



Pros and Pitfalls of Niosomes in Respect of Flavonoids in Anti-Inflammatory Activity

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ABSTRACT

Niosomes play a crucial role for the drug deliveries they are made up of non-ionic surfactant are nanosized vesicles created by spontaneous organization of nonionic surfactant molecules. With the application of niosomal media, securing a new pharmacokinetic framework is one of the best strategies of delivering drugs. The basic physical features of niosomes are similar to liposomes, whereas their chemical nature is totally different. For niosomes, nonionic surfactants are used to establish niosomal vesicles as in the case of lipid used to form liposomal vesicles. One of the major limitations is that development of niosomes is a time consuming yet gainful process because of the apparent instability of most lipids compared to surfactants. Description and comparison on the niosomes Advantages and disadvantages, application of niosomes- A review. Niosomes can be applied in countless diseases like psoriasis, leishmaniasis, cancer, migraine, Parkinsonism, anti-inflammatory, antioxidant activity, anti-microbial etc. This can be used as a diagnostic tool. Different routes of administration are available, for example, intramuscular, intravenous, peroral, and transdermal. Niosomal technology is very widely used in cosmetics. More than enough work has to be done by the researchers before niosomes become useful in drug delivery in the industrial front.

Keywords: Niosomes, liposomes, non-ionic surfactant, psoriasis, cosmetics.

INTRODUCTION

Niosomes are the newest vesicular system with an astounding array of uses, are bilayer structures made of lipidic (mainly cholesterol) and amphiphilic non-ionic surfactants. Compared to liposomes, they are more stable and can contain biologically active hydrophilic and lipophilic compounds. Niosomes and liposomes differ in that niosomes include non-ionic surfactants with or without cholesterol incorporation, whereas liposomes have a concentric bilayer of phospholipids. Liposomes are useful for targeting delivery, regulating the release of active molecules, and safeguarding medications and natural compounds. Although they are frequently employed to deliver drugs, their use is fraught with serious issues. Among their main drawbacks include aggregation or fusion during storage, sedimentation, drug leaching, and degradation by hydrolysis or oxidation. The cost and unpredictability of phospholipid purity, the difficulty of sterilizing, and the requirement for large-scale manufacture to guarantee adequate physico-chemical stability is some of the challenges facing the clinical usage of liposomes [1].

The phospholipids that make up the liposomal bilayer and the non-ionic surfactant that forms the niosomal bilayer distinguish the two systems. Non-ionic surfactants self-assemble in aqueous media to produce niosomes in a variety of shapes, including spherical, unilamellar, bilayered, multilamellar, and polyhedral structures, depending on the preparation technique and the inverse structure in the case of a non-aqueous solvent. Hydrophilic ends of the surfactant are exposed outwardly in the niosome, whereas hydrophobic ends face one another, forming a bilayer of the surfactant. Niosomes are between 10 and 1000 nm in size. Cholesterol and a tiny amount of an anionic surfactant, such as dicetyl phosphate, are added to stabilize the niosomal vesicles that the non-ionic surfactant has created. This is capable of containing both hydrophilic and hydrophobic medications. Niosomes can enhance the therapeutic efficacy of drugs by altering their surface and limiting their effects which lowers the drug clearance [2, 3].

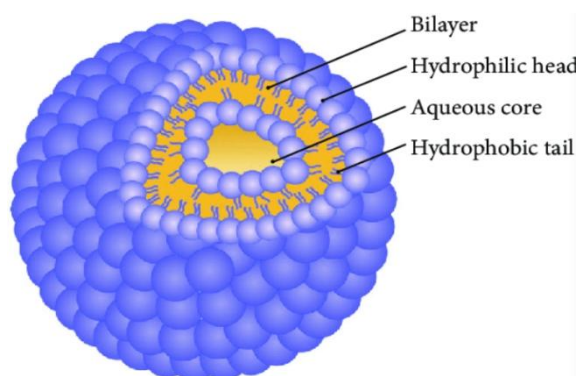


Figure 1: Niosomal structure

Advantages of niosomes

1. **Non-toxic and biocompatible:** Niosomes are safer for use in medical and cosmetic applications since they are typically less toxic than other vesicles like liposomes because they are composed of non-ionic surfactants.
2. The ability of niosomes to encapsulate a variety of hydrophilic and lipophilic medications enhances their bioavailability and therapeutic impact by enabling regulated release.
3. As a result of their resistance to oxidation and hydrolysis, niosomes are often more stable than liposomes. They are perfect for long-term preservation of medication formulations because of their stability.
4. In order to minimize the negative consequences of systemic medication administration, niosomes might be designed to target particular tissues or cells. This is especially helpful when it comes to localized therapy or cancer treatment.
5. **Versatile Formulation:** According to particular therapeutic requirements, niosomes size, charge, and release profile can be customized by combining them with various surfactants.
6. The cost-effectiveness of niosome-based formulations is attributed to the fact that non-ionic surfactants, which are employed in niosome manufacture, are frequently less expensive than liposomal components [3, 4].
7. **Sustained/Controlled Release:** Niosomes can reduce the frequency of doses and increase patient compliance by allowing the controlled or sustained release of encapsulated drugs.
8. The non-ionic surfactants that are employed in niosomes exhibit lower toxicity profiles than certain ionic surfactants, which may lessen adverse effects in therapeutic applications.
9. The skin permeability of encapsulated active substances can be improved by niosomes, which is advantageous for cosmetic formulations and transdermal medicine delivery.
10. **Versatile Administration Routes:** Niosomes can be administered orally, topically, or intravenously, providing flexibility for a range of therapeutic requirements.
11. Niosomes are a desirable alternative in fields such as medication administration, vaccine research, and cosmetic formulations because of these benefits [4].

Disadvantages

1. **Stability Issues under Harsh Conditions:** Although niosomes are more stable than liposomes, they may nevertheless become unstable in situations involving high ionic strength, pH, or temperature. This may have an impact on their performance and effectiveness, especially when they are being stored or transported.
2. The encapsulation efficiency of some medications, particularly hydrophilic chemicals, may be less effective than that of liposomes. This may restrict how much medication can be integrated into the niosome, which could lessen the efficacy of treatment.



3. The process of preparing niosomes can occasionally be more intricate and time-consuming than that of other drug delivery methods. It can be necessary to have fine control over formulation parameters and specialized equipment.
4. Despite the fact that niosomes can be successfully produced on a small scale, scaling up production for large-scale commercial Applications may make it difficult to maintain uniform size distribution, quality, and encapsulation effectiveness.
5. Irritation Potential: Certain non-ionic surfactants, especially in topical formulations, might irritate skin. The right surfactants that are kind to the skin and mucosal surfaces must be chosen with care [4, 5].
6. Certain surfactants employed in the manufacture of niosomes may still be rather harmful, even though non-ionic surfactants are typically thought to be safer than other kinds. This is particularly true when exposure is protracted or concentrations are high.
7. Difficulty in Controlling Release Profiles: Although niosomes can offer controlled release, it can be difficult to precisely regulate a drug's release profile, especially when dealing with big or complicated molecules. It might be necessary to further optimize the formulation in order to achieve consistent release throughout time.
8. The size distribution of niosomes can occasionally be broad, or polydispersed, which can affect how they behave in biological systems, including circulation time and cellular uptake.
9. Limited Commercial Applications: Despite their potential, niosomes have not been commercially adopted as widely as liposomes or other drug delivery systems. This could be because of limited clinical data, manufacturing difficulties, and regulatory barriers.
10. Storage and Handling Concerns: Niosomes, like other colloidal drug delivery systems, may be sensitive to light and temperature. To preserve their integrity, they need to be handled and stored carefully.
11. When creating niosomal formulations, these drawbacks must be taken into account because they could affect the product's viability, safety, and efficacy. But with additional study and improvement, many of these issues can be addressed [5].

Formulation of niosomes

A. Composition

1. The cholesterol

2. A surfactant that is not ionic

1) Cholesterol: Cholesterol gives niosomes their stiffness, appropriate shape, and conformation in the niosomal formulation. It gives the vesicles stability.

2) Non-ionic surfactant: are the most often utilized non-ionic surfactants in the niosome formulation.

Spans - 20, 40, 60, 80, and 85

Tweens - 20, 40, 60, and 80

Brij - 30, 35, 52, 58, 72, and 76

Their head is hydrophilic, and their tail is hydrophobic (5, 6).

Methods of preparation

The method of preparation influences the size, size distribution and number of bilayers, entrapment efficiency of the aqueous phase and the membrane permeability of the vesicles.

a. Ether injection method

b. Hand shaking method/thin film hydration method

c. Micro fluidization

- d. Multiple membrane extrusion method
- e. Reverse phase evaporation technique
- f. Sonication Method
- g. Transmembrane PH gradient drug uptake
- h. The bubble method

A. Ether injection method: surfactant dissolved in diethyl ether is added to warm water that has been kept at 60 degrees Celsius using the ether injection method. Using a 14-gauge needle, the ether solution containing surfactant is injected into an aqueous solution of material. As ether vaporizes, single-layered vesicles are created. The vesicle's diameter can range from 50 to 1000 nm, depending on the circumstances.

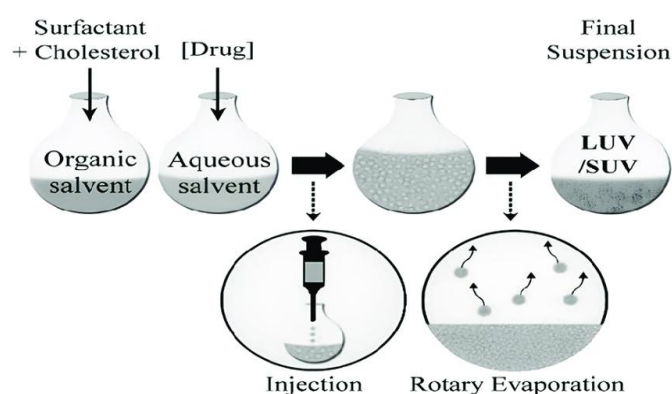


Figure 2: Ether injection method

B. Thin film hydration/hand shaking method: Surfactant and cholesterol are dissolved in a volatile organic solvent, like menthol, diethyl ether, or chloroform. At room temperature (20°C), the organic solvent is eliminated using a rotary flash evaporator, leaving a thin layer of solid mixture on the flask wall. Next, the dehydrated surfactant film is rehydrated using medication in an aqueous solution at the surfactant temperature for a predetermined amount of time (the hydration period) while being gently stirred. This process creates multilamellar niosomes¹⁴. In order to create thermosensitive niosomes, an organic solvent is evaporated at 60°C, leaving a thin layer on the rotary flask evaporator wall. The drug-containing aqueous solution is then gradually added by shaking at ambient temperature and then sonicating [6].

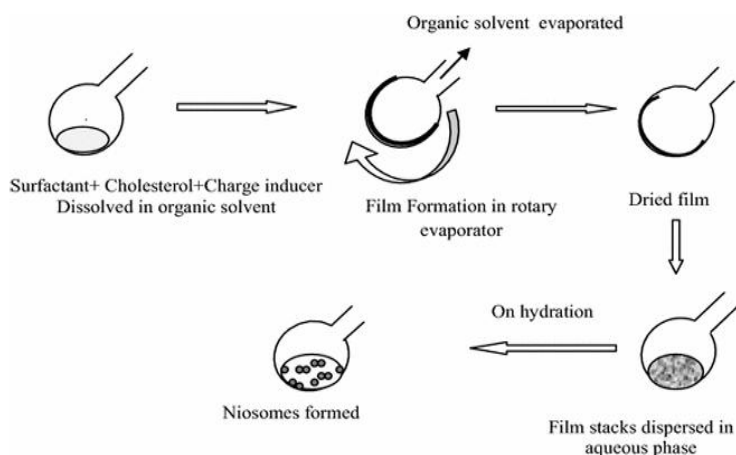


Figure 3: Thin film hydration/hand shaking method

C. Micro fluidization: The niosomes crude suspension is put into the microfluidizer and subjected to turbulence and high pressure shearing. By drastically shrinking the niosomes size, this procedure enhances the uniformity of their size distribution. The fluid undergoes high-velocity collisions, cavitation, and severe shear stresses as it moves through the microfluidizer. The breakdown of larger vesicles into smaller, more homogeneous niosomes is aided by these pressures.

Niosome size and encapsulation efficiency can be fine-tuned by varying the number of cycles and pressure, which usually ranges from 1,000 to 30,000 psi. It could be necessary to make several passes through the apparatus in order to attain the intended size distribution, which is usually between 100 and 200 nm.

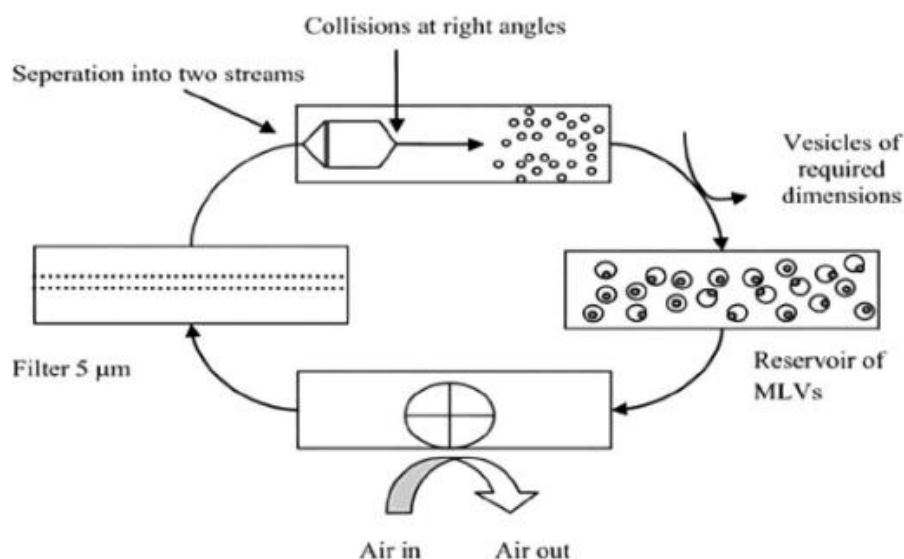


Figure 4: Micro fluidization

D. The multiple membrane extrusion method: can be used to generate vesicles of the desired size. Up to eight channels can be made by connecting polycarbonate membranes in sequence. Evaporation creates a thin layer of the mixture of surfactant, cholesterol, and dicetyl phosphate. The drug-containing aqueous solution is then used to rehydrate the film. C16G12 is used to extrude the resulting solution through a polycarbonate membrane (0.1 μ m nucleophore).

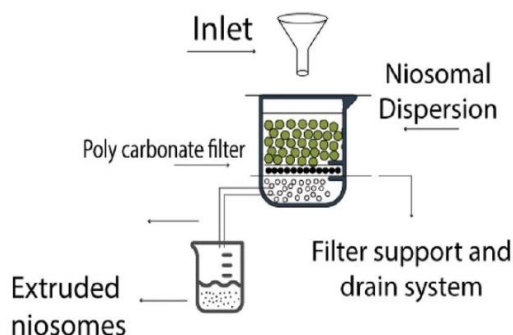


Figure 5: Multiple membrane extrusion method

E. Reverse phase evaporation technique: ether and chloroform are mixed to dissolve cholesterol and surfactant in a 1:1 ratio. This is mixed with an aqueous medication solution. At 4-5 degrees Celsius, the two phases are sonicated. The clear gel is sonicated once again after a small addition of phosphate buffered saline (PBS). It eliminates the organic phase at 40 $^{\circ}$ C and lowers the pressure. In order to produce niosomes, the viscous niosomal suspension is further diluted with PBS and heated on a water bath at 60 $^{\circ}$ C for 10 minutes (6,7).

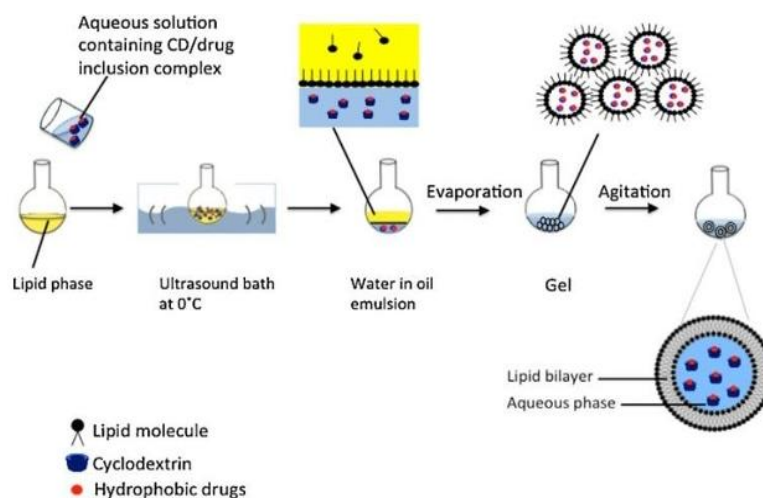


Figure 6: Reverse phase evaporation method

F. Sonication: Cable explains how vesicles are created by sonicating a solution. In a 10 ml glass vial, the surfactant/cholesterol mixture is mixed with an aliquot of drug-containing buffer solution. The liquid is then sonicated for three minutes at 60 degrees Celsius using a titanium probe in a sonicator to create niosomes.

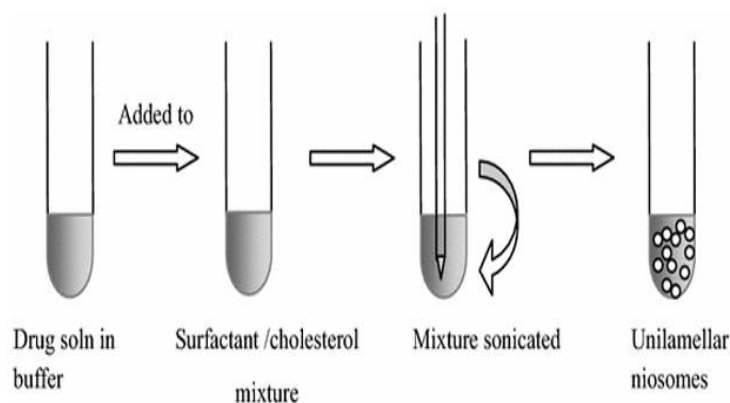


Figure 7: Sonication method

G. Trans membrane pH gradient technique: In a round-bottomed flask, cholesterol and surfactant are dissolved in chloroform to facilitate trans membrane PH gradient medication uptake. To obtain the thin film on the flak wall, the solvent is evaporated at a lower pressure. By vortex mixing, 300mm of citric acid (PH 4.0) is subsequently added to the film to hydrate it. In the end, multi lamellar vesicles are formed. They are then thawed and frozen three times before being sonicated to extract the niosomes. After adding an aqueous medication solution, the niosomal suspension is vortexed. Utilizing phosphate buffer, the PH is kept between 7.0 and 7.2. The mixture is then heated for 10 minutes at 60 degrees Celsius to produce niosomes [7].

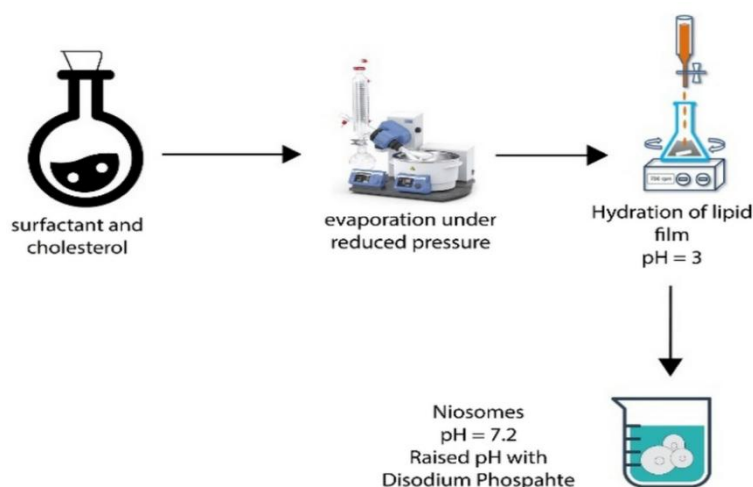


Figure 8: Transmembrane pH- gradient technique

H. The bubble method: Without the use of organic solvents, this innovative method creates niosomes in a single step. A round-bottomed flask with three necks that are positioned in a water bath to regulate the temperature is part of the bubbling unit. Water-cooled reflux is present in the first neck, a thermometer is present in the second, and a nitrogen supply is supplied through the third. PH 7.4 buffer is used to disperse cholesterol and surfactant at 70°C. The dispersion is blended with a high shear homogenizer for 15 seconds. The nitrogen gas then instantly bubbles at 70°C.

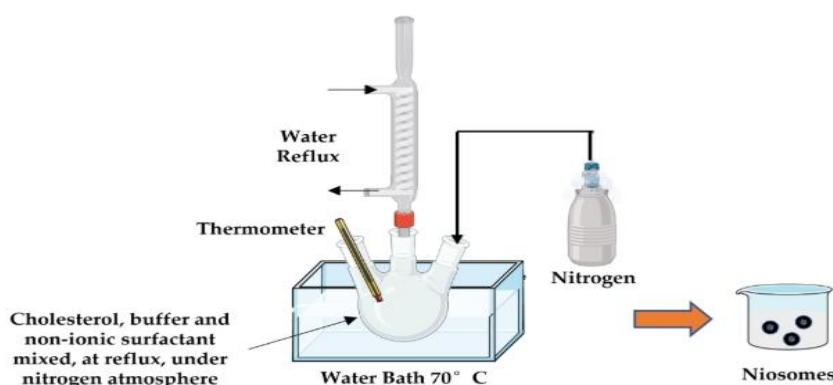


Figure 9: Bubble methods

Anti-inflammatory activity

Flavonoids can inhibit NF- κ B-dependent cytokine production, act as a scavenger of some chemokines or induce the expression of anti-inflammatory cytokines, such as IL-1ra. Example: Catechins, particularly found in green tea, exhibit significant anti-inflammatory activity by modulating various cellular pathways, including the suppression of inflammatory cytokines through inhibition of the transcription factor NF- κ B, thereby potentially helping to reduce inflammation in the body; this effect is attributed to their antioxidant properties and ability to regulate oxidative stress. Catechins can influence inflammatory responses by inhibiting the activation of key inflammatory signaling molecules like NF- κ B, which plays a central role in regulating the production of pro-inflammatory cytokines [8].

Key Mechanism of flavonoid anti-inflammatory activity:

- Inhibition of Pro-inflammatory Mediators:** Flavonoids have the ability to suppress the production and function of a number of pro-inflammatory mediators, including adhesion molecules, cytokines (like interleukin-1 β , TNF- α , and IL-6), and eicosanoids.
- Modulation of Transcription Factors:** They can alter the activity of transcription factors that are involved in the expression of pro-inflammatory genes, such as AP-1 and NF- κ B.



c) Antioxidant Pathway Activation: Flavonoids decrease oxidative stress, a major cause of inflammation, and strengthen the body's antioxidant defenses by activating pathways such as Nrf2.

d) Inhibition of Enzymes: Flavonoids can lessen the recruitment and activation of inflammatory cells at sites of inflammation by inhibiting enzymes that are involved in the production of inflammatory molecules, such as lipoxygenase, cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS).

Table 1: Flavonoids anti-inflammatory activity

S.no	Flavonoid compound	Formulation	Composition of product	Reported activity
1.	Berry fruit (quercetin)	Methanolic extraction	Goji, blue, Cran, Berry fruits(lycium barbarum)	Result suggest, rutin, phenolic compound found in these berry fruits which produces anti-inflammatory response based on modulation of oxidative stree in paw edema model [9].
2.	Diosmetin Citrus flavonoid		LPS-Induced Inflammatory Models. IMQ- induced psoriasis in mice.	DNCB -5mg/kg for 2weeks which is studied sample skin. LPS- 50mg/kg for 6days studied sample is liver. The Intial process results in the collateral tissue damage and the organ dysfunction. The Dios treatment as proven to be a significant aid in organ damage which is caused by inflammation [10]
3.	Baicalein BA	Silk worm cocoon. BA was combined with the solution of silk fibroin protein biomaterial used as drug carrier.	Sigma Aldrich, Sodium carbinat, calcium chloride.	BASF, fibroin - 18mg/ml oral for 1hr before the intra peritoneal administration. Total 6groups under Group A -0.02ml oral saline. Group B - negative 0.2ml. Group C- treated with NSAID. Group D- BASF subgroups. Group E - BA 100mg/kg. BASF, it results the good stability through the assessment of zeta potential, and the acute toxicity tests revealed that this combination is safe for the oral administration in zebrafish [11].

Table 2: Anti - Inflammatory Mechanism

S. No	Flavonoid	Method of niosomal preparation	Targeted activity	Major findings	References
1.	<i>Green tea catechin</i>	Nano delivery system	Pamdemic diseases	Improves the stability rate of absorption and bioavailability.	[12]
3.	<i>catechin</i>	Thin film hydration	Antioxidant, anti-inflammatory& anticancer properties	Favorable stability, enhanced bioavailability and a prolonged release profile, primarily governed by the diffusion controlled mechanism.	[13]
4.	<i>Gambier, catechin</i>	Nano encapsulation and DPPH method	Antioxidant activity	Based on DPPH analysis it showed that the nano emulsification process reduces the antioxidant activity. The nano encapsulated catechin as a good particle surface	[14]



				topography of the particles and emulsion stability.	
5.	ECG, catechin	Thin film hydration method	Formulation and evaluation of niosomes in in vitro drug release	In vitro studies were confirmed that catechin loaded niosomes exhibit the favorable stability, increased bioavailability and prolonged release profile.	[15]
6.	<i>Quercetin</i>	Ethanol injection method	Antioxidant activity, hepatoprotective properties.	Hepatoprotective effect of quercetin loaded niosomal preparation increases the activity of quercetin and in vivo, in vitro which significantly shows the decreases after pretreatment with quercetin niosomes.	[16]
7.	<i>Flavonoids</i>	Using the niosomal nano carrier	Treatment of glioblastoma	It Prevent elimination of poorly absorbed drug from circulation and protects the against biological environment.	[17]
8.	<i>Annona squamosa extract</i>	Thin film hydration method	Dermal delivery, antioxidant activity.	It shows the potential of both carriers to penetrate the stratum corneum.	[19]
9.	<i>Asparagus racemosus</i>	Thin film hydration method	Anti-inflammatory activity	The niosomal gel had better efficacy than the conventional gel.	[18]
10.	<i>Mefenamic acid</i>	Ether injection method	Cancer targeting	Entrapment efficiency release rate shows high accumulation in the tumor tissue. Niosomes increases the delivery of MEF to the tumor cell.	[19]

CONCLUSION

In summary, niosomes have great potential as a flexible and effective drug delivery method. They have advantages over conventional carriers like liposomes, such as increased stability, cost-effectiveness, and ease of production. They are especially appealing for improving the bioavailability of medications and targeting certain tissues because to their capability for controlled and prolonged release, as well as their ability to encapsulate both hydrophilic and lipophilic compounds. Large-scale production, long-term stability, and possible toxicity are some of the issues that require more research and improvement despite these benefits. Through further investigation and advancement, niosomes may be crucial in transforming drug delivery systems and other biological uses, providing innovative ways to enhance treatment effectiveness and patient outcomes.

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