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Review on Niosome-A Future of Targeted Drug Delivery System

Ashwini K. Shinde, Bilal Sufi, Rajlaxmi S. Deolekar, Vedika D. Bihade, Achal A. Kale
New Montfort Institute of Pharmacy, Wardha, Maharashtra, India
ashwinishinde2408@gmail.com

Abstract: *Niosome are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or their lipids. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. Niosome appears to be a well preferred drug delivery system over liposome as niosome being stable and economic. Also niosomes have great drug delivery potential for targeted delivery of anti-cancer, anti-infective agents. Niosomes can entrap both hydrophilic and lipophilic drugs and can prolong the circulation of the entrapped drug in body. Encapsulation of drug in vesicular system can be predicted to prolong the existence of drug in the systemic circulation and enhance penetration into target tissue, perhaps reduce toxicity if selective uptake can be achieved. This review article focuses on the advantages, disadvantages, preparation methods, factors affecting, characterizations, mechanism of action, and applications of noisome.*

Keywords: Niosomes, Cholesterol, Non-ionic surfactants, Amphiphile, Drug carrier, Types, Preparation methods, Characterization, Advantages, Applications

I. INTRODUCTION

Paul Ehrlich, in 1909, initiated the era of development for targeted delivery when he envisaged a drug delivery mechanism that would target directly to diseased cell. Drug targeting can be defined as the ability to direct a therapeutic agent specifically to desired site of action with little or no interaction with non target tissue. In niosomes drug delivery system the medication is encapsulated in a vesicle.[1] The aim of a target drug delivery system is to increase the selectivity and drug therapeutic index, and to reduce the toxicity of the drug. A numbers of carriers were utilized to target the drug at specific site, which include immunoglobulins, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, niosomes.[2]

The niosome can be a multicellular vesicle consisting of a non-ionic surfactant, cholesterol, and an ionic surfactant used to reduce formulation agglomeration. Hydrophilic, lipophilic and amphiphilic drugs can be incorporated into the bilayer structural pocket of the niosome. Niosomes show more stability than liposomes because liposomes can be degraded and oxidized due to their particular lipophilic nature. Niosomal formulations live longer in the bloodstream due to their non-ionic surfactants and thus their larger targeted effects.[3] The different techniques for the preparation of unilamellar and multilamellar niosomes are similar to that of liposomal preparations. Because of the various advantages offered by the niosomes over liposomes such as (i) better skin permea tion potential, (ii) higher chemical stability, (iii) sustained release characteristic, (iv) quite economic due to the ease of access of the starting materials, (v) biocompatibility, and (vi) non-immunogenicity, and (vii) cost effective handling pro cedures like no specific requirement for storage in freezer and use of nitrogen for the preparation, the niosomal formulations are grabbing the attention of researchers.[4] Non-ionic surfactants provide a few advantages over the phospholipids because they are more economical and are chemically more stable as they are not easily hydrolysed or oxidised during storage. The vesicular structure can be modified to provide sustained or controlled drug delivery thus enhancing efficacy of system for prolonged periods.[5]

II. STRUCTURE OF NOISOME

Niosomes are vesicular carriers of non-ionic surfactants with size range between 10 and 1000 nm, wherein aqueous phase is enclosed in a highly ordered bilayer of non-ionic surfactants with or without cholesterol and dicetyl phosphate. Niosomes can be used for entrapping both hydrophilic and hydrophobic drugs.[6] Niosomes are formed by the self

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assembly of non-ionic surfactants in aqueous media as spherical, unilamellar, bilayered, multilamellar system and polyhedral structures depending on the method used to prepare and the inverse structure in case of non-aqueous solvent. The orientation of the surfactant in niosome in hydrophilic ends exposed outwards while hydrophobic ends face each other forming bilayer of the surfactant.[7]

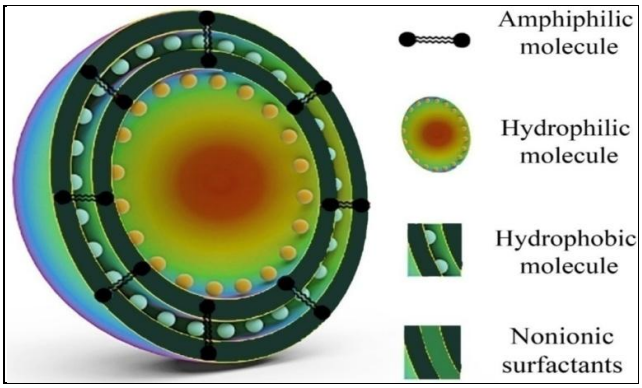

Fig.1 structure of noisome

III. COMPOSITION OF NOISOME

The two major components used for the preparation of niosomes are

- Cholesterol
- Nonionic surfactants
- Charged molecule

Cholesterol

Cholesterol is the most frequently used lipid for improving the mechanical strength and rigidity of niosomal membrane, as well as for reducing water perme ability.[8] Cholesterol is used to provide rigidity and proper shape conformation to the niosomes preparation. The amount of cholesterol to be included depends primarily on the HLB values of nonionic surfactants and needs optimization during the development process, since it has an impact not only on the membrane properties or arrangement (in case of surfactants with HLB values > 10) but also on the physicochemical characteristics of the vesicles, for instance, size, entrapment efficiency, and physical stability.[9]

Non ionic surfactant

Non-ionic surfactants are generally used for the preparation of niosomes the spans(span 60,40,20,85,80), tweens(tween 20,40,60,80) and brij (brij 30,35,52,58,72,76). The non ionic surfactants possess a hydrophillic head and a hydrophobic tail.[10,11]

Charged Molecule

Some charged molecules in order to increase the stability of some Niosomes through electrostatic repulsion to prevent the fusion will add a little Di-cetyl phosphate (DCP) and phospho lactide acid is used as negatively charged molecules. Similarly, stearylamine (STR) and stearyl pyridinium chloride is a well-known positively charged molecule used in the preparation Niosomes.[12]

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IV. ROUTES OF DRUG ADMINISTRATION

Routes of drug administration	Examples of Drugs
Intravenous route	Doxorubicin, methotrexate, sodium stibogluconate, iopromide, vincristine, diclofenac sodium, flurbiprofen, centchroman, indomethacin, colchicine, rifampicin, tretinoin, transferrin and glucose ligands, zidovudine, insulin, cisplatin, amarogentin, daunorubicin, amphotericin B, 5-fluorouracil, camptothecin, adriamycin, cytarabine hydrochloride
Peroral route	DNA vaccines, proteins, peptides, ergot alkaloids, ciprofloxacin, norfloxacin, insulin
Transdermal route	Flurbiprofen, piroxicam, estradiol, levonorgestrol, nimesulide, dithranol, ketoconazole, enoxacin, ketorolac
Ocular route	Timolol maleate, cyclopentolate
Nasal route	Sumatriptan, influenza viral vaccine
Inhalation	All-trans retinoic acids

TYPES OF NIOSOMES

- Multi Lamellar Vesicles (MLV)
- Large Unilamellar Vesicles (LUV)
- Small Unilamellar Vesicles (SUV)

Multi Lamellar Vesicles (MLV)

It comprises many bilayers that each individually enclose the aqueous lipid compartment. These vesicles range in diameter from 0.5 to 10 m. The most popular niosomes are MLV. that are easy to build and mechanically stable when kept in storage for an extended period. These cells work best as medication transporter for lipotropic drugs.[13,14]

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.

Small Unilamellar Vesicles (SUV)

These small unilamellar vesicles are mostly prepared from multilamellar vesicles by sonication method, French press extrusion method or, homogenization method. The approximate sizes of small unilamellar vesicles are 0.025-0.05 µcm diameter. They are thermodynamically unstable and are susceptible to aggregation and fusion. Their entrapped volume is small and percentage entrapment of aqueous solute is correspondingly low.[15,16]

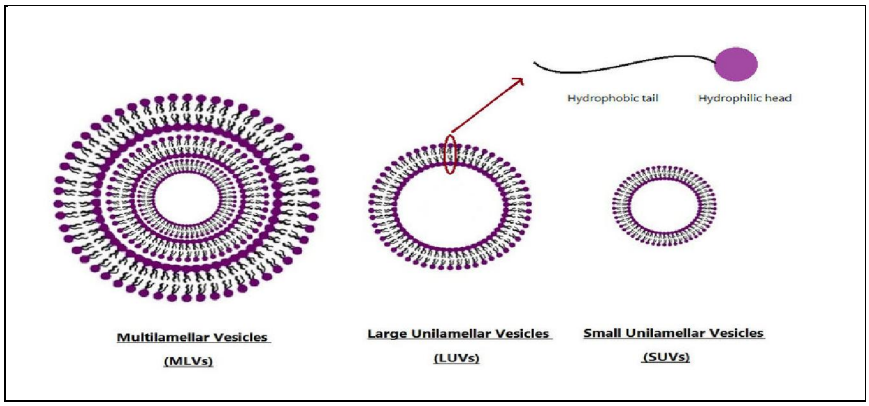

Fig.2 types of niosome

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V. METHODS OF PREPARATION

Ether injection method

The drug and lipid are added to diethyl ether and gradually to the aqueous phase through a 14-gauge needle at 0.25 ml/min, which is maintained at 60 ° C. When the organic solvent is heated above the boiling point, large unilamellar niosomes are produced, which can be further treated to obtain reduced niosomes in size. Using the ether injection method, were successful in the preparation of salbutamol niosomes with an entrapment efficiency of 67.7%[17].

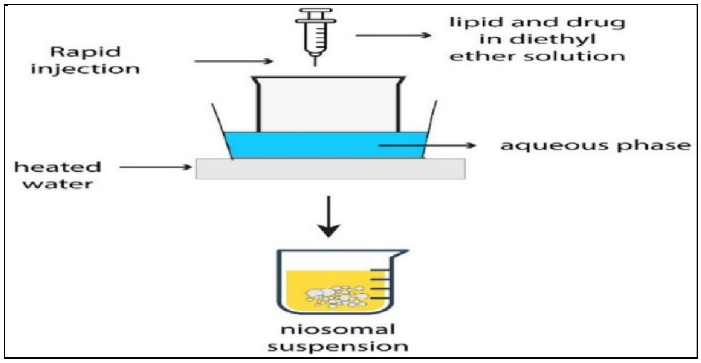

Fig 3. Ether injenction method

Sonication Method

In this method, average size of vesicles can be reduced by providing high energy by sonication. This is done by exposure of multi lamellar vesicles to ultrasonic irradiation. Sonication method is most widely used for producing small vesicles. There are two types of sonication based on the use of either probe or bath ultrasonic disintegrators. The probe is employed for dispersions, which require high energy in small volume while bath is more suitable for large volume.[18]

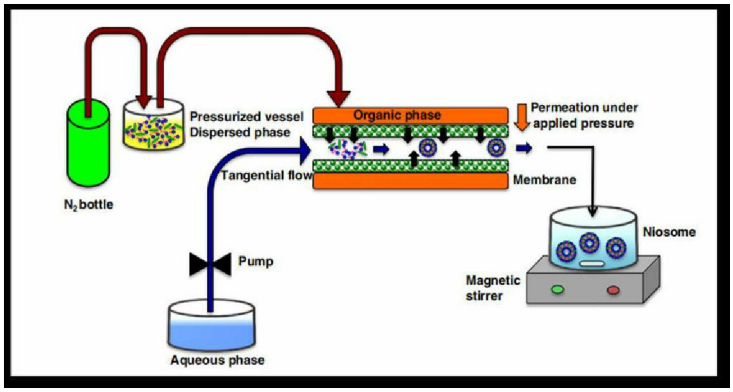

Fig 4. Sonication method

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 round-bottomed flask with three necks positioned in water bath to control the temperature. Water-cooled 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.[19]

Reverse phase evaporation method (REV)

Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to the present and therefore the resulting two phases are sonicated at 4-5°C. The clear gel formed is further

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sonicated after the addition of a little amount of phosphate buffered saline (PBS). The organic phase is removed at 40°C. The resulting viscous noisome suspension is diluted with PBS and heated on a water bath at 60°C for 10 minutes to yield niosomes.[20]

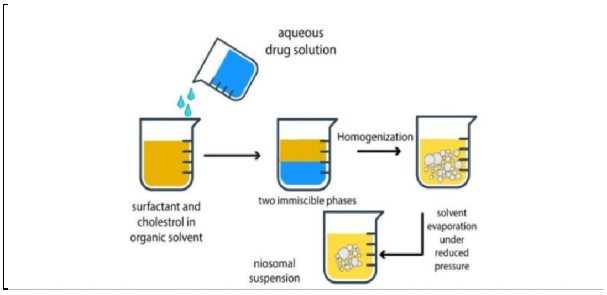

Fig 5. Reverse phase evaporation method

Micro fluidization

Micro fluidization may be a recent technique that is used to prepare unilamellar vesicles of defined size distribution. This method is predicated on submerged jet principle in which two fluidized streams interact at ultra-high velocities, in just defined micro channels within the interaction chamber. The impingement of thin liquid sheet along a typical front is arranged such the energy supplied to the system remains within the world of niosomes formation. This results a greater uniformity, smaller size and better reproducibility of niosomes.[21]

VI. SALIENT FEATURES OF NIOSOMES[39]

- Niosomes can entrap solute in a manner analogous to Liposome.
- Niosomes osmoticaly active and stable.
- Niosomes possess an infra structure consisting of hydrophobic and hydrophilic mostly together and so also accommodate the drug molecule with a wide range of solubility.
- Niosomes exhibit flexibility in their structural charecterestics (composition, fluidity and size) and can be designed according to their desired situation.
- Niosomes can improve the performance of drug molecule.
- Better availability to the particular site, just by protecting the drug from biological environment. Niosomes surfactants are biodegradable, biocompatible and nonimmunogenic.

VII. MECHANISMS OF NIOSOMES PENETRATION THROUGH THE SKIN[37]

On the surface of the skin, adsorption, and fusion of niosomes leading a high thermodynamic activity gradient at the interface for permeation of lipophilic drugs which works as a driving force. The barrier of the stratum corneum overcomes by the effect of vesicles as penetration enhancers. As surfactants are the components of niosomes, they increase transdermal permeation and percutaneous absorption by decreasing surface tension.

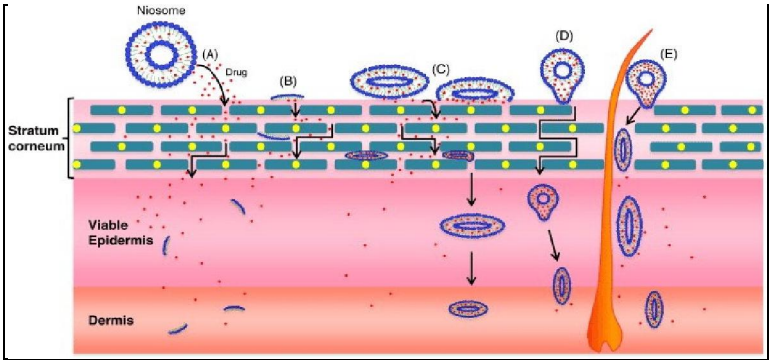

Fig.6 Mechanism of action of noisome

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VIII. CHARACTERISATION OF NIOSOMES

Bilayer formation, Membrane rigidity and Number of lamellae

Bilayer vesicle formation by assembly of non-ionic surfactants is characterized by X-cross formation under light polarization microscopy and membrane rigidity can be measured by means of mobility of fluorescence probe as function of temperature. NMR spectroscopy, small angle X-ray scattering and electron microscopy are used to determine the no of lamellae.[22,23]

Sizes and Zeta Potential

A laser scattering particle size analyzer is used to determine the polydispersity index (PDI) and size distribution. Dynamic light scattering, zeta-sizer, and microelectrophoresis are used to determine zeta potential, which is required to check the stability of niosomes in solution.[38]

In vitro Release Study

- Dialysis
- Reverse dialysis:
- Franz diffusion cell

In vivo Release Study

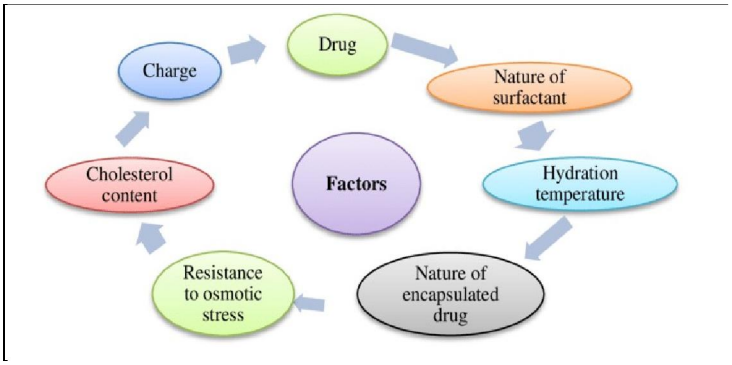
For in vivo study niosomal suspension was injected intravenously (through tail vein) to the albino rats using appropriate disposal syringe. These rats were subdivided into groups.[24]

Entrapment efficiency

After preparing niosomal dispersion, unentrapped drug is separated by dialysis, centrifugation or gel filtration as described above and the drug remained entrapped in niosomes is determined by complete vesicle disruption using 50% n- propanol or 0.1% Triton X-100 and analysing the resultant solution by appropriate assay method for the drug Where, %[25]

$$\text{Entrapment efficiency } (\text{EE}) = \left(\frac{\text{amount of encapsulated drug}}{\text{total drug added}} \right) \times 100$$

IX. FACTORS INFLUENCING NIOSOMAL FORMULATION



ADVANTAGES OF NIOSOME

- Niosomes are osmotically active and stable.
- They have the ability to increase the stability of the entrapped drug.
- Can enhance the skin penetration of drugs [26].
- They can be used for oral, parenteral as well topical.

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- Improves the therapeutic action of the drug by protecting it from the biological environment and restricting effects to target cells, thereby reducing the clearance of the drug.
- Niosomal dispersions in an aqueous phase can be emulsified in a non-aqueous phase to restrict the release rate of the drug [27].
- Niosomes are osmotically active and stable and they can increase the stability of entrapped drug [24].
- They can be made to reach the site of action by oral, parenteral as well as topical routes.
- The surfactants are biodegradable, biocompatible and non-immunogenic.[28]

DISADVANTAGES OF NIOSOME[29-30]

- Physical instability.
- Aggregation.
- Fusion.
- Leaking of entrapped drug.
- Hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion.

APPLICATIONS OF NOISOME.[31-36]

- It is used as Drug Targeting
- Transdermal Drug Delivery Systems Utilizing Niosome
- Localized Drug Action Sustained Release
- Cancer therapy
- Leishmaniasis
- Opthalmic drug delivery
- As a carrier in dermal drug delivery
- Anti-inflammatory agents
- Anti-inflammatory agents
- Use in Studying Immune Response
- Niosomes as Carriers for Haemoglobin.

X. CONCLUSION

Niosomes represent promising drug delivery systems. They present a structure similar to liposome and hence they can represent alternative vesicular systems with respect to liposomes, due to the niosome ability to encapsulate different type of drugs within their multienvironmental structure.The main object of this review the application of niosome technology is used to treat a number of diseases, niosome have good opportunity in research and beneficial for researcher and pharma industries. Niosomes have been proven to be useful in the delivery of anti infective agents, anti-cancer agents anti inflammatory agents, fairly recently as vaccine adjuvants and as diagnostic imaging agents. All this is supremely encouraging.

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