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A Review on Future Prospects of Niosomes towards Drug Delivery Applications

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Abstract:
Niosomes are self-assembled vesicles (nonionic surfactant) which are synthesized by hydration of synthetic non-ionic surfactants with or without incorporation of cholesterol or other lipids. These are similar to liposomes because of the vesicular system and they are used as carriers of amphiphilic and lipophilic drugs. Niosomes are proved to be a promising drug carrier because they have the ability to encapsulate different types of drugs within their multi-environmental structure. These non-ionic surfactant vesicles (Niosomes) have drawn a lot of importance in the area of modern drug delivery systems or target- specific drug delivery system. Niosomes as a drug carrier which improves the bioavailability of drugs and thus increase penetration through the skin. This review will focus on Niosomes, method of preparation of niosomes and its application in various fields. Formulating niosomes would be promising guide for the carrier system in novel drug delivery and thereby reduce the side effects of drugs and increase the therapeutic effects in various diseases.
Keywords: Novel drug delivery, Niosomes, Characterization, Application

I. INTRODUCTION

For several decades, medication of an acute disease or a chronic illness has been accomplished by delivering drugs to the patients through various pharmaceutical dosage forms such as tablets, capsules, pills, creams, ointments, liquids, aerosols, injectables and suppositories as carrier systems. Research is going on for finding unique and better alternatives of drug delivery system and this will continue until the drug delivery system have no side effects with optimum therapeutic action. Conventional dosage forms are still in use because of high patient compliance, though they are having side effects to achieve and maintain the concentration of drug administered within the therapeutically effective range needed for medication, it is often necessary to take this type of drug delivery systems several times in a day [1]. This results in a fluctuated drug level and consequently undesirable toxicity and poor efficiency. Several brain and CNS diseases such as neurological diseases (meningitis, encephalitis, viral, bacterial, protozoan, and fungal and worm infections), neurological disorders (epilepsy, seizures, trauma, Parkinson, multiple sclerosis, dementia, Alzheimer, mononeuropathy, polyneuropathy, and myopathy), and brain tumors (cerebral tumors and glioma) are associated with mortality. These problems needed proper drug delivery for treatment [2]. Drug delivery efficiency can be increased through ligand bindings and applying the natural drug in different surfaces of the body is performed by passive diffusion which is contingent on lipophilicity and molecular weight or through active transport systems by interacting with the blood components having the role of a mediator between the blood carrier and the brain. Nanostructures behave differently depending on the surface area and the ligand bindings as well as its mediator [3]. To minimize this fluctuation, novel drug delivery systems have been developed, which include niosomes, liposomes, nanoparticles, microspheres, microemulsions, impalatable pumps and magnetic microcapsules. Amongst these systems, particularly, liposomes and niosomes are used in treating pathological disease whose sufficiency can be enhanced by targeting permeable components passing through tissues via blood vessels [4].

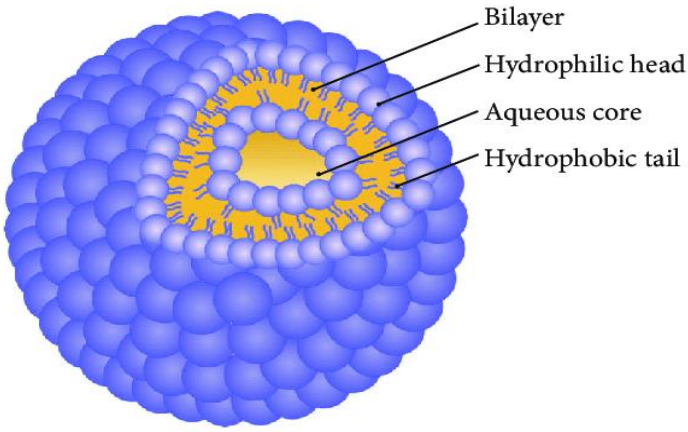
A niosome is a non-ionic surfactant-based liposome, a vesicular system is a drug-delivery platform that enables effective bioavailability of drugs through controlled release of therapeutic drugs for a prolonged period. The vesicles consist of bilayer amphiphilic molecules that surround an aqueous compartment. Niosomes are formed mostly by cholesterol incorporation as an excipient. Other excipients can also be used [5]. Niosomes are vesicles of nonionic surfactant (for example, alkyl ester and alkyl ether) and cholesterol that act as a carrier for amphiphilic and lipophilic drugs. Niosomes improve the therapeutic performance of encapsulated drug molecules by protecting the drug from harsh biological environments, resulting in their delayed clearance. Niosomes have more penetrating capability than the previous preparations of emulsions. They are structurally similar to liposomes in having a bilayer, however, the materials used to prepare niosomes make them more stable and thus niosomes offer many more advantages over liposomes [6]. The sizes of niosomes are microscopic and lie in nanometric scale. The particle size ranges from 10nm-100nm. Niosomes are unilamellar

or multilamellar vesicles formed from synthetic non-ionic surfactants. They are very similar to the liposomes. Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. Niosomes have shown promise in the release studies and serve as a better option for drug delivery system. Niosomes are promising vehicle for drug delivery and being non-ionic; it is less toxic and improves the therapeutic index of drug by restricting its action to target cells [7]. Niosomes or non-ionic surfactant vesicles are microscopic lamellar structures formed on admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media.

Structure of Noisome

A typical niosome vesicle consist of a vesicle forming amphiphilic i.e. a non-ionic surfactant such as Span-60, which is usually stabilized by the addition of cholesterol and a small amount of anionic surfactant such as dicetyl phosphate, which also helps in stabilizing the vesicle [8].

Figure 1: Structure of niosomes



The two major components used for the preparation of niosomes are

• Cholesterol

• Nonionic surfactants

1. Cholesterol: Cholesterol is employed to supply rigidity and proper shape, conformation to the niosomes preparations.

2. Nonionic surfactants: The role surfactants plays a major role in the formation of niosomes. The following non-ionic surfactants are generally used for the preparation of niosomes.

Eg. Spans (span 60, 40, 20, 85, 80) Tweens (tween 20, 40, 60, 80). The non-ionic surfactants possess a hydrophilic head and a hydrophobic tail [9].

Niosomes are spherical in shape and consist of microscopic lamellar (unilamellar or multilamellar) structures. The bilayer is formed by nonionic surfactants, with or without cholesterol and a charge inducer.

Lipid compounds are used to provide unbending nature, appropriate shape, and adaptation to the niosomes.

Nonionic surfactant-based vesicles or niosomes are capable of carrying the drug, which require a bilayer structure that are madeup of nonionic surfactant and lipid compounds (cholesterol or L-α-soya phosphatidylcholine) incorporated in an aqueous phase.

Nonionic surfactants in niosomes tend to orient themselves in such a way that hydrophilic end faces outward (toward the aqueous phase), whereas the hydrophobic end faces inward to each other to form a closed bilayer structure, which encloses solutes in an aqueous solution.

The closed bilayer structure of niosomes has hydrophilic inner and outer surfaces, with a sandwiched lipophilic area in between to form the closed bilayer structure, energy such as heat or physical agitation is required.

Various forces inside the vesicles were found to play an important role in maintaining the vesicular structure, for example, van der Waals and repulsive forces that exist among the surfactant molecules [10].

Salient Properties of Niosomes:

Surfactant-based niosomes are biodegradable, biocompatible, and nonimmunogenic.

• They act as a drug depot within the body, whereby they release drugs during a controlled manner through their closed bilayer structure, leading to a sustained release of the enclosed drug to the target site.

• The therapeutic effects of medicine enclosed in niosomes are improved by reduced clearance and specific targeting [11].

• Because of their hydrophilic, amphiphilic, and lipophilic nature, niosomes are ready to accommodate a good sort of drugs with a good range of solubility.
• Bioavailability of otherwise poorly soluble drugs could also be improved, and therefore the efficacy of topical applications would be enhanced with the utilization of niosomes.
• Furthermore, labile and sensitive drugs could also be delivered with greater ease as niosomes protect the encapsulated active pharmaceutical ingredients from deleterious conditions both inside and out of doors of the body [12].
• The stability of niosomes is especially suffering from the sort of surfactant, properties of the encapsulated drug, temperature of hydration, detergent, membrane-spanning lipids, polymerization of surfactant monomers, and charged molecules.
• It is crucial for the surfactant used for the preparation of niosomes to contains a hydrophilic head and a hydrophobic tail.
• Generally, surfactants possessing hydrophobic tails with an alkyl (chain length from C12 to C18), perfluoroalkyl, or steroidal groups are suitable for the preparation of niosomes [14].
• Ester-type surfactants are less suitable because they're easily degraded by esterases in-vivo, making them unstable within the body.
• Comparatively, ether-type surfactants are a far better choice. The dimensions of niosomes increases proportionally with the rise in hydrophilic–lipophilic balance (HLB) of surfactants. If the HLB value falls between 4 and eight, niosome vesicle formation is taken into account relatively stable and optimal [15].
• Addition of various sorts of additives alongside the drug entrapped in niosomes is in a position to enhance niosome stability, as an example, addition of cholesterol provides rigidity and reduces leaking in noisome [16].

Types of Niosomes

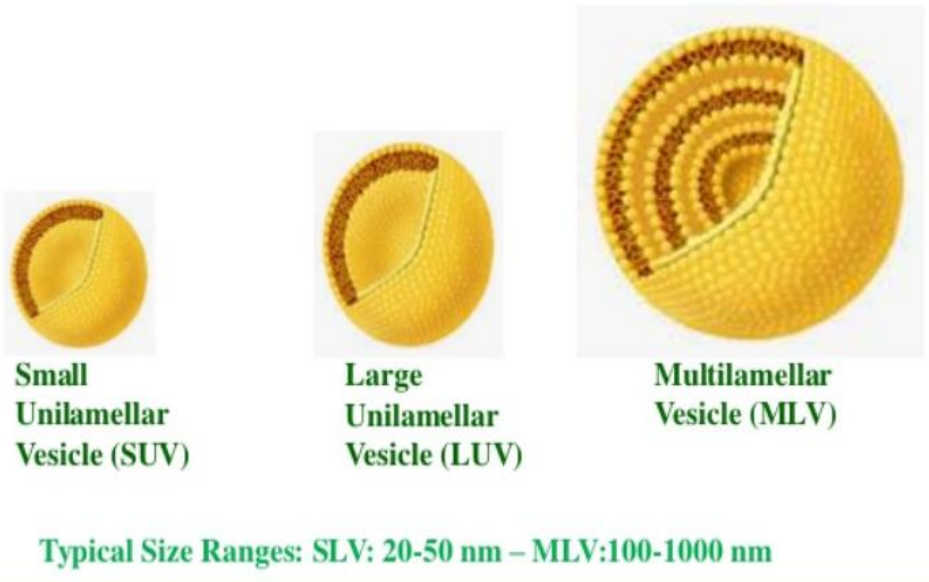
The various types of niosomes are as:
i) Multi lamellar vesicles (MLV),
ii) Large unilamellar vesicles (LUV),
iii) Small unilamellar vesicles (SUV) [17].

1. Multilamellar vesicles (mlv): It consists of a number of bi-layer surrounding the aqueous lipid compartment separately. The approximate size of those vesicles is 0.5-10 µm diameter. Multilamellar vesicles are the most widely used niosomes because which are simple to make and mechanically stable upon storage for long periods. These vesicles are highly suited as drug carrier for lipophilic compounds [18].

2. Large unilamellar vesicles (luv): This sort of vesicles have a high aqueous/lipid compartment ratio, in order that larger volumes of bio-active materials are often entrapped with a really economical use of membrane lipids [19].

3. Small unilamellar vesicles (suv): Small unilamellar vesicles are mostly prepared from multilamellar vesicles by sonication method. The approximate size of small unilamellar vesicles are 10-100 nm [20].

Figure 2: Types of Niosomal vesicles



Characterization of Niosomes [20]:

1. Vesicle diameter
2. Vesicle charge
3. Bilayer formation
4. number of lamellae
5. Membrane rigidity and homogeneity
6. Encapsulation efficiency
7. Stability study
8. Separation of unentrapped drug
9. Optical microscopy
10. In vitro drug release

a) Dialysis Tubing,
b) Reverse dialysis and
c) Franz diffusion cell.

Advantages of Niosomes:

- Niosomes are osmotically active and stable.
- They have the ability to increase the stability of the entrapped drug.
- During the preparation of niosomes, handling and storage of the surfactants do not require any special conditions.
- They can increase the oral bioavailability of drugs.
- Can enhance the skin penetration of drugs [22].
- They can be used for oral, parenteral as well topical.
- 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 [23].
- The vesicle suspension is water–based vehicle. This offers high patient compliance as compared with oily dosage forms.
- 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.
- They 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 [25].

Disadvantages of Niosomes [26]

- Niosomal aqueous suspensions owe limited shelf life due to fusion.
- We can see aggregation, leaking of entrapped drugs, and hydrolysis of encapsulated drugs.
- The techniques involved in the niosomal formulation such as extrusion, sonication are time consuming and requires specialized equipment for processing.
- Hydrolysis of encapsulated drugs which limiting the shelf-life of the dispersion.
- Physical instability
- Time consuming

Table 1: Drugs used in Niosomal delivery [27]

Route of administration	**Examples of drug**
Intravenous route	Doxorubicin,comptothecin, zidovudine,insulin,cisplatin, rifampicin
Inhalation	All trans retinoic acids
Transdermal route	Piroxicam,estradiol, nimesulide
Ocular route	Timolol maleate, cyclopentol
Nasal route	Sumatriptan

Preparation methods of Niosomes [28]:

1. Ether injection method
2. Hand shaking method
3. Sonication

4. Micro fluidization
5. Multiple membrane extrusion method
6. Reverse phase evaporation method (REV)
7. Trans membrane pH gradient Uptake process
8. The "Bubble" method
9. Formation of Niosomes from Proniosomes
10. Passive trapping technique
11. Ethanol injection method
12. Down sizing
13. Miscellaneous methods:

a) Emulsion method
b) Heating method

Ether injection method [29]: This method is used in the preparation of large unilamellar vesicles, and provides a means of making niosomes by slowly introducing the solution of cholesterol surfactant dissolved in diethyl ether into warm water maintained at 60°C with continuous stirring. The surfactant mixture in ether is injected through 14-gauge needle into an aqueous solution of material positioned at magnetic stirrer. Vaporization of ether results in formation of single layered vesicles. Depending on the conditions used the diameter of the vesicle range from 50 to 1000 nm.

Hand shaking method [30]: This is also known as thin hydration technique. In this method a mix of surfactants and cholesterol are dissolved in volatile organic solvents like ether, chloroform, methanol in a round bottom flask. The organic solvent is removed by using rotary evaporator at room temperature which leaves behind a thin layer of solid mixture deposited on the wall of the flask. This method forms multilamellar niosomes. The dried surfactant film are then rehydrated with aqueous phase at 60°C with gentle agitation results in formation of niosomes.

Sonication [31]: It is a typical method of production of the vesicles in which a 10-ml glass vial drug solution in buffer is added to the surfactant/cholesterol mixture. Then the mixture is probe sonicated at 60°C for 3 minutes employing a sonicator yields small and unilamellar niosomes.

Micro fluidization [32]: 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.

Multiple membrane extrusion method [33]: In this method, a mixture of surfactant, cholesterol and dicetyl phosphate in chloroform forms thin film by rotary evaporator. The film hydrates with aqueous drug polycarbonate membranes. Solution and resultant suspension extrude through polycarbonate membrane and placed serial for up to eight passages. It is an honest method for niosome size control.

Reverse phase evaporation method (REV) [34]: 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 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.

The "Bubble" method [35]: It is one step technique by which liposomes and niosomes are prepared without the use of any organic solvents. All the components are dispersed in the appropriate aqueous solutions and then mixed using a homogenizer to obtain the dispersion. Round bottomed flask is employed as bubbling unit with its three necks positioned in water bath to regulate the temperature. Water-cooled reflux and thermometer are positioned within the first and second neck and nitrogen supply through the third neck. At 70°C Cholesterol and surfactant are dispersed together within the buffer (pH 7.4) and mixed with high shear homogenizer for 15 seconds and immediately afterwards "bubbled" at 70°C using nitrogen gas.

Factors influencing Niosomal Formulation [36]:

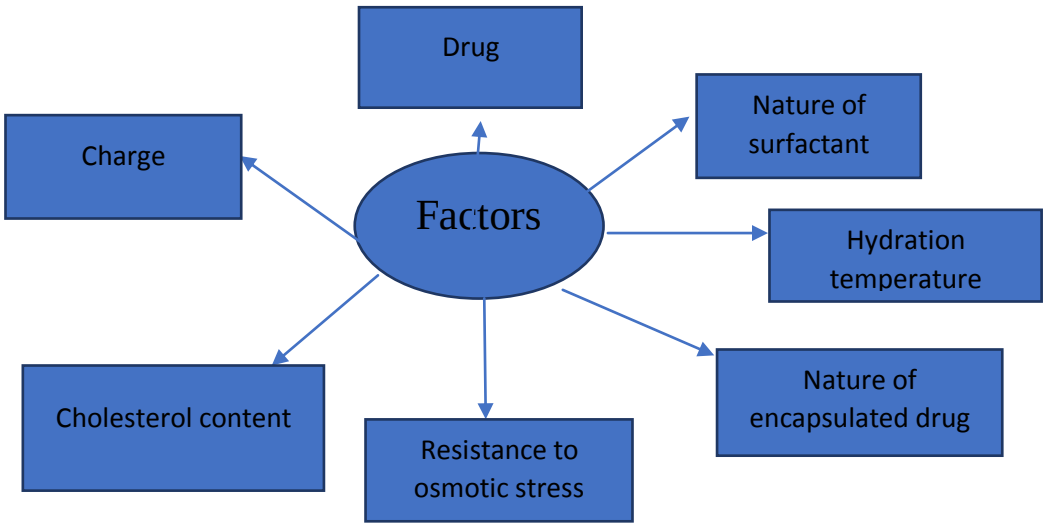


Figure 3: Factors influencing niosomal formulation:

Nature of Surfactant [37]: Increase in the HLB value of surfactants leads to the increase in the mean size of niosomes due to the decrease in surface free energy with an increase in the surfactant hydrophobicity. It depends upon the temperature, sort of surfactant and cholesterol. Alkyl chains are well ordered within the gel state, whereas disordered within the liquid state. Entrapment efficiency is affected by the gel, liquid phase change temperature (TC) of the surfactant.

Nature of Encapsulated Drug: The charge and therefore the rigidity of the niosomal bilayer are influenced by physical and chemical properties of the encapsulated drug. Entrapment of drug occurs by interacting with the surfactant head leading to the increasing charge and creates mutual repulsion of the surfactant bilayer and thus increases the vesicle size. The HLB of drug influences the degree of entrapment.

Hydration Temperature: The size and shape of the niosome are affected by the temperature of hydration. Change in temperature results the assembly of surfactants into vesicles and vesicle shape modification. Hydration time and volume of hydration medium also accounts for the modification. Improper selection of the hydration temperature, time and hydration medium produces fragile niosomes and gradually cause drug leakage problems.

Cholesterol Content: Incorporation of cholesterol increases the entrapment efficiency and hydro-dynamic diameter of niosomes. Cholesterol acts in two ways, which can increase the chain order of liquid state bilayer and also decrease the chain order of gel state bilayers. An increase within the cholesterol concentration causes a rise within the rigidity of the bilayers and reduce within the release rate of encapsulated material.

Charge: Presences of charge results rise in inter lamellar distance between successive bilayers in multi lamellar vesicle structure and greater overall entrapped volume [38].

Resistance to Osmotic Stress: Addition of hypertonic solution causes reduction in vesicle diameter. In hypotonic solution, inhibition of eluting fluid from vesicles results in the slow release initially followed by the faster release due to the mechanical loosening of vesicle structure under osmotic stress.

Separation of unentrapped drug [39]: The removal of unentrapped solute from the vesicles are often accomplished by various techniques, include:

1)Dialysis: The aqueous niosomal dispersion is dialyzed in dialysis tubing against phosphate buffer or normal saline or glucose solution.

2) Gel Filtration: The unentrapped drug is removed by gel filtration of niosomal dispersion through a SephadexG-50 column and elution with phosphate buffered saline or normal saline.

3) Centrifugation: The niosomal suspension is centrifuged and thus the supernatant is separated. The pellet is washed then resuspended to get a niosomal suspension free from unentrapped drug.

Future Prospects of Niosomes [40,41,42]:

Cancer Therapy: The drugs that are mostly used in the cancer therapy through Niosomal drug delivery are Doxorubicin HCL, Methotextrate, Bleomycin etc. There is side effect that when we administered Doxorubicin HCL as a free drug which can cause cardiac toxicity, but when we administered as a niosomal formulation the cardiac toxicity will reduce. When we use doxorubicin as niosomal formulation that can increase the level of tumor cells. It also reduces the proliferation rate of tumor cells and increases the lifetime of tumor bearing mice.

As Carrier: Niosomes being the vesicles can easily permeate to oxygen and therefore the hemoglobin dissociation curve is modified similarly to non-encapsulated hemoglobin. So they are used as the carrier for hemoglobin.

Oral Delivery: The drugs which are degraded by the proteolytic enzymes and gastric juices cannot be administered orally. This can be modified by a niosomal formulation.

Leishmaniasis: Niosomes can be used in treatment of reticulo-endothelial system based diseases. Leishmaniasis is one among the disease during which the protozoan parasites occupy the liver and therefore the spleen cells. It is treated using antimonials. Sodium stibogluconate niosomal formulation of anit-monials can permeate through the cells and target the precise cells.

Ophthalmic Drug Delivery: The occular disorders are treated by installation of medicine through eye. It can be suspension, solution or an insitu-gel. It shows better response in reduction of intraocular pressure when compared with marketed formulation. Timolol maleate as niosomal formulation with chitosin shows less cardiovascular side effects and effective reduction within the intra-ocular pressure.

Niosome as Carrier in Dermal Drug Delivery

Local Anesthesia: Lack of sensation is produced by local anesthetics through topical preparation. The penetration of the drug through the skin is poor, so niosomes acts as a carrier to improve the penetration of drug by enclosing them in vesicles which moves through the skin easily.

Psoriasis: Psoriasis is a dermal disorder which is caused by a T-lympocyte mediated autoimmune disease of dermis and epidermis. It is a chronic inflammatory condition of skin. It forms scaling erythematous plagues on skin. The drugs which are used topically for the treatment of Psoriasis are Anthralin, Methotrexate, Corticosteriods, VitD3 etc. Methotrexate is an anti-cancer drug used in the treatment of psoriasis, when administered systemically there is a chance to occur hepatotoxicity. So, topical application can be selected as an alternate to decrease the adverse effects.

Hyperpigmentation: Hyperpigmentation disorders are often controlled by noisomal preparation. N-acetyl glucosamine is a niosomal preparation used for the treatment of hyperpigmentation because it has the potential to deliver both hydrophilic and hydrophobic drugs as topical form and also has the property of preventing the thyrosine enzymes in melanocytes which treats the hyperpigmentation disorder.

Acne: Acne is a skin disease found in 70-80% of adolescence. It can be treated by topical preparations. Niosomes are often utilized in topical preparations as they need efficient dermal drug delivery. Acne can be treated by both synthetic and herbal extracts. The herbal extracts have less side effects when compared to synthetic. Benzylperoxide an artificial drug-macrolide antibiotic was utilized in the treatment of acne with other anti-acne agents. The side effects of benzyl peroxide when used as dermal delivery are itching, skin redness, irritation. Niosomal benzyl peroxide incorporated into HPMC gel was evaluated for its activity towards treatment of acne. The results showed good drug skin retention, extended release and reduced toxicity of the drug with improved drug permeation.

II. CONCLUSION:

Recent advancements within the field of research project have resulted within the endorsement of small molecules like proteins and vaccines as a serious class of therapeutic agents. Niosomal drug delivery system is one among the samples of great evolution in drug delivery technologies. They can be made by different approaches, which affect the establishment and therefore the properties of the medication, cholesterol amount, structure, type, and amounts of surfactant. Non-ionic surfactant vesicles alter the plasma clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug. The concept of incorporating the drug into or niosomes for a far better targeting of the drug at appropriate tissue destination is widely accepted by researchers and academicians. Niosome is a promising vesicular delivery system compared to liposomes because of its low cost, stability and the ability to encapsulate the different type of drugs.Niosomes having enhanced stability and low toxic drug effects, with sustained release of the encapsulated drug. In summary, niosomes represent a highly effective tool for drug delivery within the therapeutic regime of various diseases and have the potential to supply more efficacious treatment than conventional drug-delivery platforms.

Abbreviations

CNS: Central nervous system, HPMC: Hydroxypropyl methylcellulose, PBS: Phosphate buffered saline, HLB: Hydrophilic- lipophilic balance.

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Authors' contributions

PS contributed to designing the work in a stepwise manner. UU gave an eminent idea for the content needed to write this current manuscript. All authors have read and approved the manuscript.

Availability of data and materials
All data and materials are available upon request.
Ethics approval and consent to participate
Not applicable
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Not applicable
Competing interests
The authors declare that they have no competing interests.

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