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STABILIZATION OF PHYSIOLOGICAL SALINE SOLUTIONS FOR INJECTION BY LOW-FREQUENCY ACOUSTIC TREATMENT

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A B S T R A C T

Despite the large range of ready-made medicines, the extemporal formulation has not lost its significance. One of the most significant extemporal dosage forms in providing, including emergency medical care, is solutions for injection, which have technological features of manufacturing. The article presents the results of a study of the main properties of water during low-frequency acoustic treatment for the preparation of stable saline solutions. Methods of stabilization of solutions for injection were studied. The effect of low-frequency acoustic treatment on the physical and chemical properties of osmotic water has been experimentally confirmed. Using computed quantum and chemical modeling, the most probable forms of water nanoclusters formed during low-frequency acoustic treatment are determined. Prospects of using the low-frequency acoustic treatment in the Pharmaceutical Industry and pharmacies to stabilize saline solutions for injection are shown. Further research will be related to the treatment of real physiological solutions of drugs with different molecular weights.

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Introduction

Despite the large range of ready-made medicines, the extemporal formulation has not lost its significance [1]. This is due to the lack of industrial analogs for some medicines and unavailability of taking into account the individual characteristics of the patient such as body weight, the severity of the disease, and allergic reactions, etc. [2, 3].

One of the most significant extemporal dosage forms in providing, including emergency medical care, is solutions for injection, which have technological features of manufacturing. The advantage of solutions for injection as dosage forms is their high bioavailability, the accuracy of dosing, and the possibility of manufacturing in the form of an intra-apical billet [4, 5].

Despite the extensive range of injectable solutions produced at pharmaceutical enterprises, injectable solutions made in pharmacies are still in demand. [1, 6-10] The main reasons for demand are:

- lack of industrial analogs
- lower cost compared to analogs produced at pharmaceutical enterprises
- possibility of manufacturing a dosage form of a given volume

However, there is also a serious disadvantage of using injectable solutions – they need stabilization [5, 11].

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The stability of drugs means their ability to maintain the physical and chemical properties and pharmacological activity required by the Pharmacopoeia or technical documentation for a certain period of storage [12-14].
The study of stabilization of injectable solutions is an important technological task since about 90 % of medicinal substances require the use of stabilizers or special preparation conditions [15]. This is because solutions of medicinal substances undergo various changes during thermal sterilization. They can be caused by hydrolysis, oxidation-reduction, decarboxylation, polymerization, photochemical degradation, etc. [16-18, 30, 33].
To increase the stability of dosage forms for injection, stabilization is used by physical, chemical, and complex methods [19, 32, 34]. From the point of view of environmental friendliness and inertia, physical methods are the most promising [20-22, 31, 35].
Currently, the following physical methods are widely used:

- boiling water followed by rapid cooling;
- saturation of water for injection with carbon dioxide or inert gases;
- recrystallization of origin substances;
- adsorbents application.

Pharmacies usually use the first method. Using boiling and rapid cooling method the content of free oxygen in water decreases from 9 to 1.4 mg/l, which significantly reduces the intensity of redox processes in solutions, ensuring their stability [23, 24, 36]. The disadvantage of this method is the high energy consumption and duration of the process.
The method of saturating water for injection with carbon dioxide or inert gases is more effective than the boiling/cooling method since water saturated with these gases contains less oxygen than boiled water (0.18 mg/l). However, it is technically a more complicated method and requires special equipment [25, 26].
The method of recrystallization of origin substances is used to remove their impurities. It is advisable to use it for the purification of hexamethylenetetramine if the drug contains impurities of amines, ammonium salts, and para forms and does not meet the requirement "suitable for injection" [27].
Impurities contained in medicals can also be removed by adsorption from solutions of medicinal substances. Usually activated carbon grade A is used as an adsorbent. It serves as an adsorbent not only for low-molecular chemical impurities (for example calcium oxalate in calcium lactate) but also for high-molecular compounds, e.g. pyrogenic mixtures of polylipoproteins and lipopolysaccharides [28].
Thus, the main directional effect of physical methods for stabilizing physiological solutions for injection is to reduce the redox potential and active acidity. At the same time, other physical and chemical properties of water also change, which contribute to its structuring, formation of nanoclusters, and, consequently, stabilization.
Our preliminary research has shown that acoustic effects in the infrasound range can have a similar effect on water. In this regard, the purpose of this work was to study the effect of low-frequency acoustic treatment on the physical and chemical parameters of water.

Materials and Methods

Experimental studies were carried out on samples of osmotic water using an innovative acoustic water treatment equipment "ERADA" provided by "Soil Respiration" Ltd. (Stavropol, Russia). This company is engaged in the treatment of drinking water and acoustic stimulation of the growth of native soil microflora for better germination of crop seeds. The technology is developed by the company, and the processing parameters are "know-how", so it was decided not to disclose the parameters of the equipment and the radiation frequency.
The effect of infrasound radiation on the physical and chemical properties of water and its structure was studied in the laboratories of North Caucasus Federal University and Stavropol State Agrarian University. Samples of osmotic water treated with acoustic exposure from 0 to 60 minutes in 15-minute increments were examined.
Reagent grade chemicals and grade A glassware were used in the present study. The conductivity of distilled water used was less than 1 μS/cm.

pH determination
The active acidity of water was measured at room temperature using a pH meter-ionomer "Expert 001" with measurement accuracy ±0.05 (Avtomatika TH, Smolensk, Russia).

RedOx potential determination
The RedOx potential was measured at room temperature using a pH meter-ionomer "Expert 001" using an ERP-105 electrode with measurement accuracy ±0.01 mV (Avtomatika TH, Smolensk, Russia).

Investigation of specific electrical conductivity of water
The specific electrical conductivity was measured at room temperature with conductometer "Expert 002" with measurement accuracy ±0.1 μs/m (Automatika TH, Smolensk, Russia).

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Measurement of the freezing point of water

The freezing temperature of samples was measured using an automatic cryoscope (Cryostar GmbH., Germany) with measurement accuracy ±0.0001 °C.

Measurement of the boiling point of water

The boiling point of the samples was measured using an induction furnace and a laboratory thermocouple TL-2 (Altavir LLC, Belgorod, Russia) with measurement accuracy ±0.05 °C

Computed quantum and chemical modeling of water

Quantum and chemical modeling were performed in the QChem program using the IQmol molecular editor. The simulation parameters were selected according to the method of Blinov et al. (2019) [29]: Energy mode – HF (Hartree-Fock), basis – 6-31G, convergence – 5, force field – Ghemical.

Results and Discussion

When studying water samples after low-frequency acoustic treatment, nonlinear dependences were obtained that confirm the reliable effect of treatment on the physical and chemical properties of water.

Results of the obtained pH of samples are shown in **Figure 1.**

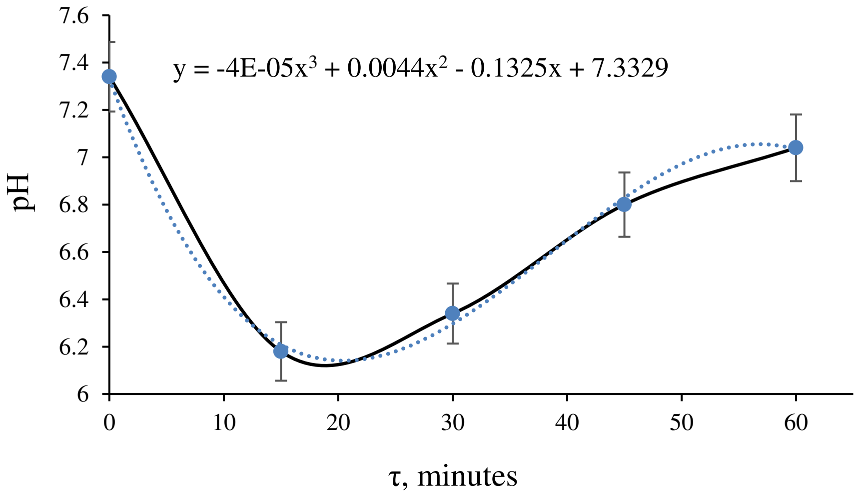


Figure 1. Dependence of the pH of osmotic water samples on the acoustic treatment duration

In the analysis of **Figure 1** data found that the most significant change of the active acidity observed in the 30-minute acoustic treatment, which is associated with an increase in the concentration of hydrogen ions [H+] and intensification of the process of dissociation of water molecules under the action of acoustic treatment.

Figure 2 shows the result of the RedOx measurement.

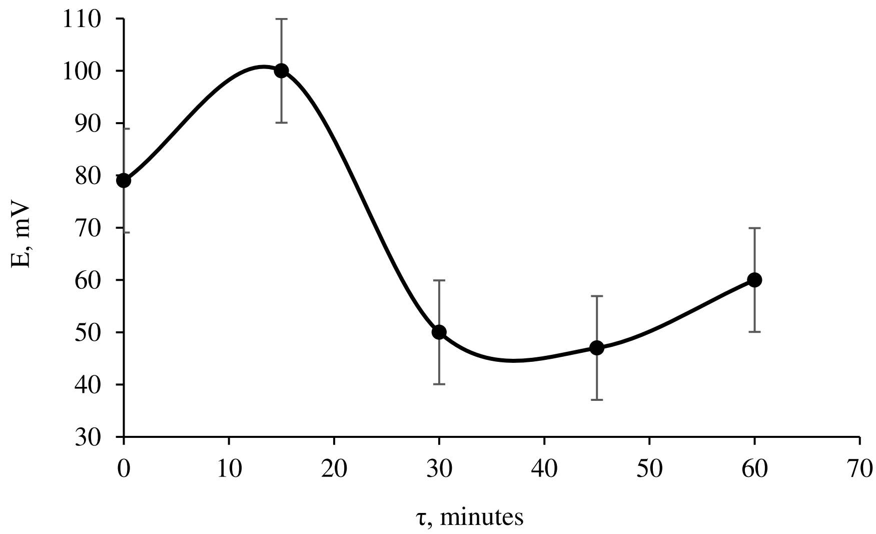


Figure 2. Dependence of the RedOx potential in samples of osmotic water on the acoustic treatment duration

Figure 2 shows that the greatest changes in the RedOx potential observed at a 30-minute acoustic treatment, which is associated with an increase in the concentration of particles (water molecules or clusters) with antioxidant properties that appear under the influence of acoustic treatment of water.

The dependence of specific electrical conductivity in samples of osmotic water on the time of acoustic treatment is shown in **Figure 3.**

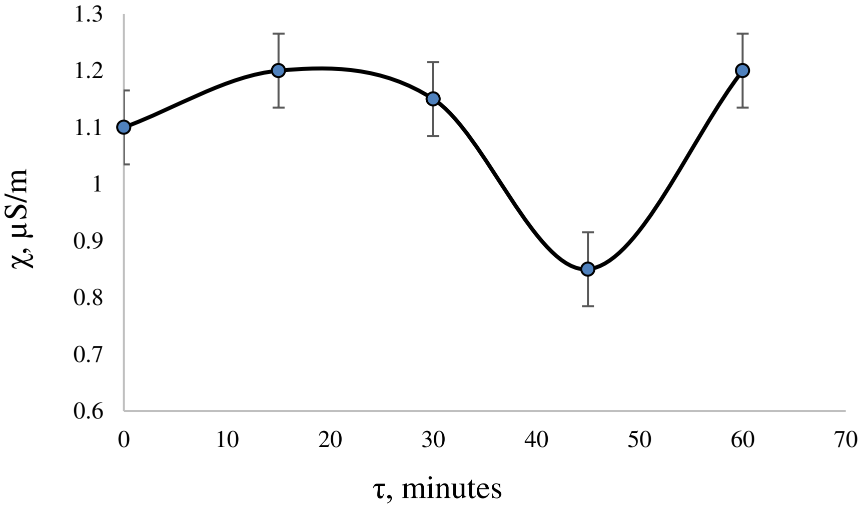


Figure 3. Dependence of specific electrical conductivity in samples of osmotic water on the acoustic treatment duration

Analysis of **Figure 3** data revealed that the greatest changes in the electrical conductivity are observed at the 30-minute acoustic treatment, which is associated with an increase in the concentration of charged pre dissolving particles (molecules or water clusters) formed by the action of acoustic treatment of samples.

The obtained dependences of the freezing point of the experimental samples are shown in **Figure 4**. The dependence of the boiling point of osmotic water on the time of acoustic treatment is shown in **Figure 5.**

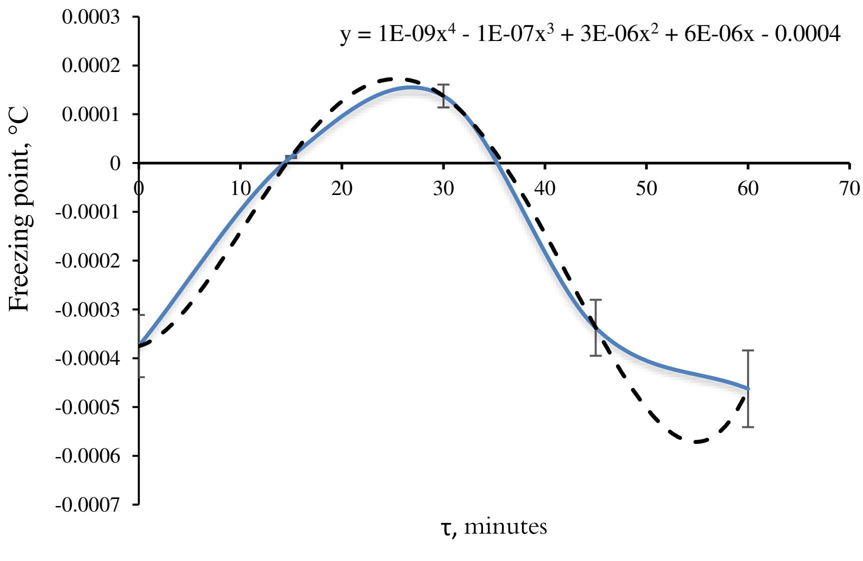


Figure 4. Dependence of the osmotic water freezing point on the acoustic treatment duration

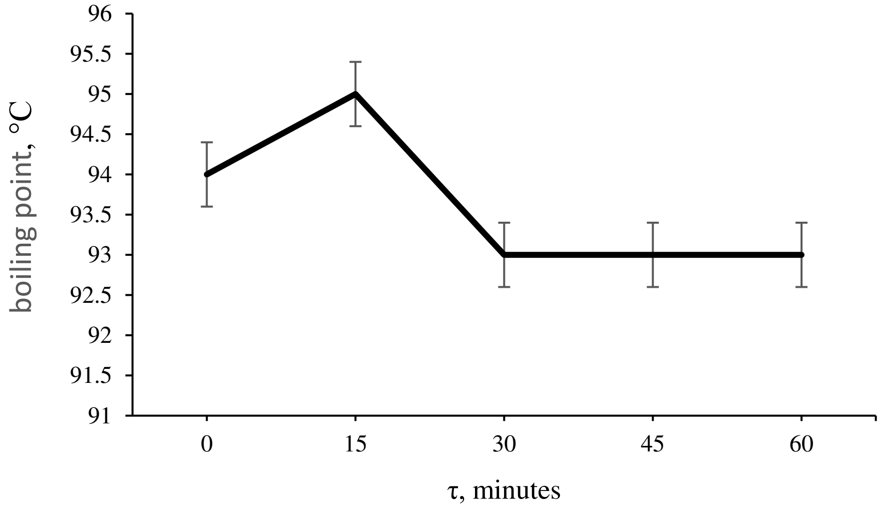


Figure 5. Dependence of the boiling point of osmotic water on the acoustic treatment duration

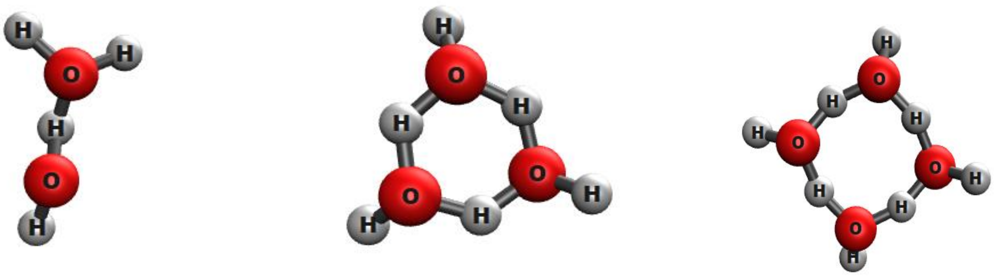
Analysis of **Figure 5** data showed that the greatest temperature change of boiling and freezing is observed at 15 – 30 minute acoustic treatment, which also correlates with previous results and, apparently, due to the increase in the number of particles and supramolecular structures (clusters or aggregates of water), destruction of which in the process of evaporation and freezing requires a lot of energy.

According to the data obtained, it was found that during acoustic processing, clusters and supramolecular formations of water molecules are formed, reaching maximum values at 15-30 minutes. In this regard, computed quantum-chemical modeling of water nanoclusters that are most likely to be formed during low-frequency acoustic treatment was performed based on the analysis of the energy characteristics of water clusters (**Table 1**).

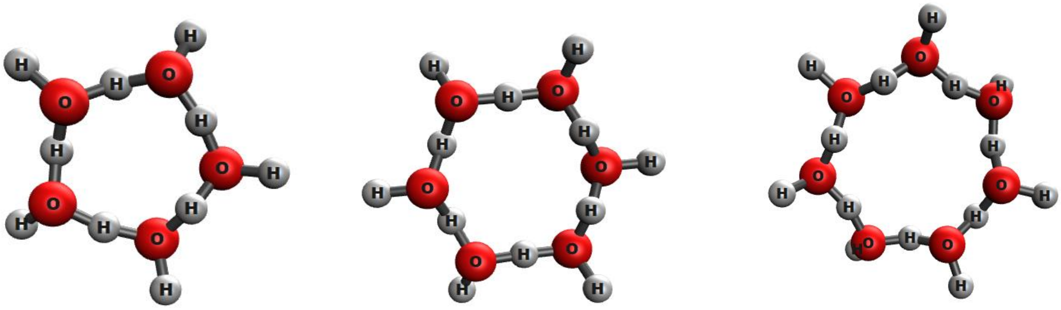
Table 1. Results of the study of energy characteristics of water clusters forming under low-frequency acoustic treatment

Cluster	Chemical energy, kJ/mol
Monomer	0,0000
Dimer	-65,8672
Trimer	-351,3552
Tetramer	-85,8265
Pentamer	-179,0214
Gexamer	-241,9691
Geptamer	-290,5196

Constructed models are represented in **Figure 6.**



a) b) c)



d) e) f)

Figure 6. 3D models of nanocluster of treated water.
a) dimer, b) trimer, c) tetramer,d) pentamer, e) gexamer, f) geptamer

As a result of computer quantum-chemical modeling, possible models of water clusters are shown and it is revealed that water clusters are stable formations from the energy point of view.

Conclusion

The experiment showed that low-frequency acoustic treatment of osmotic water helps to stabilize its pH and RedOx. The water structure changes during processing, forming stable nanoclusters and submolecular formations, the chemical binding energy of which is calculated by computer quantum chemical modeling. The results showed that an innovative method of low-frequency acoustic water treatment can be used to stabilize physiological solutions for injection. Further research will be related to the treatment of real physiological solutions of drugs with different molecular weights.

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