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ДЕФОРМАЦИОННЫЕ СВОЙСТВА ГИДРОГЕЛЕВЫХ КОМПОЗИТОВ А-ЛИПОЕВОЙ КИСЛОТЫ С КОЛЛОИДНЫМ ДИОКСИДОМ КРЕМНИЯ

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Гидрогели широко используются в качестве основы для мягких лекарственных форм и косметических композиций (мазей, кремов, гелей, масок, дермальных филлеров и т.д.). Деформационные свойства указанных продуктов являются важнейшими с точки зрения удобства и безопасности их применения, а также оптимизации процесса их производства. В данной работе неорганические гидрогели диоксида кремния рассматриваются в качестве перспективной основы для разработки новых мягких лекарственных форм и продуктов для косметологии. Были синтезированы гидрогелевые композиты диоксида кремния с α-липоевой кислотой, которая является известным мощным антиоксидантом и применяется для лечения различных заболеваний кожи. Кроме того, она оказывает омолаживающее действие на кожу. Учитывая указанное потенциальное применение гидрогелей и способ их введения (трансдермальное, инъекционное), они имели pH 6,6–7,4. Чистые гидрогели диоксида кремния и их композиты с α-липоевой кислотой были синтезированы двухступенчатым золь-гель методом. С помощью метода оптической микроскопии показано, что они имеют высоко пористую поверхность. Определены деформационные свойства синтезированных гидрогелей при сжатии, растяжении и сдвиге. Показано, что синтезированные гидрогели обладают определенной эластичностью при аксиальном сжатии, тиксотропией, проявляют псевдопластичность. Установлены эффекты условий синтеза (концентрации катализатора золеобразования диоксида кремния, количества лекарственного вещества) на деформационные свойства композитов. Эффекты объяснены с точки зрения влияния указанных факторов на прочность трехмерного каркаса диоксида кремния гидрогелевых материалов. Обнаруженные деформационные свойства гидрогелей диоксида кремния делают их перспективными для разработки новых мягких лекарственных форм для топического применения.

Ключевые слова: диоксид кремния, гидрогели, α-липоевая кислота, деформационные свойства

DEFORMATION PROPERTIES OF HYDROGEL COMPOSITES OF A-LIPOIC ACID WITH COLLOID SILICA

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Hydrogels are widely used as the basis of soft drug formulations and cosmetic compositions (ointments, creams, gels, masks, dermal fillers, etc.). Deformation properties of these products are very important from the point of view of the convenience and safety of their application, as well as optimization of their production process. In this work, inorganic silica hydrogels are considered as a promising basis for the development of new soft drug formulations and products for cosmetology.

The hydrogel composites of colloid silica with α-lipoic acid which is a well-known powerful antioxidant used for treatment of various skin diseases were synthesized. Besides, the drug has a rejuvenating effect on the skin. Taking into account the indicated potential application of the hydrogels and the methods of their administration (transdermal, injection), the hydrogels had a pH of 6.6-7.4. Pure silica hydrogels and their composites with α-lipoic acid were synthesized by a two-step sol-gel method. Using the method of optical microscopy, it was shown that they have a highly porous surface. The deformation properties of the synthesized hydrogels under compression, tension, and shear were determined. It is shown that the synthesized hydrogels have a certain elasticity under axial compression, thixotropy and exhibit pseudoplasticity. The effects of the synthesis conditions (concentration of the catalyst for silica sol formation, the amount of the introduced drug) on the deformation properties of the composites have been established. The effects were explained in terms of the influence of these factors on the strength of the three-dimensional silica framework of the hydrogel materials. The discovered deformation properties of silica hydrogels make them promising for the development of new soft drug formulations for topical application.

Key words: silica, hydrogels, α-lipoic acid, deformation properties

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INTRODUCTION

Hydrogels are widely offered and already used as the basis of soft drug formulations and cosmetic compositions (ointments, creams, gels, masks, dermal fillers, etc.). The vast majority of hydrogel materials are based on natural and synthetic polymers with a huge diversity of structures and properties [1-4] promoting their extensive use for these purposes. At the same time, inorganic hydrogels, in particular silica hydrogels are no less attractive materials for biomedical application due to their biocompatibility, nontoxicity, highly porous structure, ability to retain a large amount of aqueous phase. Unlike many polymer materials, silica is resistant to degradation by enzymes and microbial attacks [5, 6]. Therefore, in this work, inorganic silica hydrogels are considered as a promising basis for the development of new soft drug formulations and compositions for cosmetology.

The hydrogel composites of silica with a well-known antioxidant α-lipoic acid (LA) (thioctic, 1,2-dithiolane-3-pentanoic acid) as a model drug were studied. α-Lipoic acid and its derivatives were found to be effective for treatment of various skin diseases [7, 8]. Besides, the drug promotes skin rejuvenation and is promising component of cosmetic products [9-11].

In this work, we studied the mechanical properties (deformation under compression, tension, shear) of the synthesized hydrogel materials. Such studies are very important in terms of the indicated potential application of the hydrogel materials. The deformation properties influence functionality of the topical formulations (correct dosage transfer to the target site, ability to restore and maintain shape and consistency after administration), consumer properties (ease of extraction from container, application on the skin), as well as affect various steps of their production process (for example, mixing, filling, packing).

It is well known that the conditions of sol-gel synthesis affect the structure and properties of silica materials [12-13]. There is a limited number of works in the literature devoted to the study of the effects of sol-gel synthesis conditions on structure and properties of silica hydrogels. Cao et al. [14] found that silica volume fraction (φ) plays a significant role in both the structure and ultimate mechanical properties of the gels. The gel with high silica volume fraction builds a stronger network. However, salt concentration has no effect on the strength of the silica gels. Ahmed et al. [15] studied the influence of soluble silica precursor (sodium silicate) and colloidal silica (Ludox) concentration as well as pH on the structural and mechanical properties of the nanocomposite hydrogels obtained from sodium silicates/colloidal silica mixtures. They revealed that the compression Young's modulus slightly increased with silicate concentration, but the introduction of Ludox led to significantly increased mechanical stability of the silica matrix of the hydro-

gels. Serban et al. [16, 17] showed that stiffness of silica hydrogels depended on a H_2O: tetraethoxysilane (TEOS) ratio and the silica particle size. However these parameters did not influence noticeably on release properties of incorporated drugs.

In the present study, the hydrogel composites were prepared by two step sol-gel method. The effects of the concentration of catalyst of silica sol formation (HCl) and the drug loading on the deformation properties of the silica hydrogel materials were revealed.

EXPERIMENTAL

The two-step sol-gel synthesis of the hydrogel composites and pure silica hydrogels has been described in detail in [18]. The hydrogel materials were prepared using HCl concentrations of 0.125M, 0.25M and 0.50M and the drug loadings of 3.9-4.6 mg/g (low drug loading (L)) and 8.5-9.6 mg/g (high drug loading (H)), so the pure silica hydrogels and the hydrogel composites with α-lipoic acid (LA) were designated as HG1, HG2, HG3 and LA-HG1(L), LA-HG1(H), LA-HG2(L), LA0HG2(H), LA-HG3(L) and LA-HG3(H), respectively.

Morphology of the synthesized hydrogel materials was investigated using an optical microscope XSP-104 equipped with a camera Micro Ocular PCE-ME 100 (APEXLAB, Russia). For this purpose, about 2.5 mg of each hydrogel was evenly applied in a thin layer to a glass slide surface and covered with another glass slide, and the optical images were performed

Uniaxial compression and tensile tests were conducted at room temperature using a test machine [19]. Samples of height (H=5 mm) and diameter (D=20 mm) were used. The tests were performed at a constant cross-head speed of 0.021 mm·s-1. The compression strain (εc) and the tensile strain (εt) were determined as $\varepsilon_c = 1 - \lambda$, and $\varepsilon_t = \lambda - 1$, respectively, where λ=l/l0 (l0 and l) are the heights of sample before and after deformation). The compression stress (σ_c) and the tensile stress (σ_t) were calculated as $\sigma_c = F_c/A_0$ and $\sigma_t = F_t/A_0$, respectively, where F_c and F_t are the load forces at compression and tension, A_0 is the surface area. The compression and tensile Young's modulus values were calculated from the slope of initial linear part of the stress-strain curves.

Rheological tests were performed at room temperature using a Brookfield DV2T Viscosimeter (Brookfield, AMETEK, Inc. MA, USA). A hydrogel sample was placed in cylindrical cell, and a cylindrical spindle (LV-2C or LV-3C) attached to the device was accurately immersed into the cell. The hydrogel was equilibrated for 10 min prior to testing. Viscosity and shear stress were measured in a shear rate range of 0.3-8.4 s^{-1}. The experimental flow curves were fitted with the modified Bingham model (1) [20, 21], the Bingham model (2), the Casson model (3), the Ostwald- de Waele or Power Law model (4) [22]:

$$\tau = \tau_0 + \eta_B\gamma + C\gamma^2 \quad (1)$$

$$\tau = \tau_0 + \eta_B\gamma \quad (2)$$

$$\tau^{0.5} = \tau_0^{0.5} + (\eta_c\gamma)^{0.5} \quad (3)$$

$$\tau = K\gamma^n \quad (4)$$

where τ is the shear stress, γ is the shear rate, τ_0 is the yield stress, ηpl is the plastic viscosity, C is the constant, K is the consistency index, n is the flow behavior index. The predicted data for each model were evaluated using the coefficient of correlation (R2) and root mean square error (RMSE) (5):

$$RMSE = \sqrt{\frac{\sum_{i=1}^{N}(y_{i\ model} - y_{i\ exp})^2}{N}} \quad (5)$$

where y_i model and y_i exp are the predicted and actual values, respectively, N is the number of data points. A model that shows the maximum of R2 and the minimum of RMSE gives the best description of the obtained data.

The thixotropic properties were studied using the method of hysteresis loop. In this experiment, the apparent viscosity vs shear rate dependences were recorded at the increasing (from 0 to 8.4 s^{-1}) and then immediately decreasing (from 8.4 to 0 s^{-1}) shear rate. The degree of thixotropy was estimated as the thixotropy index, T, which is defined as

$$T = \frac{S_{fwd} - S_{bwd}}{S_{fwd}} \quad (6)$$

where S_{fwd} and S_{bwd} are the areas under forward and backward curves, respectively [23, 24]. The areas were calculated using the trapezoidal method.

RESULTS AND DISCUSSION

The synthesized hydrogel LA-silica composites were smooth, uniform and slightly opalescent yellowish materials. The color is due to the presence of the antioxidant. The pure silica hydrogels synthesized under the same conditions for comparison were colorless and had the same consistency and opalescence.

Optical microscopy makes it possible to study the morphology of the hydrogels containing a large amount of an aqueous medium in their original form, without freezing or drying. As an example, Fig. 1 shows the optical image of LA-HG1(H).

It is seen that the surface of the hydrogel is highly porous. The pores are round and slit-like.

The elasticity (ability of material to return to its original for and size after removal of deformation force) is very important property of soft drug formulations and cosmetic products [25- 27]. As is known, the compression Young's moduli characterize a material's stiffness. The higher stiffness of material signifies the higher its ability to resist the applied deformation forces. The modulus values were determined by the slope of the elastic region of the stress-strain curves, i.e. the initial linear portion of the curves. The ultimate tensile stress values were determined as the maximum values on the σt=f(εt) curves. The comparative diagrams of the compression modulus values and the ultimate tensile strength values are presented in Fig.2.

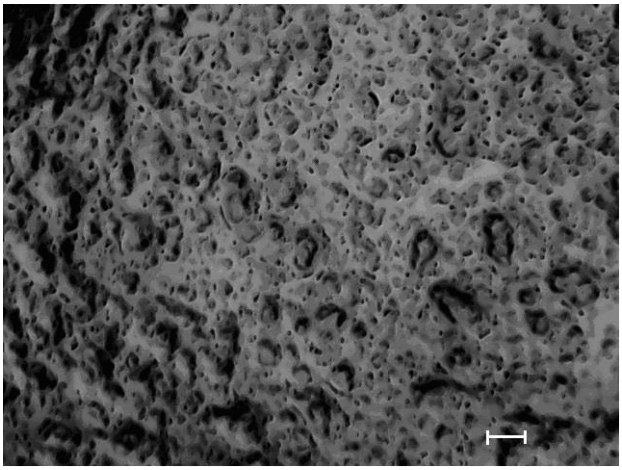

Fig. 1. Optical image of LA-HG1(H) (The scale bar is 250 μm)
Рис. 1. Снимок с оптического микроскопа для гидрогелевого композита LA-HG1(H) (Бар-метка соответствует 250 мкм)

The Young's moduli decrease with the increasing concentration of the catalyst of silica sol formation (HCl). The observed regularity can be explained by a decrease in the strength of three-dimensional silica network of the hydrogels under influence of this factor. For preparation of the hydrogels with pH ~7, larger amounts of the buffer solution with pH 7.4 were added to the sol for neutralization of the higher acid concentration. This lead to an increase in the amount of liquid phase and a decrease in volume fraction of silica in the hydrogels and, hence, their stiffness decreases [14, 16]. As for the drug loading, it is seen that the low LA loading resulted in a slight increase in the elastic modulus values. Possibly, the introduced small amounts of hydrophobic LA strengthen the hydrogel structure due to hydrophobic effect resulting in structuring of aqueous environment in the hydrogels. However the increased drug loading decreases stiffness of the hydrogel composites. T.

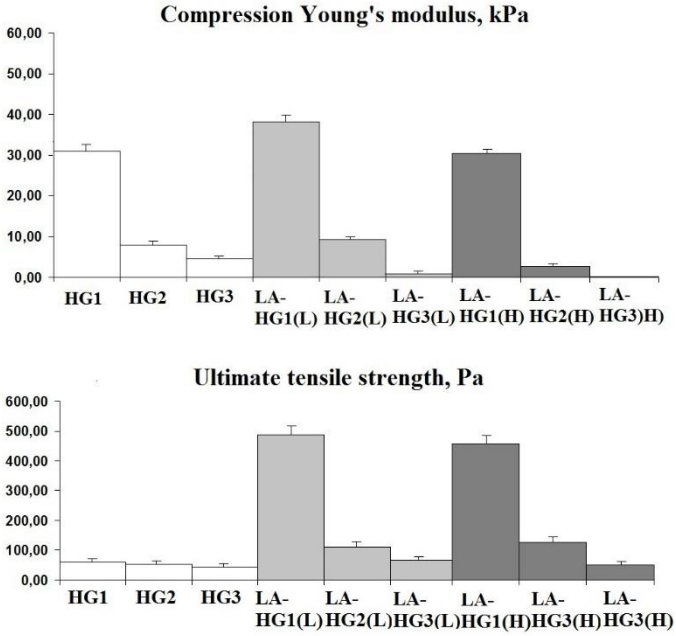

Fig. 2. Compression Young's moduli and ultimate tensile strength of the synthesized hydrogels (The data are presented as mean ± SD, n=3)
Рис. 2. Модули Юнга при сжатии и предельная прочность при растяжении синтезированных гидрогелей (Данные представлены как среднее значение ± стандартное отклонение, n=3)

The ultimate tensile strength is the maximum tensile stress that the sample can withstand without breaking. As can be seen from Fig. 2, the values of ultimate tensile strength for pure silica hydrogels are very low. Perhaps, this is due to their inorganic nature. The introduction of the organic substance contributes to an increase in the tensile strength of the hydrogels.

For potential practical application of the synthesized hydrogels as soft drug formulations and cosmetic products, their behavior under shear loading is of great interest. In order to calculate rheological characteristics of the hydrogel materials, the flow curves (shear stress via shear rate) were fitted with various rheological models. It was found that the modified Bingham model and the Ostwald- de Waele model exhibited the best description of the experimental flow curves (the R2 values for all fits were 0.96-0.99, the RMSE values were 0.045-0.776). The Bingham and the Casson models showed lower R2 and RMSE values (0.55-0.92 for the R2 and 7.03-123.44 for the RMSE). Using the modified Bingham model, the yield stress values (τ0) were determined. The consistency index (K) and the flow behavior index (n) were calculated using the Ostwald- de Waele model. The comparative diagrams of the obtained rheological characteristics for the synthesized hydrogels are presented in Fig. 3.

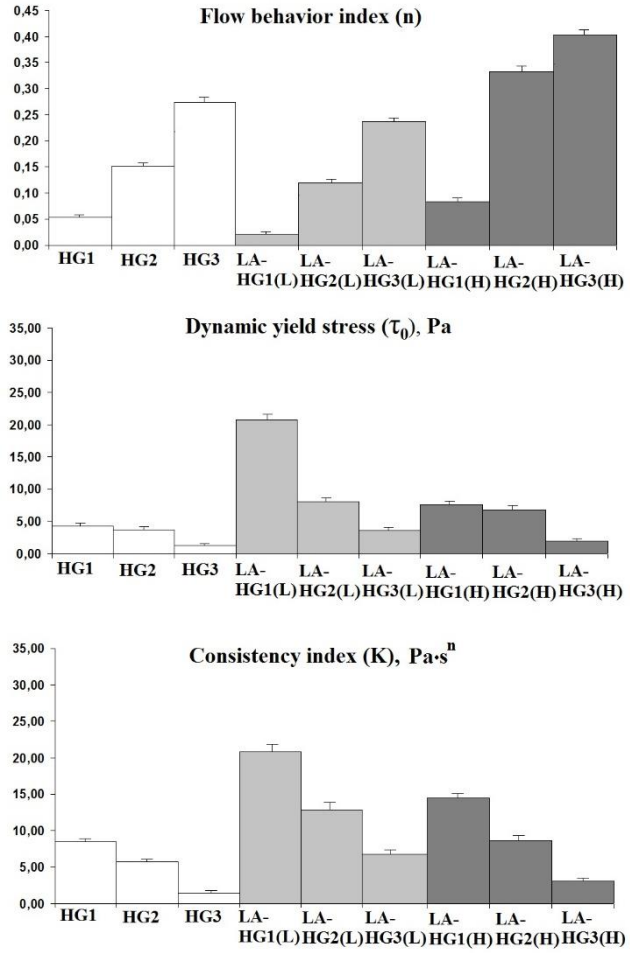

Fig. 3. Rheological characteristics of the synthesized hydrogels (The data are presented as mean ± SD, n=3)

Рис. 3. Реологические характеристики синтезированных гидрогелей (Данные представлены как среднее значение ± стандартное отклонение, n=3)

The values of flow behavior index n (0.02-0.37) indicate the shear-thinning effect or pseudoplasticity of the synthesized hydrogels [22]. It is associated with breakdown of the 3D silica framework under increasing shear rates and organization of the formed smaller particles in the flow direction resulting in the decrease in the viscosity of the hydrogels [28]. Besides, the index can be interpretated as the rate of change in the hydrogel structure during shear deformation: the higher n, the less stable the structure of the hydrogels: the higher n, the less stable the structure of the hydrogels [29, 30].

The yield stress (τ_0) determined by model fitting is dynamic yield stress, which is the minimum stress to maintain the material's flow or terminate it after the stress is removed [31, 32]. It is related to the structure of the material destroyed by shear forces and characterizes the level of structure of the material restored after removal of the shear stress (for example, after extrusion from the syringe, tube). Therefore the dynamic yield stress is very important for solution of technological problems of administration of soft drug formulations and cosmetic compositions. As can be seen from Fig. 3, the synthesized hydrogels are characterized by the dynamic yield stress of 2-22 kPa. The effects HCL concentration and the drug loading on the τ_0 values are similar to those observed for the elastic moduli and are explained by changes in the structural strength of the hydrogels under influence of these factors.

The consistency index k characterizes the viscosity properties of the hydrogels at a unit shear rate gradient. If the hydrogels become more viscous, the index increases.

Thixotropy is the ability of a material to shear-thinning (reduction of viscosity) under mechanical stress and shear-thickening (recovery of viscosity) at rest. The thixotropic properties of the synthesized hydrogels were determined using the hysteresis loop method [33]. The quantitative characteristic of the thixotropic properties is the thixotropic index (T), which is proportional to the area of hysteresis loop and is a measure of the energy required to breakdown thixotropic structures of the hydrogels by shear forces. The higher T coefficient indicates the slower the restructuring the hydrogels and the higher their thixotropic properties of the hydrogels. The index values calculated according the eq. (6) are presented in Table 1.

Table 1

Thixotropy index of the synthesized hydrogels

Таблица 1. **Индексы тиксотропности для синтезированных гидрогелей**

HG1	HG2	HG3	LA-HG1(L)	LA-HG2(L)	LA-HG3(L)	LA-HG1(H)	LA-HG2(H)	LA-HG3(H)
0.24	0.21	0.14	0.43	0.37	0.21	0.32	0.21	**0.20**

It is seen that LA-HG1(L) exhibits the highest thixotropic paroperties. The greater T value, the more energy must be expended to destroy the structure of the hydrogels and, consequently, the stronger is the structure of the hydrogels.

It should be noted that the pseudoplasticity (shear-thinning), the presence of a yield stress and thixotropic properties are desirable for soft drug formulations and cosmetic products [33-36].

CONCLUSION

In this work, the deformation properties of silica hydrogels materials under compression, tension and shear were studied. The regularities of influence of sol-gel synthesis conditions (concentration of the catalyst of silica sol formation, drug loading) on the deformation properties were revealed. The study showed that, in terms of the deformation properties, the silica hydrogels are promising platform for development of new soft drug formulations and cosmetic compositions. The synthesized hydrogels possess a certain elasticity under uniaxial compression, exhibit pseudoplasticity, thixotropy. These properties are desirable for soft drug formulations because they affect the ease and safety of administration of the products, the duration and efficiency of their functioning. They are important for the manufacture processes of the indicated products.

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The authors declare the absence a conflict of interest warranting disclosure in this article.

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