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Review Article

Niosome as Drug Carrier: Novel Approach

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ABSTRACT

Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. Noisome are non-ionic surfactant vesicles obtained by hydrating mixture of cholesterol and nonionic surfactants. It can be used as carriers of amphiphilic and lipophilic drug. The main objective of this review is application of noisome in various drug delivery systems depending upon their types and method of preparation. Niosomes improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells. The application of niosomal technology is widely used to treat a number of diseases. This article also present an overview of the techniques of preparation of niosome, types of niosomes and their evaluation parameters.

Keywords: Niosomes, Vesicles, Drug Delivery, Target Cells, Biological Environment.

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INTRODUCTION

Oral drug delivery is considered as one of the important route of drug administration. Still it has to face many significant drawbacks i.e. poor plasma availability due to pre-systemic metabolism. The probability of blood level fluctuation causes inconvenience as well as lesser economy. To overcome these complications there is a need for the development of new drug delivery systems which would improve the therapeutic efficacy and safety of drugs through various novel approaches. [3, 4]

NIOSOMES

Niosomes or non-ionic surfactant vesicles are microscopic lamellar structures formed on the admixture of a non-ionic surfactant of the alkyl or dialkyl polyglycerol ether, cholesterol and phosphate with subsequent hydration in aqueous media". Structurally, they resemble with liposomes and possess equivalent drug delivery potential. Niosomes are tiny lamellar structures (10 to 1000 nm) and consist of an admixture of non-ionic biodegradable, non-immunogenic and biocompatible surfactants and cholesterol. These are amphiphiles allowing entrapment of both hydrophilic and hydrophobic drugs within the bilayers. They are advantageous over conventional dosage forms. Niosomal drug delivery system is one of the best examples of great evolution in drug delivery technologies and nanotechnology. It is obvious that noisome appears to be a well preferred drug delivery system over other dosage form as noisome mostly stable in nature and economic. There is lot of scope to encapsulate toxic anti-cancer drugs, anti-infective drugs, anti-AIDS drugs, anti-inflammatory drugs, anti-viral drugs, etc. in noisome and to use them as promising drug carriers to achieve better bioavailability and targeting properties and for reducing the toxicity and side effects of the drugs. Thus these areas require further systemic consideration and research so as to bring out commercially and valuable available niosomal preparation.[5,6]

The concept of incorporating the drug into or noisome for a better targeting of the drug at appropriate tissue destination is widely accepted by researchers and academicians. The ionic drug carriers are relatively toxic and unsuitable whereas niosomal carriers are safer. And also handling and storage of noisome require no special conditions. Niosomes represent a promising drug delivery module. They have similar structure to liposome, to little same in property and hence they can represent alternative vesicular systems with respect to liposomes, due to the noisome ability to encapsulate different type of drugs within their multi-environmental structure. Niosomes are thoughts to be better candidate drug delivery as compared to liposomes due to various factors like cost, stability etc. Niosomes have very important and key role in various types of drug deliveries; like targeting, topical, ophthalmic and parenteral. Niosomes are very useful in bright future for pharma industries. So far only animal experimentation of this targeted drug delivery system is reported but further clinical investigations in human volunteers, pharmacological and toxicological investigations in animals and human volunteers may help to exploit noisome as prosperous drug carriers for targeting drugs more efficiently, for treating cancer, infection and AIDS.

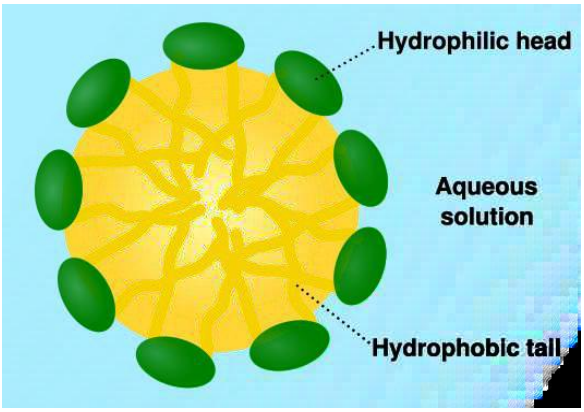

Fig 1. Structure of noisome

Advantages of Niosomes [6,8]

- The vesicle suspension is water – based vehicle.
- It offers high patient compliance in comparison to other dosage forms. ·
- They are amphiphilic in nature so can accommodate both types of moieties together i.e. hydrophilic and lipophilic.
- Niosomes are osmotically active and stable; also increase the stability of entrapped drug.
- They also act depot and release the drug in controlled manner.
- No special conditions are required for their handling and storage.
- They enhance oral bioavailability and improve penetration of poorly absorbed and permeable drugs respectively.
- They can be targeted to site of action by oral, parenteral as well as topical routes.[12]
- They also improve the therapeutic performance of the drug molecules by delayed clearance, protecting the drug from biological environment and restricting effects to target cells.
- The surfactants used are biodegradable, biocompatible and non-immunogenic.

- The drug delivery rate can be regulated by emulsifying niosomal aqueous dispersion to non-aqueous dispersion.

Types of Niosomes based on size

The noisome are classified as a function of the number of bilayers (e.g. MLV, SUV) or as a function of size. (E.g. LUV, SUV) or as a function of the method of preparation (e.g .REV, DRV). The various types of noisome are described below:

1. Multi lamellar vesicles (MLV)(MLV, (Size = > 0.05 µm)
2. Large unilamellar vesicles (LUV), (Size = > 0.10 µm).
3. Small unilamellar vesicles (SUV), (Size = 0.025-0.05 µm)

1) **Multilamellar vesicles (MLV):** It consists of a number of bilayers surrounding the aqueous lipid compartment separately. The approximate size of these vesicles is 0.5-10 µm diameter. Multilamellar vesicles are the most widely used noisome. these vesicles are highly suited as drug carrier for lipophilic compounds.

2) **Large unilamellar vesicles (LUV):** Niosomes of this type have a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materials can be entrapped with a very economical use of membrane lipids.

3) **Small unilamellar vesicles (SUV):** These small unilamellar vesicles are mostly prepared from multilamellar vesicles by Sonication method, French press extrusion electrostatic stabilization is the inclusion of dicetyl phosphate in 5(6)-carboxyfluorescein (CF) loaded Span 60 based noisome.

Types of niosomes based on ingredient use for the preparation[22]

i) Niosomes made by bola surfactants: Niosomes prepared by the surfactants, and which are composed of omega-hexadecylbis-(1-aza-18 crown-6) (bola surfactant): span- 80/ cholesterol in 2:3:1 molar ratio.

ii) Proniosomes: Proniosomes are the niosomal preparation excluding vesicles and surfactants, the proniosome have been hydrated before being used in the formulation of aqueous noisomal dispersion. The proniosomes helps in decreasing the leaking, aggregation and binding problem linked with niosomal preparation.

iii) Aspasome: Aspasome is a nano carriers it formulated by addition of highly charged mixtures like cholesterol, palmitate, and lipid diacetyl phosphate. Niosomes are prepared by primarily involving aspasomes to hydrate with water or aqueous solution and later sonicated. Aspasomes are highly been used to increase the penetration of drugs into the skin in transdermal drug delivery system. Aspasomes have gained importance for decreasing the disorders caused by reactive oxygen species (ROS) because of antioxidant property which is inbuilt.

iv) Niosome incorporated with carbopol gel: The niosomes are prepared using the mixture of spans, cholesterol and drug. The formulation of niosomes obtained were later fused into the base containing the glycerol (30% w/w) carbopol-934 gel (1%w/w) and propylene glycol{PG}(10% w/w). Thus helps in more efficient handling and stability of the system.

v) Vesicles in water and oil system (v/w/o): When aqueous niosomes are emulsified in an oil phase shows in the formation of nano carrier in water in oil emulsion (v/w/o). Which by cooling to room temperature forms nano vesicles in water in oil gel (v/w/o gel)? The v/w/o gel for the controlled release of drug or protein
the obtained gel can capture the proteinous drug or drug which is protected from degradation by enzyme after administering orally. E.g.: suspension formulated by the mixture of sorbitol monostearate, cholesterol, and solulan C24.

vi) Niosomes of hydroxyl propyl methyl cellulose {HPMC}: For this type of formulation, a base was first prepared by using 10 percentages HPMC was and later niosomes were incorporated in it wherein in this system the bioavailability of the drugs was found to be higher.

METHODS OF PREPARATION OF NIOSOMES:

Ether injection method: Niosomes are prepared by using a solution of surfactant in diethyl ether incorporated into warm water (60°C). A 14-gauge needle is used to inject into the aqueous solution. Upon vaporization, single layered vesicles are formed whose diameter ranges between 50-1000 nm.

Hand shaking method (Thin film hydration technique): A mixture of surfactant and cholesterol is dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) which is later on taken off at 20°C using rotary evaporator. The surfactant film, thus formed, is rehydrated with aqueous phase (0-60°C).

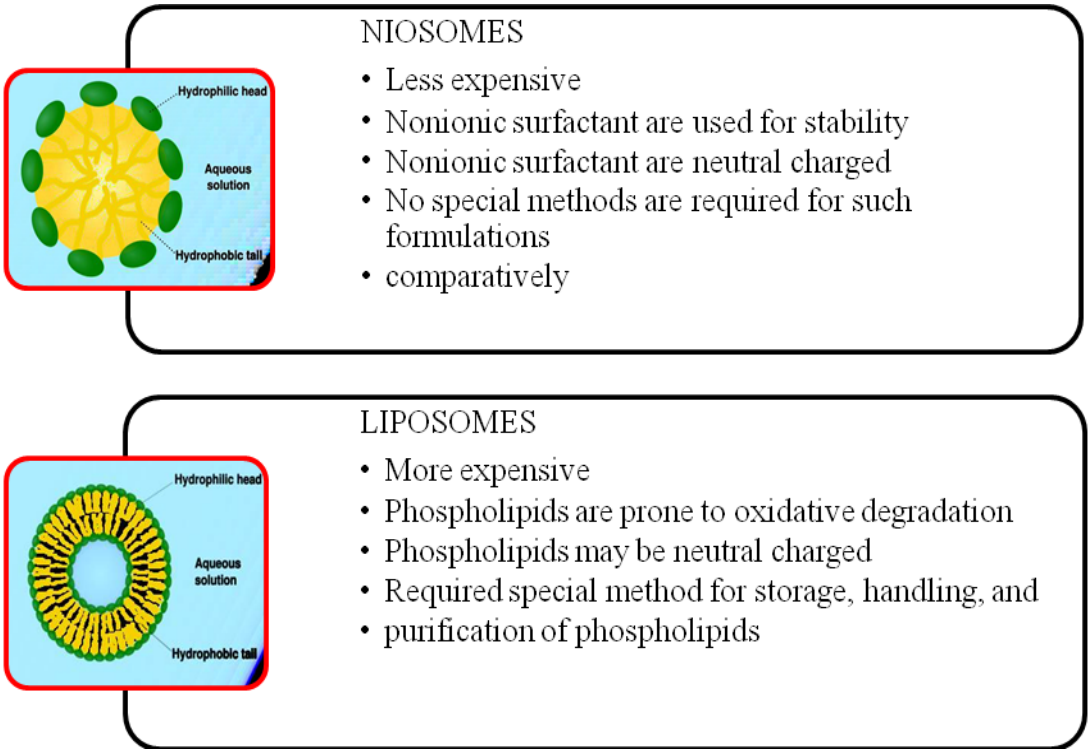

Figure 2: Major differences in characteristics between liposome and noisome.

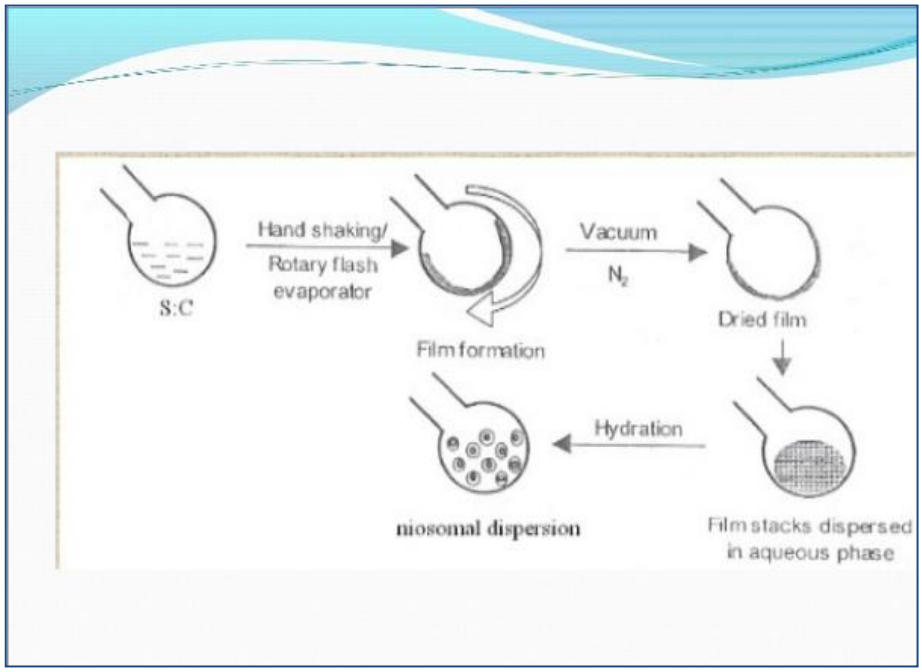

Figure 3: Hand shaking method

Sonication: The surfactant/cholesterol mixture is added with a predetermined volume of drug solution prepared in a buffer medium. The solution is further subjected to probe Sonication (at 60°C for 3 minutes). The sonicator is equipped with a titanium probe.

Micro fluidization: It is most widely used technique adopted for the preparation of noisome of unilamellar morphology. Two fluidized streams interact at ultra-high velocities (micro channels) within the interaction chamber. The impingement of thin liquid sheet along a common front is arranged such that the energy supplied to the system remains within the area of noisome formation which results in greater uniformity, smaller size and better reproducibility of noisome.

The "Bubble" Method: It is a novel technique which involves preparation of noisome and

liposome in the single step without expenditure of organic solvents. Bubbling unit comprised of three round neck flasks positioned in water bath to control the temperature. In first and second neck, water-cooled reflux and thermometer is positioned and through the third neck nitrogen supply is provided. Cholesterol and surfactant are dispersed together in pH 7.4 phosphate buffers at 70°C. Dispersion is mixed for 15 seconds with high shear homogenizer and immediately afterwards "bubbled" at 70°C using nitrogen gas.

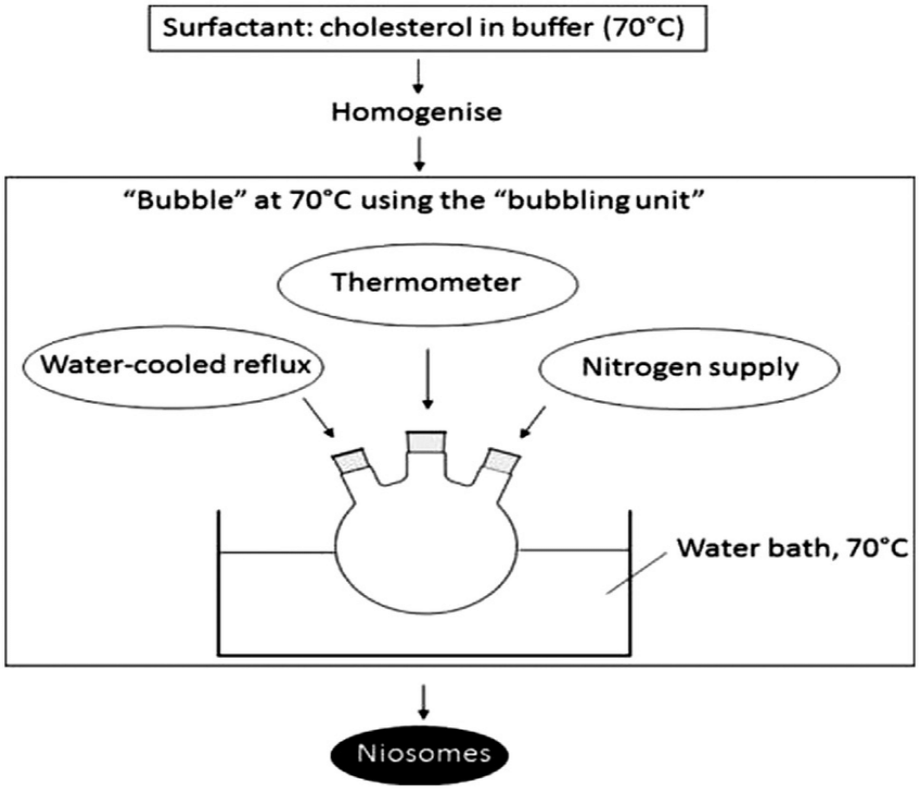

Figure 4. Figure depicting bubble method

Reverse Phase Evaporation Technique (REV): In a mixture of ether & chloroform, cholesterol and surfactant (1:1) are dissolved. An aqueous phase comprised of drug is added to the above mixture which is then sonicated at 4-5°C. The clear gel thus prepared is further sonicated after the addition of small amount of phosphate buffer 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 noisome.

Miscellaneous

Multiple membrane extrusion method: A mixture of surfactant, cholesterol and di acetyl phosphate are dissolved in chloroform and the solvent is evaporated until the formation of thin film. Using aqueous drug solution, the film is hydrated and the resultant suspension extruded through polycarbonate membrane. This method is used for controlling noisome size. [13, 14]

Preparation of noisome from proniosomes: To produce noisome the final step is to coat the carrier which is soluble in water for example glucitol with surface acting agents. The dry formulation is obtained by this technique where each particle which is soluble in water is coated with a surfactant which is thin film and dry. This formulation is called as "Proniosomes"

CHARACTERIZATION OF NOISOME (VESICLE CHARACTERIZATION)

Incompatibility studies between drugs: Incompatibility studies between drugs were performed using a stability chamber. In this study, equal amounts of each drug were taken, mixed uniformly, transferred to light resistant glass vials, and placed in a stability chamber. Individually, each drug was also placed at 65% relative humidity and 45°C temperature for 1 month. Infrared and ultraviolet (UV) spectroscopy used to investigate any interaction between the drugs. [18]

Surface morphology

The noisome vesicles characterized for their shape and surface morphology using transmission electron microscope (TEM) and scanning electron microscopy (SEM).

Procedure:

For TEM: - A drop of niosomal dispersion was smeared to a carbon film-covered copper grid and was stained with a 1% phospho-tungstic acid. Then, samples were examined and photograph with TEM at an accelerating voltage of 100 kV.

For SEM:- The samples are dried thoroughly in vacuum desiccators before mounting on brass specimen studies, using double sided adhesive tape. Gold palladium alloy of 120 °A Knees was coated on the sample sputter coating unit in Argon at ambient of 8-10 °C with plasma voltage about 20mA. The sputtering was done for nearly 5 minutes to obtain uniform coating on the sample to enable good quality SEM images.

Vesicle size and Zeta potential

The significance of zeta potential is that its value can be related to the stability of colloidal dispersions. The zeta potential indicates the degree of repulsion between adjacent, similarly charged particles in dispersion. The mean vesicle size and its distribution were estimated by using particle size analyzer based on photon correlation spectroscopy at temperature 25°C. Zeta potential of the vesicles directs the stability of the noisome and was measured by Zetasizer working on the principle of electrophoretic light scattering.[18]

Differential scanning calorimetry (DSC)

Niosomal pellets were lyophilized. Differential scanning calorimetry (DSC) thermograms for individual components, Span 60, Span 40, Cholesterol, SA and DCP, as well as the drug powder, were investigated. A heating rate of 5°C/min was employed over a temperature range (30–250)°C.

Temperature of hydration

Niosomes formed will be directly influenced by the shape and size due to hydration temperature. The systems temperature must be higher than the gel phase to liquid phase transition which affects the vesicular shape and even affects the organization of the surfactants inside the vesicle.

Stability test

The ability of the vesicles to retain the active substance was determined by storing the niosomal suspension under different temperature conditions: 4±2°C (refrigerator), 25±2°C (room temperature), and 45±2°C (high temperature) for 12 weeks. Samples were periodically tested (every 2 weeks) for active substance content, in the manner described in the entrapment efficiency procedure.

***In vitro* drug release study of noisome**

In vitro release of drug from noisome was implemented using the dialysis bag method (as reported by Bala Subramanian et al., 2002) with slight modifications. The study was carried out using methanolic phosphate buffer (pH 5.6) as release medium. Two millilitre of the niosomal dispersion was filled in dialysis bag and was suspended in a conical flask containing 50 ml of release medium. The temperature was maintained at about 37) ^{O} C in the shaking incubator with 100 rpm. Quantitative analysis was carried out immediately after withdrawal of samples at predetermined time intervals, using UV–Vis spectrophotometer under validated conditions. Percentage cumulative drug released was plotted against time.

Entrapment efficiency

Entrapment efficiency of noisome was determined by exhaustive dialysis method. The measured quantity of niosomal suspension was taken into a dialysis tube to which dialysis membrane was securely attached on one side. The dialysis tube was suspended in 100 ml PBS pH 7.4 containing 10% v/v methanol, which was stirred on a magnetic stirrer. The unentrapped drug was separated from the niosomal suspension into the medium through the membrane. At every hour, entire medium (100 ml) was replaced with fresh medium (for about 6‑7 h).

Absorbance reached a constant reading indicating no drug is available in an unentrapped form. Inclusion of CHO in noisome increases its hydrodynamic diameter and entrapment efficiency. It stabilizes noisome and decreases the permeability of vesicles to entrapped solute preventing leakage. An increase in CHO content of the bilayers resulted in a decrease in the release rate of encapsulated material and therefore, an increase of the rigidity of the bilayers obtained. Presence of charge tends to increase the inter lamellar distance between successive bilayers and leads to greater overall entrapped volume. The withdrawn samples were analyzed at 225 nm using a UV spectrophotometer. Amount of entrapped drug was obtained by subtracting amounts of unentrapped drug from the total drug incorporated. [12]

Following factors affect the entrapment efficiency.

Surfactants: The entrapment efficiency is affected by the head being hydrophilic and length of the non-ionic surfactants chain. The surfactants of tween series containing long chain alkyl group in mixture with cholesterol at 1:1 ratio comprises the maximum entrapment efficiency for water soluble drugs. HLB value of surfactants directly affects entrapment efficiency. 14 to 18 HLB value is not preferred for these noisome but it has seen that 8.6 HLB value has shown the maximum entrapment efficiency and also entrapment efficiency was

decreased with decrease from 8.6 to 1.730 in HLB value.

Cholesterol contents: The cholesterol inclusion into the bilayers of the vesicle helps in induction of membrane stabilizing activity in the noisome and thus leakiness of membrane is decreased. Thus, increases entrapment efficiency. The permeability of 5, 6-carboxy flourescein (CF) is seen to be reduced by more than ten times due to incorporation of cholesterol in the vesicle bilayers.

Table 1: Various evaluation parameters with techniques

Evaluation parameter	Generally used techniques in evaluation parameter
Morphology	SEM, TEM, freeze fracture technique
Size distribution	Dynamic light scattering particle size analyzer
Viscosity	Ostwald viscometer
Membrane thickness	X-ray scattering analysis
Thermal analysis	DSC
Turbidity	UV-Visible diode array spectrophotometer
Entrapment efficacy	Centrifugation, dialysis, gel chromatography
In-vitro release study	Dialysis membrane
Permeation study	Franz diffusion cell

CONCLUSION

Niosomes have proven useful for the delivery of anti-hypertensive, anti-cancer and anti-inflammatory agents. The literatures have also suggested that noisome has proven to target certain areas of the mammalian anatomy and exploited as diagnostic imaging agents, hence future studies based on these should conducted in noisome to exploit it in targeted and diagnostic imaging. Researchers have also suggested that hydrophobic drugs and macromolecules encapsulated in noisome are more stable than low molecular weight drugs and hence the transdermal drug delivery using noisome extended to the field of proteins and other large molecules. In addition to this, the transdermal drug delivery using niosomal carrier can be studied for certain drugs antibacterial and antifungal drugs, it is certain that pharmacokinetic problems of these drugs can be overcome by loading in the noisome carrier and also can be used to study the feasibility of the carrier. Hence, the noisome in transdermal drug deliveries are expected to achieve better bioavailability and targeting properties for reducing the toxicity and side effects of the drug.

DISCLOSURE STATEMENT

The authors declare that there is no conflict of interests regarding the publication of this paper.

REFERENCES

[1] Shakya V, Bansal B.K. Niosomes: a novel trend in drug delivery. International journal of research and Development in Pharmacy and Life Sciences. 2014; 3(4):1036-1041

[2] Vyas S.P, Khar R.K. Niosomes, Targeted and Controlled Drug Delivery. 1 st edition, CBS Publishers & Distributors Pvt. Ltd. 2012; 249- 279.

[3] Lohumi et al. A Novel Drug Delivery System: Niosomes Review. Journal of Drug Delivery & Therapeutic. 2012; 2(5): 129-135.

[4] Vashnavi V et al. Formulation and Evaluation of Nasal Niosomal in situ Gels of Loratadine. International Journal of Pharmaceutical Sciences and Drug Research. 2015; 7(1): 13-21.

[5] Jadshav SM et al. Novel Vesicular System: An Overview, Journal of Applied Pharmaceutical Science. 2012; 2(1):193-202.

[6] Prasanthi D, Lakshmi PK. Vesicles - Mechanism of Transdermal Permeation: A Review, Asian Journal of Pharmaceutical and Clinical Research. 2012; 5(1):18-25.

[7] Upadhyay R. K. Drug delivery systems, CNS protection, and the blood brain barrier. Bio Med. Research International. 2014; 2(1):46- 47.
[8] Kumari P, Gupta AK. Formulation and evaluation of aceclofenac ophthalmic gel. African Journal of Pharmacy and Pharmacology. 2013; 7(34): 2382-2391.
[9] Shivhare UD, Wasnik SV. Formulation development and evaluation of niosomal gel for transdermal delivery of an antihypertensive drug. International Journal of Biopharmaceutics. 2013; 4(3): 231-238.
[10] Ahmad U et al. Performance of Meloxicam Niosomal Gel Formulations for Transdermal Drug Delivery. British Journal of Pharmaceutical Resear. 2016; 12(2): 1-14.
[11] Balasubramaniam A et al. Formulation and in vivo evaluation of niosome-encapsulated daunorubicin hydrochloride. Drug Dev Ind Pharm 2016; 1:81–93.
[12] Malhotra M, Jain NK. Niosomes Drug Carriers. Indian Drugs. 1994; 31(3):81-86.
[13] Biswal S, et al.. Vesicles of Non-ionic Surfactants (Niosomes) and Drug Delivery Potential. Int J Pharm Sci Nanotechnology. 2008; 1(1), 342-356.
[14] Saurabh B, et al. A comparative review on vesicular drug delivery system and stability issues. International Journal of research in pharmacy and chemistry. 2012; 2(3): 704- 713.
[15] Manosroi A, et al. Transdermal absorption enhancement through rat skin of gallidermin loaded in niosomes. Int J Pharm2010; 3(2):304‑10.
[16] Vyas SP. Theory and Practice in Novel Drug Delivery System.1st Ed. New Delhi: CBS Publishers and Distributors; 2009.p. 284‑98.
[17] Ganta SK . Topical treatment in acne: current status and future aspects. Dermatology. 2003; 206:29–36.
[18] Keservani R K, Sharma A. Novel drug delivery system for the vesicular delivery of the drug by niosomes. Int J Res Control Release. 2011; 1(1):1-8.
[19] Kumar A, et al. Review on niosomes as novel drug delivery system. Int Res J Pharma 2011; 2(5):61-65.
[20] Jain A, et al. Development of antifungal emulsion based gel for topical fungal infections. International Journal of Pharmaceutical Research and Development. 2011; 2:18–25.