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Research Article

NIOSOMES: AS DRUG CARRIER

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ABSTRACT

By employing nanocarriers as a drug delivery method, such as niosomes, it is possible to address the drawbacks of conventional drug delivery systems, such as undesirable pharmacokinetics, distribution, and drug degradation. Niosomes are tiny lamellar structures that are biodegradable, biocompatible, and non-immunogenic. They are also very low in toxicity and offer high biocompatibility. The amphiphilic bilayer structure of niosomes has polar and nonpolar regions. The key benefit of employing niosomes as a drug delivery system is that it may be used to administer a range of medications since it has the potential to entrap hydrophilic, lipophilic, and amphiphilic medications. Niosomes are more superior to liposomes as they are more physically and chemically stable than liposomes as niosomes are less vulnerable to chemical degradation or oxidation than phospholipids. The major application of niosomes is the controlled and the targeted release of the drugs. Niosomes have been thoroughly investigated in recent years for their potential to function as a vehicle for the transport of medications, antigens, hormones, and other bioactive molecules. Niosomes have also been employed to address the issues of drug insolubility, instability, and fast degradation. To increase the therapeutic efficacy of some anti-inflammatory medications, such as flurbiprofen and piroxicam, and sex hormones, such as estradiol and levonorgestrel, niosomes are widely used in transdermal administration. Better drug concentration at the site of action is also provided by this vesicular system when drugs are delivered topically, parenterally, or orally. Niosomes' sustained release activity can be used to deliver medicines with poor therapeutic indices and water solubilities.

INTRODUCTION

Conventional drug delivery systems face some significant challenges, such as unfavourable pharmacokinetics and distribution, which can lead to unwanted side effects [1]. Drug degradation in blood circulation by the reticulo-endothelial system and insufficient drug uptake at the target site can reduce drug efficacy[2]. Nanocarriers have been extensively investigated in the past decades to overcome the challenges associated with conventional drug delivery systems, due to the following advantages:

a] facilitate targeted drug delivery to the diseased site; b] enhance absorption as surface area increases and hence increase bioavailability;c] improve pharmacokinetics and bio-distribution of therapeutic agents; d] increase retention in biological systems and prolong the efficacy of drugs.

Niosomes are microscopic lamellar structures composed of non-ionic surfactants and cholesterol. The niosomes have amphiphilic bilayer structure in a way that polar region is oriented outside and inside the vesicles where the hydrophilic drug will be entrapped and nonpolar region is formed within the bilayer where hydrophobic drug can be entrapped [3].One of the potential bilayer drug delivery systems is the niosome. Niosomes are non-immunogenic, biocompatible, and immune-inactive. They are very stable, have a long shelf life, and allow for regulated and/or continuous drug administration at the target location. To improve the effectiveness of niosomes for drug administration, the composition, size, number of lamellae, and surface charge may be changed and tuned [4]. Due to their small size and poor penetration into connective tissue and epithelium, niosome drug delivery is one method for achieving localised drug activity. This method maintains the medication localised at the site of administration. When a drug acts locally, its effectiveness and potency are increased while its systemic toxic effects are decreased. For example, when antimonial contained in niosomes is taken up by mononuclear cells, the drug is localised, its potency is increased, and as a result, the drug's dose and toxicity are reduced. [5] Niosomal drug delivery technology is in in its early stages of development, although it

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has showed promise in leishmaniasis treatment and cancer chemotherapy.

NIOSOMES AS DRUG CARRIERS

Niosomes are incredibly promising delivery systems for many pharmacological and diagnostic substances. They offer great biocompatibility and minimal toxicity due to their non-ionic nature. Niosomes' distinctive structure allows the development of efficient, cutting-edge drug delivery devices that can accommodate both hydrophilic and lipophilic medicines. Drugs that are lipophilic and hydrophilic are entrapped in the membrane bilayer and aqueous core of niosomes, respectively.

Anticancer Drug Delivery

Many anticancer medications' therapeutic efficiency is constrained by their low tumour tissue absorption and their damaging side effects on healthy cells. Many attempts have been taken to combat these drawbacks, including the use of niosomes as a novel drug delivery system. Some studies are explained below:

Melanoma

A 10-amino-artemisinin derivative known as artemisone has both antimalarial and anticancer properties. Artemisone was encapsulated in niosomes by Dwivedi *et al*. utilising the thin-film hydration technique. The formulations demonstrated little toxicity toward normal skin cells while exhibiting highly selective cytotoxicity versus melanoma cells [6]. A novel bola-niosomal system comprised of,-hexadecyl-bis-[1-aza-18-crown-6] [bola-surfactant], Span 80, and cholesterol was utilised to encapsulate the drug 5-fluorouracil [5-FU], which is primarily used to treat various kinds of skin cancer. Human stratum corneum and epidermis membranes were used to assess the percutaneous penetration of 5-FU-loaded bola-niosomes. When compared to free drug aqueous solution, the drug penetration was increased by 8 and 4 times, respectively, by bola-niosomes. Because of its harmful toxic effects, cisplatin usage is restricted. Using Span 60 and cholesterol to create niosomal cisplatin, Gude *et al*. looked into the antimetastatic efficacy in an experimental metastatic form of B16F10 melanoma. According to their findings, niosome-encapsulated cisplatin has strong antimetastatic effectiveness and less toxicity than free cisplatin. [7].

Breast Cancer

Cosco *et al*. created 5-FU-loaded PEG-coated and uncoated bola-niosomes and tested them on the breast cancer cell lines MCF7 and T47D. In comparison to the free medication, the cytotoxic impact was enhanced in both bola-niosome formulations. After a 30-day course of therapy, in vivo tests using SCID mice models of the MCF-7 xenograft tumour revealed that PEGylated Niosomal 5-FU had a more potent antitumor impact at a concentration ten times lower [8 mg/kg] than the Free Solution of the Drug [80 mg/kg] [8]. By using an injectable technique, cantharidin-entrapped niosomes were created. On the human breast cancer cell line MCF-7, their potential in boosting the anticancer effects of the medication and lowering its toxicity was assessed. Additionally, the effectiveness of the treatment in mice carrying the S180 tumour was examined. With an inhibition rate of 52.76%, mice treated with 1.0 mg/kg of niosomal cantharidin shown the strongest anticancer activity, which was noticeably greater than that of mice treated with the same quantity of free cantharidin (1.0 mg/kg, 31.05%) [9]. Recently, tamoxifen citrate niosomes were created using the film hydration process for localised cancer treatment using both in vivo and in vitro breast cancer cytotoxicity. Tamoxifen's enhanced niosomal formulation demonstrated noticeably improved cellular absorption [2.8-fold] and dramatically increased cytotoxic action against the MCF-7 breast cancer cell line. When compared to free tamoxifen, in vivo studies indicated that niosomal tamoxifen caused a greater reduction in tumour volume [10].

Ovarian Cancer

Niosomes loaded with doxorubicin were created by Uchegbu *et al*. The effectiveness of doxorubicin against a human ovarian cancer cell line and its doxorubicin-resistant subline was investigated in hexadecyl diglycerol ether [C16G2] and Span 60 niosomes. The results showed that when the medication was enclosed in Span 60 niosomes as opposed to being loose in solution, there was a small decrease in the IC50 against the resistant cell line [11].

Lung Cancer

In order to evaluate the efficacy of niosomal adriamycin to free adriamycin solution on human lung tumour cells cultivated in monolayer and spheroid culture as well as in tumour xenografted nude mice, Kerr *et al*. encapsulated adriamycin into the noisome using a monoalkyl triglycerol ether. Adriamycin and niosomal adriamycin caused a growth delay (i.e., the time it took for the tumour volume to double) that was much longer than the control's growth delay of 5.8 days (15 days). Adriamycin treatment in niosomal form has the potential to substantially improve its therapeutic ratio[12]. In a different work, lipid film hydration was used to create pentoxifylline-loaded niosomes. In an experimental metastatic B16F10 model, intravenous treatment of niosomal pentoxifylline [6 mg/kg and 10 mg/kg] caused a substantial decrease in lung nodules, indicating accumulation of pentoxifylline in a distant target. Histologic sections examined under light microscopy revealed fewer tumour islands in the lung.[13].

Targeted Delivery

By actively targeting tumour therapy with a ligand coupled to the surface of niosomes, which could be actively taken up, for instance, via a receptor-mediated endocytosis, the effectiveness and, in particular, the specificity of cellular targeting of niosomal drug delivery systems can be further enhanced. Cell-specific targeting is made possible by conjugating niosome surfaces with small molecules or macromolecular targeting ligands [14]. The most popular compounds that precisely attach to a target that is overexpressed on the cell surface include proteins, peptides, carbohydrates, aptamers, antibodies, and antibody fragments [15]. The glucose derivative was used by Bragagni *et al*. to create a brain-targeted niosomal formulation. They created niosomal doxorubicin using the following components: span; cholesterol; solulan; and N-palmitoyl glucosamine Compared to the commercial formulation, intravenous administration of a single dose of the developed targeted-niosomal formulation was able to significantly reduce the drug's accumulation in the heart and keep it in the bloodstream longer as well as enable the achievement of well detectable doxorubicin brain concentrations in rats [16]. Furthermore, Tavano *et al*. created a powerful tumor-targeted niosomal delivery method. Cholesterol and Pluronic L64 surfactant were combined to create niosomes, which were then

filled with doxorubicin. Using EDC [N-[3-[dimethylamino] propyl]-N ethylcarbodiimide hydrochloride] chemistry, transferrin was coupled to niosome surfaces after synthesis. MCF-7 and MDA-MB-231 tumour cell lines were subjected to doxorubicin-loaded niosome anticancer activity, and a substantial reduction in viability in a dosage and time related way was detected. The information about some recent studies on niosomal targeted drug delivery:

Co-drug Delivery

Nanoparticles have become a potential type of medication delivery systems for combination treatment in recent years. Combinational treatments reduce dose while achieving same or better levels of efficacy and lowering drug resistance [17]. They also improve therapeutic efficacy. Anticancer medications frequently have negative side effects. In comparison to free drug therapy, Pasut *et al*. found that multidrug delivery system increased anticancer activity for carcinoma cells while reducing cytotoxicity against endothelial cells and cardiomyocytes. Nitric oxide and the anticancer medication epirubicin were covalently attached to each terminal of PEG in their system, which they devised to deliver both substances simultaneously. Nitric oxide actas not only protecting reagent against anthracycline induced cardiomyopathy but also sensitizer of anticancer drug treatment. They employed branched PEG as the polymer backbone instead of linear one in order to maximise anticancer activity and improve cardiocyte protective capabilities of codelivery system [18]. Malignant neoplasm multidrug resistance (MDR) refers to the capacity of cancer cells to survive when treated with structurally and functionally different anticancer medicines. The majority of 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 responsible for increased drug efflux. Numerous medicinal drugs' intracellular concentration is significantly reduced by these drug efflux pumps [19]. Chemosensitizers including verapamil, elacridar, tariquidar, and cyclosporine A primarily work as P-gp antagonists to decrease drug efflux and restore chemosensitivity in MDR cancer cells. Together, paclitaxel and cyclosporine A were encapsulated in actively targeted polymeric lipid-core micelles. Cyclosporine A's P-gp inhibition increased the cytotoxicity of paclitaxel. Micelles that included both of these cargoes were substantially more hazardous to MDCKII-MDR1 cells than those that contained just paclitaxel. In applications involving multiple medication delivery, niosomes are potential nanocarriers. The simultaneous encapsulation of hydrophobic curcumin and hydrophilic doxorubicin in niosomes for cancer multidrug administration was recently described by Sharma *et al*. [20]. According to the findings, dual-drug loaded niosomes were more hazardous to HeLa cells than free medicines.The effects of the drugs' coencapsulation on the physicochemical characteristics of the carriers, on their antioxidant properties, and on their capacity to release the encapsulated materials, were assessed in another study using gallic acid, ascorbic acid, curcumin, and quercetin either alone or in combination [21]. Marianecci *et al*. also created, characterised, and delivered multidrug niosomes using lidocaine and ibuprofen. The findings suggest that niosomes might be used as effective carriers for the simultaneous dermal delivery of two drugs in the same pharmaceutical formulation to treat various skin conditions, such as acute and chronic inflammations accompanied by discomfort.[22]

Antibiotics

Antibiotic and anti-inflammatory drug delivery can be accomplished using niosomal carriers. These carriers have been employed often to increase medication retention in the skin and to improve ineffective skin penetration. Rifampicin, a niosomal delivery system-encapsulated wide range antibiotic, was created by Begum and her colleagues. This work demonstrated that the niosomal formulation of rifampicin is capable of providing constant and sustained release of the medication [23]. They studied the activity of this system in in vitro settings. In a separate study, Akbari *et al*. created ciprofloxacin-loaded niosomes via film hydration technique utilising various nonionic surfactants and cholesterol in varying quantities to boost the antibiotics' effectiveness and decrease the dose. Drug release through bilayers and niosome antibacterial activity were examined. The outcomes demonstrated that the performance of niosomes was impacted by the cholesterol content and phase transition temperature of the surfactants. Additionally, compared to free ciprofloxacin, all formulations showed greater antibacterial activity [24]. Niosomes and liposomes are the two most common vesicular delivery methods employed in ocular medicine. Niosomes were put to the test as a potential vehicle for the controlled ocular administration of the antibiotic gentamicin by Abdelbary and ElGendy. Cholesterol and the negative charge inducer dicetyl phosphate were mixed with a variety of surfactants (Tween 60, Tween 80, or Brij 35) in varying molar ratios. The effectiveness of these vesicles to entrap the chosen medication was assessed, and the outcomes demonstrated that the presence of charge inducers, the kind of surfactant used, and the cholesterol content all influence how quickly gentamicin is released. In terms of extending in vitro drug release, gentamicin-loaded niosomes made of Tween 60, cholesterol, and dicetyl phosphate were the most successful[25].

Anti-Inflammatory Drugs

The preparation of NSAID-loaded niosomes has been done by a number of different teams. These medications may have undesirable consequences, such irritated mucous membranes. Niosomes loaded with NSAIDs that are administered topically can significantly enhance drug penetration. Marianecci *et al*. created ammonium glycyrrhizinate [AG] loaded niosomes using a variety of surfactants and cholesterol at varied concentrations to examine the possible use of niosomes for the delivery of anti-inflammatory medicines. For characterisation, tests for drug entrapment effectiveness, anisotropy, cytotoxicity, skin tolerability, and other factors have been carried out. The AG-loaded niosomes had excellent skin tolerance, no toxicity, and they were able to enhance the anti-inflammatory action in mice. Additionally, when applied to chemically produce human skin erythema, the anti-inflammatory effect of the medication supplied through niosomes was shown to be enhanced[26].

Antiviral Drugs

The capacity of niosomes to distribute different antiviral medications has also been established. Zidovudine, the first anti-HIV drug licenced for clinical use, was created by Ruckmani and Sankar. Niosomes were then entrapped, and their effectiveness and sustainability of release were studied. Tween, Span, and cholesterol were combined in the proper

ratios to create niosomes. Zidovudine was tightly bound in niosomes that made up Tween 80, and the inclusion of dicetyl phosphate prolonged the duration of drug release[27]. Comparing the drug leakage from Tween 80 formulations held at ambient temperature to niosomes stored at 4 °C for 90 days, the difference was considerable. In addition, the outcomes of a pharmacokinetic investigation in rabbits demonstrated that Tween 80 formulations containing dicetyl phosphate were eliminated from the bloodstream in just five hours.

Physical Stability of Niosomes

One of the most important features of niosomes compared with liposomes is their chemical stability. Compared to phospholipids, niosomes are less susceptible to chemical oxidation or destruction. However, issues with physical stability can occur with both niosomes and liposomes. The most frequent physical alterations include drug leakage, bilayer fusion, and vesicle aggregation. Physically stable niosomal dispersions must maintain a steady drug concentration and particle size throughout time.

It has been established that niosomes are more stably generated than liposomes. Aceclofenac Span 60 niosomes, for instance, demonstrated greater physical durability than liposomes when maintained at 4°C for three months in terms of particle aggregation and drug leakage. Additionally, when kept at 4 and 20 °C for 3 months, Span 20-based niosomes were both more physically stable than liposomes. Additionally, within three months, Tween 61 and Span 60 elastic niosomes with 25% and 20% ethanol respectively showed no sedimentation, no layer separation, and an unaltered particle size.It is important to note that surfactant/lipid type, initial size, and storage temperature are the primary determinants of niosome stability. The bilayer membrane's fluidity is firstly determined by the surfactant selection. Niosomes have been reported to have higher drug-retentive qualities the higher the gel-liquid transition temperature. This is as a result of the bilayer membranes' constant gel state under storage conditions. It was discovered that Span 604Span 404Span 204Span 80 had the highest risk of leaking carboxyfluorescein-loaded niosomes. Furthermore, it has been discovered that niosomes with a size between 1 and 10 mm are more stable than those with a submicron size. Thermodynamically, smaller niosomes have higher surface free energy and tend to aggregate more than larger ones in order to lower the excess free energy[28]. For example, niosomes composed of hexadecyl diglycerol: cholesterol: Solulan C24 at a 40:40:10 molar ratio with an original size of 70 nm were monitored for changes in size. Niosome size increased by 250 times. This finding showed that the stability of niosomes is significantly influenced by the initial size. Thirdly, as a change in temperature frequently results in a change in the composition of the surfactant bilayer membranes, the storage temperature for niosomes needs to be kept under control. Since Span 40 has a greater transition temperature than phospholipids, it has been discovered that Span 40 niosomes are more stable than liposomes in this situation at higher storage temperatures, such as 25 °C and 37 °C [29].

APPLICATIONS OF NIOSOMES

The applications of niosomes can be mainly classified into three categories

1. To Improve the Stability and Physical Properties of the Drugs.
2. To Increase Oral Bioavailability.
3. To Modify the Physicochemical Properties of Drugs.
4. For Improvement of Stability of Peptide Drugs**.**
5. To Promote Transdermal Delivery of Drugs.
6. As a Tool for Improvement of Stability of Immunological Products.
7. To Improve Anti-inflammatory Activity.
8. To Controlled Release of Drugs like prolong drug delivery [gliclazide niosomes], enhanced Ophthalamic Drug Delivery of gentamicin sulphate & timolol meleate [0.25%]. For Targeting and Retention of Drug in Blood Circulation ,
9. To Increased Uptake by A431 Cells.
10. To Improve the Efficacy of Drugs in Cancer Therapy.
11. In Treatment of Localized Psoriasis: Methotrexate, a drug used in psoriasis has limited applications due to its formulation problem. In the treatment of localized psoriasis, niosomes of methotrexate taking chitosan as polymer have shown promising results.
12. In Leismaniasis: The leismaniasis parasite mainly infects liver and spleen cells. Antimonials, a class of regularly used medications, can harm many human organs, including the heart, liver, and kidneys. It has been discovered that integration of sodium stibogluconate in niosomes increases its effectiveness [30].
13. In Diagnostic Imaging: It has been studied that niosomes can also act as a carrier radiopharmaceuticals and showed site specificity for spleen and liver for their imaging studies using 99mTc labeled DTPA containing niosomes. Conjugated niosomal formulations of gadobenate with [Npalmitoyl-glucosamine, NPG], PEG 4400 and both PEG and NPG can be used to increased tumor targeting of a paramagnetic agent.
14. Carrier for Haemoglobin: Niosomes play an important role as a carrier for haemoglobin. The niosomal haemoglobin suspension was found to give superimposable curve on free haemoglobin curve [2].

FUTURE PROSPECTIVE

There are two approaches to improve the physical stability of lipid vesicles at ambient conditions. Dispersing liposomes in a viscous gel has been used either to reduce the rapid leakage of the encapsulated drug from liposomes or to minimize the burst release effect observed with liposomes This approach may be extrapolated to improve the physical stability of ocular niosomes. However, the drug release from such a system is likely to be complex, as the drug molecules have to release from the bilayer membranes and diffuse through the viscous gel. Furthermore, the improvement in the physical stability of the niosomes can be offset by reducing the ocular bioavailability of the administered drug. Additionally, a topical application of a viscous gel is less convenient than eye drops in terms of ocular administration and the adjustment of the dose. To Change In addition to the previous method, lyophilization [freeze-drying] or spray-drying the final liposomal/niosomal liquid dispersion into a powder form improves the physical stability of the vesicles while also significantly reducing the oxidative instability of oxidizable drug molecules by reducing the formation of hydroxyl free radicals.

These benefits may be outweighed by the disadvantages of expensive manufacture, extended production times, and more complex formulations incorporating cryoprotectants. The

simplest and most practical dose form to create and deliver is ready-to-use niosomal dispersion. Therefore, the focus of our future niosomes research will be on investigating various methods for enhancing niosomes physical stability.

CONCLUSION

Small molecules including proteins and vaccines have been endorsed as a prominent class of medicinal agents as a consequence of recent advances in scientific study. However, they present a number of drug-related difficulties, including low bioavailability, adequate drug administration methods, chemical and physical instability, and possibly dangerous side effects. Niosomes have been criticised for being ineffective in delivering proteins and biologicals, yet they are capable of encapsulating deadly medications like those for AIDS, cancer, and viruses. In contrast to ionic drug carriers, which are generally harmful and inappropriate, it offers a viable carrier system.. The niosomes technology, however, remains in its infancy. As a result, research is being done to create a technology that is appropriate for mass manufacturing since it is a promising approach for delivering tailored medications.

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