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Original Research Article

Chemical and Judgmental Examination of Niosomes or Vesicles of Non-Ionic Surfactants

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ABSTRACT

Niosomes or vesicles of nonionic surfactants are very small layered structures obtained from a mixture of nonalionic surfactants of alkyl or diakyl polyglycerol ether and cholesterol and then hydration in aqueous (aqueous) medium. Today, overuse of antibiotics in the treatment of human and animal diseases has caused the multidrug resistance of bacteria to antibiotics. In addition, if a new type of antibiotic is used, resistance genes will begin to appear. After a period of widespread transmission to other bacteria, the spread of resistance and the need for new antibiotics, which requires millions of dollars. Vancomycin is used to treat infections of many gram-positive and gram-negative bacteria. Consumption of this antibiotic is very high due to the bacterial resistance that has been created against it as well as the side effects that it causes in some parts of the body. Many studies have been done on antibiotics to find a solution to eliminate the toxicity caused by their long-term use.

Keywords: Newsome, Dialkyl Polyglycerol Ether, Antibiotic, Vancomycin, Bacteria.

Introduction

Staphylococcus aureus is a gram-positive pathogenic bacterium that is the leading cause of many nosocomial diseases including pneumonia, jaundice, toxic staphylococcal shock syndrome, gastrointestinal infections and urinary tract infections [1-3]. This bacterium can be comprehensively involved in human and animal diseases due to its genes encoding pathogens such as genes that synthesize toxins and biofilms and other pathogens [4-6].

Today, this bacterium can also show resistance to various antibiotics due to its genes encoding antibiotic resistance as well as mutations in their genomic structure. This bacterium has been resistant to many antibiotics for decades, especially the penicillin family [7-9]. But today vancomycin has been introduced as a potential drug to fight bacterial infections. However, in the last decade, resistance to this antibiotic has been observed in clinical strains of Staphylococcus aureus, which necessitates a new approach to combat this problem. An ideal antimicrobial agent has bactericidal action, not bacteriostatic, meaning that an ideal antimicrobial agent is one to which a susceptible organism has not been resistant, either phenotypically or genetically [10].

It is desirable that the antimicrobial agent be effective against a wide range of common microorganisms. The ideal antimicrobial agent should not be allergenic and high-dose decomposition should have side effects. For effective drug delivery to scar tissue and control of microbial colonization and prevention of the development of invasive infections, use of new drug delivery systems including liposomes, autosomes, niosomes and ... instead of creams, ointments, solutions and suspensions in topical dermatology due to increased drug permeability, slow and controlled release, reducing the required dose and finally reducing toxicity and cost-effectiveness, etc. have received much attention [11-13]. Niosomes are a special type of vesicular drug delivery system based on nonionic surfactants and cholesterol that produce microscopic lamellar structures. Finally, following hydration in aqueous medium, sonication and homogenization of small monolayer vesicles are created. In these vesicular systems, nonionic surfactants have replaced phospholipids in liposomes. Niosomes can be used to enclose hydrophilic and hydrophobic drugs (in the aqueous fraction or in the membrane of vesicles made from fatty substances. niosomes, like other vesicular systems, have many advantages, such as prolonging the residence time of the drug in the circulatory system, targeted drug delivery to specific organs and tissues, and controlled release of the drug, and being biodegradable and non-immunogenic. niosomes are more stable than liposomes. Due to their cholesterol content, they increase the encapsulation efficiency of the drug [14-16]. Unlike liposomes, they do not require low temperatures or the use of neutral gases in packaging and storage, and the materials used to make them are inexpensive.

Nanotechnology

Nanotechnology is a new technology that has spread all over the world, and to be more precise, nanotechnology is not part of the future but the whole future [17-19]. Nanotechnology is the ability to produce new materials, tools, and systems by taking control of molecular and atomic levels and using the properties that appear on those surfaces. From this simple definition it follows that nanotechnology is not a new discipline, but a new approach in all disciplines. In general, this technology is the application of particles in nanoscale. These particles can be accessed in two ways: a top-down access path and a bottom-up design and fabrication. In the first type, nanostructures are obtained by crushing larger particles with the help of precision tools and equipment. In bottom-up design, also called molecular technology, structures are produced, atom to atom, and molecule to molecule. According to the Executive Director of Nanotechnology in the United Kingdom, nanotechnology is a continuation and expansion of the process of miniaturization, and in this way the production of materials, equipment and systems with Nano dimensions is done [20-22]. In fact, nanotechnology allows us to make and design materials that have completely new properties [23].

The nanometer is equivalent to one billionth of a meter, or the equivalent of ten hydrogen atoms stacked next to each other. If humans were on the nanometer scale, we could fit all the humans who lived on the planet in the space needed to park a car [24]. The specialized field of nanotechnology is structures and devices that are in the spatial dimensions of 1 to 100 nanometers and the activities of these structures take place in a period of phantom seconds. Shrinking beyond the nanoscale will cause us major problems. Because if the nanotechnology cornerstone is made up of single atoms, the smallest of which, the hydrogen atom, is one-tenth of a nanometer in diameter, the pico-tech cornerstone will be particles that must necessarily be on a smaller scale than the atom, such as Electrons, neutrons and protons. The main problem here is that the energies needed to create such particles are not naturally found on our planet, and we have to create such particles by spending high energies [21]. From this point of view, nanotechnology is the end point of downsizing, and the nanoscale is the most basic level of organization and formation of physical and biological matter. Because it is at this scale that the overlap of atoms, molecules, and finally the interaction and overlap of tissues is formed.

Niosome and their history in drug delivery

Niosome was first introduced as a factor for the cosmetics industry in 1970, and then potential drug delivery plans were explored. Niosomes are one of the most prominent vesicles in the drug delivery system, which have attracted a lot of attention for drug delivery [8]. These structures are

single- or multi-layered vesicles based on nonionic surfactants, which are used as carriers of lipophilic and hydrophilic drugs. In many cases, cholesterol and its derivatives are used to make niosome. They are formed by the self-aggregation of nonionic surfactants in aqueous medium and form concentric bilayer vesicles that have a liposome-like structure. Based on the size of the vesicles, the niosome can be divided into three groups.

1. Small unilamellar vesicle (size between 0.25-0.5)
2. mlv (multi lamellar vesicle) vesicles (size <0.5)
3. Large unilamellar vesicles (0.1 <= size).

Niosomes are a new drug delivery system that has done a lot of research on the use of niosomes as drug carriers, to name a few [19].

Parthasarthi et al. prepared niosomes containing vincristine sulfate, which had lower toxicity and improved anticancer activity [10].

Paolino et al. developed a niosome system consisting of span80 and fluorouracil-containing cholesterol for the treatment of skin cancer, which was more toxic to cancer cells in assessing cytotoxic activity than the free drug [1].

Phytochemicals such as lawsone have low solubility in water, which leads to low permeability and instability. In 2018, Barani et al. synthesized lawsone-containing niosome that showed higher cytotoxic activity than free drug in the MCF7 cell line. In 2018, Asgharkhani et al. loaded Artemisine into Newsome and Pegyle Newsome with two different techniques [14].

Pegylation of the niosome results in slower release, increased stability, and greater efficacy of artemisinin. The results showed that pegylated niosomes have many advantages in terms of interaction with MCF7 cell membranes [12]. Askari et al., niosomes Nano carriers containing pomegranate peel extract evaluated encapsulation efficiency, size and surface charge of 861.61%, 6.143 nm and -9.40%, respectively, and their effect on MCF7 cell line.

The results of cytotoxicity showed that the toxicity of free extract and niosomes was dependent on concentration and time. niosomes containing pomegranate peel extract were also more toxic than free extract [3].

Using cationic lipids DOTAP, DOTIMA, DOAB and DDAB along with phospholipid levels of cholesterol, dppc and dspe-Mpeg, Nikonahad et al. evaluated their cationic liposomal formulations and evaluated their cytotoxicity in two cell lines at 48 and 72. Based on the results, dotap-based cationic liposomes can be used effectively in the gene therapy process, especially for miRNA transfer as a novel therapeutic agent, especially in the treatment of various cancers [6].

In a study, Nikonahad et al. used lipofectamine 2000 as a cationic liposome for miR-101 transfection to evaluate cytotoxicity and its effect on the expression of ubiquitin ligase in acute myeloid leukemia (AML) cells [17].

The results showed that lipofectamine, as a cationic liposome, could effectively transfect miR-101 into the cell and also exert its antitumor effects by increasing the expression of $HECTH_9$ [18].

Niosome preparation methods

Niosome preparation methods include: thin film hydration, freeze-drying, reverse phase evaporation, ether injection, sonication, micro fluidization, bubble, etc., which are described below.

1. Sonication: In this method, some of the drug is dissolved in a buffer and added to a mixture of surfactant and cholesterol in a vial. The mixture is homogenized using a sonic probe at 60 ° C for 3 minutes. As a result, homogeneous vesicles are formed.

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

3. Ether Injection Method: First, a certain amount of surfactant is slowly dissolved in diethyl ether and placed in a hot water bath at 60 °C. The surfactant mixture is injected into an aqueous solution with a 14-degree needle. Evaporation of ether leads to the formation of monolayer vesicles. Depending on the conditions used, vesicles with a diameter of 50-1000 nm are formed.

4. Thin Film Hydration Technique First: all molecules that make up vesicles such as surfactants, cholesterol and charge inducers in a volatile organic solvent such as diethyl ether, methanol, chloroform, etc. are dissolved in a round bottom balloon and used. From a rotary evaporator, organic solvents evaporate at room temperature to form a thin, dry film of soluble components. The thin film dried with the aqueous phase is gently hydrated by stimulation, which leads to the formation of niosomes. In this method, multilayered niosomes are created.

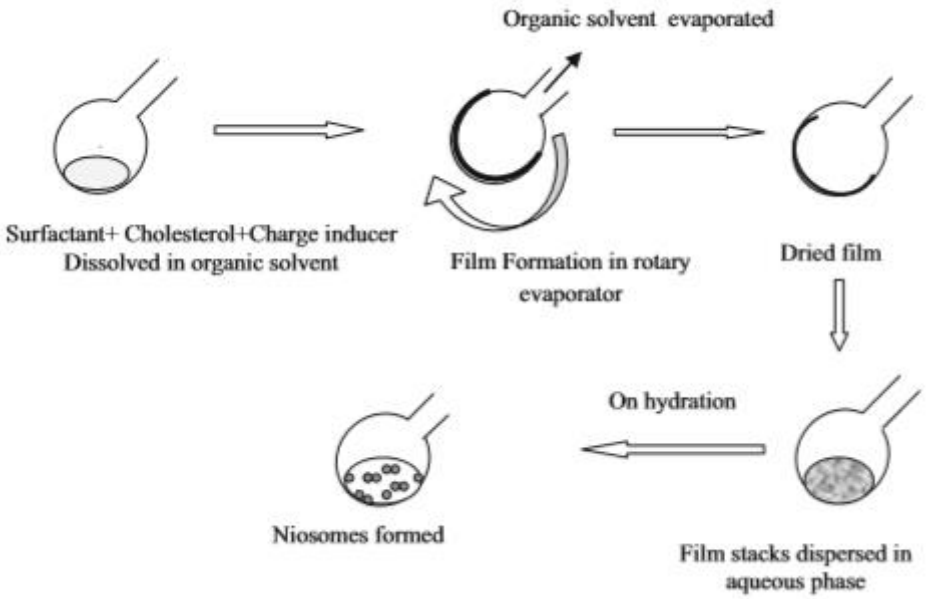

Figure 1: Thin film watering method

Formulate Niosome

Niosome formulation is the most important parameter that can affect niosome properties. Surfactants form a unique class of chemical compounds. They are amphiphilic molecules with two distinct regions that have 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. If the head of a surfactant has a negative charge, it is called anionic, it contains: fatty acid salts (soap), sulfates, ether sulfates and phosphate esters.

If the head has a positive charge, it is called a cationic surfactant, and if the head contains both a positive and a negative charge, it is called amphoteric. Cationic types are often irritating and sometimes even toxic, so their use is limited. Non-ionic surfactants have no charge on their heads. Therefore, in solutions, structures are created in which hydrophilic heads are placed in front of the aqueous solution and hydrophobic tails are placed in front of the organic solutions. Nonionic amphiphilic used in niosomes are classified into four categories: alkyl esters, alkyl amides, alkylates, and fatty acid esters [1]. Most of the surfactants used in Newsome are based on the hydrophilic-lipophilic balance below. The choice of surfactant type depends on the hydrophilic-lipophilic balance (HLB) and the critical packing parameters (CPP). Hydrophilic-Lipophilic Balance is a guide for selecting a surfactant, and its amount plays an important role in controlling drug capsule efficacy [14]. So far, depending on the niosome management, a large number of nonionic surfactants with different HLB values such as polyglycerol alkylates, glycosyl dialkylates, polyoxyethylenes and esters including Brij, Tween, Span series have been used.

Surfactants with HLB between 3-8 are compatible with the preparation of bilayer surfaces. The HLB scale is between 0-20. Lower HLB refers to lipophilic surfactant and higher HLB refers to more hydrophilic surfactant. 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. Critical Packing Parameter in addition to HLB, various other factors play a key role in predicting vesicle formation ability. CPP is a dimensionless scale for surfactants as defined below.

$$Cpp = V / Lca0$$

V = volume of the hydrophobic group.

LC = critical hydrophobic group length.

a0 = Head area of the hydrophilic group.

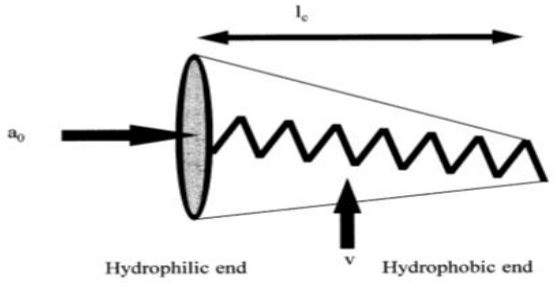

Figure 2: Critical parameter of the packaging of an amphibian

The type of vesicle can be predicted by the CPP value of the surfactant. CPP between 1-5.1 indicates that the surfactant is probably in the form of vesicles. CPP less than 0.5 indicates that the micelles are spherical due to the large hydrophilic head, and CPP more than 1 indicates reverse micelles due to the large amount of hydrophobic group, which probably occurs only on the fat or sediment phase.

Influential parameters in selecting the appropriate niosome

Phase transfer temperature (TC)

The phase transition temperature has a direct effect on the surfactant encapsulation efficiency. Span60, for example, is a surfactant with a high phase transfer temperature that exhibits the highest encapsulation efficiency.

Additive agents

In addition to the nature of surfactants, encapsulation and the method of preparing the niosome, an additive can be an effective parameter in the self-aggregation of surfactants. So far, various additives have been used for niosomes, the most common and important of which is cholesterol.

Cholesterol content affects the properties of vesicles such as encapsulation efficiency, storage time, release and stability [4].

Charging inductors

Charging inducers are another membrane additive often found in niosomes, as they increase surface charge density and prevent dissolution, aggregation, and fusion. Negative and positively charged molecules are used to induce charge in myosin. Dicetyl phosphate and stearyl amine, which result in a negative or positive charge, are examples of these membrane additives [6].

Niosome size

Zeta size and potential are very important for vesicle movement in the body, bio-distribution, toxicity and stability of niosome. The shape of the niosomes vesicle is assumed to be spherical, and methods such as laser light scattering, electron microscopy, and molecular sieve chromatography are used to determine their average diameter and shape [7].

Formation of two layers, membrane stiffness and number of layers

The formation of two layers by non-ionic surfactants is determined by X-cross in a light polarizing 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.

Efficacy of the drug loaded

The free drug in the niosomal suspension is removed by dialysis bag, filtration gel or centrifuge. The amount of drug loaded in them is calculated by lubricating the vesicles using 50% propanol or Triton x-100. To determine the drug loading percentage, the lysozyme 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.

100 * (total amount of drug / amount of drug in Newsome) = loading percentage

Isolation of unloaded drug from niosome solution is also done by the following methods.

Filtration gel

The unloaded drug in the niosome is separated by a Sephadex-G-50 column and washed with a saline phosphate buffer or ordinary salt.

Dialysis bag

The aqueous solution around the niosome is dialyzed by dialysis bag into phosphate saline buffer or glucose solution or natural salt.

Centrifuge

The suspension of the niosomes is centrifuged, the resulting precipitate is washed to obtain a niosome solution without free drug.

Measuring the release rate of the drug from the niosome

Dialysis bag: The release of the drug from the suspension of Newsome is affected by several factors including the concentration of the drug and the volume of hydration [24]. In this method, the niosome is placed in a cultured dialysis bag, and phosphate saline buffer is placed around it (PH =5.7,100-300) at a temperature of 37 °C and dialyzed on a magnetic stirrer. Samples are taken out of the dialysis bag at regular intervals and centrifuged, then examined by conventional spectroscopic methods such as UV and HPLC.

Reverse dialysis: In this procedure, a number of small dialysis bags containing 1 ml of phosphate buffer are placed in the niosome solution. Direct dilution of niosome is possible with this method; However, its rapid propagation cannot be measured using this method.

Niosomes Benefits

- These vesicles are water-based carriers, which increase patient satisfaction compared to oily drug forms.
- They have a substructure consisting of hydrophilic, amphiphilic and lipophilic components and as a result can accommodate drug molecules with a wide range of solubility.
- The properties of the vesicle formulation can be changed and controlled. By changing the composition of the vesicle, the size, lamellarity, surface load 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 the stability of the drug.
- Administration and maintenance of surfactants do not require special conditions.

- They improve the bioavailability and low absorption of oral drugs and increase the penetration of the drug into the skin.
- Niosome can be reached orally, topically, and by injection [9].
- Surfactants are biocompatible and do not produce an immune response.
- Improve the therapeutic function of drug molecules by delaying drug release from the bloodstream, protecting the drug in the biological environment, and limiting the effect of the drug on target cells.

Advantages of using niosomes as drug carriers

- Niosomes dissolve water-insoluble drugs and provide a stable liquid environment.
- Niosomes provide controlled release for the drug, thereby preventing rapid drug release, which improves the therapeutic function of drug molecules (by protecting the drug from biological environments). By changing the bio-distribution of drugs, niosomes increase their cumulative concentration in the target tissue and prevent the accumulation of the drug in non-targeted and healthy tissues. In this way, the therapeutic effect of the drug will be more and on the other hand, its toxicity and side effects will be much less.
- Niosomes can deliver drugs in the desired conformation state or in combination with compounds that increase the activity of the immune system.
- Biodegradable, compatible with biological systems, very low toxicity (non-ionic nature) and non-immunogenic.
- Raw materials are easy to prepare, store, store and transfer niosomes.
- Oral bioavailability of the drug is increased by using niosomes. They have the ability to accumulate a wide range of hydrophilic drugs (in their aqueous part), hydrophobic (in their vesicular bilayer membrane) and dual-friendly.
- Niosomes increase the penetration of the drug into the skin.
  Increases the stability of accumulated drug (trapped in them) (due to drug retention inside the niosome).

Conclusion

The aim of the study by Abdulaziz et al. in 2014 was to optimize norfloxacin niosomes to increase antibacterial activity and reduce bacterial resistance. In this study, Pseudomonas aeruginosa, a bacterium that forms a biofilm, was used as the test organism. Different norfloxacin niosomes were examined in vitro and in vivo for antibacterial activity in comparison with aqueous drug solution, respectively. The effect of norfloxacin niosomes on biofilm formation was investigated.

The interaction of niosome with bacterial cells was also monitored using scanning electron microscopy (SEM). The findings showed that the effect of niosomes depends on their composition. The standard niosomes of Span 60 and cholesterol were similar to the drug solution. Mixing tween 80, oleic acid (OA), OA/propylene glycol or lecithin produces liquid niosome that reduce MIC and inhibit biofilm formation compared to drug solution. Mixing a positively charged agent in liquid niosomes increases antibacterial activity and significantly reduces biofilm formation. SEM showed evidence of vesicle uptake into bacteria with the possibility of adhesion or fusion to the cell membrane. The in vivo dermal model confirmed the laboratory results that optimal niosomes are more effective than the drug solution. They suggested that niosomes promise to increase antibacterial activity and reduce antibiotic resistance.

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