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Review Article

FOCUS ON NIOSOMAL–BASED DRUG DELIVERY SYSTEMS FOR NASAL ROUTE: APPLICATIONS AND CHALLENGES

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ABSTRACT

For decades, the nasal route of administration is principally used for many therapeutic applications owing to the non-invasive nature of the nasal pathway. Besides, it circumvents blood-brain-barrier (BBB) and hepatic first-pass effect. Consequently, the nasal route is much preferred over other invasive approaches like intravenous, intracerebral, and transcranial for the systemic delivery of drugs and the treatment of central nervous systems (CNS) disorders such as depression, Alzheimer's disease (AD), multiple sclerosis, and Parkinson's disease (PD) *via* the nose-to-brain pathway. Drug applied *via* the nasal route displays some difficulty to reach the brain, like the dose limitation of the nasal pathway, mucociliary clearance, etc. The efficiency of the nasal route depends on the application delivery system. Lipidic-based drug delivery systems (liposomes, solid lipid nanoparticles …etc.) have been confirmed for their promising impact on the nasal delivery approach. Furthermore, the sensitivity of the nasal route and the touched-complications of clinical trials in CNS disorders assigns the necessity of consideration to the clinical trials and approval process of the niosomal-based nasal drug delivery approach. This review describes different approaches to nasal delivery, lipidic-based delivery systems with a focus on niosomes as a promising nasal delivery system, along with different formulation methodologies, and applications.

Keywords: Nasal delivery, Niosomal-based delivery systems, Methods of preparations, Nose-to-brain delivery, Systemic delivery

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INTRODUCTION

A long time ago and till now, nasal drug delivery has been utilized as a very good alternative route of administration. In Indian literature of medicine, the nasal route was used in what is renowned as Ayurveda, which applied nasal delivery of active volatile oils, smoke, steam, and powders for alleviating many different systemic/local ailments [1]. At present, the intranasal application of drugs has been considered the first choice for easing nasal congestion and treating common rhinitis, allergic rhinitis, and local inflammations. Examples of the most commonly used nasal sprays/drops globally are decongestants, glucocorticoids, or antihistaminic drugs [2].

One of the pros of using the nasal route of administration is the fast absorption of drugs owing to the physiological nature of the nose, such as the high vascularity of the nasal mucosa. This will potentially cause the hasty/rapid local effect, decreasing any unintended systemic drug distribution, and thus, avoiding related side effects [2]. On the other hand, the systemic nasal delivery of drugs has also been considered a promising alternative to parenteral and/or oral routes of administration. As the nasal route is advantaged with the avoidance of the hepatic first-pass effect, the fast onset of action owing to the high penetrability of many active moieties, and the enhanced patient compliance. In addition, the nasal delivery dosage form has the probability to be designed and thus gain a sustained/prolonged effect with the aid of a suitable advanced delivery system [1].

Interestingly, the nasal route can be potentially considered a very successful alternative route for any oral-problematic drugs, such as acid-sensitive drugs (proteins/peptide hormones), drugs with an active polar group, and drugs that are weakly orally absorbed. Besides, the use of permeation enhancers and advanced delivery systems for the nasal route can enhance further drug absorption as well as nasal-drug uptake [3]. Other benefits of using nasal drug administration are being a form of non-invasive/painless route of administration, the ease of application by yourself or by nursing staff, with a much lower risk of infection for blood-borne diseases (such as HIV or hepatitis B) or injury, than parenteral route [3]. In this review, different approaches to nasal delivery and delivery systems, with a focus on niosomal delivery systems and their applications as nasal formulations, have been discussed and illustrated.

It is worthy to mention that data collection for this review was done mainly from Innovare Academic Sciences (IAS) journals and other sources and publishers through the Egyptian Knowledge Bank (EKB) platform. Search criteria have been undertaken via using keywords (nasal delivery, niosomal-based delivery systems, methods of niosomal preparations, nose-to-brain delivery, niosomal systemic delivery) to collect data from research articles and review articles that have been published in the last twenty years and related to the selected keywords. The outcomes of data collection from the aforementioned sources have been systematically gathered, analyzed, interpreted, and cited in this review accordingly.

Approaches to nasal drug delivery

The drug-physicochemical properties are having a major influence on nasal-drug absorption small sized, hydrophilic, or highly unionizable drugs are characterized by their high penetration ability through the mucosa and a large proportion of the absorbed drug can avoid systemic degradation/elimination and vice versa. Accordingly, many factors can affect the nasal delivery of drugs, such as the pH of a drug, which influences its degree of ionization and stability and can irritate the nasal mucosa. Highly hypertonic or hypotonic formulations can significantly alter the ciliary movement, which will potentially lead to much lower absorption. Other factors like the surface and the physical condition of the dosage form, viscosity of formulations, the drug concentration/quantity, and even the position of the patient's head during application are playing a significant role in the process of drug absorption [4]. Therefore, utilizing the suitable factors will strongly result in controlling the desired behavior of the drug delivery system, either for local, systemic, or even brain targeting by bypassing blood-brain barriers, which will be discussed in the next sections.

Nasal drug delivery for local effect

As abovementioned, the nasal application of drugs for local effect is well-known. Nasal drops/sprays for local alleviation of

inflammation or congested nose are almost world-widely available. Drugs with hydrophobic nature or with low molecular weight are the best to be utilized for nasal local effectiveness. Examples of nasal pharmaceutical products with local effects are Allergodil®, Pollicrom®, Levocamed®, Rhinivict®, Budapp®, Avamys®, MomeAllerg®, Rhinex®, Nasivin®, and Olynth®. Such drugs with local effects have been manufactured with a lower drug dose than the systemic alternative dosage form, which leads to a lower risk of systemic side effects like drowsiness related to oral antihistaminics [1].

Systemic drug delivery

The interior of the nasal cavity can be divided into four main segments: the atrium, the nasal vestibule, the olfactory region, and the respiratory region. Many transport routes are available for systemic drug delivery. One of them is *via* the transcellular route (mainly for small hydrophobic molecules) to pass through the nasal epithelium reaching the blood or lymphatic system (fig. 1). On this specific route, the drug will suffer from the hepatic first-pass effect after passing through the blood-brain barrier "BBB" to enter the brain. Drugs can be transferred directly through the respiratory region into the stem and further areas of the brain. A much greater amount of the drug can be transmitted to the brain through the olfactory region. Generally, there are three routes of transport, either intracellular and/or neuronal route *via* internalization with neurons (transport route I), the extracellular route *via* the gaps between the cells (transport route II), or transcellular *via* the basal epithelial cells (transport route III) as displayed in fig. 1 [5]. Regarding route I, the drug can be internalized *via* endocytosis/pinocytosis within the olfactory sensory neurons, released in the olfactory bulb by exocytosis, and then passed more to the brain region. This route is comparatively slow transport, which may last from many hours to days. The fastest route of drug transport can be considered *via* the extracellular route II. The lamina propria directly under the epithelium in the olfactory region is responsible for the extracellular transfer of hydrophobic compounds either *via* passive diffusion or active transport (as a neuronal source of olfactory axon bundles), which allows this route of transport [5].

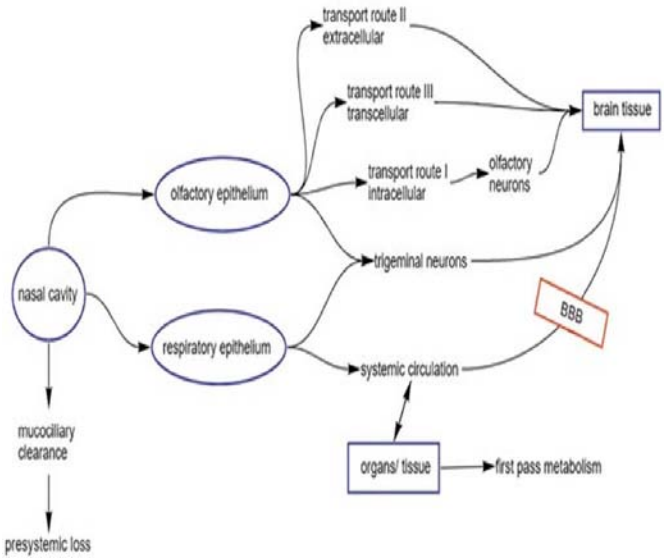

Fig. 1: Drug transport pathways to the lungs or the brain, after nasal application [1]

Nose-to-brain drug delivery

The BBB comprises a tightly-closed monolayer net of blood vessels bargained by polarized endothelial cells that form the brain and spinal cord capillaries. This monolayer blocks the flow of most ingredients from the blood circulation to the brain and vice versa. The epithelial cells of the brain are closely connected by tight junctions and adherent junctions, which strictly control the passageway of ingredients between the brain and the blood [6]. Furthermore, the BBB guards the brain versus infiltration of pathogens, neurotoxic plasma components, transmitters, and even blood cells [7]. One possibility to circumvent the BBB is injections administered intrathecally, intracerebroventricularly, or intraparenchymally. With this approach, the drug can be delivered directly to the cerebrospinal fluid of the CNS. However, these routes of administration are considered invasive and can only be performed by well-trained professionals. Besides, these routes have a furthermore risk of infection [8]. An alternative/noninvasive technique to dodge both the blood-cerebrospinal fluid barrier and the BBB is to deliver drugs *via* the nose-to-the-brain (N-to-B) approach. The nose is not only placed just near the brain, but it also comprises distinct nerves (the olfactory and the trigeminal nerve), which have a direct connection to the brain, independent from the limitations of the BBB. Studies confirmed that the absorption of many moieties such as proteins, peptides, stem cells, viruses as well as possible nucleotides can be granted *via* the N-to-B route, not only small active ingredients [8].

Nasal vaccines

Vaccination is renowned for the administration of non-disease-causing microorganisms, sections of microorganisms, or live-attenuated vaccine microorganisms, with the purpose of immunization versus certain infectious diseases. It is very popular that most conventional vaccines are administered parenterally, owing to the difficulty to be absorbed through the mucous membranes and having little stability in the GIT. However, many drawbacks are also encountered like the increased risk of infection, poor patient compliance, and the need for trained personnel in vaccination [9]. Nasal vaccines are one of the emerging approaches to nasal delivery of moieties for augmented bioavailability and stability. Nasal delivery systems should possess some specifications. They should not exceed 100 nm in size to be able to penetrate the nasal mucosa barriers. Therefore, the optimal size range is between 20 and 80 nm in diameter [10]. Besides, and to be effective, the nasal vaccine needs a significant degree of interaction with the immune system (interaction with the nasopharynx-associated lymphoid tissue). Such stimulation causes a strong humoral/cellular immune response in the body, which takes place on the mucosal as well as on the systemic level [11]. Nasal vaccination is painless to use, non-invasive and can be economically manufactured. However, few products are available on the market, and preclinical investigations are mostly conducted on rodents. In addition, the differences between a human nose and a rodent render some difficulties in implementation, prediction of efficacy, and application safety [10].

Lipidic-based nasal delivery systems

To optimize and improve nasal drug uptake, various drug delivery systems are under investigation. Lipidic-based nasal delivery systems like niosomes, liposomes, *in-situ* gel systems, cyclodextrins, microemulsions, and nanoemulsions [12–14], can be considered as one type of the most emerging drug delivery systems utilized in the nasal delivery route (fig. 2).

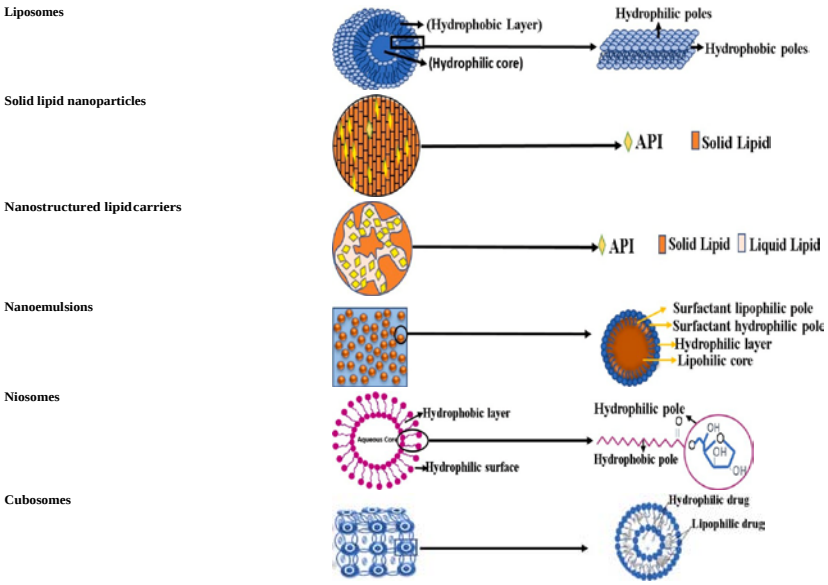

Fig. 2: Different lipid-based nanocarriers with their structures [2]

Many successful research works confirmed the significance of such a delivery system being utilized for nasal delivery. In earlier research work, the anti-schizophrenic quetiapine fumarate-loaded lipidic-based drug delivery systems were investigated. The outcomes revealed that the 7–8% poor oral bioavailability of Quetiapine fumarate (due to its low water solubility and sensitivity to the first pass effect) has been improved and increased to reach 32.61% of drug oral bioavailability with the drug-loaded lipidic nanocarriers [15]. Another example is the basic fibroblast growth factor (a 16.5 kDa protein), which has neuroprotective properties and is used in stroke. Owing to its comparatively large size, it cannot pass the BBB and must be administered invasively *via* the intracerebroventricular or intraparenchymal route. This protein was encapsulated in a nano-liposomal drug delivery system and was investigated for its efficacy and distribution in rats by intranasal route of administration. The experimental animals were observed and examined for 21 d. The rats treated with the drug nanoliposome-complex displayed an enhancement of the damaged-brain tissue and the survival rate was 57% [16]. Previous research investigated the efficacy of ovalbumin-loaded cationic liposomes, as the positively-charged liposomal formulation was found to be a safe/potent nasal drug delivery system. The results displayed that the intranasal ovalbumin-loaded positively-charged liposomal formulation enhanced the antigen uptake by dendritic cells in nasal-associated lymphoid tissue, and the immune response is induced *via* antigen-specific Th2 reaction [17].

Therefore, further investigations utilizing lipidic-based nasal delivery systems are very promising and crucial for safety, compliance, and efficacy applications. Niosomes, as one of the lipidic-based delivery systems, will be discussed for the applicability of nasal administration in the following sections.

Niosomes

Niosomes, the well-renowned nonionic surfactant vesicles, can be best described as unilamellar/multilamellar vesicles mainly prepared from a combination of nonionic surfactants and cholesterol [18]. A niosomal formulation can also be described as a self-assembly system that can be assembled from a variety of hydrophilic moieties along with molecules with a hydrophobic alkyl group, resulting in the entrapment of hydrophilic and/or hydrophobic active ingredients in these vesicles (fig. 3).

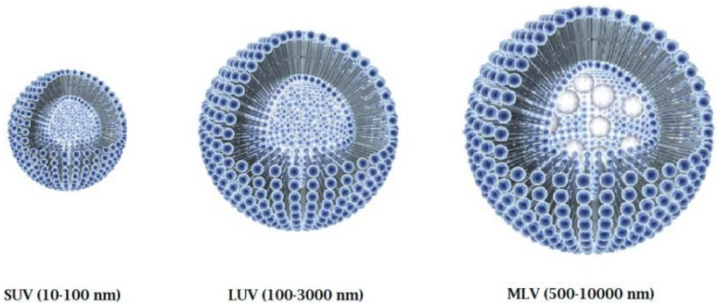

Fig. 3: Classification of niosomes (according to size and number of lamella) [19]

According to configuration and physical assets, niosomes (in comparison with liposomes) offer many added pros regarding biodegradability and biocompatibility. Like liposomes, niosomes can boost the bioavailability and solubility of low water-soluble

medicaments, and reduce the required quantity of used medication, along with targeting ability [20]. They can also augment the stability of the loaded drug, like enhanced protection/drug encapsulation [21], prolonged circulation, targeted and controlled drug delivery [22] photostability [23], and improved chemical/physical stability [24]. In addition, niosomes are much more feasible in production, less costly, more economic, more stable, and easier to store than liposomal formulations [23]. Niosomes can encapsulate aqueous solutions leading to either the encapsulation of hydrophobic or hydrophilic mixtures of pharmaceuticals, micronutrients, antioxidants, nutraceuticals and other active molecules [25, 26]. From an economical perspective, the amendment/improvement/ functionalization of niosomes utilizes a relatively simple/suitable approach by using the least amount of suitable pharmaceutical solvents [27]. Additionally, the characteristics of these particular niosomal nanovesicle formulizations (such as lamellarity, surface charge, size, and concentration) can be easily and feasibly well-controlled [28].

Niosomes elaboration via different procedures

At raised temperatures, the hydration of surfactant/lipid combination followed by niosomal size reduction (optional) to produce a colloidal suspension of homogenous niosomes with a low polydispersity index value. There are many well-established procedures for the elaboration of niosomes. Furthermore, comparatively more economic and facility of production make niosomes with high potential for applications in several arenas. Procedures like the Thin-Film hydration method, Ether injection method, Bubble method, and Microfluidization technique are some of the well-known procedures employed to elaborate niosomes (fig. 4) [29].

Thin-film hydration method

This technique includes solubilizing the total amount of lipids in a proper organic solvent or mixture of solvents used as a vehicle [30], followed by eliminating this vehicle to form structured lipid thin films and then hydrating these films *via* an aqueous environment comprising water-soluble ingredients [31]. The next step is vesicle formation, which comprises the direct combining/coalescing of lipids and aqueous medium at rea latively high temperature (higher than the phase transfer temperature of used surfactants), with the aid of applying reduced pressure to eliminate the dangerous influence of trace sediments of organic solvents on encapsulated material or biologically practical situations [20]. The thin-film hydration method (TFH) is regarded as the most common method of niosomal formulation. Usually, multilaminar vesicular (MLV) niosomes are produced by this technique, which contributes to a larger particle size distribution (fig. 4A). The niosomes of epigallocatechin gallate, pyrazolopyrimidines, citicoline, curcumin and methotrexate were prepared by this technique [26].

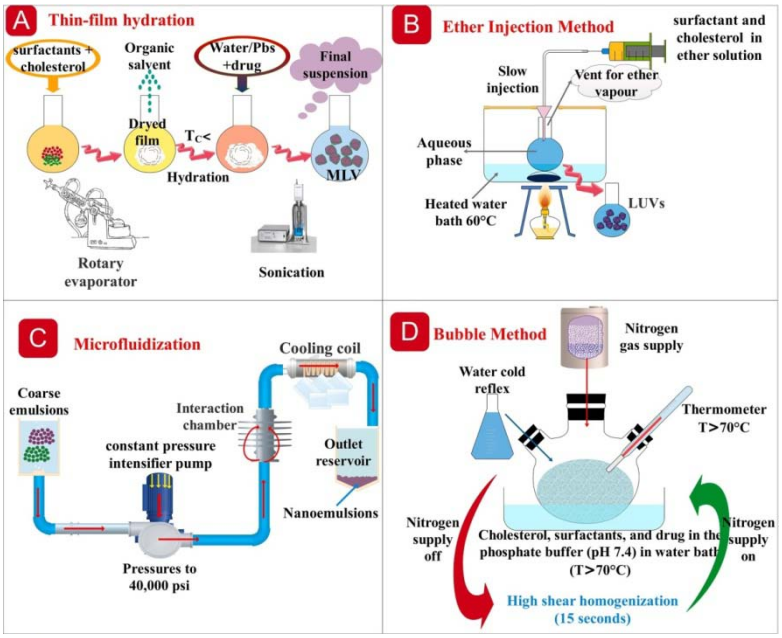

Fig. 4: Different niosomal formulation processes [26]

Ether injection method

By utilizing the ether injection method (EIM), various designs of niosomes can be prepared. Surfactants with additives are solubilized in diethyl ether and then inserted/injected slowly via a certain needle into the previously prepared aqueous drug solution and kept at a high temperature (above the boiling point of the organic solvent). The organic solvents are then evaporated using a rotary evaporator. Through the vaporization step, the controlled formation of uni-layered vesicles takes place (fig. 4B). The niosomes of resveratrol and pilocarpine hydrochloride were elaborated *via* this simple method [26, 32].

Microfluidization method

The main feature of this method is that it can be utilized for generating large unilamellar vesicles (LUVs) with a particular uniform size dispersion. The submerged jet principle was employed in this procedure, which introduced two fluidized streams moving at ultra-high speeds in microchannels inside the interaction chamber. The collision of a thin liquid sheet with a common foreside was arranged in a mode that the energy equipped for the procedure remains in the zone of niosomes formation. Accordingly, the elaborated niosomes had high uniformity, were smaller in size, and had better reproducibility of niosomal formulation (fig. 4C). The topotecan (TPT)-loaded PEGylated niosomes were formulated via the microfluidics technique [26].

The Bubble method

The "Bubble" procedure is a unique technique for the assembly of liposomes and niosomes without utilizing any organic solvents, using a round-bottomed flask with three temperature-controlling necks in the water bath. There is water-cooled reflux in the first neck, a thermometer in the second neck, and nitrogen is supplied *via* the third neck. Cholesterol and surfactants are dispersed together in a 7.4 pH phosphate buffer at 70 ℃, then mixed for 0.25 min with a high shear homogenizer, and then instantaneously bubbled with

nitrogen gas at 70 °C, to form the desired niosomal formulation [26, 33] (fig. 4D).

Applications of niosomes–based nasal drug delivery systems

As previously mentioned, niosomes are vesicular systems that gained much consideration owing to their inimitable characteristics like utilization of non-ionic surfactant, probability of including poorly-soluble drugs, and structurally similar to liposomes but with improved stability/economical features. They are characterized to have a multi-thin-layer vesicular structure and comprise mostly non-ionic surfactants, a hydration medium, and lipids such as cholesterol [34]. Surfactants like Tween mimics apolipoprotein and the niosomes molecule as a low-density lipoprotein in the body which are absorbed by epithelial cells. Niosomes, which are prepared by following the same procedures and under the same variety of conditions, are structurally analogous to liposomes [35]. Besides, niosomes have several advantages over liposomes such as the ability to target the brain *via* using Receptor Facilitated Transcytosis (RFT), lower cost, scaling-up, and ease of formulation [36].

Lately, niosomes have been an interesting consideration in neurodegeneration treatment applications for many reasons. The first is owing to their potential opportunity to upsurge nose-to-brain drug delivery as well as augment drug chemical and biological stability. The second is due to their particular structures, which make them able of encapsulating both hydrophilic and lipophilic types of substances. The third is because of the probability of governing niosomes' properties like surface charge and size. The fourth is the absence of any special conditions that might be required for handling and storage [2].

Many systemically-administered drugs cannot spread to the brain owing to the presence of BBB. The nasal route can help boost drug delivery to the brain by evading the BBB. The results of many previous studies showed that the nose can be a very potential inlet to deliver drugs that cannot bypass the BBB. Both olfactory neurons and facial trigeminal have a significant role in transferring drugs from the nasal cavity to the brain. Niosomes, as nano-sized vesicular carriers, can entrap, encapsulate, or solubilize the active molecules to deliver the loaded substances to the brain. Niosomal vesicles augment cellular uptake, enhance chemical stability, and decrease systemic side effects [19, 37]. They can also enhance the passage of drugs through the olfactory region, boost bioavailability and improve patient compliance. Examples of many niosomal formulations that were studied for nasal administration and thoroughly investigated are presented and reviewed in table 1.

Table 1: Examples of research work on niosomal–based nasal drug delivery systems (for nose-to-brain delivery) [19]

Loaded drug/substance	Compositions	Indication(s)	Aim(s)	EE (%)	Experimental model		Year	Reference
					In vitro	*In vivo*		
Sumatriptan succinate	Span 60 Cholesterol Dicetyl Phosphate Sephadex,	Acute migraine attacks Cluster headaches	To increase bioavailability To accelerate the absorption rate in comparison to oral ways.	57.9	Dialysis bag	Wistar albino rats	2000	[38]
Melatonin	Span 60 Sodium deoxycholate Dimethyl sulfoxide Cholesterol	Sleep disorder	To reduce side effects such as unconsciousness, GI disturbance, etc. To prevent the first-pass metabolism.	95	-	Male wistar rats	2012	[39]
Folic acid	Span 60 Cholesterol	Prevention of depression in Alzheimer's disease	To provide a faster therapeutic effect (faster onset of action)	69.42	-	-	2013	[40]
Diltiazem	Span 60 Brij 52 Cholesterol	Hypertension angina pectoris some types of arrhythmia	To achieve high bioavailability to prolong the duration of action	66.26	-	Male wistar rats	2017	[41]
Nefopam	Span 40 Cholesterol	Moderate and acute pain	To improve bioavailability	80.5	Vertical Franz diffusion cell	Male wistar albino rats	2018	[42]
Buspirone	Span 40 Cholesterol	Anxiety disorders	To improve bioavailability	87.7	-	-	2018	[43]
Pentamidine	Tween 20 Cholesterol Dicetyl phosphate	Alzheimer's disease	To improve pentamidine permeability and reduce the side effects	10.96	-	-	2018	[44]
Olanzapine	Cholesterol/ Span 60 (1:4)	Schizophrenia	To improve brain targeting	95	-	Male white albino rats	2019	[45]

Interestingly, the intranasal route for the administration of antipsychotics may be an appealing alternative route of administration. The advantage of the nasal route in comparison with other routes is its capacity to directly deliver drugs to the brain *via* the olfactory region and its ability to avoid the first-pass effect to improve bioavailability and reduce adverse events. In an earlier study, olanzapine (OL)-loaded surface-modified niosomes were elaborated for improving permeability to the brain *via* the nasal route, which proved to have improved characteristics and effectiveness over the pharmaceutical solution. Functionalization of niosomal surfaces proved to increase drug penetration even further, and the nasal delivery of the produced vesicles successfully transported OL into the brain [26, 45]. Niosomes were also reported to be absorbed by the olfactory epithelium in the nasal mucosa and then distributed to the brain [46]. Bromocriptine-loaded niosomal formulation for the intranasal route in rats displayed greater brain targeting and enhanced efficiency over the oral route which decrease its dose by $1/10^{th}$, thus almost diminishing the risk of toxicity [47, 48]. Another research was designed to formulate non-ionic surfactant vesicles loaded with Bromocriptine Mesylate (BCM) to enhance brain absorption *via* the nose-to-brain route. Compared to the BCM pharmaceutical solution, penetration through nasal mucosa was found to be elevated up to 6.4 times over the conventional drug solution in a 24-hour *ex vivo* study [36]. Depending on the theory that the low blood level of folates is the main cause of depression in Alzheimer's disease (AD), many studies investigated and studied possible facilitated delivery of folic acid, since folic acid is a water-soluble vitamin with significant difficulty in bypassing the BBB. An earlier study reported that prepared folic acid-loaded niosomes (with 1: 1 molar ratio Span 60: Cholesterol

composition) exhibited better entrapment efficiency (69.42 %) and better *in vitro* cumulative drug release (64.2 %) after 12 h [2].

On the other hand, many niosomal enhancement approaches should be carefully studied. For example, the PEGylation of lipidic nanocarriers is known to prolong their half-life after being administrated. However, the utilization of such an approach was limited because the lipid bilayer can maximally tolerate about 5 to 6% mol of PEGylation. Above this percentage, some stability complications like the lysis of lipid-based vesicles at high PEG concentrations can potentially encounter [49]. In a previous study, drug-free and pentamidine-loaded chitosan-glutamate (CG) coated niosomes were formulated and characterized for delivery to the brain *via* the intranasal route. Entrapment efficacy was found to be 10.96%, which is significantly high and can be considered valuable to attain therapeutic effectiveness. Moreover, PEGylation of the niosomal surface enhanced the mucoadhesive properties. Furthermore, niosomal surface functionalization *via* CG was found to be of great influence due to its penetration-enhancing ability [44].

Limitations (challenges) and how to defeat (future directions)

Several studies reported that there are some limitations in using niosomes in a wide-scale drug delivery system, including aggregation, fusion, and leakage, possible chemical reactions with the encapsulated drug, and other factors related to the proper stability of niosomes. In other words, niosomes' physical stability is one of the main barriers challenging their use as prospective drug delivery vehicles [50]. However, it is required to face such limitations as challenges that can be defeated via various approaches. Therefore, the focus of our future directions in niosome research should be on investigating various methods for enhancing niosome physical stability. Some examples of stability challenges and how to investigate and defeat them were mentioned in the next paragraphs.

The property of aggregation can be encountered in many types of niosomes which need much focus while designing and formulating any type of niosomes. In many studies, it was investigated by applying the sedimentation behavior and stability tests, and found that using some surfactants like Span 60 and Pluronic P85 in the mixed noisome formulation may potentially show excellent stability and drug release [51]. Pluronics are polymers composed of triblock (PEO-PPO-PEO) of polyethylene oxide (PEO, which is water soluble) and propylene oxide (PPO, which is water insoluble), and they are used as drug carriers because of their assembly property which behaved as drug container. In addition, the cholesterol and surfactant ratio has a significant influence on the stability of niosomes [50].

The chemical reaction of the encapsulated drug is another important issue needed to be also considered. It has been found that the hydration media and the molecular weight of loaded drugs are important determinants of the chemical reaction of the encapsulated medicine. The efficiency of encapsulation is increased with increasing vesicle size and the composition of hydrated media will affect the bilayer packing and physical properties of niosomes [52]. Generally, the hydration media that is used in the preparation of niosomes is phosphate buffer, but the desired pH depends on the encapsulated drug solubility [53]. Both the quick leakage of the medication from the niosomes and the burst release effect associated with niosomes have been reduced by dispersing niosomes in a viscous gel. Using this method, the niosomes' physical stability might be increased. In addition to the previous method, lyophilization (freeze-drying) or spray-drying the final niosomal liquid dispersion to a powder form improves the physical stability of the vesicles and significantly lowers the oxidative instability of oxidizable drug molecules by reducing the production of hydroxyl-free radicals [50].

The aforementioned techniques might be useful for creating stable niosomes, so studying how each one affects the niosomes' physical stability could be a promising area/future direction for further potential investigation.

CONCLUSION

Niosomal-based drug delivery systems for the nasal route, as nano-sized vesicular nanocarriers, have a diversity of pros and are well-favored delivery platforms over other lipidic-based delivery systems. With understanding the different approaches to nasal delivery, and selecting the appropriate compositions, these nonionic surfactant vesicular carriers are promising means for significantly controlling the drug release profile, targeting exact body tissues or cells, minimizing the systemic side effects and toxicity, and enhancing the efficacy and bio-distribution profile in the body. Niosomes facilitate drug delivery *via* the nasal route (mainly *via* the olfactory region) by increasing the solubility of low water-soluble-loaded molecules and improving drug transmission through the biological membranes, which leads to bioavailability enhancement. On the other hand, the expected toxicity from niosomes (according to the selected ingredients for formulation and their composition) must be well-thought-out. Additional research studies are expected to be conducted concerning the synthesis/production of non-toxic nonionic surfactants with recognized metabolic mechanisms.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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