Chapter 14
Niosomes-Based Drug Delivery in Targeting the Brain Tumors Via Nasal Delivery

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Abstract Targeting tumors has always been a herculean task. Moreover, the presence of blood brain barrier (BBB) acts as a physical barrier and restricts the transportation of therapeutic molecules across the brain. Targeted delivery of the therapeutic payload across the blood brain barrier has gained widespread attention over the past few years. Intranasal route offers delivery to the brain via the trigeminal and olfactory route surpassing BBB. It also offers various other advantages such as surpassing biotransformation, and systemic absorption increasing the efficacy. Over the last few decades, several novel drug delivery systems such as liposomes and other lipid nanoparticles targeting brain, have gained widespread attention. The Niosomes are vesicular nanoparticle flatforms comprised of non-ionic surfactants, which are biodegradable, more stable than liposomes. This current review discusses the potential use of niosomes as a delivery vehicle for targeting brain tumors via the nasal route.

Keywords Niosomes · Nasal route · Blood brain barrier · Nanoparticles · Tumours

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1 Introduction

Chemotherapy, radiation therapy, and targeted drug therapy play a significant role in the treatment of glioblastoma and central nervous system (CNS) diseases to decrease the mortality rate [1]. The main problem is the inability of drugs to cross the blood-brain barrier (BBB) to reach the brain tissue in sufficient quantities to achieve therapeutic levels. It is estimated that the BBB prevents intrusion of approximately 98% of low molecular weight drugs and about 100% of macromolecules drugs leads to poor bioavailability for drug delivery to the CNS [2]. Different strategies including intracerebroventricular or intraparenchymal injections, mini-pump-assisted intracranial delivery, catheter infusions, accurate ultrasound methods, or electromagnetic force-field are used to deliver active drug agents. However, these methods are aggressive and dangerous for patients [3]. BBB is the first limiting factor to the delivery of drugs to the brain through systemic circulation [1]. Several studies are underway to cross the BBB through the nose-to-brain approach. Intranasal delivery is a promising alternative approach compared to the invasive methods mentioned above for drug delivery to the brain, because the nasal cavity has so many arteries that provide a high absorption level for the prescribed drug. It also allows this pathway to bypass the BBB and provide fast and direct drug delivery to the brain [4]. Also, this route (delivery through the nose) limits unnecessary drug systemic exposure and reduces systemic toxicity [5].

As the olfactory nasal segment cavity extends to the cranial cavity, nasal drug delivery can provide direct access to the brain [3]. At present, nanotechnology-based drug delivery systems provide a great opportunity for intranasal drug delivery to the brain. Nano-drug delivery systems have been widely studied in the last decades as a new strategy to solve the problem of poor bioavailability of various drugs [6]. Successful delivery of the drug to the brain through liposomes, dendrimers, microspheres, nanoemulsions, carbon-based nanoformulations, microspheres, and dendrimers has been reported in different studies [7].

The major goal of vesicular structure development is to change distribution profiles, control drug release over time, and deliver drugs to target sites. Vesicular systems can handle high amounts of drugs and generate an appropriate surface for targeting. It enables the drugs to carry both hydrophilic and lipophilic components. The non-ionic surfactant vesicles (Niosomes), systems with the advantages of liposomes and the permeability of membranes, are created in the aqueous phase from non-ionic surfactants. The integrity of niosomes in biological fluids is a critical requirement for their function as a medication carrier. Niosomes are to circulate in the body while simultaneously protecting the medicine for a certain period, connect with the target site, and convey their contents into the target cells as a carrier. Niosomes are preferred in comparison to other bilayer structures, because of chemical stability, biodegradability, biocompatibility, low production cost, low toxicity, and easy storage and handling. Niosomes have been used by different delivery routes, such as oral, intramuscular, intravenous, transdermal, and so on. In this chapter, we will discuss and suggest the niosomes as versatile nasal formulations for brain targeting of drugs.

2 Nasal Drug Delivery Route

2.1 The Blood-Brain Barrier (BBB) and Targeted Drug Delivery to the Brain

Despite advances in the treatment of brain diseases, the blood-brain barrier (BBB) is a major barrier to the delivery of drugs to the central nervous system (CNS). Crossing BBB barrier is a challenging problem for most of the effective drugs on central nervous system diseases such as neuropeptides, proteins, chemotherapeutic agents, monoclonal antibodies, recombinant proteins, and antisense or gene therapy agents. The BBB is made up of tight junctions between the brain capillaries endothelial cells with low endocytic activity. This structure leads to a capillary wall that, like the lipid bilayer of the cell membrane, prevents the passage of polar and insoluble substances across the BBB. With significant advances in nanotechnology, several strategies have been developed for drug delivery to the CNS. Some strategies, such as modifying the drug itself, binding it to the transcytosis vector, and using appropriate carriers, increase the capacity of therapeutic agents to cross the BBB. One of the current challenges is to develop a targeted drug delivery system that can effectively cross the BBB barrier while the drug agent remains intact [8, 9].

2.2 Transmitting to the Brain Through Nasal Passages

Understanding the anatomy and physiology of the nasal cavity is essential to the success of nasal drug delivery systems. The nasal cavity can be divided into three areas: the olfactory area, respiratory area, and vestibule. The respiratory area is rich in blood vessels; thus, it can provide systemic absorption of the drug after intranasal administration and subsequent indirect delivery of the drug to the brain. The vestibule is a small area and the drug absorbed through this area is very low [10, 11]. The respiratory area is suitable for the delivery of the vaccines by the intranasal route. The olfactory area also plays an important role in the direct delivery of drugs to the brain and cerebrospinal fluid (CSF) [1, 12]. The main purpose of these drug delivery routes is to deliver the desired drug concentration to the drug activity site. Due to the permeability of the nasal epithelium, high overall flow, porous endothelial membrane, large surface area, and evading of the first passage metabolism cause the drug to be rapidly absorbed into the brain. Methods of drug delivery through the nasal route can transfer a wide range of therapeutic agents (small molecules and macromolecules) to the CNS. Several studies have shown that, when administered nasally to the CNS, the drug offers effective therapeutic effects in lower doses (Fig. 14.1). The transmission of therapeutic agents from nose to brain is described below.

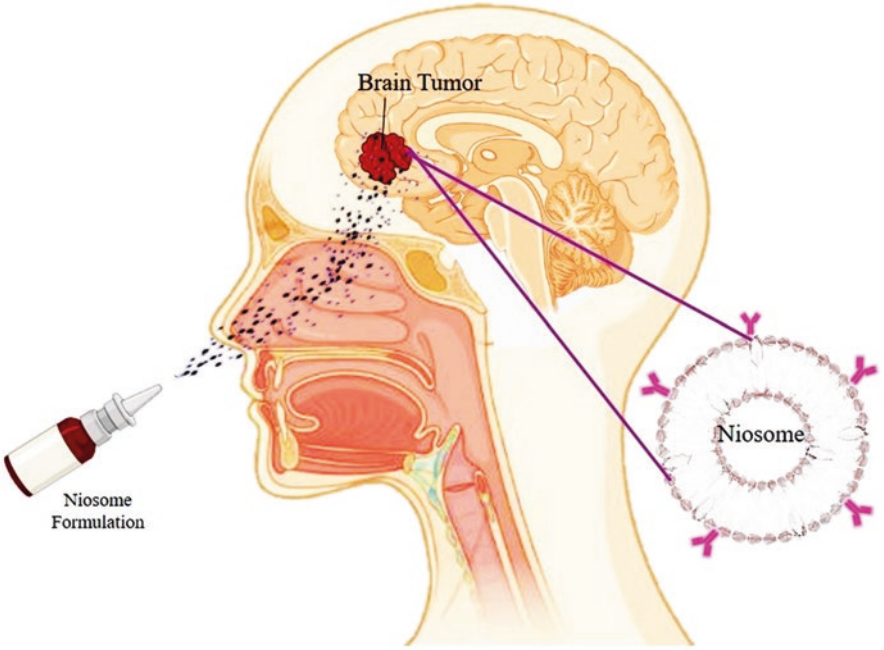

Fig. 14.1 Schematic of the niosomal nasal delivery route for brain targeting

2.2.1 Olfactory Pathway

The olfactory area at the top of the nasal cavity is known as the possibility of drug delivery through the nose to the brain for the treatment of various CNS diseases [13]. Drugs can pass through the olfactory epithelial space through the tight interstitial space with passive diffusion, or through transmission through cell membranes with endocytosis, or neuron transfer [5, 14]. Most drugs that deposit in the olfactory area are extracellularly transported between cells. Various studies on drug delivery through the nose have suggested the role of P-glycoprotein in this pathway. In addition, a study was performed to test the penetration and transfer of the drug in the three-dimensional culture of these cells (3D MucilAir) as a model of nasal structure [15]. The olfactory neurons play an important role in targeting drugs to the brain through the nasal path [16]. The path of the drugs for transmission is from the intracellular axon to the olfactory bulb and then to the brain [17]. The diameter of the olfactory axon in humans is about 0.1–0.7 micrometers, indicating that molecules that have a diameter in this range can easily deliver their pharmaceutical agents through this route. Since nanosystems used in drug delivery are usually nano sized, they seem to be suitable for transmission through this pathway [7].

Drug delivery through the epithelium is faster than axonal transport. Drug delivery from the olfactory pathways occurs through extracellular and intracellular mechanisms. Most lipophilic drugs are transported through passive diffusion, while most hydrophilic drugs are transported through the paracellular pathway. The hydrophilic and molecular weight of drugs has a significant effect on drug absorption. Drugs with high lipophilicity are usually absorbed through the transcellular pathway [5].

2.2.2 Trigeminal Pathway

The trigeminal pathway for drug delivery from the nose to the brain has been less studied. The main function of the trigeminal nerve is to transmit chemical and thermal information to the nose, mouth, and ocular mucosa [18, 19]. The trigeminal nerve pathway can be an important site for drug delivery to the brain through the nasal route. For example, insulin-like growth factor 1 was transmitted to the brain through the trigeminal and olfactory pathways [20].

2.2.3 Lymphatic Pathway

Drugs can be transferred through several extracellular pathways such as perineural, perivascular, and lymphatic channels in the olfactory region. These extracellular pathways are connected to the olfactory bulb of the brain by olfactory nerves [7, 21]. Therefore, the lymphatic pathway also plays an important role in drug delivery from the nose to the brain.

2.2.4 Systemic Pathway

The systemic pathway is an indirect transmission from the nose to the brain and can be a promising approach for low molecular weight lipophilic drugs [22, 23]. Drugs are absorbed by the vascular regions of the epithelial membrane of the nasal mucosa and lymphatic system and then are transported to the systemic circulation to avoid the first-pass metabolism of the drug [22, 24].

2.3 Advantages and Disadvantages of the Nasal Drug Delivery Route

Targeted drug delivery through the nasal route to the brain reliably, effectively, non-invasively, and directly transmits drug agents to the CNS via neural connections between the nose and the brain [25]. The nasal cavity has high blood vessels that are

also highly permeable and therefore one of the best places to prescribe drugs [10, 26]. The following are some of the unique benefits of nasal transmission:

1. Has a large surface area for drug absorption.
2. Facilities and patients are comfortable.
3. In this method, the level of drugs in the bloodstream rises rapidly.
4. Drugs penetrate this pathway well, especially low molecular weight lipophilic drugs.
5. Circumvent difficult conditions of absorption through the intestine.
6. Circumvent hepatic metabolism, which is the first-line metabolism for drugs that are absorbed from the intestine.
7. It is possible to transfer the drug directly to the brain through the olfactory nerves.
8. This pathway is adjacent to the lymphatic tissue; the vaccine is administered through the nasal route directly to the lymphatic tissue.
9. This route is suitable for people who are undergoing long-term drug treatment.
10. Suitable for prescribing drugs that have low fluid stability.

In the nasal uptake pathway, drug agents reach the olfactory bulb and brainstem after passing through the surface of the nasal epithelium, and through the pulsating current, that spaces around the cerebral blood vessels and contributes to drug absorption, drug agents spread to other areas of the CNS. In some cases, nasal transmission is almost equivalent to intravenous injection because there is a unique connection between the nasal cavity and brain [27–29].

Nasal administration is the only way to administer directly to the brain without non-invasive methods [22]. Because proteins, peptides, nucleic acids, and even stem cells can be transported through the nasal passage, this route has received considerable attention for drug delivery. In addition, via the nasal passage drugs can be administered both locally and systematically. Drugs in the form of suspensions, solutions, gels, surfactants bases, and emulsions can be administered through the nose, and administration through this route increases the efficiency of targeted delivery and decreases the side effects of systematic administration [30–33]. Some factors that affect nasal absorption are as follows:

1. Some physicochemical properties of drugs: including drug or nanocarriers containing drug size, molecular weight, hydrophilic or lipophilic, and resistance to enzymatic degradation
2. Nasal condition: rate of mucociliary clearance, nasal pH condition, and endothelial cell permeability
3. Including drug formulation, drug solubility, and viscosity [34–37]

For example, a drug with low molecular weight, lipophilic, and resistance to enzymatic degradation with high endothelial permeability and low clearance of the nasal cavity is well absorbed from the nasal route. The anatomy of the nasal cavity and the condition of the nasal mucosa can affect the process of drug absorption such as enzymatic degradation, mucociliary clearance, nasal cavity blood flow, nasal health conditions [38–45].

2.4 Mechanism of Drug Absorption from the Nasal Route

The main step in absorbing drugs from the nasal cavity is to cross the mucus. Large particles find it relatively hard to pass through the mucus layer, but small particles pass easily [46]. The nasal mucosa contains mucin, a protein that can bind to solutes, and the presence of this mucin affects the absorption process. Environmental or physiological changes cause structural changes in the mucosal layer, and this influences the rate of absorption through the nose [47]. After the drug passes through the mucosa, there are several mechanisms for absorption through the mucosa. These include simple diffusion from the membrane, transcellular transcytosis by vesicular carriers across the cell, and paracellular transmission between cells. Among the several mechanisms mentioned, paracellular and transcellular pathways are predominant [48]. Transmission from the paracellular pathway is slow and passive. The lower the molecular weight of the drug or nanocarriers containing the drug, the faster it is absorbed through nasal passages. In contrast, low bioavailability has been reported for drugs with molecular weight above 1000 Daltons [46]. Lipid drugs are often transported through a lipoid pathway, also known as the intercellular process; the transfer of this pathway depends on the lipophilicity of the drug. Other drug routes include passing through the cell membrane through active transport facilitated by the carrier and passing through the opening of tight junctions [48]. Barriers to drug absorption are potential metabolism before reaching systemic circulation and improper length of stay in the nasal cavity [49]. Many water-soluble drugs are poorly absorbed through the nose and therefore do not have sufficient bioavailability. Penetration enhancers are often used to increase the absorption and bioavailability of such drugs [50]. The mechanism of action of penetration enhancers is that they increase the rate of drug absorption by making reversible changes in the structure of the nasal epithelial barrier [49]. Researchers have been drawn to investigate the intranasal drug delivery method based on the findings so far. Nonetheless, it is critical to comprehend medication uptake across the nasal mucosa. The nose is a complex organ from a kinetic standpoint since three separate processes, such as drug disposal, clearance, and absorption, occur simultaneously inside the nasal cavity. Understanding the nasal anatomy and related physiological aspects is critical for optimal drug absorption across the nasal mucosa.

2.5 Nasal Anatomy and Physiology of the Nose

The human nasal cavity is separated into two nasal cavities by the septum and has a total volume of 16 to 19 mL and a total surface area of 180 cm^2 [51]. Each cavity has a volume of around 7.5 mL and a surface area of about 75 cm^2 [52]. A solute can be deposited in one or more of three anatomically distinct locations following medication administration into the nasal cavity: the vestibular, respiratory, or olfactory regions. The vestibular area is responsible for filtering airborne particles and is

located at the entry of the nasal passages [53, 54]. When it comes to medication absorption, it is thought to be the least essential of the three zones [55]. The respiratory system is the largest and most vascularized, and it is primarily responsible for drug absorption. The olfactory region has a surface area of around 10 cm^2 and is important for drug delivery to the brain and CSF. In the nasal cavity, there are three main anatomical zones. A mucus layer covers the epithelium of the nose canal, trapping particles. Cilia clean the mucus layer from the nasal cavity, which is replenished every 10 to 15 min [56]. Mucosal secretions have a pH of 5.5 to 6.5 in adults and 5.0 to 6.7 in children [57], which retains particles and allows cilia to remove them from the nasal cavity. The mucus moves through the nose at an approximate rate of 5 to 6 mm/min resulting in particle clearance within the nose every 15 to 20 minutes [58, 59]. Numerous enzymes [51], for instance, cytochrome P450, enzyme isoforms [60] (CYP1A, CYP2A, and CYP2E), carboxylesterases, and glutathione S-transferases are found in the nasal cavity [61, 62].

2.6 Brain Targeting Through the Nasal Route

Because of the BBB's poor distribution into the CNS, the development of numerous potentially interesting CNS therapeutic candidates has been hampered for some time. The intranasal route can deliver therapeutic drugs to the brain without passing through the BBB because of the unique connection between the nose and the CNS [63].

A unique characteristic and superior choice is the capacity to transfer therapeutic drugs to the brain via drug absorption across the olfactory region of the nose [58]. When drugs were administered nasally to rats, some drugs produced significantly higher CSF and olfactory bulb drug levels than when administered intravenously [25]. Many scientists have identified evidence of nose-to-brain transfer [64]. Many previously abandoned potent CNS medication candidates with intranasal delivery have the potential to become successful CNS therapeutic drugs. Thus, several nasal intranasal injection formulations were developed for the treatment of disorders such as epilepsy, migraine, MS, depression, and erectile dysfunction [65].

2.7 Drugs for Glioblastoma Treatment Administered Intranasally

Several studies have been carried out to discover the optimal intranasal treatment for glioblastoma (GBM) utilizing monotherapy or in combination with other drugs, including natural and/or synthetic agents. The research that was done to develop a viable treatment for this aggressive brain tumor is summarized here.

Intranasal delivery of curcumin, as a natural compound, combined with a glioblastoma-specific antibody was suggested by Mukherjee et al. The targeted

curcumin-CD68 Ab conjugate was intranasally administered to mice in which glioma GL261 cells were xenografted in the brain. Adult male C57BL/6 mice were given a curcumin-CD68 Ab solution in PBS intranasally every 72 h ten days after GL261 cells were xenografted, whereas another set of animals got an intraperitoneal injection of a commercially available lipid-complexed form of curcumin, that is, Curcumin Phytosome. Curcumin-CD68 Ab conjugate intranasal delivery and Curcumin Phytosome intraperitoneal injection both caused GL261 brain tumor remission in 50% of mice, confirming that CD68 Ab could be delivered to the brain via the intranasal route and that CD68 Ab had a targeted therapeutic effect after intranasal delivery. Furthermore, on day 90, 70% of the animals given curcumin-CD68 Ab intranasally and 60% of those given Curcumin Phytosome intraperitoneal were still alive, whereas all the control group animals, that is, vehicle-treated mice, were already dead. As the obtained results, intranasally delivered curcumin-targeted conjugates can directly kill GBM cells and also lead to repolarizing tumor-associated microglial cells (TAMs) to a tumoricidal state [66].

Rhein (4, 5- dihydroxyanthraquinone-2-carboxylic acid) is a natural compound with anti-inflammatory, antioxidant, anti-fibrosis, neuroprotective, and anti-tumor properties [67]. The CD38 enzymatic activity is inhibited by rhein, which leads to attenuating glioma progression. To demonstrate this, Blacher et al. conducted a study while using a syngeneic mouse glioma progression model (CD38-deficient C57BL/6J (CD38-/-) mice) [68]. Glioma cells (GL261) were intracranially implanted into the mice's brains after 24 h, and vehicle or rhein was administered three times each week for 22 days. Rhein can suppress CD38 enzymatic activity, which leads to reduced microglia activation that is supportive of tumor progression. The intranasal administration of rhein suppressed the glioma progression significantly in WT mice, showing that CD38 is a therapeutic target in the tumor microenvironment and that small-molecule inhibitors of CD38 could be a potential treatment for glioma [68]. Furthermore, Shingaki et al. evaluated the direct brain uptake of 5-fluorouracil (5-FU) from the nasal cavity, as well as whether the inhibition of CSF secretion by choroid plexus could lead to increased brain concentration of the free drug [69]. In this study, male Wistar animals were administered 5-FU intravenously or nasally in the presence or absence of intravenous infusion of acetazolamide (AZA).

AZA (25 mg/kg) was injected for 15 min before initiating the nasal perfusion of 5-FU in the n groups of co-treatment. CSF secretion by choroid plexus epithelial cells is inhibited by AZA. The active transport of Na+ ions is connected to CSF secretion in these cells, and AZA significantly reduces the activity of the Na/K ATPase [70]. The results found that intravenous administration of AZA increased the CSF content of nasally given 5-FU by 200–300% when compared to 5-FU nasal perfusion without pre-treatment with AZA. By reducing CSF secretion from the choroid plexus and so maintaining the concentration of the nasally administered drug in the CSF, AZA was able to improve nose-to-brain drug transport [69]. It was concluded that co-administration of therapeutic agents to treat neurological diseases with drugs that reduce CSF secretion from the choroid plexus could be an interesting alternative to treating diseases of the brain, such as GBM, because the concentrations of therapeutic agents in the brain are improved.

In another report, the same group found a similar effect in male Wistar rats after methotrexate (MTX) administration by nasal injection [71]. MTX is a folic acid antagonist that inhibits the enzyme dihydrofolate reductase and has been used in treating a variety of cancers [72]. Because MTX has a poor penetration across the BBB, therapeutic options for GBM via oral administration are limited [73]. In the study, MTX was administered nasally with sodium carboxymethyl cellulose (CMC) added to improve the nasal residence time of the formulation, and AZA was given orally 30 min later. The amount of MTX measured in the CSF was higher than that measured in plasma 15 minutes after intranasal injection, indicating that MTX was transported directly from the nasal cavity to the CSF. When compared to the concentrations found in the CSF following intraperitoneal administration, plasma had a greater concentration. Simultaneously, the effect of oral AZA 30 min before nasal MTX administration was investigated, and it was shown that the co-treatment enhanced the concentration of MTX in CSF by 195% [71].

In another research, MTX-loaded chitosan microspheres were prepared by spray-drying technique. In this way, different molecular weights of chitosan were used to fabricate chitosan microspheres owing to promote the nose-to-brain delivery of the MTX. The animals were given MTX solution, and MTX-loaded chitosan microspheres were intranasally administered. According to the obtained results, a higher concentration of MTX in rat brain tissues was shown after intranasal administration of the MTX-loaded chitosan microspheres when compared to the MTX solution, which was attributed to the presence of chitosan. In fact, chitosan is known to be a safe mucoadhesive polymer that could effectively improve the brain hydrophilic drug delivery, like MTX, via intranasal administration [74].

Another study [75] suggested that temozolomide (TMZ) be delivered by the nose. After oral administration, TMZ is efficiently absorbed and is available in capsule form. TMZ has also shown good penetration via the BBB and an acceptable toxicity profile [76]. However, a significant increase in overall survival was observed in multimodal treatment with TMZ and radiotherapy group as compared to the radiotherapy alone group. This study suggested that 60–75% of patients with GBM present no clinical benefit from treatment with TMZ [77]. Based on these findings, a rat model with orthotopic C6 glioma xenografts was employed to investigate the therapeutic efficacy of intranasal administration of TMZ to take benefit of the drug's brain-targeting capabilities. In fact, it was proposed that TMZ be administered intranasally to restrict systemic exposure to the drug and therefore reduce toxic effects on healthy organs. During the 40-day experiment, the rats were given saline solution or TMZ via three distinct delivery routes: intravenous, oral, or intranasal, and tumor size, rat survival time, and pathological changes were evaluated. When compared to all other groups, including controls, magnetic resonance imaging revealed a significant reduction in the volume of glioma xenografts in the intranasal TMZ group ($p < 0.05$). Immunohistochemistry and a terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay were also used to examine proliferating cell nuclear antigen (PCNA) and tumor cell apoptosis. High tumor cell apoptosis rate as well as a reduction in protein expression of PCNA were observed in treatment by the intranasal route.

When comparing the three groups of C6 glioma-bearing rats, the intranasal TMZ group had a significantly higher median survival time. Control animals given saline solution survived 20 days, while animals treated with TMZ orally, TMZ intravenously, and intranasally survived 21.5, 19, and 31 days, respectively [75]. The findings of this study suggest that intranasal TMZ delivery can inhibit the growth of C6 glioma in vivo and that it could be an effective glioma treatment strategy.

Pineda et al. evaluated a solution of TMZ in dimethyl sulfoxide (DMSO) in nude mice xenografted models bearing human glioblastoma tumors derived from the human glioma stem cell lines TG16, TG1N, and TG20 [78]. TG16, TG1N, and TG20 human glioma cell lines were injected intrastriatal into ten-week-old female Swiss nu/nu mice. The anesthetized mice received 10 L of TMZ or vehicle intranasally 1 month after the graft, and this treatment was repeated three times a week for 2 weeks. Intranasally administered TMZ slowed tumor growth and significantly increased the lifetime of mice engrafted with TG16 and TG1N cells, without any effect on tumors produced by TG20 cells, which are resistant to TMZ in vitro. The findings showed that the intranasal route for TMZ delivery into the brain for the treatment of intrastriatal brain tumors should be investigated further [78].

The studies that are reviewed above collectively demonstrate that the intranasal administration of anticancer drugs can induce benefits in the treatment of GBM and the intranasal route of administration might allow for direct access of the drugs to the brain, serving as an effective strategy for glioblastoma treatment. However, the use of nanotechnology to design a nanosystem as an intranasal drug delivery system could be a promising strategy for clinical employment of nose-to-brain administration over more traditional methods.

3 Nanotechnology-Based Drug Delivery

The notion of medicine administration in traditional dose forms is shifting because of nanotechnology. Nanoparticles are a type of particulate medication delivery technology in which the particle size is in the nanometer range (1–1000 nm). Nanoparticles are being studied in great detail to develop medication delivery methods that can penetrate physiological barriers [62]. There has been a lot of interest in developing nanotechnology by employing nanoparticles as carriers for tiny and large molecules throughout the last few decades. Nanoparticles have been created using a variety of polymers. The term “nano” comes from a Latin word that means “dwarf.” A nanometer is one thousand millionth of a meter (i.e., 1n = Nanosize, size refers to one thousand millionth of a given unit). For several decades, the word “nanotechnology” has been most widely used in fields of science such as electronics, physics, and engineering. Biomedical and pharmacological disciplines, on the other hand, have yet to be investigated [79].

The nanomaterial has several advantages including increased surface, enhanced solubility, increased rate of dissolution and bioavailability, rapid onset of action, and less amount dose required in the field of pharmacy [80]. These materials and technologies can be developed to interact with a high degree of functional specificity for

applications in medicine and physiology, offering a level of interaction between technology and biological systems not previously possible [81]. In this chapter, we focused on niosomes as key nanocarriers in nasal drug delivery.

3.1 Structure of Niosomes

The structure of niosomes is spherical and consists of one or more microscopic layers. This structure formed by non-ionic surfactants that cholesterol and charge inducers can also be used in this structure [82]. Different types of surfactants used to form niosomes differ in the number of combinations and the molar ratio [83]. Examples of surfactants used to synthesize niosomes include polyoxyethylene fatty acid esters, sorbitan fatty acid esters, alkyl glyceryl ethers, and alkyl ethers [84]. The addition of cholesterol to the bilayer of surfactant in niosomes maintains the strength of the bilayer and reduces its leakage. Also, charge inducers provide charge to vesicles, and the size of these vesicles increases, thus increasing the encapsulation efficiency of the drug in niosomal structures. Negative charge inducers include lipoamino acids, dihexadecyl phosphate, and dicetyl phosphate and positive inducers include cetylpyridinium chloride and stearyl amines; these compounds increase the stability of niosomes structures [85, 86]. In an aqueous solution, non-ionic surfactants orient the hydrophilic end of the amphipathic surfactant molecules outward (i.e., toward the aqueous phase), while the hydrophobic ends of the two surfactant molecules orient each other (i.e., toward the lipophilic environment) and form a bilayer structure resembling a cell membrane [82].

In the structure of closed niosomes, the inner and outer bilayer surfactant is an aqueous phase and a lipophilic space is in the middle of these two phases [86]. Energy is required to form the closed bilayer structure of the niosomes, which is supplied by thermal energy or physical stimulation. Van der Waals forces and repulsive forces between surfactant molecules are the most important stabilizing forces of vesicles in the structure of niosomes. Variables such as changes in vesicle components (type, concentration, and composition), surface charge, size, and volume will alter the properties of the niosomes [87]. As shown in Fig. 14.2, niosomes can be classified into three groups based on their vesicle size: small unilamellar vesicles (SUV; 10–100 nm), large unilamellar vesicles (LUV; 100–500 nm), and multilamellar vesicles (MLV > 500 nm) [88].

3.2 Advantages and Disadvantages of Niosomes-Based Drug Delivery Systems

Niosomes have several advantages over other nano-carriers:

1. Surfactants used for synthesis niosomes are non-immunogenic, biocompatible, and biodegradable.
2. The method used to produce niosomes does not involve very toxic solvents.

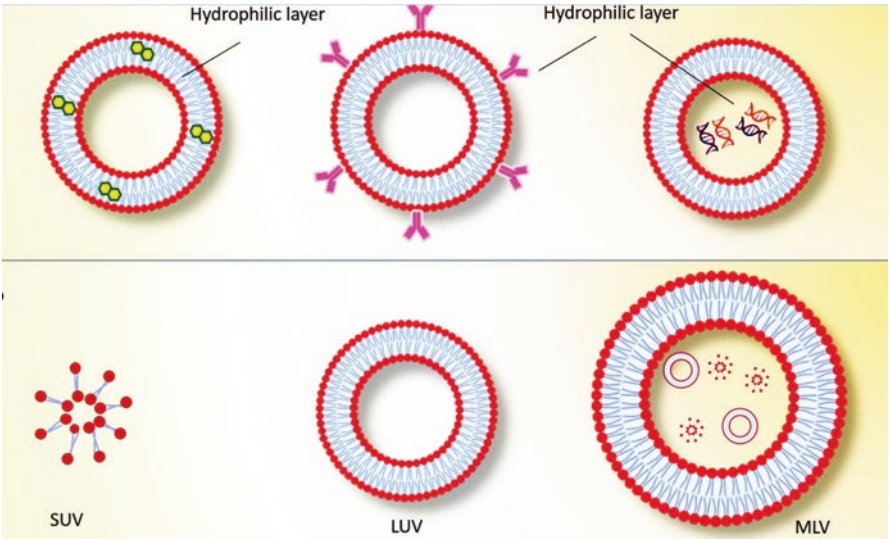

Fig. 14.2 Schematic typical vesicle size of niosomes

3. The chemical stability of niosomes components is high, so their storage and transportation do not require special conditions.
4. By changing the structural composition and production method of niosomes, their physicochemical properties such as size, shape, and fluidity can be easily changed.
5. Niosomes can carry large amounts of drugs.
6. Niosomes can be used to deliver unstable and sensitive drugs because they protect drug ingredients against heterogeneous conditions inside and outside the body.
7. Niosomes improve the therapeutic function of drug molecules because they have high circulation time and limit the effects of the drug on the target cell.
8. Niosomes can be administered in a variety of ways, such as topical, oral, and injectable.
9. Niosomes have different drug formulations: semi-solid, powder, and suspension.
10. Niosomes increase the bioavailability of insoluble drugs when used orally.
11. Niosomes increase the penetration of drugs when used for skin delivery.
12. Niosomes-based drug delivery formulation leads to better patient compliance compared to free oil forms.
13. To regulate the rate of drug release from the structure of the niosomes, becoming an aqueous phase, it can be emulsified in the non-aqueous phase.

In contrast, niosomes have disadvantages including aggregation, physical and chemical instability, decomposition of vesicles, and leakage encapsulated drugs. Also, the methods required to prepare multilayer vesicles are time-consuming and require specialized equipment [89, 90].

3.3 Formulation Components of Niosomes

3.3.1 Non-ionic Surfactants

Non-ionic surfactants are a group of surfactants that have no charge in the structure of their head group. Non-ionic surfactants have high stability and biocompatibility compared to positive, negative, and amphoteric surfactants. Non-ionic surfactants have an amphiphilic structure, that is, they have a distinct hydrophilic part and a distinct hydrophobic part [91].

Non-ionic surfactants play a major role in the structure of niosomes and are the most abundant factor in the structure of niosomes. Non-ionic surfactants used in niosomes synthesis have an amphipathic structure and these include polysorbates [92], terpenoids [93], spans [94], alkyl oxyethylene [95], and so squalene belongs to the group of terpenes, a natural lipid, used in the synthesis of niosomes.

The advantage of squalene in niosomes synthesis is that it stabilizes the structure of niosomes and is also slightly toxic in vivo and in vitro [93]. Polysorbate is another group of non-ionic surfactants used in the structure of niosomes; for example, niosomes synthesized with 80 Polysorbates are an excellent vector for gene delivery because they have a polyethylene glycol (PEG) group in their structure. Niosomes with a structure of Span 60/Tween 60/cholesterol are a carrier with a high percentage of drug encapsulation because the interaction is established between the acyl group of 60 Span and the drug [94].

3.3.2 Cholesterol

Steroids are an important part of cell membranes, and their presence affects membrane fluidity and permeability. Cholesterol is the most important steroid that is often used to synthesize niosomes. Cholesterol binds to non-ionic surfactants using a hydrogen bond.

Although cholesterol may not play a role in lipid formation, it plays a role in stabilizing and controlling the properties of niosomes nanostructures. The addition of cholesterol to niosomes formulation affects the properties of the nanosystem, such as lipid layer permeability, rigidity, increased drug encapsulation efficiency, easier hydration of frozen niosomes, and increased biocompatibility of nanocarriers. Cholesterol reduces leaky niosomal nanocarriers by inhibiting phase shifts from gel to liquid [96].

3.3.3 Charge Inducer Molecules

In the synthesis of niosomes, charge inducer molecules may also be added. Charge inducer molecules, by inducing positive or negative electrostatic charges on the surface of niosomal vesicles, maintain the suspension state of nanocarriers, prevent aggregation, and ultimately increase stability. Negative inducers of electric charge include diacetyl phosphate (DCP) and phosphatidic acid. Stearylamine (STR) and

stearyl pyridinium chloride are negatively charged inducer molecules. For niosomes synthesis, a percentage of charge-inducing material of 2.5–5 M is acceptable; adding more than this amount prevents synthesis [97].

3.4 Types of Niosomes

3.4.1 Proniosomes

Proniosomes is a new vesicle system for delivering medication to the skin and ocular. Proniosomes overcome a variety of disadvantages of previous structures, such as physical stability, aggregation, and leaking. Proniosomes are suitable for drug delivery because they have no first-pass hepatic metabolism, no adverse effects on oral delivery, and no gastrointestinal tract (GIT) [98]. Proniosomes are composed of non-ionic surfactants whose outer part is hydrophobic and the inner part is hydrophilic. Because peroxisomes increase the permeability of the skin layers, they are very suitable for transporting drugs through the skin. Proniosomes are dehydrated niosomes that become niosomes with the absorption of water. Proniosomes are more stable than other carrier vesicles [98]. Proniosomes are inactive and must be transformed to the active form, niosomes, to function. The proniosomes become niosomes by passing through the skin layer or adding an aqueous solution. When proniosomes are administered to the skin, they hydrate in the skin and form one-side concentration on the outer surface of the skin, which increase the permeability of the skin. When niosomes lysis into the endosomes of subcutaneous tissue, encapsulate drugs are released [99, 100]. Non-ionic surfactants used in the synthesis of niosomes are also used to synthesize proniosomes. These non-ionic surfactants are used in combination with cholesterol and lecithin, a structure-stabilizing phospholipid. To hydrate the lipid layer, hot water, phosphate buffer with pH = 7.4, and 1% glycerol are used to synthesize proniosomes [100]. Proniosomes have been successfully used as a carrier for better delivery of various drugs, including Roxithromicin, Tazarotene, α-Mangostin, Tolterodine tartrate, and so on [98].

3.4.2 Ethosomes

Ethosomes were first introduced by Touitou et al. in 1997 [101]. Ethosomes arose from the modification of liposomes and were composed of phospholipids, high concentrations of ethanol, and water [102]. Ethosomes nanocarriers compared to liposomes have (1) reduced particle size, (2) negative zeta potential, (3) higher drug encapsulation percentage, and (4) are more stable [103]. However, to develop a more efficient delivery system, a new generation of ethosomes, that is, binary ethosomes, and transethosomes developed. Zhou et al reported different form of ethosomes such as binary ethosmes by adding alcohol to the conventional form [104]. In the formulation of binary ethosomes, in addition to ethanol, another alcohol is usually propylene glycol (PG), and isopropyl alcohol is also present [103, 105, 106].

PG increases permeability, low toxicity, low skin irritation, high viscosity, as well as greater stability than ethanol [103, 107]. This specificity of PG causes the drug to increase its affinity to the skin and also the drug to accumulate into deeper levels of the skin. Adjusting the ratio of PG and ethanol is very important to achieve proper penetration of the drug into the skin [105, 108]. Sung et al. introduced a new generation of ethosomes in 2012. The advantages of this new generation autosome were the same as those of previous generation ethosomes and liposomes [109]. Transethosomes are identical to ethosomes in composition, but they also contain a penetration enhancer (surfactant) [109]. Evidence suggests that transethosomes are smaller in size, more elastic, and have more permeability to the skin – the "more permeability to skin" probably due to the synergistic effect between ethanol and surfactant [110].

3.4.3 Bola-Surfactant Niosomes

Bola surfactant is used to synthesize bola niosomes. Surfactants of this type were initially discovered in the membrane of *Archaebacteria* in 1980. These surfactants have two hydrophilic heads that are connected by one or two lipophilic bonds. In 2010, Zakharova et al. showed that bola surfactants have low critical micelle concentrations, high surface tension, high self-assembly, and high tolerance in vitro and in vivo compared to conventional surfactants [111, 112].

3.4.4 Aspasomes

Vesicles synthesized by supramolecular amphiphiles that have antioxidant properties, such as aspartic acid and its derivatives, are used therapeutically for diseases in which active oxygen species are produced. Ascorbyl palmitate (ASP) combination with cholesterol and a negative charge inducer can be used to synthesize bilayer lipid of niosomes. Aspasomes are prepared by film hydration method and then hydration with aqueous solution along with sonication is synthesized.

Gopinath et al. introduced the nanoparticle formulation of aspasomes (ASC-P) [113]. Submicron-sized aspasomes are synthesized by thin layer hydration. A lipid film is synthesized with ascorbyl palmitate and cholesterol (27.63 to 72.18) and dicetyl phosphate at 10% mol of total lipid and hydrated with phosphate saline buffer (PBS, pH 7.4). For example, for hydration of zidovudine (AZT) hydrophilic drug, it is first dissolved in PBS and then the solution is hydrated on a thin layer. Then the prepared suspension is sonicated in an ultrasonicator to obtain AZT-encapsulated aspasomes. In a study for zidovudine (AZT) encapsulation in aspasomes, adding cholesterol to the lipid layer showed no change in size, zeta potential, and zidovudine (AZT) encapsulation percentage. But release rate of zidovudine (AZT) varied with the presence of cholesterol. The antioxidant property of ascorbyl was maintained even after ascorbyl palmitate was converted to aspasomes. Aspasomes also showed increased skin penetration and AZT preservation properties [114].

3.5 Methods of Preparation

The qualities of niosomes can vary widely depending on how they are synthesized. In this chapter, different approaches were reviewed:

3.5.1 Thin-Film Hydration (TFH)/Handshaking Method (HSM)

These two methods are mostly put into one category for the similarities they have (although some articles have separated them to be two different methods) [115]. Based on the research and the lab practices done, they seem to be the most common technique to prepare niosomes: need a round bottom flask, a volatile organic solvent like diethyl ether or chloroform, etc. (for dissolving surfactant), cholesterol, and charge inducers (rotary evaporator). Using TFH/HSM, the solvent will be evaporated at room temperature which creates a thin dry film of dissolved components, and then the dried film must be hydrated, so an aqueous phase will be added with gentle agitation [116]. As can be seen in Fig. 14.3, depending on the structure of the drug (hydrophilic or hydrophobic) decide where the aqueous phase must be added:

(A) Aqueous phase if it is hydrophilic
(B) Organic solvent if it is hydrophobic

3.5.2 The "Bubble" Method

An organic solvent won't be used for this method, but a three-neck flask will be needed (fabric must be glass) to be in a water bath for maintaining the temperature. The first neck flask must be able to place the thermometer, the second one is used to pass the nitrogen, and the third (last) one is attached for the water-cooled reflux. So, using this method first cholesterol, then surfactant, and finally, phosphate buffer is mixed together and then these particles are dispersed at 70 °C. Afterward, a high-shear homogenizer will be used for 15 s and afterward, nitrogen gas will be immediately supplied to the mixture (bubbling of the nitrogen gas must be at 70 °C). The vesicles produced this way are large and unilamellar [89].

3.5.3 Ether Injection Method (EIM)

In this method, an aqueous solution is used so that the solution of cholesterol and surfactant dissolved in diethyl ether (volatile organic solvent) will be injected with the help of a 14 gauge needle, and then they must be put into preheated warm water (maintained at 60 °C). Finally, niosomes are formed by vaporization of diethyl ether (volatile organic solvent) using a rotary evaporator. These single-layered niosomes can have a diameter varying from 50 to 1000 μm [115–117].

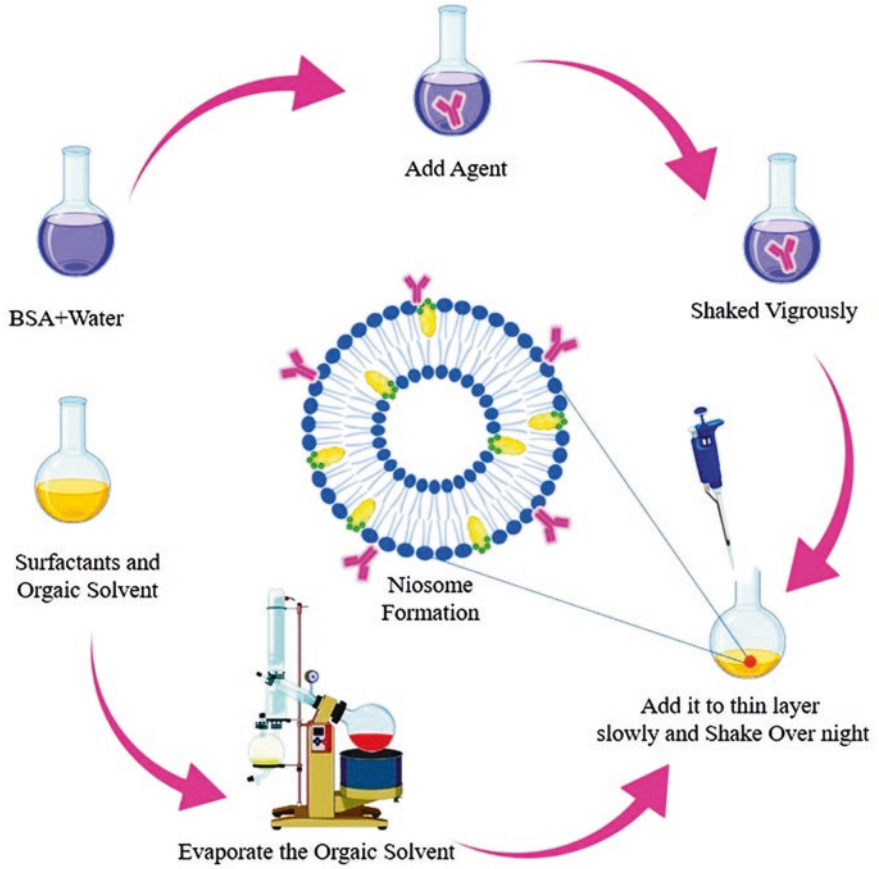

Fig. 14.3 Schematic non-ionic surfactant vesicles (niosomes) formation by lipid layer hydration method

3.5.4 Sonication Method

It is one of the conventional methods; sonication is used to prepare niosomes. In this method, solution of the drug in the buffer must be prepared so that afterward surfactant and cholesterol can add up [118]. The next necessary step to produce multilamellar vesicles is probe sonication (they require high levels of energy) at 60 °C for 3 min. It's possible to produce unilamellar vesicles if it would be a further ultrasonicator. So, the ability to control niosomes particle sizes can be achieved by sonication of the mixture at a particular frequency, temperature, and time [116].

3.5.5 Reverse Phase Evaporation Method (REV)

In this method, an organic solvent will be used like ether and chloroform, and then surfactant and cholesterol (as the aqueous drug solution) will be mixed in (taken in the ratio 1:1 ratio) [116] and then the mixture will be added to aqueous phase containing the drug afterward resulting in a two-phase system, then they must be homogenized so that organic phase is evaporated under negative pressure to form niosomes. Now large unilamellar vesicles are formed [91]. To form a semi-solid gel of large vesicles this emulsion must be dried in a rotary evaporator at 40 C. To form small stable uniform vesicles small quantities of the buffer will be added and the semi-solid form is sonicated at 4–5 C [118]. REV can be the ideal method for creating niosomes of hydroxychloroquine, isoniazid, ellagic acid, and bovine serum albumin due to: high % EE, large particles size with a small variation to encapsulate large hydrophilic macromolecules with relatively higher EE than other methods [97]. Keep in mind that if the structure of the used drug is deformed (for being in temperatures greater than 50 °C or in organic solvents), direct entrapment method cannot be used [115].

3.5.6 Micro-Fluidization Method

This method is based on the submerged jet principle. Surfactants and the drug solution are pumped through an interaction chamber under the pressure of 100 ml/min, and a cooling loop is required to remove the heat produced from before the micro-fluidization. Using this method, it is possible to create different forms of niosomes with greater uniformity, small size, unilamellar vesicles, and better reproducibility of niosomes [91].

3.5.7 Trans-Membrane pH Gradient (Inside Acidic)

In this method, multilamellar vesicles are produced; so to create niosomal suspension,a round bottom flask is being used. Firstly, the surfactant and cholesterol must be mixed so they can dissolve together in chloroform, and then the mixture must be put under pressure to evaporate chloroform. The mixture should be vortex with 300 mM and citric acid (pH 4.0) to hydrate film. But still, the job is not done; an aqueous solution containing 10 mg/ml of the drug must be added to the solution and vortex. Set the pH of the final solution to 7.0–7.2 by adding 1 M disodium phosphate. Finally heat the mixture at 60 °C for 10 min [116].

3.5.8 Single-Pass Technique

This is a patented technique for creating niosomes within the range of 50–500 nm. It has also been mentioned as a multiple membrane extrusion. In this method, a lipid-containing drug suspension must be passed through a porous device and then through a nozzle. Finally, the uniform-sized niosomes are prepared [89].

3.5.9 Heating Method (HM)

The heating method was introduced by Mozafari et al. [119, 120] in 2005. In this method, surfactants and cholesterol were hydrated in PBS (pH = 7.4) separately at room temperature for one hour under a nitrogen atmosphere. The solution then is stirred and heated up to 120 °C to dissolve cholesterol. At the next level, the temperature must reach 60 °C. Afterward, surfactants and other additives should be added to the buffer while stirring (meant for cholesterol) continues for another 15 min and after all niosomes nanocarriers were designed. At the end stage, created niosomes must be kept at room temperature for 30 min, and then for future needs, they will be stored at 4–5 °C in a nitrogen atmosphere [115].

3.5.10 Freeze and Thaw Method (FAT)

This method enables us to create frozen and thawed multilamellar vesicles (FAT-MLVs). First, niosomes are prepared with the TFH method (thin-film hydration), then niosomal suspensions are frozen in liquid nitrogen for 1 min and are thawed in a water bath at 60 °C for 1 min [121].

3.5.11 Microfluidic Hydrodynamic Focusing

This method provides better-sized niosomes for distribution compared to a conventional method. Lo et al. created niosomes out of two miscible liquids via diffusive mixing based on microfluidic hydrodynamics [122, 123]. Hence, a rapid and controlled manner is required to mix the miscible liquids in microchannels.

The following are the factors that can affect the assembly of niosomes:

(a) Microfluidic mixing conditions.
(b) Chemical structure of the surfactant.
(c) Material: the micro-channels fabrication, for example; large-sized niosomes will be produced If we use aider micro-channels for it and increase the diffusive mixing time & hence.
(d) Low-rate ratio: This factor can affect the size of the produced niosomes, for example, if the rate increases it will be decreasing diffusive mixing time. So, the manufactured niosomes will be small-sized [89].

3.5.12 Dehydration-Rehydration Method

The initiator of this method was Kirby and Gregoriadis in 1984 [124]. In this method, vesicles must first be prepared by the thin-film hydration method. Next, liquid nitrogen should be used to frizz vesicles and then it should be freeze-dried overnight; this will form powder niosomes, and then phosphate buffer saline (pH 7.4, at 60 °C) should be used for hydration.

3.5.13 Supercritical Carbon Dioxide Fluid Method (scCO2)

The advantages are:

(a) One-step production
(b) Easy scale-up

Manosroi et al. designed this method for creating niosomes [125, 126]. To sum up, Tween 61, cholesterol, glucose, PBS, and ethanol must be added into the view cell and the CO_2 gas should be introduced into the view cell, next equilibrium must be reached through magnetic stirring, and after this level, the pressure should be released and finally, niosomal dispersions can be found (Niosomes created by this method will be in the range of 100–440 nm) [91]. So, keep in mind that this method requires solvents that are non-inflammable, non-toxic, and volatile.

3.5.14 The Handjani-Vila Method

In this method, the aqueous solution of the drug must be mixed with cholesterol and surfactant. Then, ultracentrifugation or agitation should be used to homogenize the mixture at a controlled temperature [127].

3.6 Characterization of Niosomes

The parameters that characterize niosomes are as follows:

3.6.1 Size, Morphology, and Size Distribution of Niosomes

Light microscopy, coulter counter, photon correlation spectroscopy, electron microscopic analysis, SEM (scanning electron microscope), TEM (transmission electron microscope), freeze-fracture replicator, light scattering, and zetasizer can be used to determine the size and morphology of niosomes. Because the two methods use different measurement concepts, the particle size determined by the transmission electron microscope is smaller than the dynamic light scattering (DLS) [115, 128–130]. Rinaldi et al. [131] investigated the size, shape, and size distribution of the niosomes sample using atomic force microscopy.

3.6.2 Entrapment Efficiency

It can be computed by subtracting the total amount of drug added from the amount of unloaded drug [84]. Exhaustive dialysis, filtration, gel chromatography, and centrifugation can all be used to determine the unloaded drug [131]. By dissolving niosomes in 50% n-propranolol or 0.1% Triton X–100, the concentration of loaded medicines can be measured [132]. The percent entrapment efficiency can be calculated using the calculation below [115].

$$\%\text{Entrapment Efficiency} = \frac{\text{Quantity of drug} - \text{loaded in the niosomes}}{\text{The total quantity of drugs in the suspension}} \times 100$$

3.6.3 Charge on Niosomes and Zeta Potential

Because of the charge on them, niosomes repel one other. By inhibiting aggregation and fusion, electrostatic repulsion keeps them stable [133]. The *zeta* potential is used to determine the charge on niosomes. The *zeta* potential is determined using a *zeta* potential analyzer, mastersizer, microelectrophoresis, pH-sensitive fluorophores, high-performance capillary electrophoresis, and a DLS apparatus [134]. Henry's equation is the formula for calculating *zeta* potential [135, 136].

$$£ = \frac{\mu E \pi \eta}{\Sigma}$$

where $£$ = *zeta* potential, μE = electrophoretic mobility, η = viscosity of medium, and Σ = dielectric constant.

Because of electrostatic repulsion between particles, Bayindir and Yuksel [122] employed dicetyl phosphate (DCP) to give the surface charge on niosomes and found that a negative *zeta* potential in the range of 41.7 to 58.4 mV is enough to keep the system stable. Manosroi et al. [137] used two different charges to manufacture gallidermin niosomes (anionic and cationic). They noticed differences in niosomes size because, in anionic vesicles, the charge was neutralized by the positive charge of gallidermin, resulting in small niosomes, whereas in cationic vesicles, the charge was neutralized by repulsion between the cationic charges, resulting in big niosomes.

3.6.4 Number of Lamellae

The number of lamellae can be determined using a variety of techniques such as AFM, NMR, small-angle X-ray spectroscopy, and electron microscopy [138, 139]. Small-angle X-ray scattering combined with in situ energy-dispersive X-ray diffraction can be utilized to characterize the thickness of bilayers [140, 141].

3.6.5 Membrane Rigidity

The mobility of a fluorescent probe as a function of temperature can be utilized to evaluate membrane stiffness [142]. Fluorescence polarization can be used to determine the micro-viscosity of the niosomal membrane to better understand its packing structure [125]. The membrane characterization of pentamidine niosomes was done by Rinaldi et al. DPH and pyrene were utilized because DPH indicates lipid order and pyrene indicates lateral diffusion inside the bilayer [143]. The fluorescent measurements (λ = 350–425 nm) were made with a luminescence spectrometer, and the fluorescence anisotropy (r) was calculated using the equation below:

$$\text{Fluorescence Anisotropy}\left(r\right) = \frac{\left(IVV - \text{GIVH}\right)}{\left(IVV + 2\text{GIVH}\right)}$$

3.6.6 In Vitro Release

The dialysis membrane method is used to investigate in vitro release. Niosomes are placed in a dialysis bag, which is then placed in a container with dissolving media, usually buffer, in this procedure. This entire assembly is kept at a constant temperature of 37 °C on a magnetic stirrer. A sample is obtained from the receptor compartment at specific time intervals, and drug concentration is measured using any method described in the literature [136, 137, 144].

The dialysis approach was used to release temozolomide niosomes [145], benazepril hydrochloride niosomes [146], paclitaxel, curcumin cationic PEGylated niosomes [147], and diltiazem niosomes [148]. Aboul Einien [129] studied the release of ascorbic acid derivative from aspasomes using a cellophane membrane (mol. Wt. cut off = 500–1000) soaked in glycerin: water (1:3) for 15 min; 0.5 g of aspasomes were packed in this membrane, firmly knotted, and placed in a USP dissolution apparatus I. The experiment was carried out in 250 mL of phosphate buffer (pH 7.4) at 32 °C ± 0.5 °C temperature and 50 rpm speed. At a predefined time interval, the samples were spectrophotometrically examined. To investigate the diffusion of morusin from niosomes, Agarwal et al. [149] utilized a different approach. They dispersed 15 mg of preparation in 15 ml of phosphate buffer between pH 4.5 and 7.4. This sample was taken in 15 Eppendorf tubes. These tubes were revolved at a constant speed of 130 rpm and a temperature of 37 °C for 9 days. The tube is removed at a predetermined time interval and centrifuged at 15000 rpm for 30 min. The drug concentration of the resulting supernatant was determined using spectrophotometry.

3.6.7 Tissue Distribution/In Vivo Study

The method of delivery, drug concentration, effect, and present time of the drug in tissues such as the liver, lung, spleen, and bone marrow all influence in vivo investigations for niosomes [115, 133]. Animal models can be used to investigate a drug's tissue distribution. Animals must be sacrificed, and various tissues such as the liver, kidney, heart, lungs, and spleen must be taken, washed with buffer, homogenized, and centrifuged to investigate the distribution pattern. The drug content of the supernatant is determined [136]. Onochie et al. [150] studied the bioavailability of benzyl penicillin niosomes in albino rats in vivo.

The intubation tube was used to administer each formulation (0.1 ml) orally. Blood samples were taken at predefined intervals for 24 h using the retro-orbital puncture method, and the supernatant was utilized to measure serum drug concentration.

3.6.8 Stability Studies

On storage, the drug may leak from the niosomes, because of aggregation and fusion [115]. Kopermsub et al. [151] performed the stability studies of niosomes by exposing the preparation to different conditions of temperature (4°, room temperature, and 45°) for 2 months. Niosomes are also exposed to various humidity and light (UV) conditions. During stability studies, parameters like size, shape, and entrapment efficiency are evaluated periodically. In the same manner stability of green tea extract niosomes [152], lornoxicam niosomes [153], cefdinir niosomes [154], and *Ginkgo biloba* [154] niosomes have been performed. Bayindir and Yuskel [122] studied the effect of gastrointestinal enzymes on the stability of niosomes. This study was performed by exposing the drug and drug-loaded niosomes in different gastrointestinal enzymes like pepsin, trypsin, and chymotrypsin and found that niosomes protect the drug from degradation by gastrointestinal enzymes.

3.7 Routes of Administration

Drug-loaded niosomes can be supplied via a variety of routes, depending on the condition, drug characteristics, and the site of administration. These administration paths are briefly described below.

3.7.1 Intravenous

Intravascular delivery of niosomes is possible. The advantage of injecting the medicine is that it enters the systemic circulation immediately; also, the niosomes improve the drug's stability and prolong its time in the blood. With minimal changes,

the drug can also be administered to a specific location. Many medications' niosomes are delivered using the intravenous method [87, 155]. Niosomes of morin hydrate were produced by A. Y. Waddad et al. [156] for intravascular injection. To increase the stability and bioavailability of phenol, He et al. [157] developed PEGylated niosomes. PEGylated niosomes can block uptake from the mononuclear phagocytic system, allowing to improve circulation time.

3.7.2 Intramuscular

Niosomes can also be given via the intramuscular method. Jitender Singh Wilkhu [158] fabricated niosomes for the oral and intramuscular administration of subunit influenza antigen.

3.7.3 Dermal and Transdermal

In the event of skin problems, the dermal route is employed to deliver drugs locally. It is solely employed for local activity. This approach has the advantage of preventing the medicine from entering the systemic circulation, resulting in fewer side effects. The medicine enters the systemic circulation via transdermal distribution; however, drugs confront a barrier in the form of the skin. The vesicular system is extremely useful in enhancing medication delivery via both *dermal* and transdermal routes [139]. Niosomes operate as a drug reservoir, allowing the drug to penetrate deeper into the body. To avoid gastrointestinal problems, NSAIDs are delivered by a transdermal administration method [84].

Clomipramine is provided encapsulated in niosomes to reduce first-pass metabolism and increase bioavailability [159]. Manosroi et al. [137] produced gallidermin niosomes for transdermal administration. They demonstrated improved transdermal medication delivery with increased drug accumulation in the skin and no systemic adverse effects. Patel et al. [160] improved lopinavir transdermal administration from niosomal gel. They compared the niosomal gel to the ethosomal gel of the same medication and discovered that the ethosomal gel deposition was better using ex vivo permeation experiments. Niosomes were found to be safer than ethosomes in histopathological investigations and their in vivo bioavailability was substantially higher than the oral suspension of lopinavir. A papain-loaded elastic niosomal gel with a molecular mass of 23.5 kDa was effectively developed for scar therapy by transdermal application [161]. Sandeep et al. [162] produced a fluconazole proniosomal gel for topical use. Ex vivo skin penetration and permeation experiments revealed that a large amount of drug has collected in the skin, improving local drug delivery for a longer period. Abdelbary et al. [163] developed methotrexate niosomes for topical administration of methotrexate to patients with psoriasis. This preparation has the highest proportion of drug deposition in the skin (22.45%). To achieve continuous medication delivery, Narayana Charyulu R et al. [164] combined penetration enhancers with methotrexate. Junyaprasert et al. [165] used different

surfactants (Span 60 and Tween 60) and solubilizers to make ellagic acid niosomes (propylene glycol 400, propylene glycol, and methanol).

The niosomes size, entrapment efficiency, and drug permeability were all modified by the formulation. Junyaprasert et al. [166] investigated the effects of chemical penetration enhancers on ellagic acid skin permeability. The penetration enhancer has altered the permeation of ellagic acid from niosomes at 24 hours, according to in vitro skin permeation tests in the human epidermis. The DMSO niosomes have the highest drug concentration in the epidermis, while N-methyl-2-pyrrolidone niosomes have the highest concentration in the acceptor compartment. This research shows that DMSO niosomes are effective for epidermal distribution of ellagic acid, while N-methyl 2-pyrrolidone (NMP) niosomes are effective for dermal delivery. Niosomes of the following drugs are also made and evaluated: ascorbic acid derivative (topical delivery) [129], green tea extract (transdermal) [152], diacerein (topical) [89], etodolac (topical) [167], celecoxib (transdermal) [168], baclofen (topical) [169], and resveratrol (topical) [170]. For transdermal drug delivery, phenol ethosomes [130] and pentazocine proniosomes [171] are also created.

3.7.4 Oral

As the oral route is the preferred approach for drug administration, niosomes are also given this way. The acidic environment and digestive enzymes, which may degrade the medication, are a difficulty in the oral distribution of the medicine [122]. However, niosomes have been demonstrated to successfully carry the medication to the gastric mucosa [172]. To improve oral bioavailability, niosomes containing tenofovir disoproxil fumarate [173], cefdinir [154], paclitaxel [122], and *Ginkgo biloba* extract are produced. To improve the oral activity, microbiological activity, and duration of action, Onochie et al. [150] developed benzylpenicillin niosomes. Lornoxicam niosomes were developed to prolong the drug's action when taken orally [153]. Samyukta Rani et al. [174] made orlistat niosomes from proniosomes to improve solubility, regulate release, and length of action. To improve insulin penetration through the intestinal membrane, Moghassemi et al. [175] produced trimethyl chitosan (TMC)-coated niosomes of insulin.

3.7.5 Ocular

When a medicine must be given in the anterior location of the eye, topical ocular administration is usually preferred [115]. Drugs delivered in conventional forms have a bioavailability of just 1–3%, and they are subject to precorneal loss due to tear production and insufficient residence time in the conjunctival sac [176, 177]. To distribute naltrexone via the ocular pathway, Abdelkader et al. [178] produced controlled release niosomes and discomes. They discovered that anionic niosomes

outperform neutral niosomes in improving naltrexone penetration across the cornea. By covering tacrolimus niosomes with mucoadhesive hyaluronic acid, Zeng et al. [179] created tacrolimus niosomes. Because of its high lipophilicity and molecular weight, tacrolimus has a poor corneal penetration (822.5 D). The hyaluronic acid–coated niosomes improve corneal permeability and ocular contact time. Abdelkader et al. [180] also created unique nano-sized elastic niosomes for ocular delivery of prednisolone acetate and sodium phosphate. They tested for ocular irritation, bioavailability, and anti-inflammatory properties, as well as compared the results to those of traditional eye drops (both suspension and solution). Using a modified Draize test, researchers discovered that both forms of prednisolone have good ocular tolerability and bioavailability. A side effect elevation in intraocular pressure created by prednisolone was greatly reduced by niosomes preparations.

3.7.6 Pulmonary

The pulmonary route of administration of niosomal drugs has various advantages, including enhanced mucus permeability, sustained drug delivery, targeting, and superior therapeutic outcomes. The interaction of niosomes for pulmonary glucocorticoid administration with human lung fibroblasts is created and tested. At all incubation durations, these niosomes showed no appreciable toxicity in the concentration range of 0.01 to 1 M. Vesicular carriers have been discovered to be located in the cytoplasm using confocal laser scanning (site for glucocorticoid receptors). These vesicles were shown to significantly increase drug absorption by human lung fibroblasts as well as drug activity [181].

3.7.7 Nasal Administration

Nasal delivery is an excellent option for medicines with a high first-pass metabolism. Diltiazem is rapidly absorbed from the mouth, although its bioavailability is only 30–60% due to substantial hepatic first-pass metabolism by cytochrome P450 enzymes. Nasal administration has some drawbacks, such as a short residence time in the nasal cavity due to mucociliary clearance, airflow restriction, and nasal mucosa sensitivity, all of which impair drug penetration and systemic bioavailability. Nasal niosomal diltiazem has been demonstrated to have higher absorption and less elimination [148].

3.8 Applications of Niosomes

Niosomes can be employed as a delivery device for a range of pharmaceutical reasons. Table 14.1 provides a summary of some of the prior studies on the application of niosomes in a tabular format.

Table 14.1 Recent studies in drug delivery using niosomes and applications

Application	Surfactant	Method	Therapeutic agent	Route administration	Reference
Protein delivery	Tween 60	Lipid layer hydration	Glutathione	In vitro	[182]
	Span 60	Lipid layer hydration	Insulin	In vitro	[175]
	Brij 92	Lipid layer hydration	Insulin	Oral	[183]
	Span 60	Lipid layer hydration	Insulin	Oral	[184]
	Span 40	Lipid layer hydration	N-acetyl glucosamine	Topical	[185]
	Span 60	Lipid layer hydration	Bovine serum albumin	Oral	[186]
Anticancer drugs delivery	Span 60	Lipid layer hydration	Cisplatin		[187]
	Span 60	Lipid layer hydration	5-Flourouracil	Topical	[188]
	Span 80	Sonication	Curcumin		[188]
	Bola surfactant	Lipid layer hydration	5-Fluorouracil	Intravenous	[111]
	Span 60	Lipid layer hydration	5-Fluorouracil	Topical	[189]
	Span 60	Lipid layer hydration	Flutamide	Oral	[190]
	Pluronic P123	Lipid layer hydration	Doxorubicin	In vitro	[191]
	Tween 80	Lipid layer hydration	Curcumin	Vein injection	[192]
	Tween-100/ span 80	Lipid layer hydration	Curcumin	In vitro	[193]
	Span 60	Ethanol injection	Gambogenic acid	In vitro	[194]
	Tween 80	Lipid layer hydration	Paclitaxel and curcumin	In vitro	[147]
	Tween 80	Lipid layer hydration	Doxorubicin and curcumin	In vitro	[195]
Carrier for hemoglobin	Span 60	Lipid layer hydration	Hemoglobin	Intravenous	[196]
Treatment of HIV-AIDS	Span 60	Lipid layer hydration	Lamivudine		[197]
	Span 60	Ether injection	Stavudine		[198]
	Span 60	Lipid layer hydration	Stavudine		[199]
	Span 80	Ether injection	Zidovudine		[200]

(continued)

Table 14.1 (continued)

Application	Surfactant	Method	Therapeutic agent	Route administration	Reference
Vaccine and antigen delivery	Span 60	Lipid layer hydration	Tetanus toxoid		[201]
	Span 20	Lipid layer hydration	Newcastle disease vaccine	Parenteral	[202]
	Span 60	Lipid layer hydration	Ovalbumin		[203]
	Span 60/ Span 85	Reversed phase evaporation	Bovine serum albumin	Topical vaccine	[204]
Management of psoriasis	Span 60	Lipid layer hydration	Methotrexate	Topical	[163]
	Free surfactant	Lipid layer hydration	Methotrexate	Topical	[205]
	Span 60	Lipid layer hydration	Acitretin	Topical	[206]
Treatment of leishmaniasis	Span 40/ Tween 40	Lipid layer hydration	Selenium and glucantime	In vitro	[207]
	Span 40/ Tween 40	Lipid layer hydration	Amphotericin B and glucantime	intramuscularly	[208]

3.8.1 Delivery of Proteins and Peptides

Protein and peptide medications have long been challenging to deliver orally due to their degradation by the acidic environment and enzymes of the gastrointestinal tract. Niosomes, on the other hand, shield these drugs from protolithic enzymes [84, 132]. Moghassemi et al. [153] developed bovine serum albumin niosomes (BSA). The formulation was tuned for loading and release as a function of cholesterol to span 60 M ratios, and an inverted light microscope was utilized to monitor the position of protein in the vesicle. To improve insulin penetration, niosomes of trimethyl chitosan-coated insulin are also produced for oral delivery [175].

3.8.2 Delivery of Anticancer Drugs

Niosomes can deliver anticancer drugs to a specific organ. This targeting could be passive [209] (deposition of niosomes within the tumor due to unique properties of tumor cells not found in normal cells) [210], physical (delivery based on specific environmental conditions such as pH or magnetic fields) [118], or active [209] (delivery based on specific environmental conditions such as pH or magnetic fields) (active uptake of niosomes by the tumor cell). Active targeting can be accomplished by altering the surface's structural features or by binding the ligand to the niosomes. Curcumin, which is hydrophobic, and doxorubicin hydrochloride, which is hydrophilic, were encapsulated in niosomes for anticancer treatment in this study. They

observed two distinct release phases: doxorubicin release during the first 2 days, followed by curcumin release for 7 days. Against HeLa cell lines, the cytotoxic impact was amplified (synergistic). For the co-administration of curcumin and paclitaxel, Alemi et al. [147] developed cationic PEGylated niosomes. The improved synergistic anticancer effects of these niosomes were reported. Agarwal et al. [149] created the morusin niosomes for anticancer therapy potentiation. He noticed that the drug was released in a dependent manner. The release of morusin from niosomes was lower at pH 7.4 than it was at pH 4.5. In acidic settings (pH 4.5), drug release was 58.1% after 120 hours, but it was only 43.3% at physiological pH 7.4. It suggests that in the acidic environments of cancer cells, significant drug release can be achieved.

3.8.3 Delivery of Vaccine and Antigen

Wilkhu et al. [211] developed bilosomes for vaccine administration orally. Bile salt is incorporated into the bilayer of vesicles to manufacture bilosomes. The antigens are protected by these bilosomes from being degraded by enzymes found in the gastrointestinal system (GIT).

3.8.4 Carrier for Hemoglobin

Because of their strong oxygen absorptive capabilities, niosomes can also be used as a hemoglobin carrier in the blood [212].

3.8.5 Treatment of HIV-AIDS

Niosomes can be used to deliver drugs for sustained delivery in AIDS patients. The low efficacy and toxicity of these drugs pose an issue in their delivery, which could be solved by constructing a niosomal system. Due to dose-dependent hematological toxicity, significant first-pass metabolism, short biological half-life, and poor absorption, zidovudine is an anti-HIV drug with limited therapeutic efficiency [146, 213]. Niosomes have been reported to solve zidovudine issues [199]. Lopinavir is an HIV protease inhibitor that is reversible. Because of its low aqueous solubility, high log P value, cytochrome P450 3A4 sensitivity, and susceptibility to P-glycoprotein efflux transporters, its systemic bioavailability via the oral route is limited. Transdermal niosomes were created and compared to the ethosomal gel to address these concerns. Ex vivo skin permeation experiments revealed that the ethosomal gel deposition of a drug into the skin was higher than the niosomal gel, but niosomes permeated deeper through the skin and had a better drug release profile [160]. Kamboj et al. developed niosomes to improve the oral bioavailability of tenofovir disoproxil fumarate [173]. They discovered a twofold increase in bioavailability and a considerable improvement in the drug's mean residence time, indicating a

longer drug release time. Stavudine niosomes were manufactured by Shreedevi et al. [214] for targeting and controlled release.

3.8.6 Management of Psoriasis

Psoriasis is an inflammatory skin condition that lasts for a long time. It has been reported to affect joints and is recurring [180, 215]. Topical treatment is often used for mild to moderate psoriasis [173]. When more than 20% of the patient's body is affected, systemic therapy is recommended. Emollients, keratolytic agents, coal tar, anthralin, calcipotriene, and corticosteroids are some of the topical treatments for psoriasis. Phototherapy may be combined with systemic therapy. Systemic therapy for psoriasis includes methotrexate, cyclosporine, corticosteroids, and etretinate [152]. Nausea, diarrhea, dizziness, and mouth ulcers are all common side effects of systemic methotrexate treatment [133, 216]. Hematological and liver damage are potentially possible side effects [217]. Topical methotrexate may help prevent these issues. For better psoriasis care, Abdelbary and AbouGhaly [163] created and optimized niosomes containing methotrexate for topical application. In comparison to the oral solution, the niosomes were optimized using the Box-Behnken design and reported to have a much higher area under curve and skin deposition amount of drug. The safety of niosomes was proven by histopathological examinations. Hashim et al. [206] developed an acitretin nano-vesicular gel for topical use to combat the drug's low solubility, stability issues, skin irritation, and substantial systemic adverse effects. Moghaddam et al. [89] used topical application to prepare the diacerein niosomes for targeted distribution.

3.8.7 Treatment of Leishmaniasis

Because niosomes are taken up by the reticuloendothelial system and accumulate there, they can be used to treat disorders like leishmaniasis [87, 218]. Niosomes have also been utilized to treat malignancies that have spread to the liver and spleen [132]. The Leishmania parasite primarily infects the liver and spleen. Antimonial (drugs used to treat leishmaniasis) might affect the liver, kidneys, and other organs [219]. The niosomal formulation can increase the drug's absorption in the liver, reducing the drug's negative effects on other organs [132]. Positively charged niosomes entrapped with autoclaved Leishmania major against cutaneous leishmaniasis had a moderate effect and successfully delayed the formation of lesions in BALB/c mice, according to Pardakhty et al. [220]. For *Leishmania tropica*, Mostafavi et al. [207] produced selenium niosomes with glucantime. In vitro testing revealed that selenium niosomes combined with glucantime have effective antileishmanial action and improved potent lethal activity. For *Leishmania tropica*, Parizi et al. [207] investigated the immune-modulatory and antileishmanial action of benzoxonium chloride niosomes. They discovered that as the concentration of the drug was increased, the expression of interleukin IL-10 decreased while that of interleukin-12 increased.

3.8.8 Diagnostic Imaging

Niosomes have the potential to be employed as a carrier for radiopharmaceuticals, making them valuable in diagnostic imaging of organs such as the liver and spleen. For imaging, ^{99m}Tc labeled DTPA is utilized [136, 221]. Iobitridol (diagnostic agent) is utilized with niosomes for x-ray imaging [222]. Gadobenate dimeglcemine in a conjugated niosomal formulation with [N-palmitoylglucosamine (NPG)], PEG 4400, and both PEG and NPG have been found to increase tumor targeting of an encapsulated paramagnetic drug as measured by MR imaging [138, 223]. By adding contrast agents or dyes (near-infrared) in the inner aqueous or non-aqueous compartment or conjugating onto the surface of niosomes, A. Massotti [224] created unique biconjugate niosomes for imaging. Gd (EDTA) 2- may be utilized as a contrast agent for incorporation [225]. Optical imaging combined with magnetic resonance imaging is also a useful method for tumor diagnosis [226–228]. In vivo imaging can be achieved by combining polyethylene amino groups with near-infrared probes [229].

3.8.9 Enhancement of Bioavailability

Drug bioavailability can be improved with niosomes. To improve oral bioavailability, niosomes of paclitaxel [122], cefdinir [154], benzylpenicillin [150], and tenofovir disoproxil fumarate [173] are produced. Diltiazem niosomes were developed for nasal delivery to improve bioavailability [148].

3.9 Targeted Drug Delivery

Tavano et al. [209] and A. Massotti [224] prepared niosomes for targeted delivery of drugs to tumor cells. Tavano et al. prepared to transfer conjugated pluronic niosomes of doxorubicin for delivery to tumor cells. A. Massotti prepared pH-sensitive niosomes for delivery of a drug to hepatoblastoma. Targeting was done using surface modification and no pH-sensitive molecule was used. These niosomes undergo protonation of amino groups present on their surface after penetration into the cell and release their cargo by “sponge effect.”

3.10 Brain Targeting

As illustrated above, niosomes can entrap lipophilic or hydrophilic drugs and deliver the drug molecules to the target site in a sustained and/or controlled way [75, 115]. Drug organ distribution and metabolic stability have been reported to be affected by niosomes. Surface modification of niosomes has been shown to improve target

selectivity for cancer drug delivery systems [118]. De et al. reported that modification of temozolomide-loaded niosomes with chlorotoxin, a target-specific peptide, significantly improved the temozolomide glioma targeting efficacy [145]. In comparison to the intranasal solution of the drug, surface-modified niosomes containing olanzapine (an atypical antipsychotic medicine) demonstrated a three-fold increase in olanzapine concentration in the brain [230]. Pentamidine is an antiprotozoal drug, also having an anti-inflammatory and neuroprotective effect in Alzheimer's disease [231–233]. Its clinical efficacy is limited due to poor permeability across blood-brain-barrier and high hepatotoxicity. To overcome these issues chitosan-glutamate coated pentamidine niosomes were prepared for intranasal drug delivery to reach the brain. Approach to the brain via intranasal delivery bypasses the first-pass hepatic metabolism and blood-brain barrier [11, 17, 22].

4 Summary

Despite the great advances in drug discovery, still, neurologic diseases are the second cause of death around the world [234]. Conventional drug delivery methods such as peripheral routes including oral and parenteral administrations are one of the most common routes for drug delivery whenever systemic effects are intended [235]. Besides the fact that the parenteral route is usually painful and also requires technical assistance, conventional methods also showed other major drawbacks in the efficient delivery of therapeutic agents to the brain. First of all, due to the presence of the blood-brain barrier (BBB), the drug administered via conventional routes results in dramatically lower drug concentration in the brain [5]. Secondly, systemic clearance as well as first-pass metabolism and enzymatic degradation hinder the efficacy of the drug and significantly reduce the drug bioavailability [236]. There are two barriers between blood and brain extracellular fluids: BBB and the blood-cerebrospinal fluid barrier (BCSFB) which mediate communication between the central nervous system (CNS) and the periphery [237, 238]. The BBB consists of a tight layer of endothelial capillary cell junctions which are surrounded by astrocyte foot processes. The BBB plays a key role in regulating CNS homeostasis and function by protecting the CNS from pathogens, toxins, inflammation, and injury. It is a highly regulated barrier that allows highly selective transport of essential molecules to the brain [239]. BBB loss or dysfunction by various diseases such as brain traumas, stroke, multiple sclerosis (MS), and neurodegenerative disorders could result in neuronal dysfunction and degeneration. Although the BBB is a critical component of CNS, it is a significant barrier for drug transport from the blood to the brain, and just the drugs with molecular weight less than 400 Da, high polarity, and not multicyclic can across the BBB successfully [234, 240]. All of these factors trigger the hunt for an alternative delivery system that directly reaches the brain. Different strategies that are mostly invasive such as intraventricular, intraparenchymal, and intrathecal delivery (disruption of the BBB) have been investigated for this purpose [240]. Over the past decades, several studies have described the

nose-to-brain route as a promising approach that could offer an opportunity to serve as a noninvasive direct route to the CNS. The concept of the nose-to-brain drug delivery, for the first time, was introduced by W. H. Frey II in 1989 (William H, Frey I. Inventor Neurologic Agents for nasal administration to the brain. US1991 1990-12-04). This method previously was often used for brain targeting of insulin or insulin-like growth factor and later was developed for delivery of larger molecular weight substances like proteins, peptides, and bioactive [236].

As previously mentioned, nose-to-brain drug delivery is an invasive alternative and patient-friendly route over the traditional and invasive drug administration routes which could provide faster onset of action, high blood flow, and porous endothelial membrane to absorb drugs efficiently while circumventing the hepatic first-pass metabolism, BBB, and potentially lowering the systemic exposure, which enables the easy and self-administration possibilities. Furthermore, this route is optimal for drugs that are susceptible to enzymatic degradation and gastrointestinal tract acidic environment [239]. Generally, there are two main pathways for drugs to reach the brain from the nasal cavity: (1) neuronal pathway as the major route and (2) crossing the BBB through systemic circulation as the minor route.

Desired drugs could be located in the deeper region of the nasal cavity which is firstly absorbed by olfactory and trigeminal neurons, and then through cellular transport can reach the olfactory bulbs [235, 236]. The nasal cavity includes three main regions: vestibular, respiratory, and olfactory regions. After a drug enters the nasal cavity, it encounters mucociliary clearance and then moves forward to reach respiratory and olfactory regions. From these regions, depending on the formulation, physiological condition, and the administration device, the drug can be transported to the brain by several mechanisms such as trigeminal nerve pathway, lymphatic and vascular pathway, olfactory nerve pathway, and cerebrospinal fluid. When the drug reaches the brain, it is distributed throughout the CNS by perivascular transport [235]. Although the nasal to brain route is a promising method for fast, easy, efficient, and targeted drug delivery, some limitations must be acknowledged when developing new therapeutics to be administered via this route. First of all, this route can be used just for potent drugs with a dose volume of 100–250 ml for liquids and 20–50 mg for powders [235]. Secondly, there is a possibility of poor drug permeation through the nasal mucosa due to the low drug retention caused by mucociliary clearance and enzymatic degradation. For this reason, drugs to be delivered by this route should be protected from degradation [236]. Thirdly, due to high vascularization, there is a possibility of peripheral side effects through systemic absorption which also reduces the drug concentration in the brain [236]. Finally, there is a need to use the proper nasal delivery device to install the right amount of drug correctly in the nasal cavity [234]. However, different approaches such as permeation enhancers, protective drug capsulation and colloidal carriers, suitable mucoadhesive system, controlled delivery system, and other novel approaches have been employed to improve the drug delivery through the nasal to brain route [236]. Niosomes are non-ionic surfactant vesicles fabricated by hydrating synthetic non-ionic surfactants, either with or without cholesterol or lipids. They're vesicular structures that appear similar to liposomes and can transport both amphiphilic and

lipophilic medicines. Niosomes are a viable vehicle for drug administration because of their non-ionic nature and are biodegradable, biocompatible, non-immunogenic, and structurally flexible. For the treatment of cancer, viral infections, and other microbial diseases, niosomes have been extensively studied for controlled release and targeted administration. Niosomes can entrap both hydrophilic and lipophilic drugs, allowing them to circulate in the body for a prolonged period. Encapsulation of a drug in the vesicular system is expected to prolong its presence in the systemic circulation and improve penetration into a target tissue, perhaps reducing toxicity if selective absorption is possible. This chapter focuses on the nasal drug delivery route, advantages and disadvantages of niosomes, types of niosomes, methods of preparation, characterization, routes of administration, and applications of niosomes.

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