REVIEW ARTICLE

Recent Advancements and Therapeutic Applications of the Niosomal Drug Delivery System

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Abstract

Niosomes are a novel class of creative vesicular structures. They are made of biodegradable and essentially harmless non-ionic surfactants. They were created as more affordable and reliable alternatives to liposomes. Their function has expanded to include various application areas since they were first introduced to the cosmetics sector. They are currently being investigated as prospective medication delivery systems for focused and sustained delivery. They can be administered through ocular, transdermal, vaginal, and inhalation in addition to traditional, oral, and parenteral methods. Niosome delivery of biotechnological goods, like vaccines, is another fascinating and promising study topic. These systems have become even more relevant in developing a particular strategy in the form of proteasomes. Further, focused research efforts are still needed to fully exploit these innovative technologies. With a focus on their function in drug targeting, this review examines the current state and promise of niosomes in drug delivery. Their preparation techniques, formulation features, benefits, drawbacks, and applications are also described.

Key words: Drug delivery system, liposomes, niosomes, sustained delivery

INTRODUCTION

An "ideal system" would target the active ingredient at the site and supply the medication at a pace determined by the body's demands during treatment in motion. Strategies are modified to accomplish this by carefully considering medication delivery. It is managed by including it in formulation via changing the active pharmaceutical ingredients (API) composition using molecular mechanisms, or by operating the contribution of the medication into the biosphere to certify a suitable distribution. According to previous years, a tonne of research has been done on this topic and drug delivery. Researchers are working non-stop to create innovative systems that can overcome the restrictions and drawbacks of traditional therapy. Victory in possibly addressing some or all of these difficulties would increase effectiveness and patient compliance and limit negative effects.[1,2]

Until now, research has focused heavily on vesicular system evaluation for improving medication performance.[3,4] Including liposomal carriers, niosomal carriers, transpersonal carriers, pyrosomes, and autosomal carriers are the main components of vesicular systems. Vesicular systems have several benefits, including incorporating hydrophilic and lipophilic API, sustained delivery, the improved oral bioavailability of biopharmaceutical classification system Class II drugs, postponed API excretion of quickly metabolized APIs, and improved biopharmaceutical issues of the APIs. In addition, the systemic phagocytic absorption of a drug-loaded vesicular delivery system provides an attractive route to administer the API directly into the site of infection, decreasing API side effects.[5,6]

Mostly, the vesicle-based formulations being researched for API administration are liposomal[7-11] and niosomal

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formulations.[12] The simple tiny vesicles called liposomes have an aqueous compartment and a core of lipid bilayers.[13] Liposomes are favorable when it comes to medication protection, controlled delivery of the API component combined with the site of administration, and endocytosis-based drug uptake. Nevertheless, there are still a lot of issues with using liposomes in general for medication delivery. Leaching of pharmaceuticals, sedimentation, destruction by oxidation or hydrolysis, and fusion of liposomal carriers throughout storage are a few of their main drawbacks.[14-16] Sterilization challenges and manufacturing at large scale offer formulations with good pharmaceutical stability are issues with therapeutic applications of liposomes.[17] Other limiting considerations are phospholipids' price and fluctuating purity.[18] They are suitable for parenteral administration but cannot be given orally due to liposomes' inability to withstand bile salts and phospholipase action. Liposomes are challenging to handle in a cold environment, which has led to the usage of surfactant (non-ionic) vesicles, that is, niosomal carriers.

Niosomes have different advantages over liposomes despite behaving similarly to them *in vivo*.[19] They are less prone to instability and lack the disadvantages of liposomes, such as the requirement for inert processing conditions and variable purity of phospholipids. Niosomes, or vesicular nanocarriers, have garnered a lot of attention as potential drug delivery vehicles during the past 30 years due to their unique advantages. They are contained in an aquatic compartment and have lamellar (bilayer) structures based on amphiphilic molecules. Amphiphilic molecules, such as surfactants, can self-assemble into a variety of shapes, including micelles and planar lamellar bilayers.[20] Drug delivery strategies that might be employed include sorbitan esters, sugar, polyoxymethylene, polyglycerol, and membrane lipids like cholesterol or its derivatives. Non-ionic surfactants are preferred over cationic surfactants due to the latter's greater propensity to irritate skin.[21]

Niosomes are vesicular systems with specialized features that encapsulate hydrophilic and lipophilic molecules. Lipophilic compounds are trapped within the lipophilic part of the phospholipid's bilayers via a partition mechanism, whereas hydrophilic medicines are often enclosed in the aqueous core. All the experimental procedure analyses involve hydrating a mixture of amphiphiles above the gel to the system liquid transition phase temperature. Following this an optional size reduction step produces a colloidal dispersion, as the development of vesicular formulations needs the participation of energy.[22] Colloidal vesicles were exploited as nanocarriers to enable drug targets, controlled delivery, and permeability enrichment due to their potential capacity to transport various treatments.[4] In fact, by modifying the content, concentration, and charges of the developed vesicle and membrane components, niosomes formulations could operate as therapeutic nanocarriers for the regulated distribution of an API to increase bioavailability and obtain a therapeutic impact over a longer time.[23] In addition, it has been discovered that drug ionization modifies the physicochemical characteristics of the niosomes and their transdermal penetration patterns since it can readily be derivatized to increase vesicle flexibility to enhance the attraction for the site of the region.[24]

Basic properties of Niosomal carrier

- The basic properties of niosomes are discussed below:
- They are stable on their own and osmotically active. It strengthens the stability of trapped as well as on one's drugs.[25]
- Niosomes can accommodate hydrophobic and hydrophilic enhance the oral therapeutic bioavailability of API.
- Structural characteristics of niosomal formulations, for instance, their formulations composition, vesicle size, entrapped volume, and surface charge are flexible.
- Niosomes allow hydrophilic moieties to adhere to their surface in a bilayer, changing the way they behave *in vivo*. Positive, neutral, or negative charges can bind or anchor these moieties to the polar groups of amphiphilic monomers. Niosomes charge type and density impact their permeability and stability.
- Niosomal amphiphiles show biocompatibility, non-immunogenicity, and degradable. They are mainly harmless since they are non-ionic.
- Niosomes may entrap small to large DNA substances with various molecular weights.
- Niosomal vesicles through intravenous route are sent to RES. When RES is incorporated, this passive targeting aspect can be effectively used, for instance, hepatotoxicity, metal poisoning in the hepatic cells, inflammatory diseases, and leishmaniasis.[26]

Advantages and disadvantages of niosomal carrier

- No undesirable solvents are utilized in the procedure employed to produce niosomes on a regular and enormous scale.
- Niosomes handling and storage do not require any specific circumstances because physic-chemical issues of their structural makeup.
- By modifying their structural makeup and manufacturing process, niosomes physicochemical characteristics could be changed.
- Niosomes can pack a lot of information into a small vesicular volume.
- Niosomes can be employed to deliver labile and sensitive medications since their structure shields therapeutic ingredients from diverse influences both within and outside the body.
- By confining effects to specific cells and delayed clearance through circulation, niosomes enhance the therapeutic effectiveness of drug compounds.

- Niosomes can be used to administer medications through various routes and in various drug delivery carriers. This increases the efficacy and permeation of APIs through the skin.
- Niosomes exhibit more effectiveness than traditional oily formulations and increase patient adherence and satisfaction.[27]

In Figure 1 there are various Methods of preparation of niosomal carriers are mention.

PREPARATION TECHNOLOGIES OF NIOSOMAL CARRIERS

Thin film formation

This preparation technique is simple, economical, and extensively employed. In this procedure, 100 mL RBF containing an organic solvent is mixed with the formulation components such as amphiphiles, cholesterol, and positive or negative charged compounds.[28,29]

Injection method

The amphiphiles and additional components are combined with diethyl ether, dissolved, and then gradually injected using a syringe into an aqueous-based API solution that is maintained at a temperature that is consistently higher than the organic solution's boiling point. The vesicles develop and take on characteristics during evaporation.[31,30]

Reverse phase evaporation

The niosomal components are mixed with the dissolved combination of ether-chloroform solution before being introduced to the drug-containing aqueous phase. The developed solution was ultrasonicated forming an emulsion. From this, the organic phase is evaporated. The organic solvent's evaporation results in sizable unilamellar vesicles.[32-34]

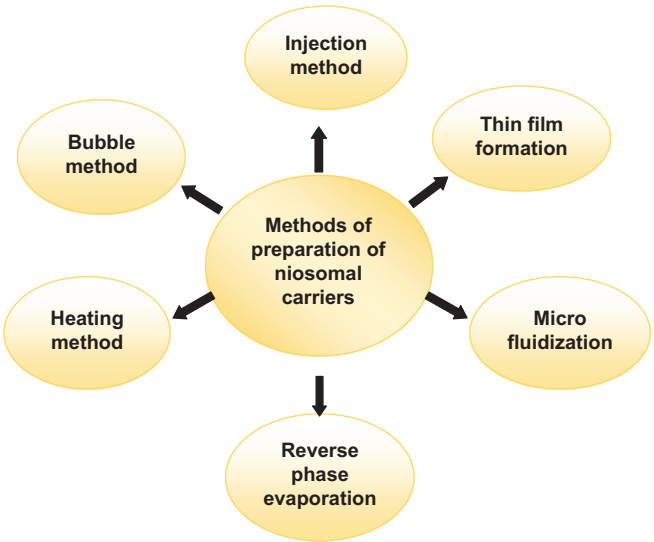

Figure 1: Methods of preparation of niosomal carriers

Micro fluidization

The micro fluidization technique is based on the submerged jet concept. Using this method, the reaction chamber's tiny; precisely defined microchannels saw very high speeds of interaction between the fluidized streams of drug and surfactant. The impact's high speed and energy cause niosomes to form. This method yields unilamellar-based vesicles, homogeneity, and optimal size and shape in niosome creation.[35,36]

Heating method

The heating method was patented and developed earlier. Hydrating the amphiphiles and the cholesterol in the buffer solution independently. The prepared mixture is subjected to heat at 120°C to provide easy dissolution of cholesterol. After this, continued stirring is required to maintain the dissolution status of amphiphiles and cholesterol. At this point, niosomal formulations are formed, allowed to cool to 25°C, preserved at a lower temperature in the presence of nitrogen, and characterized.[37,38]

Bubble method

A glass flask with three necks that is loaded with buffer, additives, and surfactants is used in the bubble technique. The components of a niosome are distributed at 70°C and then mixed using a homogenizer. The contents of the flask are immediately immersed in a water bath as 70°C nitrogen gas bubbles. Propelling N2 gas through a homogenized amphiphile sample causes the formation of large unilamellar vesicles.[39]

PHYSICO-CHEMICAL AND FUNCTIONAL CHARACTERIZATION OF NIOSOMAL CARRIERS

Particle size

The methods most often employed to ascertain the sizes and forms of niosomes. Among its components are transmission electron microscopy, electron microscopy for freeze-fracture replication, electron microscopy for scanning, dynamic light scattering, and cryogenic transmission electron microscopy.[40,41] DLS provides useful information on the homogeneity of a solution and cumulative information regarding particle size at the same time. The PI is advantageous

in this sense. In colloidal systems, a homogenous population is indicated by a value smaller than 0.3. Microscopic inspection is the most often used technique to study the morphology of niosomes.[42]

Bilayer characteristics

It is possible to evaluate the membrane stiffness of niosomal formulations by examining the fluorescent probe's mobility in relation to temperature. The most popular fluorescent probe, 1,6 diphenyl1,3,5-hexatriene, which usually sits in the hydrophobic area of the bilayer membrane, is paired with niosomal formulations. Fluorescence polarization measures the microviscosity of the niosomal membrane; a high fluorescence polarization[43] suggests a significant microviscosity of the membrane. Energy-dispersive X-ray diffraction *in situ*, as well as the previously described.[44]

Percent entrapment efficiency (EE)

The percentage of an API that niosomal formulations are able to capture is known as EE%. Three methods can be used to extract the unencapsulated free medication from the niosomal fluid: Gel chromatography, dialysis bag, and centrifugation.[45] By rupturing the vesicles, the encapsulated drug was liberated from the niosomal carrier. Methanol or 0.1% Triton X-100 can be added to get niosome-free niosomal solution. Spectrophotometers or high-performance liquid chromatography (HPLC) can be used to determine the drug concentration in both the loaded and free states.[46]

Stability studies

The stability of niosomes may be evaluated by calculating the average niosomal carrier size and percent entrapment effectiveness in comparison to many storage times at different temperatures. Throughout storage, niosomes are routinely evaluated to ascertain the amount of medicine retained in the niosomes, which is then ascertained through the use of ultraviolet spectroscopic or HPLC techniques.[47,48]

Dissolution studies

One approach that is frequently used to study API dissolution is based on the use of a dialysis membrane. A dialysis membrane is cleaned and given a freshly prepared aqueous solution to soak in. The API-encapsulated niosomal dispersion was loaded into a freshly prepared dialysis bag. The vesicle-loaded bag was submerged in a buffer media and vigorously shaken at a temperature of 25°C or 37°C. Samples were taken out from the dissolution media at a scheduled interval and replenished with the same media. Using the proper test method, the samples are examined for the presence of drugs.[49]

In Figure 2 various Therapeutic applications of niosomal carrier are involved.

THERAPEUTIC APPLICATIONS OF NIOSOMAL CARRIER

For lung administration

In-depth research on lung cancer and other malignant diseases has been done on all-trans-retinoic acid (ATRA).[50] Chronic administration of retinoids in patients is linked to adverse consequences, like many other anticancer medications.[51] According to Desai and Finlay (2002), niosomal ATRA was released to the lungs at higher doses through aerosolization with no discernible adverse effects. To accomplish the best encapsulation efficiencies, a variety of non-ionic surfactants were utilized. The niosomal formulations were produced using the association of span and tweens with an ATRA (1 mg/mL). Following this, the aerosol created with the chosen niosomal formulations was examined to determine the vesicle size and EE on separate phases of an Anderson cascade impactor. It prevented false sizing brought on by droplet evaporation. The optimized formulations produced mass median aerodynamic diameters of ~ 3.7 0.3 and ~ 3.58 0.03 m, geometric standard deviation values of ~ 1.59 0.17 and ~ 1.51 0.01, and entrapment efficiencies considerably >50%. The positive outcomes provided a different method for delivering ATRA via aerosolization to the respiratory system.[52] Conventional niosomal formulations were first created using the reverse phase evaporation method. Proniosomes were hydrated with 0.9% saline at 50°C and mixed for about 2 min to produce proteasome-derived niosomes. When proniosomes were prepared by covering the niosomal carrier surface with the amphiphile-phospholipids mixture, resulting vesicles had a high drug EE. The proteasome-derived niosomes successfully retarded the drug release rate compared to a typical drug solution, with the t50% value of the release pattern. They also obtained good physical stability and a high nebulization efficiency percentage. Their research suggested that prolonged-release p-derived niosomes might be produced as suitable API nanocarriers for the nebulized delivery of cromolyn sodium.[53]

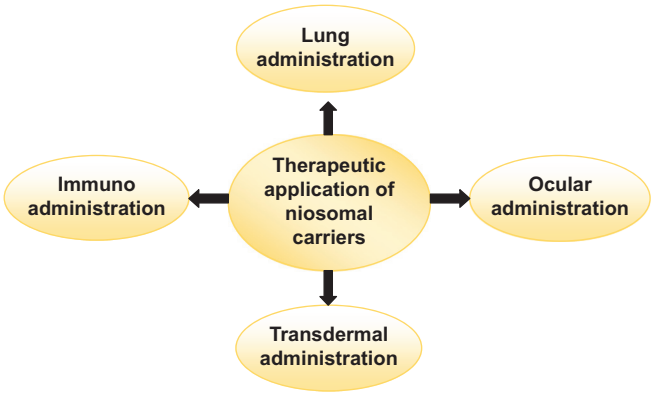

Figure 2: Therapeutic applications of niosomal carrier

For ocular administration

The niosomal formulations aid in extending and regulating the effect at the surface of the cornea and halting the drug biotransformation through the enzymatic system found at the corneal surface. The medicine is more able to divide and go through the cornea thanks to the vesicles' encapsulated drug. Niosomes also present a viable path to meet the demand for an ocular drug delivery technology that is as convenient as a conventional formulation, however, it could localize and preserve API efficacy at the ocular site.[54]

Niosomal carriers were mentioned by Guinedi *et al*. as a potential solution to the limited bioavailability and corneal penetration characteristics displayed by standard ophthalmic vehicles. Two techniques, that is, thin film hydration and reverse phase evaporation were used to create niosomal carriers using Spans and cholesterol in the molar ratios of ~ (7:4), ~ (7:6), and ~ (7:7). Ashot tonometer, the ability of acetazolamide niosomal formulations to reduce intraocular pressure (IOP) in rabbits was assessed. Their findings demonstrated that the API inclusion effectiveness and its dissolution rate from niosomal formulations were significantly impacted via surfactant type, cholesterol level, and manufacturing technique. Niosomal formulations (multilamellar) prepared from the components of (span 60 and cholesterol at a 7:6 molar ratio) produced higher inclusion efficiency. As compared to the API and plain niosomal formulations, each of the evaluated acetazolamide niosomes made using either approach resulted in a considerable reduction in IOP. It was discovered that acetazolamide-loaded niosomal formulations (containing span 60 and cholesterol in a 7:4 molar ratio) were the most efficient and demonstrated a sustained reduction in IOP. After 40 days of niosomal formulation instillation, histological analysis of corneal tissues revealed minor irritation to the eye.[55]

For transdermal administration

Proniosomes and niosomes have been extensively studied to improve different medicine penetrations. Following a topical administration, proniosomes transform into niosomal carriers because of the skin-assisted hydration mechanism. Proniosomal gel, unlike niosomes, may be made directly into a transdermal patch without the need for vesicles to be dispersed into a polymer matrix.[56,57]

For Immuno administration

Public health organizations are placing a high premium on non-invasive vaccine administration because traditional immunization methods are risky and have a lot of drawbacks. Skin administration of vaccinations has recently gained attention as a viable alternate route. Utilizing vesicular systems is one way to improve the bioactive ability to penetrate the skin. Vesicles, that is, transpersonal, niosomal, and liposomal formulations were used by Gupta *et al*. to examine their potential for non-invasive tetanus toxoid delivery (TT). After topical immunization, the serum anti-TT immunoglobulin G (IgG) titer was used to measure the immunoactivity of the above-mentioned vesicles. They compare the immunological response induced by topical immunization to that induced by intramuscular injection of the same amount of alum-adsorbed TT. According to an *in vivo* investigation, applying TT-containing transferosomes topically after a secondary immunization can cause an immunological response (anti-TT-IgG) comparable to that following an intramuscular injection of a TT-based vaccine. Niosomes and liposomes elicited a lesser immunological response than transferosomes.

A monoclonal antibody attached to CD44 (IM7) was coupled with niosomes made by Hood *et al*. through association between cyanuric chloride and polyoxyethylene group of the Tween 61. The niosomes were made of components (i.e., span 60, tween 61, cholesterol, and diacetyl phosphate). Compared to span 60 niosomes, an adequate quantity of tween 61 in the amphiphilic part of niosomal carrier was created using thin-film hydration methods. Synovial lining cells expressing CD44 were added to the immuno-niosomes for incubation. Niosome attachment was obvious and demonstrated selectivity and specificity, respectively. This study revealed that the resulting niosomal formulations would offer a valuable way to deliver drugs to specific targets.[58]

CONCLUSION AND FUTURE PERSPECTIVES

The current data provides a thorough overview of niosomes makeup, benefits, applications, function (as percutaneous permeation enhancer), and more updated uses as transdermal formulations. The percutaneous administration of hydrophilic and lipophilic medicines is a promising application for niosomes as controlled delivery systems. Utilizing new methods for niosome preparation, loading, and customization can increase their potential. These regions require additional investigation and study to create niosomal preparations that can be sold commercially. In consideration of its physical stability, potential for medicinal purposes, and skin toxicity, the amphiphiles category represents a viable parameter in the development of niosomal formulations. Researchers should be aware of the need for an appropriate selection of suitable surfactants for the preparation of niosomes.

AUTHOR CONTRIBUTION STATEMENT

Mayur Dandekar and Prajakta Dandekar collected the information and discussed it with the corresponding author. Following the discussion, Mayur Dandekar prepared the initial draft. Prajakta Dandekar and Sejal Telrandhe wrote the second draft of the manuscript. The co-author offered

feedback on an initial draft of the paper before it was polished. After reading and giving their approval, each author signed the text in its final form. For this work, the sequence of authorship was approved by the corresponding author.

REFERENCES

1. Elsayed MM, Abdallah OY, Naggar VF, Khalafallah NM. Deformable liposomes and ethosomes: Mechanism of enhanced skin delivery. Int J Pharm 2006;322:60-6.
2. Cosco D, Celia C, Cilurzo F, Trapasso E, Paolino D. Colloidal carriers for the enhanced delivery through the skin. Expert Opin Drug Deliv 2008;5:737-55.
3. Mokhtar M, Sammour OA, Hammad MA, Megrab NA. Effect of some formulation parameters on flurbiprofen encapsulation and release rates of niosomes prepared from proniosomes. Int J Pharm 2008;361:104-11.
4. Rai K, Gupta Y, Jain A, Jain SK. Transfersomes: Self-optimizing carriers for bioactives. PDA J Pharm Sci Technol 2008;62:362-79.
5. Rao Y, Zheng F, Zhang X, Gao J, Liang W. *In vitro* percutaneous permeation and skin accumulation of finasteride using vesicular ethosomal carriers. AAPS PharmSciTech 2008;9:860-5.
6. Azeem A, Khan ZI, Aqil M, Ahmad FJ, Khar RK, Talegaonkar S. Microemulsions as a surrogate carrier for dermal drug delivery. Drug Dev Ind Pharm 2009;35:525-47.
7. Caddeo C, Teskac K, Sinico C, Kristl J. Effect of resveratrol incorporated in liposomes on proliferation and UV-B protection of cells. Int J Pharm 2008;363:183-91.
8. Katanasaka Y, Ida T, Asai T, Maeda N, Oku N. Effective delivery of an angiogenesis inhibitor by neo-vessel-targeted liposomes. Int J Pharm 2008;360:219-24.
9. Garg A, Tisdale AW, Haidari E, Kokkoli E. Targeting colon cancer cells using PEGylated liposomes modified with a fibronectin-mimetic peptide. Int J Pharm 2009;366:201-10.
10. Zheng X, Lu J, Deng L, Xiong Y, Chen J. Preparation and characterization of magnetic cationic liposome in gene delivery. Int J Pharm 2009;366:211-7.
11. Zhu L, Huo Z, Wang L, Tong X, Xiao Y, Ni K. Targeted delivery of methotrexate to skeletal muscular tissue by thermosensitive magneto liposomes. Int J Pharm 2009;370:136-43.
12. Hood E, Gonzalez M, Plaas A, Strom J, VanAuker M. Immuno-targeting of non-ionic surfactant vesicles to inflammation. Int J Pharm 2007;339:222-30.
13. Bangham AD, Standish MM, Watkins JC. Diffusion of univalent ions across the lamellae of swollen phospholipids. J Mol Biol 1965;13:238-52.
14. Frokjaer S, Hjorth EL, Worts O. Liposome Technology. Vol. 1. Florida: CRC Press; 2019 Jul 23. p. 235-45.
15. Arien A, Dupuy B. Encapsulation of calcitonin in liposomes depends on the vesicle preparation method. J Microencapsul 1997;14:753-60.
16. Alsarra IA. Evaluation of proniosomes as an alternative strategy to optimize piroxicam transdermal delivery. J Microencapsul 2009;26:272-8.
17. Müller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Adv Drug Deliv Rev 2002;54 Suppl 1:S131-55.
18. Vora B, Khopade AJ, Jain NK. Proniosome based transdermal delivery of levonorgestrel for effective contraception. J Control Release 1998;54:149-65.
19. Azmin MN, Florence AT, Handjani-Vila RM, Stuart JF, Vanlerberghe G, Whittaker JS. The effect of non-ionic surfactant vesicle (niosome) entrapment on the absorption and distribution of methotrexate in mice. J Pharm Pharmacol 1985;37:237-42.
20. Uchegbu IF, Florence AT. Non-ionic surfactant vesicles (niosomes): Physical and pharmaceutical chemistry. Adv Colloid Interface Sci 1995;58:1-55.
21. Moghassemi S, Hadjizadeh A. Nano-niosomes as nanoscale drug delivery systems: An illustrated review. J Control Release 2014;185:22-36.
22. Lasic DD. On the thermodynamic stability of liposomes. J Colloid Interface Sci 1990;140:302-4.
23. Mahale NB, Thakkar PD, Mali RG, Walunj DR, Chaudhari SR. Niosomes: Novel sustained release nonionic stable vesicular systems--an overview. Adv Colloid Interface Sci 2012;183:46-54.
24. Obata Y, Takayama K, Maitani Y, Machida Y, Nagai T. Effect of pretreatment of skin with cyclic monoterpenes on permeation of diclofenac in hairless rat. Biol Pharm Bull 1993;16:312-4.
25. Baillie AJ, Florence AT, Hume LR, Muirhead GT, Rogerson A. The preparation and properties of niosomes--non-ionic surfactant vesicles. J Pharm Pharmacol 1985;37:863-8.
26. Schreier H, Bouwstra J. Liposomes and niosomes as topical drug carriers: Dermal and transdermal drug delivery. J Controlled Release 1994;30:1-5.
27. Khoee S, Yaghoobian M. Niosomes: A novel approach in modern drug delivery systems. In: Nanostructures for Drug Delivery. Netherlands: Elsevier; 2017. p. 207-37.
28. Bhaskaran S, Lakshmi PK. Comparative evaluation of niosome formulations prepared by different techniques. Acta Pharm Sci 2009;51:20-5.
29. Rajera R, Nagpal K, Singh SK, Mishra DN. Niosomes: a controlled and novel drug delivery system. Biol Pharm Bull. 2011;34:945-53.
30. Abedullahh MH. Preparation and *in-vitro* evaluation of diclofenac sodium niosomal formulations. Int J Pharm Sci Res 2013;4:1757-65.
31. Rogerson A, Cummings J, Willmott N, Florence AT. The distribution of doxorubicin in mice following administration in niosomes. J Pharm Pharmacol 1988;40:337-42.
32. Moghassemi S, Parnian E, Hakamivala A, Darzianiazizi M, Vardanjani MM, Kashanian S, *et al*. Uptake and transport of insulin across intestinal

membrane model using trimethyl chitosan coated insulin niosomes. Mater Sci Eng C Mater Biol Appl 2015;46:333-40.
33. Budhiraja A, Dhingra G. Development and characterization of a novel antiacne niosomal gel of rosmarinic acid. Drug Deliv 2015;22:723-30.
34. Kiwada H, Niimura H, Fujisaki Y, Yamada S, Kato Y. Application of synthetic alkyl glycoside vesicles as drug carriers. I. Preparation and physical properties. Chem Pharm Bull (Tokyo) 1985;33:753-9.
35. Zidan AS, Rahman Z, Khan MA. Product and process understanding of a novel pediatric anti-HIV tenofovir niosomes with a high-pressure homogenizer. Eur J Pharm Sci 2011;44:93-102.
36. Verma S, Singh SK, Syan N, Mathur P, Valecha V. Nanoparticle vesicular systems: A versatile tool for drug delivery. J Chem Pharm Res 2010;2:496-509.
37. Mozafari MR. A new technique for the preparation of non-toxic liposomes and nanoliposomes: The heating method. In: Nanoliposomes: From Fundamentals to Recent Developments. United States: Trafford Publishing; 2005. p. 91-8.
38. Mozafari MR, Reed CJ, Rostron C. Cytotoxicity evaluation of anionic nanoliposomes and nanolipoplexes prepared by the heating method without employing volatile solvents and detergents. Pharmazie 2007;62:205-9.
39. Talsma H, Van Steenbergen MJ, Borchert JC, Crommelin DJ. A novel technique for the one-step preparation of liposomes and non-ionic surfactant vesicles without the use of organic solvents. Liposome formation in a continuous gas stream: The 'Bubble'method. J Pharm Sci 1994;83:276-80.
40. Tavano L, Aiello R, Ioele G, Picci N, Muzzalupo R. Niosomes from glucuronic acid-based surfactant as new carriers for cancer therapy: Preparation, characterization and biological properties. Colloids Surf B Biointerfaces 2014;118:7-13.
41. Priprem A, Janpim K, Nualkaew S, Mahakunakorn P. Topical niosome gel of *Zingiber cassumunar* Roxb. Extract for anti-inflammatory activity enhanced skin permeation and stability of compound D. AAPS PharmSciTech 2016;17:631-9.
42. Hua W, Liu T. Preparation and properties of highly stable innocuous niosome in Span 80/PEG 400/H2O system. Colloids Surf A Physicochem Eng Aspects 2007;302:377-82.
43. Manosroi A, Wongtrakul P, Manosroi J, Sakai H, Sugawara F, Yuasa M, Abe M. Characterization of vesicles prepared with various non-ionic surfactants mixed with cholesterol. Colloids Surf B Biointerfaces 2003;30:129-38.
44. Pozzi D, Caminiti R, Marianecci C, Carafa M, Santucci E, De Sanctis SC, *et al*. Effect of cholesterol on the formation and hydration behavior of solid-supported niosomal membranes. Langmuir 2010;26:2268-73.
45. Pando D, Gutiérrez G, Coca J, Pazos C. Preparation and characterization of niosomes containing resveratrol. J Food Eng 2013;117:227-34.
46. Mehta SK, Jindal N. Formulation of Tyloxapol niosomes for encapsulation, stabilization and dissolution of anti-tubercular drugs. Colloids Surf B Biointerfaces 2013;101:434-41.
47. Waddad AY, Abbad S, Yu F, Munyendo WL, Wang J, Lv H, *et al*. Formulation, characterization and pharmacokinetics of Morin hydrate niosomes prepared from various non-ionic surfactants. Int J Pharm 2013;456:446-58.
48. Hao Y, Zhao F, Li N, Yang Y, Li K. Studies on a high encapsulation of colchicine by a niosome system. Int J Pharm 2002;244:73-80.
49. Akhilesh D, Bini KB, Kamath JV. Review on span-60 based non-ionic surfactant vesicles (niosomes) as novel drug delivery. Int J Res Pharm Biomed Sci 2012;3:6-12.
50. Lokshin A, Zhang H, Mayotte J, Lokshin M, Levitt ML. Early effects of retinoic acid on proliferation, differentiation and apoptosis in non-small cell lung cancer cell lines. Anticancer Res 1999;19:5251-4.
51. Lippman SM, Kessler JF, Meyskens FL Jr. Retinoids as preventive and therapeutic anticancer agents (Part I). Cancer Treat Rep 1987;71:391-405.
52. Desai TR, Finlay WH. Nebulization of niosomal all-trans-retinoic acid: An inexpensive alternative to conventional liposomes. Int J Pharm 2002;241:311-7.
53. Abd-Elbary A, El-Laithy HM, Tadros MI. Sucrose stearate-based proniosome-derived niosomes for the nebulisable delivery of cromolyn sodium. Int J Pharm 2008;357:189-98.
54. Kaur IP, Garg A, Singla AK, Aggarwal D. Vesicular systems in ocular drug delivery: An overview. Int J Pharm 2004;269:1-14.
55. Guinedi AS, Mortada ND, Mansour S, Hathout RM. Preparation and evaluation of reverse-phase evaporation and multilamellar niosomes as ophthalmic carriers of acetazolamide. Int J Pharm 2005;306:71-82.
56. Azeem A, Jain N, Iqbal Z, Ahmad FJ, Aqil M, Talegaonkar S. Feasibility of proniosomes-based transdermal delivery of frusemide: Formulation optimization and pharmacotechnical evaluation. Pharm Dev Technol 2008;13:155-63.
57. Paolino D, Cosco D, Muzzalupo R, Trapasso E, Picci N, Fresta M. Innovative bola-surfactant niosomes as topical delivery systems of 5-fluorouracil for the treatment of skin cancer. Int J Pharm 2008;353:233-42.
58. Gupta PN, Mishra V, Rawat A, Dubey P, Mahor S, Jain S, *et al*. Non-invasive vaccine delivery in transfersomes, niosomes and liposomes: A comparative study. Int J Pharm 2005;293:73-82.

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