Available online on 15.06.2024 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Full Text Article

Review Article

A Comprehensive Review on Niosomes in Drug Delivery and Recent Advancements

Charlisar Teron *, Abhranil Bhuyan, Prasurjya Saikia, Sunmon Raj Dutta, Himanshu Gogoi, Shivam Rongpi

Faculty of Pharmaceutical Science, Assam down town University, Sankar Madhab Path, Gandhi Nagar, Panikhaiti, Guwahati, Assam, India, PIN – 781026

Article Info:

Article History:

Received 28 March 2024
Reviewed 07 May 2024
Accepted 25 May 2024
Published 15 June 2024

Cite this article as:

Teron C, Bhuyan A, Saikia P, Dutta SR, Gogoi H, Rongpi S, A Comprehensive Review on Niosomes in Drug Delivery and Recent Advancements, Journal of Drug Delivery and Therapeutics. 2024; 14(6):262-273

DOI: http://dx.doi.org/10.22270/jddt.v14i6.6651

*Address for Correspondence:

Charlisar Teron, Assam down town University, Sankar Madhab Path, Gandhi Nagar, Panikhaiti, Guwahati, Assam, India, PIN – 781026

Abstract

The recent emphasis on nanocarrier development for drug delivery stems from the need to target specific diseased areas while sparing healthy tissues. Effective and safe drug administration has long posed challenges in medicine. Over the past decade, the emergence of vesicles as a means to enhance drug delivery has captivated researchers in the field of drug delivery systems. Among vesicular systems, niosomes have gained attention due to their nonionic features. Unlike liposomes, niosomes offer superior stability, making them a preferred choice. Non-ionic in nature niosomes offer unique advantages in drug delivery providing a versatile platform for encapsulating various drugs to enhance bioavailability and ensure controlled release. Understanding preparation techniques enables tailored applications from oral to transdermal delivery. Characterization methods such as morphology and particles size are pivotal in ensuring the stability and effectiveness of niosomes. Applications span cancer therapy, diagnostic imaging, and vaccination adjuvants, showcasing niosomes versatility. Ongoing research reflects dynamic efforts to enhance capabilities, emphasizing their pivotal role in evolving drug delivery systems. In this comprehensive review, we aim to encapsulate fundamental aspects of niosomes, encompassing diverse preparation methods, various niosomal types, methods for characterization and the advancements witnessed in niosomal research over the past decade, drawing insights from a literature review.

Keywords: Niosomes, Drug delivery, Nanocarrier, Vesicles, Nanomedicines

1. INTRODUCTION:

The rapid advancement of nanotechnology has revolutionized the study of medication delivery and disease treatment. This progress has led to the development of numerous nanocarriers formed by shaping nanoparticles into vesicles, facilitating the targeted transport of medications and therapeutic agents to specific areas within the body. Researchers have placed significant emphasis on achieving controlled and precise drug delivery, resulting in the creation of multifunctional nanoparticles capable of transporting a wide range of medications. These nanocarriers offer several benefits, including protection of drugs from degradation, controlled release, and the ability to direct drug molecules to specific locations in the body, particularly in targeted delivery systems.[1,2]

Currently, the goal is to combine biotechnology with nanotechnology by promoting a green chemistry-driven and environmentally benign approach to nanomaterial manufacture, characterization, and application.[3] Examples include gold and silver nanoparticles, nanovesicle systems, solid lipid nanoparticles, nanostructured lipid carriers, nano-micelles, dendrimers, polymeric nanoparticles, mesoporous silica nanoparticles, and other similar entities.[4,5,6] Furthermore, advances in biotechnology, nanotechnology, pharmaceutical science, artificial intelligence, and genetic engineering may be used to healthcare systems, a field known as nanomedicine.[7,8,9,10]

Researchers are focusing on the creation of new nano-systems that control the release of diverse physiologically active substances, as well as the manufacturing of nanomaterials. Nanocarriers and novel pharmacological formulations are critical in increasing the bioavailability of medicines or natural chemicals by precisely targeting targeted areas. Vesicular systems make it easier to transport payloads to precise places, which improve overall efficiency.[10,11]

Synthetic drug delivery technologies include liposomes, micelles, dendrimers, nanocapsules, nanosponges and peptide-based nanoparticles. Among these liposomes are the oldest and most thoroughly explored.[12] Liposomes and niosomes exhibit differences with liposomes characterized by a concentric bilayer of phospholipids while niosomes consist of nonionic surfactants with or without cholesterol. Although both are commonly utilized for drug delivery, liposomes present significant drawbacks including susceptibility to degradation through hydrolysis or oxidation, sedimentation, drug leakage and aggregation or fusion during storage. The therapeutic application of liposomes faces challenges such as sterilization the need for large-scale production for optimal physicochemical stability and the cost and variability of phospholipid purity. In contrast, niosomes address many stability issues and shortcomings associated with liposomes making them suitable for industrial production and cost-effective manufacturing.[10,13,14,15,16,56]

As a consequence of these advancements, researchers are currently exploring niosomes, or non-ionic surfactant vesicles, as a potential alternative to liposomes. Various types of surfactants have shown the capacity to form vesicles capable of encapsulating both hydrophilic and hydrophobic solute particles. Niosomes, resembling liposomes in their bilayer structure and physical characteristics, boast enhanced stability due to the components employed in their production. These nano-sized structures typically range from 10nm to 100nm in particle size.[16,17]

Initially utilized in the beauty industry, niosomes research has expanded into potential applications in medication delivery. The first patent for niosomes formulations was attributed to L'Oreal in 1975. These vesicles, resembling liposomes, consist of hydrated blends of cholesterol, charge-inducing agents, and nonionic surfactants like monoalkyl or dialkyl polyoxyethylene ether. Niosomes formulations offer versatility and can be administered through various routes, including transdermal, parenteral, oral, ocular, and subcutaneous routes.[18,19]

In targeted drug delivery, a diverse range of carriers such as immunoglobulin, plasma protein, microspheres, synthetic polymers, erythrocytes, and liposomes are employed. Nevertheless, liposomes and niosomes remain widely acknowledged and established as effective drug delivery systems.[20]

While our primary emphasis in this review centers on conventional niosomes, it is imperative to recognize the substantial advantage offered by multifunctionality.[10] The incorporation of specific structural elements like functional groups, segments, and nanoparticles, facilitated by diverse modification techniques, paves the way for the creation of multifunctional niosomes. This growing interest has spawned the development of numerous applications for drug and natural molecule-loaded niosomes as a nanocarrier. These applications leverage the inherent benefits of niosomes, encompassing biodegradability, biocompatibility, non-immunogenicity, improved bioavailability, controlled size, stability, higher encapsulation efficiency for drugs/natural molecules and an accelerated release rate. This review articles explores the composition, formulation procedures, and recent strides in utilizing niosomes as versatile carriers for drug delivery.

2. STRUCTURES AND COMPOSTION OF NIOSOMES:

Niosomes are vesicular structures composed of nonionic surfactants, resembling liposomes but distinguished by their use of nonionic surfactants instead of phospholipids, the primary components of liposomes.[16,21] Niosomes manifest as spherical structures consisting of small lamellar arrangements, which can be either unilamellar or multilamellar. The bilayer formation in niosomes is created by combining non-ionic surfactants, sometimes with cholesterol, and a charge-inducing agent. These niosomes comprise a diverse array of surfactants combined in different compositions and molar ratios.[21]

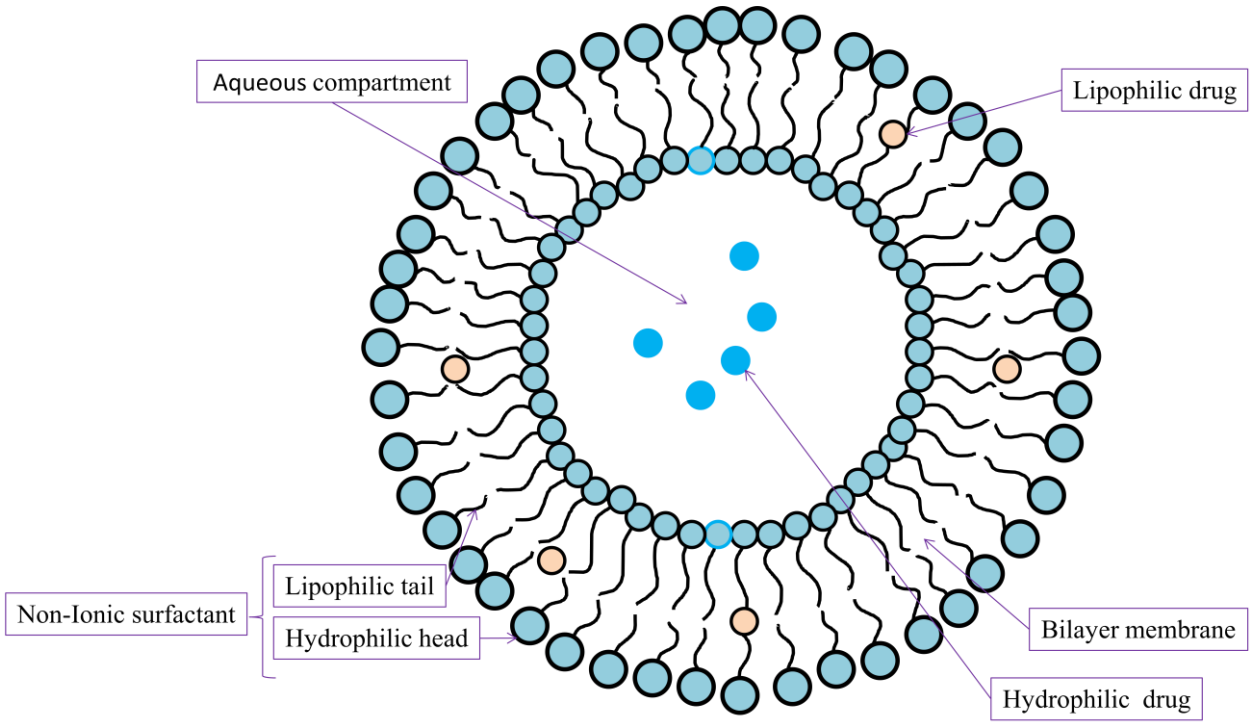

Figure 1: Structure of niosomes[17]

2.1 Non-ionic surfactant: Niosomes, vesicles made from non-ionic surfactants, form via the self-assembly of non-ionic amphiphiles in aqueous solutions, generating enclosed bilayer structures.[22] Nonionic surfactants are the preferred surface-active agents in vesicle preparation due to their superior stability, compatibility and lower toxicity in comparison to anionic, amphoteric or cationic counterparts. These versatile surfactants function as solubilizing agents, wetting agents, emulsifiers and enhancers of permeability. Nonionic surfactants possess both polar and non-polar segments, displaying high interfacial activity.[23] The attainment of thermodynamic stability involves the curvature of each bilayer which create continuous membranes that form vesicles and ultimately eliminating exposure of the hydrocarbon or water interface.[26]

2.2 Cholesterol: Cholesterol possesses the unique capability to enhance lipid organization within fluid membranes while maintaining their fluidity and facilitating diffusion rates. It contributes mechanical stability and establishes low permeability barriers within lipid membranes. A single cholesterol molecule can span nearly half of a bilayer, playing

a crucial role in regulating lipid chain order. The inclusion of cholesterol significantly increases the ordering of lipid molecules in the membrane structure.[24] Cholesterol influences membrane permeability, stiffness, entrapment efficiency, ease of rehydration of freeze-dried niosomes, stability, storage duration, and potential toxicity. When combined with low HLB surfactants, cholesterol enhances vesicle stability, whereas an HLB value exceeding 6 facilitates the formation of bilayer vesicles. Additionally, the addition of cholesterol elevates the viscosity and subsequently augments the stiffness of the preparation.[25]

2.3 Charge molecule: Some charged molecules are introduced to niosomes to strengthen their stability by electrostatic repulsion, which inhibits coalescence. These charged motes are substantially employed to inhibit niosomes aggregation.[26] Certain charged compounds are incorporated into niosomes to enhance their stability through electrostatic repulsion, thereby preventing coalescence. These compounds elevate surface charge density, effectively averting vesicle aggregation. Among the commonly used negatively charged substances in niosomes production are dicetyl phosphate and phosphatidic acid. Typically, niosomes formulations include 2.5-5 mol% of the charged molecule. However, augmenting the quantity of charged molecules can hinder the formation of niosomes.[2,3]

2.4 Types of Niosomes:

According to the nature of lamellarity:

1. Small uni-lamellar vesicles (SUV): 0.025-0.05µm or 25-50nm.[20]
2. Multilamellar vesicles (MLV): 0.5-10 µm
3. Large unilamellar vesicles (LUV): 100nm.

According to the size:

1. Smaller niosomes: 100 nm - 200 nm
2. Larger niosomes: 800 nm – 900 nm
3. Bigger niosomes: 2 µm – 4 µm

3. EXISTING ADVANCEMENT OF NIOSOMES AS A TOOL:

Rather than solely seeking new medications, the current research and development strategy prioritizes the enhancement of drug delivery methods that enable established pharmaceuticals to function optimally in therapy. The primary goal of any medication delivery approach should always be to maximize therapeutic efficacy while minimizing adverse effects.[27] The application that comes with using niosomes as a targeted medication delivery method is now being addressed by a number of ways. Among the noteworthy developments are:

3.1 Anticancer drug delivery: The utilization of niosomes facilitates the precise delivery of anticancer medications. This targeting can occur through passive means (niosomes deposition within the tumor due to unique properties of tumor cells not found in normal cells), physical mechanisms (delivery reliant on specific environmental conditions like pH or magnetic fields) or active methods (direct uptake of niosomes by the tumor cell). Active targeting can be achieved by modifying the surface properties or by attaching ligand to the niosomes. To facilitate ligand attachment, a combination of cholesterol, polyethylene glycol (PEG) and the ligand may be used or the ligand can be linked to cholesterol or the end of the PEG chain.[28] An experiment done by kulkarni, et al.[29] Niosomes loaded with Tamoxifen and Doxorubicin were formulated for combined breast cancer therapy, utilizing statistical optimization through the Box-Behnken experimental design. Atomic force microscopy demonstrated a spherical morphology of the niosomes with Tamoxifen and Doxorubicin exhibiting entrapment efficiencies of 74.3% and 72.7%, respectively.[29]

3.2 Ophthalmic drug delivery: Due to physiological barriers in the eyes such as the retinal pigment epithelium barrier properties and the endothelium lining the inner side of retinal blood vessels, traditional ocular drug delivery methods like eye drops, ointments and suspensions often fail to achieve high bioavailability. A significant portion of the dosage is also lost through drainage into the nasolacrimal ducts. Research indicates that niosomes can help overcome some of these challenges and serve as suitable carriers for ocular administration. Firstly, nano-sized niosomes show resistance to drainage caused by reflex tearing and blinking. Additionally, compared to other carriers, niosomes exhibit better retention on the ocular surface.[30] Researchers Gugleva, et al.[31] found that niosomal formulation with Span 60 and cholesterol in a molar ratio of 6:4, resulting in a monomodal size distribution, slower release rate and no significant change in the amount of encapsulated doxycycline hyclate formulation. Niosomal preparations were non-irritating and well-tolerated by the eye, as proven by the Draize test.[31]

3.3 Dermal and transdermal drug delivery: Dermal drug administration offers localized high concentrations at the site of action, reducing systemic absorption and subsequently lowering adverse effects. The transdermal route provides several advantages, including being a noninvasive technique, bypassing first-pass hepatic metabolism, thereby increasing drug bioavailability, circumventing gastrointestinal degradation, maintaining steady-state plasma concentration, enabling self-administration and enhancing patient compliance. However, the transdermal method faces limitations due to the stratum corneum, a major barrier to drug permeation which restricts the penetration of certain medications through the skin. Niosomal drug delivery systems have emerged as an alternative to conventional physical or chemical methods for overcoming skin barriers. This approach advantage lies in avoiding first-pass metabolism but it suffers from slow drug absorption through the skin.[27,32] Researchers conduct an experiment by Tran, et al.[33] that niosomes containing diclofenac produced through ethanol injection, exhibited a spherical shape with a small diameter of approximately 100 nm and a limited distribution. *Ex-vivo* and i*n-vivo* studies indicated that the diclofenac niosomes hydrogel enhanced both the quantity and speed of diclofenac transport through the skin along with its concentration in the muscle, surpassing that of the commercial medication. These results underscore the potential application of diclofenac niosomes in transdermal drug administration.[33]

3.4 Oral drug delivery: Drug are administered through this method to address challenges associated with issues such as susceptibility to stomach acids and digestive enzymes, inadequate absorption and fluctuating medication bioavailability. Consequently, novel drug delivery mechanisms such as niosomes have been employed to enhance drug bioavailability. In a separate study, niosomes were found to improve the weak and inconsistent oral bioavailability of Cefdinir, categorized as a class IV medicine in the Biopharmaceutics Classification Scheme (BCS). Recently, mixed niosomes were developed for the oral administration of Candesartan Cilexetil, serving as a model for weakly water-soluble medications in a particular investigation.[34] The research conducted by Sadeghi-Ghadi, Zaynab, et al.[35] determined that polymeric niosomes incorporating hyaluronic acid serve as a viable nanocarrier for enhancing the oral delivery of quercetin, leading to heightened pharmacological

activity. Results indicated that polymeric formulations encapsulating quercetin exhibited superior anti-inflammatory and antioxidant activity compared to quercetin simple suspensions and empty polymeric niosomes.[35]

3.5 Pulmonary drug delivery: A drug carrier can serve as a mechanism to overcome specific limitations of an existing medication, thereby enhancing the effectiveness of therapy. For various reasons, aerosolized delivery methods may be particularly advantageous for treating lung infections. Multiple studies have indicated that aerosolized niosomes could offer additional advantages in targeted drug delivery, enhance therapeutic outcomes and reduce the toxicity of certain medications. In comparison to liposomes, niosomes present an attractive colloidal carrier option due to their cost-effectiveness, improved stability and ease of storage and manufacturing. However, there remains a paucity of research focusing on the aerosolization behavior of niosomes formulations.[36] The developed formulation that conducted by Mohamad Saimi, Norfatin Izzatie, et al.[37] exhibits favorable attributes for controlled drug release, ensuring safety and demonstrating an inhibitory effect on cell proliferation in A549 lung cancer cells. These experiments suggest that the enhanced NGC formulation holds promise for cancer treatment, offering high entrapment efficiency and efficient aerosol emission.[37]

3.6 Nasal drug delivery: The nasal route for systemic medication delivery is gaining popularity as an alternative for medications with limited oral bioavailability, particularly those susceptible to degradation by gastrointestinal fluids or hepatic enzymes. Nasal administration is considered a convenient, safe and non-invasive method for drug delivery with a faster onset of action compared to other routes. Concerning nasal delivery, niosomes emerge as the preferred vesicular system due to their superior chemical and physical stability in comparison to liposomes. Additionally, their capacity to transport both lipophilic and hydrophilic drugs, non-ionic nature contributing to low toxicity, high permeability through biological membranes, and biodegradability make them an advantageous choice.[38] An experiment done by Teaima, Mahmoud H., et al.[39] found that *in-vitro* and *in-vivo* release studies revealed that the nasal in-situ gel exhibited higher relative bioavailability and prolonged release compared to oral tablets with the same dosage. The niosomal nasal thermosensitive in-situ gel proves to be a more efficient and convenient method for administering anti-emetic medications compared to oral tablets.[39]

3.7 Gene delivery: Numerous research teams worldwide are diligently working towards the development of novel, safe and effective vaccines. Sub-unit proteins or DNA derived from various species despite being potentially less effective are considered safer alternatives compared to live organism-based vaccines. Adjuvanted systems have demonstrated the ability to enhance the immunogenicity of these subunit vaccines by ensuring protection such as inhibiting antigen degradation in vivo and facilitating improved targeting of antigens to professional antigen-presenting cells.[40] Brewer and Alexander documented the initial utilization of niosomes-based antigen delivery to immunize Balb/c mice against bovine serum albumin (BSA). They concluded that niosomes might possess superior Th1 lymphocyte stimulatory properties compared to Freund's complete adjuvant, thereby acting as robust stimulants of cellular immunity.[41] A studies conducted by Carballo-Pedrares, Natalia, et al.[42] that niosomes composed of DOTMA, cholesterol and polysorbate 60 serve as effective nonviral gene delivery systems for immortalized MSCs. Unfiltered 15% DOTMA niosomes demonstrate DNA protection and complexation, achieving transfection values similar to Lipofectamine but with lower cytotoxicity in iMSCs.[42]

3.8 Drug delivery: An essential attribute of niosomes is their ability to facilitate targeted drug delivery. Niosomes offer the potential to target medications specifically to the reticuloendothelial system (RES) which demonstrates a preference for absorbing niosomes vesicles. Moreover, aside from the RES, niosomes hold promise for targeting medications to various tissues within the body. To achieve organ-specific targeting, niosomes can be modified by attaching a carrier system such as antibodies given their rapid binding to the lipid surface of the niosomes.[43] A researcher Rathee, Jyoti, et al.[44] conducted an experiment that the integration of Toll-Like Receptor 7 agonist (BBIQ) and IDO inhibitor (D-1MT) into niosomes systems was successfully accomplished. Stable and biocompatible niosomes were produced using the sonication method with the Triton X-100/PEG 2000/water/Span 80 system. The drug-loaded niosomes exhibited enhanced stability and compatibility, suggesting an extended shelf life. Solubility tests revealed increased drug solubility in the niosomes formulations.[44]

3.9 Immunological application: Niosomes are being employed in immune response research owing to their immunological selectivity, low toxicity and enhanced stability. Non-ionic surfactant vesicles have demonstrated considerable potential as adjuvants following the parenteral administration of diverse antigens and peptides. Leveraging their immunological selectivity, niosomes with lower toxicity and increased stability serve as a valuable tool for investigating immune responses triggered by antigens. In parenteral delivery, non-ionic surfactant vesicles have exhibited promising potential to act as antibacterial agents in conjunction with various antigens and peptides.[27,43] A research conducted by Fallarini, Silvia, et al.[45] found that glycosylated niosomes have the potential to induce macrophage differentiation towards an M1 phenotype. This phenotype is crucial for presenting antigens to responsive T cells in a proinflammatory environment, essential for generating an effective anticancer immune response. This demonstrated the capability of niosomes to deliver Tumor Associated Antigens (TACAs), eliciting an immunological response in vitro without requiring external adjuvants. It also confirmed the involvement of TnThr mimics in protective immune stimulation. This approach proves to be ideal for the development of synthetic tumor vaccines.[45]

3.10 Diagnostic imaging: Theranostic nano-platforms have gained considerable attention due to their extensive potential in therapy and diagnostics using niosomes, stemming from their remarkable success and advancements in producing unique nanostructures. Consequently, theranostics has emerged as a prevalent method for tailored therapy. Moreover, conventional therapy approaches impose limitations on the use of chemotherapeutic drugs tailored for individual patients, necessitating more efficient drug carrier systems by designing drug formulations in a specific manner. The increasing emphasis on developing innovative and more effective therapeutic approaches in combating cancer has unveiled numerous opportunities, mandating a multidisciplinary approach. To keep pace with this trend, researchers have been focusing on multifunctional nanocarriers that enable multimodal treatment, diagnostics, and their integration.[46] In this method, InP/ZnS quantum dots and CA-MIONs were incorporated into a niosomes structure by the researchers Ag Seleci, Didem, et al.[47] resulting in fluorescent and magnetic properties with low cytotoxicity. CA-MIONs enabled MR imaging and magnetic targeting. PEGNIO/QDs/MIONs/Tf efficiently bound to Tf-positive glioma cells, showing a negative-contrast enhancement in MRI

and increased fluorescence intensity. These findings suggest the promising potential of multifunctional niosomes for targeted imaging of glioblastoma.[47]

Table 1: shows the application of niosomes in the field of therapeutic drug delivery using various methods for the development and efficacy of drug:

Table 1: Application of niosomes and method

Drugs	Application	Method	References
Doxirubicin	Anticancer drug delivery	Sonication method	54
Pilocarpine hydrochloride	Ophthalmic drug delivery	Sonication method	55
Ammonium glycyrrhiinate	Transdermal drug delivery	Film hydration method	56
Nefopam	Nasal drug delivery	Film hydration method	58
Insulin	Peptide drug delivery	Film hydration method	59
Ketoprofen	Drug delivery	Film hydration method	60
Ag85B-ESAT-6	Immunological response	Dehydration–rehydration method	61
Gadobenate	Diagnostic imaging	Hand shaking/Ether injection method	62,63
Zanamivir	Pulmonary drug delivery	Thin layer hydration	57
Paclitaxel	Anticancer/oral drug delivery	Thin layer hydration	64

4. RECENT STUDIES AND PROGRESS IN NIOSOMES:

Recent discoveries and advances in the field of niosomes have piqued the interest of those involved in pharmaceutical research. Niosomes which are nano-sized vesicular structures made up of non-ionic surfactants and cholesterol have emerged as a focus for researchers looking for novel drug delivery options. This emerging field of study seeks to solve obstacles inherent in existing medication delivery systems by investigating the multifarious capabilities of niosomes. Recent research has focused on improving the composition, production methods and uses of niosomes demonstrating their flexibility and adaptability across several therapeutic areas. This introduction lays the groundwork for an examination of the most recent advances and achievements in niosomes research emphasizing their increasing significance in revolutionizing drug transport, controlled release mechanisms and therapeutic effectiveness.[48] As the scientific community works to understand the complexity of niosomes, these nanostructures have the potential to reshape pharmaceutical methods and contribute to the development of more effective and tailored therapeutic treatments.

Drug Delivery in Neurodegenerative Diseases - The recent progress in nanotechnology has given rise to cutting-edge and remarkably effective drug delivery systems (DDS), customizable for transporting drug molecules and therapeutic substances across the blood-brain barrier (BBB). The transfer of drugs from the nasal cavity to the brain can take place directly through olfactory and trigeminal neural pathways or indirectly through systemic absorption. In response to the latest advancements and achievements in the field of nanomedicine, novel nano-sized carriers have been developed.[49] A new studies conducted by the Kulkarni et al.[50] that Rivastigmine (RIV) functions by inhibiting the enzymes AChE and BChE, thereby diminishing the release of acetylcholine (ACh) and butyrylcholine (BCh) from cholinergic neurons. This reduction in ACh degradation has demonstrated clinically significant benefits. N-Acetyl cysteine (NAC), recognized as a neuroprotective drug, has been observed to maintain the neuronal tissue environment, potentially fostering growth post-injury. NAC enhances glutathione levels and diminishes reactive oxygen species, mitigating inflammation-related neuronal damage implicated in conditions such as Alzheimer's and other dementias.[50]

Drug delivery as Antibacterial – Recently an investigation on antibacterial that drug which is resistance can be made effective and targeted for the specific site by changing is formuation like as niosomes. This investigation delves into the physicochemical characteristics of non-ionic surfactants employed in the formulation of niosomal suspension. Spans and Tweens represent two non-ionic surfactants, providing diverse advantages such as enhanced stability, broad compatibility, and formulation adaptability. The robust hydrophobic nature of Tween 60 surfactant prevents the formation of a rigid membrane during niosomal formulation. By combining Span 60, which exhibits heightened hydrophobicity, with cholesterol and surfactants in a 1:1 M ratio, condensed niosomal films can be generated.[51] A study conducted on P. aeruginosa, a prevalent nosocomial organism, exhibits resistance to medications and poses a threat of life-threatening infections, especially in individuals with compromised immune systems. Consequently, ongoing research is focused on identifying methods to overcome and/or diminish this resistance. The findings of this study indicate that encapsulating tobramycin in niosomes enhances antibacterial effectiveness and mitigates drug resistance.[52] Some researcher Kashef, Mona T., et al.[53] investigated on bio film that the anti-biofilm efficacy of ciprofloxacin-loaded niosomes was evaluated against free ciprofloxacin using MBICs and MBECs. In 14 out of 24 tested isolates, ciprofloxacin-loaded niosomes demonstrated a 2-4 times reduction in MBIC compared to free ciprofloxacin.[53] Making it more effective against multi drug resistant bacteria.

5. METHOD FOR THE PREPARATION OF NIOSOMES:

Niosomes preparation processes may vary but they all essentially entail hydrating a lipid film created by the thin-film hydration method, which may also incorporate additional methods such reverse-phase evaporation and other various techniques. The ensuing niosomes have distinct physicochemical characteristics, such as size, charge, and membrane fluidity, which may be adjusted in accordance with the demands of the medication and the intended delivery location. All things considered, niosomes present a potential

method of drug administration; their adaptability and flexibility make them a desirable choice for a range of pharmaceutical applications. The various techniques or processes used for the preparation of niosomes are given below: -

5.1 Thin film hydration: The widely employed thin-film hydration method for niosomes production includes dissolving surfactants and cholesterol in an organic solvent within a round-bottomed flask using a rotary evaporator, followed by solvent evaporation to form a dried film at the flask base. Upon introducing an aqueous medium (such as water or PBS) to the film at a temperature above the surfactant's transition temperature, continuous moderate agitation induces the formation of multilamellar vesicles (MLVs), which can be subjected to sonication for unilamellar vesicle production. Drugs intended for encapsulation are dissolved in either the aqueous or organic phases based on their solubility. Typically, sonication is employed subsequently to ensure a uniform size distribution of niosomes.[54] This frequently employed thin-film hydration method (TFH) involves dissolving surfactants and cholesterol in an organic solvent, evaporating the solvent to create a thin film on the inner wall of the flask. Adding an aqueous solution of medication hydrates the dry film above the surfactant transition temperature (Tc), leading to the generation of MLVs during the hydration process. TFH has been extensively used in synthesizing niosomes entrapping various drugs.[18]

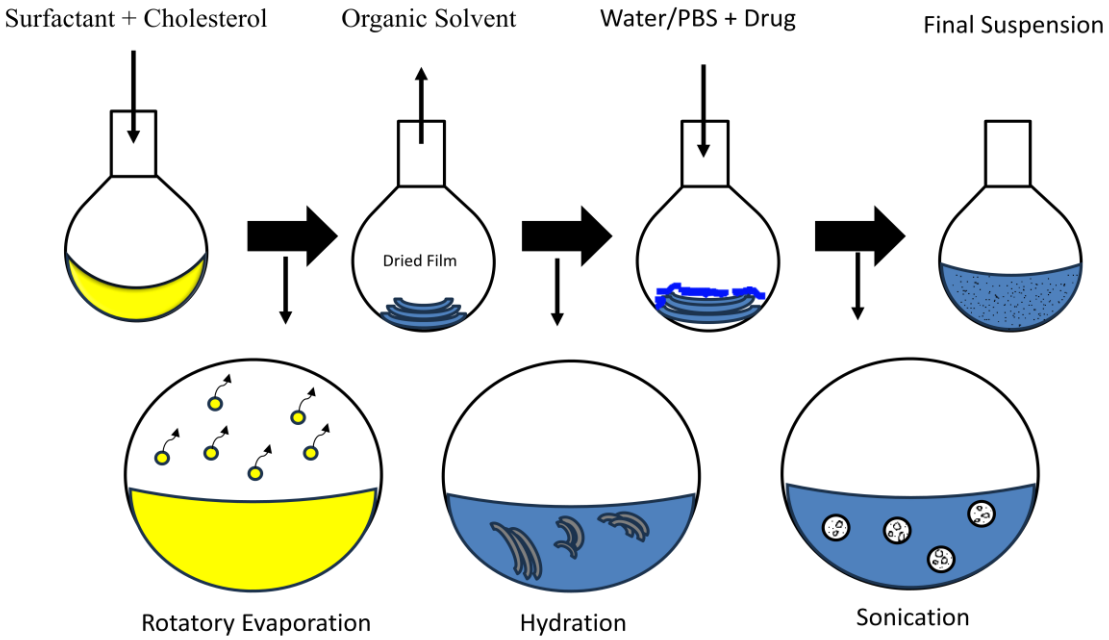

Figure 2: Thin film hydration[18]

5.2 Reverse-phase evaporation method: Initially described by Szoka and Papahadjopoulos, the reverse phase evaporation method allows for control over niosomes size, albeit with challenges related to the drug solubility in ether and the complete removal of ether from the final formulation. The pivotal step involves solvent evaporation from the emulsion. To create the emulsion, cholesterol and surfactant are dissolved in a 1:1 combination of ether and chloroform, followed by the addition of an aqueous phase containing the medication. Sonication of the resulting phases at 4-5°C is performed, and buffer addition creates a transparent gel. The organic phase is then evaporated at 40-60°C and low pressure. The resulting viscous niosome suspension is diluted with PBS and subjected to heating in a water bath at 60°C for 10 minutes, completing the hydration process until full water evaporation. This final step leads to the formation of Large Unilamellar Vesicles (LUVs) as the organic solvent evaporates.[34,43]

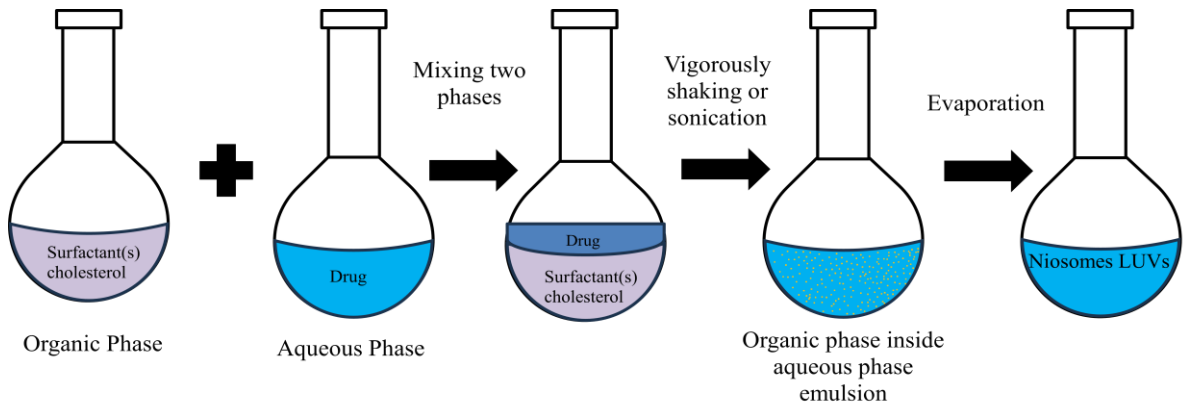

Figure 3: Reverse phase evaporation[18]

5.3 **Ether injection method:** The method in involves dissolving surfactants with additives in diethyl ether and slowly injecting them through a needle into an aqueous drug solution maintained at a constant temperature. Employing a rotary evaporator, the organic solvent is extracted, leading to the formation of single-layered vesicles during the vaporization process. Simultaneously, through the ether injection technique, niosomes components dissolved in ether are gradually injected using a 14-gauge needle at a rate of approximately 0.25 ml/min into a heated aqueous phase held at 60°C. The gradual evaporation of the solvent likely contributes to the production of larger unilamellar vesicles by establishing an ether gradient extending towards the aqueous-non aqueous interface, facilitating the formation of the bilayer structure. However, a notable challenge with this method is the effective removal of trace amounts of ether from the vesicle suspension.[2,67]

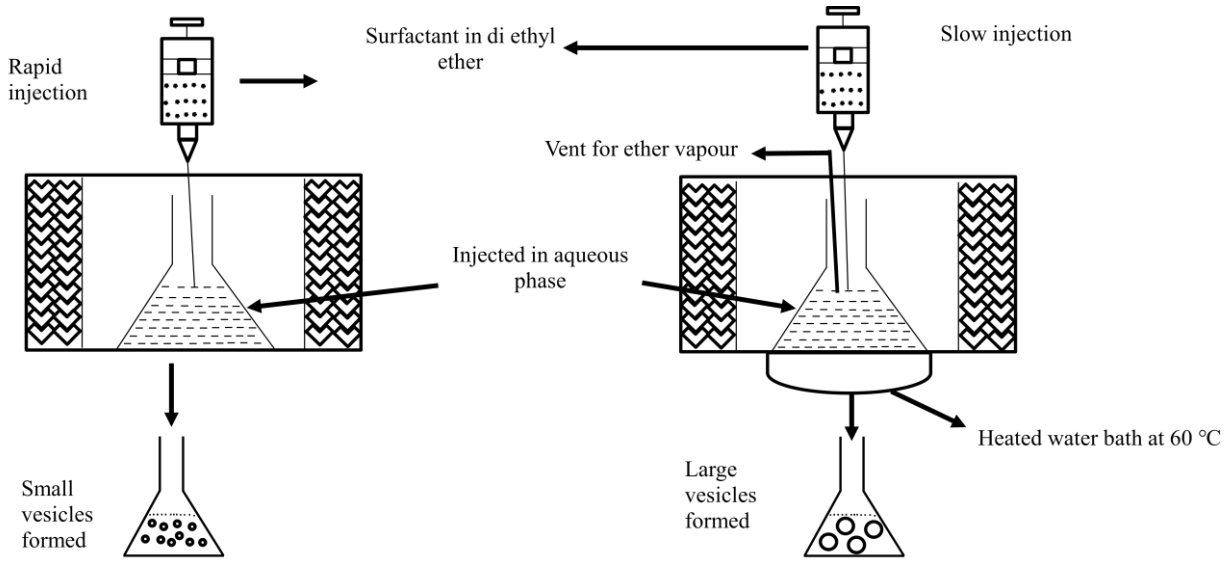

Figure 4: Ether injection method[67]

5.4 **Emulsion method:** The procedure involves dissolving surfactant and medication in diethyl ether and gently introducing this mixture into an aqueous phase, subsequently heating it above the boiling point of the organic solvent. This method yields Large Unilamellar Vesicles (LUVs), which can be further treated to reduce their size if necessary. Additionally, an oil-in-water (o/w) emulsion is created by combining an organic solution containing surfactant and cholesterol with an aqueous solution containing the medication. Subsequently, the organic solvent is removed, resulting in the distribution of niosomes within the aqueous phase.[30,67]

5.5 **Microfluidization method:** The microfluidization method represents a recent advancement in producing vesicular particles. It involves transporting two fluidized streams of organic and aqueous phases through a specific micro-scale channel, where they swiftly interact within an interaction chamber at high speeds. The design of the interface ensures that the energy input remains concentrated at the site of niosomes formation.[68] In summary, Span 60, cholesterol, and PEG were dissolved in chloroform (organic phase), while topotecan was dissolved in the aqueous phase. These distinct phases were introduced through separate inlets and merged within the microfluidic channel, subsequently heated to 65°C. The resulting niosomes were collected from the outflow, exhibiting a drug encapsulation efficiency exceeding 37.5% and diameters ranging from 100 to 200 nm.[69]

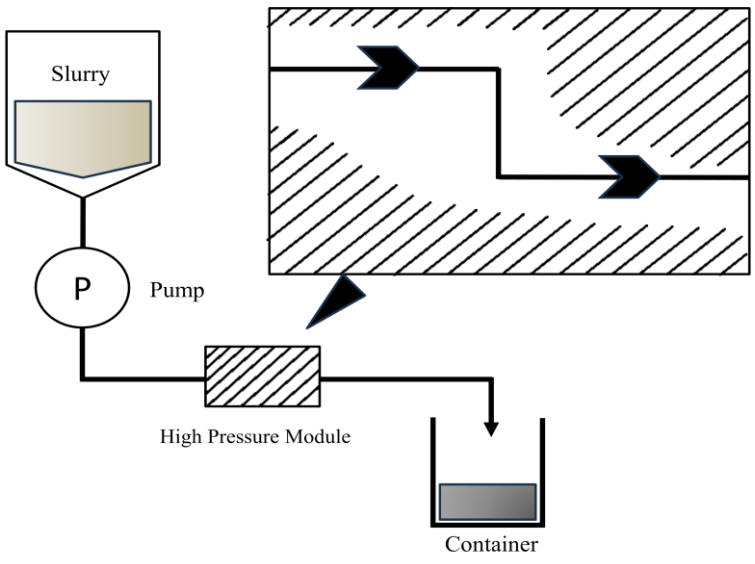

Figure 5: Microfluidization method[69]

5.6 Bubble method: The "bubble" approach enables the creation of niosomes devoid of organic solvents. This technique involves a "bubbling unit," which consists of a round-bottomed flask equipped with three necks immersed in water. The first neck contains a water-cooled reflux condenser, the second houses a thermometer, while the third is used for nitrogen delivery. The process involves homogenizing surfactant and cholesterol, which are then introduced and "bubbled" into a buffer at 70°C using this "bubbling unit."[21]

5.7 Transmembrane pH gradient method: A mixture of cholesterol and surfactant was dissolved in chloroform within a round-bottom flask. The organic solvent was subsequently eliminated using a rotary evaporator at room temperature (20 °C), leaving a thin solid coating on the flask walls. This coating was rehydrated with 300 ml of citric acid (pH 4.0), sonicated, and subjected to three consecutive freeze-thaw cycles. Upon addition of the aqueous drug solution and vortexing, the pH was adjusted to 7.0-7.2 using disodium phosphate (1 M) and heated for 10 minutes at 60 °C to yield niosomes.[70,71] The study explored niosomes of various compositions and conducted a comparative analysis with liposomes. It was observed that the freeze-thaw cycle reduced niosomes made with unsaturated surfactants, consequently impacting the niosome entrapment efficiency.[72]

5.8 Sonication method: The sonication process, as outlined by Cable, represents a widely utilized technique for vesicle production. In this method, a portion of the drug solution in buffer is added to the surfactant/cholesterol combination within a 10-ml glass vial. To generate niosomes, the mixture undergoes probe sonication at 60°C for 3 minutes using a sonicator equipped with a titanium probe. The resulting vesicles are both unilamellar and diminutive. In contrast to liposomes, niosomes typically exhibit larger sizes, measuring no less than 100 nm in diameter.[17,86]

Various methods for the preparation of niosomes with its advantages and disadvantages in table (2) shows the challenges in the preparation of niosomes:

Table 2: Method, advantages and disadvantages of Niosomes

Preparation Method	Advantages	Disadvantages	References
Thin film hydration	Easy method for laboratory research	There must be organic solvent	18
Emulsion method			1
Transmembrane pH gradient cycle of drug absorption	The Entrapment efficiency is high		75
Reverse-phase evaporation method			73
Microfluidization method	Organic solvent does not require	Only can be used in high melting point drugs	1
Bubble method			16
Sonication method			34
Ether injection method	Easy method for laboratory research		74

6. CHARACTERIZATION STUDIES OF NIOSOMES:

Niosomes characterization is critical to ensuring their quality, stability, and applicability for drug delivery applications. The physicochemical characteristics of niosomes, which are lipid-based vesicular systems made of cholesterol and non-ionic surfactants, are critical in determining how well they function as drug carriers. Niosomes characterization methods that are often employed include evaluating the morphology, size, distribution, surface charge, drug encapsulation efficiency, and drug release profile of the particles. Researchers can create more effective pharmaceutical formulations by developing a better understanding of niosomes' stability, function in biological settings, and potential for tailored drug delivery.

6.1 Stability of niosomes: Evaluating the stability of niosomes holds paramount importance in their formulation development, which is significantly influenced by diverse factors such as the preparation process, the nature of loaded medications, and the membrane-forming materials employed. Assessing the storage stability involves monitoring variations in particle size, zeta potential, shape alterations and the rate of loaded drug leakage. To simulate the conditions niosomes encounter during circulation *in-vivo*, incubating drug-loaded vesicles at 37°C in serum or subjecting them to more stringent environments become essential. An analysis of niosomes stability necessitates continuous monitoring of parameters such as diameters, zeta potential alterations, and the release rate of encapsulated drugs over specific durations.[76,77]

6.2 Morphology of niosomes: Morphology plays a pivotal role in providing insights into the shape, size and structure of various formulations. It serves as a rapid method to gain an overview of the surface morphology of the formulated product. Techniques like AFM, FESEM, and TEM are instrumental in visualizing intricate structures with precision concerning shape and size. For instance, Confocal Laser Scanning Microscopy (CLSM) facilitates the identification of hydrophobic and hydrophilic layers within niosomes by employing appropriate dyes, allowing visualization of the encapsulated medicinal components. On the other hand, Leica microscopy serves as a valuable tool to scrutinize the fundamental architecture of niosomes, including the observation of specific formations such as ring-like structures.[66,78,79]

6.3 Particle size and zeta potential: Understanding the zeta potential, which characterizes the surface charge of nanoparticles and is crucial in defining niosomes structures, is pivotal for determining particle solidity. Charged niosomes typically exhibit enhanced stability against aggregation and fusion compared to their uncharged counterparts. Laser Doppler velocimetry is utilized to measure the zeta potential, providing insights

into the electrostatic interactions between neighboring nanoparticles. Research suggests that zeta potentials exceeding or falling below 30 mV indicate adequate stability.[80,81,82] Additionally, the size of niosomes particles significantly impacts their stability and physical properties, varying in dimensions from approximately 10 nm to about 50 mm various techniques are employed to determine niosomes size, including Dynamic Light Scattering (DLS)[18] and microscopy. DLS, when transformed into Photon Correlation Spectroscopy (PCS)[1], offers rapid and non-destructive measurements with minimal particle sample concentration. It provides insights not only into average particle size but also particle size dispersion.[30] Furthermore, electron microscopy methods such as Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM) and Freeze-Fracture Replication-Electron Microscopy (FF-TEM) are utilized for comprehensive analysis of niosomes structures.[82]

6.4 Entrapment efficiency (EE): The assessment of entrapment efficiency involves the separation of un-entrapped medication through a suitable process such as centrifugation, after which the resulting solution is separated, and the liquid supernatant is collected. This collected supernatant is then properly diluted and quantified following the specific procedure outlined in the drug's monograph.[16,22,83,84] Separation of the drug remaining entrapped in niosomes is conducted through methods like dialysis, centrifugation or gel filtration as previously described. The evaluation of the entrapped drug within niosomes is determined by complete vesicles rupture, accomplished using 50% n-propanol or 0.1% Triton X-100, followed by assessing the resulting solution using the appropriate test technique designed for the drug.[26,85] Entrapment efficiency is calculated by using the formula:

$$EE = \frac{amount\ of\ entrapped\ drug}{total\ amount\ added} \times 100\%$$

The instrumentation used for the characterization of niosomes are given in the table (3):

Table 3: Instrument used for characterization of niosomes

Characterization	Instruments	Ref
Stability of niosomes	DLS (The size and zeta potential measurements are conducted at 37°C or within serum to simulate the in vivo solution)	[76, 77]
Morphology of niosomes	AFM, FESEM, TEM and CLSM	[66, 78, 79]
Particle size and zeta potential	DLS, PCS, SEM, TEM, FF-TEM	[1, 18, 30, 80, 81, 82]
Entrapment efficiency	$EE = \frac{amount\ of\ entrapped\ drug}{total\ amount\ added} \times 100\%$, UV/VIS, Fluorescene	[26, 77, 85]

7. RESULTS AND DISCUSSION:

Niosomes, a versatile drug delivery system comprising non-ionic surfactants and cholesterol are prepared through diverse methods influenced by additives, surfactant characteristics and osmotic stress resistance. They outperform liposomes with osmotic activity, chemical stability and improved drug stability. Niosomes requiring no specialized handling, provide structural flexibility and extensive applications in pharmaceuticals. Their efficacy in incorporating therapeutic agents and targeting specific sites underscores their potential for diverse applications. While resembling liposomes, niosomes offer added benefits such as versatile drug encapsulation, increased bioavailability, reduced toxicity and evasion of significant metabolism by the reticuloendothelial system (RES). The ease of handling and storage without special conditions enhances the appeal of niosomes as a drug delivery system which is a promising advancement in various therapeutic contexts.

8. CONCLUSION:

Niosomes showcase significant potential as a versatile and innovative platform within the evolving landscape of drug delivery methodologies. Researchers are actively striving to overcome challenges, refine formulations and explore novel approaches to amplify the therapeutic impact of niosomes across diverse medical applications. Global research is progressively delving into sustainable concepts and the amalgamation of sustainability with nanotechnology suggests a promising trajectory for niosomes technology in therapeutic drug delivery. The anticipation is that research in the field of niosomes will continue to expand, potentially culminating in the development of successful market formulations within the pharmaceutical industry.

Acknowledgement:

We extend our heartfelt thanks and gratitude to Faculty of Pharmaceutical Science, Assam down town University for their invaluable support and excellent education. Their dedication to fostering academic and personal growth has profoundly impacted my journey.

Authors Contribution:

All the authors have contributed equally.

Funding Source:

Nil

Conflict of Interest:

The author declares that there is no conflict of interest.

REFERENCES:

1. Marianecci C, Di Marzio L, Rinaldi F, Celia C, Paolino D, Alhaique F, Esposito S, Carafa M. Niosomes from 80s to present: the state of the art. Advances in colloid and interface science. 2014 Mar 1;205:187-206. DOI: https://doi.org/10.1016/j.cis.2013.11.018
2. Ag Seleci D, Seleci M, Walter JG, Stahl F, Scheper T. Niosomes as nanoparticular drug carriers: fundamentals and recent applications. Journal of nanomaterials. 2016 Oct;2016. DOI: https://doi.org/10.1155/2016/7372306
3. Soni RA, Rizwan MA, Singh S. Opportunities and potential of green chemistry in nanotechnology. Nanotechnology for Environmental Engineering. 2022 Sep;7(3):661-73. DOI: https://doi.org/10.1007/s41204-022-00233-5
4. Kanwar R, Rathee J, Salunke DB, Mehta SK. Green nanotechnology-driven drug delivery assemblies. ACS omega. 2019 May

22;4(5):8804-15. DOI: https://doi.org/10.1021/acsomega.9b00304

5. Malik S, Muhammad K, Waheed Y. Emerging applications of nanotechnology in healthcare and medicine. Molecules. 2023 Sep 14;28(18):6624. DOI: https://doi.org/10.3390/molecules28186624

6. Kántor I, Dreavă D, Todea A, Péter F, May Z, Biró E, Babos G, Feczkó T. Co-Entrapment of Sorafenib and Cisplatin Drugs and iRGD Tumour Homing Peptide by Poly [ε-caprolactone-co-(12-hydroxystearate)] Copolymer. Biomedicines. 2021 Dec 26;10(1):43. DOI: https://doi.org/10.3390/biomedicines10010043

7. Bayda S, Adeel M, Tuccinardi T, Cordani M, Rizzolio F. The history of nanoscience and nanotechnology: from chemical–physical applications to nanomedicine. Molecules. 2019 Dec 27;25(1):112. DOI: https://doi.org/10.3390/molecules25010112

8. Mbunge E, Muchemwa B, Batani J. Sensors and healthcare 5.0: transformative shift in virtual care through emerging digital health technologies. Global Health Journal. 2021 Dec 1;5(4):169-77. DOI: https://doi.org/10.1016/j.glohj.2021.11.008

9. Anjum S, Ishaque S, Fatima H, Farooq W, Hano C, Abbasi BH, Anjum I. Emerging applications of nanotechnology in healthcare systems: Grand challenges and perspectives. Pharmaceuticals. 2021 Jul 21;14(8):707. DOI: https://doi.org/10.3390/ph14080707

10. Liga S, Paul C, Moacă EA, Péter F. Niosomes: Composition, Formulation Techniques, and Recent Progress as Delivery Systems in Cancer Therapy. Pharmaceutics. 2024 Feb 4;16(2):223. DOI: https://doi.org/10.3390/pharmaceutics16020223

11. Prajapati SK, Maurya SD, Das MK, Tilak VK, Verma KK, Dhakar RC, Dendrimers in drug delivery, diagnosis and therapy: basics and potential applications, Journal of Drug Delivery and Therapeutics, 2016;6(1)67-92. https://doi.org/10.22270/jddt.v6i1.1190

12. Elsharkasy OM, Nordin JZ, Hagey DW, de Jong OG, Schiffelers RM, Andaloussi SE, Vader P. Extracellular vesicles as drug delivery systems: Why and how?. Advanced drug delivery reviews. 2020 Jan 1;159:332-43. DOI: https://doi.org/10.1016/j.addr.2020.04.004

13. Kauslya A, Borawake PD, Shinde JV, Chavan RS. Niosomes: a novel carrier drug delivery system. Journal of Drug Delivery and Therapeutics. 2021 Jan 15;11(1):162-70. DOI: https://doi.org/10.22270/jddt.v11i1.4479

14. Maja L, Željko K, Mateja P. Sustainable technologies for liposome preparation. The Journal of Supercritical Fluids. 2020 Nov 1;165:104984. DOI: https://doi.org/10.1016/j.supflu.2020.104984

15. Azeem A, Anwer MK, Talegaonkar S. Niosomes in sustained and targeted drug delivery: some recent advances. Journal of drug targeting. 2009 Nov 1;17(9):671-89. DOI: https://doi.org/10.3109/10611860903079454

16. Maurya SD, Prajapati S, Gupta A, Saxena G, Dhakar RC, Formulation development and evaluation of ethosome of stavudine, Int J Pharm Edu Res 2010;13(16).

17. Chandu VP, Arunachalam A, Jeganath S, Yamini K, Tharangini K, Chaitanya G. Niosomes: a novel drug delivery system. International journal of novel trends in pharmaceutical sciences. 2012 Feb;2(1):25-31.

18. Moghassemi S, Hadjizadeh A. Nano-niosomes as nanoscale drug delivery systems: an illustrated review. Journal of controlled release. 2014 Jul 10;185:22-36. DOI: https://doi.org/10.1016/j.jconrel.2014.04.015

19. Sahin NO. Niosomes as nanocarrier systems. Nanomaterials and nanosystems for biomedical applications. 2007:67-81. DOI: https://doi.org/10.1007/978-1-4020-6289-6_4

20. Umbarkar MG. Niosome as a Novel Pharmaceutical Drug Delivery: A Brief Review Highlighting Formulation, Types, Composition and Application. Indian Journal of Pharmaceutical Education & Research. 2021 Jan 2;55. DOI: https://doi.org/10.5530/ijper.55.1s.34

21. Yeo PL, Lim CL, Chye SM, Ling AP, Koh RY. Niosomes: a review of their structure, properties, methods of preparation, and medical applications. Asian Biomedicine. 2017 Aug 1;11(4):301-14. DOI: https://doi.org/10.1515/abm-2018-0002

22. Srivastava RC, Nagappa AN. Surface activity in drug action. Elsevier; 2005 Mar 1.

23. Kumar GP, Rajeshwarrao P. Nonionic surfactant vesicular systems for effective drug delivery—an overview. Acta pharmaceutica sinica B. 2011 Dec 1;1(4):208-19. DOI: https://doi.org/10.1016/j.apsb.2011.09.002

24. Mouritsen OG, Zuckermann MJ. What's so special about cholesterol?. Lipids. 2004 Nov;39(11):1101-13. DOI: https://doi.org/10.1007/s11745-004-1336-x

25. Bhardwaj P, Tripathi P, Gupta R, Pandey S. Niosomes: A review on niosomal research in the last decade. Journal of Drug Delivery Science and Technology. 2020 Apr 1;56:101581. DOI: https://doi.org/10.1016/j.jddst.2020.101581

26. Sharma A, Kumar L, Kumar P, Prasad N, Rastogi V. Niosomes: a promising approach in drug delivery systems. Journal of Drug Delivery and Therapeutics. 2019 Jul 15;9(4):635-42. DOI: https://doi.org/10.22270/jddt.v9i4.3064

27. Mishra V, Nayak P, Singh M, Sriram P, Suttee A. Niosomes: potential nanocarriers for drug delivery. J Pharm Clin Res. 2020;11(03):389-94. DOI: https://doi.org/10.25258/ijpqa.11.3.13

28. Mehta S. Anti-cancer drugs targeting using nanocarrier niosomes-a review. TMR Cancer. 2020;3(4):169-74. DOI: https://doi.org/10.12032/TMRC201800078

29. Kulkarni P, Rawtani D. Application of box-behnken design in the preparation, optimization, and in vitro evaluation of self-assembly–based tamoxifen-and doxorubicin-loaded and dual drug–loaded niosomes for combinatorial breast cancer treatment. Journal of pharmaceutical sciences. 2019 Aug 1;108(8):2643-53. DOI: https://doi.org/10.1016/j.xphs.2019.03.020

30. Chen S, Hanning S, Falconer J, Locke M, Wen J. Recent advances in non-ionic surfactant vesicles (niosomes): Fabrication, characterization, pharmaceutical and cosmetic applications. European journal of pharmaceutics and biopharmaceutics. 2019 Nov 1;144:18-39. DOI: https://doi.org/10.1016/j.ejpb.2019.08.015

31. Gugleva V, Titeva S, Rangelov S, Momekova D. Design and in vitro evaluation of doxycycline hyclate niosomes as a potential ocular delivery system. International journal of pharmaceutics. 2019 Aug 15;567:118431. DOI: https://doi.org/10.1016/j.ijpharm.2019.06.022

32. Khatoon M, Shah KU, Din FU, Shah SU, Rehman AU, Dilawar N, Khan AN. Proniosomes derived niosomes: recent advancements in drug delivery and targeting. Drug delivery. 2017 Nov 1;24(2):56-69. DOI: https://doi.org/10.1080/10717544.2017.1384520

33. Tran YT, Tran GN, Hoang AL, Vu GT. Niosomes loaded with diclofenac for transdermal administration: Physico-chemical characterization, ex vivo and in vivo skin permeation studies. Journal of applied pharmaceutical science. 2020 Dec 5;10(12):053-61. DOI: https://doi.org/10.7324/JAPS.2020.101207

34. Khoee S, Yaghoobian M. Niosomes: A novel approach in modern drug delivery systems. InNanostructures for drug delivery 2017 Jan 1 (pp. 207-237). Elsevier. DOI: https://doi.org/10.1016/B978-0-323-46143-6.00006-3

35. Sadeghi-Ghadi Z, Ebrahimnejad P, Talebpour Amiri F, Nokhodchi A. Improved oral delivery of quercetin with hyaluronic acid containing niosomes as a promising formulation. Journal of drug targeting. 2021 Feb 7;29(2):225-34. DOI: https://doi.org/10.1080/1061186X.2020.1830408

36. Moazeni E, Gilani K, Sotoudegan F, Pardakhty A, Najafabadi AR, Ghalandari R, Fazeli MR, Jamalifar H. Formulation and in vitro evaluation of ciprofloxacin containing niosomes for pulmonary delivery. Journal of microencapsulation. 2010 Nov 1;27(7):618-27. DOI: https://doi.org/10.3109/02652048.2010.506579

37. Mohamad Saimi NI, Salim N, Ahmad N, Abdulmalek E, Abdul Rahman MB. Aerosolized niosome formulation containing gemcitabine and cisplatin for lung cancer treatment: Optimization, characterization and in vitro evaluation. Pharmaceutics. 2021 Jan 5;13(1):59. DOI: https://doi.org/10.3390/pharmaceutics13010059

38. Abou-Taleb HA, Khallaf RA, Abdel-Aleem JA. Intranasal niosomes of nefopam with improved bioavailability: preparation, optimization, and in-vivo evaluation. Drug design, development and therapy. 2018 Oct 17:3501-16. DOI: https://doi.org/10.2147/DDDT.S177746

39. Teaima MH, El Mohamady AM, El-Nabarawi MA, Mohamed AI. Formulation and evaluation of niosomal vesicles containing ondansetron HCL for trans-mucosal nasal drug delivery. Drug development and industrial pharmacy. 2020 May 3;46(5):751-61. DOI: https://doi.org/10.1080/03639045.2020.1753061

40. Pardakhty A, Moazeni E. Nano-niosomes in drug, vaccine and gene delivery: a rapid overview. Nanomedicine Journal. 2013 Oct 1;1(1):1-2. DOI: https://doi.org/10.22038/NMJ.2013.697

41. Brewer JM, Alexander J. The adjuvant activity of non-ionic surfactant vesicles (niosomes) on the BALB/c humoral response to bovine serum albumin. Immunology. 1992 Apr;75(4):570.

42. Carballo-Pedrares N, Kattar A, Concheiro A, Alvarez-Lorenzo C, Rey-Rico A. Niosomes-based gene delivery systems for effective transfection of human mesenchymal stem cells. Materials Science and Engineering: C. 2021 Sep 1;128:112307. DOI: https://doi.org/10.1016/j.msec.2021.112307

43. Jain AP, Sharma P, Pandey P, Gupta R, Roshan S, Garg A, Sahu A, Jain A. Niosome a novel approach for drug delivery system: an overview. Asian J Pharm Sci Res. 2013;3(5):18-30.

44. Rathee J, Kanwar R, Kaushik D, Salunke DB, Mehta SK. Niosomes as efficient drug delivery modules for encapsulation of Toll-like receptor 7 agonists and IDO-inhibitor. Applied Surface Science. 2020 Mar 1;505:144078. DOI: https://doi.org/10.1016/j.apsusc.2019.144078

45. Fallarini S, Papi F, Licciardi F, Natali F, Lombardi G, Maestrelli F, Nativi C. Niosomes as Biocompatible Scaffolds for the Multivalent Presentation of Tumor-Associated Antigens (TACAs) to the Immune System. Bioconjugate Chemistry. 2022 Dec 15;34(1):181-92. DOI: https://doi.org/10.1021/acs.bioconjchem.2c00383

46. Demir B, Barlas FB, Gumus ZP, Unak P, Timur S. Theranostic niosomes as a promising tool for combined therapy and diagnosis:"All-in-One" Approach. ACS Applied Nano Materials. 2018 Jun 1;1(6):2827-35. DOI: https://doi.org/10.1021/acsanm.8b00468

47. Ag Seleci D, Maurer V, Barlas FB, Porsiel JC, Temel B, Ceylan E, Timur S, Stahl F, Scheper T, Garnweitner G. Transferrin-decorated niosomes with integrated InP/ZnS quantum dots and magnetic iron oxide nanoparticles: dual targeting and imaging of glioma. International journal of molecular sciences. 2021 Apr 27;22(9):4556. DOI: https://doi.org/10.3390/ijms22094556

48. Mawazi SM, Ann TJ, Widodo RT. Application of niosomes in cosmetics: a systematic review. Cosmetics. 2022 Nov 25;9(6):127. DOI: https://doi.org/10.3390/cosmetics9060127

49. Al Jayoush AR, Hassan HA, Asiri H, Jafar M, Saeed R, Harati R, Haider M. Niosomes for nose-to-brain delivery: a non-invasive versatile carrier system for drug delivery in neurodegenerative diseases. Journal of Drug Delivery Science and Technology. 2023 Sep 28:105007. DOI: https://doi.org/10.1016/j.jddst.2023.105007.

50. Kulkarni P, Rawtani D, Barot T. Design, development and in-vitro/in-vivo evaluation of intranasally delivered Rivastigmine and N-Acetyl Cysteine loaded bifunctional niosomes for applications in combinative treatment of Alzheimer's disease. European journal of pharmaceutics and biopharmaceutics. 2021 Jun 1;163:1-5. DOI: https://doi.org/10.1016/j.ejpb.2021.02.015

51. Mirzaie A, Peirovi N, Akbarzadeh I, Moghtaderi M, Heidari F, Yeganeh FE, Noorbazargan H, Mirzazadeh S, Bakhtiari R. Preparation and optimization of ciprofloxacin encapsulated niosomes: A new approach for enhanced antibacterial activity, biofilm inhibition and reduced antibiotic resistance in ciprofloxacin-resistant methicillin-resistance Staphylococcus aureus. Bioorganic chemistry. 2020 Oct 1;103:104231. DOI: https://doi.org/10.1016/j.bioorg.2020.104231

52. Hedayati Ch M, Abolhassani Targhi A, Shamsi F, Heidari F, Salehi Moghadam Z, Mirzaie A, Behdad R, Moghtaderi M, Akbarzadeh I. Niosome-encapsulated tobramycin reduced antibiotic resistance and enhanced antibacterial activity against multidrug-resistant clinical strains of Pseudomonas aeruginosa. Journal of Biomedical Materials Research Part A. 2021 Jun;109(6):966-80. DOI: https://doi.org/10.1002/jbm.a.37086

53. Kashef MT, Saleh NM, Assar NH, Ramadan MA. The antimicrobial activity of ciprofloxacin-loaded niosomes against ciprofloxacin-resistant and biofilm-forming Staphylococcus aureus. Infection and Drug Resistance. 2020 Jun 8:1619-29. DOI: https://doi.org/10.2147/IDR.S249628

54. Moammeri A, Chegeni MM, Sahrayi H, Ghafelehbashi R, Memarzadeh F, Mansouri A, Akbarzadeh I, Hejabi F, Abtahi MS, Ren Q. Current advances in niosomes applications for drug delivery and cancer treatment. Materials Today Bio. 2023 Oct 21:100837. DOI: https://doi.org/10.1016/j.mtbio.2023.100837

55. Owodeha-Ashaka K, Ilomuanya MO, Iyire A. Evaluation of sonication on stability-indicating properties of optimized pilocarpine hydrochloride-loaded niosomes in ocular drug delivery. Progress in biomaterials. 2021 Sep;10:207-20. DOI: https://doi.org/10.1007/s40204-021-00164-5

56. Junyaprasert VB, Teeranachaideekul V, Supaperm T. Effect of charged and non-ionic membrane additives on physicochemical properties and stability of niosomes. AAPS pharmscitech. 2008 Sep;9:851-9. DOI: https://doi.org/10.1208/s12249-008-9121-1

57. Kulkarni AS, Jadhav AN, Babar CV, Patil SR, Mirajkar ND, Jadhav SD. Design and characterization of zanamivir loaded niosomes. World J. Pharm. Res.. 2020 Jun 22;9:2485-515. DOI: https://doi.org/10.20959/wjpr20208-18343

58. Abou-Taleb HA, Khallaf RA, Abdel-Aleem JA. Intranasal niosomes of nefopam with improved bioavailability: preparation, optimization, and in-vivo evaluation. Drug design, development and therapy. 2018 Oct 17:3501-16. DOI: https://doi.org/10.2147/DDDT.S177746

59. Pardakhty A, Varshosaz J, Rouholamini A. In vitro study of polyoxyethylene alkyl ether niosomes for delivery of insulin. International journal of pharmaceutics. 2007 Jan 10;328(2):130-41. DOI: https://doi.org/10.1016/j.ijpharm.2006.08.002

60. Arora R, Chawla R, Marwah R, Arora P, Sharma RK, Kaushik V, Goel R, Kaur A, Silambarasan M, Tripathi RP, Bhardwaj JR. Potential of complementary and alternative medicine in preventive management of novel H1N1 flu (Swine flu) pandemic: thwarting potential disasters in the bud. Evidence-Based complementary and alternative medicine. 2010;2011. DOI: https://doi.org/10.1155/2011/586506

61. Vangala A, Kirby D, Rosenkrands I, Agger EM, Andersen P, Perrie Y. A comparative study of cationic liposome and niosome-based adjuvant systems for protein subunit vaccines: characterisation, environmental scanning electron microscopy and immunisation studies in mice. Journal of pharmacy and pharmacology. 2006 Jun;58(6):787-99. DOI: https://doi.org/10.1211/jpp.58.6.0009

62. Dufes C, Schätzlein AG, Tetley L, Gray AI, Watson DG, Olivier JC, Couet W, Uchegbu IF. Niosomes and polymeric chitosan based vesicles bearing transferrin and glucose ligands for drug targeting. Pharmaceutical research. 2000 Oct;17:1250-8. DOI: https://doi.org/10.1023/A:1026422915326

63. Luciani A, Olivier JC, Clement O, Siauve N, Brillet PY, Bessoud B, Gazeau F, Uchegbu IF, Kahn E, Frija G, Cuenod CA. Glucose-receptor MR imaging of tumors: study in mice with PEGylated paramagnetic niosomes. Radiology. 2004 Apr;231(1):135-42. DOI: https://doi.org/10.1148/radiol.2311021559

64. Bayindir ZS, Yuksel N. Characterization of niosomes prepared with various nonionic surfactants for paclitaxel oral delivery. Journal of pharmaceutical sciences. 2010 Apr 1;99(4):2049-60. DOI: https://doi.org/10.1002/jps.21944

65. Thabet Y, Elsabahy M, Eissa NG. Methods for preparation of niosomes: A focus on thin-film hydration method. Methods. 2022 Mar 1;199:9-15. DOI: https://doi.org/10.1016/j.ymeth.2021.05.004

66. Tangri P, Khurana S. Niosomes: Formulation and evaluation. International Journal. 2011;2229:7499.

67. Kazi KM, Mandal AS, Biswas N, Guha A, Chatterjee S, Behera M, Kuotsu K. Niosome: a future of targeted drug delivery systems. Journal of advanced pharmaceutical technology & research. 2010 Oct 1;1(4):374-80. DOI: https://doi.org/10.4103/0110-5558.76435

68. Durak S, Esmaeili Rad M, Alp Yetisgin A, Eda Sutova H, Kutlu O, Cetinel S, Zarrabi A. Niosomal drug delivery systems for ocular disease—Recent advances and future prospects. Nanomaterials. 2020 Jun 18;10(6):1191. DOI: https://doi.org/10.3390/nano10061191

69. Ag Seleci D, Maurer V, Stahl F, Scheper T, Garnweitner G. Rapid microfluidic preparation of niosomes for targeted drug delivery. International journal of molecular sciences. 2019 Sep 22;20(19):4696. DOI: https://doi.org/10.3390/ijms20194696

70. Durga B, Veera L. Recent advances of non-ionic surfactant-based nano-vesicles (niosomes and proniosomes): A brief review of these in enhancing transdermal delivery of drug. Futur J Pharm Sci. 2020;6:100. DOI: https://doi.org/10.1186/s43094-020-00117-y

71. Nikam NR, Patil PR, Vakhariya RR, Magdum CS. Liposomes: A novel drug delivery system: An overview. Asian journal of pharmaceutical research. 2020;10(1):23-8. DOI: https://doi.org/10.5958/2231-5691.2020.00005.2

72. Bartelds R, Nematollahi MH, Pols T, Stuart MC, Pardakhty A, Asadikaram G, Poolman B. Niosomes, an alternative for liposomal delivery. PLoS One. 2018 Apr 12;13(4):e0194179. DOI: https://doi.org/10.1371/journal.pone.0194179

73. Jain S, Singh P, Mishra V, Vyas SP. Mannosylated niosomes as adjuvant–carrier system for oral genetic immunization against Hepatitis B. Immunology letters. 2005 Oct 15;101(1):41-9. DOI: https://doi.org/10.1016/j.imlet.2005.04.002

74. Devaraj GN, Parakh SR, Devraj R, Apte SS, Rao BR, Rambhau D. Release studies on niosomes containing fatty alcohols as bilayer stabilizers instead of cholesterol. Journal of colloid and interface science. 2002 Jul 15;251(2):360-5. DOI: https://doi.org/10.1006/jcis.2002.8399

75. Bhaskaran S, Lakshmi PK. Comparative evaluation of niosome formulations prepared by different techniques. Acta Pharmaceutica Sciencia. 2009;51(1).

76. Celia C, Trapasso E, Cosco D, Paolino D, Fresta M. Turbiscan Lab® Expert analysis of the stability of ethosomes® and ultradeformable liposomes containing a bilayer fluidizing agent. Colloids and Surfaces B: Biointerfaces. 2009 Aug 1;72(1):155-60. DOI: https://doi.org/10.1016/j.colsurfb.2009.03.007

77. Ge X, Wei M, He S, Yuan WE. Advances of non-ionic surfactant vesicles (niosomes) and their application in drug delivery. Pharmaceutics. 2019 Jan 29;11(2):55. DOI: https://doi.org/10.3390/pharmaceutics11020055

78. Verma S, Singh SK, Syan N, Mathur P, Valecha V. Nanoparticle vesicular systems: a versatile tool for drug delivery. J Chem Pharm Res. 2010;2(2):496-509.

79. Aparajay P, Dev A. Functionalized niosomes as a smart delivery device in cancer and fungal infection. European Journal of Pharmaceutical Sciences. 2022 Jan 1;168:106052. DOI: https://doi.org/10.1016/j.ejps.2021.106052

80. Shilpa S, Srinivasan BP, Chauhan M. Niosomes as vesicular carriers for delivery of proteins and biologicals. International Journal of Drug Delivery. 2011 Jan 1;3(1). DOI: https://doi.org/10.5138/ijdd.2010.0975.0215.03050

81. Escudero I, Geanta RM, Ruiz MO, Benito JM. Formulation and characterization of Tween 80/cholestherol niosomes modified with tri-n-octylmethylammonium chloride (TOMAC) for carboxylic acids entrapment. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 2014 Nov 5;461:167-77. DOI: https://doi.org/10.1016/j.colsurfa.2014.07.042

82. Akbarzadeh I, Sedaghatnia K, Bourbour M, Moghaddam Z, Moghtaderi M, Samimi-Sohrforozani E, Quazi S, Far B. Niosomes: a novel targeted drug delivery system. 2021 DOI: https://doi.org/10.20944/preprints202112.0315.v1

83. Yue PF, Lu XY, Zhang ZZ, Yuan HL, Zhu WF, Zheng Q, Yang M. The study on the entrapment efficiency and in vitro release of puerarin submicron emulsion. Aaps Pharmscitech. 2009 Jun;10:376-83. DOI: https://doi.org/10.1208/s12249-009-9216-3

84. Bahrololoumi S, Nikazar S. Niosomes as a promising nanovesicular drug delivery. InAdvanced and Modern Approaches for Drug Delivery 2023 Jan 1 (pp. 223-258). Academic Press. DOI: https://doi.org/10.1016/B978-0-323-91668-4.00011-3

85. Karki R, Mamatha GC, Subramanya G, Udupa N. Preparation, characterization and tissue disposition of niosomes containing isoniazid. 2008

86. Yadav JD, Kulkarni PR, Vaidya KA, Shelke GT. Niosomes: a review. Journal of Pharmacy Research. 2011 Mar;4(3):632-6. DOI: https://doi.org/10.22270/ajprd.v11i4.1295