

Lipid nanocapsules: A Novel Strategy for Brain Targeting via Nasal Administration

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ABSTRACT: In spite of the great advance in drug delivery systems (DDSs) for the control of the neurological disorders like Alzheimer's disease, Parkinson's disease, epilepsy and seizures, yet there is a demand for innovative DDSs for brain targeting. The biggest hurdle for directing the drug to the brain is the presence of the blood-brain barrier (BBB) which hampers the passage of medicants to the brain. Many recent approaches to allow carriage of medicaments to the brain have come out during the last twenty years. Intranasal delivery of drugs is one of these approaches which can bypass the BBB in a noninvasive way. Lipid nanocapsules (LNCs) act as an appropriate platform and novel strategy for nose to brain drug delivery due to their several advantages. They can be produced in a quick, simple, solvent-free and scalable-up process. Therefore, this review depicts mechanisms of nose-to-brain drug delivery and the several approaches for improving nasal absorption of drugs with a special emphasis on lipid nanocapsules-based approaches. It discusses the composition and method of preparation of LNCs, their advantages and their application in nose to brain drug delivery. The upcoming prospect of nasal drug delivery to the brain is also discussed.

KEYWORDS: Neurological disorders; Blood-brain barrier; Brain targeting; Intranasal delivery; Nanocapsules.

1. INTRODUCTION

The blood-brain barrier (BBB) is an extremely discriminating semipermeable borderline of endothelial cells which hinders elements in the flowing blood from the non-selective passage into the extracellular fluid of the central nervous system (CNS) where neurons locate [1]. The BBB is made up by endothelial cells of the capillary wall, astrocyte end-feet surrounding the capillary, and pericytes inserted in the capillary basement membrane [2]. The BBB permits the entrance of certain small molecules by passive diffusion, besides the selective and active transport of different nutrients, ions and macromolecules like glucose and amino acids which are essential to neurological function [3].

The major objection to the management of the majority brain diseases is how to defeat the obstacle of bringing medicaments to certain areas of the brain. According to its protective function, the BBB serves to hamper the passage of various possibly crucial and beneficial agents to the brain. These agents do not traverse the BBB in sufficient extents to be clinically active [4]. From the eighties, nasal drug delivery has attained expanding attention. Nasal passageway serves as a non-invasive route for administering pharmacologically active agents for systemic, local and central nervous system action. Due to the distinctive linkage between the nose and brain, the intranasal route can transport medicaments to the brain evading the blood-brain barrier. Therefore, the intranasal pathway is able to convey drugs in a direct way to the brain from the nasal space alongside the olfactory and trigeminal nerves. Moreover, drugs administered through the nasal route have frequently greater bioavailability, lower side effects and give rise to greater brain entrance at analogous dosage than the orally administered drugs. From the patient standpoint of view, the nasal administration route still exhibits numerous benefits such as self-administration, little cost and greater patient compliance.

Several attempts were tried to improve the brain delivery of drugs through the intranasal route, the most significant of which is the use of nanocarriers. An example of these nanocarriers, is the lipid nanocapsules (LNCs) which are nanocarriers consisting of a tensioactive shield around a lipophilic core [5]. They are

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prepared by solvent-free method using the principle of phase inversion during the heat treatment of water and oil. LNCs can better encapsulate lipophilic drugs. Furthermore, the method of preparation of LNCs is simple and repeatable and doesn't need the use of large amount of surfactant and cosurfactant or organic solvent, therefore, LNCs are considered to be safe [6]. Also, the study of Thomas et al. 2013 [7] showed that lipid nanocapsules could be scaled up. Lipid nanocapsules are stable and have particle size in the nano range, so, they are considered as a better choice comparing to nano and microemulsions or liposomes [8]. LNCs can increase the drug nasal permeability and realize controlled drug release as well as efficient drug targeting.

This article gives an idea about the construction and function of the human nasal passage and processes participating in transnasal crossing of the drug into the brain. Afterwards, different models for evaluating direct nose-to-brain delivery will be discussed. Moreover, the strategies for enhancing nasal drug absorption will be summarized. Finally, LNCs as a drug nanocarrier focalizing on the recent applications of LNCs for intranasal drug transmission into the brain.

2. ANATOMY AND FUNCTION OF HUMAN NASAL CAVITY

The nose has responsibility for numerous biological roles like respiration as well as the sense-of-smell. It is built up of two similar holes, divided by the septum [9]. The nasal and buccal cavities are isolated from one another by the palatine bone. The nasal holes are coated with a mucosal layer, and the whole area of both nasal holes is about 150–160 cm² [10-12]. These cavities are more subdivided into 3 regions: vestibular, respiratory and olfactory regions. The features of these regions are listed in Table 1.

Table 1. Features of the various regions of the nasal cavity [13-18].

Region	Location	Surface Area	Characteristics	Vascularization	Epithelium
Vestibular region	Anterior part	0.6 cm ²	<ul style="list-style-type: none"> - Low permeability as well as limited surface area which restricts absorption of drug. - Existence of mucus and hairs or vibrissae, that represent an essential defence mechanism, precluding the entry of toxic materials from the outer atmosphere to the body. 	Low	Squamous Epithelium
Respiratory region	Central part and lateral walls	130 cm ²	<ul style="list-style-type: none"> - High permeability as well as great surface area, so it is the region in which the highest drug absorption takes place. - Separated to 3 nasal turbinates: inferior, middle and superior. - Direct passageway of drug passage into the brain through the trigeminal nerve. - Presence of mucus, cilia and microvilli. - Incidence of mucociliary clearance process. 	High	Respiratory epithelium: ciliated pseudostratified and columnar epithelium
Olfactory region	Upper part	10 cm ²	<ul style="list-style-type: none"> - Found above the respiratory region and beneath the cribriform plate. - Comprises superior turbinate, and a slight upper part of the middle turbinate. - Allows passage of the drug from the nose into the brain through the olfactory bulb, bypassing BBB. - In charge of the sense-of-smell. 	High	Olfactory epithelium

3. PROCESSES PARTICIPATING IN TRANSNASAL DRUG PASSAGES TO THE BRAIN

Transfer of drugs from the nose into the brain takes place via the olfactory as well as the trigeminal nerves. As soon as the drug is carried to the origins of the nerves in the cerebrum and pons, respectively, it will be capable to diffuse all over the brain taking certain passageways. Such transport takes place by way of both intracellular and extracellular pathways. The intracellular path begins with embodying the molecule by an olfactory neuron, transporting of the endocytic vesicle inside the cell to the projection site of the neuron, and lastly discharge by exocytosis. The extracellular way begins with traversing the drug the nasal epithelium

to the lamina propria in which neurons are found specially in the olfactory area of the nasal cavity, then the drug is transported outwardly alongside the length of the neuronal axon by bulk flow processes. The axon directs into the brain, wherein the drug is more dispersed through fluid movement. The entrance of drugs to the brain parenchyma through endothelial cells in the lamina propria or from the subarachnoid CSF supposes the capability of the drug to traverse BBB and B-CSF-B [9]. However, intracellular means of transport is a slowly moving process, needing between several hours to several days [19]. Extracellular transport, on the contrary, is fast and may account for great of the quick transfer and onset of action noticed in CNS drugs taken intranasally [20, 21]. Rapid intranasal transfer of therapeutics to the CNS, within 5–10 min in some cases, has been exhibited by many intranasally administered drugs, verifying the significance of the extracellular transport mechanism [12, 22–26]. This high rate of transportation supposes that for many drugs, a notable portion of intranasal drug delivery to the CNS occurs by extracellular drug transport through the olfactory and trigeminal nerves [12].

4. ESSENTIAL REQUIREMENTS FOR NASAL FORMULATIONS

Certain aspects of the nasally administered formulations can hinder drug absorption and should be taken into consideration. For example, to evade irritation of the mucous membrane and/or impairment of the cilia, such formulations should be isotonic and of a pH around that of the nasal cavity (5.0–6.8) [18, 27]. Moreover, excipients used with the drug should be harmonious with the mucous membrane of the nose [28, 29].

Accelerated elimination of the drug via mucociliary clearance is one of the major drawbacks of intranasal drug delivery. This can be circumvented by adding to the formulations, materials that interact with the mucus. The mucus is mainly composed of mucin [13]. Mucin being negatively charged, formulations which are positively charged can freely attach to it via electrostatic interactions, which assist mucoadhesion. On the contrary, formulations having a negative charge can pass through the mucin chains and form hydrogen bonds, and this also improves mucoadhesion [18, 30].

New approaches to control the limitations of nasal formulations were studied. For instance, the use of nanocarriers to attain extended release, allow shielding against enzymatic impairment and enhance directing to the brain. The usage of in situ gels and polymers of mucoadhesive properties to extend drug retaining time in the nasal mucosa and, in consequence, improve drug absorption is also a frequently applied approach [31]. In addition, nasal formulations that increase in viscosity after administration were prepared to extend the time of drug contact within the nose [18].

5. MODELS FOR ESTIMATING DIRECT NOSE-TO-BRAIN DELIVERY

Different models can be utilized for assessment of nasal drug absorption and penetration, for pharmacokinetics/pharmacodynamics evaluations, and also for toxicological and electrophysiological studies. These models include in vitro, in vivo and ex vivo models which have been applied for different studies as will be discussed below [32].

5.1. In vivo models

Adequate in vivo models are crucial for effectively examining the nasal delivery systems. Studying the structure of the animal nasal hole is imperative prior to choosing the proper animal model for an in vivo nasal absorption study. The first animal used in the nasal absorption studies was the rat, and then, the mouse, dog, monkey, sheep and rabbit were utilized too [33]. Nevertheless, outcomes of studies attained from animal models are not every time consistent with those of humans, due to the anatomical and biological dissimilarities of their nasal cavities [34]. The direct transport of drugs from the olfactory region to the brain is generally branched into transfer within the nerve axon and outside the nerve. The two passageways afford possibility for evading the BBB.

The solubility and potency of the drug are generally the controlling features owing to the limited absorption capacity. It is significant to notice that the nose-to-brain absorption circumvents the pre-absorption metabolism, besides the dilution brought about by distribution and protein binding. The dose to be conveyed to the olfactory region or to be absorbed through the neurons may be only just 0.01–1% of the oral one. Besides, it is necessary that the drug must be soluble in the little microliters that are going to be administered through the nose. The clearance within the nose is so speedy that the time needed for the drug to be dissolved prior to absorption is mostly insufficient.

Nasal drug formulations are commonly administered into the animal nasal opening with a pipette or by a polyethylene tube connected to a micropipette. In a study of Westin and co-workers [35], the volumes of the administered intranasal formulation were 5 μ l and 50 μ l for mice and rats respectively, while the drug was administered into the right nostril, and the left olfactory bulb served as a control. The animals must be maintained at a supine position so that the drug can reach the olfactory area or the upper part of the nasal cavity to be in a direct contact to the brain. The olfactory region in humans makes up approximately 10% of the nasal cavity with limited access. In monkeys, the olfactory region is like that of humans and exists in the upper part of the nasal cavity. However, in rats and mice, the olfactory region makes up nearly 50% of the nasal cavity. Rabbits and dogs resemble each other with respect to their nasal anatomy, although dogs have greater surface area and their olfactory region is found primarily on the ethmoidal conchae [36].

5.2. In vitro models

While in vivo evaluations are best valuable for any nasal drug absorption and permeation tests, in vitro studies are beneficial to anticipate drug permeability, permitting inspection of the principal mechanisms of drug absorption and transport through the nasal way [37]. Mainly three cell lines (RPMI 2650, CaCo-2 and Calu-3) are utilized to evaluate nasal absorption and permeability. These cellular models can afford information on both intracellular and extracellular transport, however, simultaneous agents like mucus, clearance, physiological and anatomical factors participating in maintaining the nose functioning, may also influence the absorption. Moreover, the cellular models have a receiving lumen that does not entirely demonstrate the required transport from the mucosa to the receiving nerves. However, in vitro cell culture models showed numerous benefits when compared to other models, since they permit the fast estimation of the permeability of the drug, and the chance to examine materials that may be dangerous if examined directly in vivo [38]. In addition, using in vitro models with human cells doesn't encompass the same regulatory and ethical limitations as the studies implemented with in vivo models [38, 39].

5.2.1. The RPMI 2650, CaCo-2 and Calu-3 cell lines

The RPMI 2650, CaCo-2 and Calu-3 cell lines were used as models of the nasal epithelial barrier by several researchers [40-43]. These cell lines vary with respect to derivation of the cells (nasal origin of RPMI 2650 versus bronchial origin of Calu-3), and production of monolayers (Calu-3) or multilayers (RPMI 2650) [39, 44]. The CaCo-2 cell line, on the other hand, is originated from human colon carcinoma and converts to different monolayers gradually [42]. These cell models have been used by several researchers to assess in vitro permeation of many drugs from various intranasal formulations [18, 41, 45-49].

5.2.2. Reconstructed human nasal mucosa

The three-dimensional reconstructed nasal mucosa model uses isolated hominoid nasal fibroblasts in collagen matrix concealed by RPMI 2650 epithelial cells. The collagen matrix enclosing fibroblasts is utilized to support growth of the epithelial cells. The three-dimensional reconstructed nasal mucosa model displays similar penetration barrier characteristics and 4 to 5 times more rapid paracellular permeation than in the epithelial cell model. Though such three-dimensional model has the drawback of the more difficult management of the constructs, it is an encouraging model to assess passive permeation of materials through the nasal mucosa [48, 50].

5.3. Ex vivo models

These models are highly favored as drug investigation models, particularly for drug delivery investigations, throughout the initial stage of drug developing. Assessment of toxic properties of excipients and transmucosal transport of drugs are typically carried out ex-vivo utilizing nasal mucosa from experimental or slaughtered animals. Ex vivo excised animal tissue models are most commonly taken from rats, dogs, monkeys, sheep, rabbit as well as human being.

Studies with ex vivo models are helpful to get details on permeation, metabolism, efflux as well as toxicity. In spite of their many benefits, the ex vivo models have also certain restrictions, the greatest of which are the thickness of nasal epithelium of animals as well as the absence of interstitial flow rate beneath the mucosa. To get details on permeability, it may be hard to generalize the outcomes of the ex vivo models to in vivo models [34].

The most popular ex vivo model for nasal permeability is the Ussing chamber innovated by the Danish zoologist and physiologist Hans Henriksen Ussing in 1946. The usage of this model is easy, therefore it is effortless to check and keep viability of tissues all over the study. Moreover, the Ussing chamber model has

been used to correlate the nasal transport of analgesic medications across nasal olfactory and respiratory mucosa in rodents [51].

6. STRATEGIES FOR ENHANCING NASAL DRUG ABSORPTION

Drug penetration through the nasal mucosa can be enhanced by varying the drug formulation, utilizing different nasal devices as well as by administration of transporter modulators that may aid in transcellular transport of the drug.

6.1. Drug formulation design

Drug formulation design was found to aid in breaking several barriers for immediate drug transfer from the nose to the brain. Table 2 exhibits a number of formulations that were employed to improve nose to-brain drug delivery such as microemulsions, nanoemulsions, nanoparticles, nanovesicles, nanocrystals, utilizing the prodrug approach, co-administration with vasoconstrictors and the use of penetration enhancers.

Table 2. Examples of formulation designs for intranasally administered drugs.

Drug	Disease	formulation design	Therapeutic Outcomes	References
Phenytoin	Epilepsy	Chitosan-lecithin nanoparticles	High drug transport into the brain with sustained drug accumulation in the brain	[52]
Rivastigmine	Alzheimer's disease	Lipid nanocarriers and nanoemulsion	Improved brain delivery	[53]
Lamotrigine	Epilepsy	PLGA nanoparticles	Improved brain delivery	[54]
Tacrine	Alzheimer's disease	PLGA nanoparticles	A good brain targeting efficiency	[55]
Agomelatine	Antidepressant	Solid lipid nanoparticles	enhanced drug absorption and brain delivery	[56]
Olanzapine	Schizophrenia and mania	Polymeric micelles	Enhanced drug targeting to brain	[57]
Quetiapine Fumarate	Schizophrenia	Nanoliposomes	Higher brain uptake	[58]
Clonazepam	Status epilepticus	Transferosomes	greater drug accumulation in the brain	[59]
Zolmitriptan	A pain terminator in migraine	Bilosomes	Successful brain targeting with improved brain bioavailability	[60]
Olanzapine	Antipsychotic drug	Nanocubic Vesicles	Efficient drug targeting to the brain with increased bioavailability	[61]
Paeoniflorin	Parkinson's disease	Nanocrystals	greater drug accumulation in the brain	[45]
D-264	Parkinson's disease	Cysteine based prodrug	Enhanced drug bioavailability in the brain	[62]
hypocretin-1 & L-Tyr-D-Arg	Appetite and sleep regulation (hypocretin-1) & morphine-like analgesic activity (L-Tyr-D-Arg)	Co-administration with a short-acting vasoconstrictor	Enhanced nose-into-brain drug transport	[63]
Geniposide	Stroke treatment	Co-administration with a permeation enhancer	Higher drug bioavailability in the brain	[64]
Zolmitriptan	Migraine treatment	Terpesomes	Improvement the drug bioavailability with high brain targeting efficiency	[65]
Zopiclone	Insomnia treatment	nano-structured lipid carriers	effective drug targeting to the brain with improved brain bioavailability	[66]
Clonazepam	Brain tumor	phospholipid magnesome	Enhancing the diagnosis and/or radiotherapy of particular brain diseases with high brain targeting	[67]

6.2. Nasal delivery devices

For successful nose-to-brain drug targeting, a special delivery device is needed so that the amount of drug transported to the olfactory epithelium can be maximized. Although numerous studies have been concentrated on formulations to enhance drug transport to the brain as seen in Table 2, however, the studies focalized on the nasal delivery devices designed to direct these drugs to the brain are still few. Nasal drops are among the first nasal delivery systems [68]. When properly applied, nasal drops can diffuse over a greater area, though they are frequently more rapidly cleared in comparison to nasal sprays [69].

Novel nasal devices have been invented to control the drawbacks of common nasal delivery systems. These devices may be propellant-activated like Vianase device [70], precision olfactory device [71] and Alchemy Pharmatech's Naltos device [70], or they may be breath-activated like the Optinose device [72]. The Vianase device, invented by Kurve Technology®, is an electronic atomizer which throws liquid droplets in size of 15–20 μm to the whole nasal cavity, together with the olfactory region [70, 73]. The precision olfactory device conveys liquids and powders to the olfactory region using hydrofluoroalkane as an inert gas propellant. In Alchemy Pharmatech's Naltos device, the powder is forced through the nostrils by actuation of an inert gas. Lastly, the Optinose device utilizes the patient's own outbreath, which directs the dose deeply into the nose while concurrently isolating the oral cavity from the nasal cavity [74]. So far, only the Vianase, precision olfactory and Optinose devices have been utilized in human nose to brain investigations.

6.3. Transporter interactions

An earlier study has proved that efflux transporters decrease drug uptake by the brain upon its intranasal administration, but this decrease could be overwhelmed by intranasal administration of suitable transporter inhibitors [75].

Nano-drug delivery systems combined with specific ligands to target selective cell-surface receptors or transporters can improve the effectiveness of drug delivery and hence therapy. Transporters are expressed divergently on the cell-surface of different cell types. Moreover, specific transporters are expressed at elevated levels in particular cell types under pathologic disorders [76]. The majority of transporters have a site-specific expression, which convey ideal targets for drug delivery to enhance uptake at definite site or improve permeation through biological barriers like the BBB. Usually, transporters have wide substrate selectivity while the ligands for the receptors are far more specific. These differences could essentially provide certain advantages in selecting cell-surface transporters for nano-drug delivery systems as it affords numerous selections of ligands for modification of the surface of the nanoparticles to target the transporters [77]. Absence of immunogenicity of such ligands is also a strong point. It has been observed that imatinib, a P-glycoprotein (Pgp) substrate, was rapidly delivered to the brain through the olfactory region upon its nasal administration and it was proved that it is possible to increase the brain uptake of imatinib together with its residence time inside the brain, preventing it from elimination by the P-gp, after its intranasal administration [78]. These findings have opened the way for emerging a large variety of central nervous system active agents which were formerly removed from consideration as drug candidates owing to insufficiency of their entrance into the central nervous system.

7. ADVANTAGES AND DISADVANTAGES OF INTRANASAL ROUTE OF DRUG ADMINISTRATION [12, 79, 80]

7.1. Advantages

1. Great penetrability of the mucous membrane of the nose in comparison to that of the skin or gastrointestinal tract.
2. Exceptionally vascularized subepithelial tissue.
3. Fast absorption, mostly in less than thirty minutes.
4. Circumvention of first-pass metabolism that takes place following absorption of drugs from the alimentary tract.
5. Evasion of the influence of gastric stasis and emesis, for instance, in patients suffering from migraine.
6. Little risks of infections
7. Easy self-administration

7.2. Disadvantages

1. Nasal administration of drugs is restricted to minute volumes (25–200 μL), and therefore only suitable for potent medications with great water solubility.

2. It is necessary for the active agent to possess a molecular mass less than 1 kDa otherwise it will not be absorbed.
3. Drugs that are irritating or harmful to the mucous membrane of nose are not suitable candidates for nasal administration.
4. Absorption may be reduced in certain nasal diseases like common cold characterized by a congested or runny nose which may throw out the medication from the nose.
5. Drug dose is restricted due to the rather limited area accessible for absorption.
6. The process of mucociliary clearance leads to a short contact between the drug and the nose.
7. Certain drugs as proteins may be incompletely absorbed from the nose owing to reduced membrane penetrability, rapid mucociliary clearance and enzymatic degeneration.
8. Chronic nasal application may eventually damage the cilia and affect body's defenses.
9. Interpersonal variability.
10. There is a need of a suitable delivery device to carry the medication through the nose into the brain.

8. LNCs COMPOSITION AND PREPARATION

LNCs are an example of nanosystem that could be prepared using simple phase-inversion technology which doesn't involve using harmful organic substances that must be removed after preparation (like dichloromethane and chloroform) [5, 81-83]. To put it briefly, the process involves combining a lipophilic substance with 2 amphiphilic surfactants with the existence of salty water. Various excipients could be utilized to act as each of the single components of the LNCs, like medium chain triglycerides (Labrafac® CC or Labrafac® WL 1349), ethyl oleate, Labrafil® M1944CS, among many others. The lipidic surfactant is often a derivative of lecithin at varying hydrogenation degrees (Phospholipon® 80H, Lipoid® S75-3, Phospholipon® 90H), whereas the amphiphilic surfactant is typically a PEG-based product, which is usually being a combination of free PEG and PEG 660 (Solutol® HS-15). Besides the presence of these three main components in the LNCs, an extensive variety of excipients can be used for preparation of LNCs. The selection of an excipient is dependent on the potential affinity of the encapsulated drug to the oily phase as well as the stability that the surfactant shell will provide for the LNCs. Respecting a three-way balance between the water, amphiphilic surfactant, and oil amounts is essential for the production of LNCs; otherwise, the product might not assemble to the structure of LNCs, preferring to form micelles or not even associate at all [82, 84]. Therefore, a specific designed ternary diagram which incorporates the concentrations of the oil, the amphiphilic surfactant and the aqueous phase should be used to produce LNCs. LNCs can usually be obtained by maintaining a constant concentration of one amphiphilic surfactant (usually the non-PEG surfactant) and changing the concentration of the other one. The study of Heurtault et al. describes this ternary design diagram in details [8]. To put it briefly, the three components' percentages should be as follows: the oily phase must have a concentration between 10 and 25%, the surfactant between 10 and 50%, and the watery phase between 50 and 90%, all in w/w, of the original mixture. To adjust the LNCs's characteristics, these components can be changed within these ranges [8].

Following the complete mixing of the components, a sequence of heating and cooling cycles is carried out to elevate the mixture's temperature over the phase-inversion zone which is detected by a sudden shift in the mixture's conductimetry. This significant change in conductimetry indicates that the mixture has changed from being an emulsion of oil in water to one of water in oil. At these temperatures, organoleptic alterations are typically also discernible. Following 3 or more cycles, an amount of cold water (almost 4 °C) is suddenly added to the mixture and the LNCs is produced. Typically, the drug is dissolved earlier in the oil phase, or added before the cold-water addition. The end product is a lipid core surrounded by an external shell of surfactants, where the amphiphilic or hydrophobic drug is safely encapsulated within [5]. This technique makes it possible to produce lipidic nanomedicines that have stable characteristics, ideal size for nose to brain delivery and great encapsulation efficiency. Normally, the lipophilic or amphiphilic drug can be earlier dispersed in the lipid phase of the mixture and exposed to the heating cycles to ensure its association with the lipid structure after the dilution step.

Nevertheless, if the drug is thermolabile, it could be added in form of solution a few degrees above the phase-inversion zone, just before the dilution step in the last heating cycle, to guarantee its encapsulation with minimum degradation owing to elevated temperatures [82, 85]. This appears to be a viable approach for facilitating the encapsulation of medicinal substances that are challenging to deal with, such as antibodies and proteins, which are degraded at high temperatures. On the other hand, if encapsulation efficiency using this method is not acceptable, the phase-inversion zone can be achieved at significantly lower temperatures by

addition of high amount of sodium chloride to the mixture [84]. It should be emphasized that scaling up a nanosystem can be extremely difficult and seriously hinders the improvement of most clinical candidates when it comes to the possible LNC scale-up procedure. The production stage is always the primary constraint. Maintaining enough energy in the stirring process to accurately simulate what happens in pilot-scale formulations is one of the difficulties in moving the LNC from a pilot-based scale to a big industrial scale. This work by Thomas et al. clearly illustrates the behavior of ibuprofen loaded-LNC during a scale-up procedure. The scaled-up LNC exhibited the typical long term stability of the LNCs, and its physio-chemical characteristics were similar to those of formulations used on pilot scales [7].

9. THE POTENTIAL ROLE OF LNCs IN DRUG DELIVERY

When it comes to drug delivery, LNCs offer a versatile platform. When building nanosystems, their application related to innovative therapeutic options must be given careful consideration because of their adjustable properties and easily scaled-up production process. LNCs are similar to lipoproteins. Compared with other lipid-based delivery systems like liposomes, LNCs provide several benefits since they are produced without the use of hazardous solvents, they can encapsulate hydrophobic drugs much better, and they are more stable in *in vivo* environments [84]. Because polyethylene glycol (PEG) makes up the LNCs' outer shell, they enjoy extended circulation because they efficiently evade quick digestion by the mononuclear phagocyte system and have capability to transiently inhibit P-glycoprotein function. LNCs-based treatment is therefore a promising option for malignancies that often have poor therapeutic rates of active ingredients reaching them. As an example of these LNC applications, Lamprecht et al. study revealed that LNCs were designed to vehiculate etoposide, the first-line therapy for glioblastoma, resulting in 5 to 6 times raise in concentration in glioblastoma cells in comparison with the free drug. This may be related to the formerly described impact of PEG supply, in which the PEG shell transiently inhibits P-glycoprotein following the release of the drug payload, enabling larger concentrations of intracellular etoposide compared to the free drug [86]. Furthermore, LNCs are excellent choices for encapsulating other nanosystems and fixing their flaws. Resnier et al.'s study demonstrated how LNCs encapsulated liposomes and modified their properties to improve their effects [87]. The potential of LNCs was further proven by Tsakiris et al. who utilized an *in vivo* colorectal cancer model to demonstrate the anti-cancer effect of 5 of the 6 suggested active ingredients, resulting in high encapsulation efficiencies [88]. Concerning brain delivery in diseases other than malignance, LNCs were utilized for neurodegenerative disorders such as Alzheimer's disease, like the study of Giacomeli et al. demonstrated. Curcumin was given to a mouse model of Alzheimer's disease after being encapsulated in LNCs. The LNCs revealed neuroprotective effects against the pro-inflammatory environment at the brain and successfully raised the drug's bioavailability to the brain [89]. Finally, because of their lipophilicity, which can aid in the sequestration of greatly hydrophobic drugs *in vivo* and lower their concentrations to non-toxic degrees, LNCs were even used as antidotes for drug overdoses [90].

LNCs are typically used to encapsulate hydrophobic or amphiphilic drugs because they are lipid in nature. LNCs are also capable of encapsulating hydrophilic drugs. The process begins with the formation of an initial water-in-oil emulsion (micelles) that encapsulates the drug. Later, an aqueous phase replaces the oily phase at this interface due to the production of a polymer shell, producing an aqueous core inside the lipid shell [91].

Moreover, studies have shown that conventional LNCs can provide a sustained release system, remain stable at 4 °C for up to 18 months [7, 85, 92], and can reach high shelf-life without the need for freeze-drying. Additionally, they still have the same physio-chemical characteristics as when they were initially created. This here could be important, as because of their lipid nature and the sublimation properties of the lipids that form the LNCs, freeze-drying may show a challenge. But aqueous core LNCs are not as stable as they tend to experience a burst release of the payload.

Depending on the desired purpose of the LNCs, the process for developing them can be adjusted. The influence of LNCs modifications on LNCs properties is presented in detail in the research by Huynh et al. [84]. The key conclusions presented in this well-written paper are that by adjusting the concentration of the amphiphilic surfactant or the oil, LNCs may be optimized to be generated at minimal sizes in a greatly monodisperse system. The LNCs' size is primarily affected by its oily phase concentration; a higher percentage of the oily phase will result in a larger size. Since the lipophilic surfactant is mostly important for maintaining the shell's rigidity and stability, it is typically maintained in fixed, well-established concentrations. Additionally, the quantity of water added in the cooling step may help in lowering polydispersity index (PDI) because it results in decreasing in the LNCs' average size. The number of heating/cooling cycles achieved also

appears to enhance the PDI of the LNCs, but after three cycles, the properties do not appear to change significantly [8]. Finally, the amphiphilic surfactant (normally PEG-based) has a significant impact on the stability and formulation of LNCs structures and no other micellar structures.

10. APPLICATIONS OF LIPID NANOCAPSULES IN NOSE-TO-BRAIN DRUG DELIVERY

The nasal cavity is composed mainly of two regions which are the olfactory and the respiratory regions. The respiratory region is greatly vascularized, whereas the olfactory region is stimulated by the olfactory nerve [93]. LNCs were investigated for intranasal applications for delivery of drugs into the brain. Intranasally administered nano-carriers including LNCs can transport drugs via the olfactory pathway (nose-brain delivery) [94-96]. Alternatively, it can reach the brain by passing the nasal epithelium reaching the systemic circulation passing through blood brain barrier to the brain (nose-blood-brain delivery) [97]. To explain that in detail, there are two pathways through which the drug can enter the brain following intranasal administration of the drug loaded LNCs as clarified by earlier studies [60]. First one is the absorption of the drug from the respiratory region of the nasal cavity across the nasal mucosa to the systemic circulation, then crossing the blood brain barrier to enter the brain. A previous study was done and it was successful in improving nimodipine delivery to the brain via penetration of the BBB from systemic circulation following Intranasal administration of nimodipine loaded LNCs [98]. On the other hand, in second pathway (direct nose to brain pathway), the drug is transferred from nasal cavity's olfactory region into the olfactory bulb and then directly to the brain [9]. Direct nose to brain pathway in order to bypass the blood brain barrier and transport drugs directly into brain is of significant interest [99], even though the olfactory region just comprises around 5 % of the entire volume of the nasal cavity [100]. Moreover, there are 2 various ways through which drugs can be transferred to the olfactory bulb from the olfactory area and subsequently to several sections in brain. Those ways are the intracellular and extracellular pathways. Concerning the intracellular pathway, the olfactory neurons take in the drug which is then emitted via exocytosis from the projection region of the neurons. On the other hand, at extracellular mechanism, the drug primarily passes the nasal epithelium into the lamina propria region which contains neurons in the olfactory region [9]. Therefore, utilizing the intranasal route to enhance the drug delivery to the brain is considered a non-invasive way to bypass the blood brain barrier. The nasal route is tempting in therapy because of the medications' quick absorption, which leads in higher pharmacokinetic parameters and, as a result, a more rapid onset of the therapeutic effects of the drugs [33]. Because mucus-producing cells are present at the nasal epithelium, nanoparticles need to have moderate mucus-permeating characteristics in order to pass through the nasal epithelia. Obtaining sufficient free drug delivery rates is difficult since the nasal epithelium expresses a large range of metabolic defenses and serves as a main point of communication for direct exposure and contact to most pathogens and xenobiotics. Therefore, an association with LNCs will be crucial to protecting the drugs and promoting efflux inhibition [101].

Regarding the particular use of lipid-based nanosystems like LNCs for nose-to-brain delivery of drugs, the optimization of some factors is essential to improve such transport. For example: i) size should be around 100-200 nm to allow transport through olfactory and trigeminal nerves; ii) surface charge must be positive to interact with the nasal mucosa which is negatively charged in order to increase adhesion and extend contact time; iii) surface modifications may be required such as addition of surface ligands like cell penetrating peptides [97, 102]. Using in situ gel-forming agents to prolong nasal contact time of the formula was also studied [103].

LNCs have a diversity of applications in pharmaceutical field as drug delivery carriers. One of these applications is their use in nose-into-brain drug delivery. Fraga Dias et al. have established and described nose to brain LNCs loaded with bozepinib as a potential treatment for glioblastoma. They proved that the prepared drug loaded LNCs have lessened the in vivo glioma growth by about 81 % [104]. Also, Bseiso et al. concluded that melatonin loaded LNCs may be an encouraging delivery system for nose to brain delivery for the remedy of cerebral ischemia [105]. Successful preparation of melatonin loaded LNCs with suitable physicochemical properties resulted in high ex vivo nasal permeation and promising neuroprotective effects in vivo, suggesting the therapeutic potential of LNCs in lessening the effects of ischemic stroke. Additionally, Bruinsmann et al. proved that the nose-to-brain administration of chitosan-coated lipid nanocapsules loaded with simvastatin can be considered as a novel potential method for the treatment of glioblastoma [106]. As simvastatin loaded LNCs greatly increased (2.4-fold) the quantity of drug in brain tissue of rats following intranasal delivery in comparison with the free drug. Glioma-bearing rats treated with Simvastatin loaded LNCs showed a substantial reduction in tumor development and malignancy when compared with the control and free

drug groups. Also, simvastatin loaded LNCs did not result in any toxicity in the rats. Alves et al. proved that using nose-into-brain delivery of bevacizumab lipid nanocapsules could represent a new and hopeful approach against glioblastoma [107]. Moreover, Clementino research team scrutinized the nose-to-brain administration of lecithin/chitosan nanocapsules loaded with simvastatin in rats. They concluded that these nanocapsules increased the nose-into-brain drug delivery as proved by preliminary gamma scintigraphy studies and the cytotoxicity of these nanocapsules was noticed to be much less than that of the drug solution [108]. Furthermore, Mwema et al. proved that LNC is a good carrier to effectively deliver Prostaglandin D2-glycerol Ester (PGD2-G) to the brain [109]. Furthermore, our research group has recently succeeded in enhancing the delivery of antidepressant drug (mirtazapine) to the brain through the direct nose-to-brain pathway after the intranasal administration of mirtazapine loaded LNCs [110]. Also, Gad et al. proved that nose to brain delivery of 18 β -Glycyrrhetic acid (GA) loaded LNCs can provide a promising treatment for Alzheimer's disease patients with 50 times lower dose [111]. GA loaded LNCs were able to achieve a sustained drug release, increase drug penetration through the nasal mucosa, and improve the rats' memory in the Alzheimer's disease model, proving the anti-oxidant and neuroprotective effects of GA.

11. UPCOMING PROSPECT OF NASAL DRUG DELIVERY TO THE BRAIN

Dealing with neurological diseases is still one of the most major dares and progresses in nanotechnology have offered encouraging keys to this problem. Various nanocarriers like nanoemulsions, nanoparticles, nanovesicles and nanocrystals have been investigated for the delivery of drugs to the brain. It is predictable that in the nearest coming times, extra drugs will invade the market for the treatment of brain diseases via intranasal route. Nevertheless, a lot of researches are required because up till now there are definite unsolved issues during intranasal delivery. The present lipid nanocapsule-based drug delivery approach is required to be more developed such that it can be targeted, harmless, efficient, and economical. In addition, development of CNS nanocarriers necessitates concentration on enhancing their BBB penetrability, lessening neurotoxicity and improving their drug- targeting for brain tissue using innovative targeting elements. Moreover, it is imperative to bear in mind formulation approaches, drug delivery devices and muco-adhesive properties of polymers, so as to enhance bioavailability, extend retention and intensify the outcome of drugs. Many CNS-related diseases such as stroke, obesity, eating disorders, addiction, seizure, autism, anxiety, Huntington Disease (HD), depression, Alzheimer's Disease (AD) and Parkinson's Disease (PD) have already been treated with intranasal drug administration and many more promising drugs are being developed for intranasal application [112]. New trends should be directed towards the Intranasal administration of LNCs for brain targeting to treat various CNS diseases.

12. CONCLUSION

Actually, there is a great number of CNS disorders that need the medication to get to the brain evading the complications caused by the blood-brain barrier and the difficulties related to systemic administration like biological availability and side-effects of the drug. Therefore, many attempts have been tried for the design of strategies to overcome these problems. One of these is the usage of the nose-to-brain delivery route which is an easy and safe approach for targeting the drug to the brain. The immediate link between the nose and brain allows the passage of drugs from the nose to the brain alongside both the olfactory and trigeminal nerves. This transportation process takes place through two passageways; intracellular and extracellular. Nevertheless, the nose-into-brain delivery represents a big dare primarily owing to fast removal of the drug through mucociliary clearance, in addition to other factors such as enzymatic degradation. Therefore, a variety of nasal formulations were developed to bypass the shortcomings of the nasal formulations such as the use of nanocarriers. Out of these nanocarriers, lipid nanocapsules have acquired a great attention owing to their capability to achieve targeted and sustained drug delivery for hydrophilic as well as hydrophobic drugs in addition to their protection of the encapsulated drug from tissue environment. As a final conclusion, lipid nanocapsules will proceed to provide solutions for several significant challenges. However, the impact of lipid nanocapsules and other nanoscale materials on human healthiness are still not fully understood due to the relatively new nature of nanotechnology. Therefore, multiple studies are so far in progress to determine the long-term safety of lipid nanocapsules.

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