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FUNDAMENTALS, CONCEPTS, AND ADVANCEMENTS IN NIOSOMES DRUG CARRIER SYSTEMS

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ABESTRACT

Formulations aimed at transporting medication to the intended region of action inside the body are known as drug delivery systems. A suitable carrier shields the medication from fast breakdown or removal, resulting in increased drug concentration in target tissues. Niosomes, which are produced by self-association of non-ionic surfactants and cholesterol in an aqueous phase, are potential drug carriers because of their biodegradable, biocompatible, and non-immunogenic nature. Numerous research papers published in scientific journals in recent years have reported on the ability of niosomes to act as a carrier for the delivery of various kinds of medicines. The current review discusses production methods, characterization techniques, and recent research on niosomal drug delivery systems, as well as providing up-to-date information on new niosomal drug delivery applications.

KEYWORDS: Niosomes, Vesicular drug delivery system, Components, Applications, Characterizations, Preparation methods.

1. INTRODUCTION[1,2]

In recent years, medication delivery with a regulated rate and focused distribution has gotten a lot of attention. The use of nanotechnology in medicine has resulted in the creation of multifunctional nanoparticles that can be loaded with various medicines and serve as drug carriers. Nanocarriers provide a potential method to drug delivery, with characteristics such as drug protection against degradation and cleavage, controlled release, and, in the case of targeted delivery techniques, drug molecule distribution to the target locations. Niosomes, which have a bilayer structure and are produced by self-association of non-ionic surfactants and cholesterol in an aqueous phase, is one of the most promising drug carriers. Niosomes are non-immunogenic, biodegradable, and biocompatible. They have a long shelf life, are very stable, and allow for regulated and/or continuous drug administration at the target location. The potential of niosomes as a medicine carrier has been widely researched in recent years. Various non-ionic surfactants have been reported to produce niosomes, which allow a broad variety of medicines with varying solubilities to be entrapped. To improve the efficacy of niosomes for drug delivery, the composition, size, number of lamellae, and surface charge of niosomes may be changed and adjusted. The goal of this study is to provide the basics of niosome production and characterization, as well as a description of their use in drug administration, with a focus on more recent research. This study will provide an overview of the growing interest in niosomes as drug delivery vehicles.

2. STRUCTURE AND COMPONENTS OF NIOSOMES[3-5]

Non-ionic surfactants, hydration medium, and lipids such as cholesterol are the primary components of niosomes. Examples include hexadecyl diglycerol ether ($C_{16}G_2$), Brij 30, Brij 52, Brij 72, Brij 76, Brij 78, Bola, Span 20, Span 40, Span 60, Span 80, Span 65, Span 85, Tween 20, Tween 40, Tween 60, Tween 80, Tween 65, Tween 85, C-Glycoside derivative surfactant (BRM-BG), octyl-decyl polyglucoside (OrCG110), decyl polyglucoside (OrNS10), stearyl alcohol, cetyl alcohol, myristyl alcohol, Stearic acid, palmitic acid, myristic acid, Pluronic L64, Pluronic 105, Diacetyl phosphate, phosphatidic acid, lipoamino acid, dihexadecyl phosphate, Stearylamine, stearyl pyridinium chloride, cetyl pyridinium chloride, etc. Non-ionic surfactants self-assemble in aqueous environments to form closed bilayer structures (**Figure 1**). Water and the amphiphile's hydrophobic tails provide an interfacial tension that drives them to interact. The steric and hydrophilic repulsion between the non-ionic surfactant's head groups ensures that the hydrophilic termini point outwards and come into touch with water. The formation of closed bilayers generally requires some kind of energy input,

such as mechanical or thermal. Niosomes are divided into three categories based on their size and bilayer structure. SUVs (small unilamellar vesicles) (10–100 nm), LUVs (large unilamellar vesicles) (100–3000 nm), and MLVs (multilamellar vesicles) are examples of multilayer vesicles.

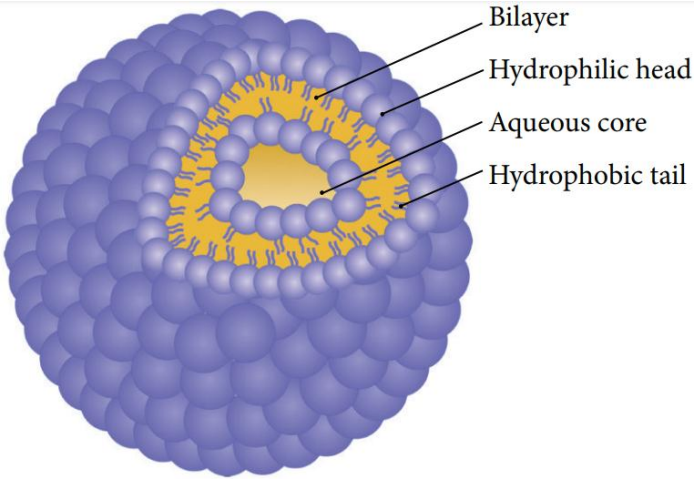

Figure 1: Structure of niosomes.

2.1. Non-ionic surfactants

Surfactants with no charged groups in their hydrophilic heads are known as non-ionic surfactants. When compared to anionic, amphoteric, or cationic equivalents, they are more stable, biocompatible, and less poisonous. As a result, they are favored for the *in vitro* and *in vivo* production of stable niosomes. Non-ionic surfactants are amphiphilic compounds with two distinct regions: one is hydrophilic (water-soluble) and the other is hydrophobic (water-insoluble) (organic-soluble). The major non-ionic surfactant classes utilized in niosome synthesis include alkyl ethers, alkyl esters, alkyl amides, and fatty acids. In the selection of surfactant molecules for niosome production, the hydrophilic-lipophilic balance (HLB) and critical packing parameter (CPP) values are crucial.

2.1.1. Hydrophilic-Lipophilic balance

The Hydrophilic-Lipophilic Balance (HLB) is a dimensionless measure that indicates the surfactant molecule's solubility. The HLB value reflects the balance between the non-ionic surfactant's hydrophilic and lipophilic portions. For non-ionic surfactants, the HLB range is 0 to 20. It is observed that the lower the HLB, the more lipophilic the surfactant, and the higher the HLB, the more hydrophilic. Surfactants having an HLB of 4 to 8 may be utilized for vesicle preparation. Due to their high water solubility, hydrophilic surfactants with an HLB value of 14 to 17 are not appropriate for forming a bilayer membrane. Polysorbate 80 (HLB value = 15) and Tween 20 (HLB value = 16.7) do, however, produce niosomes when an optimal amount of cholesterol is added. In the presence of equimolar cholesterol concentrations, Tween 20 produces persistent niosomes. At an equimolar ratio, the hydrophobic portion of the amphiphile adjacent to the head group interacts with the 3-OH group of cholesterol, which may explain cholesterol's impact on the formation and hydration behavior of Tween 20 niosomal membranes. The HLB value of the surfactant has an effect on the drug entrapment efficiency of niosomes. By altering the HLB, experimenters were able to integrate nimesulide into niosomes utilizing the lipid film hydration method. Entrapment efficiency falls when the HLB value of the surfactant drops from 8.6 to 1.7.

2.1.2. Critical Packing Parameter (CPP)

The essential packing parameter determines the shape of the vesicle during niosomal preparation. The shape of nanostructures produced by self-assembly of amphiphilic molecules may be predicted using the CPP of a surfactant. The critical packing parameter is determined by the surfactant's symmetry and may be calculated using the following equation:

$$\mathbf{CPP} = \frac{\boldsymbol{V}}{\boldsymbol{lc} \times \boldsymbol{a0}}$$

where *v* is the volume of the hydrophobic group, *lc* is the critical length of the hydrophobic group, and *a0* is the area of the hydrophilic head group. Small hydrophobic tail spherical micelles may develop if CPP ≤ 1/3, which corresponds to a bulky head group, for example. If 1/3 ≤ CPP ≤ 1/2, non-spherical micelles may form, and bilayer vesicles may form if 1/2 ≤ CPP ≤ 1. When the surfactant has a large hydrophobic tail and a small voluminous tail, inverted micelles develop (CPP ≥ 1). CPP may be used to see, rationalize, and forecast self-assembled structures and their morphological transitions in amphiphilic fluids.

2.2. Cholesterol

Cholesterol creates hydrogen bonds with the hydrophilic head of a surfactant in the bilayer structure of niosomes. The amount of cholesterol in niosomes affects their structure as well as physical characteristics including entrapment efficiency, long-term stability, payload release, and biostability. Cholesterol increases vesicle stiffness and stabilizes niosomes against destabilizing

effects caused by plasma and serum components, as well as lowering vesicle permeability for encapsulated molecules, preventing leakage. In niosomal formulations, drug entrapment efficiency is essential, and it may be changed by changing the cholesterol concentration. With increasing cholesterol content, studies showed that cholesterol enhances the stability of enoxacin-loaded niosomes, resulting in increased entrapment efficiency. Researchers investigated the impact of cholesterol on flurbiprofen entrapment and discovered that cholesterol had minimal influence on flurbiprofen entrapment into Span 20 and Span 80 niosomes. When 10 percent cholesterol was integrated into niosomes made from Span 40 and Span 60, however, there was a substantial rise in flurbiprofen entrapment efficiency, followed by a reduction in encapsulation efficiency when the cholesterol concentration was increased further. According to the findings, the quantity of cholesterol added and how much is added should be adjusted based on the physical-chemical properties of surfactants and loaded medicines.

2.3. Charged Molecule

The addition of charged groups to the bilayer of vesicles by charged molecules increases the stability of the vesicles. They inhibit vesicles from aggregating by increasing surface charge density. Negatively charged compounds such as dicetyl phosphate and phosphatidic acid are often employed in niosomal preparations, whereas positively charged molecules such as stearylamine and stearyl pyridinium chloride are also commonly used. Normally, 2.5–5 mol percent of the charged molecule is added to the niosomal formulation. However, increasing the number of charged molecules may prevent the development of niosomes.

3. METHODS OF PREPARATION[6-8]

3.1. Thin-Film hydration method

The thin-film hydration technique is a well-known and easy method of preparation. Surfactants, cholesterol, and other additives like charged molecules are dissolved in an organic solvent in a round-bottomed flask in this technique. The organic solvent is then evaporated using a rotating vacuum evaporator to leave a thin coating on the flask's inner wall. The aqueous drug solution is added, and the dry film is hydrated above the surfactant's transition temperature (Tc) for a predetermined period with continuous shaking. This technique produces multilamellar niosomes.

3.2. Ether injection method

The surfactants with additions are dissolved in diethyl ether and injected slowly via a needle into an aqueous drug solution kept at a steady temperature above the boiling point of the organic solvent in the ether injection technique. A rotary evaporator is used to evaporate the organic solvent. Single-layered vesicles are formed during the vaporization process.

3.3. Reverse phase evaporation method

Niosomal components are dissolved in a combination of ether and chloroform and then added to an aqueous phase containing the medication in this technique. The organic phase is evaporated after the mixture has been sonicated to create an emulsion. During the evaporation of the organic solvent, large unilamellar vesicles develop.

3.4. Microfluidization method

The submerged jet concept is used in the microfluidization technique. The drug and surfactant fluidized streams interact in precisely specified microchannels inside the interaction chamber at ultrahigh velocities in this technique. Niosomes are formed as a result of the high-speed impact and the energy involved. In the formation of niosomes, this technique provides better homogeneity, smaller size, unilamellar vesicles, and excellent repeatability.

3.5. Supercritical carbon dioxide fluid

The supercritical reverse-phase evaporation method for niosome production was reported. Tween 61, cholesterol, glucose, PBS, and ethanol were added to the view cell, and then CO_2 gas was injected. The pressure was released after magnetic stirring until equilibrium was reached, and niosomal dispersions were produced. This technique allows for simple scale-up and one-step manufacturing.

3.6. Proniosome

A water-soluble carrier, such as sorbitol or mannitol, is coated with surfactant in the proniosome method. A dry formulation is formed as a consequence of the coating process. This preparation is known as Proniosomes, and it must be hydrated before usage. The inclusion of the aqueous phase results in the formation of niosomes. When compared to traditional niosomes, this technique reduces physical stability issues such as aggregation, leakage, and fusing while also providing simplicity in dosing, distribution, transportation, and storage.

3.7. Transmembrane pH gradient

Surfactant and cholesterol are dissolved in chloroform and evaporated to create a thin lipid layer on the flask's wall in this technique. By vortex mixing, the film is hydrated with a citric acid solution (pH = 4) and the resultant product is freeze-thawed for niosome production. The drug's aqueous solution is added to the niosomal suspension, followed by phosphate buffer to keep the pH between 7.0 and 7.2. The core of the niosome, according to this technique, has a lower pH than the outside medium. The additional unionized medication enters the niosome after passing through the niosome membrane. In an acidic environment, the medication ionizes and is unable to pass through the niosomal bilayer.

3.8. Heating method

Surfactants and cholesterol are hydrated separately in buffer, then heated to 120°C with stirring to dissolve

cholesterol. While stirring continues, the temperature is lowered and surfactants and other chemicals are introduced to the buffer in which cholesterol is dissolved. Niosomes are formed at this step, then left to cool to ambient temperature before being stored at 4-5°C in a nitrogen environment until needed.

3.9. Bubble method

Surfactants, additives, and the buffer are placed in a glass flask with three necks in this technique. The components of niosomes are distributed at 70°C and combined using a homogenizer. After that, the flask is immediately put in a water bath and nitrogen gas is bubbled at 70°C. Large unilamellar vesicles are formed when nitrogen gas is fed over a sample of homogenized surfactants.

4. CHARACTERIZATION OF NIOSOMES[9-11]

For clinical uses, niosome characterization is critical. The stability of niosomes is directly influenced by characterization criteria, which also have a major impact on their *in vivo* performance. As a result, these characteristics must be assessed, including shape, size, polydispersity index (PI), number of lamellae, zeta potential, encapsulation efficiency, and stability.

4.1. Size and Morphology

The most common techniques for determining niosome sizes and morphology are dynamic light scattering (DLS), scanning electron microscopy (SEM), transmission electron microscopy (TEM), frozen fracture replication electron microscopy (FF-TEM), and cryotransmission electron microscopy (cryo-TEM). DLS offers both cumulative particle size information and important information on the homogeneity of the solution at the same time. A single sharp peak in the DLS profile indicates the presence of a single scatterer population. In this regard, the PI is beneficial. For colloidal systems, a value of less than 0.3 corresponds to a homogeneous population. Characterizing the morphology of niosomes is usually done using microscopic methods.

4.2. Zeta potential

The zetasizer and DLS devices may be used to measure the surface zeta potential of niosomes. The surface charge of a niosome has a significant impact on its behavior. Charged niosomes are more resistant to aggregation than uncharged vesicles in general. Experimenters made paclitaxel-loaded niosomes and studied their physicochemical characteristics, such as their zeta potential. Negative zeta potential levels ranging from -41.7 mV to -58.4 mV were found to be adequate for niosome electrostatic stabilization.

4.3. Bilayer characterization

The effectiveness of drug entrapment is influenced by the bilayer properties of niosomes. For multilamellar vesicles, AFM, NMR, and small-angle X-ray scattering (SAXS) may be used to measure the number of lamellae. The mobility of a fluorescent probe as a function of temperature may be used to determine the membrane stiffness of niosomal formulations. The most often utilized fluorescent probe is DPH (1,6 diphenyl-1,3,5-hexatriene), which is added to niosomal dispersion. DPH is usually found in the bilayer membrane's hydrophobic area. Fluorescence polarisation determines the microviscosity of the niosomal membrane. High fluorescence polarisation indicates a high membrane microviscosity. Furthermore, employing the latter technique in conjunction with in situ energy-dispersive X-ray diffraction (EDXD), the bilayer thickness may be determined.

4.4. Entrapment efficiency

The percentage of the applied medication that is captured by the niosomes is known as entrapment efficiency (EE percent). Centrifugation, dialysis, or gel chromatography may be used to extract unencapsulated free medication from the niosomal solution. By destroying vesicles after this process, the loaded medication may be released from niosomes. The addition of 0.1 percent Triton X-100 or methanol to niosomal suspension may kill them. A spectrophotometer or high-performance liquid chromatography (HPLC) may be used to determine the loaded and free drug concentrations.

4.5. Stability

The stability of niosomes may be assessed by measuring the mean vesicle size, size distribution, and entrapment efficiency over many months at various temperatures. Niosomes are collected at regular intervals throughout storage, and the proportion of medication retained in the niosomes is determined using UV spectroscopy or HPLC techniques.

4.6. *In vitro* release

The use of dialysis tubing is a common technique for studying *in vitro* release. A dialysis bag is immersed in distilled water after being cleaned. The drug-loaded niosomal suspension is put into this bag after 30 minutes. At 25°C or 37°C, the bag holding the vesicles is submerged in buffer solution and constantly shaken. Samples were withdrawn from the outer buffer (release medium) and replaced with the same amount of fresh buffer at predetermined intervals. An appropriate assay technique is used to determine the drug content of the samples.

5. NIOSOMES AS DRUG CARRIERS[12-15]

Niosomes have shown to be effective carriers for a variety of pharmacological and diagnostic substances. The production, characterization, and usage of niosomes as drug carriers have been described in a number of articles. They have high biocompatibility and minimal toxicity due to their non-ionic nature. Because of their unusual structure, niosomes may be used to create new drug delivery systems that can load both hydrophilic and lipophilic medicines. Drugs that are hydrophilic and lipophilic are entrapped in the niosome's aqueous core and membrane bilayer, respectively (**Figure 2**).

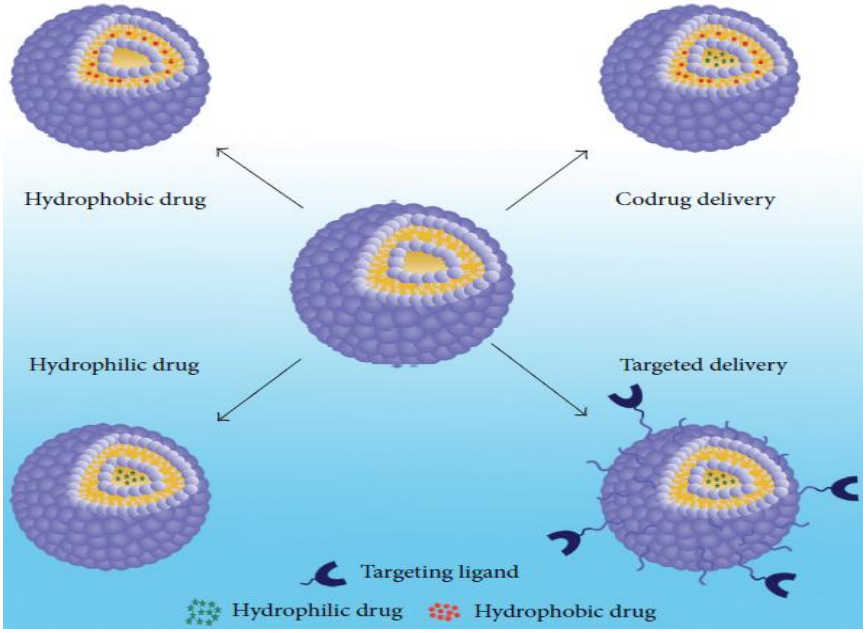

Figure 2: Applications of niosomes in modern drug delivery.

5.1. Anti-cancer drug delivery

Chemotherapy is the most common cancer treatment. Many anti-cancer medicines' therapeutic effectiveness is hampered by their inability to penetrate tumor tissue and their significant adverse effects on healthy cells. Various approaches, including the use of niosomes as a new drug delivery method, have been attempted to address these limitations.

5.1.1. Melanoma

Artemisone is a 10-amino-artemisinin derivative with anti-malarial and anti-cancer properties. Investigators used a thin-film hydration technique to encapsulate artemisone in niosomes. The formulations exhibited extremely selective cytotoxicity against melanoma cells while having minimal toxicity against normal skin cells. 5-Fluorouracil (5-FU) was encapsulated in a novel bola-niosomal system built up of,-hexadecyl-bis-(1-aza-18-crown-6) (bola-surfactant), Span 80, and cholesterol to treat various types of skin malignancies. Human stratum corneum and epidermis membranes were used to test the percutaneous penetration of 5-FU-loaded bola-niosomes. Bola-niosomes increased drug penetration by 8-times and 4-times, respectively, as compared to free drug aqueous solution. Because of its high toxicity, the use of cisplatin is restricted. Innovators used Span 60 and cholesterol to make niosomal cisplatin and tested its anti-metastatic efficacy in an experimental metastatic form of B16F10 melanoma. When compared to free cisplatin, their findings indicate that cisplatin encapsulated in niosomes has substantial anti-metastatic efficacy and lower toxicity.

5.1.2. Breast cancer

Experimenters produced 5-FU-loaded polyethylene glycol-coated and -uncoated bola-niosomes and tested them on breast cancer cell lines (MCF-7 and T-47D). In comparison to the free medication, both bola-niosome formulations increased the cytotoxic impact. After 30 days of therapy, *in vivo* studies on MCF-7 xenograft tumor SCID mice models revealed that the PEGylated niosomal 5-FU had more effective anti-cancer activity at a concentration ten times lower (8 mg/kg) than the free solution of the medication (80 mg/kg). The injection technique was used to create cantharidin-entrapped niosomes. On the human breast cancer cell line MCF-7, their ability to improve the drug's anti-cancer effects while lowering its toxicity was tested. In addition, *in vivo* therapeutic effectiveness in S180 tumor-bearing mice was examined. The anti-cancer activity of mice treated with 1.0 mg/kg niosomal cantharidin was 52.76 percent, which was considerably greater than that of mice treated with the same dosage of free cantharidin (1.0 mg/kg, 31.05 percent). Tamoxifen citrate niosomes were recently produced using a film hydration method for localized cancer treatment, as shown by *in vitro* breast cancer cytotoxicity and *in vivo* solid anti-tumor effectiveness. On the MCF-7 breast cancer cell line, the improved niosomal formulation of tamoxifen demonstrated substantially increased cellular absorption (2.8-fold) and much higher cytotoxic action. When compared to free tamoxifen, niosomal tamoxifen caused greater tumor volume reduction in *in vivo* studies.

5.1.3. Ovarian cancer

Doxorubicin-loaded niosomes were produced. A human ovarian cancer cell line and its doxorubicin-resistant subline were tested using doxorubicin in hexadecyl diglycerol ether ($C_{16}G_2$) and Span 60 niosomes. In contrast to the free drug in solution, the IC_{50} against the resistant cell line was slightly reduced when the medication was encapsulated in Span 60 niosomes, according to the findings.

5.1.4. Lung cancer

Scientists used monoalkyl triglycerol ether to encapsulate adriamycin into the noisome, and the activity of niosomal adriamycin was compared to free adriamycin solution on human lung tumor cells cultured in monolayer and spheroid culture, as well as tumor xenografted nude mice. The time it took for adriamycin (15 days) and niosomal adriamycin (11 days) to double the tumor volume was considerably longer than it was for control (5.8 days). It is conceivable that administering adriamycin in niosomal form would improve the therapeutic ratio even more. Another research used the lipid film hydration technique to make pentoxifylline-loaded niosomes. In an experimental metastatic B16F10 model, intravenous treatment of niosomal pentoxifylline (6 mg/kg and 10 mg/kg) resulted in a substantial decrease in lung nodules, indicating accumulation of pentoxifylline in a distant target. The number of tumor islands in the lung was reduced when light microscopic examination of histologic sections was performed.

5.2. Targeted delivery

Active targeting for tumor treatment, utilizing a ligand linked to the surface of niosomes, which may be actively taken up, for example, through receptor-mediated endocytosis, can enhance the efficiency and specifically the specificity of cellular targeting of niosomal drug delivery systems. To allow cell-specific targeting, niosome surfaces may be coupled with small molecules and/or macromolecular targeting ligands. The most frequently utilized compounds that bind selectively to an overexpressed target on the cell surface include proteins and peptides, polysaccharides, aptamers, antibodies, and antibody fragments. Innovators created a brain-targeted niosomal formulation that included a glucose derivative as a targeting ligand. They created niosomal doxorubicin, which is made up of the following ingredients: span: cholesterol: solulan: *N*-palmitoylglucosamine. Preliminary *in vivo* studies in rats showed that intravenous administration of a single dose of the developed targeted-niosomal formulation was able to significantly reduce hearth accumulation of the drug and keep it longer in the blood circulation, as well as achieve well detectable doxorubicin brain concentrations, compared to the commercial formulation. Researchers also developed an effective tumor-targeted niosomal delivery method. Niosomes were made from a combination of Pluronic L64 surfactant and cholesterol, with doxorubicin entrapped within. Transferrin was attached to the surface of niosomes using EDC (*N*-[3-(dimethylamino)propyl]-*N*-ethylcarbodiimide hydrochloride) chemistry after synthesis. Anti-cancer activity of doxorubicin-loaded niosomes was found in MCF-7 and MDA-MB-231 tumor cell lines, with a substantial decrease in viability seen in a dosage and time-dependent manner.

5.3. Co-drug delivery

Nanoparticles have emerged as a potential class of carriers for the delivery of several medicines in combination treatment in recent years. Combination treatments improve the therapeutic effectiveness and reduce dose while maintaining or improving efficacy and decreasing drug resistance. Anti-cancer medications often have severe adverse effects. In comparison to free drug therapy, studies demonstrated greater anti-cancer activity for carcinoma cells using a multidrug delivery system, but the multidrug delivery system reduced cytotoxicity against endothelial cells and cardiomyocytes. They created simultaneous anti-cancer drug epirubicin and nitric oxide transport system in which nitric oxide and epirubicin were covalently conjugated to each terminal of PEG in their system. Nitric oxide is a protective reagent against anthracycline-induced cardiomyopathy as well as an anti-cancer drug sensitizer. They utilized branched PEG instead of linear PEG as the polymer backbone to boost anti-cancer effectiveness and improve the cardiocyte-protecting capabilities of the co-delivery method. The capacity of cancer cells to survive treatment with structurally and functionally varied anti-cancer medicines is known as multidrug resistance (MDR) of malignant neoplasm. ATP-driven extrusion pump proteins of the ATP-binding cassette (ABC) superfamily, including P-glycoprotein (P-gp) encoded by MDR1, multidrug resistance (MDR) proteins (MRPs/ABCC), and breast cancer resistance protein (BCRP/ABCG2), are primarily responsible for increased drug efflux. Several medicinal medicines' intracellular concentrations are significantly reduced by these drug efflux pumps. Chemosensitizers including Verapamil, Elacridar, Tariquidar, and Cyclosporine A primarily work as P-gp antagonists, suppressing drug efflux and restoring chemosensitivity in MDR cancer cells. Paclitaxel was co-encapsulated with cyclosporine A in polymeric lipid-core micelles that were actively targeted. Paclitaxel cytotoxicity was increased when P-gp was inhibited by cyclosporine A. Micelles containing this dual cargo caused substantially more cytotoxicity in MDCKII-MDR1 cells than micellars containing just paclitaxel. In multidrug delivery applications, niosomes are a potential nanocarrier. It is recently described the use of niosomes to encapsulate both hydrophobic curcumin and hydrophilic doxorubicin for cancer treatment delivery. When compared to free medicines, dual-drug-loaded niosomes exhibited greater cytotoxicity on HeLa cells, according to the findings. Gallic acid, ascorbic acid, curcumin, and quercetin were encapsulated into the niosome as single agents or in combination in another study, and the effect of the drugs co-encapsulation on the carriers' physicochemical properties, anti-oxidant properties, and ability to release the encapsulated materials was assessed. Scientists also used lidocaine and ibuprofen to produce, characterize, and apply multidrug niosomes. The findings point to the possible use of niosomes as carriers for the treatment of different skin disorders, including acute and chronic inflammations in the presence of pain, when both

medicines are administered dermally at the same time in the same pharmaceutical formulation.

5.4. Antibiotics

Antibiotics and anti-inflammatory drugs may also be delivered via niosomal carriers. These carriers have been widely utilized to ease poor skin penetration and improve medication retention in the skin. Rifampicin, a broad-spectrum anti-biotic encapsulated in a niosomal delivery system was created. They tested the system's functionality *in vitro*, and the results indicated that a niosomal formulation of rifampicin may provide constant and long-lasting drug release. Researchers used the film hydration technique to manufacture ciprofloxacin-loaded niosomes using different non-ionic surfactants and cholesterol in varied concentrations to enhance anti-biotic effectiveness and decrease the dosage. The anti-bacterial activity of niosomes and drug release via bilayers were investigated. The findings revealed that cholesterol concentration and surfactant phase transition temperature affected niosome performance. Furthermore, as compared to free ciprofloxacin, all formulations showed higher anti-bacterial activity. In ocular-controlled delivery, vesicular systems, niosomes, and liposomes are often utilized. Research groups investigated if niosomes might be used as a carrier for ocular-controlled administration of the antibiotic gentamicin. In various molar ratios, different surfactants (Tween 60, Tween 80, or Brij 35) were mixed with cholesterol and a negative charge inducer dicetyl phosphate. The capacity of these vesicles to entrap the chosen medication was tested, and the findings revealed that cholesterol content, surfactant type, and the presence of a charge inducer all influence gentamicin entrapment efficiency and release rate. In terms of prolonging *in vitro* drug release, gentamicin-loaded niosomes made of Tween 60, cholesterol, and dicetyl phosphate were the most effective.

5.5. Anti-Inflammatory drugs

NSAID-loaded niosomes have been produced by a number of research organizations. These medications have the potential to produce side effects such as mucosal inflammation. NSAID-loaded niosomes used topically may significantly enhance medication penetration. Investigators produced ammonium glycyrrhizinate (AG) loaded niosomes using different surfactants and cholesterol at varied concentrations to explore the possible use of niosomes for anti-inflammatory drug delivery. For characterization, researchers looked at drug entrapment efficiency, anisotropy, cytotoxicity, and skin tolerability, as well as several other factors. The AG-loaded niosomes had no toxicity and were able to enhance anti-inflammatory efficacy in mice with excellent skin tolerability. Furthermore, on chemically produced cutaneous erythema in humans, the anti-inflammatory efficacy of the niosome-delivered medication was enhanced.

5.6. Anti-viral drugs

Niosomes have also been shown to be capable of delivering anti-viral medicines. Investigators produced zidovudine, the first anti-HIV drug authorized for clinical use, encased niosomes, and investigated their entrapment efficiency as well as their release sustainability. Tween, Span, and cholesterol proportions were combined to create the niosomes. Tween 80-derived niosomes captured significant quantities of zidovudine, and the addition of dicetyl phosphate prolonged drug release. In comparison to niosomes kept at 4°C for 90 days, medication leakage from Tween 80 formulations held at ambient temperature was considerable. Tween 80 formulations containing dicetyl phosphate were similarly removed from the circulation in rabbits after five hours, according to the findings of a pharmacokinetic investigation.

6. RECENT STUDIES[16-18]

Niosomes have been effectively utilized as drug carriers to address several key biopharmaceutical issues such as insolubility, side effects, and poor chemical stability of therapeutic molecules during the last three decades. The most recent uses of niosomes as drug delivery methods are summarized in **Table 1**.

Table 1: Recent studies on niosomes drug delivery systems.

Drug	Composition	Experimental model
Candesartan cilexetil	Span 60, cholesterol, dicetyl phosphate, maltodextrin	*In vitro* dissolution test for proniosomal tablets, *in vivo* evaluation of proniosomal tablets, and pharmacokinetic analysis
Cefixime	*C*-Glycoside derivative surfactant, cholesterol	*In vitro* release study, biocompatibility, and bioavailability studies using experimental animals
Dexamethasone	Span 60, cholesterol	Characterization of niosomes, *in vitro* release studies, and stability test
Doxorubicin	Span 60, cholesterol, dicetyl phosphate, *N*-lauryl glucosamine	Optimization studies for the formulation, skin irritancy, and histopathological investigation of rat skin
Famotidine	Span 60, cholesterol	Kinetic analysis of drug-release profiles and *ex vivo* permeability study
Moxifloxacin	Tween 60, cholesterol	*In vitro* release studies and antimicrobial activity
Naproxen	Tween 80, Tween 20,	*In vitro* drug release study and preformulation study

	cholesterol	
Nevirapine	Tyloxapol, cholesterol	Diffusion kinetics of drug, microviscosity studies, and *in vitro* release study
Paclitaxel	Span 40, cholesterol, dicetyl phosphate	Formulation studies, Pharmacokinetic, and tissue distribution studies

7. STRENGTHS AND LIMITATIONS[19,20]

Chemical stability is one of the most significant advantages of niosomes over liposomes. In comparison to liposomes, niosomes are more resistant to chemical destruction or oxidation and have a longer storage period. Surfactants utilized in the production of niosomes are biodegradable, biocompatible, and non-immunogenic. Surfactant handling and storage conditions do not need any standards. Furthermore, the kind of production technique, surfactant, cholesterol content, surface charge additions, and suspension concentration may all affect the composition, size, lamellarity, stability, and surface charge of niosomes. On the other hand, niosomes have issues with physical stability. Niosomes in dispersion is susceptible to aggregation, fusion, drug leakage, and hydrolysis of encapsulated medicines during storage. Furthermore, sterilizing niosomes requires a significant amount of work. Niosomes are not suited for heat sterilization or membrane filtration. As a result, further study is needed in these areas in order to develop economically viable niosomal preparations.

8. CONCLUSION

Niosomes are a new kind of nano-drug carrier that may be used to create efficient drug delivery systems. They provide an excellent way to load hydrophilic, lipophilic, or both medicines at the same time. Numerous researches have been conducted using various kinds of niosomes in the administration of anti-cancer, anti-inflammatory, and anti-infective drugs, among other things. Niosomes enhance the stability of the entrapped medication, decrease the dosage, and allow targeted administration to a particular kind of tissue, according to the research. Novel preparations, loading, and modification techniques for specific routes of administration may improve the structural features and attributes of niosomes. As a result, niosomes seem to be potential therapeutic instruments in commercially accessible therapies.

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CONFLICT OF INTEREST

The authors declare no Conflict of Interest regarding the publication of the article.

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