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DEHYDRATED FILMS OF PROTEIN SOLUTIONS: STRUCTURAL PROPERTIES

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In this paper, the formation of various characteristic dissipative structures in the films of aqueous and aqueous-salt solutions of albumin protein in dehydration processes is considered. It has been shown that a number of parameters for conducting experiments on solution dehydration affect the shape and spatial distribution of two-dimensional structural formations in films of protein solutions. A conclusion was drawn on the importance of the structural self-organization of films in the process of their dehydration.

Keywords: self-organization process, dissipative structure, protein film

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СТРУКТУРНЫЕ СВОЙСТВА ДЕГИДРАТИРОВАННЫХ ПЛЕНОК БЕЛКОВЫХ РАСТВОРОВ

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В данной работе рассмотрено образование различных характерных диссипативных структур в пленках водного и водно-солевого растворов белка альбумина в процессах дегидратации. Показано, что условия проведения экспериментов по дегидратации растворов влияет на форму и пространственное распределение двумерных структурных образований в пленках растворов белков. Сделан вывод о значении структурной самоорганизации пленок в процессе их дегидратации.

Ключевые слова: процесс самоорганизации, диссипативная структура, белковая пленка

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Introduction

The properties of films formed upon dehydration of protein solutions or their fragments (peptides) are currently the focus of much attention. Such materials are used in physics, chemistry, biology, medicine, as well as in electronics and nanotechnologies [1–8]. The conditions for rapid phase transition of substances during dehydration are far from equilibrium; according to classical theory, this should be accompanied by self-assembly and by appearance of ordered spatial structures.

These processes can occur, for example, during dehydration of aqueous solutions of proteins [9–11]. Understanding the mechanisms of protein folding is the key to studying self-assembly processes in biological films [9]. A peculiar ordered morphological structure is observed as water evaporates from protein films [9]. Such evaporated film is an interesting subject as a natural model of a self-organizing system with a rich set of variables affecting the process, depending on its composition, substrate properties, and external conditions [10, 12].

Dehydrated films of biological fluids are commonly used in medical diagnostics, obtained by wedge-shaped dehydration. There is a well-known correlation between the parameters of the structures formed in self-organized films of biofluids and different types of pathologies [13, 14]. Different experimental factors affect the physical component of self-assembly processes in protein films.

To correctly interpret the structures formed in complex biological fluids, we considered aqueous solutions of egg albumin (ovalbumin) with different experimental conditions, analyzing the effect of different dehydration parameters on formation of structures in ovalbumin films.

Description of self-assembly processes

From the standpoint of molecular biology, protein folding occurs during self-assembly, i.e., with the tertiary structure (three-dimensional conformation) evolving in accordance with structural information encoded in the primary structure (sequence of amino acid residues). Physically speaking, self-assembly means that macroscopically ordered spatio-temporal structures form in complex nonlinear systems [15]. Physical and chemical aspects of self-assembly of proteins are described in detail in [16].

Self-assembly processes can only occur in systems with a high level of complexity and a large number of elements. There are several approaches to describing and interpreting the physical nature of these processes. For example, Prigogine offered an approach determining the entropy of open systems [17], while Rudenko formulated an approach from the standpoint of evolutionary catalysis [18]. While both of these approaches are identical in estimating the anti-entropic nature of self-assembly, they differ greatly in interpreting the conditions, causes and driving forces of self-assembly, explaining its mechanisms and establishing its measure. These approaches are close in choice of characteristics of an open system for describing its self-assembly and estimating its measure. However, dissipative flow is considered in the first case and that of internal useful work in the second. In other words, dissipation and its functions serve as measures of self-assembly in the first approach, and internal useful work and its functions do so in the second. The difference between these approaches, the benefits and drawbacks found by comparing them are described in monograph [19].

Study of self-assembly processes should include unstable states of systems and conditions of phase transitions accompanied by diffusion and dissipation of energy. Mathematical modeling, for example, the framework of differential equations, is used to describe these processes [20, 21]. Probability theory combined with computer simulation is used for analyzing processes with a small number of molecules.

Self-assembly during protein folding is described using methods of physical chemistry and optics, i.e., considering the interaction of matter with light in the entire wavelength range: from X-rays to radio waves. Self-assembly of proteins after destruction of their tertiary structure (renaturation) and their structural formation are of particular interest for such fields as drug design, molecular bioelectronics, including biomolecular robotics, and nanotechnology [9, 22].

There are a number of techniques for studying self-assembly processes. X-ray diffraction provides direct information about the arrangement of atoms in molecular crystals. This method was used to describe the structure of some vitamins and also to discover denaturation of protein molecules. Structural formation of proteins at the molecular level is studied by this method. This allows to detect lattices with long-range order with strong covalent chemical bonds [23]. X-ray

diffraction methods are not quite satisfactory for describing systems without long-range order.

Synchrotron radiation is a very promising method for studying biological processes associated with conformational and other structural transformations at molecular and supramolecular levels [20]. The electric field affects a wide range of processes, for example, phase transitions in substances, reducing the evaporation heat of water and increasing the heat transfer rate in liquids. The electric field induces conformational transformation of spiral single-stranded polynucleotide in the solution into clusters, where the degree of transition is a linear function of field strength [24].

Optical methods make it possible to observe the progress of biological processes in real time virtually without interfering with them.

Experimental procedure

The simplest and most accessible method for studying self-assembly is visual (or hardware-based) monitoring of dynamics of protein condensation and its phase transitions under nonequilibrium conditions: in an open protein-water system, far from thermodynamic equilibrium. This technique consists in evaporating water from a colloidal protein-water system (dehydration) with subsequent dynamic visualization of protein condensation and self-assembly under equilibrium and nonequilibrium conditions *in vitro*. Different types of colloidal protein-water systems (with albumin or thrombin) are placed on a solid wetted substrate (glass) and dried in an open system at room temperature and atmospheric pressure. The dynamics of the process is recorded with an optical microscope and a sensitive CCD camera.

Certain reproducible structures form through self-assembly in drying films of aqueous protein solutions. Depending on the chemical composition of the solution of a particular protein and on experimental conditions, these structures can take a variety of shapes and volumes. It was found in [9] that there are two main types of structures: spirals and dendrites. Fig. 1 shows these types of structures.

The next section describes the procedure for obtaining these structures and the results of experimental studies.

Experimental studies

These studies were aimed at analyzing the effect that experimental conditions have on formation of different structures in ovalbumin films. We considered the following factors:

initial volume of solution;
protein concentration in solution;
presence of salt;
acidity of solution.

Ovalbumin with an initial concentration of 20 wt% was selected for the experiments. Next, different samples were prepared in accordance with the experimental design. Liquid samples with a volume of 1, 2, 3, and 4 ml were placed in glass Petri dishes 28 mm in diameter and subjected to dehydration for 48 h at a temperature of 36.6 °C and a humidity of 20%. The temperature selected corresponded to the temperature of the human body under normal conditions. The degree of acidity of the solutions was changed by adding 99% acetic acid to the solution.

Eight measurements were performed for each experimental set. Images of the films with a resolution of 896 × 684 pixels were recorded with an optical microscope and a USB camera connected to it.

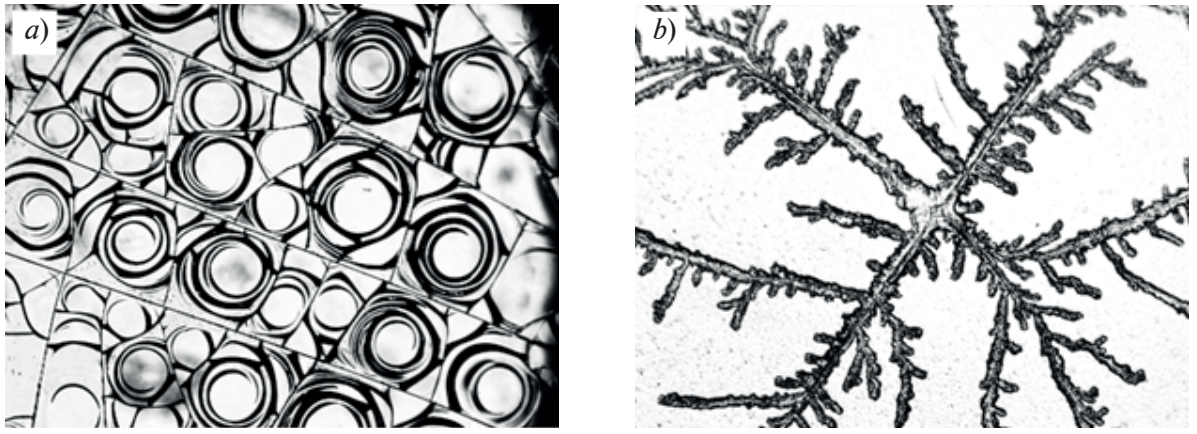

Fig. 1 [9]. Dissipative structures found in dehydrated film of ovalbumin protein: spirals (*a)*; dendrites (*b)*

Transparent protein films formed in Petri dishes as the samples dried. Structures varying in type, shape and size formed In some films, depending on their composition and experimental conditions. The structures were found in separate areas of the Petri dish rather than over its entire surface (Fig. 2). A small spot containing cracks formed in the protein film in the center of the Petri dish (region *3*).

A ring of spiral structures located on polygonal fragments of the film, separated by cracks, formed closer to the edge of the dish (region *2*). Film fragments in this ring had a smaller total area than in the central region. Hemispherical cracks with elongated branch-like structures were observed at the edge of the Petri dish (region *1*).

The reason for this localization was that the colloidal phase (particles) were driven to the periphery as water evaporated.

Dependence of the structures on protein concentration. We considered the structures forming in albumin films depending on the protein concentration both in the initial aqueous solution and in the sodium chloride (NaCl) solution. We used 3 ml samples with different protein concentrations in the solution (wt%): 2.5; 5.0; 10 and 20. The experimental results obtained are shown in Fig. 3. Evidently, the higher the initial protein concentration in aqueous solution given a constant volume, the denser the spiral structures in the protein film. The average geometric dimensions of the spirals and the cells were obtained by calibrating the microscope chamber. The outer circumference and area for spiral structures were approximately 180 μm and 2500 μm^2, respectively. The circumference and area of the cells were about 200 μm and 5000 μm^2.

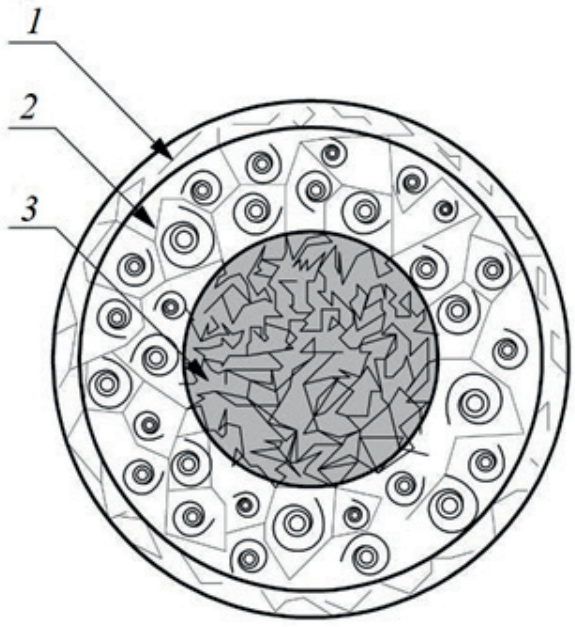

Fig. 2. Schematic of Petri dish with dried egg albumin sample showing different regions of film: dish edge *1* with salt residue; region *2* with spiral structures and cracks; central region *3* with cracks

We also analyzed the structures forming in ovalbumin films depending on protein concentration in dry film. Because protein concentration in the film could not be measured or changed, the samples in these experiments were selected by the initial volume of the aqueous solution. A 20% solution was chosen for the experiment. Solutions of 1, 2, 3, and 4 ml were then placed in Petri dishes and subjected to dehydration for 48 h. The experimental results obtained are shown in Fig. 4.

To assess the nature of film structuring, we calculated the approximate number of structures formed (in one spiral) in the photograph of the film. Fig. 5 illustrates this calculation.

It follows from the data in Figs. 4 and 5 that the larger the initial volume of the solution, the more structures form in protein film and the larger they are. A possible reason for this is that protein concentration in dry film is higher with a larger volume of the initial solution.

Dependence of the structures on solution acidity. We prepared aqueous solutions of albumin with different pH values. Acetic acid was added to the protein solution to obtain a certain degree of acidity. The same as in the previous experiment, 3 ml samples were taken. Fig. 6 shows photographs of ovalbumin films with different pH and similar aqueous solutions.

It follows from the data in Fig. 6 that the closer the pH of the initial solution to 4.8, the less structures are formed in albumin film. Additionally, if the pH of the solution abruptly shifts from 4.8 towards acidic or alkaline values, the structures take the shape of incorrectly formed spirals. Notably, pH = 4.8 is the isoelectric point of the protein (the pH value at which the total charge of the protein molecules is zero).

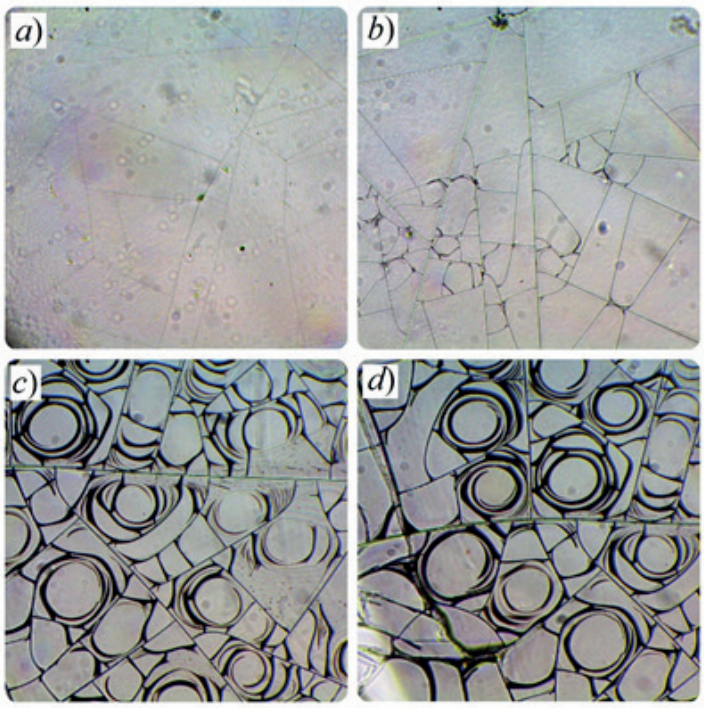

Fig. 3. Structural changes in ovalbumin films depending on ovalbumin concentration in aqueous solution (wt%): 2.5 (*a*), 5.0 (*b*), 10 (*c*) and 20 (*d*)

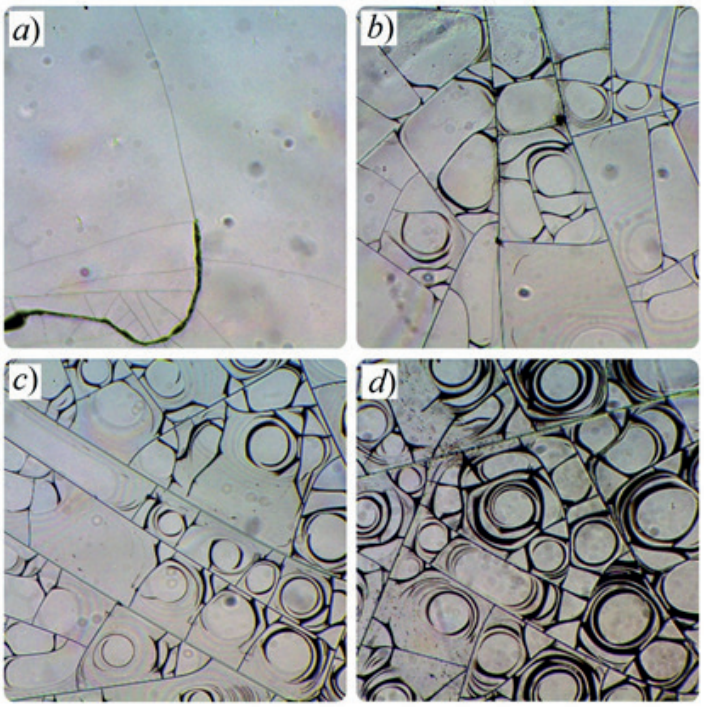

Fig. 4. Structural changes in ovalbumin films depending on volume of initial 20% aqueous solution, ml: 1 (*a*); 2 (*b*), 3 (*c*), 4 (*d*)

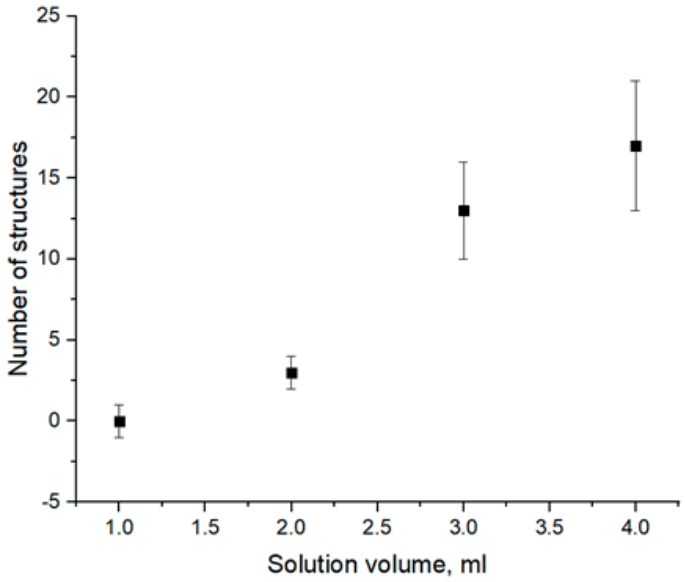

Fig. 5. Number of structures formed in ovalbumin film depending on volume of initial 20% aqueous solution

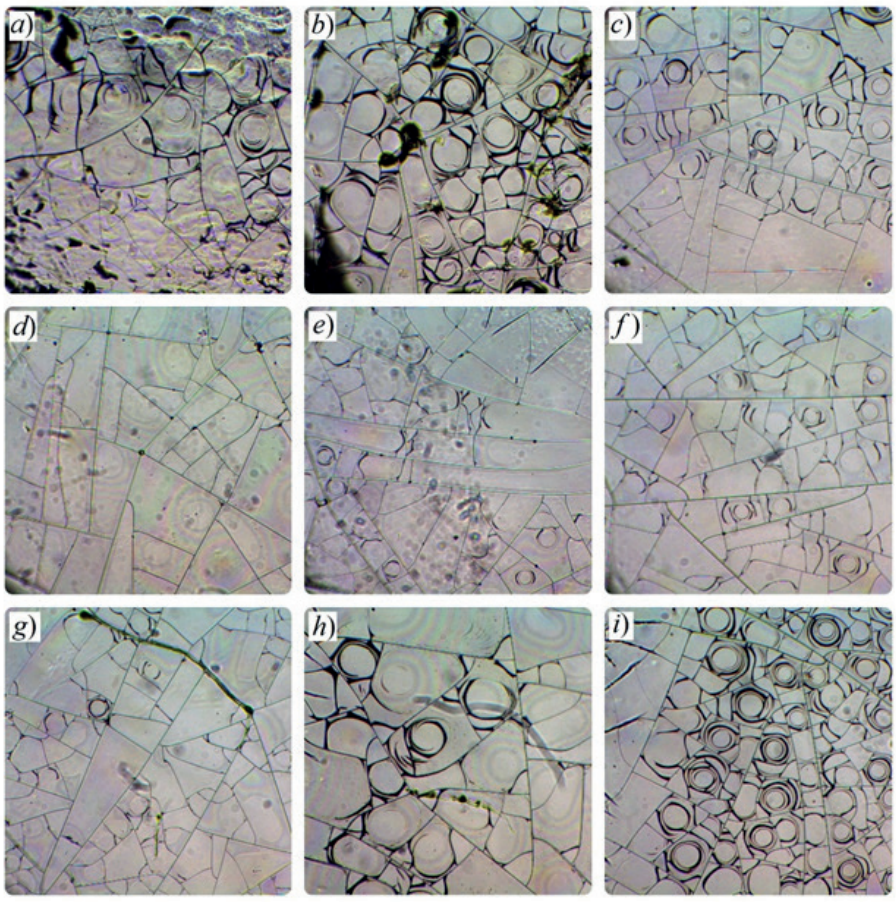

Fig. 6. Structural changes in ovalbumin films depending on pH value of initial aqueous solution: 3.0 (*a*), 4.2 (*b*), 4.4 (*c*), 4.8 (*d*) 5.2 (*e*), 5.8 (*f*), 6.2 (*g*), 7.0 (*h*), 7.8 (*i*)

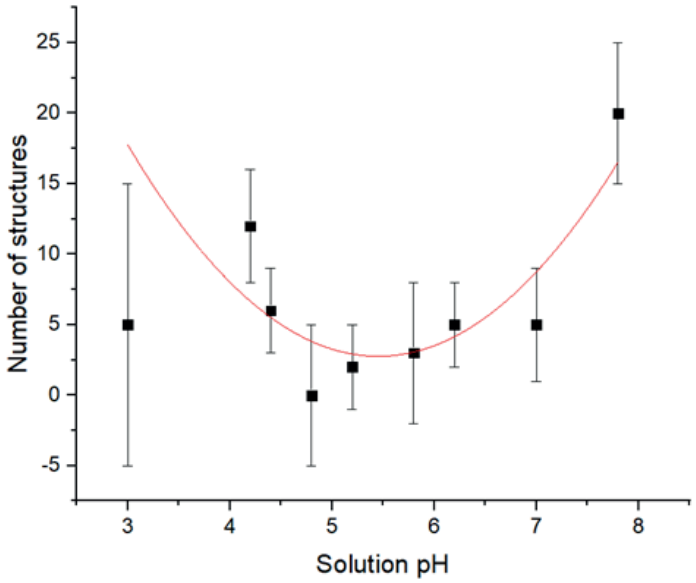

Fig. 7. Number of structures in ovalbumin films depending on pH of initial aqueous solution

Fig. 7 shows the number of structures formed, i.e., the number of structures per unit area, depending on the pH of the initial solution.

It can be seen from Fig. 7 that a large number of structures form if the acidity of the initial solution ranges from 7.0 to 7.8. The same thing happens with pH ranging from 3.0 to 4.4. There are no structures with pH = 4.8. Most likely, structures cannot form near the isoelectric point due to absence of uncompensated charge. We can then conclude that protein's ability to form structures in dehydrated film is directly related to charge of the protein molecule. Even though errors extend beyond the trend, we decided to preserve this line, since this graph shows only measurement errors and does account for the specifics of producing an aqueous protein solution and performing dehydration.

Presence of salts in solution. In addition to films obtained from purely aqueous solutions, we considered structures forming in ovalbumin films from a solution containing NaCl. For this purpose, we prepared protein solutions with different concentrations where an aqueous NaCl solution with a concentration of 0.9% (0.15 M) served as solvent. Experimental samples of 3 ml were dehydrated for 8 h. The experimental results are shown in Fig. 8.

Unlike the structures forming in films prepared from aqueous solution, so-called tree-like structures formed in films prepared from water-salt solution. The higher the concentration of NaCl in the initial solution, the denser the branches. The structure of the 'trees' is disrupted with a very low protein concentration, and a dense field of crystals is formed. The structures shown in Fig. 9 are two-dimensional self-affine fractals. The main property of such structures is invariance after a simultaneous but quantitatively different change in distance along different directions in space. In other words, in contrast to a simple fractal, self-affine fractals cannot be obtained by simple stretching of self-replicating fractals, since the ratios of stretching in different directions should depend on size [26].

However, if protein concentration in the initial water-salt solutions is progressively reduced, fractal structures of a different type form. Examples of such structures are shown in Fig. 9. Evidently, as protein concentration decreases, structures become more and more branched. Fig. 9,*b* shows a NaCl crystal surrounded by fine structures. We used the Witten–Sander model to interpret the results obtained. According to this model, particles are added one after another to a growing cluster. The aggregation process is induced by a fixed initial particle in the original version. The aggregate then keeps growing [26]. The structures shown in Fig. 8 are Witten–Sander aggregates.

Results and discussion

We examined some features of the structures forming in ovalbumin films upon dehydration self-assembly. We confirmed experimentally that two types of film predominantly form as a result of dehydration and accompanying self-assembly of protein solutions. We analyzed how different factors affect the structures forming: acidity of protein solution, presence of NaCl in the solution, protein concentration, and initial volume of aqueous solution. The experiments showed that all of the above conditions influence the structuring of the 'spirals'. As a whole, the nature of protein self-assembly depends on general physicochemical properties of polymer biomacromolecules [16]. However, mechanisms of interaction of protein with water have to be understood to take into account all aspects of the studies conducted.

The protein chain is polar like water and also has total zero charge. Some side groups are also partially charged. Charged amino acid residues are even more polar. Both the peptide groups of the main chain and the polar side groups act as donors and acceptors of hydrogen bonds. They can form bonds with each other or with water molecules; almost all of them create such bonds, since the typical energy of hydrogen bonds is 5 kcal/mol, which is significantly higher than the energy of thermal motion.

If the intramolecular bond between the donor and the acceptor of the hydrogen bond in protein forms in an aqueous medium, it replaces two hydrogen bonds of the protein with water molecules, with a bond simultaneously created between the molecules of the water released.

From a thermodynamic standpoint, the energy balance of the given reaction is close to zero, since the number of hydrogen bonds has not changed [16]. However, the entropy of water generally increases, since water is no longer bound to the protein chain, and molecules with an H-bond can move freely.

Let us consider the so-called hydrophobic effect. Proteins contain many amino acids with hydrocarbon side groups that form the hydrophobic core of the protein globule. The hydrophobic effect plays a crucial role in maintaining the stability of the protein structure, serving to transform the protein chain into a compact dense globule. The effects opposite to 'hardening' are associated with entropy of rotations and displacements of molecules in liquid. This is because each molecule in a liquid moves more or less freely, while it is restrained by the crystal lattice in a solid. As a matter of fact, the entropy of displacements of a molecule does not depend on its size, in contrast to the enthalpy that grows with increasing number of contacts of the molecule

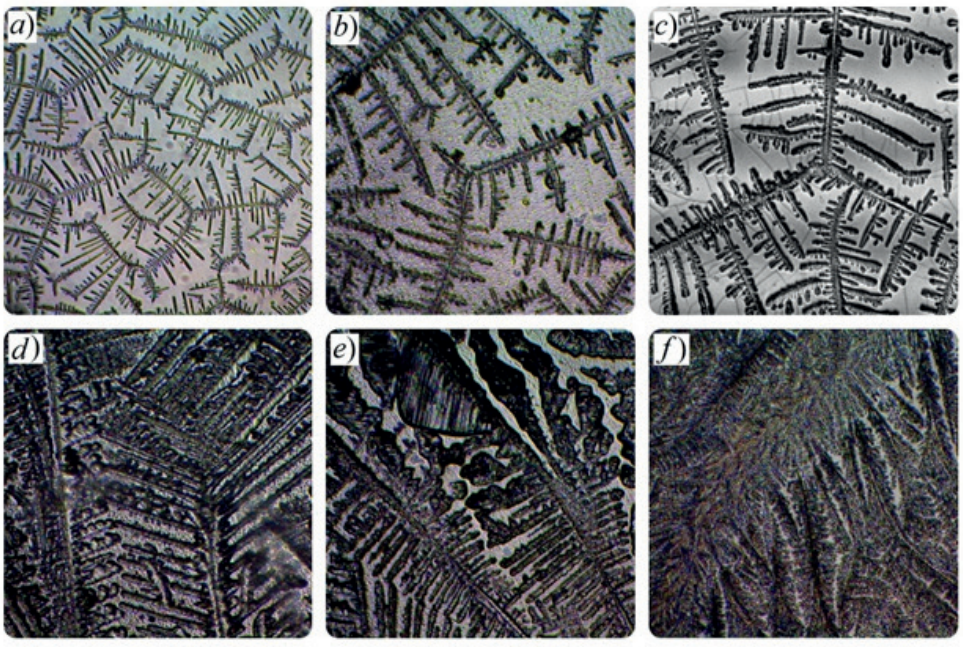

Fig. 8. Changes in dendritic structures in ovalbumin films depending on protein concentration, %: 10 (*a*), 5 (*b*), 2.5 (*c*), 1.0 (*d*), 0.5 (*e*), 0.1 (*f*).
Films were obtained from water-salt solutions (0.1 M NaCl)

Fig. 9. Changes in dendritic structures in ovalbumin films depending on protein concentration c_p in initial water-salt solutions (0.15 M NaCl); c_p = 0.05% (*a*), 0.02% (*b*), 0.01% (*c*)

with the others. Displacement entropy plays a smaller role in the protein chain, since amino acid residues are linked by a chain, that is, they cannot move independently of each other, making the protein 'harden'.

The hydrophobic effect accounts for 90% of the process in which a protein globule is created. But it cannot produce its own 'solid' protein, generating only a liquid protein globule. Accordingly, we can conclude that aqueous protein solutions should serve as a basis for studying self-assembly of proteins *in vitro*. However, protein concentration should be maintained in a certain range to achieve proper self-assembly [16].

As already established (and confirmed by our experiments), the water content affects the structure of proteins, and the structure is in turn responsible for the functionality of the protein. Thus, if concentration of proteins in aqueous solutions has a known effect on the formation of structures during dehydration, it is possible to estimate the functionality of proteins during dehydration of complex biological fluids in medical diagnostics.

Conclusion

We have carried out experimental studies aimed at understanding how the sizes and shapes of structures in protein films depend on experimental conditions.

Analyzing the results of the experiments conducted, we have reached the following conclusions.

Acidity of the initial solution and the concentration of protein in the solution significantly affected the formation of spiral structures.

We have found that acidity considerably different from the isoelectric point of ovalbumin, neither critically acidic nor alkaline, was required to obtain stable structures in ovalbumin films. The required pH of the solution was less than 3.0 or greater than 8.0.

We determined the specific values of the parameters in experimental conditions. For example, dense structures could form with a sufficiently large volume of the initial solution: 3-4 ml for a Petri dish of 28 mm, i.e., with film thickness in liquid phase at least 4–5 mm.

Notably, self-assembly processes can occur in samples with the smallest volume. However, it is extremely difficult to detect dissipative structures in such samples.

We plan to carry out further quantitative studies of the structures formed in protein films, including by varying the pH value of salt solutions, measuring the geometric parameters of structures, determining whether these parameters correspond to experimental conditions for self-assembly during dehydration.

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