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НАУЧНО-ТЕХНИЧЕСКИЙ ВЕСТНИК УНИВЕРСИТЕТ ИТМО ИНФОРМАЦИОННЫХ ТЕХНОЛОГИЙ, МЕХАНИКИ И ОПТИКИ

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REVIEW OF METHODS FOR SIZE AND MORPHOLOGY DETERMINATION OF VESICLES IN NIOSOME DISPERSION

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Abstract
The paper provides comparative analysis of direct and indirect methods for assessing the size and morphological characteristics of niosome dispersions. Niosome sizes vary over a wide range: from 20 nm to 10 μm and more. The vesicle shape can also vary from perfectly spherical to elliptical and complexly curved in the case of aggregation. The size and shape of large particles with a diameter greater than 1 μm can be assessed by light microscopy. To study smaller vesicles, about 0.1–0.5 μm, it is advisable to use the technique of dynamic light scattering. Photometric method is reasonable to be used for an indirect assessment of the size of niosome vesicles in the range of 40–130 nm. For surface morphology study of the smallest niosomes, the method of scanning electron microscopy seems to be optimal.

Keywords
niosome dispersions, niosome vesicle size, dynamic light scattering, scanning electron microscopy, photometric method

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ОБЗОР МЕТОДОВ ОПРЕДЕЛЕНИЯ РАЗМЕРОВ И МОРФОЛОГИИ ВЕЗИКУЛ НИОСОМАЛЬНОЙ ДИСПЕРСИИ

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Аннотация
Выполнен сравнительный анализ прямых и косвенных методов оценки размеров и морфологических характеристик ниосомальных дисперсий. Размеры ниосом варьируются в широких пределах: от 20 нм до 10 мкм и более. Форма везикул также может изменяться – от идеально сферической до эллиптической, и сложно изогнутой в случае агрегации. Размеры и форму крупных ниосом, диаметром более 1 мкм, можно оценить с помощью световой микроскопии. Для исследования более мелких везикул, размером около 0,1–0,5 мкм, целесообразно использовать метод динамического рассеяния света. Для косвенной оценки размера ниосомальных везикул в диапазоне 40–130 нм целесообразно использовать фотометрический метод. При исследовании морфологии поверхности мельчайших ниосом оптимальным представляется метод сканирующей электронной микроскопии.

Ключевые слова
ниосомальная дисперсия, размер ниосомальных везикул, динамическое рассеяние света, сканирующая электронная микроскопия, фотометрический метод

Introduction

Recently, creation of innovative dosage forms of existing drugs has been developing intensively in parallel with the development of new drugs. The objective is to increase the bioavailability of drugs that have already proven their effectiveness together with the decrease in the administered dose and the risk of possible side-effects [1–4]. One of these promising "delivery systems" of drugs is the aqueous niosome dispersion. Niosomes are stable, single-layer or multi-layer vesicles of non-ionic surfactants. Non-ionic surfactants have advantages over ionic ones, since they are usually biocompatible and minimally bind to proteins [5]. Various components can be integrated into the bilayer lipid membranes by means of niosomes, affecting their stability, electrophoretic mobility and controllability by external electromagnetic fields. Besides, the problem of the prolonged drug action can be solved by the size control of the niosomes and the time of the substance release from them [6–8].

Currently, there are no experimental and theoretical approaches for a comprehensive description of the niosome vesicle properties that affect their ability to transport drugs into the aqueous environment. The possibility of obtaining morphologically homogeneous dispersed compounds with desired sizes provides to move forward in the direction of drug development.

Material and Methods

We used a water solution of niosomes consisted of a shell in the form of a water-insoluble double layer of a nonionic surfactant, which is a group of dimethiconcopolyol substances. They are esters of polyethylene glycol and polydimethylsiloxane (PDMS) backbone [9–11]. To obtain the capsules of silicone nature, physicochemical methods for the synthesis of molecules were applied. The shell of the obtained niosome vesicles were generated from PEG-12 Dimethicone [12]. Samples were diluted with ultrapure water (with concentration $C = 0.01$ %).

The vesicle formation process is the self-organization of molecules and their simultaneous assembly into associates. Wherein, solution phase separation happens, and the resulting vesicles have significant anisotropy of physical properties in the radial direction. Significant influence on the size and shape of niosomes is exerted by their concentration in an aqueous solution. The growth in the content of the vesicles per volume unit inevitably leads to their fusion and violation of the form symmetry.

Results and Discussion

Optical microscopy. Light microscopy can be used for estimation of size and morphology of niosomes with micron and submicron diameter.

Microscopy of the sample of the above described niosome dispersion was performed by Micromed 2–20 microscope with magnification factor equal to 400 and LOMO digital camera.

The microphotograph on Fig.1 shows that the sample is a fraction containing a number of conglomerates formed

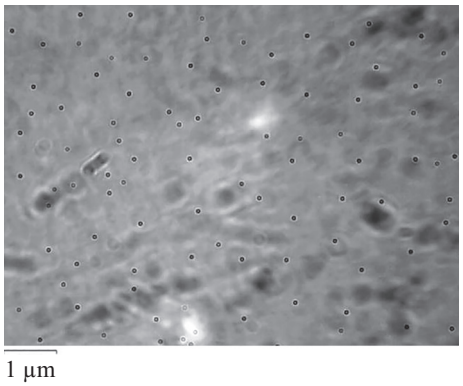

Fig. 1. Microphotography of niosome dispersion

by the merger of the individual niosomes. In general, the sample looks fairly homogeneous, since most of them have dimensions smaller than the resolution limit of an optical microscope.

Thus, the microphotograph obtained by optical microscopy can assess the homogeneity of the niosome solution only in the first approximation revealing the presence of large aggregates in the finely dispersed system.

Dynamic light scattering (DLS). Particle size can be determined by measuring the random changes in the intensity of light scattered from a niosome solution. The limitations imposed by this method on the dimensions of the particles being measured give the possibility to be used for the research of niosome solutions with the effective diameters from a few nanometers to several microns.

The linear dimensions of the niosome dispersion particles were measured using the PHOTOCORCOMPLEX multifunctional spectrometer for dynamic and static light scattering (He-Ne laser, 633 nm). Vesicle sizes were calculated applying FAST Version 2.8.3 software. (Alango Ltd.) According to the Einstein-Stokes formula, which relates the particle size to their diffusion coefficient and fluid viscosity:

$$R = \frac{kT}{6\pi\eta D},$$

where k — Boltzmann constant; T — absolute temperature; η — shear viscosity of the medium; D — diffusion coefficient.

Analysis of the obtained results (Fig. 2) provides for the conclusion that the size of the niosomes in the sample varies considerably. The size distribution is polymodal with

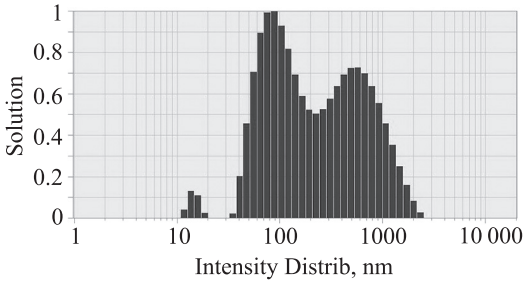

Fig. 2. The results of light scattering on niosomes obtained by PHOTOCORCOMPLEX multifunctional spectrometer

three peaks corresponding to 15 nm, 100 nm and 657 nm, respectively. The latter result, apparently, is associated with the scattering not on individual vesicles, but on their conglomerates.

The method gives a large error related to non-ideal spherical form of the particles and the presence of a certain number of randomly arranged aggregates in the sample, as it was shown in case of optical microscopy application.

Now, the method of dynamic light scattering is one of the most popular methods for estimating the size of nanoparticles, since it provides the possibility to obtain data and carry out their mathematical processing automatically with relatively low material costs and short duration of the experiment [13, 14].

Scanning electron microscopy. The size of nanoparticles can be defined using scanning electron microscopic method (Scanning Electron Microscopy (SEM) Tescan Mira 3 Im). The particle size determined by Image J, Excel statistical package program was used to perform the analysis.

Fig. 3 shows that water solution of niosomes consists of particles with various diameter sand niosomes, that are spherical particles in their majority.

This fact implies that for equivalent diameter determination of the particles the projected diameter can be used. The area of the projected diameter will be equal to the area of the particle projection image [15].

The cumulative distribution function (distribution density) was used to evaluate the average particle size.

Particle probability density function of the size of niosomes is shown in Fig. 4.

Research results present two most probable values for sizes of 100 nm and 160 nm, which do not contradict the data obtained by the method of dynamic light scattering.

This method makes it possible to determine accurately the niosome sizes in the sample, as well as to carry out morphological and dispersion analysis. In addition, the possibility of visual control excludes large conglomerates of vesicles from the study.

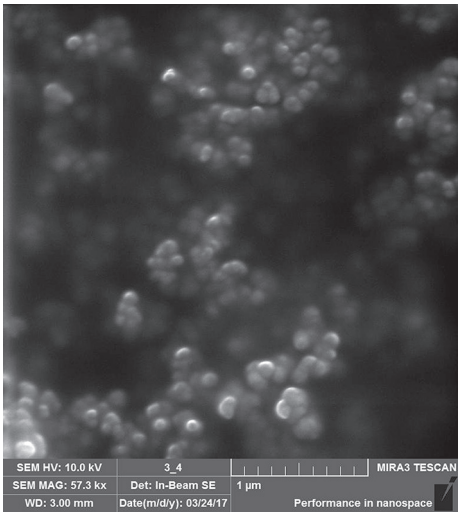

Fig. 3. Micrograph of niosomes obtained by Scanning Electron Microscopy

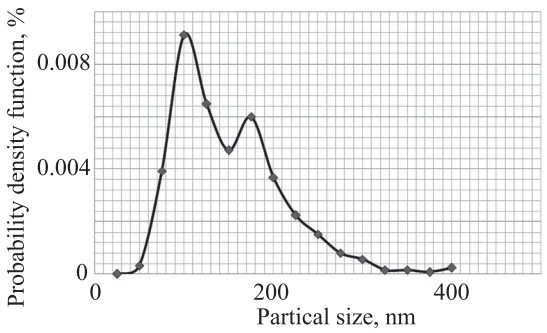

Fig. 4. Probability density function of particle size distribution

However, this method has some limitations, since it is impossible to study sufficiently large amount of material, as well as the complexity of the measurement process itself. In addition, the lack of automation in the selection of measured particles gives a subjective contribution to the results of the study.

Photometric method. With monochromatic radiation passages and a wavelength from 400 to 750 nm, through a solution of niosomes with the dimensions much smaller than these quantities, the light rays are not reflected from them, but scattered.

In this case, the Geller formula is applicable related to the optical density of the solution of the incident light wavelength. The formula contains a coefficient and its value depends on the average particle size:

$$D = K\lambda^{-\chi},$$

where D — optical density; K — coefficient independent of the light wavelength; λ — light wavelength; χ — coefficient, the value of which varies from 1 to 4 depending on the size of the scattering particles.

The Geller calibration curve is shown in Fig. 5. It can be used to determine graphically the radius of particles.

For particles with a radius from 40 to 130 nm, the calibration dependence is linear. Therefore, we can establish the analytical dependence $r = f(\chi)$. In the specified range it has the form:

$$r = \frac{4.875 - \chi}{0.031}.$$

This expression is true for $\chi = 0.9750 - 3.6750$.

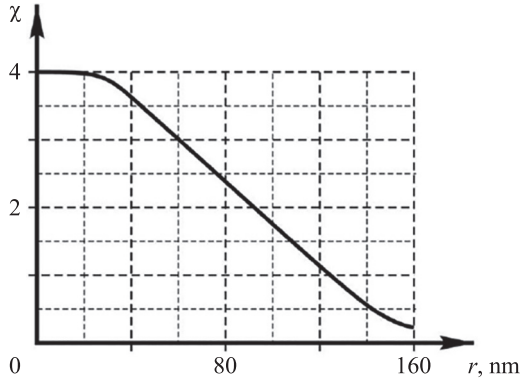

Fig. 5. Geller curve

The algorithm for the size determination of niosome vesicles by photometric method is described in details [16]. According to the experiment results, the effective diameter of the niosomes was equal to108 ± 12 nm.

Photometric method does not provide information on the dispersion composition of the niosome solution, however, due to its implementation simplicity and the absence of the complex equipment requirements, it seems to be a good alternative to SEM Tescan Mira 3 Im or Photocor Complex application for the express estimation of the vesicle sizes by coagulation.

Conclusion

Niosome creation with controlled size parameters, shape and morphology is one of the promising tasks of modern science. The methods for producing of single-layer and multilayer vesicles with sizes from 20 nm to 10 μm and more are described.

Range of sizes and morphological properties of niosomes can be set by the conditions of production and various components. Thus, the application of a certain preparation technology determines the expected particle sizes.

Methods for estimation of the niosomes sizes are based on the interaction of particles with light waves, or by the flow of electrons in case of scanning electron microscopy. Therefore, when choosing a method, we are guided by the ratio of the light wavelength and the expected diameter of the vesicles.

In the study of large particles with a diameter in excess of 1 μm, light microscopy is used in combination with various methods of increasing resolution. To estimate the particle sizes in the order of 0.1–0.5 μm, it is advisable to apply the technique of dynamic light scattering and photometric method is reasonable for niosomes with the diameter in the range of 40–130 nm. The method of scanning electron microscopy seems to be optimal in the surface morphology study of the smallest niosomes.

To obtain detailed information about the shape of niosomes and their size distribution, methods directly evaluating images should be applied. For preliminary assessment the method of dynamic light scattering or photometric method can be used.

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