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Niosomes As Potential Vesicular Carrier for Drug Targeting: A Review

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Abstract
Vesicular frameworks are innovative methods for medication conveyance that can improve bioavailability of encapsulated drug. They also provide therapeutic activity for a long period of time in controlled manner. Niosomes is a nonionic surfactant vesicular framework acquired by hydrating the blend of cholesterol and nonionic surfactant. The interesting structure of niosome presents a viable novel medication conveyance framework (NDDS) with capacity of stacking both hydrophilic and lipophilic medications. Niosomes have been generally utilized for medication focusing on and controlled discharged medication conveyance for the treatment of malignancy, viral contaminations and other microbial diseases. Niosomes are monetarily, artificially and once in a while physically steady and substitution to liposomes. This article additionally introduces a review of the strategy for planning of niosome, sorts of niosomes, characterization and their applications.

Keywords
Niosomes, Nonionic surfactants, Composition, Method of Preperation, Factors, Applications.

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INTRODUCTION
Medication focusing on can be characterized as the capacity to coordinate a restorative specialist particularly to wanted site of activity with practically zero association with non-target tissue [1].The idea of focused medication conveyance is intended for endeavoring to move the medication in the tissues of intrigue while decreasing the overall centralization of the drug in the rest of the tissues. This outcome indicates sedate is confined at the focused-on location. Consequently, encompassing tissues are not influenced by the medication. Moreover, loss of medication does not occur because of localisation of medication, prompting get greatest viability of the medicine. Distinctive transporters have been utilized for focusing of medication, for example, immunoglobulin, serum proteins, engineered polymers, liposome, microspheres, erythrocytes and baneful [2]. Vesicles are colloidal particles in which a concentric bilayer made up of amphiphilic atoms encompasses a fluid compartment [3-5]. They are valuable vehicle for medication conveyance of both hydrophobic medications, which connect with the lipid bilayer and hydrophilic medications, which are exemplified in the inside fluid compartment. Vesicles made up of regular or engineered phospholipids are called liposomes though those made of nonionic surfactants (e.g. alkyl ethers and alkyl esters) and cholesterol establishes a nonionic-surfactant vesicular framework called niosomes [6-7].

NIOSOMES
Niosomes are non-ionic surfactant vesicles with bilayer structure framed without anyone else's input

relationship of hydrated surfactant monomers. The multilamellar or unilamellar structure of niosomes is framed by blending non-ionic surfactant, cholesterol and diethyl ether alongside consequent hydration in fluid media [8]. Niosomes are a novel medication conveyance framework in which both hydrophilic and hydrophobic medication is embodied in a vesicle [9]. Niosomes are minute lamellar structures of the size range between 10 to1000 nm. The niosome comprises of non-immunogenic, biodegradable and biocompatible surfactants. Niosomes are superior to liposomes and its higher synthetic security of surfactants than phospholipids which are effortlessly hydrolyzed because of the ester bond and financially savvy [10].

STRUCTURE OF NIOSOME

Niosomes are fundamentally comprised of a bilayer which is comprised of non-ionic surface dynamic specialists. Niosomes might be unilamellar or multilamellar relying upon strategy for preparation. Most surface dynamic operators which inundated in water yield miceller structures, anyway a few surfactants can yield bilayer vesicles which are niosomes. An average niosome comprises of non-ionic surfactant like Span-60. Cholesterol and a little measure of non-ionic surfactant, for example, diacetyl phosphate is utilized to settle the vesicle (Fig-1) [11, 12, 13].

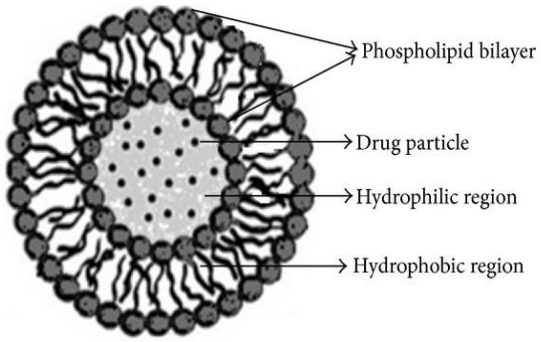

Fig-1: Structure of Noisome Encapsulated Drug Particle

COMPOSITION OF NIOSOMES

Two segments use in niosome preparation are:

1. Cholesterol

Cholesterol is a waxy steroid metabolite found in the cell film. The fuse of cholesterol into bilayer organization of dangerous gives film soundness and declines the brokenness of layer. Subsequently consolidation of cholesterol into bilayer expands ensnarement effectiveness [14]. Cholesterol is added for the most part to the nonionic surfactants to give unbending nature and introduction request to the niosomal bilayer [15]. Cholesterol is otherwise called annul gel to fluid stage change of niosomal framework bringing about niosomes that are less flawed [16].

2. Non-ionic surfactants

Non-ionic surfactant has hydrophilic head gathering and hydrophobic tail. The hydrophobic moiety may comprise of 1/2/3 alkyl chains or per fluro gathering or at times a solitary stearyl bunch [17]. Hydrophilic head aggregate influences the entanglement effectiveness of medication. As HLB esteem increments i.e alkyl chain builds, the measure of pernicious expands [18].Hence HLB esteems 14-17 is not reasonable for niosome definition. HLB esteem 8.6 has most astounding entanglement effectiveness [19]. HLB number somewhere in the range of 4 and 8 was observed to be good with vesicle development [20]. The accompanying non-ionic surfactants are by and large utilized for the readiness of niosomes.

- Spans (60, 40, 20, 85, 80)
- Tweens (20, 40, 60, 80) and
- Brijs (30, 35, 52, 58, 72, 76).

ADVANTAGES [21]

The characteristics, for example, measure, lamellarity and so forth of the vesicles can fluctuate contingent upon the necessity.

- The vesicles can go about as warehouse to discharge the medication gradually and offer a controlled discharge.
- They are osmotically dynamic and stable.
- They increment the dependability of ensnared tranquilize.
- They can be made to achieve the site of activity by oral, parenteral and in addition topical courses.
- They enhance oral bioavailability of ineffectively ingested medications and improve skin infiltration of medications.

- The surfactants are biodegradable, biocompatible and non-immunogenic.
- Handling and capacity of surfactants don't require any exceptional conditions.
- These vesicles have capacity to epitomize hydrophilic, lipophillic also ampiphillic sedate moieties.

DISADVANTAGES [21]

- Fusion
- Aggregation.
- Leaking of entangled medication.
- Physical precariousness.
- Hydrolysis of exemplified drugs which constraining the timeframe of realistic usability of scattering

METHOD OF PREPERATION OF NIOSOMES

1. Sonication method

Blend of medication arrangement in the cushion, surfactant and cholesterol

Sonicated with a titanium test sonicator at 60°C for 3 minutes to yield niosomes[22].

2. Ether injection method

Niosomes by slowly introduce in a solution of surfactant dissolve in diethyl ether into warm water maintain at 60°C

Blend in ether is infused through 14-check needle into a fluid arrangement of material

Vaporization of ether prompts the arrangement of the single layer vesicles

Diameter of the vesicle extend from 50 to 1000 nm relies on the conditions utilize [23,24].

3. The bubble method

Foaming unit includes round-bottomed flask with three neck position in water bath to Control the temperature

Water-cool reflux is situated in the primary neck and thermometer is situated in the second neck and nitrogen supply through the third neck

Cholesterol and surfactant are scattered in the cushion (pH 7.4) at 70°C

Scattering blending for 15 seconds with high shear homogenizer

“Bubbled” at 70°C utilizing nitrogen gas [25]

4. Hand Shaking Method (Thin Film Hydration Technique/Rotary Evaporator)

The blending ingredients - surfactant and cholesterol and charge inducer

↓

Dissolves in a volatile organic solvent (chloroform, diethyl ether or methanol) in a round bottom flask (Fig-2)

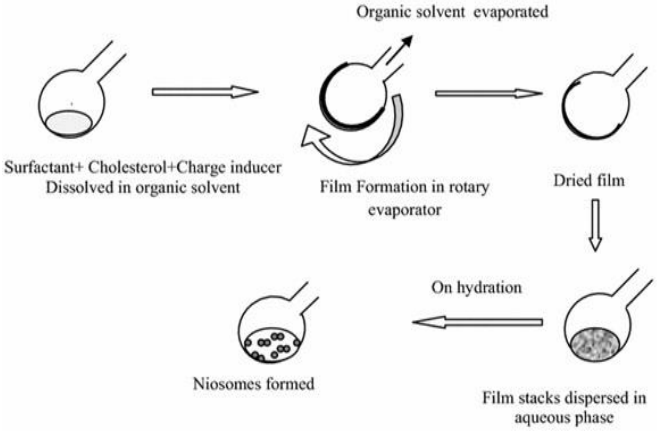

Fig-2: Formation of Niosomes by Using Thin Film Hydration Method

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By utilizing a rotary evaporator organic solvent is evaporated at room temperature 20°C

↓

Shaping a thin layer of solid blend

↓

The dry surfactant film can be re-hydrated with a fluid stage at 0-60°C with gentle agitation

↓

Arrangement of niosomes [26]

5. Ethanol Injection Method

An ethanol solution of surfactant is infused quickly through a fine needle

↓

Into excess of saline or different aqueous medium

↓

Vaporization of ethanol

↓

Development of vesicles [27]

6. **Reverse Phase Evaporation Technique** - Cholesterol and surfactant (proportion of 1:1) breakdown in the blend of organic solvent (ether and chloroform). Expansion of the aqueous drug solution to this and water in oil emulsion is framed; two stages are sonicated at 4-5ºC. The emulsion is dried in a rotary evaporator at 40°C to form a semisolid gel of large vesicles. Little measures of phosphate buffered saline (PBS) are added to the reasonable gel and sonicate once more. The organic phase is expelled at 40ºC and lower pressure. Thick niosomal suspension is additionally diluted with phosphate buffered saline, then heat on a water bath at 60ºC for 10 min to shape niosomes [28].
7. **Micro Fluidization** - In this procedure the standards includes is submerged jet rule in which two fluidized streams collaborate with each other at ultra-high speeds and in the smaller scale channels inside the interaction chamber. Thin fluid sheet impingements along with common front are arranged such as that the energy supplies remain same within the area of niosomes formation, development of niosomal vesicles of more uniformity, littler size and better reproducibility [29].

MISCELLANOUS METHODS

1. **Emulsion Method** - This is a straightforward strategy to shape niosome in which oil in water (o/w) emulsion is set up from an organic solution of surfactant, cholesterol, and an aqueous solution of the medication. At long last, the organic solvent is evaporated leaving niosomes scattered in the fluid Phase [38].
2. **Heating Method** - This technique is in one-step, scalable and non-dangerous and furthermore dependent on the patent system. An appropriate aqueous medium for example buffer distilled water, etc. in which blends of non-ionic surfactants, cholesterol and charge inciting particles are included the nearness of the polyol like as glycerol. The blend is warmed with low shear powers until the point that the vesicles were form [39].
3. **Formation of Niosomes from Proniosomes** - Proniosome is a dry formulation in which each water-soluble particle is covered with a thin film of dry surfactant. The niosomes are recognizing by the adding aqueous phase at T > Tm with brief agitation. T is the Temperature and Tm is the mean stage transition temperature [40].
   Carrier + surfactant = proniosomes,
   Proniosomes + water = niosomes.
4. **Lipid Injection Method** - This strategy does not require costly organic stage. Blends of lipids and surfactant is first melted and then infused into a highly agitate warmed aqueous phase contains the dissolved medication. Medication dissolves in molten lipid and the blend will be infused into agitate, warm aqueous phase containing surfactant.

FACTOR INFLUENCING NIOSOMAL FORMULATUION

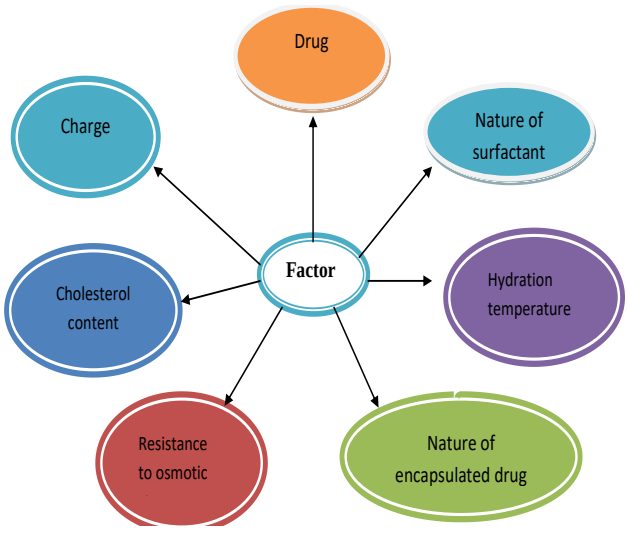

Fig-3: Various Factors Effecting Niosomal Formulation

1. **Medication** - Entrapment of medication in niosomes influence charge and rigidity of the noisome bilayer. The hydrophilic lipophilic parity of the medication influences level of entrapment [30].

2. **Nature of Surfactant -** Increase in the HLB estimation of surfactants prompts the expansion in the mean size of niosomes because of the decrease in surface free energy with an increment in the surfactant hydrophobicity. The bilayers of the niosomes can exist either as a fluid state or in a gel state. It relies on the temperature, sort of surfactant and cholesterol. Alkyl chains are all around requested in the gel state, though scattered in the fluid state. Entrapment efficiency is influenced by the gel, liquid phase transition temperature (TC) of the surfactant**.** Eg**:** span 60 with higher TC exhibits better entrapment. The HLB estimation extending somewhere in the range of 14 and 17 are not reasonable for niosomal preparations. Decrease in the HLB estimation of surfactants from 8.6 to 1.7 decreases the entrapment efficiency and highest entrapment efficiency is found with the HLB estimation of 8.6[41].
3. **Nature of Encapsulated Drug -** The charge and the rigidity of the niosomal bilayer are extraordinarily affected by physical compound properties of the encapsulated medication. Entrapment of medication happens by interacting with the surfactant head groups leading to the increasing charge and creates mutual repulsion of the surfactant bilayer and thus increases the vesicle size. The HLB of medication impact the level of entrapment [42].
4. **Cholesterol content and charge -** Hydrodynamic diameter and entrapment efficiency of niosomes relies upon the incorporation of cholesterol. Cholesterol decreases the chain order of gel state bilayers and increases the chain order of liquid state bilayers. The discharge rate of encapsulated material can be decreased by increasing cholesterol content because high cholesterol content increases the rigidity of the bilayers [43].
5. **Resistance to osmotic stress -** Vesicles diameter and discharge design additionally relies upon the addition of hypertonic or hypotonic salt solution. Diameter can be diminished by expansion of hypertonic salt solution whereas initial slow release due to the retardation of eluting fluid from vesicles followed by faster release due to mechanical loosening of vesicles structure under osmotic stress should obtained by expansion of hypotonic salt solution.
6. **Temperature of Hydration:** Hydration temperature impacts the shape and size of niosome[30].

CHARACTERIZATION OF NIOSOMES

1. **Measurement of angle of repose -** Angle of repose of dry niosomes powder is estimated by funnel technique. A funnel is settled with stand and empties the niosomes powder into funnel. At the point when powder streams down from the funnel cone is formed on the surface. The angle of repose is estimated by measuring the diameter of its base and height of the cone by utilizing following condition:
   Tan ɵ = H/R or ɵ = tan-1 H/R
   Where **ɵ** = Angle of repose **H**= Height of the granules **R** = Radius of the granules [31].
2. **Scanning electron microscopy -** Scanning Electron Microscopy (SEM) is utilized to contemplate the surface morphology (roundness, smoothness, and formation of aggregates) and the size circulation of niosomes [32].
3. **Optical Microscopy -** The niosomes were mounted on glass slides and saw under a magnifying instrument with an amplification of 1200X for morphological perception after reasonable dilution.
4. **Measurement of vesicle size -** Particle size analyzer is utilized to measure the Vesicle estimate. Before deciding the vesicle estimate the example is blended by utilizing a stirrer [33].
5. **Entrapment efficiency-**After planning niosomal scattering, unentrapped sedate is isolated and the medication remained entangled in niosomes is dictated by entire vesicle disturbance utilizing half n-propanol or 0.1% Triton X-100 and investigating the resultant arrangement by suitable measure technique for the drug [32]. It can be spoken to as:

Entrapment efficiency (EF) = (Amount entrapped / total amount) × 100

6. **Osmotic shock -** Niosomes definitions are hatched with hypotonic, isotonic, hypertonic answers for 3 hours to decide the difference in vesicle measure by osmotic investigations. Optical magnifying lens is utilized to watch the adjustments in the measure of vesicles in the formulations [34].
7. **Stability studies -** Niosomal formulations are liable to stability studies by storing at 4°C, 25°C and 37°C in thermostatic oven for the time of three months. After one month, drug content of all the formulations are checked by entrapping efficiency parameter.
8. **Zeta potential analysis -** Zeta potential analyzer dependent on electrophoretic light dissipating and laser Doppler velocimetry technique is

utilized to examine the Zeta potential which is done for determining the colloidal properties of the prepared formulations. The temperature is set at 25°C [35].

9. **Membrane rigidity** - Membrane unbending nature can be estimated by methods for versatility of fluorescence test as a component of temperature.
10. **In-vitro discharge investigation of niosomes [37]**

In vitro medicate discharge should be possible by three techniques:

- Dialysis tubing
- Reverse dialysis
- Franz diffusion cell

a. Dialysis Tubing - A strategy for in-vitro discharge rate think about incorporates the utilization of dialysis tubing. Washed the dialysis sac and then soaked into distilled water. The vesicle suspension is pipetted into a sac. The sack is comprised of the tubing and fixed. The vesicles containing sack is set in 200ml of buffer solution in a 250ml beaker with continous shaking at 37°C. At different time intervals, the medication content of buffer is analyzed by an appropriate assay method.

b. Reverse Dialysis - 1m of dissolution medium containing number of little dialysis is put in proniosomes. Proniosomes are then uprooted into dissolution medium. By utilizing this strategy, the immediate weakening of the proniosomes is conceivable yet the quick discharge can't be accomplished by this technique.

c. Franz Diffusion Cell -By utilizing Franz diffusion cell the in vitro diffusion studies can be performed. In the donor chamber of a Franz diffusion cell that is fitted with cellophane membrane in which proniosomes are placed. The dialysis of proniosomes are performed against an appropriate dissolution medium at room temperature; the withdrawn of sample from the medium is done at suitable intervals and medication content is examine by utilizing reasonable technique, for example, U.V spectroscopy, HPLC, etc. the sink conditions are essential to maintain.

APPLICATION OF NIOSOMES

The utilization of niosomal innovation is broadly shifted and can be utilized to treat various ailments. A portion of their restorative applications are talked about beneath: -

- Niosomes have been utilized for concentrate the idea of the insusceptible reaction incited by antigens.
- It is utilized as Drug Targeting.
- It is utilized as Anti-neoplastic Treatment i.e. malignant growth Disease.
- It is utilized as Leishmaniasis i.e. Dermal and Mucocutaneous diseases e.g. Sodium stibogluconate.
- Niosomes as Carriers for Hemoglobin.
- It is utilized go about as Delivery of Peptide Drugs.
- Niosomes can be utilized as a transporter for hemoglobin.
- It is utilized in Studying Immune Response.
- Transdermal Drug Delivery Systems Utilizing Niosomes.
- It is utilized in ophthalmic medication conveyance.
- Niosomal framework can be utilized as analytic specialists. [44]

1. Niosomes as Drug Carriers

Niosomes are fill in as a vesicular carrier for, an analytic specialist utilized for X-beam imaging, iobitridol.

2. Targeting of Bioactive Agents

(a) To reticulo-endothelial system (RES) - The vesicles are specially taken up by the cells of RES. The niosomes take up by the cells is also by circulating serum factors known as opsonins, which mark them for clearance. Creature tumors known to metastasize to the liver and spleen and in parasitic infestation of liver have been treated by such localized medication amassing.

(b) To organs other than RES - By utilizing the antibodies bearer framework can be coordinated to particular destinations in the body. Immunoglobulins appear to tie promptly to the lipid surface, consequently offering a helpful means for focusing of medication bearer [44]. The intrinsic capacity of numerous cells to perceive and bind specific sugar determinants and this can be abused to guide carriers' frameworks to specific cells.

3. Ophthalmic drug delivery

In the ocular medication conveyance framework, it is extremely hard to accomplish brilliant bioavailability like ophthalmic solution, suspension and ointment because of tear production, impermeability of corneal epithelium, non-productive absorption and transient residence time. Niosomal vesicular framework has been purposed to accomplish better medication bioavailability [29]. Carter *et al*. announced that stacked niosomes demonstrate better medication bioavailability with numerous portions of sodium stibogluconate against parasites

in the liver, spleen and bone marrow as compared to simple solution of sodium stibogluconate [45, 46].

4. Anti-inflammatory operators

Niosomal formulation of Diclofenac sodium with 70% cholesterol displays more anti-inflammator activity as compare to free medication, similarly formulation of Nimesulide and Flurbiprofen shows more anti-inflammatory activity as compared to free drug. For the treatment of parasitic disease span-60 niosomal oral suspension of fluconazole was produced by sharma et al (2009). It is more powerful as contrast with tablet and capsules [47].

5. Anti - malignancy Treatment

Most anticancer medications cause serious symptoms. Niosomes can modify the metabolism prolong the circulation and half-life of the drug, they also decreasing the side effects of the medications. They diminish the rate of multiplication of tumor and higher plasma levels by slower elimination [49].

6. Leishmaniasis

It is a sickness in which the cells of liver and spleen get attacked by the parasite of sort leishmania. Niosomes use in tests, conduct and demonstrates that it was conceivable to administer larger amount of the medication without the activating of the reactions, that permits more prominent and better adequacy in the treatment [50].

7. Delivery for peptides drugs

Niosomes are effectively shield the peptides from the gastrointestinal peptide breakdown is being examined. In an in-vitro study conducts by oral conveyance of a vasopressin entrap derivative in niosomes demonstrates that capture of the medication expands the strength of the peptide [51].

8. Cosmetics

The first report of non-ionic surfactant vesicles originated from the cosmetic applications reconsidered by L'Oreal. Niosomes create and patent by L'Oreal in the 1970s and 80s. The main item 'Niosome' present in 1987 by Lancome. Niosome advantage in cosmetic and healthy skin incorporate their capacity to expand the stability of entrapped medications and furthermore enhance the bioavailability of poorly absorbs ingredients and improves skin penetration [52].

9. Use in Studying Immune Response

Due to their immune framework choice, low poisonous quality, more prominent stability niosomes are utilized to study the nature of the immune response provoke by antigens. Non-ionic surfactant vesicles have obviously exhibited their capacity to work as adjuvant as parenteral organization with various diverse antigens and peptides [53].

Other Applications [54]

a) **Localized Drug Action -** Approach of niosome medication conveyance is to accomplish local drug action, since their size and low vulnerability through the epithelium and connective tissue keeps the medication restricted at the site of organization.

b) **Sustained Release -** Sustained discharge activity of niosomes can be connected to drugs having a low therapeutic index and low water solubility then they keep up in the circulation through niosomal encapsulation.

c) **Delivery Carrier for Hemoglobin -** Niosomes can be utilized as a transporter for hemoglobin. Niosomal suspension demonstrates a visible spectrum super-imposable to that of free hemoglobin. Vesicles are penetrable to oxygen and hemoglobin dissociation curve can be modified similarly to non-encapsulate hemoglobin.

Table-1: Comparison Between Liposomes And Niosomes[48]:

Liposomes	Niosomes
Require unique techniques for storage and handling of the final formulation.	No unique techniques for such formulations
Phospholipids might be neutral and charged	Non-ionic surfactant is uncharged
More Expensive	More affordable

Table-2: Marketed Formulations of Niosomes:

S;No	Brand	Name of Product
1	Loris Azzaro – Chrome	Chrome Eau De Toilette Spray 200 ml
2	Britney Spears – Curious	Curious Coffret: Edp Spray 100ml +Dualended Parfum and Pink Lipgloss + Body soufflé 100 ml
3	Lancome- Foundation and complexation	Flash Retouch Brush on Concealer
4	Orlane – Lipcolor and Lipstick	Lip Gloss

CONCLUSION

Niosomes are novel medication conveyance framework which offers countless over other ordinary and vesicular conveyance frameworks. This is inferred that Niosomes are enhanced adaptation of liposomes. Due to the niosomal ability to encapsulate wide assortment of medications inside their multi ecological structure and furthermore in view of various components like cost, stability. These few advantages over the liposomes improve it a focusing on operator. Visual, topical, parenteral and different courses are utilized for focusing on the medication at the site of activity for better adequacy. Niosomes represent a promising medication conveyance particle for enhanced medication security. They additionally have capacity to encapsulate toxic anti-cancer drugs, anti-infective drugs, anti-AIDS drugs, anti-inflammatory medications, anti-viral medications, and so on in niosomes and to utilize them as therapeutic tranquilize bearers to accomplish better oral and topical bioavailability. Due to their focusing on the additionally diminishes the toxicity and reaction of medications.

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