International Journal of Research in Pharmacy and Pharmaceutical Sciences
www.pharmacyjournal.in
ISSN: 2455-698X
Received: 06-01-2024, Accepted: 21-01-2024, Published: 05-02-2024
Volume 9, Issue 1, 2024, Page No. 25-32

Nanostructured lipid carriers: An emerging approach for nose to brain delivery of drugs in the treatment of various CNS disorders

Divya B Jagdale*, Indrajeet D Gonjari, Yash B Kadam, Pranita K More, Akshay B Jadhav
Department of Pharmaceutics, Government College of Pharmacy, Vidyanagar Karad, Satara, Maharashtra, India

Abstract
The administration of medications for illnesses affecting the central nervous system (CNS) is difficult since these medications must pass through the blood-brain barrier (BBB) to reach the brain. The use of the intranasal route to deliver medications straight from the nose to the brain has shown encouraging results among the many approaches that have been researched to get around this problem. Furthermore, by enhancing the bioavailability and site-specific delivery, the encapsulation of the medications in lipid-based nanocarriers, such as nanostructured lipid carriers (NLCs), can enhance nose-to-brain transport. The most recent *in vivo* research using lipid-based nanocarriers (NLCs) for nose-to-brain transfer is reviewed in this study. Drawing from the body of research published in the last 24 months, we offer an understanding of the various pathways that medications may take to enter the brain following intranasal delivery. The findings of research on pharmacokinetics and pharmacodynamics are presented, together with a careful examination of the variations in the nasal cavity anatomy among the many animal species employed in *in vivo* investigations. Drugs tend to be more effectively targeted to the brain when taken via the intranasal route in conjunction with NLCs, despite the fact that the precise mechanism of drug transport from the nasal passages to the brain is still unclear and its efficacy in humans is uncertain. These systems are anticipated to be approved by regulatory bodies in the upcoming years since it has been demonstrated that they are more efficacious for nose-to-brain transport than other routes or preparations with non-encapsulated medicines.

Keywords: CNS targeting, (BBB) blood brain barrier, nose-to-brain delivery, intranasal administration, nanostructured lipid carriers, NLC

Introduction

Because parenteral and oral routes have not produced sufficient results, research on alternate methods to better medication targeting for the management of illnesses affecting the central nervous system (CNS) has become imperative [1]. The nose-to-brain pathway presents itself as a viable substitute in this situation, enabling drug delivery straight from the nose to the brain without the need to pass through the blood-brain barrier (BBB) [2]. The latter is a sophisticated barrier that blocks approximately 98% of molecules from entering the brain from the circulation and shields the brain from infections and xenobiotics. It is made up of closely spaced endothelial capillary cells, pericytes, astroglia, and perivascular mast cells [3-5]. The second-generation lipid-based nanoparticulate structure known as nanostructured lipid carrier (NLC) is created by substituting a combination of liquid and solid lipids for the oily phase of an emulsion. In order to deliver drugs via oral, cutaneous, parenteral injection, nasal, ocular, and buccal routes, NLC is often used as a carrier [6]. Because of their smaller sizes, nanoparticles can diffuse more quickly by transcellular transport, which, depending on the carrier's nature, can lead to a faster onset of action, better bioavailability, and enhanced dispersion in the target tissue. Nanoparticles provide protection against enzymatic degradation and allow for regulated drug release [7]. The highly researched nanocarrier system known as nanostructured lipid carrier (NLC) is made up of a mixture of liquid and solid lipid. It has been claimed that NLC can overcome the drawbacks of solid lipid nanoparticles (SLN), including their reduced capacity for drug loading and inability to exclude entrapped drugs during storage [8].

Need of nose to brain delivery of NLCs

Drug concentrations in the brain are crucial for the successful treatment of CNS diseases. Drugs that are targeted to the brain may have higher concentrations of the medicine there, which would reduce side effects. The inability of some medications to be absorbed appropriately, first-pass metabolism, and problems with drug transit through the blood brain barrier (BBB) limit the targeting by oral route [9]. Treatment of CNS disorders is extremely tough and hard when the BBB is present. Tight junctions, which limit molecule movement by paracellular transport and only allow drug transit via transcellular, carrier-mediated, and receptor-mediated endocytosis, are characteristics of the blood-brain barrier (BBB) [10]. P-glycoprotein, an efflux transporter that is extensively expressed, further regulates drug uptake in the brain. A different method of brain targeting is called "nose to brain delivery," which allows drugs to be delivered by a variety of channels, including the perivascular, trigeminal, olfactory, and cerebrospinal fluid pathways. Enhanced nose-to-brain targeting can be accomplished by a number of techniques, such as employing mucoadhesive polymer to lengthen the nasal residency duration, applying nanocarriers for more effective drug penetration and regulated release, and using enzyme inhibitors and permeation enhancers [11].

Mechanism of drug transport to brain when administered through nasal route

There are two primary routes via which drugs are delivered across the nasal cavity: the respiratory region and the olfactory area. While the later region has exposed olfactory neurons in the upper part of the nares, the former region is extensively vascularized. The nasal epithelium, which is

vascularized, carries medication substances through the respiratory area primarily through the trigeminal nerves. Molecules from the olfactory region are transported by a transcellular route across the olfactory bulb and into the brain by olfactory neurons [12–14].

Limitations

When creating a formulation that targets the central nervous system directly through the nasal route, certain constraints occur. Some of the constraints that are thought to be crucial for formulators when creating a formulation are the drug-excipient stability, the volume of dose in the case of a liquid formulation, the size of the dose in the case of a powdered formulation—hence, potent drugs are preferred. Their safety and toxicity evaluation is one of the most important factors in the development of nose-to-brain medication delivery systems. Extended contact between the nasal mucosa and the mucoadhesive formulation may cause tissue damage, irritation, ciliotoxicity, or epithelial toxicity, as well as create an environment that is conducive to the growth of microorganisms [15, 16].

Advantages and disadvantages of Nanostructured Lipid Carriers [17-19]

Advantages

- Reduce the amount of water in the dispersion;
- Increase the loading capacity for some medications;
- Prevent or reduce drug ejection during storage
- Delivery systems still need to be fully utilized.
- Control and targeted drug release.
- Possibilities to load both lipophilic and hydrophilic drugs.
- Use of biocompatible and biodegradable lipids.
- Avoidance of organic solvents.
- Costlier (less costly than polymeric/surfactant based carriers).
- Better physical stability.
- Easier to prepare for and scale up.
- Increased skin hydration and elasticity.
- Small dimensions ensures close interactions with the stratum corneum.
- Improved retention of drugs.

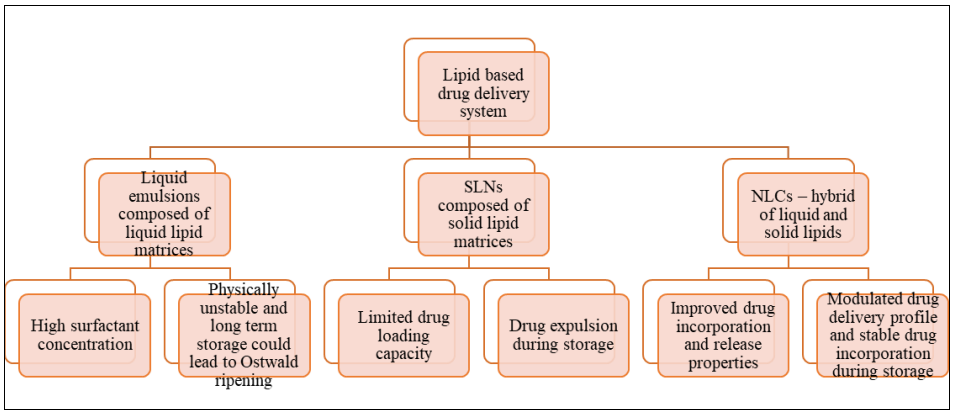

Fig 1: Lipid-based drug delivery system classification illustrating the possible benefits of hybrid matrices that combine liquid and solid lipids over solely liquid or solid formulations

Disadvantages

- Application and effectiveness in the case of protein and peptide medications and gene therapy;
- Cytotoxic effects associated with the type and concentration of lipid matrix;
- Itching and hypersensitive action of surfactants;
- Lipid Stability

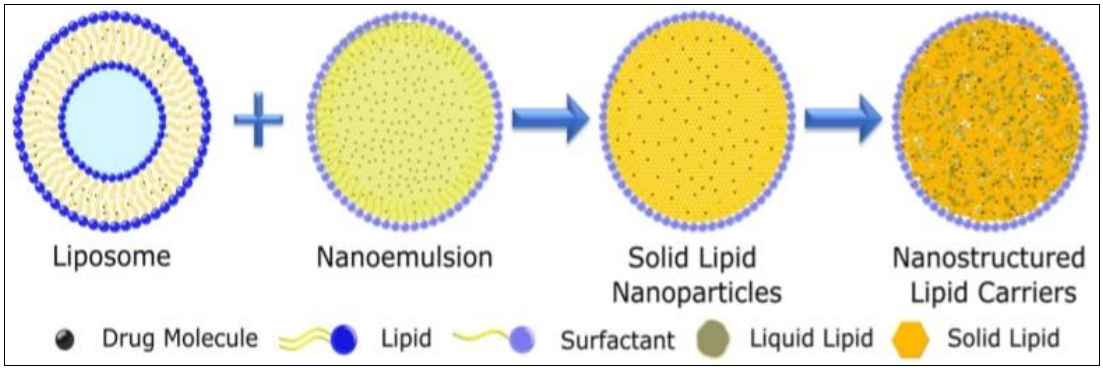

Fig 2: Evolution of lipid based nanocarriers

Composition of nanostructured lipid carriers

At room temperature, NLCs are a type of binary mixture of liquid and solid lipids, or fats and oils, respectively. In a formulation, the ratio of liquid to solid lipid typically varies from 50:50 to 90:10 [20, 21]. The preparation contains surfactants in the entire range of 1–5% (w/v). Because surfactants reduce the surface tension between the lipid and aqueous phases, they have a significant role in both the creation of stable formulations and the stability of NLC [22]. Drugs are loaded into liquid lipids, which are subsequently loaded into solid lipids. This provides double protection

from external degradation factors in the form of a core structure. The choice of liquid and solid lipids is crucial for the long-term stability of NLCs. According to regulatory organizations, every ingredient utilized to create a nanostructured lipid carrier must be GRAS (generally regarded as safe) [23].

Various types of nanostructured lipid carriers

The imperfect type NLC (type 1)

The solid matrix of an imperfect form of NLC has an uneven shape. The assimilation of a portion of solid lipid by liquid lipid (or oil) results in imperfect form. This causes tiny cavities to emerge. As a result, this occurrence results in more space being available for drug molecules to occupy, increasing the drug pay load. Using minuscule amounts of glycerides can help resolve this issue. Therefore, the creation of irregular shapes allows for more room for the loading of drugs, preventing the construction of a highly ordered and structured matrix that would have forced the medicament out of the core [24].

The multiple type NLC (type 2)

This kind of NLC is essentially oil-in-solid or fat-in-water, and it can only be produced via the phase separation technique. Pharmaceuticals that are more soluble in oil or liquid lipid than different types of NLC are more suited for phase separation technology manufacture. It enhances the stability and capacity of medication loading as a result. Small oil droplets are first distributed in the solid lipid phase and then in the aqueous phase. The phase separation process is covered in more detail in the section on NLC production methods below [25].

The amorphous type NLC (type 3)

When solid lipid that is still in the alpha polymorph after the process of solidification and storage is combined with liquid lipid or oils, an amorphous core is produced in the form of NLC. A crystalline core or matrix is produced by solid lipid in its beta polymorph form. Since no crystalline structure is forced, the medication remains incorporated in the core of this type of NLC, which offers additional advantages [26].

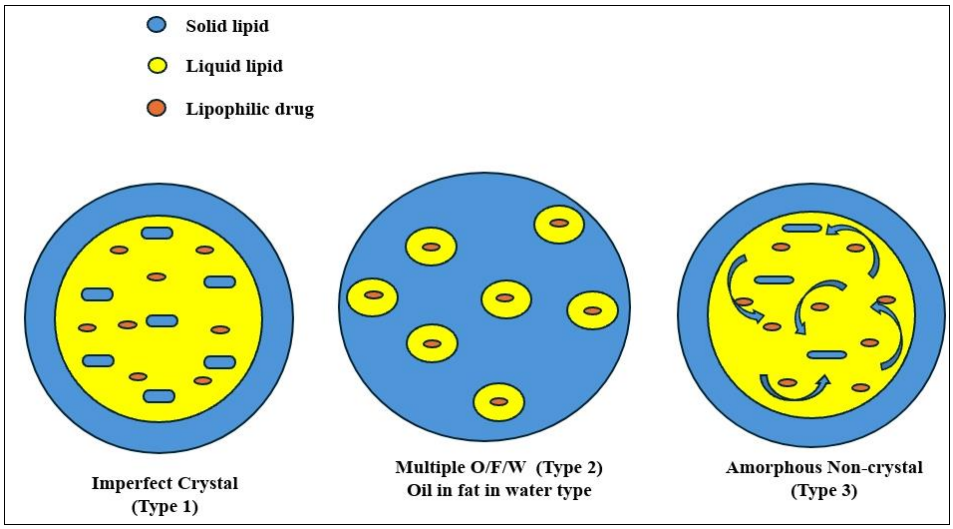

Fig 3: Various types of NLCs

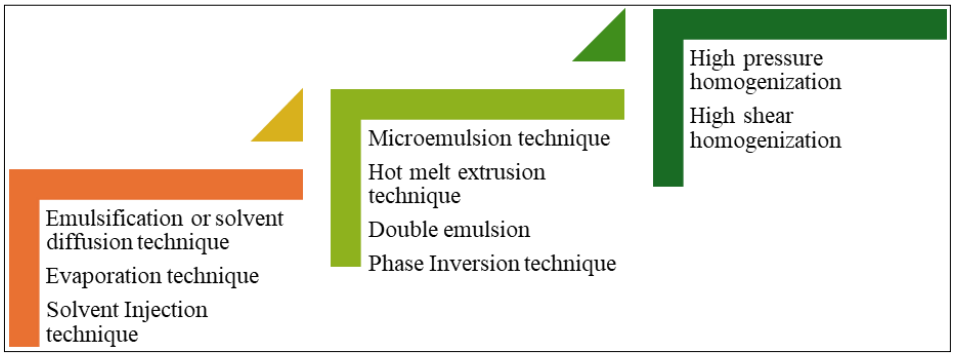

Fig 4: Methods of preparation of NLCs as per energy requirement

Methods of preparation of NLCs

Various techniques have been documented for the preparation of NLCs. Some of the several ways to prepare are as follows:

1. High pressure homogenization technique
2. High speed/shear homogenization technique
3. Microemulsion technique
4. Hot melt extrusion
5. Double emulsion technique
6. Phase inversion technique
7. Emulsification technique
8. Solvent diffusion and evaporation technique
9. Solvent injection technique

A. High energy required methods

1. High pressure homogenization technique

a. Hot high-pressure homogenization technique

An energy-intensive and scalable method for creating nano-sized colloidal molecules (NLC, SLN, and nanoemulsions) is high-pressure homogenization. With the aid of applied

pressure, it employs a top-down method to reduce microemulsion particles to nanoscale size [27]. This method created a hot lipid phase by melting solid lipid and then adding liquid lipid. To create an aqueous phase, surfactants—with or without cosurfactants—are added to water. To make a microemulsion, the heated aqueous phase and the preheated lipid phase are combined while being constantly stirred. A high-pressure homogenizer is used to reduce the size of this heated microemulsion. Different cycles of homogenization might be used according to the target particle size. To transform this nanoemulsion into NLC, it is cooled [28, 29]. NLC with a particle size of less than 100 nm is produced over an extended period of time at an intermediate pressure of 1000 bar [30]. For medications or materials that deteriorate at high temperatures, this method is not recommended.

b. Cold high-pressure homogenization technique

This procedure, which is comparable to hot high-pressure homogenization, combines a lipid phase with a cold aqueous solution that is constantly stirred and kept at a temperature of about between 2 and 6 degrees Celsius. At low temperatures, a high-pressure homogenizer is used to homogenize this coarse NLC suspension. Materials and medications that shouldn't be subjected to high temperatures can be processed using this method [31].

2. High shear homogenization technique

The preparation of NLC using this approach is the same as hot high-pressure homogenization. In this procedure, a high shear rate takes the place of high pressure. Liquid lipid is combined with melted solid lipid to form the lipid phase, and surfactant is combined with water to form the aqueous phase. A homogenizer is used to homogenize the heated lipid and the aqueous phase for a prolonged period of time (10–30 minutes) at a high rotation per minute (rpm). NLC is created by cooling the resultant solution to ambient temperature [32, 33]. The size of particles of nanocarriers is linearly influenced by the speed of homogenization [34]. To further lower the NLC particle size, liquid nanoemulsion can additionally be sonicated for five minutes with an ultrasonic probe before cooling [35]. The melt emulsification approach, which used the same process but with slower homogenization and longer sonication times, was described in certain literature [36, 37].

B. Low energy required methods

3. Microemulsion

Liquid lipid is added to molten solid lipid in the microemulsion process. To create a microemulsion, the final solution is combined with an aqueous phase. The NLC dispersion system is created by quickly cooling this microemulsion with cold water. The NLC particle size is determined by the difference between the microemulsion and water. Although this method of preparing NLC is straightforward, a significant quantity of surfactants and the cosurfactant is needed [38].

4. Hot melt extrusion technique

In order to obtain NLC, the hot melt extrusion technique pumps raw material into a barrel and then sonicates it. Using a volumetric feeder, the mixture of medication and solid lipid was delivered into an extruder barrel. Using a peristaltic pump, liquid lipid and aqueous solutions were introduced at extrusion temperature. To create a pre-emulsion, this mixture had been extrude at the component melt temperature. To decrease NLC particle size, the resulting hot pre-emulsion is subjected to further sonication [39].

5. Double emulsion

This approach facilitates the precipitation of uniformly dispersed NLCs particles by adding the produced microemulsion to cold water (2–10 C) [40].

6. Phase inversion

This procedure involves exposing the mixture of all the components to three cycles of heating and cooling. Phase inversion causes NLCs to form after the hot mixture is shocked by being diluted with cold water [40].

C. Very low or no energy required methods

7. Emulsification technique

This approach involves dissolving the active ingredient and lipids in an organic solvent that has been saturated with water to achieve thermodynamic equilibrium. The resulting brief o/w emulsion is added to water and stirred until the dispersed phase solidifies [40].

8. Solvent diffusion and evaporation technique

This method involves adding liquid lipid to molten solid lipid that has been dissolved at a high temperature in one or more organic solvents. After that, this lipid solution is stirred into an aqueous solution containing surfactant. To create an oil in water nanoemulsion, this prepared dispersion is ultrasonicated and then chilled with gentle stirring until the organic solvent evaporates [41]. This method uses less energy and prevents physical stress from shear or high pressure, but it requires an extra step to remove any remaining harmful solvent because it uses an organic solvent [27].

9. Solvent injection technique

This method involves melting solid lipid by dissolving the lipid phase in a water-miscible solvent or in a combination of them. With continuous stirring, the resulting organic phase is quickly injected into an aqueous phase containing a surfactant or buffer solution. Lipid precipitation and lipid nanocarrier production cause the solvent to disperse. Diffusion of the solvent and emulsifier content determine particle size [27].

Table 1: Overview of how NLCs overcome various barriers for the efficient absorption of poorly water soluble drugs [42].

Sr. No.	Barriers	NLCs overcoming the barrier
1.	Unstirred water layer (UWL)	Formation of submicron micelles enhances solubilization across UWL
2.	Reduced biliary secretion emulsification	Induction of biliary and pancreatic secretions
3.	Intraenterocyte metabolism	Lipids acts as protective core and prevent such metabolism
4.	Pgp efflux of the drug	Modulatory activity of lipids on efflux transporters
5.	Extensive first pass metabolism	Promotion of lymphatic uptake and surpassing liver

Characterization Techniques of NLCs

Techniques for characterizing NLCs are crucial for evaluating their chemical, biological, and physical characteristics. These methods offer useful data for enhancing NLC formulations and guaranteeing their quality. The following are some typical methods of characterizing NLCs that are covered in detail in the research literature [21, 43, 44]:

1. **Particle size analysis**

a. **Dynamic light scattering (DLS):** The hydrodynamic diameter of NLC particles in suspension is measured by DLS. It offers details on polydispersity and the distribution of particle sizes.

2. **Zeta potential measurement**

a. **Electrophoretic light scattering (ELS):** The zeta potential of NLCs is measured using ELS. Zeta potential is a surface charge reflection that can reveal a particle's stability and aggregation potential.

3. **Morphological analysis**

a. **Transmission electron microscopy (TEM):** High-resolution imaging of NLCs is made possible by TEM, which offers details on the morphology, size, and shape of the particles.

b. **Scanning electron microscopy (SEM):** NLCs can also be seen with SEM, even though it only gives surface morphological data.

4. **Drug loading and encapsulation efficiency:** Drug content in NLC formulations is commonly measured using HPLC and UV-Vis spectroscopy, which is also used to determine encapsulation efficiency.

5. **Physical stability**

a. **Centrifugation:** Centrifugation experiments, which watch for particle sedimentation or creaming, can evaluate the physical stability of NLC dispersions.

b. **Freeze-thaw cycling:** It is possible to evaluate the stability of NLC formulations under stress circumstances by performing repeated cycles of freeze-thaw.

6. ***In vitro* drug release studies**

a. **Dialysis or membrane diffusion:** Using methods that mimic drug release *in vivo*, these approaches are utilized to investigate the kinetics of drug release from NLCs over time.

b. **Franz diffusion cell:** Technique makes it possible to monitor the amount of medication released from NLCs via a biological or synthetic membrane.

7. **Thermal analysis**

a. **Differential scanning calorimetry (DSC):** Drug-lipid interactions and the thermal behavior of NLC constituents can be ascertained by DSC.

b. **Thermogravimetric analysis (TGA):** The thermal stability and degradation patterns of NLC formulations are evaluated by TGA.

8. **X-ray diffraction (XRD):** Understanding lipid component crystalline structure and any variations in drug crystallinity inside NLCs is aided by XRD.

9. **Nuclear magnetic resonance (NMR):** Drug-lipid interactions and the distribution of drug molecules within the lipid matrix can be examined using NMR spectroscopy.

10. **Fourier-transform infrared spectroscopy (FTIR):** Drug-lipid interactions are evaluated and chemical bonds and functional groups in NLC components are analyzed using FTIR spectroscopy.

11. **Rheological analysis:** Rheological testing can reveal details on the viscosity and flow characteristics of NLC dispersions, which is crucial for the stability and administration of the formulation.

12. **Biological studies**

a. **Cellular uptake studies:** These investigations use methods like flow cytometry and confocal imaging to evaluate the cellular internalization of NLCs loaded with medicines.

b. ***In vivo* studies:** Studies on humans or animals can assess the therapeutic effectiveness, biodistribution, and pharmacokinetics of NLC-based drug delivery systems.

13. **Stability and shelf-life testing:** Accelerated stability tests can evaluate how stable NLC formulations are over the long term under a variety of storage scenarios.

The particular characteristics and goals of the NLC formulation determine which characterisation approaches are best, and a combination of these techniques is frequently employed to thoroughly evaluate NLCs for drug delivery applications.

Table 2: Drug Delivery through Nasal route by NLC

Drug	Purpose	Solid lipid	Liquid lipid	Surfactant	Formation method	Outcome	Ref.
Almotriptan malate	Nasal delivery of antimigraine drug	Compritol	Labrafil	Tween 80 and lauroglycol	Hot homogenization and ultrasonication technique	Chitosan-coated NLC demonstrated improved mucoadhesion and high drug permeability in the nasal mucosa of sheep. An *in vivo* investigation in albino rabbits revealed a higher Cmax than the solution and oral commercial formulation.	45
Lorazepam	Nasal delivery of drug for status epilepticus	Glyceryl monostearate	Oleic acid	Tween 80 and pluronic F127	Solvent diffusion and evaporation method	Rats with convulsion models treated with chitosan-based NLC exhibit improved *in vivo* outcomes and a sustained *in vitro* medication release rate.	46

Mosapride citrate	Nasal delivery of prokinetic agent for GERD	Stearic acid	isopropyl myristate	L-alpha lecithin And Lutrol F127	Melt–Emulsification Low temperature–Solidification Technique	Drug-loaded NLC demonstrates a three-fold rise in drug penetration in the nasal mucosa of sheep. and better bioavailability and stomach emptying rate compared to a medicine suspension and commercially available oral preparation.	47
Oleuropein	Phytochemical loaded NLC for treatment of meningitis	Tefose	Capmul	Poloxamer 188, polysorbate 80, and soya lecithin	Melt emulsification and ultrasonication method	There is a high medication penetration rate in the nasal mucosa. Studies conducted *in vitro* demonstrate an initial burst release followed by a persistent release.	37
Carbamazepine	For fast action Of anti-epileptic drug through nose-to-brain targeting	Precirol ATO 5	Capmul MCM	Tween 80 and span 20	Microemulsion technique followed by probe sonication	Poloxamer 407 (P407), poloxamer 188 (P188), and the mucoadhesive polymer were employed in thermosensitive in situ gel. Gel based on NLC shows increased drug dispersion. Anticonvulsant activity in MES model rats and sheep nasal mucosa are superior than non-NLC-Based gel and drug dispersion.	48
Flibanserin	Nose-to-brain delivery of seratonergic agent	Glyceryl behenate	Sweet almond oil	L-phosphatidyl choline and gelucire 44/14	High speed homogenization followed by sonication	Improved formulation results in improved medication release. Drug concentrations in the brain and plasma are higher in *in vivo* assessment than in raw form.	49
Escitalopram and Paroxetine	Nose to brain drug delivery for treatment of depression	Precirol ATO 5	Lauroglycol 90	Tween 80	High Pressure Homogenization Technique	NLC *in vivo* experiments demonstrate comparable systemic drug response compared to intravenous drug treatment. With reduced systemic exposure, borneal encapsulation produces a five-fold increase in brain drug concentration.	50

Conclusion and future perspectives

The intranasal route has garnered a lot of attention in recent decades due to research on how it can bypass the necessity for medications to penetrate the blood-brain barrier. Based on the published research, we draw the conclusion that the intranasal route, in conjunction with lipid-based nanocarriers like NLCs, is beneficial for delivering medications to the brain. When delivered via the nose to the brain, these methods have proven to be more successful than when free drug suspensions or solutions are administered intravenously. It is crucial to determine the parameters that affect the medication's nasal absorption when creating a lipid-based nanocarrier formulation. This will help to guarantee that the drug reaches the brain with the least amount of losses due to mucociliary clearance, enzymatic breakdown, or systemic circulation absorption. Developing an appropriate device that targets the medicine to the upper area of the nasal cavity also requires a deeper knowledge of the nose-brain transport process.

The lipids utilized in the NLC formulation are readily available, biocompatible, biodegradable, and most importantly approved as GRAS status. Because straightforward production techniques like high-pressure homogenization are employed, NLCs may be produced on a large scale and scaled without any problems. The liquid lipids, or natural oils, used in the creation of NLCs are crucial to the effective treatment of disorders. In this study, we have attempted to compile data from nearly all studies conducted in the past few years that have used NLC as a carrier system to treat different types of brain diseases. Additionally, the review covered the various NLC varieties based on lipid blends, NLC manufacturing methods, and NLC stability profiles. With the growth of technologies over the years, fabrication techniques and drug delivery tactics also more improved and smarter which allows the development of more viable remedies to treat brain problem. By altering the surface with mucoadhesive substances like chitosan, natural gum, or in conjunction with an in situ gelling system, it is possible to improve nasal permeability by increasing drug retention in the nasal mucosa. All of these tactics aim to improve the medication's performance and bioavailability when treating brain disorders. However, despite a number of promising experimental claims, not a single method is offered for sale for use in clinical settings. The majority of the work was either abandoned at the preclinical or early phases of clinical trials, which is the cause for this failure. Other than this, no worldwide standard operating procedures or equipment specifications exist for the creation of innovative carrier systems as of yet. Different methodologies are used by different researchers and laboratories, which could have an impact on the commercial development of this kind of delivery system. Pharmaceutical companies and scientists have, nevertheless, made some attempts to create a commercial product that targets the brain with NLC; these attempts are unsuccessful at first, but persistent efforts will undoubtedly pay off in the long run.

Acknowledgment

The authors are thankful to AICTE New Delhi for providing the financial support during M. Pharm study tenure. Also, thankful to the principle of GOVERNMENT COLLEGE OF

PHARMACY, KARAD for allowing to publish this article and gave us other facilities.

References

1. Costa CP, Moreira JN, Lobo JM, Silva AC. Intranasal delivery of nanostructured lipid carriers, solid lipid nanoparticles and nanoemulsions: A current overview of *in vivo* studies. Acta Pharmaceutica Sinica B,2021:11(4):925-40.
2. Alexander A, Agrawal M, Bhupal Chougule M, Saraf S, Saraf S. Chapter 9 – nose-to-brain drug delivery: an alternative approach for effective brain drug targeting. In: Shegokar R, editor. nano-pharmaceuticals. Elsevier, 2020. P. 175e200.
3. Pottoo FH, Sharma S, Javed MN, Barkat MA, Harshita, Alam MS, *et al*. Lipid-based nanoformulations in the treatment of neurological disorders. Drug Metab Rev,2020:52:185e204.
4. Weiss N, Miller F, Cazaubon S, Couraud PO. The blood–brain barrier in brain homeostasis and neurological diseases. Biochim Biophys Acta,2009:1788:842e57.
5. Kaur IP, Bhandari R, Bhandari S, Kakkar V. Potential of solid lipid nanoparticles in brain targeting. J Control Release,2008:127:97e109.
6. Beloqui A, Solınıs MA, Rodr ıguez-Gascon A, *et al*. Nanostructured lipid carriers: promising drug delivery sysTems for future clinics. Nanomedicine,2016:12(1):143–161.
7. Chaudhari PD. A review on nose-to-brain drug delivery. Int J Pharm Chem Sci,2013:2(1):516-25.
8. Abolhasanzadeh Z, Ashrafi H, Badr P, Azadi A. Traditional Neurotherapeutics approach intended for direct nose to Brain delivery. J Ethnopharmacol,2017:209:116-23. doi: 10.1016/j.jep.2017.07.026.
9. Joseph E, Saha RN. Advances in brain targeted drug delivery: Nanoparticulate systems. J PharmaSciTech,2013:3(1):1-8.
10. Phukan K, Nandy M, Sharma RB, Sharma HK. Nanosized drug delivery systems for direct nose to brain targeting: a review. Recent Pat Drug Deliv Formul,2016:10(2):156-64. doi: 10.2174/1872211310666160321123936.
11. Bhise SB, Yadav AV, Avachat AM, Malayandi R. Bioavailability of intranasal drug delivery system. Asian J Pharm,2008:2(4):201-15. Doi: 10.22377/ajp.v2i4.203.
12. Mistry A, Stolnik S, Illum L. Nanoparticles for direct nose-to-brain delivery of drugs. Int J Pharm,2009:379(1):146-57. doi: 10.1016/j.ijpharm.2009.06.019.
13. Crowe TP, Greenlee MHW, Kanthasamy AG, Hsu WH. Mechanism of intranasal drug delivery directly to the brain. Life Sci,2018:195:44-52. doi: 10.1016/j.lfs.2017.12.025.
14. Pardeshi CV, Belgamwar VS. Direct nose to brain drug delivery via integrated nerve pathways bypassing the blood-brain barrier: an excellent platform for brain targeting. Expert Opin Drug Deliv,2013:10(7):957-72. doi: 10.1517/17425247.2013.790887.
15. Wang Z, Xiong G, Tsang WC, Schätzlein AG, Uchegbu IF. Nose-to-brain delivery. J Pharmacol Exp Ther,2019:370(3):593-601. doi: 10.1124/jpet.119.258152
16. Erdő F, Bors LA, Farkas D, Bajza Á, Gizurarson S. Evaluation of intranasal delivery route of drug administration for brain targeting. Brain research bulletin,2018:143:155-70. doi: 10.1016/j.brainresbull.2018.10.009.
17. Jaiswal P, Gidwani B, Vyas A. Nanostructured lipid carriers and their current application in targeted drug delivery. Artif Cells Nanomed Biotechnol,2016:44(1):27-40. doi: 10.3109/21691401.2014.909822.
18. Naseri N, Valizadeh H, Zakeri-Milani P. Solid lipid nanoparticles and nanostructured lipid carriers: structure, preparation and application. Adv Pharm Bull,2015:5(3):305-13. doi: 10.15171/apb.2015.043.
19. Kaur S, Nautyal U, Singh R, Singh S, Devi A. Nanostructure lipid carrier (NLC): the new generation of lipid nanoparticles. Asian Pac J Health Sci,2015:2(2):76-93. doi: 10.21276/apjhs.2015.2.2.14.1.
20. Li Q, Cai T, Huang Y, Xia X, Cole SPC, Cai Y. A review of the structure, preparation, and application of NLCs, PNPs, and PLNs. Nanomaterials (Basel),2017:7(6):122. doi: 10.3390/nano7060122.
21. Khosa A, Reddi S, Saha RN. Nanostructured lipid carriers for site-specific drug delivery. Biomed Pharmacother,2018:103:598-613. doi: 10.1016/j.biopha.2018.04.055.
22. Han F, Li S, Yin R, Liu H, Xu L. Effect of surfactants on the formation and characterization of a new type of colloidal drug delivery system: nanostructured lipid carriers. Colloids Surf A Physicochem Eng Asp,2008:315(1-3):210-6. doi: 10.1016/j.Colsurfa.2007.08.005.
23. Tekade AR, Mittha PS, Pisal CS. Nanostructured Lipid Carriers for Nose to Brain Delivery Targeting CNS: Diversified Role of Liquid Lipids for Synergistic Action. Advanced pharmaceutical bulletin,2022:12(4):763–771. https://doi.org/10.34172/apb.2022.078.
24. Salvi VR, Pawar P. Nanostructured lipid carriers (NLC) system: a novel drug targeting carrier. J Drug Deliv Sci Technol2019:51:255-67. Doi: 10.1016/j.jddst.2019.02.017.
25. Jaiswal P, Gidwani B, Vyas A. Nanostructured lipid carriers and their current application in targeted drug delivery. Artif Cells Nanomed Biotechnol,2016:44(1):27-40. doi: 10.3109/21691401.2014.909822
26. Sharma A, Baldi A. Nanostructured lipid carriers: a review. J Dev Drugs,2018:7(1):192. doi: 10.4172/2329-6631.1000191
27. Duong VA, Nguyen TT, Maeng HJ. Preparation of solid lipid nanoparticles and nanostructured lipid carriers for drug delivery and the effects of preparation parameters of solvent injection method. Molecules,2020:25(20):4781. doi: 10.3390/Molecules25204781
28. Nimtrakul P, Sermsappasuk P, Tiyaboonchai W. Strategies to enhance oral delivery of amphotericin B: a comparison of uncoated and enteric-coated nanostructured lipid carriers. Drug

Deliv,2020:27(1):1054-62. doi: 10.1080/10717544.2020.1785050
29. Patil GB, Patil ND, Deshmukh PK, Patil PO, Bari SB. Nanostructured lipid carriers as a potential vehicle for carvedilol delivery: application of factorial design approach. Artif Cells Nanomed Biotechnol,2016:44(1):12-9. doi: 10.3109/21691401.2014.909820
30. Mendes M, Basso J, Silva J, Cova T, Sousa J, Pais A, *et al*. Biomimeting ultra-small lipid nanoconstructs for glioblastoma treatment: a computationally guided experimental approach. Int J Pharm,2020:587:119661. doi: 10.1016/j.ijpharm.2020.119661
31. Duong VA, Nguyen TT, Maeng HJ, Chi SC. Data on optimization and drug release kinetics of nanostructured lipid carriers containing ondansetron hydrochloride prepared by cold high-pressure homogenization method. Data Brief,2019:26:104475. doi: 10.1016/j.dib.2019.104475
32. Rouco H, Diaz-Rodriguez P, Gaspar DP, Gonçalves LMD, Cuerva M, Remuñán-López C, *et al*. Rifabutin-loaded nanostructured lipid carriers as a tool in oral anti-mycobacterial treatment of Crohn's disease. Nanomaterials (Basel),2020:10(11):2138. doi: 10.3390/nano10112138
33. Khan AA, Mudassir J, Akhtar S, Murugaiyah V, Darwis Y. Freeze-dried lopinavir-loaded nanostructured lipid carriers for enhanced cellular uptake and bioavailability: statistical optimization, *in vitro* and *in vivo* evaluations. Pharmaceutics,2019:11(2):97. doi: 10.3390/pharmaceutics11020097
34. Mulia K, Safiera A, Pane IF, Krisanti EA. Effect of high speed homogenizer speed on particle size of polylactic acid. J Phys Conf Ser 2019:1198(6):062006. doi: 10.1088/1742-6596/1198/6/062006
35. Ajiboye AL, Nandi U, Galli M, Trivedi V. Olanzapine loaded nanostructured lipid carriers via high shear homogenization and ultrasonication. Sci Pharm 2021:89(2):25. doi: 10.3390/scipharm89020025
36. Yu Y, Feng R, Li J, Wang Y, Song Y, Tan G, *et al*. A hybrid genipin-crosslinked dual-sensitive hydrogel/nanostructured lipid carrier ocular drug delivery platform. Asian J Pharm Sci,2019:14(4):423-34. doi: 10.1016/j.ajps.2018.08.002
37. Palagati S, Sv S, Kesavan BR. Application of computational tools for the designing of oleuropein loaded nanostructured lipid carrier for brain targeting through nasal route. Daru,2019:27(2):695-708. Doi: 10.1007/s40199-019-00304-0
38. Li Q, Cai T, Huang Y, Xia X, Cole SPC, Cai Y. A review of the structure, preparation, and application of NLCs, PNPs, and PLNs. Nanomaterials (Basel),2017:7(6):122. doi: 10.3390/nano7060122
39. Shadambikar G, Marathe S, Ji N, Almutairi M, Bandari S, Zhang F, *et al*. Formulation development of itraconazole PEGylated nano-lipid carriers for pulmonary aspergillosis using hot-melt extrusion technology. Int J Pharm X,2021:3:100074. doi: 10.1016/j.ijpx.2021.100074
40. M. Elmowafy and M.M. Al-Sanea, Nanostructured lipid carriers (NLCs) as drug delivery platform: Advances in formulation and delivery strategies, Saudi Pharmaceutical Journal, https://doi.org/10.1016/j.jsps.2021.07.015
41. Shamma RN, Aburahma MH. Follicular delivery of spironolactone via nanostructured lipid carriers for management of alopecia. Int J Nanomedicine,2014:9:5449-60. doi: 10.2147/ijn.s73010
42. Khan S, Baboota S, Ali J, Khan S, Narang RS, Narang JK. Nanostructured lipid carriers: An emerging platform for improving oral bioavailability of lipophilic drugs. Int J Pharma Investig,2015:5:182-91.
43. V. Andonova and P. Peneva, "Characterization methods for solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC)," Current Pharmaceutical Design,2018:23(43):6630–6642.
44. G. Poovi, T. M. Vijayakumar, and N. Damodharan, "Solid lipid nanoparticles and nanostructured lipid carriers:a review of the efect of physicochemical formulation factors in the optimization process, diferent preparation technique, characterization, and toxicity, "Current Nanoscience,2018:15:436–453.
45. Salem LH, El-Feky GS, Fahmy RH, El Gazayerly ON, Abdelbary A. Coated lipidic nanoparticles as a new strategy for enhancing nose-to-brain delivery of a hydrophilic drug molecule. J Pharm Sci,2020:109(7):2237-51. doi: 10.1016/j.Xphs.2020.04.007
46. Taymouri S, Minaiyan M, Ebrahimi F, Tavakoli N. *In-vitro* and *in-vivo* evaluation of chitosan-based thermosensitive gel containing lorazepam NLCs for the treatment of status epilepticus. IET Nanobiotechnol,2020:14(2):148-54. doi: 10.1049/iet-nbt.2019.0156
47. Hammad RW, Sanad RAB, Abdelmalk NS, Aziz RL, Torad FA. Intranasal surface-modified mosapride citrate-loaded nanostructured lipid carriers (MOS-SMNLCs) for treatment of reflux diseases: *in vitro* optimization, pharmacodynamics, and pharmacokinetic studies. AAPS PharmSciTech,2018:19(8):3791-808. doi: 10.1208/s12249-018-1142-9
48. Deshkar SS, Jadhav MS, Shirolkar SV. Development of carbamazepine nanostructured lipid carrier loaded thermosensitive gel for intranasal delivery. Adv Pharm Bull,2021:11(1):150-62. doi: 10.34172/apb.2021.016
49. Fahmy UA, Ahmed OAA, Badr-Eldin SM, Aldawsari HM, Okbazghi SZ, Awan ZA, *et al*. Optimized nanostructured lipid carriers integrated into in situ nasal gel for enhancing brain delivery of flibanserin. Int J Nanomedicine,2020:15:5253-64. doi: 10.2147/ijn.s258791
50. Silva S, Bicker J, Fonseca C, Ferreira NR, Vitorino C, Alves G, *et al*. Encapsulated escitalopram and paroxetine intranasal co-administration: *in vitro*/*in vivo* evaluation. Front Pharmacol,2021:12:751321. doi: 10.3389/fphar.2021.751321