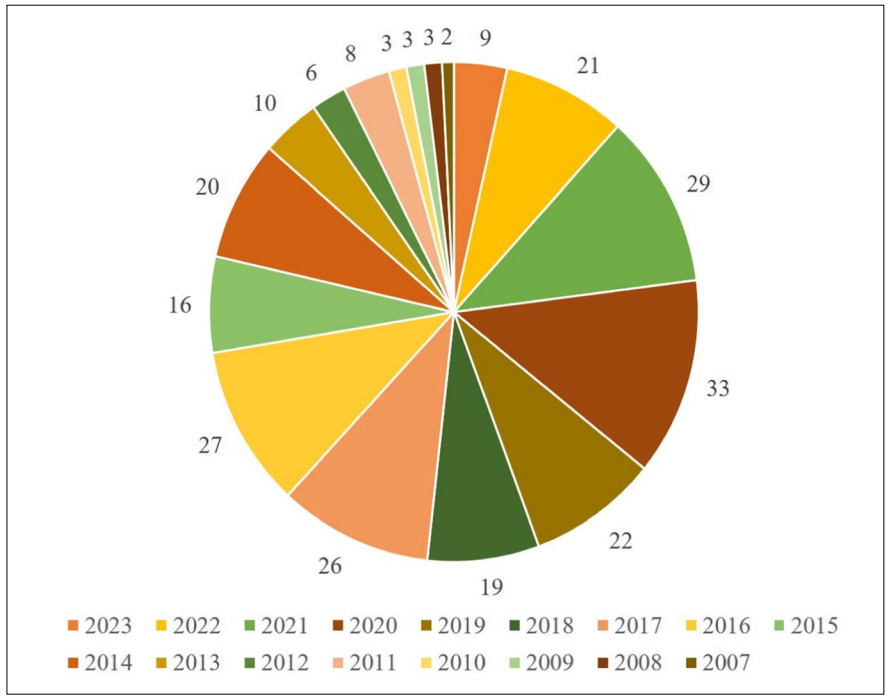

Fig. 9 NLCs prepared for oral drug delivery

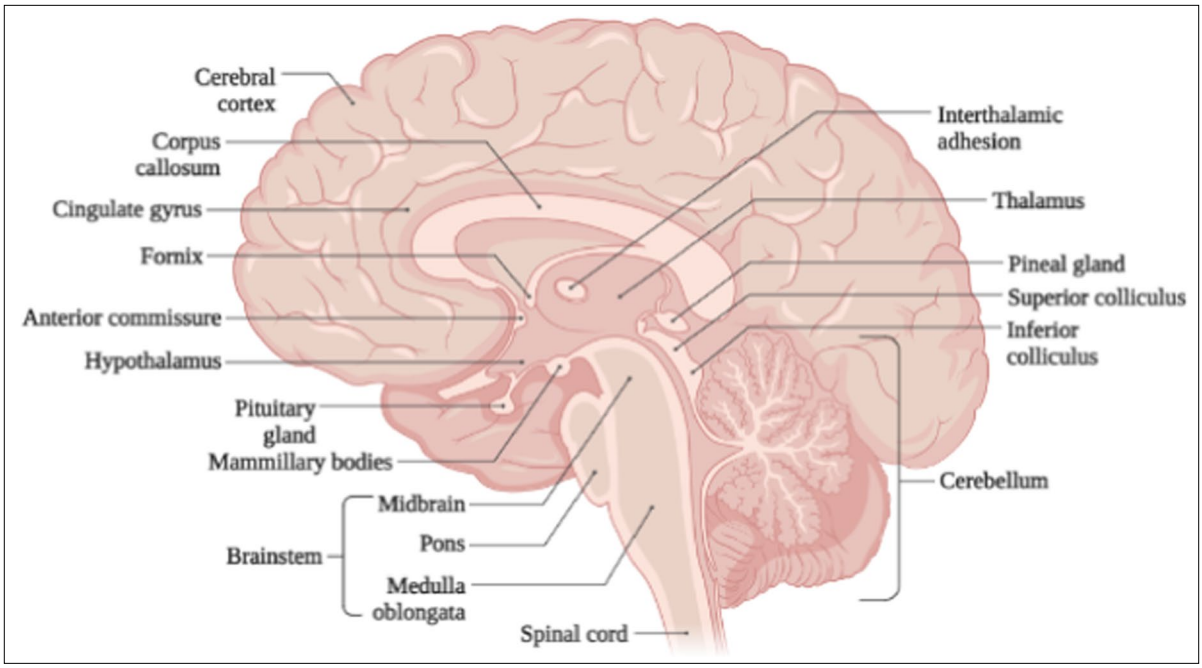

Fig. 10 Anatomy of the brain

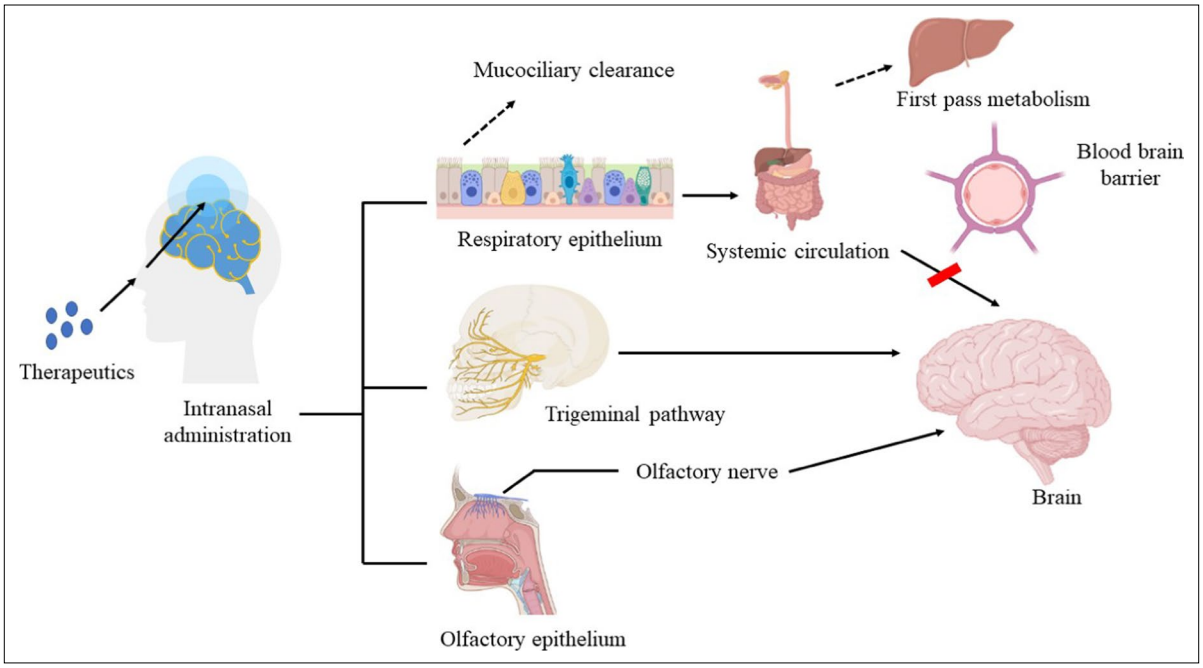

Fig. 11 Pathway of intranasal administration

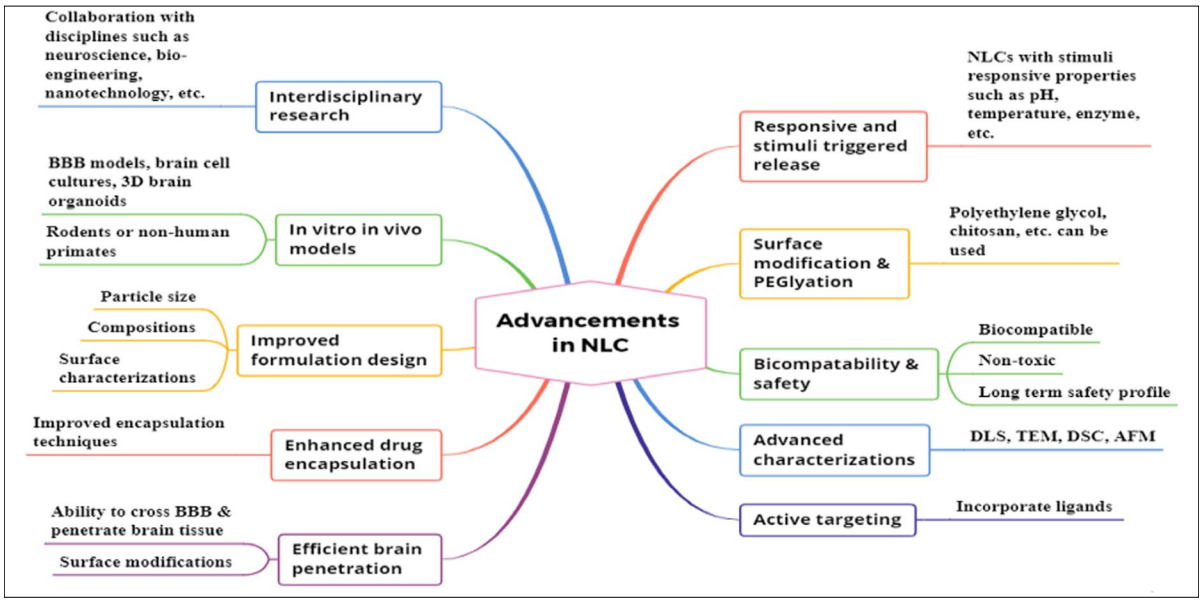

Fig. 12 Principles to develop NLC

variety of classes. Formulation techniques are insufficient to utilize this route to deliver human drugs. To target formulation deposition in the nasal passage's olfactory region and circumvent its architecture limitations, novel technologies are currently being developed. The Vianase™ was used to administer insulin intranasally in one of the few experiments on brain delivery via the nose in humans. Kurve Technology® created the Vianase™

Table 4 NLCs in the nose to brain drug delivery

Sr. no	Drug	Disease	Excipients	Method	Characteristics	Outcomes	Year	Reference
1	Rivastigmine	Alzheimer's	-	-	PS: 114.00 ± 1.91 nm PDI: 0.45 ± 0.00 ZP: − 3.58 ± 1.62 mV %EE: 95.13 ± 0.34% Loading capacity: 9.30 ± 0.03% pH: 6.47 ± 0.01 Osmolarity: 275 ± 0.02 mOsm/kg	Good long-term stability Prolonged drug release and appropriate nasal mucoadhesion were noted Low cytotoxicity varies with the concentration In the olfactory region, 4.0% of the drug deposited Lipid-based nanosystems' thermosensitive in situ gels demonstrated an 8.0% drug deposition rate	2022	[69]
2	Rizatriptan benzoate	For treatment of CNS disorders like migraine	P407 and liquid Carbopol 934P	Melt-emulsification ultrasonication	PS: 189 nm %EE: 84.5%	Drug release was 83.9% after 24 h C_{max}: 5.1 ng/Ml AUC: 829 ng/(min·mL) Drug targeting index: 2.76 Nose-to-brain drug direct transport: 63.69%	2022	[70]
3	Salvia officinalis	Alzheimer's	-	Solvent evaporation	PS: 127 ± 0.68 nm to 140 ± 0.74 nm ZP: − 25.6 ± 0.404 mV	Prolonged and regulated release that adhered to the in vitro Peppas-Sahlin release kinetic model Antioxidative activity: 95.31 ± 1.86%	2022	[71]
4	Teriflunomide (TFM)	Glioma	Gellan gum, carbopol 974P, Compritol 888 ATO, Gelucire 44/14, and glyceryl mono-linoleate	-	Globule size: 117.80 nm PDI: 0.56 ZP: − 21.86 mV %EE − 81.16% Mucoadhesive strength: 4.80 g Nasal permeation: 904 µg/cm^2	IC_{50} for: TNLCGHG: 7.0 µg/mL Pure TFM: 4.8 µg/mL TNLC: 78.5 µg/mL twofold higher brain C_{max} for ^{99m}TC labeled (i.n.) ^{99m}TC-TNLCGHG compared to ^{99m}TC-TNLC (i.n.) and ^{99m}TC-TNLC (i.v.) Improved drug permeability	2021	[72]

Table 4 (continued)

Sr. no	Drug	Disease	Excipients	Method	Characteristics	Outcomes	Year	Reference
5	Olanzapine	Schizophrenia	Isopropyl alcohol, stearic acid as solid lipid, OA, chitosan, and P 407	Solvent injection	Average size: 227.0 ± 6.3 nm PDI: 0.460 %EE: 87.25% pH: 5.7 ± 0.05 Viscosity: 78 centipoises	In-vitro mucoadhesion: 15 ± 2 min In vitro release: 91.96% Ex-vivo permeation drug permeated after 210 min: 84.03%	2021	[73]
6	Astaxanthin	Parkinsonism	Poloxamer-127	Melt-emulsification	PS: 225.6 ± 3.04 nm %EE: 65.91 ± 1.22% ZP: 52.64 mV	Drug release: 92.5 ± 5.42% Compared to drug-loaded in-situ gel, drug-loaded NLC has a better availability	2021	[74]
7	Sumatriptan	Migraine	Triolein, cholesterol, acetone, stearic acid, Brij 35, glacial acetic acid, Brij 72, sodium hydroxide, ammonium acetate, and ethyl acetate	Solvent diffusion evaporation	PS: 101 nm PDI: 0.27 %EE: 91%	Drug targeting efficiency (DTE): 258.02% Direct transport percentage (DTP): 61.23%	2020	[75]
8	Almotriptan maleate (ALM)	Migraine and to check the capability of mucoadhesive chitosan-coated NLCs	Glyceryl behenate, Transcutol®HP, Lauroglycol™90, Precirol® ATO 5, Labrasol®, Labrafil®M2125CS, Chitosan, Tween® 80, and stearic acid	Hot homogenization and ultrasonication	PS: 255 nm PDI: 0.27 ZP: 34.1 mV %EE: 80%	In vitro drug release having biphasic pattern Mucoadhesive property and ex-vivo permeability were enhnaced Brain C_{max} of: IN ALM-NLC: 3.64 µg/mL Oral ALM market product: 0.5 µg/mL IN ALM solution: 0.48 µg/mL	2020	[76]

Table 4 (continued)

Sr. no	Drug	Disease	Excipients	Method	Characteristics	Outcomes	Year	Reference
9	Ketoconazole	Cryptococcal meningoencephalitis	Coumarin, cyanine 5.5, Miglyol 812N, Sasol, Compritol 888 ATO, Solutol HS 15, Polysorbate 80	High-pressure homogenization	PS: 102.1 ± 0.44 nm PDI: 0.195 ± 0.005 ZP: − 2.1 ± 0.18 mV %EE: 70.4% ± 3.4%	Approximately 92% of growth was inhibited compared to 50% in keto-treated cells With a cell inhibition rate of 0.0625 g/mL, the keto-NLC treatment group's cell inhibition rate was nearly fourfold higher than that of the keto treatment group NLCs increase the effectiveness of antifungal medications NLCs can enter brain tissues by bypassing the BBB	2019	[77]
10	Teriflunomide (TFM)	Multiple sclerosis	Glyceryl behenate, Maisine 35–1, Peceol, GMS, stearic acid, Gelucire 44/14, Tween 80, HPMC K4M, and Tween 20	Melt emulsification ultrasonication	PS: 99.82 ± 1.36 nm ZP: 22.29 ± 1.8 mV %EE: 83.39 ± 1.24%	Ex vivo permeation: TFM- MNLC: 830 ± 7.6 µg/cm2 TFM-NLC: 651 ± 9.8 µg/cm2 TFM-MNLC displays almost two times as much Jss than TFM-NLC	2019	[78]

Table 4 (continued)

Sr. no	Drug	Disease	Excipients	Method	Characteristics	Outcomes	Year	Reference
11	Olanzapine (OLZ)	Agranulocytosis	Carbopol 974P and the combination of P407 and HPMC K4M	Melt emulsification	PS: 88.95 nm ± 1.7 nm ZP: − 22.62 mV ± 1.9 mV %EE: 88.94% ± 3.9%	Ex vivo permeation of: OLZ-NLC: 545.12 µg/cm^2 ± 12.8 µg/cm^2 OLZ-MNLC (P + H): 940.02 µg/cm^2 ± 15.5 µg/cm^2 OLZ-MNLC (C): 820.10 µg/cm^2 ± 11.3 µg/cm^2 Drug permeation was seen quickly in OLZ-MNLC (P + H) Comparing the OLZ-MNLC I and OLZ-NLC to the OLZ-MNLC (P + H), there are 13.57 and 27.64 times more Jss, respectively The Cmax of i.n was 3.98 times greater than that of i.v Sustained release of up to 8 h	2019	[79]
12	Selegiline hydrochloride	Parkinson's	-	Hot homogenization	%EE: 93 ± 5.25% Loading capacity: 51.96%	70% of the drug is released after 10 h, while the remaining 97% of the medicine is released continuously for 22 h	2019	[80]
13	Pioglitazone	Alzheimer's	Tripalmitin, tween 80, and Pluronic F68	Microemulsion	PS: 211.4 ± 3.54 nm ZP: 14.9 ± 1.09 mv PDI: 0.257 ± 0.108 %EE: 70.18 ± 4.5%	NLCs were stable at 4 °C and 25 °C Sustained medication delivery from the NLC Ex vivo studies show improved nasal permeability Direct drug delivery from the IN-NLC to the brain is demonstrated by in vivo investigations	2019	[81]

Table 4 (continued)

Sr. no	Drug	Disease	Excipients	Method	Characteristics	Outcomes	Year	Reference
14	Rivastigmine	To enhance brain distribution and pharmacodynamics	Capmul MCM C8, Gellan gum, P407, Tween 80, stearyl amine, and sodium deoxycholate	Ethanol injection	PS: 123.2 ± 2.3 nm ZP: 32 ± 1.2 mV PDI: 0.257 ± 0.108 %EE: 68.3 ± 3.4%	Enhanced penetration in IN- NLCs compared to IV-NLCs No evidence of inflammation was found in the nasal toxicity trials with NLCs	2017	[82]
15	To study the in vivo neuroprotective effect of investigate administered GDNF	Parkinson's	Precirol ATO5, Miglyol, Sasol, Tween 80, P188, chitosan	Melt-emulsification	PS: 136.70 ± 14.14 nm ZP: + 30 mV %EE: 98.10 ± 0.36%	After 2 weeks, achieved a behavioral improvement in rats	2016	[83]
16	Rivastigmine	-	Capmul MCM C8, GMS, gellan gum, lecithin, polysorbate 80, and Lutrol F 127	-	PS: 123.2 ± 2.3 nm %EE: 68.34 ± 3.4%	Nasal permeability and enzyme inhibition efficacy were both increased twofold and threefold, respectively, by NLC-based in situ gel	2015	[84]
17	Chitosan	Neurodegenerative diseases	Miglyol, Precirol ATO® 5, sodium citrate, Dynasan 114®, Tween 80, P 188, and paraformaldehyde	-	PS: 114 nm ZP: + 28 mV	16HBE14o- cells' cellular absorption of the nanocarrier and its biocompatibility were confirmed by in vitro tests Nasal mucosa showed no signs of either toxicity or hemolysis processes	2015	[85]
18	Delonix regia gum with ondansetron hydrochloride	In order to successfully deliver drugs to the brain via the nasal route	GMS, soya lecithin, P188 and Capryol 90	High-pressure homogenization	PS: 92.28–135 nm PDI: 0.32–0.46 ZP: − 11.5 to − 36.2 mV	DTE: 506% DTP: 97.14% Thermodynamically stable and control release pattern	2014	[86]
19	Duloxetine (DLX)	Depression	GMS, pluronic F-68, and capryol PGMC	-	Radiolabeling efficiency of DLX-NLC was 98.87 ± 0.82	Higher DTP (86.80%) and DTE (757.74%) show better brain targeting than the DLX solution When compared to i.v. DLX solution treatment, the brain had an eight-fold greater concentration of DLX	2014	[87]

Table 4 (continued)

Sr. no	Drug	Disease	Excipients	Method	Characteristics	Outcomes	Year	Reference
20	-	To investigate the influence of the nanocarrier surface charge on brain delivery of a model hydrophilic drug via the nasal route	Compritol 888 ATO, Labrafac Stearylamine, P407 and P188, polysorbate 80	Hot high-shear homogenization	PS: < 200 nm ZP: ≈ 34 mV	When compared to anionic NLCs in situ gel, cationic NLCs revealed a non-significantly greater Cmax in the brain Enhanced absolute bioavailability 77.3% compared to the solution (44%) Anionic NLCs in situ gel has the highest DTE% with a value of 158.5, which is nearly 1.2 times that of the cationic NLCs in situ gel	2014	[88]
21	Artemether (ARM)	To treat cerebral malaria, a neurological complication of plasmodium falciparum infection	Trimyristin and Pluronic F 68, sucrose	Microemulsion	PS: 123.4 nm ZP: 34.4 mV	Non-toxic Up to 96 h of sustained release DTE: 278.16% DTP: 64.02% ARM-NLC showed flux that was substantially lower than the medication solution Brain-to-blood ratios for ARM-NLC (i.n.) are 2.619, which is more compared to ARM-SOL (i.n.) and ARM-SOL (i.v.)		[89]
22	Duloxetine (DLX)	To estimate in brain and blood	GMS, Pluronic F-68, capryol PGMC, bile salt, and mannitol	Homogenization and ultrasonication	-	The permeation of DLX-NLC was 2.5 times more than that of DLX solution Estimates of the levels of DLX in the blood and brain were made, and the levels for DLX-NLC were greater	2013	[90]

Table 4 (continued)

Sr. no	Drug	Disease	Excipients	Method	Characteristics	Outcomes	Year	Reference
23	Lamotrigine	To enhance the brain targeting in epilepsy	Cutina CP, Precirol ATO 5, glyceryl behenate, Apifil and Labrafac CC, almond oil, castor oil, olive oil, OA, and Tween 80	Solvent evaporation	PS: 151.6 ± 7.6 nm PDI: 0.249 ± 0.035 ZP: 11.75 ± 2.96 mV %EE: 96.64 ± 4.27%	Sustained drug concentration was obtained after 24 h Scintigraphy research also demonstrated that there is a significant drug buildup in the brain	2015	[91]

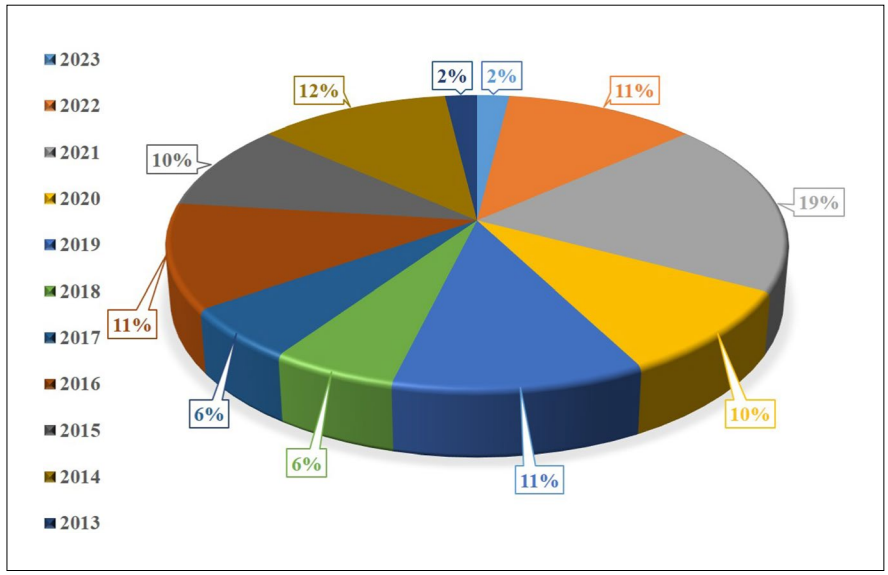

Fig. 13 NLCs prepared for nose-to-brain drug delivery

electronic atomizer, comprising a nebulizer coupled to a vortex chamber. The vortex chamber, where the nebulized drug particles move, maintains this flow after the particles have left the device. Increased transit to the brain encourages deposition to the olfactory area [94]. The necessity for additional administration routes for new medications and to address various targets is driving the growth of the nasal drug delivery industry. A non-invasive drug delivery method for both localized and systemic effects is aerosolization. The formulation will likely reach the olfactory area and achieve direct brain targeting if deeper nasal penetration beyond the nasal valve can be accomplished [95]. Table 5 shows the comprehensive work done in NLCs with the combination of the medical device to deliver drugs at different target sites.

The medium- and long-term fate of nanoparticles is likely to depend on several factors, including tissue distribution, clearance from the body, potential toxicity, metabolism, biodegradation, and environmental factors, including their stability, associations with other environmental elements, and exposure circumstances. It is still emerging, and continuous studies are geared at better comprehending their behavior and possible threats and creating techniques to lessen negative impacts.

Patent search

The patent search was carried out using the licensed version of the PatSeer® PRO database using search strings shown in Table 6. Researchers have thoroughly worked on the synthesis and solubility of the NLCs. Here we have presented formulation-based patents, including formulations with enhanced drug solubility and loading capacity, improved encapsulation efficiency, lowered dose frequency, in vitro studies, etc., as shown in Table 7. This type of literature suggests that these formulations have achieved targeted delivery of drugs and thus lessened side effects related to drug and dose.

Conclusion

With better drug incorporation and enhanced bioavailability, NLCs are chemically and physically stable systems. In recent years, improvements have been significantly accelerated by the industry's growing interest in lipid carrier systems. Currently, the industry offers more than 30 commercial NLC formulations with ingredients for drugs and cosmetics. NLCs can increase bioavailability and reduce dosing frequency, indirectly reducing dose-related side effects. Intervening NLCs directly on the targeted site displays site specificity and many more benefits than conventional dosage forms. Thus, the use of NLCs in nose-to-brain drug delivery is invigorating. NLCs provide advantageous aerosolization properties and practical stability for pulmonary use. Additionally, they can get past local defenses and gather in the lung. NLCs can enter the brain by furnishing the surface of

Table 5 NLCs in combination with medical device

Sr. no	Drug	Purpose	Formulation	Ingredients	Method	Characterization	Outcomes	Year	Reference
1	Beclomethasone dipropionate	For pulmonary drug delivery	NLC with air-jet nebulizer	Glycerol trimyristate, glyceryl tributyrate, glycerol trilaurate, cetyl palmitate, isopropyl palmitate GMS, stearic acid and propylene glycol dicaprylate/dicaprate	Ultrasonication method	Desirable stability (1 week at 25 °C) PS: ~ 241 nm Drug entrapment: > 91% Fine particle fraction (FPF): 70 and 54% Respirable fraction: 92 and 69%	The nebulization time was 42 min or more with the air jet nebulizer Provided improved performance Higher fine particle dose (FPD): 90 and 69 µg Lower mass median aerodynamic diameter (MMAD): 1.15 and 1.62 µm	2021	[94]
2	Ciprofloxacin	For treatment of non-cystic fibrosis bronchiectasis	NLC – Dry powder inhaler (DPI)	Stearic acid, OA, and tween 80	Hot homogenization	PS: 102.3 ± 4.6 nm PDI: 0.267 ± 0.12 %EE: 98.75% ± 0.048% ZP: – 18.3 ± 0.153 FPD: 45.0 µg FPF: 49.2%	NLCs released 80% of the drug in vitro within 10 h Nanocomposite microparticles were produced by spray drying prepared NLCs with chitosan in various ratios with a high yield (> 65%) MMAD: 3.9–5.1 µm	2021	[96]
3	Rosuvastatin	Treatment of airway remodeling in chronic obstructive pulmonary disease	NLC—DPI	Lauric acid and Capryol- 90	Melt-emulsification and ultrasonication	MMAD: < 3 µm FPF: > 90% at 60 L/mi	Significant improvements in t1/2 (fivefold), Cmax (1.14-fold), and AUC0- (35-fold) all pointed to increased bioavailability of NLC-DPI	2016	[97]

Table 5 (continued)

Sr. no	Drug	Purpose	Formulation	Ingredients	Method	Characterization	Outcomes	Year	Reference
4	Montelukast	For pulmonary application	Montelukast NLC (MNLC)–DPI	Precirol ATO5, Capryol-90, and DL-pyrrolidone-carboxylic acid salt of L-cocyl arginine ethyl ester	Melt-emulsification-homogenization method	PS: 184.6 ± 2.7 nm %EE: > 95% Mass median diameters: 15.1 ± 1.4 µm Density for MNLC-DPI: 0.051 ± 0.002 g/cc	A performance evaluation of in vitro aerosols revealed that more than 95% of the dose was released MNLC was found to be safer than the pure drug in an in vitro cytotoxicity assay on A549 cells Prolonged drug retention in the lung and increased bioavailability	2014	[98]
5	Ciprofloxacin hydrochloride (CIP) and N-acetyl cysteine (NAC)	For cystic fibrosis and chronic obstructive pulmonary disorder	NLC–DPI	Cetyl palmitate, OA, and Tween80	Emulsification and ultrasonication	PS: 199.1 ± 1.859 nm ZP: − 38.27 ± 0.384 mV %EE: 72.143 ± 1.8%	Drug release was delayed, and stability was improved with DPI preparation 15 h later, CIP-NLC exhibited a 55% release rate, but CIP-NLC-DPI formulation revealed a 60% release rate	2012	[99]
6	Itraconazole	For pulmonary application	NLC combined with the nebulizing system with an ultrasonic nebulizer and jet stream	Precirol ATO 5 and OA, Eumulgin SLM 20	-	%EE: 98.78%	Drug released in a burst from the designed carrier system The particle size and Itraconazole's ability to entrap itself in the particle matrix were unaffected by the nebulization of Itraconazole-loaded NLC using either a jet stream or an ultrasonic nebulizer	2011	[100]

Table 6 Search strings for patent search

Search string	Number of patents
(Nanostructured lipid carriers) wp (brain)	4
(Nanostructured lipid carriers) wp (nose to the brain)	3
(Nanostructured lipid carriers) wp (intranasal)	4
(Lipid carrier) wp (brain)	30
(NLC) and (brain)	44

the formidable barrier enclosing it, and they can then pass the BBB by receptor-mediated transcytosis. Given the recent increase in patent filings, NLCs should have the same opportunity for accurate clinical translation and pharmaceutical marketing in all cases. Success in this field can be imagined if the pharmaceutical business takes academic study to design this carrier system for diverse therapeutic and cosmetic agents.

Table 7 Patents of NLCs in nose-to-brain drug delivery

Sr. no	Patent number	Description	Abstract	Reference
1	CN110013471B	Brain glioma treatment using an NLC, its manufacture, and application	• NLC is prepared from GMS, triglyceride, temozolomide, curcumin, P188, and absolute ethyl alcohol by a microemulsion method • Particle size: less than 100 nm • Uniform particle size distribution • Zeta potential: − 8.54 + / − 0.51 mV • High encapsulation efficiency • The preparation method is simple to operate and high in repeatability • The NLC prepared by the invention has the sequential release performance of two drugs and a synergistic treatment effect on glioma	[101]
2	IN-MUM-2015-00667A	Brain-targeting novel nanocarrier composition	• A mucoadhesive polymer or its derivative, a hydrophilic cationic neurotherapeutic agent, an anionic polymer, surfactant/s, and cosurfactant/s, solid lipids or triglycerides, liquid lipids or natural oils, are all constituents of the lipid-based nasal nanocarrier • For targeted brain delivery in Parkinson's disease, the suggested nanocarrier formulation entailed integrating a drug-polymer complex into NLC, which was then given a mucoadhesive polymer surface modification	[102]
3	AU2021104270A4	Nasal delivery of desvenlafaxine succinate-loaded NLC for brain targeting	• High-pressure homogenization and melt emulsification techniques were used to prepare them • These compositions are designed to increase the lipophilic drug's bioavailability so that it can more easily traverse the BBB and cerebrospinal fluid barriers • Both solid lipid (GMS) and liquid lipid (OA) were used. P188 is used as a polymer for the formulation • Eight hours of drug release was monitored, and 81.21% of the total release was seen • The maximum %EE was 80.45% • The zeta potential result showed that the system was stable	[103]
4	IN202021023420A	Improved bioavailability in a novel pharmaceutical formulation of ziprasidone hydrochloride	• The NLC was formulated by high-pressure homogenization technique using stearic acid as a SL with Capmul MCM as LL and Tween 80 as the surfactant • The release profile of NLC in phosphate buffer pH 6.4 demonstrated a prolonged release pattern with the full release of 83.50% and 2.15% of the drug at 24 h, showing its slow and continuous release • The nasal ciliotoxicity study indicated no apparent detrimental effect of the developed formulation on the cilia movement • In vivo study demonstrated improved bioavailability	[104]

Abbreviations *NLCs*: **Nanostructured lipid carriers;** *NPs*: **Nanoparticles;** *SLNs*: **Solid lipid nanoparticles;** *PNPs*: **Polymeric nanoparticles;** *SL*: **Solid lipid;** *LL*: **Liquid lipids;** *GMS*: **Glyceryl monostearate;** *OA*: **Oleic acid;** *P188*: **Poloxamer 188;** *RNA*: **Ribonucleic acid;** *DNA*: **Deoxyribonucleic acid;** *SCF*: **Supercritical fluid;** *PS*: **Particle size;** *ZP*: **Zeta potential;** *PDI*: **Polydispersity index;** *%EE*: **% Entrapment efficiency;** *P407*: **Poloxamer 407;** *AUC*: **Area under curve;** *BBB*: **Blood-brain barrier;** *CNS*: **Central nervous system;** *GBD*: **Global burden of disease;** *DALYs*: **Disability-adjusted life years;** *TFM*: **Teriflunomide;** *TNLCGHG*: **Teriflunomide loaded nanolipid carrier–carbopol-gellan gum in situ gel;** *TNLC*: **Teriflunomide loaded nanolipid carrier;** ^{99m}*TC*: **Technetium;** *DTE*: **Drug targeting efficiency;** *DTP* **: Drug transport percentage;** *ALM*: **Almotriptan maleate;** *IN-ALM-NLC*: **Intranasal almotriptan maleate NLC;** *TFM-MNLC*: **TFM mucoadhesive NLC;** *OLZ*: **Olanzapine;** *OLZ-MNLC (P + H)*: **OLZ mucoadhesive NLC (Poloxamer 407 and HPMC K4M);** *OLZ-MNLC (C)*: **OLZ mucoadhesive NLC (Carbopol 974P);** *IN-NLC*: **Intranasal NLC;** *IV-NLC*: **Intravenous NLC;** *DLX*: **Duloxetine;** *ARM*: **Artemether;** *ARM-SOL*: **Artemether solution;** *FPF*: **Fine particle fraction;** *FPD*: **Fine particle dose;** *MMAD*: **Mass median aerodynamic diameter;** *DPI*: **Dry powder inhaler;** *MNLC*: **Montelukast NLC;** *CIP*: **Ciprofloxacin hydrochloride;** *NAC*: **N-acetyl cysteine**

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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