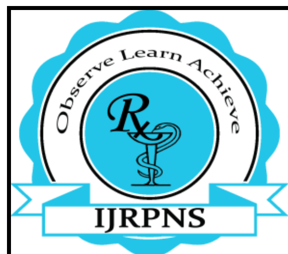
Review Article **CODEN: IJRPJK** **ISSN: 2319 – 9563**



International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: www.ijrpns.com

https://doi.org/10.36673/IJRPNS.2024.v13.i03.A05

ADVANCES IN NIOSOME TECHNOLOGY: A REVIEW ON RECENT DEVELOPMENTS

Jasmin*[1], J. Adlin Jino Nesalin[1], Ganesh N S[1], Vineeth Chandy[1]

[1*]Department of Pharmaceutics, T. John College of Pharmacy, Bengalore, Karnataka, India.

ABSTRACT

Niosomes are non-ionic surfactant-based vesicular drug delivery systems that enhance drug stability, controlled release and targeted delivery. They encapsulate hydrophilic and lipophilic drugs, offering advantages such as improved bioavailability, reduced toxicity and suitability for multiple administration routes. Various preparation methods, including ether injection, ethanol injection, sonication and novel techniques like ball milling, influence their size, stability and drug entrapment efficiency. Characterization techniques such as scanning electron microscopy (SEM), vesicle size measurement and zeta potential analysis assess their properties. Niosomes have broad pharmaceutical applications, including cancer therapy, transdermal and ophthalmic drug delivery and immune response modulation. Their ability to enhance drug stability and enable site-specific delivery makes them a promising platform for advanced drug delivery systems.

KEYWORDS

Niosomes, Drug delivery, Surfactant vesicles, Targeted therapy, Controlled release, Bioavailability, Nanotechnology and Encapsulation efficiency.

Author for Correspondence:

Jasmin,

Department of Pharmaceutics,

T. John College of Pharmacy,

Bengalore, Karnataka, India.

Email: jasminenaveen30@gmail.com

INTRODUCTION

A drug-delivery system is a method of administering pharmaceutical compounds at a controlled rate to achieve a therapeutic effect at a targeted site in humans or animals, while minimizing the concentration of the medication in surrounding tissues. Localized drug action improves the drug's efficacy and reduces the potential for systemic toxicity in other tissues.

Paul Ehrlich proposed the idea of targeted delivery directly to the diseased cell without damaging healthy cells in 1909 and this strategy has been known as the “magic bullet”. Since then, a number

of drug carrier systems have emerged, including immunoglobulins, serum proteins, synthetic polymers, liposomes, microspheres, and niosomes[1]. Niosomes, or non-ionic surfactant vesicles, are tiny lamellar structures formed when non-ionic surfactants from the alkyl or dialkyl polyglycerol ether class are combined with cholesterol and then hydrated in aqueous media. These vesicular systems, which are similar to liposomes, can serve as carriers for both amphiphilic and lipophilic drugs[2]. Niosomes are novel drug delivery system which can be used for sustained, controlled, and targeted drug delivery. While liposomes were the first vesicular systems developed for drug delivery, they have several drawbacks, such as toxicity, high cost and stability issues across different pH levels. These limitations led to a shift in research focus towards niosomes[3]. One of the reasons for preparing niosomes is the assumed higher chemical stability of the surfactants than that of phospholipids, which are used in the preparation of liposomes. Due to the presence of ester bond, phospholipids are easily hydrolysed. Unreliable reproducibilty arising from the use of lecithin's in liposomes leads to additional problems and has led scientist to search for vesicles prepared from other material, such as non-ionic surfactants[4]. In niosomes, the surfactant molecules arrange themselves with their hydrophilic ends facing outward, while the hydrophobic tails are directed inward, creating a bilayer structure. Niosomes typically range in size from 10 to 1000nm. The inclusion of cholesterol and a small amount of anionic surfactants, such as diacetyl phosphate, helps stabilize the niosomal vesicles formed by the non-ionic surfactant[5].

STRUCTURAL COMPONENTS

Niosomes are vesicular nanocarriers composed of non-ionic surfactants and cholesterol, used for drug delivery. Their structure resembles liposomes but with greater stability and biocompatibility. Figure No.1 shows the structural components of niosomes.

Bilayer Membrane

Formed by non-ionic surfactants (e.g., Span, Tween, Brij).

Provides a hydrophobic barrier, entrapping hydrophobic drugs.

Stability is enhanced by cholesterol, which regulates fluidity and permeability.

Aqueous Core

Encloses hydrophilic drugs within the vesicle.

Surfactant Head Groups

Hydrophilic heads face outward, interacting with water, ensuring vesicle stability.

Cholesterol

Improves membrane rigidity, reducing vesicle permeability and leakage.

Charge Inducers

Electrostatic stabilizers (e.g., dicetyl phosphate, stearyl amine) help prevent aggregation.

ADVANTAGES OF NIOSOMES[6]

Enhanced Patient Compliance

Being water-based, niosomal suspensions are more patient-friendly compared to oil-based drug delivery systems.

Versatile Drug Encapsulation

Their unique structure allows the incorporation of hydrophilic, lipophilic, and amphiphilic drug molecules, making them suitable for a wide range of drugs.

Customizable Characteristics

Parameters such as vesicle size and lamellarity can be adjusted based on specific therapeutic needs.

Controlled Drug Release

Niosomes function as a drug depot, enabling sustained and controlled drug release for prolonged therapeutic effects.

OTHER ADVANTAGES OF NIOSOMES[7,8]

They are osmotically active and highly stable.

They enhance the stability of the encapsulated drug.

Surfactants used in niosomes require no special storage or handling conditions.

They improve the oral bioavailability of drugs.

Niosomes enhance skin penetration, making them effective for transdermal drug delivery.

They are versatile and can be administered via oral, parenteral, and topical routes.

The surfactants used are biodegradable, biocompatible, and non-immunogenic.

They enhance therapeutic efficacy by protecting the drug from the biological environment, limiting its effects to target cells, and reducing drug clearance.

Niosomal dispersions in an aqueous phase can be emulsified in a non-aqueous phase to regulate drug release and administer vesicles in an external non-aqueous medium.

DISADVANTAGES[9]

Physical Instability – Niosomes may undergo structural changes over time.

Aggregation – Vesicles can clump together, affecting drug delivery efficiency.

Fusion – Niosomes may merge, altering their size and drug-release properties.

Drug Leakage – The encapsulated drug may gradually escape from the vesicles.

Hydrolysis of Encapsulated Drugs – This can limit the shelf life of the niosomal dispersion.

COMPOSITION OF NIOSOMES[10-12]

Niosomes are primarily composed of two key components:

Cholesterol

Provides rigidity, structural stability and proper shape to the niosomal vesicles.

Non-ionic Surfactants

Play a crucial role in niosome formation by stabilizing the vesicular structure.

Various non-ionic surfactants are commonly used in the preparation of niosomes to enhance their stability and functionality.

E.g. Spans (span 60, 40, 20, 85, 80) Tweens (tween 20, 40, 60, 80) and Brijs (brij 30, 35, 52, 58, 72, 76). The non-ionic surfactants possess a hydrophilic head and a hydrophobic tail 5.

HLB VALUE

The concept of hydrophile-lipophile balance (HLB) was introduced to define the activity of surfactants based on the contributions of different groups in their molecular structure[13]. First used by Griffin in 1949, the HLB number helps describe the types of surface-active agents[14]. According to Zheng *et al*, HLB typically refers to the balance between the hydrophilic and lipophilic components in a surfactant molecule[15]. The HLB scale ranges from 0 to 20, with lower values indicating a greater affinity for oil, while higher values suggest better water solubility[16]. The characterization of niosome formulations depends on the HLB number of the surfactant used and the solubility of the encapsulated drug. Studies show that as the HLB number of Span increases, the mean particle size gradually increases[17,18]. A high hydrophobicity (low HLB number) can result in smaller niosome particles due to lower surface energy[19]. Consistent with findings from Das and Palei (2011), previous studies have also shown that, for different surfactant types and HLB numbers, the mean size of niosomes increases with a higher HLB value 7[20-22].

BILAYER INDUCING AGENT IN NIOSOME

Niosome formulations typically involve mixing a non-ionic surfactant with a bilayer-inducing agent, such as cholesterol, which acts as a membrane stabilizer. The interaction between non-ionic surfactants and cholesterol in niosome formulations has been extensively studied[23-25]. The inclusion of cholesterol is known to impact both the stability and permeability of niosomes. Most niosome formulations rely on cholesterol during their preparation. Moghassemi and Hadjizadeh (2014) highlighted the main benefits of using cholesterol in niosome formation, which include,

Improving niosome stability through two mechanisms

By forming the bilayer vesicle (acting as a bilayer-inducing agent)

By increasing the gel-liquid transition temperature (TC) of the vesicle;

Enhancing drug encapsulation efficiency. Similarly, Devara *et al*, (2002) found that cholesterol helps stabilize the niosomal bilayer, reduce leakage, and slow down the permeability of the core molecule. Generally, increasing the proportion of the bilayer-inducing agent, cholesterol, improves the

entrapment efficiency in most prepared formulations 7[26].

CHARGE INDUCER AGENTS IN NIOSOMES

Niosomal vesicles tend to aggregate significantly when charge inducer agents are not used. Current research on charge inducer agents focuses on two main approaches: one involves using agents that induce a negative charge, while the other uses agents that create a positive charge. Both strategies aim to prevent aggregation and stabilize the vesicles for improved performance in drug delivery systems[27,28]. Negative charge inducer agents like diacetyl phosphate (DCP) and phosphatidic acid, as well as positive charge inducer agents such as stearyl amine (SA) and stearyl pyridinium chloride, are commonly used in niosomal preparations[29]. These agents help prevent particle aggregation by inducing surface charges on the prepared vesicles[30,31]. By modifying the surface charge, they improve the stability and dispersion of the niosomal particles, ensuring more effective drug delivery and reduced risk of aggregation during storage or administration. Typically, 2.5-5mol percent of charged molecules are added to the niosomal formulation[32]. However, increasing the concentration of charge-inducing agents can impact the stability of the niosomes and may lead to a decrease in the encapsulation efficiency of the incorporated drug.

FORMATION OF NIOSOMES FROM PRONIOSOMES[33,34]

The niosomes can be prepared from the proniosomes by adding the aqueous phase with the drug to the proniosomes with brief agitation at a temperature greater than the mean transition phase temperature of the surfactant.

$T > T_m$

Where,

T = Temperature

Tm = mean phase transition temperature

Blazek8Walsh A.I. *et al* has reported the formulation of niosomes from maltodextrin based Proniosomes. This provides rapid reconstitution of niosomes with minimal residual carrier. Slurry of maltodextrin and surfactant was dried to form a free-flowing powder, which could be rehydrated by addition of warm water. Figure No.2 depicts the formation of niosomes from proniosomes.

METHOD OF PREPARATION[35-41]

The preparation of niosomes starts with hydrating a mixture of surfactant and lipid at elevated temperatures, followed by an optional size reduction step to achieve a colloidal suspension. Several established methods for preparing niosomes are commonly used, including ether injection, hand shaking, sonication and micro fluidization. Afterward the unentrapped drug is separated from the encapsulated drug using techniques like centrifugation, gel filtration, or dialysis.

Ether injection method

This method provides a means of making niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether into warm water maintained at 60°C. The surfactant mixture in ether is injected through 148gauge needle into an aqueous solution of material. Vaporization of ether leads to formation of single layered vesicles. Depending upon the conditions used the diameter of the vesicle range from 50 to 1000nm. Figure No.3 shows the schematic representation of ether injection method.

Preparation steps

Surfactant is dissolved in diethyl ether

Then injected in warm water maintained at 60°C through a 14-gauze needle

Ether is vaporized to form single layered niosomes.

Ethanol injection method

Ethanol injection is a fast and simple technique for the preparation of small uni-lamellar vesicles. The technique consists of the injection of an ethanolic solution of lipids into an aqueous phase, where spontaneous vesicle formation takes place. Co-solvents, such as isopropanol, can be used with ethanol in order to optimize lipid solubility and enhance encapsulation efficiency. Furthermore, the speed of injection and temperature can be change in

order to modify vesicle size and prevent aggregation, which makes this method even more versatile. The method is inexpensive, does not require sophisticated equipment, has the possibility of scaling up, and is easy to set up. The size of the niosomes obtained by this method is smaller compared to the thin film hydration and microfluidics methods. Figure No.4 indicates the preparation of niosomes by ethanol injection method.

Hand shaking method

The vesicle-forming ingredients, such as surfactant and cholesterol, are dissolved in a volatile organic solvent (like diethyl ether, chloroform, or methanol) in a round-bottom flask. The solvent is then removed at room temperature (20°C) using a rotary evaporator, leaving behind a thin layer of the solid mixture on the flask's walls. The dried surfactant film is rehydrated with an aqueous phase at 60-80°C while gently agitating. This process results in the formation of typical multilamellar niosomes. Figure No.5 shows preparation of niosomes by hand shaking method.

Preparation steps

Surfactant + cholesterol + solvent

↓

Remove organic solvent at room temperature

↓

Thin layer formed on the walls of flask

↓

Film can be rehydrated to form multilamellar niosomes.

Sonication method

A common method for producing vesicles involves sonication of the solution, as described by Cable. In this technique, a portion of a drug solution in buffer is combined with a surfactant/cholesterol mixture in a 108ml glass vial. The mixture is then subjected to probe sonication at 60°C for 3 minutes using a titanium probe on a sonicator. This process results in the formation of niosomes. The application of sonication helps to break up the mixture, ensuring the creation of stable vesicles. Figure No.6 indicates the preparation of sonication method.

Preparation steps

Drug in buffer + surfactant/cholesterol in 10ml

↓

Above mixture is sonicated for 3 mints at 60°C using titanium probe yielding niosomes.

Micro fluidization method

Micro fluidization is a modern technique used to create unilamellar vesicles with a controlled size distribution. It operates on the submerged jet principle, where two fluidized streams collide at extremely high velocities within precisely defined microchannels in the interaction chamber. The thin liquid sheets collide along a common front, ensuring that the energy supplied is concentrated within the area where niosomes are formed. This method results in more uniform, smaller-sized niosomes with improved reproducibility. Figure No.7 indicates the schematic representation of noisome preparation by micro fluidization method.

Preparation steps

Two ultra-high-speed jets inside interaction chamber

↓

Impingement of thin layer of liquid in micro channels

↓

Formation of uniform niosomes.

Multiple membrane extrusion method

A mixture of surfactant, cholesterol and diacetyl phosphate in chloroform is evaporated to form a thin film. This film is then hydrated with an aqueous drug solution, and the resulting suspension is extruded through polycarbonate membranes. The suspension is passed through a series of membranes for up to 8 passages. This method is effective for controlling the size of the niosomes. Figure No.8 shows the preparation of niosomes by multiple membrane extrusion method.

Reverse phase evaporation technique

Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 485°C. The clear gel formed is further sonicated after the addition of a small amount of phosphate buffered saline (PBS).

The organic phase is removed at 40°C under low pressure. The resulting viscous noisome suspension is diluted with PBS and heated on a water bath at 60°C for 10 min to yield niosomes. Figure No.9 depicts the formation of niosomes by reverse phase evaporation technique.

Preparation steps

Cholesterol + surfactant dissolved in ether + chloroform
↓
Sonicated at 5oc and again sonicated after adding PBS
↓
Drug in aqueous phase is added to above mixture
↓
Viscous niosomes suspension is diluted with PBS
↓
Organic phase is removed at 40°C at low pressure
↓
Heated on a water bath for 60°C for 10 mints to yield niosomes.

Trans membrane pH gradient (inside acidic) Drug uptake process: or remote loading technique

Surfactant and cholesterol are dissolved in chloroform and the solvent is evaporated under reduced pressure to form a thin film on the wall of a round-bottom flask. The film is then hydrated with 300mM citric acid (pH 4.00) by vortex mixing. The multilamellar vesicles are frozen, thawed three times, and then sonicated. An aqueous solution containing 10mg/mL of the drug is added to the niosomal suspension and vortexed. The pH of the mixture is adjusted to 7.0–7.2 using 1M disodium phosphate. Finally, the mixture is heated at 60°C for 10 minutes to form the niosomes**.** Figure No.10 shows the preparation of niosomes by trans membrane pH gradient method.

Preparation steps

Surfactant + cholesterol in chloroform
↓
Solvent is evaporated under reduced pressure
Thin film is deposited on the walls of RBF
↓
Hydrated with citric acid by vortex mixing
↓
3 cycles of freezing and thawing then sonication
↓
Addition of aqueous drug solution and vortoxing
↓
pH raised to 7.087.2 by 1M disodium phosphate
↓
RBF as bubbling unit with three necks in water bath
↓
Reflux, thermometer and nitrogen supply by three necks
↓
Cholesterol + surfactant dispersed in buffer pH 7.4 at 70oC
↓
Above dispersion is homogenized for 15 sec and then bubbled with nitrogen gas at 70°C
↓
To get niosomes.

The bubble method

It is novel technique for the one step preparation of liposomes and niosomes without the use of organic solvents. The bubbling unit consists of round8bottomed flask with three necks positioned in water bath to control the temperature. Water8cooled reflux and thermometer is positioned in the first and second neck and nitrogen supply through the third neck. Cholesterol and surfactant are dispersed together in this buffer (PH 7.4) at 70°C, the dispersion mixed for 15 seconds with high shear homogenizer and immediately afterwards “bubbled” at 70°C using nitrogen gas. Figure No.11 shows the preparation of niosomes by bubble method.

Novel ball milling method[42]

The ball milling (BM) method is an innovative technique that enhances the quality and efficiency of niosome production. It involves using a rotating container filled with spherical balls to break apart and compress drug and surfactant particles, forming uniform niosomes. This method offers better size control, improved encapsulation efficiency, and enhanced stability compared to traditional techniques like thin film hydration or reverse-phase evaporation. By adjusting parameters such as ball

size and rotation speed, particle uniformity can be optimized. BM is simpler, reproducible, and scalable, making it highly suitable for pharmaceutical applications. Originating from the ball mill machine used in various industries, this technique ensures precise drug delivery by producing niosomes with customizable sizes and shapes. Figure No.12 shows the preparation of niosome by ball milling method.

CHARACTERIZATION OF NIOSOME[43-45]

Measurement of angle of repose

The angle of repose of dry niosome powder was determined using the funnel method. The powder was poured into a funnel fixed in place, with the 13mm outlet orifice positioned 5cm above a flat black surface. As the powder flowed from the funnel, it formed a cone on the surface. The angle of repose was then calculated by measuring the height of the cone and the diameter of its base.

Scanning electron microscopy

The particle size of niosomes is a crucial characteristic. To examine the surface morphology (including roundness, smoothness, and the formation of aggregates) and size distribution, Scanning Electron Microscopy (SEM) was used. Niosomes were lightly sprinkled onto double-sided tape, which was then attached to aluminium stubs. These stubs were placed inside the vacuum chamber of a scanning electron microscope (XL 30 ESEM with EDAX, Philips, Netherlands). The samples were observed for morphological analysis using a gaseous secondary electron detector, with a working pressure of 0.8 torr and an acceleration voltage of 30.00kV.

Optical microscopy

The niosomes were placed on glass slides and examined under a microscope (Medi lux 8207RII, Kyowa-Getner, Ambala, India) at a magnification of 1200X for morphological analysis after appropriate dilution. Photomicrographs of the preparation were captured using a digital SLR camera attached to the microscope.

Measurement of vesicle size

The vesicle dispersions were diluted approximately 100 times with the same medium used for their preparation. The vesicle size was then measured using a particle size analyser (Laser diffraction particle size analyser, Sympatec, Germany). The device uses a 632.8nm He-Ne laser beam, focused with a minimum power of 5mW using a Fourier lens, aimed at the centre of a multielement detector and a small sample holding cell (Su cell). Before measuring the vesicle size, the sample was stirred with a stirrer to ensure proper dispersion. According to a study by Hu C. and Rhodes in 1999, the average particle size of niosomes derived from the method is approximately 6 µm, while conventional niosomes typically measure around 14µm.

Entrapment efficiency

The entrapment efficiency of the niosomal dispersion can be determined by separating the unentrapped drug using methods such as dialysis, centrifugation, or gel filtration, as described earlier. The drug that remains entrapped in the niosomes is then released by fully disrupting the vesicles with 50% isopropanol or 0.1% Triton X-100. The resulting solution is analysed using an appropriate assay method to quantify the drug.

$$\%EE = (Drug\ loading\ /Theoritical\ drug\ loading\ ) \times 100$$

Osmotic shock

The change in vesicle size can be assessed through osmotic studies. Niosome formulations are incubated in hypotonic, isotonic, and hypertonic solutions for 3 hours. Afterward, the size changes of the vesicles in the formulations are observed under optical microscopy.

Stability studies

To assess the stability of niosomes, the optimized batch was stored in airtight sealed vials at various temperatures. The evaluation focused on surface characteristics and the percentage of drug retained in both niosomes and niosomes derived from proniosomes. Instability in the formulation would be indicated by drug leakage and a reduction in the percentage of drug retained. Niosome samples were collected at regular intervals (0, 1, 2 and 3 months) and examined for colour changes, surface

characteristics, and the percentage of drug retained after hydration to form niosomes. The drug retention was analysed using appropriate analytical methods such as UV spectroscopy or HPLC.

Zeta potential analysis

Zeta potential analysis is performed to assess the colloidal properties of the prepared formulations. The suitably diluted niosomes derived from the proniosome dispersion were analysed using a zeta potential analyser that employs electrophoretic light scattering and laser Doppler velocimetry (Zeta Plus™, Brookhaven Instrument Corporation, New York, USA). The temperature was maintained at 25°C. The charge on the vesicles and their mean zeta potential values, along with the standard deviation of measurements, were directly obtained from the analysis.

APPLICATIONS OF NIOSOMES[46-49]

The application of niosomes technology is widely varied and can be used to treat a number of diseases. The following are a few uses of niosomes which are either proven or under research.

Delivery of proteins and peptides

Delivering protein and peptide drugs orally has always been challenging due to their degradation by the acidic environment and enzymes in the gastrointestinal tract (GIT). However, niosomes offer protection against proteolytic enzymes. Moghassemi *et al*, developed niosomes containing Bovine Serum Albumin (BSA) and optimized the formulation for drug loading and release based on cholesterol-to-Span 60 molar ratios. They used methyl orange as an indicator to determine the protein's location within the vesicle using an inverted light microscope. Additionally, trimethyl chitosan-coated insulin niosomes have been formulated for oral delivery to enhance insulin permeation.

Delivery of anticancer drugs

Targeted delivery of anticancer drugs using niosomes can be achieved through passive, physical, or active mechanisms. Passive targeting relies on tumour-specific properties, while physical targeting depends on environmental conditions like pH or magnetic fields. Active targeting involves modifying the niosome surface or attaching ligands via cholesterol-PEG conjugates. Paclitaxel niosomes have been successfully developed for oral delivery, improving bioavailability and stability. Lin *et al*, formulated PEGylated niosomes of gambogenic acid for anticancer therapy. Sharma *et al*, designed self-degrading niosomes encapsulating curcumin and doxorubicin, demonstrating a synergistic cytotoxic effect against HeLa cells. Alemi *et al*, developed cationic PEGylated niosomes for co-administering curcumin and paclitaxel, enhancing antitumor efficacy. Agarwal et al. prepared niosomes, showing a pH-dependent release favouring acidic tumour environments. Wilkhu *et al*, created bilosomes incorporating bile salts for oral vaccine delivery, protecting antigens from enzymatic degradation in the GIT.

Carrier for haemoglobin

Niosomes can serve as carriers for haemoglobin in the blood due to their excellent oxygen absorption properties.

Treatment of HIV-AIDS

Niosomes can be used for the sustained delivery of drugs in AIDS treatment, addressing challenges like low potency and toxicity. Zidovudine, an anti-HIV drug, faces limitations such as dose-dependent haematological toxicity, extensive first-pass metabolism, short half-life, and poor bioavailability, which niosomes help overcome. Lopinavir, a reversible HIV protease inhibitor, has low oral bioavailability due to poor aqueous solubility, high log P value, sensitivity to cytochrome P450 3A4, and susceptibility to P-glycoprotein efflux. To address these issues, transdermal niosomes were developed and compared with ethosomal gel, showing deeper skin penetration and an improved drug release profile. Kamboj et al. formulated niosomes of tenofovir disoproxil fumarate, reporting a twofold increase in bioavailability and prolonged drug release. Shreedevi et al. designed niosomes of stavudine for targeted and controlled drug release.

Diagnostic imaging

Niosomes can serve as carriers for radiopharmaceuticals, making them useful in diagnostic imaging of organs such as the liver and spleen. 99mTc-labeled DTPA is commonly used for imaging, while niosomes are also utilized with iobitridol, a diagnostic agent for X-ray imaging. A conjugated niosomal formulation of gadobenate dimeglumine with N-palmitoylglucosamine (NPG), PEG 4400, or a combination of both has demonstrated enhanced tumour targeting of an encapsulated paramagnetic agent, as assessed by MRI. A. Massotti developed novel biconjugate niosomes for imaging by incorporating contrast agents or near-infrared dyes into the inner aqueous or non-aqueous compartments or by conjugation onto the niosome surface. Additionally, Gd (EDTA) can be incorporated as a contrast agent for enhanced imaging. Optical imaging combined with MRI is a valuable tool for tumour diagnosis, and conjugating polyethylene amino groups with near-infrared probes enables effective in vivo imaging.

Brain targeting

De et al. demonstrated improved drug delivery to the brain in glioblastoma using smart niosomes of temozolomide. To specifically target gliomas, the surface of the niosomes was modified with chlorotoxin, a 36-amino acid peptide derived from the venom of the scorpion *Leiurus quinquestriatus*. Pentamidine, an antiprotozoal drug with anti-inflammatory and neuroprotective properties for Alzheimer’s disease, faces challenges such as poor blood-brain barrier permeability and high hepatotoxicity. To address these limitations, chitosan-glutamate-coated pentamidine niosomes were developed for intranasal delivery, facilitating direct transport to the brain. This intranasal approach bypasses first-pass hepatic metabolism and the blood-brain barrier, enhancing drug efficacy.

Targeted drug delivery

Tavano *et al* and A. Massotti developed niosomes for targeted drug delivery to tumour cells. Tavano *et al*, designed Pluronic-conjugated niosomes for doxorubicin delivery to tumour cells, while A. Massotti formulated pH-sensitive niosomes for drug delivery to hepatoblastoma. The targeting was achieved through surface modification without incorporating a pH-sensitive molecule. These niosomes undergo protonation of amino groups upon entering the cell, triggering drug release through a "sponge effect".

Other Applications: Niosomes can also be utilized for sustained drug release and localized drug action to greatly increase the safety and efficacy of many drugs. Toxic drugs which need higher doses can possibly be delivered safely using niosomal encapsulation.

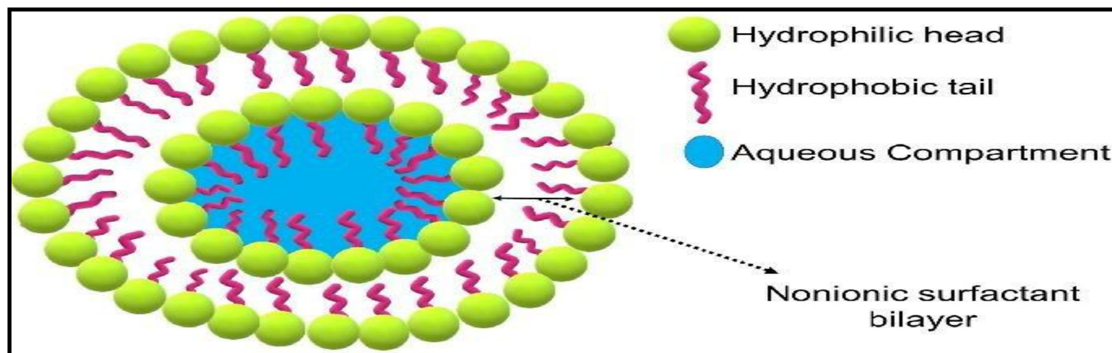


Figure No.1: Structure of niosome

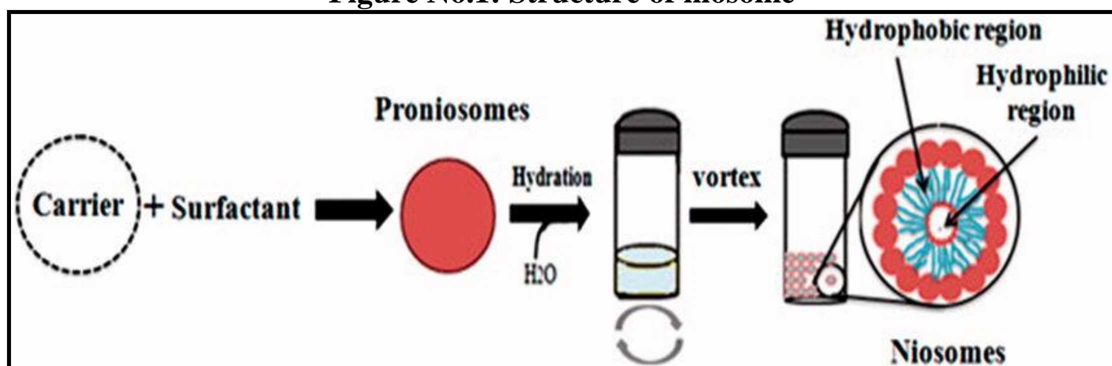


Figure No.2: Formation of niosomes

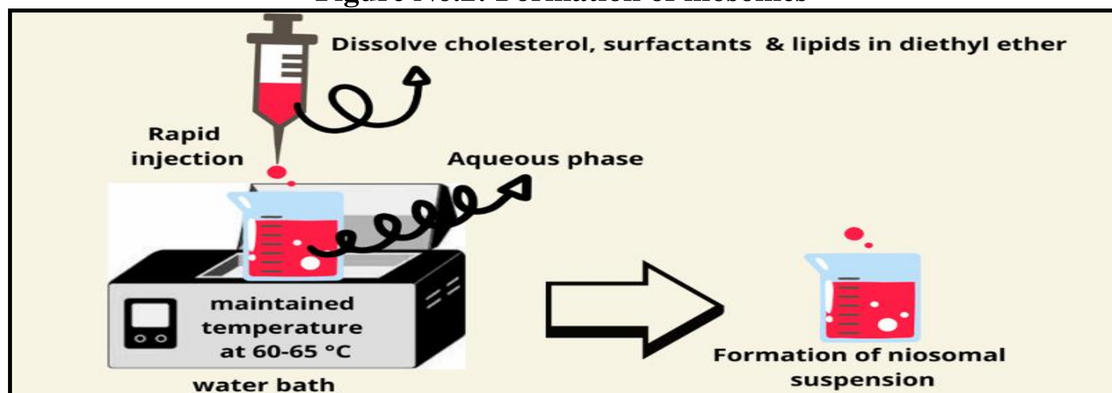


Figure No.3: Ether injection method

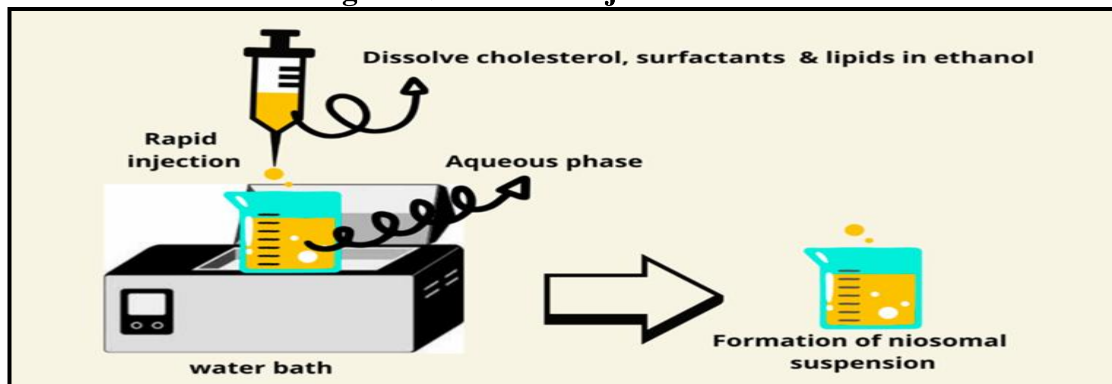


Figure No.4: Ethanol injection method

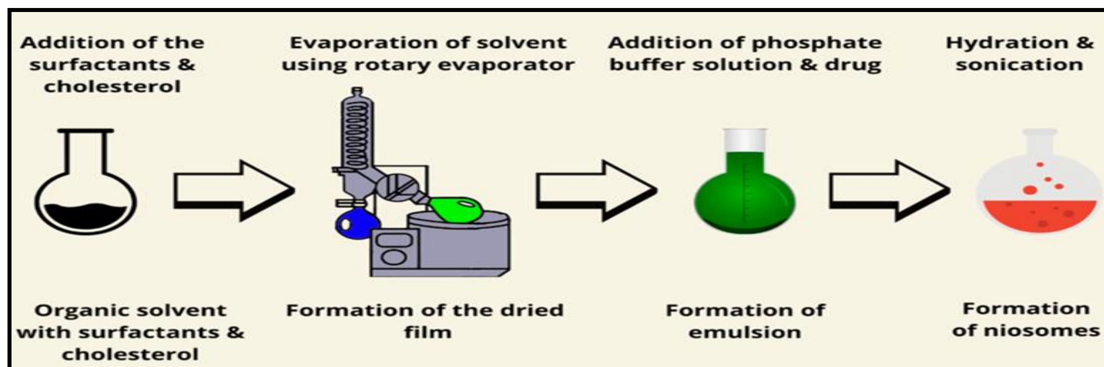


Figure No.5: Hand shaking method

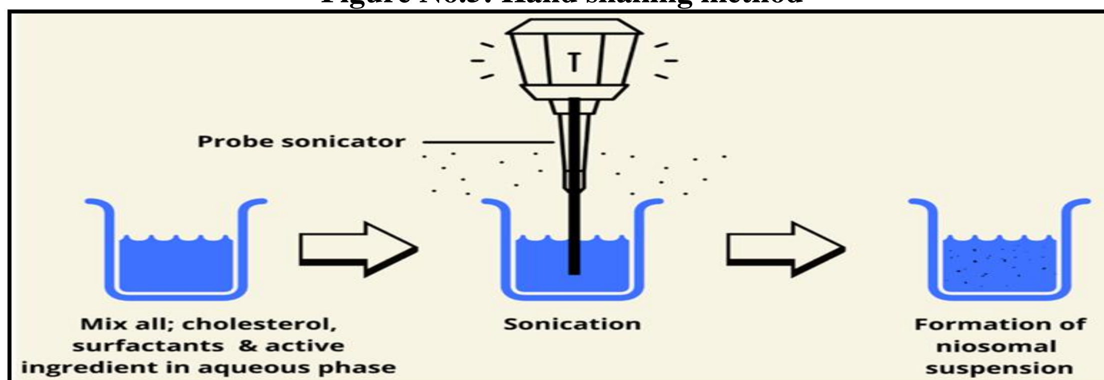


Figure No.6: Sonication method

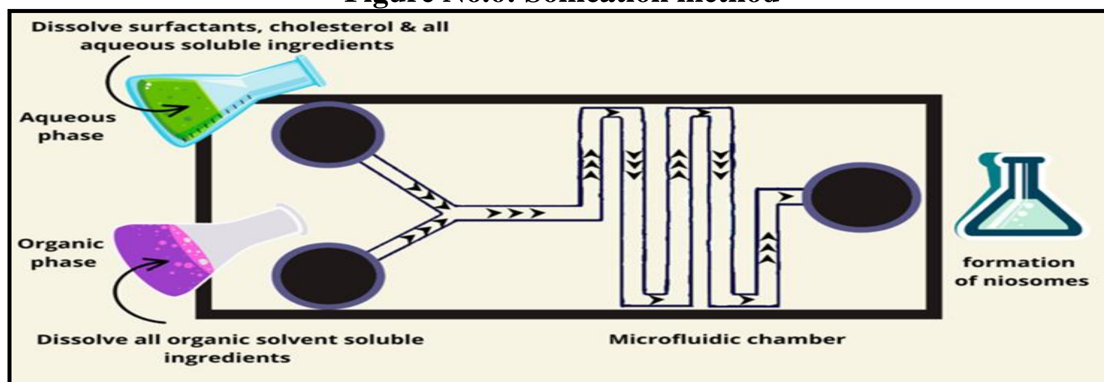


Figure No.7: Micro fluidization method

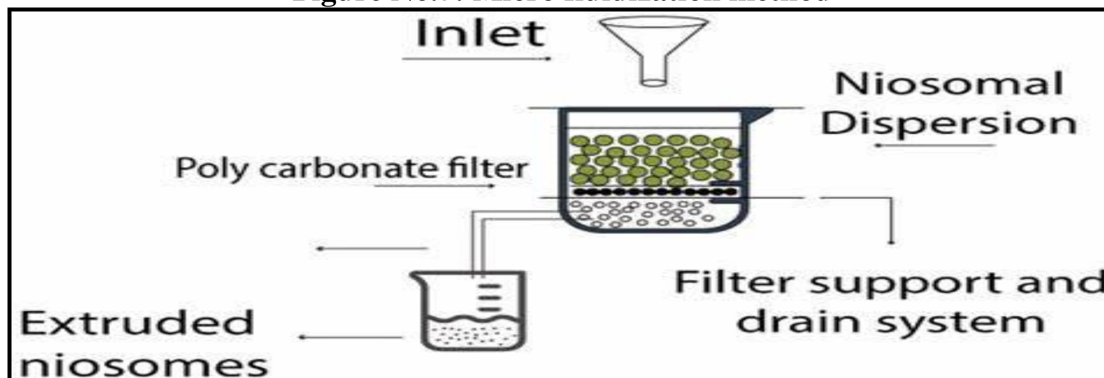


Figure No.8: Multiple membrane extrusion method

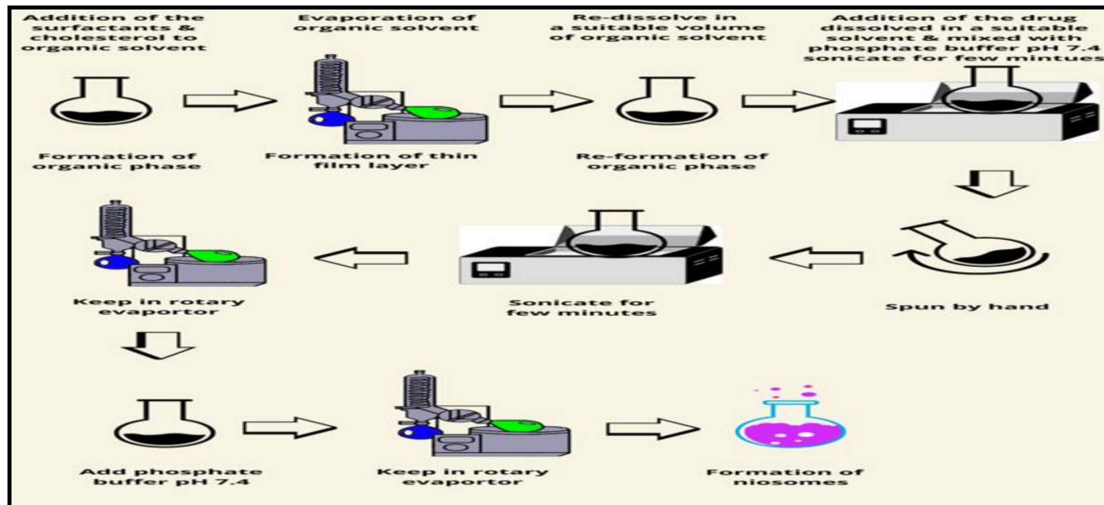


Figure No.9: Reverse phase evaporation technique

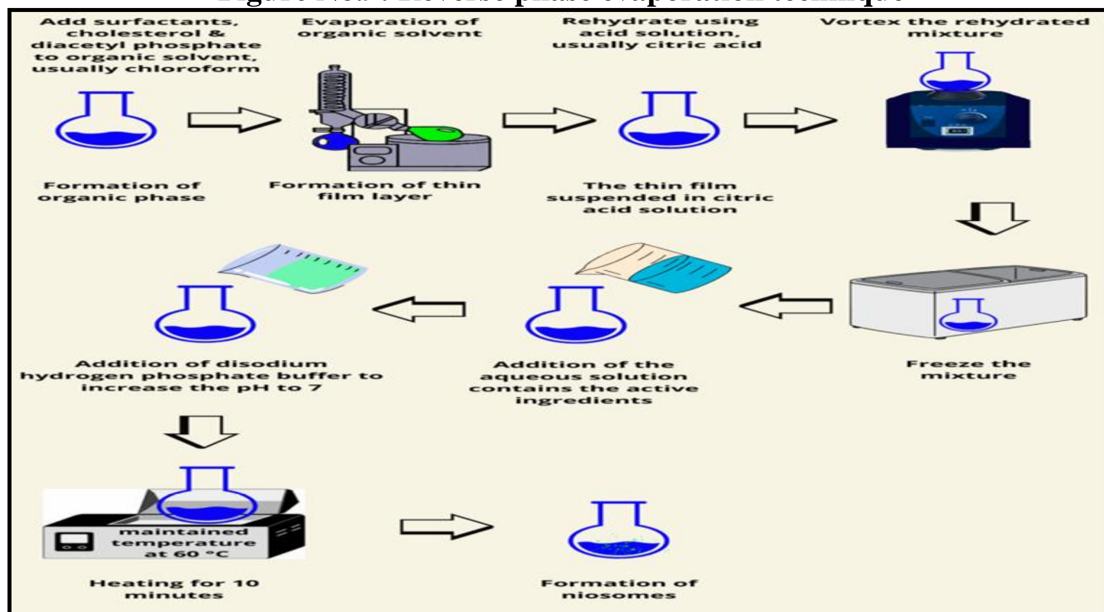


Figure No.10: Trans membrane pH gradient

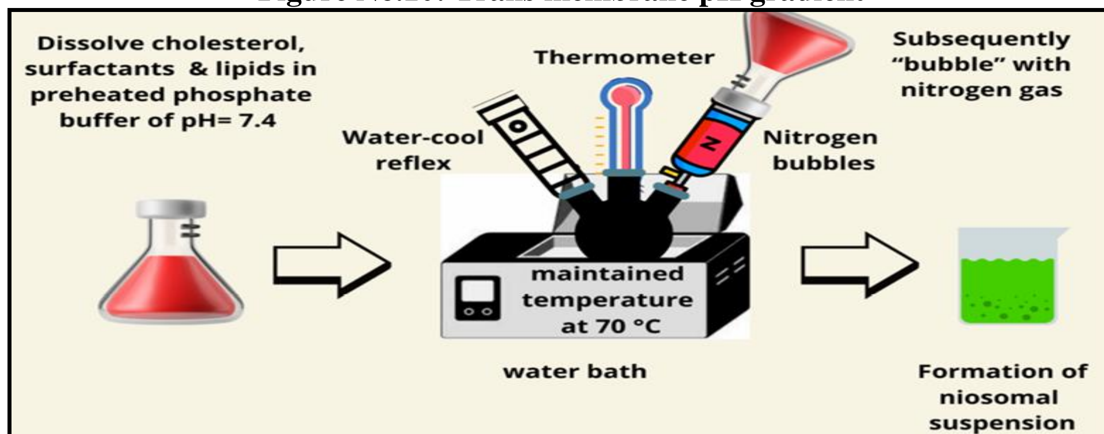


Figure No.11: Bubble method

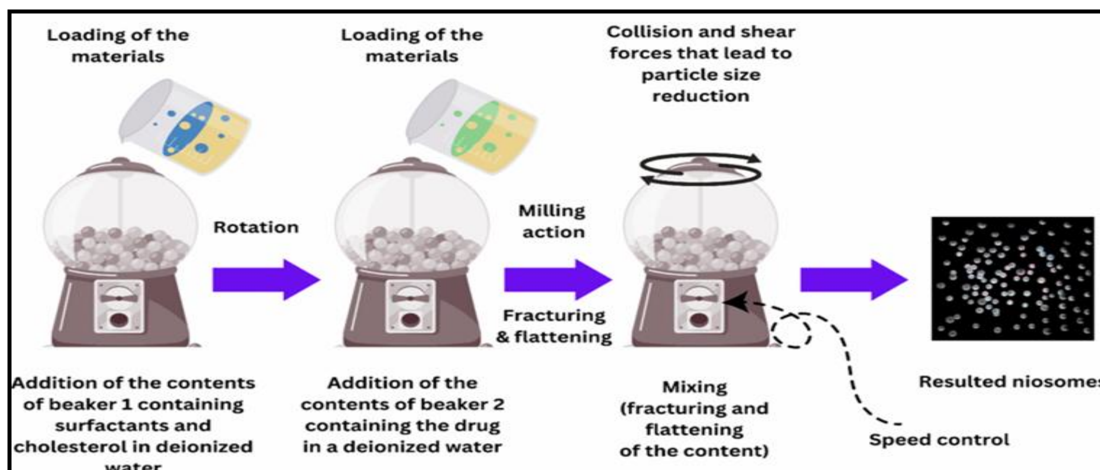


Figure No.12: Ball milling method

CONCLUSION

Niosomes represent a significant advancement in drug delivery, offering improved drug stability, targeted release and enhanced bioavailability. Their ability to encapsulate hydrophilic, lipophilic and amphiphilic drugs makes them highly versatile for pharmaceutical applications. Compared to liposomes, niosomes provide superior chemical stability, lower production costs and reduced toxicity. Various preparation methods, such as ether injection, ethanol injection and sonication, allow for precise control over vesicle size and encapsulation efficiency. Characterization techniques, including microscopy, vesicle size measurement, and entrapment efficiency analysis, ensure formulation reliability.

Niosomes have broad applications in cancer treatment, transdermal drug delivery and ophthalmic drug administration. Despite some limitations like physical instability and drug leakage, strategies such as cholesterol incorporation enhance stability. The development of proniosomes further simplifies preparation and storage. Overall, niosomes hold great potential for controlled and site-specific drug delivery, making them a valuable tool for future pharmaceutical innovations. Further research will help optimize their formulation and maximize clinical benefits.

ACKNOWLEDGEMENT

The authors wish to express their sincere gratitude to Department of Pharmaceutics, T. John College of Pharmacy, Bengalore, Karnataka, India for providing necessary facilities to carry out this review work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

REFERENCES

1. Yeo P L, Lim C L, Chye S M, Ling A P, Koh R Y. Niosomes: A review of their structure, properties, methods of preparation and medical applications, *Asian Biomed,* 11(4), 2017, 301-314.
2. Tangri P, Khurana S. Niosomes: Formulation and evaluation, *Int. J. Biopharma,* 2(1), 2011, 47-53.
3. Yadav J D, Kulkarni P R, Vaidya K A, Shelke G T. Niosomes: A review, *J. Pharm. Res,* 4(3), 2011, 632-636.
4. Vadlamudi H C, Sevukarajan M. Niosomal drug delivery system-a review, *Indo Am. J. Pharm. Res,* 2(9), 2012, 1-22.
5. Chandu V P, Arunachalam A, Jeganath S, Yamini K, Tharangini K, Chaitanya G. Niosomes: A novel drug delivery system, *IJNTPS,* 2(1), 2012, 25-31.

6. Biju S S, Talegaonkar S, Misra P R, Khar R K. Vesicular systems: An overview, *Indian J. Pharm. Sci,* 68(2), 2006, 1418-153.
7. Ijeoma F, Suresh P, Vyas. Non-ionic surfactant-based vesicles (niosomes) in drug delivery, *Int. J. Pharm,* 172(2), 998, 33-70.
8. Malhotra M, Jain N K. Niosomes as drug carriers, *Indian Drugs, Indian J. Pharm. Sci,* 58(2), 1995, 41-46.
9. Alsarra A, Bosela A, Ahmed S M, Mahrous G M. Proniosomes as a drug carrier for transdermal delivery of ketorolac, *Eur. J. Pharm and Biopharm,* 2(1), 2004, 186-192.
10. Hu C, Rhodes D G. Proniosomes: A novel drug carrier preparation, *Int. J. Pharm,* 185(1), 1999, 23-35.
11. Blazek–Welsh A I, Rhodes D G. SEM imaging predicts quality of niosomes from maltodextrin-based proniosomes, *Pharm. Res,* 18(5), 2001, 656-661.
12. Yoshioka T, Florence A T. Preparation and properties of vesicles (niosomes) of sorbitan monoesters (Span 20, 40, 60 and 80) and a sorbitan tri ester (Span 85), *Int. J. Pharm,* 105(1), 1994, 1-6.
13. Corin K C. A proposal to use excess Gibbs energy rather than HLB number as an indicator of the hydrophilic-liphophilic behavior of surfactants, *Miner. Eng,* 58, 2014, 17-21.
14. Griffin W C. Classification of surface-active agents by" HLB", *J. Soc. Cosmet. Chem,* 1, 1949, 311-325.
15. Zheng Y, Zheng M, Ma Z, Xin B, Guo R, Xu X. Sugar fatty acid esters in Polar lipids, *Elsevier Sci,* 3(5), 2015, 215-243.
16. Ranjith H P, Wijewardene U. Lipid emulsifiers and surfactants in dairy and bakery products, *CABI,* 3(2), 2006, 1-9.
17. Ruckmani K, Jayakar B, Ghosal S K. Non-ionic surfactant vesicles (niosomes) of cytarabine hydrochloride for effective treatment of leukemias: Encapsulation, storage and *in vitro* release, *Drug Dev. Ind. Pharm,* 26(2), 2000, 217-222.
18. Das M K, Palei N N. Sorbitan ester niosomes for topical delivery of rofecoxib, *NIScPR,* 49(6), 2011, 438-445.
19. Baillie A J, Rogerson A. The preparation and properties of niosomes-non-ionic surfactant vesicles, *J. Pharm. Pharmacol,* 37(12), 1985, 863-868.
20. Khazaeli P. Caffeine-loaded niosomes: Characterization and *in vitro* release studies, *Drug Deliv,* 14(7), 2007, 447-452.
21. Kamboj S. Formulation and characterization of drug loaded nonionic surfactant vesicles (niosomes) for oral bioavailability enhancement, *TSWJ,* 4(1), 2014, 95-121.
22. Gugleva V, Titeva S, Rangelov S, Momekova D. Design and *in vitro* evaluation of doxycycline hyclate niosomes as a potential ocular delivery system, *Int. J. Pharm,* 5(7), 2019, 11-31.
23. Ahad A, Raish M, Al-Jenoobi F I, Al-Mohizea A M. Sorbitane monostearate and cholesterol based niosomes for oral delivery of telmisartan, *Curr Drug Deliv,* 15(2), 2018, 260-266.
24. Ruckmani K, Sankar V. Formulation and optimization of zidovudine niosomes, *AAPS Pharm Sci Tech,* 3(1), 2010, 1119-1127.
25. Hunter C A, Dolan T F, Coombs G H, Baillie A J. Vesicular systems (niosomes and liposomes) for delivery of sodium stibogluconate in experimental murine visceral leishmaniasis, *J. Pharm. Pharmacol,* 40(3), 1988, 161-165.
26. Devaraj G N, Apte S S, Rao B R, Rambhau D. Release studies on niosomes containing fatty alcohol as bilayer stabilizers instead of cholesterol, *J. Colloid Interface Sci,* 2(1), 2002, 360-365.
27. Kalsin A M, Grzybowski B A. Controlling the growth of “ionic” nanoparticle supra crystals, *Nano Lett,* 7(4), 2007, 1018-1021.
28. Elci S G, Jackson L C, Rotello V M, Vachet R W. Surface charge controls the suborgan biodistributions of gold nanoparticles, *ACS Nano,* 10(5), 2016, 5536-5542.

29. Ag Seleci D, Scheper T. Niosomes as nanoparticular drug carriers: Fundamentals and recent applications, *J. Nanomater,* 2016(1), 73-86.
30. Sezgin-Bayindir Z, Yuksel N. Investigation of formulation variables and excipient interaction on the production of niosomes, *AAPS Pharm Sci Tech,* 13(1), 2012, 826-835.
31. Blazek–Welsh A I. SEM imaging predicts quality of niosomes from maltodextrin-based proniosomes, *Pha. Res,* 18(5), 2001, 656-661.
32. Junyaprasert V B. Effect of charged and non-ionic membrane additives on physicochemical properties and stability of niosomes, *AAPS Pharm Sci Tech,* 9(3), 2008, 851-859.
33. Mokhtar M. Effect of some formulation parameters on flurbiprofen encapsulation and release rates of niosomes prepared from proniosomes, *International Journal of Pharmaceutics,* 361(1-2), 2008, 104-111.
34. Sudhamani T. Proniosomes-a promising drug carriers, *Int. J. Ph Re,* 2(2), 2010, 1446-1454.
35. Yoshida H, Lehr C M, Kok W, Jun ginger H E, Verhoef J C, Bouwstra J A. Niosomes for oral delivery of peptide drugs, *J of Controlled Release,* 21(1-3), 1992, 145-153.
36. Satturwar P M, Fulzele` S V, Nande V S, Khandare J N. Formulation and evaluation of ketoconazole niosomes, *Indian J Pharm Sci,* 64(2), 2002, 155-158.
37. Vyas S P, Khar R K. Niosomes Targeted and controlled drug delivery, 2008, 249-279.
38. Gibaldi M, Perrier D. Pharmacokinetics, *Marcel Dekker, Inc, New York,* 2nd Edition, 1982, 127-134.
39. Ritthe P V, Rudrurkar M N, Kazi A J, Patil S R, Sante R U, Shaikh I. Unlocking the potential of niosomes: A Comprehensive review, *AJPRD,* 11(3), 2024, 239-246.
40. Bhaskaran S, Panigrahi L. Formulation and evaluation of niosomes using different non-ionic surfactants, *Indian J Pharm Sci,* 64(1), 2002, 63-65.
41. Ritthe P V, Fugate A, Shafi S, Rudrurkar M N, Kazi A J, Patil S R, Sante R U, Shaikh I. Unlocking the potential of niosomes: A comprehensive review, *AJPRD,* 11(3), 2024, 239-246.
42. Temprom L, Priperm A, Namuangruk S. A novel preparation and characterization of melatonin loaded niosomes based on using a ball milling method, *Mater. Today Commun,* 31(7), 2022, 1033-1040.
43. Schreier H, Bouwstra J. Liposomes and niosomes as topical drug carriers: Dermal and transdermal drug delivery, *J Control Release,* 30(1), 1994, 1-5.
44. Buckton G. Interfacial phenomena in drug delivery and targeting, *CRC Press, London,* 1st Edition, 2000, 304.
45. Bairwa N K, Choudhary D. Proniosome: A review, *Asian J. Pharm. Biol Res,* 2(1), 2011, 690-694.
46. Bhardwaj P, Tripathi P, Gupta R, Pandey S. Niosomes: A review on niosomal research in the last decade, *J Drug Deliv Sci Technol,* 56(2), 2020, 1-17.
47. Kumar G P, Rajeshwar Rao P. Nonionic surfactant vesicular systems for effective drug delivery-an overview, *Acta Pharm. Sin. B,* 1(4), 2011, 208-219.
48. Lin T, Fang Q, Peng D, Huang X, Zhu T, Luo Q, Zhou K, Chen W. PEGylated non-ionic surfactant vesicles as drug delivery systems for Gambogenic acid, *Drug Delivery,* 20(7), 2013, 277-284.
49. De A, Venkatesh N, Senthil M, Sanapalli B K, Shanmugham R, Karri V V. Smart niosomes of temozolomide for enhancement of brain targeting, *Nanobiomedicine,* 5(9), 2018, 1-11.

Please cite this article in press as: Jasmin, *et al*. Advances in niosome technology: A review on recent developments, *International Journal of Research in Pharmaceutical and Nano Sciences,* 13(3), 2024, 48-62.