SHORT REVIEW

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Niosomes as an Effective Phytochemical Nanocarrier: A short review

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ABSTRACT

Niosomes are a new class of nanocarrier systems for the delivery of phytochemicals made from biocompatible, stable, and hydrophilic and hydrophobic encapsulating non-ionic surface-active agents. This review looks at the role that niosomes can play in enhancing the solubility, stability, and bioavailability of the phytochemicals, as well as how they can be used for the therapy of targeted and controlled drug delivery. Nanocarriers are membranes around cells or tissues composed of electronically neutral lipids that protrude from a biological cell membrane and serve to increase efficacy of natural resources. This review looks at the variety of advancements as well as challenges existing in the quest for integrating Phytochemicals using liposomal technology and the perspectives on the way forward in enhancing the efficacy of Phytochemicals through liposomes. These advances also aim at giving a better understanding of this novel drug delivery system.

KEYWORDS: Niosome, Method of Preparation, Phytochemicals.

INTRODUCTION

Phytochemicals are bioactive compounds originating from plants and have shown significant therapeutic potential in the treatment and prevention of various diseases such as cancer, diabetes, cardiovascular diseases, and neurodegenerative disorders. (1)(2) Despite the potential that exists, their ability to succeed in the clinic is restricted by factors such as low water solubility, low bioavailability, unstable in physiological environment and rapid systemic clearance among others. (3) As an improvement of the pharmacotherapeutic characteristics of these molecules, Nanotechnology-based drug delivery systems like niosomes operating through pharmacotherapy. Niosomes has been improved to possess structural and functional versatility which has made them to be a strong carrier for the phytochemical agents delivery. (4) This review delves into the fundamental principles, technological advancements, and application domains of niosomes in phytochemical delivery.

Niosomes are bilayer vesicular systems formed by the assemblies of non-ionic surface active agents in aqueous environments.(5) Their structural integrity is often enhanced by incorporating cholesterol or other stabilizing agents. The bilayer is amphiphilic in nature, with hydrophobic tails forming the interior and hydrophilic heads exposed to the aqueous environment.(6) This dual property allows the capsulation of both hydrophilic substances in the core and hydrophobic substances within the bilayer.(7)

Non-ionic surface-active agents are important in the formation of niosomes and contribute to their stabilization, flexibility, and biocompatibility. Surfactants commonly used in the preparation of niosomes include the Span series, which include Span 20, 40, 60, and 80. These are hydrophobic in nature and form stable bilayer structures. The Tween series (Tween 20, 40, 60, 80), being hydrophilic surfactants, increase the flexibility of the bilayer, hence making niosomes more flexible and stronger. Further, Brij series surfactants are polyethylene glycol-based surfactants with better biocompatibility and lower immunogenicity; therefore, they find application in pharmaceutical and therapeutic industries. Surfactant selection influences the physicochemical properties of niosomes. (8) Cholesterol is an essential constituent of niosomes, which provides rigidity and decreases the permeability of the bilayer. Stabilizers like stearylamine and dicetyl phosphate are also used to control charge and enhance vesicle stability. (9)

Niosomes have great advantages in the delivery of phytochemicals, addressing most of the challenges encountered in conventional drug delivery systems. One of the primary advantages of niosomes is improved bioavailability. Poorly soluble phytochemicals encapsulated within niosomes enhance their solubility and absorption in the gastrointestinal tract, thereby providing higher systemic availability.(10) Moreover, surface modification of niosomes with ligands, antibodies, or peptides allows for targeted delivery, thus ensuring site-specific action and reducing off-target actions while enhancing therapeutic efficacy. Niosomes also allow for controlled and

sustained release of encapsulated phytochemicals, maintaining therapeutic levels for extended periods, thus reducing dosing frequency and improving patient compliance.(11)(12) In addition, niosomal vesicles protect the degradable phytochemicals from degradation via light, heat, or enzymes, ensuring longer shelf life and thus maintaining their effectiveness. In addition, the niosomes' composition of non-ionic surfactants ensures low toxicity and high biocompatibility, rendering them safer and more effective for phytochemical delivery in therapeutic applications. (13)(5)

Niosomes have now emerged as a promising delivery system for phytochemicals, with enhanced therapeutic potential across various applications. Thus, for example, antioxidant delivery such as curcumin, resveratrol, and quercetin, which are extremely potent antioxidants but have poor water solubility and rapid metabolism, is enhanced by niosomal encapsulation.(9) This technique improves their solubility, bioavailability, and stability to provide better therapeutic efficacies against oxidative stress-associated diseases. Similarly, niosomes have proven their extraordinary efficacy in anticancer drug delivery by encapsulating phytochemicals like paclitaxel, vincristine, and epigallocatechin gallate. Functionalization with targeting ligands allows selective enrichment in cancerous tissues to reduce systemic toxicity and inhibit tumor growth effectively.(14)

Niosomal formulations of phytochemicals, such as boswellic acid, curcuminoids, and flavonoids, have been improved in terms of therapeutic index through targeted inflamed tissues to reduce systemic side effects. Niosomes have been shown to increase antimicrobial and antiviral activity by encapsulating phytochemicals such as berberine, eugenol, and tea tree oil. The formulation is improved for efficacy against resistant bacterial strains and for potent antiviral activity. Niosomes show flexibility in addressing a wide range of therapeutic challenges.

NIOSOME PREPARATION TECHNIQUES

Niosome preparation varies with technique, each of them optimized in the formation of vesicles and drug loading. Commonly used approaches of thin-film hydration make a thin film of surfactants, hydrates it, and produces the vesicles. Such a technique is simple yet effective enough to be utilized in all research and development purposes.(15)(5) The reverse phase evaporation technique, famous for having high encapsulation efficiency, makes surfactants emulsified within the organic and aqueous phases, generating stable vesicles that are able to carry drug loads substantially. More sophisticated techniques such as microfluidic methods ensure the production of uniformly sized and distributed vesicles. The choice of process depends on the expected properties of the niosomes, such as size, stability, and encapsulation efficiency, making it an important aspect in tailoring niosomes for specific applications.(10)

SOME OF THE RECENT ADVANCES

Diosgenin-loaded niosomal nanocarrier

Diosgenin is a plant-derived phytochemical with recognized anticancer potential, though it has low solubility in water, which can be one of the significant limitations to its therapeutic applications. To solve this problem, Hajizadeh et al. used the thin-film hydration process to encapsulate diosgenin into niosomeal vescicles. Diosgenin-loaded niosomes prepared via this process were found to have nanometric size, spherical morphology, and a high loading efficiency of approximately 89%. Techniques like optical microscopy, DLS, SEM, and UV-visible spectrophotometry further authenticated the structural integrity and optimal design of the nanocarrier. The encapsulation highly improved controlled release and solubility of diosgenin; therefore, its anticancer activity was increased significantly with a reduced HepG2 cell viability of 28.32%, while for free diosgenin it remained 61.25%. This study uncovers the prospective use of niosomes as nanocarriers for enhancing therapeutic efficacy in hydrophobic phytochemicals.(16)

PEGylated niosomal nanoparticles co-loaded with ART-MET

PEGylated niosomal nanoparticles are a promising nanocarrier system for the co-delivery of artemisinin (ART) and metformin (MET), which are known to be plagued by issues such as dose-dependent side effects and poor bioavailability. A study by Shahbazi et al. demonstrated the successful synthesis and characterization of ART-MET-loaded PEGylated niosomal composition using the thin-film hydration technique. It possessed a particle size of 256 nm, encapsulation efficiency of 95%, and a polydispersity index of 0.202, making it suitable for therapeutic use. The in vitro cytotoxicity study showed dose-dependent inhibition on the proliferation of A549 lung cancer cells, the niosomal formulation proved to be more effective against anticancer activity than free ART-MET. In addition, results from RT-PCR analyses confirmed that these nanoparticles suppressed the anti-apoptotic genes and enhanced the expressions of pro-apoptotic genes. This makes them a promising advance in therapy for human lung carcinoma.(17)

Carum-loaded Niosomes

Thymoquinone (TQ), a bioactive compound extracted from

Carum carvil seeds, has good promise for application in cancer therapy. Due to its hydrophobic nature, it has a lower limit of solubility and permeability and bioavailability in the biological system. To improve these limitations, a novel herbal carrier system was prepared using ergosterol-a herbal lipid, Carum carvil extract, and nonionic surfactants. The niosomes encapsulated TQ and Carum carvil extract, namely Nio/TQ and Nio/Carum, respectively, and the physicochemical and biological properties of these formulations were compared in a systematic manner. The morphology of both formulations appeared spherical with nanometric size and a negative zeta potential; the encapsulation efficiencies of TQ and Carum carvil extract were found to be 92.32% ± 2.32 and 86.25% ± 1.85, respectively. Controlled release profiles were noted and it enhanced the therapeutic potential of the encapsulated compounds. In vitro cytotoxic activity study with MCF-7 cell line showed the niosomal formulations had higher anticancer activity compared to free TQ and free Carum carvil extract. Flow cytometric analysis further confirmed G2/M cell cycle arrest. In addition, both Nio/TQ and Nio/Carum significantly inhibited cancer cell migration. Thus, these findings underscore the potential of niosomal carriers as effective delivery systems for hydrophobic phytochemicals and offer a promising strategy for breast cancer treatment.(18)

D-limonene niosomes

The low solubility of phytochemical agents such as D-limonene is highly challenging in their application for the treatment of cancer. In this regard, D-limonene-loaded niosomes (D-limonene/Nio) have been developed to improve therapeutic efficacy. The niosomal formulation obtained by the film hydration method with a Span® 40: Tween® 40: cholesterol molar ratio of 35:35:30 was found to be nanosized, spherical in morphology, and had a good entrapment efficiency at 87 ± 1.8%. In vitro studies proved the maintained release of D-limonene from niosomes in comparison to the free compound while overcoming the solubility problem. Further, cytotoxicity assays carried out against HepG2, MCF-7, and A549 cell lines resulted in notably improved anti-cancer activity by a concentration of 20 µM. Therefore, findings prove that niosome-based delivery systems hold promise to be effective nano-carriers for enhancing bioavailability as well as therapeutic values of phytochemicals in the treatment of cancer.(19)

Lawsone-loaded Niosome

Lawsone is a phytochemical isolated from Henna and exhibits good promise against tumor development. It has limitations like poor solubility, low bioavailability, and instability in biological environments. In an effort to overcome these difficulties, nanoniosomes have been prepared as the delivery system using non-ionic surfactants and cholesterol. The thin film hydration method was used. These nanoniosomes encapsulated either standard Lawsone (SLaw) or Henna extract containing Lawsone (HLaw), which both presented spherical shapes, a particle size of about 250 nm, and negative zeta potentials, thereby stabilizing the formulations for two months at 4 °C. The entrapment efficiency of around 70% showed sustained release profiles and significantly enhanced antitumor activity in MCF-7 cells compared with free Lawsone. This study indicates the potential of niosomes as an effective carrier system for improving the therapeutic efficacy of phytochemicals with solubility-related limitations.(14)

Carvacrol Oil-Loaded Niosomal Gel

Niosomes have now emerged as promising carriers for effective delivery of active ingredients into the skin, overcoming the deficiencies of poor penetration and biodegradation of bioactive compounds. Carvacrol oil (CVC) is a constituent of essential oils with known anti-inflammatory properties that was formulated into a niosomal gel to enhance stability and penetration into the skin. The thin-film hydration technique along with Box-Behnken Design (BBD) for optimization was used to develop various formulations by varying the ratios of drug, cholesterol, and surfactant. The optimized formulation (F4) showed a vesicle size of 180.23 nm, PDI of 0.265, zeta potential of −31.70 mV, and an entrapment efficiency of 90.61%. In vitro drug release experiment revealed a significantly higher discharge rate of 70.24% for CVC-loaded niosomes as compared to 32.87% for the CVC suspension. The release kinetics followed the Higuchi model and exhibited non-Fickian diffusion behavior. Dermatokinetic studies showed that the niosomal gel facilitated deeper penetration into the skin layers (25.0 µm) compared to conventional formulations (5.0 µm), as evidenced by confocal laser scanning microscopy (CLSM). Additionally, the gel of CVC niosome showed enhanced antioxidant activity and good anti-inflammatory efficacy compared with free CVC.(20)

DISCUSSION

Niosomes have shown great promise in overcoming the problems associated with the delivery of phytochemicals, such as poor solubility, low bioavailability, and rapid systemic elimination. This review emphasizes key advancements in niosomal drug delivery systems, underlining their potential as innovative

platforms for improving the pharmacokinetic and pharmacodynamic properties of phytochemicals. The most remarkable structural adaptability of niosomes is their ability to absorb a wide variety of non-ionic surfactants and stabilizing agents. For example, the introduction of Span and Tween surfactants improves the elasticity and stability of the vesicles, while cholesterol rigidifies the bilayer; this contributes to long-term stability with controlled drug release. The choice of surfactant and the method of formulation greatly affect the size, zeta potential, and encapsulation efficiency of niosomes, which are crucial factors in determining their therapeutic performance.(9)

The studies reviewed above clearly show that niosomal formulations increase the solubility and bioavailability of phytochemicals, as well as provide targeted and sustained release capabilities. This is very helpful in anticancer and anti-inflammatory therapies, where localized delivery and prolonged drug action are essential for efficacy and safety. Additionally, surface functionalization of niosomes with ligands, antibodies, or peptides further enhances their targeting capabilities, thereby reducing systemic side effects and improving therapeutic outcomes.(16)(20)(9) (14)

The latest developments in the area, including PEGylation and co-delivery of multiple drugs, have greatly broadened the scope of niosomal applications. For instance, PEGylated niosomes have shown longer circulation times and decreased immunogenicity, making them useful for chronic conditions. Co-loaded formulations, such as ART-MET-loaded PEGylated niosomes, exemplify the potential of niosomes in addressing multifactorial diseases like cancer by delivering synergistic combinations of drugs.(17)

Future studies should focus on the formulation challenges using new techniques of novel formulations, advanced characterization techniques, and comprehensive in vivo evaluation. Advanced technologies, including microfluidics and artificial intelligence, could be used in niosome design and optimization for further rapid development and scalability. Another possibility would be to utilize natural surfactants and biopolymers for niosome formulation to improve biocompatibility and lower the cost of production.

CONCLUSION

Material science advances such as stimulus-responsive materials will revolutionize niosome technology. Emerging strategies such as 3D printing of precise drug delivery systems, integration with smart drug delivery devices, hold great promise. The collaboration of pharmaceutical scientists, material engineers, and clinicians will be key in overcoming the current challenges and unearthing the full potential of niosomes in phytochemical delivery. Niosomes are an excellent and efficient nanocarrier system for the delivery of phytochemicals. The limitation of phytochemicals, poor solubility, and low bioavailability, can be overcome by niosomes, which can open up novel therapeutic interventions. Future studies should focus on overcoming current challenges and innovative applications that can maximize their impact in clinical settings.

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