INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Niosomes Used In Treatment Of Cancer: A Review

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ARTICLE INFO

Received: 03 April 2024
Accepted: 07 April 2024
Published: 13 April 2024
Keywords:
Cancer, Niosomes, Nanoparticles, Herbal drugs, Applications.
DOI:
10.5281/zenodo.10966570

ABSTRACT

Cancer is one of the leading causes of death worldwide, killing about 6 million people every year. Cancer is caused by genetic and epigenetic changes. As a result, apoptosis, metastasis, angiogenesis and unlimited cell proliferation can occur. Many advanced drugs have been developed from the scientific study of plants used in various forms of traditional drugs such as taxol, camptothecin, vincristine and vinblastine. Niosomes are bi-structured non-ionic surfactant vesicles that function to transport various medicinal components such as hormones, antigens, therapeutic agents, genes and peptides. In recent years, niosomes have gained popularity as drug delivery systems, especially for drugs with unpredictable stability, limited solubility, or rapid release. Additionally, niosomes have shown great potential as drug delivery systems in cancer research. Nisome therapy aims to increase the bioavailability of anticancer drugs, proteins, peptides and natural products. This review will focus on various niosomes used in cancer treatment, herbal medicines and clinical and non-clinical applications of niosomes in cancer treatment.

INTRODUCTION

Cancer is one of the most destructive human pathologies, which shows a wide variety of clinical manifestations and causes the death of millions of people worldwide every year. This group of diseases represents more than 100 distinct genetic conditions with many similarities in molecular mechanisms and metabolic changes [1,2]. The direct involvement of tissue microenvironment and survival in tumor growth is well established [3,4]. However, a clear understanding of underlying causes and factors is still unclear and requires further research. It has been reported that normal human cells have many genetic mutations that can lead to tumorigenesis and cancer development [5,6]. To date, various scientific and technological approaches have been taken to understand, identify, investigate and combat this disease that worries many people. Various approaches used in oncology research include

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

genetics; molecules, biochemistry, biophysics, immunology, genomics, proteomics, systems and computational biology, and none of these have yet met the requirements of a successful therapeutic strategy [7]. The field of oncology research is well documented but has evolved to such an extent those researchers and clinicians find it difficult to update and report new data and developments [8]. Cancer is caused by genetic and epigenetic changes. As a result, apoptosis, metastasis, angiogenesis and unlimited cell proliferation can occur. Many highly effective drugs have been prepared from plants used in various forms of traditional medicine such as taxol, camptothecin, vincristine and vinblastine [9]. Curcumin has been shown to have anticancer effects (alone or in combination with conventional chemotherapy drugs) in the treatment of cancers such as prostate and ovarian cancer [10,11]. According to in vitro and in vivo studies, curcumin suppresses carcinogenesis by regulating two important processes: angiogenesis and tumor progression [12]. Recently, more attention has been paid to the use of nanotechnology for the development of new targeted drug delivery systems. The unique properties of nano-sized drug delivery systems consisting of small particles and large surface vesicles can improve the passive targeting properties of drugs. In addition, the latter helps to maintain drug-containing vesicles in tumor cells by increasing permeability and retention effect. They increase the efficacy of the dose, reduce side effects, and support the use of chemotherapy at lower concentrations, which overcomes many limitations of conventional chemotherapy [13-15]. Niosomes are a type of nanoparticle drug delivery system known as nonionic surfactant vehicles (NSVs). Niosomes act as self-sealing spherical structures of non-ionic amphiphiles in aqueous media [16]. It has the ability to encapsulate hydrophilic and hydrophobic drugs between the core and bilayer, respectively [17]. Therefore, phytochemicals are considered as excellent drug delivery systems for many active substances such as extracts, drugs, and many anticancer drugs (methotrexate, doxorubicin, cisplatin, etc.) [18,19]. Compared to many other nanocarriers that can be used for cancer treatment and diagnosis, niosomes are considered simple, cheap and highly stable nanocarriers [20]. They have many advantages that overcome the disadvantages associated with lipid-based drug delivery systems such as liposomes, such as chemical stability, longevity, increased purity, material homogeneity, low cost, and ease of storage [21]. Encapsulated drugs have the ability to prolong blood circulation and reduce drug degradation and inactivation, thereby preventing adverse side effects and toxicity, increasing drug bioavailability, and making drugs more susceptible to disease. It is useful for targeting physical regions [22-24]. (MPS), mostly fixed Kupffer's cells in the liver and spleen. Some liposomal drug delivery techniques show better pharmacological characteristics than those found in traditional formulations. In the present review, we will discuss on the various types of liposomes, their production procedures and characterization parameters along with the applications in pharmaceutical field. Also list of clinically approved liposomal products are given to have an updated idea on the current status. [2,3,4,5,6]

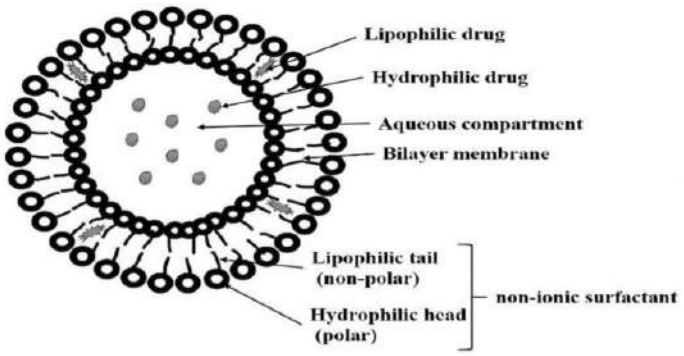

Figure 1: Structure of Niosome [25]

COMPOSITION OF NOISOME:

Two components are required for the formation of nisome vesicles.

1. Cholesterol

It is a steroid product that helps to form the correct shape and structure of niosomes [26].

2. Non-ionic surfactant

The amount of hydrophilic-lipophilic balance (HLB) of surfactants is important in niosome formation. To produce drug-compatible and optimally stable vesicles, the HLB range should be between 4 and 8 [27, 28]. Different types of nonionic surfactants are listed with examples in Table 1. Additionally, a charge manager is added to induce repulsion in the vesicles and create a high zeta potential. Thus, it helps prevent aggregation and increase vesicle stability [29, 30].

Table 1: Types of non-ionic surfactants

Non-ionic surfactants	Examples
Esters	Spans, polysorbates, glyceryl laurate
Ethers	Brij, octyl glucoside, decylglucoside, lauryl glucoside
Black copolymers	Poloxamers
Fatty alcohols	Cetyl alcohol, stearyl alcohol, cetostearyl alcohol

Types of niosomes:

Based on the size and number of layers, niosomes can be classified into small unilamellar vesicles (SUVs), large unilamellar vesicles (LUVs) and multilamellar vesicles (MLVs) (Figure 3). The size of light vehicles varies from 10 to 100 nm. It can be synthesized by sonication, high pressure extrusion, and high shear homogenization [30]. Light vehicles are thermodynamically unstable and prone to aggregation. It also has lower retention efficiency for hydrophilic drugs [30]. LUVs are 100-1000 nm in diameter and can be prepared by transmembrane pH gradient (remote charging), reversed-phase evaporation, solvent injection, heating, dehydration, and rehydration techniques. LUV is an effective option for large-scale production due to the low use of nonionic surfactants [25]. MLV ranges from 0.5 to 10 µm. They have a special double layer that specifically covers the water environment. MLV is the most widely used nisome carrier with favorable mechanical stability for encapsulating lipophilic bioactive compounds with a simple preparation method. Particle size is one of the important characteristics of niosomes and plays an important role in determining the pharmacodynamic and pharmacokinetic parameters of loaded drugs [25]. Different characterization methods were used to

determine the morphological and physicochemical characteristics of the studied niosomes as described below [31].

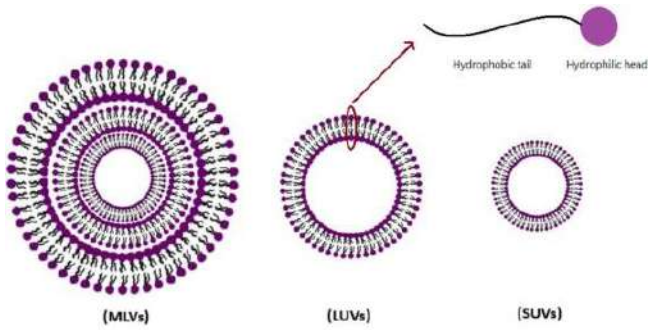

Figure 2: Types Of Niosomes

The mechanism of action of niosomes in drug delivery through the skin:

A key requirement for transdermal delivery is that the drug carried in the vehicle can reach the skin surface in sufficient quantity. Due to its ability to deliver medicine to the deeper layers of the skin, many applications and methods have been reported. In general, there are three possible ways to use the epidermis permanently. Cellular pathways include protein-bound lipid domains of corneocytes, cellular pathways, and lateral pathways through hair follicles, sebaceous glands, and sweat ducts. Depending on the nature of the drug, the mechanisms of drug transport may be different [32]. Mechanisms of absorption through the skin of hydrophilic drugs include (1) increasing the thermodynamic activity of drug-containing vesicles that are absorbed and internalized on the skin surface. A thermodynamic activity gradient then occurs, increasing the diffusion pressure at the drug surface, which acts as the driving force for drug penetration into the stratum corneum (SC). (2) Changes in the surface charge of ionic drugs. (iii) Sebum lysis by vesicles to promote hair follicle relaxation. (iv) pore permeability of large water-soluble molecules loaded into niosomes [33-35]. Mechanisms of percutaneous absorption of hydrophobic drugs include: (i) disruption of the stratum corneum (SC) – structural changes in the stratum corneum, a dense lipid bilayer, open the extracellular space; It helps you meet entrance level; (2) increasing skin penetration in the nano scale. (iii) Alteration of drug distribution across skin layers) release encapsulated drugs into the system using lysozyme [25] and (v) alter the delivery pathway of follicular lipophilic transporters [36]. Nonionic surfactants play an important role as enhancers of intracellular lipids by endocytosis. A possible mechanism of action to improve skin penetration is shown in Figure 3 [37,38].

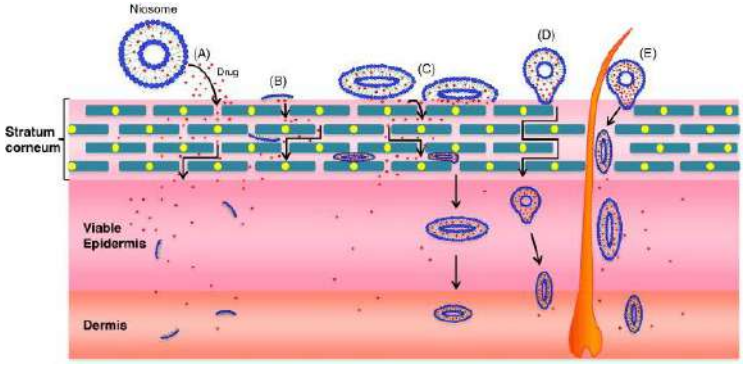

Figure 3: The mechanism of action of niosomes in drug delivery systems through the skin

Current applications of niosomes

Drug delivery systems using niosomes through transdermal, injectable and ocular routes have also been investigated [39,40]. Newsome delivery via the transdermal route overcomes the slow penetration of traditional transdermal approaches. The bioavailability and therapeutic effectiveness of drugs such as diclofenac, flurbiprofen, and nimesulide are increased by combining them in niosomal formulations. For ocular drug delivery, a niosomal formulation of chitosan-encapsulated timolol maleate was shown to be more effective in reducing intraocular pressure than commercially available formulations with less cardiovascular effects. Newsome's formulation is used for many other therapeutic applications due to its highly desirable properties [40].

Niosomes for cancer therapy:

Niosomes are a promising drug delivery system in cancer therapy because they help target drugs to cancer cells, prolong treatment duration, and improve drug stability while reducing severe toxic effects [41]. Various treatments have been studied to treat acne. Cancer treatment presents many challenges, including non-targeted delivery, short-term drug profiles, and antitumor effects of drugs [42]. Therefore, cancer treatment strategies are changing to support the effectiveness and efficiency of cancer cell-targeted therapies. Passive targeting facilitates the deposition of niosomes in the tumor microenvironment due to the unique characteristics of the tumor environment that are not normally present in normal tissues. In addition, active targeting facilitates niosome uptake by tumor cells. Customized molecules can be used to create drug vesicles that target tumor cells [43]. Stimulus-sensitive targeting is important for the development of future neosomal drug technologies because it is sensitive to signals from physiological systems that can be influenced by the environment and perturbations caused by pathological defects [44]. Dual targeting is a new concept for the synthesis of dual receptor targeting formulations to enhance the cell targeting specificity of nisome formulations without destroying healthy connective tissue cells [45]. In addition, dual targeting through dual drug loading strategies using two or more drugs is a combination therapy that promotes synergistic effects, and delivery in multifunctional niosomes has shown great potential for cancer therapy [46]. Another new way to fight cancer is immunotherapy, which uses the immune system to fight the disease. To increase the efficiency of immunotherapy and reduce side effects, niosomes coated with immunostimulants must be properly delivered to the target area [47].

Table 2: Drugs/compounds stored in niosomes and their anticancer agents [41-47]:

Drugs/Compounds	Therapeutic effects
Artemisinin	Cytotoxicity to melanoma cells
Bleomycin	It is highly concentrated in plant cells
Ciplatin	Cytotoxicity to breast cancer cells
Curcumin	Cytotoxic and apoptotic effects on ovarian cancer cells
Curcumin and doxorubicin hydrochloride	Cytotoxicity against cervical cancer cells
Daunorubicin	Dalton kills lymphoma cells with acetate
Doxorubicin	Proliferation of sarcoma cells
5-Fluorouracil	Improvement of drugs in the treatment of skin cancer
Methotrexate	It increases the activity of anti-sarcoma antibodies
Mitoxantrone	Higher cytotoxicity against human ovarian and breast cell lines

Tamoxifen citrate	Higher cytotoxicity against human ovarian and breast cell lines
Tocotrienol	Cytotoxicity for breast cancer
Vincristine	It increases the activity of anti-sarcoma antibodies

Herbs that show anticancer activity of niosomes:

Traditional medicine plays an important role in many health care systems around the world. The medicinal and economic benefits of this plant are increasingly recognized and cultivated in developing and developed countries. Herbs or plant compounds used for aroma, flavor and/or medicinal properties are known as herbs. Herbal medicines and herbal medicine are terms that describe plant products that are used to protect or promote health [48,49]. It is estimated that herbal medicines currently constitute a quarter of the Indian pharmacopoeia. Traditional medicinal plants are medicines obtained from organically existing plants and used in local or regional healing traditions to treat diseases without chemical modification [50]. Preventive care, disease management, severe side effects associated with synthetic drugs, and inadequate treatment options for serious diseases are some of the factors promoting the use of herbal medicines [49,51]. While traditional Tibetan medicine is still somewhat limited to its country of origin, other medicines such as Ayurveda and traditional Chinese medicine are widely used around the world. Herbs coated with chemicals with chemopreventive properties are in clinical trials [52]. Niosomes have been shown to function as part of advanced drug delivery strategies, delivering drugs via intravenous, transdermal, vascular, and pulmonary routes. Other applications of nisome-based drug delivery include cancer treatment, gene therapy, and intranasal drug targeting. It is also used as a hemoglobin carrier and in immune supplements for cosmetic reasons [53]. Murcin-loaded niosomes have been developed for cancer therapy [54]. It has been shown that nanomurcin is easily separated in aqueous media, unlike free murcin. Murcin showed very high drug absorption efficiency (97%), regulated and sustained release, and therapeutic efficacy in four different cancer cell lines. Another study evaluated the anticancer activity of niosomes containing curcumin and methotrexate against colon cancer cells [55]. Niosomal formulation showed higher cytotoxicity in vitro than the free compound. The anti-arthritic effect of luteolin (LT) niosomes formulated with different nonionic surfactants was tested in vitro and in vivo for encapsulation efficiency and high transdermal flux in mouse skin exudates. Cytotoxicity studies showed lower IC50 values for LT-NV than pure LT [56]. Therefore, it can be concluded that LT-NV is a natural alternative to synthetic drugs in the treatment of lung cancer. Nisome therapy aims to increase the bioavailability of anticancer drugs, proteins, peptides and natural products. Many experts are interested in introducing natural compounds such as curcumin, which have low solubility and low bioavailability [53]. Finally, a clinical trial combining Curcuma longa L. with doxorubicin is ongoing (NCT04996004). In addition to curcumin, there is a powerful natural antibacterial, anti-inflammatory and anti-cancer compound called myrcin. Rahman et al developed a formulation of murcin containing niosomes as a carrier that overcomes the barriers of low solubility and stability to target specific cells [57].

NON-CLINICAL AND CLINICAL APPLICATION OF NIOSOME IN CANCER TREATMENT:

Non-clinical application:

In order to commercialize or launch a particular drug, it is important to meet the standards of

clinical and non-clinical testing. Clinical trials play an important role in analyzing human responses to potential treatments. However, before examining and studying the efficacy and safety of the drug in humans, non-clinical studies are necessary. A number of niosomal formulations have been investigated to reduce toxicity, particularly to increase efficacy in cancer [58,59]. It can be concluded that niosomes are suitable delivery systems for hydrophilic, hydrophobic and lipophilic drugs for therapeutic purposes. Studies in in vivo models have shown that niosomes have high drug loading capacity, controlled therapeutic efficacy and long shelf life. Additionally, in vitro experiments published in this paper show that nisome delivery systems can be more successful than free drug delivery. This prolongs the release of the drug at the target site. In addition, it has been shown to have a long-lasting colloidal delivery system with improved bioavailability in experimental subjects such as mice and rats. Because it is possible to control and keep the concentration of the drug used above the minimum effective concentration for 24 to 48 hours [60,61].

Clinical application:

In recent years, several studies have been published on nisome formulations containing various anticancer drugs. Many authors have investigated different nisome formulations to improve efficacy and limit vesicle toxicity. For example, Span 80 vesicles have been shown to be successfully delivered into the cytoplasm of tumor cells with a drug loading efficiency of 63%, where the vesicles are in direct contact with the cell membrane [62]. Newsome's formulation contains non-ionic surfactants and cholesterol. Cholesterol is the main component of niosomes [63]. Most formulations contain vesicles at a 1:1 M ratio to prevent aggregation. That is, by adding molecules that stabilizes the system against the occurrence of aggregation caused by spatial or electrostatic forces [64]. In most of these clinical trials, Newsome's formulations produced nanometer-sized vesicles with spherical morphology in the range of 100–500 nm. Moreover, compared to the free drug solution, the efficiency of the drug delivery system is significantly increased after encapsulating therapeutic agents in niosomes. Additionally, the clinical use of niosomes has shown excellent efficacy against human cancers originating from tumors located in the breast, ovary, lung, and colon. High pH-dependent release of anticancer drugs in vitro. Collectively, these findings provide proof-of-concept for the therapeutic benefits of incorporating anticancer drugs into niosomes formulations [61,64].

CONCLUSION:

Cancer is one of the leading causes of death worldwide, killing nearly 6 million people annually. Cancer is caused by genetic and epigenetic changes. As a result, apoptosis, metastasis, angiogenesis and unlimited cell proliferation can occur. Niosomes are bi-structured non-ionic surfactant vesicles that function to transport a variety of medicinal components such as hormones, antigens, therapeutic agents, genes and peptides. In recent years, niosomes have gained popularity as drug delivery systems, especially for drugs with unpredictable stability, limited solubility, or rapid release. In addition, niosomes have shown great potential as drug delivery systems in cancer research. Despite the number of formulations and drugs available, cancer treatment remains a major challenge for researchers. One of the main challenges in the development and treatment of new drug delivery systems that target cancer cells is to increase the efficiency of eradicating cancer cells while maintaining sufficient systemic biocompatibility in vivo and in vitro. Curcumin is widely used as a therapeutic agent in the treatment of cancer. However, limited absorption and rapid elimination are the main therapeutic limitations in clinical use. Using niosomes as a curcumin

delivery system is a cheap, simple, and low-toxicity strategy to increase curcumin uptake and delay its release by cells.

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HOW TO CITE: Sudarshan Kale, Shradhha Vaishnav, Chaitali Markand , Vinit Khairnar, Niosomes Used In Treatment Of Cancer: A Review, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 4, 735-745. https://doi.org/10.5281/zenodo.10966570