Investigating the Use of Niosomes in Pharmaceuticals and Drug Delivery

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ABSTRACT

The treatment of infectious and autoimmune diseases has experienced many changes in the past few years. Currently, cancer treatment is usually based on pathological and clinical methods. The most common cancer treatment is limited to chemotherapy, radiation therapy, and surgery, however, the treatment is still not optimal. Common problems in some diseases treatment, especially cancer, include non-specific and systematic distribution of medicinal agents, insufficient drug concentration at the operation site, intolerable toxicity, and drug resistance. The application and development of nanotechnology for cancer treatment have attracted a lot of attention in recent years. This technology provides a unique approach to cancer through early detection and cancer treatment. The design and development of new drug delivery systems not only increase the activity of the drug in the target tissue but also reduce the toxicity of the drug to a great extent and release it at the site of operation in a controlled manner. Niosomal vesicles contain non-ionic surfactants, which are non-toxic, biodegradable, stable, and cheap and can be utilized for targeted drug delivery. High purity, greater chemical stability, proper drug storage, various types of availability of non-ionic surfactants, and cheapness are the most important advantages of niosomes.

Key Words: *Treatment, Niosomes, Drug delivery, Nanotechnology*

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INTRODUCTION

Biotechnology and nanobiotechnology are two promising technologies of the 21st century. Nanobiotechnology is defined as the design, development, and application of materials and devices at the nanometer scale. Nanotechnology is dealing with or developing materials, devices, or other structures with a minimum size between 0-100 nanometers [1, 2].

Nanotechnology provides an event for the targeted delivery of genes, drugs, and proteins to tumor tissues, thus reducing the anticancer agent's toxicity in healthy tissues. Cancer is the leading cause of death in the world, especially in developing countries, according to the American National Cancer Institute (NCI), nanotechnology will change the important foundations of cancer diagnosis, treatment, and prevention [3, 4]. The use of nanoscale engineering materials for cancer treatment provides preferential removal of cancer cells without serious damage to normal cells [5].

Niosomes were first introduced in the 1970s as a factor for the cosmetic industry and then explored for potential applications for drug delivery. Niosomes are one of the most distinguished vesicles in the drug delivery system, which have attracted much attention for drug delivery [6-8]. These structures are single or multi-layered vesicles based on non-ionic surfactants, which are used as carriers of lipophilic and hydrophilic drugs [9, 10].

In many cases, cholesterol and its derivatives are used to prepare niosomes [6]. They are formed using the self-assembly of non-ionic surfactants in aqueous medium and form concentric bilayer vesicles that have a liposome-like structure [8]. The structure of Nisome is shown in **Figure 1** [11].

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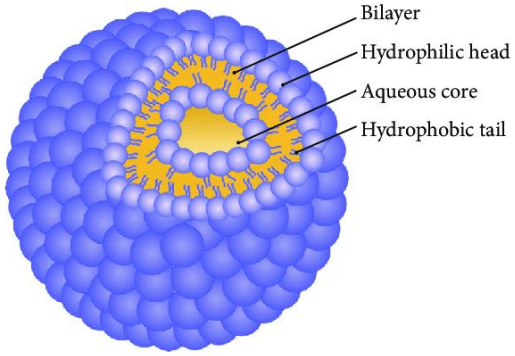

Figure 1. The structure of Nisomes.

Niosomes, a new drug delivery system

A lot of research has been done on the use of niosomes as drug carriers, and we will mention a few. Parthasarathi *et al*. prepared niosomes containing vincristine sulfate, which had lower toxicity and improved anticancer activity [12]. Paolino *et al*. prepared a niosomal system consisting of span80 and cholesterol-containing fluorouracil for the treatment of skin cancer, which was more toxic to the cancer cell than the free drug in the evaluation of cytotoxic activity [13]. Phytochemical compounds such as Lawsone have low solubility in water, which causes low permeability and instability. Barani *et al*. synthesized niosomes containing lawsone, which showed more cytotoxic activity than the free drug in the MCF7 cell line [14]. Asgharkhani *et al*. loaded artemisinin into nisomes and pegylated niosomes by two different techniques. Pegylation of nisome causes slower release, increased stability, and greater effect of artemisinin. The results showed that pegylated niosomes have many advantages in terms of interacting with the membrane of MCF7 cells [15]. Based on the vesicle size, niosomes can be divided into 3 groups: small unilamellar vesicles (size between 0.25-0.5), multi-lamellar vesicles (size > 0.5), and large unilamellar vesicle (size ≥ 0.1) [16].

Niosomes preparation methods

Niosome preparation methods contain freeze-drying, thin-film hydration, ether injection, reverse phase evaporation, bubble, microfluidization, sonication, etc. We will explain some methods below [17].

Sonication

In this method, some of the drug is dissolved in the buffer and added to the surfactant and cholesterol mixture in a vial. This mixture is homogenized by a sonic probe at a temperature of 60°C for 3 minutes. As a result, homogeneous and uniform vesicles are formed [18].

Technique of reverse phase evaporation

In this method, surfactant and cholesterol are dissolved in a mixture of chloroform and ether. The aqueous phase containing the drug is added to these materials and the resulting two phases are homogenized at a temperature of 4-5 degrees Celsius. A small amount of phosphate buffer salt is added to the formed clear gel. The organic phase is removed at 40-60°C and low pressure. As a result, the viscous suspension of niosomes is diluted with phosphate salt and heated in a water bath at a temperature of 60 degrees for 10 minutes to form niosomes [19].

Ether injection method

First, a certain amount of surfactant is slowly dissolved in diethyl ether and placed in a hot water bath at a temperature of 60 degrees. The surfactant mixture is injected into an aqueous solution by a 14-degree needle. Evaporation of ether causes the formation of unilamellar vesicles. Depending on the conditions used, vesicles with a diameter of 50-1000 nm are formed [20].

Thin film hydration technique

First, all the vesicle-forming molecules such as cholesterol, surfactants, and charge inducers are dissolved in a volatile organic solvent such as chloroform, methanol, diethyl ether, etc. It evaporates and a dry and thin film is formed from the dissolved components. The dried thin film is hydrated with the aqueous phase upon gentle stimulation, leading to the formation of niosomes [21]. In this method, multi-layered niosomes are created [11] **(Figure 2)**.

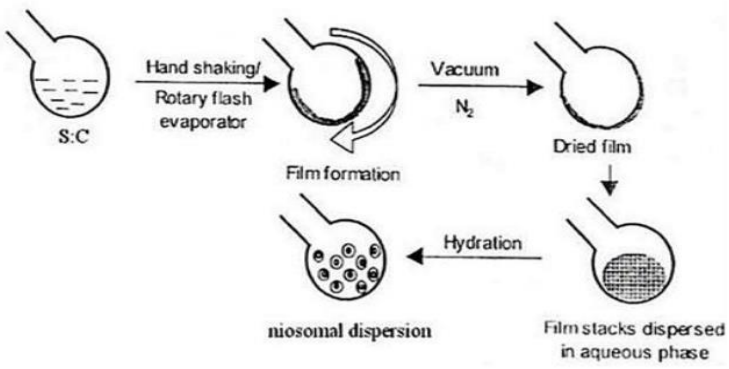

Figure 2. Thin film hydration method.

Niosomes formulation

Niosomes formulation is the most significant parameter that can affect the niosomes characteristics [22].

Surfactants

Surfactants constitute a unique class of chemical compounds. They are amphiphilic molecules with two different regions of very different solubility, a hydrophilic end and a lipophilic end that is hydrophobic. Surfactants can be classified into four groups: anionic, cationic, amphoteric, and nonionic [23]. If the head part of a surfactant has a negative charge, it is called anionic, including fatty acid salts (soap), phosphate esters, ether sulfates, and sulfates. If the head part has a positive charge, it is called a cationic surfactant, and if the head contains both positive and negative charges, it is called amphoteric. Cationic species often cause irritation and sometimes even toxicity, so their use is limited. Non-ionic surfactants have no charge on their head. Therefore, they create structures in solutions where hydrophilic heads are placed in front of aqueous solution and hydrophobic tails are placed in front of organic solutions. Non-ionic amphiphiles utilized in niosomes are classified into four categories: alkyl amides, alkyl esters, alkylators, and fatty acid esters. Most surfactants used in Nisome are listed below based on hydrophilic-lipophilic balance, the choice of surfactant type depends on HLB (hydrophilic-lipophilic balance) and CPP (critical packing parameters) [24].

Hydrophilic-Lipophilic Balance is a guide for selecting surfactant and its amount plays a vital role in controlling drug encapsulation efficiency. Until now, depending on Nisome's management, a large number of non-ionic surfactants with different HLB values, such as polyglycerol alkyl ethers, glucosyl dialkyl ethers, polyoxyethylene ethers, and esters, including Brij, Tween, Span series, have been used. Surfactants with HLB between 3-8 are compatible with the preparation of bilayer surfaces [6]. The HLB scale is between 0-20 values. A lower HLB indicates a lipophilic surfactant and a higher HLB indicates a more hydrophilic surfactant [16].

Hydrophilic surfactants with HLB values between 14 and 17 are not suitable for the formation of bilayer vesicles due to their high solubility in water [25]. Critical packing parameters (Critical packing parameter) In addition to HLB, various other factors also play a role in predicting the ability of vesicle formation **(Figure 3)**.

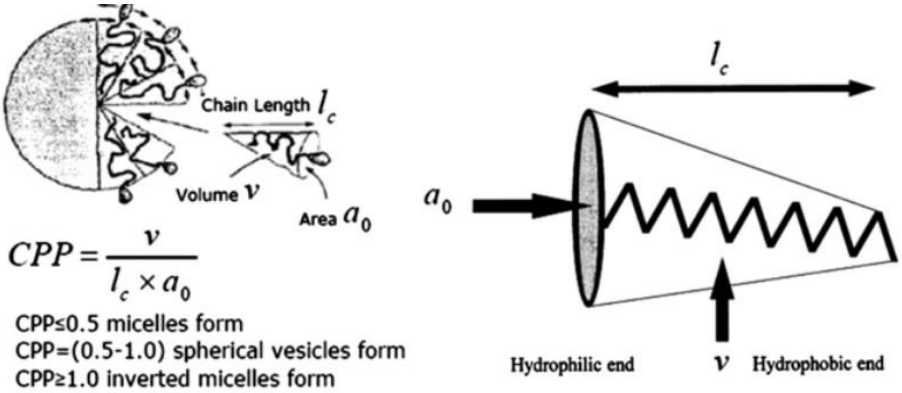

Figure 3. Critical packing parameter of an amphiphile.

The vesicle type can be predicted using the CPP value of the surfactant. CPP between 1.5-1.1 indicates that the surfactant is probably in vesicle form. A CPP less than 0.5 indicates that the micelles are spherical due to the large hydrophilic head, and a CPP greater than 1 produces reverse micelles due to the large amount of hydrophobic groups, which probably only occurs on the lipid or sediment phase [26].

Phase transition temperature (TC)

The phase transition temperature has a direct effect on the surfactant encapsulation efficiency. For example, Span60 is a surfactant with a high phase transition temperature that shows the highest encapsulation efficiency [27].

Additive agents

In addition to the nature of surfactants, encapsulation, and preparation method of niosomes, an additive agent can be an important parameter in the self-aggregation of surfactants. So far, different additives have been utilized for niosomes, among which cholesterol is the most common and important. Cholesterol content affects the properties of vesicles such as encapsulation efficiency, retention time, release, and stability [28].

Charge inductors

Charge inducers are another membrane additive often found in niosomes because they enhance the surface charge density and prevent dissolution, fusion, and aggregation. Positively and negatively charged molecules are used to induce charge in the niosomes. Diacetyl phosphate and

stearyl amine, which lead to negative or positive charges, are examples of these membrane additives [9].

Niosomes features

Size and zeta potential are very important for vesicle movement in the body, biodistribution, toxicity, and stability of niosomes [29]. The shape of the nisome vesicle is assumed to be spherical, and methods such as laser light scattering, electron microscopy, and molecular sieve chromatography are utilized to determine their average diameter and shape [30].

Formation of two layers, membrane stiffness, and number of layers

The formation of two layers by non-ionic surfactants is characterized by X-cross in the optical polarization microscope and can be measured using a fluorescence probe tool. NMR spectroscopy, X-ray scattering, and electron microscopy are used to determine the number of layers [31].

Efficiency of loaded drug

The free drug in the Niosome suspension is separated by dialysis bag, gel filtration, or centrifugation. The amount of drug loaded in them is calculated by lysing the vesicles using 50% propanol or Triton x-100. To determine the drug loading percentage, the lysed Niosomal suspension is centrifuged, the supernatant is removed and the precipitate is washed twice with distilled water to remove the loaded drug. Loading efficiency is calculated using the following formula [32].

$$\text{Loading percentage} = (\text{Total amount of drug}/\text{Amount of drug in Niosome}) \times 100 \quad (1)$$

Separation of unloaded drug from niosome solution

Filtration gel

The unloaded drug in niosomes is separated by a Sephadex-G-50 column and washed with phosphate-buffered saline or normal saline.

Dialysis bag

The aqueous solution around the nisome is dialyzed by the dialysis bag in phosphate-buffered saline, glucose solution, or natural salt.

Centrifuge

The suspension of niosomes is centrifuged, and the precipitate is washed to obtain a niosomes solution without free drug [33].

Measurement of drug release rate from niosomes

Dialysis bag

Drug release from nisome suspension is influenced by several factors including drug concentration and hydration volume. In this method, niosomes are placed in a cultured dialysis bag, surrounded by phosphate buffer (pH = 5.7-100) at a temperature of 37 degrees, and dialyzed on a magnetic stirrer. From around the dialysis bag, samples are taken out and centrifuged at specific time intervals, then they are analyzed using common spectroscopic methods such as UV, and HPLC [34].

Reverse dialysis

In this method, several small dialysis bags containing 1 ml of phosphate buffer are placed in Nisome's solution. Direct dilution of niosomes is possible with this method; however, its rapid release cannot be measured using this method [19].

Niosomes benefits

These vesicles are water-based carriers, which enhance patient satisfaction compared to oily dosage forms. They have a substructure consisting of lipophilic, amphiphilic, and hydrophilic components and thus can accommodate drug molecules with a wide range of solubility. The vesicle formulation characteristics can be changed and controlled. By changing the composition of the vesicle, the lamellarity, size, surface charge and concentration of the vesicle can be controlled. These vesicles can act as a reservoir and release the drug in a controlled manner. They are osmotically active and stable and also increase drug stability [34].

Administration and maintenance of surfactants do not require special conditions. They improve bioavailability and poor absorption of oral drugs and increase drug penetration into the skin. Niosomes can reach the target site through oral, topical, and injection routes. Surfactants are biocompatible and biological and do not produce an immune response. They improve the therapeutic effect of drug molecules by delaying drug clearance from the blood circulation, protecting the drug in the biological environment, and limiting the effect of the drug on the target cells [35].

CONCLUSION

In recent years, the systems of vesicular drug delivery have attracted much attention. Niosomes are a convenient, effective, and targeted drug delivery system that can load both hydrophobic and hydrophilic drugs. Surfactants as structural components of niosomes play a vital role in the properties and formation of these nanocarriers, so any progress in the new surfactants synthesis that is non-toxic, biodegradable, biocompatible, and low-cost will increase the niosomes efficiency. In summary, niosomes are a very

useful tool. They are effective for drug delivery in the treatment of many diseases and have a higher capability than conventional drug treatments.

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