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MATHEMATICAL SUBSTANTIATION OF THE TECHNOLOGY OF CREATING A PHARMACEUTICAL COMPOSITION IN THE FORM OF CRYOGEL

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ABSTRACT

The comprehensive study of cryogels is of both theoretical and practical interest. They can serve as a new promising material in pharmacy for the production of new drugs. Cryotropic polymer structures based on polyvinyl alcohol are interesting. This is due to the good mechanical, thermophysical properties of polyvinyl alcohol, the availability of the polymer, non-toxicity, biocompatibility, as well as the relatively simple, cheap method of forming cryotropic polymer structures. This determines the relevance of this study to mathematically substantiate the technology of creating a pharmaceutical composition in the form of cryogel. During the research, substances were used to obtain cryogel - polyvinyl alcohol, propylene glycol, glycerin, polyethylene oxide-400. In the course of the research mathematical methods of research were used, and also the method of crosslinking of a polymeric solution - cryoshewing (a freezing method) is offered. The article presents the results of mathematical calculations of substantiation of the technology of obtaining a pharmaceutical composition in the form of a cryogel based on a polymer of polyvinyl alcohol. The author investigated the indicators of cryogel production, researched the production of crosslinked (physical method) cryogel based on polyvinyl alcohol polymer.

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Introduction

Modern medicine and pharmacy are interested in cryotropic polymer structures both scientifically and appliedly [1]. Of particular interest are cryotropic polymer structures based on polyvinyl alcohol (PVA). This is due to the good mechanical, thermophysical properties of PVA, polymer availability, non-toxicity, biocompatibility, as well as the relatively simple, cheap method of forming cryotropic polymer structures [2-4].

Cryotropic polymeric structures are new perspective material in pharmacy for receiving new medicines and in medicine for the treatment of a certain number of diseases [5-10].

Cryogel is a supermacroporous hydrogel, is formed at subzero temperature by polymerization of monomers or cryogelation of oligomers without the use of toxic organic solvents and with controlled textural, structural characteristics [11, 12]. Such materials provide necessary surface area sufficient for fastening and proliferation of cells; the improved transfer of oxygen, substances, and removal of products of metabolism [13, 14].

The key parameters that affect the physical properties of hydrogels are [15]:

- Degree and type of stitching. The main way of formation - chemical or physical crosslinking. Chemically crosslinked hydrogel has a large pore size. Physically crosslinked cryogels do not contain unreacted agents that can affect cell viability;
- Composition of the solution. Low-molecular polymers lead to the formation of a big-time, in comparison with solutions of high-molecular polymers. In case of change of concentration of polymer in solution, its higher values lead to the reduction of the average size of a time;
- gelation temperature. At lower temperatures, solvent crystallizes quicker. As a result, the growth of the number of smaller crystals of solvent increases;

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- Freezing speed. The High (low) speed of freezing of water leads to the formation of small (less well-planned) or larger (more well-planned) crystals of ice. At a low speed of freezing, big crystals of ice which can destroy walls of a time, cellular membranes, etc. are formed;
- Cryoconcentration. There is a "pushing out" of solute in a liquid phase, to the gradual reduction of temperature of freezing [16]. It increases bodying speed that does more effective cryotropic gelation under optimal conditions.

Usually, the solution for gelation is cooled up to a temperature between –5 and –25ºC [17]. The formed properties of polymeric matrixes depend on the concentration of monomers, their physical and chemical properties [18], and freezing conditions [19]. Because of that development of this direction of the creation of medicines is reasonable, and in this article, the mathematical calculations proved the technology of receiving pharmaceutical composition in the form of cryogel based on PVA polymer [2-4, 20].

Research Objective
to mathematically prove technology of creation of pharmaceutical composition in the form of cryogel.

Materials and Methods

Cryogel production substances - polyvinyl alcohol, propylene glycol (PG), glycerin (Loba Chemie Pvt. Ltd., Mumbai, India), polyethylene oxide-400 (PEG-400) were used in the research. In the course of the research mathematical methods of research were used, and also the method of crosslinking of a polymeric solution - cryocrosslinking (freezing method) is offered.

Results and Discussion

According to Patent [20], the crosslinking of the polymer occurs due to the physical method of freezing-thawing. The author proved that for polymers of PVA, Na-carboxymethylcellulose at a temperature of -15 - -30 ° C the optimal concentration of polymers is 10%; at a temperature of -15 - -20 ° C - 13%, and a temperature of -10 - -30 ° C - 15%. The method of obtaining cryogel includes the following stages: dissolution of self-structured polymers, freezing at a temperature of -20 ° C, keeping at this temperature for 24 h, then thawing at room temperature for 2-5 h.
Based on these indicators of cryogel production, studies were conducted to obtain crosslinked (physical method) cryogel based on PVA polymer.
To obtain a polymer film, first, dissolve PVA in water, then add a plasticizer (PG, glycerin, PEG-400). We chose PG as a plasticizer. After complete dissolution of PVA in water and addition of PG, the quantitative proportion of PVA in the total solution decreases. Therefore, for research, we obtained samples of PVA solution with PVA concentration from 10% to 20%. For experimental research, we will consider the following indicators: the size of the polymer film is 10 cm, which corresponds to the diameter of the Petri dish, and the film thickness should be from 3 to 4 mm. These characteristics are substantiated in the works of prof. LL Davtyan [6, 21]. For the convenience of calculations, we will choose the average value of the film thickness - 3.5 mm.
First, we need to determine the volume of the solution. The calculated volume of the polymer solution was determined by the formula (1):

$$V = \pi r^2 S \rho \quad (1)$$

where: V – solution volume, g;
r – radius of a cup, cm;
π – constant equal 3,14;
S – thickness of solution, cm;
ρ – specific mass of solution, g/cm^3.

In our Petri dish, the radius of a cup is equal to 5 cm, and film layer thickness is – 0,35 cm. The specific weight of the solution was calculated as the total value of the specific mass of each component concerning the mass of the solution. Considering that polymeric weight consists of water with a specific weight ρ_{aq} = 1 g/cm^3, PG with ρ_{PG} = 1,0363 g/cm^3 and PVA (ρ_{PVA} from 1.019 g/cm^3 to 1.031 g/cm^3), for predesigns value of the specific weight (ρ) us will be accepted for unit: ρ = 1 g/cm^3.
Substituting the corresponding values in formula 1, we calculated solution volume (V), subject to watering on a surface of a Petri dish:

$$V = 3.14 \times 5^2 \times 1.02 \times 0.35 \quad (2)$$

V = 28,83 г
The rated volume of polymeric solution is 28,83 g.

Because polymeric weight consists of PVA and PG solution in the ratio of 70% to 30% respectively, for convenience the rated volume of polymeric solution will be conditionally taken by us for 30 g.

First, we received a PVA solution (20 g) with a concentration from 10% to 20%. The quantitative ratio of PVA (at %) in solution and mass of a volume of solution was calculated by formulas 3 and 4.

$$C=\frac{m}{(M1+M2)}\times 100\% = \frac{m}{(M_{aq}+M_{\mathrm{PVA}})}\times 100\ \% \quad (3)$$

where: C – concentration, %;
m_{PVA} – the mass of PVA, g;
m_{aq} – the mass of water, g;
M – the volume of solution, g.

Mass (g) of the volume of solution was calculated by the formula (4)

$$m_{aq} = M - m_{\mathrm{PVA}} \quad (4)$$

where: M – number of volumes of solution, g;
m – mass of PVA (water), g.

The settlement amount of water and PVA in polymeric solution is given in **Table 1**.

Table 1. A settlement amount of water and PVA in polymeric solution

Components	Concentration PVA, %										
	10	11	12	13	14	15	16	17	18	19	20
	number of components, g										
Water	18,0	17,8	17,6	17,4	17,2	17,0	16,8	16,6	16,4	16,2	16,0
PVA	2,0	2,2	2,4	2,6	2,8	3,0	3,2	3,4	3,6	3,8	4,0

To obtain solutions in the volumetric flask was added the required amount of water (according to the table data) and PVA. The flask was placed in a water bath with a temperature of 70–75 ° C with constant stirring (from 0.5 to 1.5 h) until complete dissolution of PVA. The polymer solution was adjusted to 20 g with purified water. After obtaining a homogeneous mass, the flask was left at room temperature until the solution was cooled for 0.5–1 h. To the resulting mass (20 g) was added 10 g of PG and a polymeric mass with a total mass of 30 g was obtained. Stirred (slowly to avoid the formation of bubbles) for 30 min to obtain a homogeneous mass.

The resulting mass by watering was transferred to a glass surface (Petri dish) with a diameter of 10 cm. Quantity of PVA calculated by the formula (5):

$$C_{\mathrm{PVA}} = \frac{m}{M}100\% \quad (5)$$

where: C_{PVA} – the maintenance of PVA in solution, %;
M – the mass of solution;
m – PVA contents, g.

The quantitative ratio of PVA and water in a Petri dish with a diameter of 10 cm and weighing 30 g is provided in **Table 2**.

Table 2. Estimated concentration of PVA in the polymer solution

Substances	The concentration of substances, %										
	C_{10}	C_{11}	C_{12}	C_{13}	C_{14}	C_{15}	C_{16}	C_{17}	C_{18}	C_{19}	C_{20}
PVA	6,6	7,3	8	8,6	9,3	10	10,6	11,3	12	12,7	13,3
Water	13,3	12,7	12,0	11,3	10,7	10,0	9,3	8,7	8,0	7,3	6,7

After receiving model samples with various concentrations of PVA ($C_{10\%}$ – $C_{20\%}$) we carried out their polymerization. All samples were left at room temperature within 24 hours. During the day polymeric films in process of their drying find a certain form. Samples were removed from a glass surface and dried up with the next weighing.

As in films, there are free water / residual dry matters, films depending on concentration will have different weights **(Table 3)**.

Table 3. Rated mass of samples (n=5; P 95%)

Indicator	Number of samples									
	1	2	3	4	5	6	7	8	9	10
Concentration PVA, %	6,6	7,3	8,0	8,6	9,3	10,0	10,6	11,3	12,0	13,3
Mass	25,22±0,01	25,32 ±0,02	25,36±0,01	25,41±0,02	25,47±0,02	25,52±0,01	25,52±0,01	25,37±0,01	25,24±0,01	25,22±0,01

The analysis of this **Table 3** showed that with the increase in the concentration of PVA the mass of samples increases. However, it should be noted that the linear dependence between the concentration of PVA in a film and the mass of a sample **(Figure 1)** is not observed.

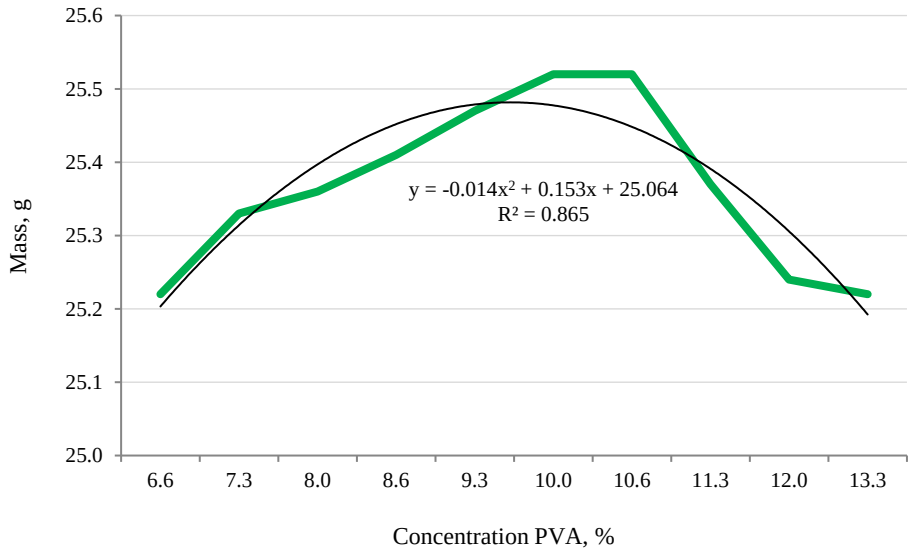

Figure 1. Graphic dependence of weight on the concentration of PVA

The **Figure 1** shows that increase in mass of a sample happens in 3 stages: from 6,6 to 7,3%; from 8,0 to 10,0% and from 10,0 to 10,6%.

Increase in concentration of PVA by 0,7% (from 6,6% to 7,3%) the mass of a sample increases by 0,1 g (from 25,22 to 25,32 g). At concentration of 8,0% (from 7,3 to 8,0%) the increase in weight by 0,04 g is observed. Further increase in the concentration of PVA (from 10,6 to 11,3%) leads to degrowth of samples on 0,15 g. From **Figure 1** it is visible that within the concentration of 10,0-10,6% the plateau is formed. At these values of concentration of PVA the mass of samples is 25,52 g.

The decrease in the mass of the samples occurs with an increase in the concentration of PVA from 10.6% to 13.3%. This process occurs in 2 stages: from 10.6% to 12.0% and from 12% to 13.3%. The mass of the samples decreases from 25.52 to 25.22 g. The change in the mass of the samples is probably due to thermodynamic changes that occur in the polymer solution - crosslinking of the polymer or polymerization of the polymer.

Given that within the concentrations of PVA 10.0–10.6%, the maximum mass of the sample does not change and is 25.52 g, we have chosen the optimal concentration of PVA 10% in the polymer solution (total amount 30.0) consisting of a solution of polymer PVA and PG in a ratio of 70% and 30%. Technologically, to obtain a solution of the polymer, we will separately make a solution of PVA of a certain concentration and to this solution will be added PG. To maintain the concentration of PVA in the polymer mass of 10%, we will make samples with a concentration of PVA of 15% in the amount of 20 g and added PG in the amount of 10 g

The optimal sample has minimal shrinkage and weight loss relative to the solution. Experimental data show that the loss of mass of the samples (relative to the mass of the solution) sets from 4.5 to 4.8 g. It is proved that the shrinkage of all samples is approximately the same **(Table 3, Figure 1)**.

From the very beginning, we conducted researches on the polymeric solution having a mass of 30 g. Based on this indicator (30,0 g), we calculated shrinkage of both polymer solution to stitching (polymerization) and a polymeric film after polymerization on formula (6).

$$S_p = \frac{Vp}{\pi r^2 \rho} \qquad (6)$$

where: S_p – thickness of solution, mm;
V – solution volume, g;

r – radius of a cup, mm;
ρ – the specific mass of solution, g/cm^3.
To polymerization

$$S_p = \frac{Vp}{\pi r^2 \rho} = \frac{30}{3.14 \times 5^2 \times 1.04} = 3.67 \text{ mm} \quad (7)$$

After polymerization

$$S_p = \frac{Vp}{\pi r^2 \rho} = \frac{25.52}{3.14 \times 5^2 \times 1.04} = 0.34 \text{ mm} \quad (8)$$

Analyzing the mathematical calculations for the difference (in mm) between the diameter of the Petri dish and the final diameter of the polymer film after washing and drying, we can say that shrinkage (shrinkage size) is the difference between the mass of samples due to thermodynamic changes during polymerization. This value from 100 mm (diameter of the polymer solution covering the Petri dish with a diameter of 100 mm) is reduced to 98 mm (diameter of the film after polymerization). That is, the shrinkage of the film is 2% (formula 9):

$$\text{У} = \frac{Ds - Dp}{Ds} 100\% = \frac{100 - 98}{100} 100 = 2\% \quad (9)$$

where: Ds – diameter of the solution, mm;
Dp – diameter of polymer, mm;
У – shrinkage, %.

Considering the loss of mass of samples (4,5-4,8 g) at shrinkage of 2%, we calculated the concentration of PVA in solution by formula (10).

$$C_{\text{PVA}} = \frac{m_1}{m_0} 100\% = \frac{4.5}{30} 100 = 15\% \quad (10)$$

where: C_{PVA} – concentration of PVA, %;
m_1 – lot of loss, g;
m_0 – mass of initial solution, g.

The concentration of PVA at an indicator loss of mass of 4,5 g establishes 15% and weighing 4,8 g – 16%. That is the concentration of PVA from 15% to 16% is optimum. We for further researches will use an indicator of the concentration of 15%.

So, by the mathematical justification of experimental data us it is established that the concentration of PVA in polymer solution of 15% is optimum.

To receive a volume and uniform stitching of polymer to solution enter the agent who promotes sewing together of solution or influences polymer β-radiation. We offered a method of stitching of polymeric solution – cryo-stitching (freezing method). We made a model example of the following Ingredients: PVA solution of 15% – 20,0 and PG 10,0.

On 20 g of this solution brought in Petri dishes (25 cups). Subjected to a research 20 samples, and – left 5 for comparative characteristic. After that Petri dishes with samples were placed in the fridge at a constant temperature of -20 °C for 6, 8, 10, and 12 h. On the expiration of the time of an experiment of a Petri dish (5 samples) took out from the fridge and left at room temperature (15-25 °C) for defrosting. We carried out calculations proceeding from average temperature -20 °C. Freezing of aqueous solutions of polymer, their keeping in the crystalline state (T < 0 °C) during certain time with the subsequent stage of a defrosting (T > 0 °C) leads to the formation of cryogel that in terms of rheology is characterized as an elastic body.

The formation of the phase of the elastic body (gel) can occur at one of the stages of freezing: either directly during the freezing of the initial solution or during keeping the samples in the freezing state or in the process of thawing crosslinked cryogels.

According to our observations, freezing of all samples occurs within 44-45 minutes. Thawing of samples takes 47-48 minutes, regardless of the duration (time) of freezing.

The process of freezing and thawing of polymer solutions depends on certain factors: the cooling rate, the geometry of the sample, the substrate material, the freezing time.

The difference in freezing time (44–45 min) and thawing time (47–48 min) is probably due to both the intensive cooling of the sample and the air conversion, which is characterized by the closed space of the refrigerator compartment.

In the process of freezing and thawing the sample, heat is obtained or released from the sample. The amount of heat obtained or released by the polymer can be calculated based on the formula of specific heat (11).

$$C = \frac{Q}{M \times \Delta T} \quad (11)$$

where: C – specific heat;
Q – the amount of heat which will receive a sample at heating/discharge from a sample during the cooling, J/kg × K;
ΔT – the difference between final and reference temperature;
M – the mass of a sample, kg.

The amount of heat of Q is equal:

$$Q = C \times \text{M} \times \Delta T \quad (12)$$

Polymeric weight consists of PVA (C_{PVA} = 4186 J/kg × K), waters (C_{aq} = 4200 J/kg × K) and PG (C_{PG} = 2483 J/kg × K). The specific heat of polymeric weight (C_{pw}) equals (9)

$$C_{pw} = \frac{M_{aq} \times C_{aq} + M_{PVS} \times C_{PVS} + M_{PG} \times C_{PG}}{M_{aq} + M_{PVS} + M_{PG}} = \frac{0.017 \times 4200 + 0.003 \times 4186 + 0.01 \times 2483}{0.017 + 0.003 + 0.01}$$

$$= \frac{7.14 + 12.558 + 24.83}{0.03} \quad (13)$$

$$= 3626{,}3 \text{ J/kg} \times \text{K} = 3{,}6 \text{ кJ/kg} \times \text{s}$$

where: M_{aq}; M_{PVS}; M_{PG} – mass of water; PVA; PG respectively in polymeric weight, g;
C_{aq}; C_{PVS}; C_{PG} – specific heat of water; PVA; PG, J/kg × K;
C_{pw} – specific heat of polymeric weight, J/kg × K.

Note: calculations are given for polymeric weight on 30,0 g (0,03 kg).

The amount of heat (Q) on formula 12 is equal:

$$Q = C_{\text{пм}} \times M(t_1 - t_2) \quad (14)$$

where: Q – the amount of heat which will receive a sample when heating / is allocated from a sample during the cooling, J/kg × K;
C_{pw} – specific heat of polymeric weight;
M – the mass of polymer, kg;
t_1 – average room temperature, °C;
t_2 – temperature of the fridge, °C.

$$Q = C_{pw} \times M(t_1 - t_2) \quad (15)$$

Q = 3,6 кJ/kg × s × 0,03 kg 40 °C = 4,32 кJ = 4320 J
1 J = 0,2388 cal
Q = 4320 × 0,2388 = 1031,6 cal

Therefore, the amount of heat received by the sample when thawed or given off during freezing is 1031.6 cal.
After defrosting the temperature of all samples in the room that reached (20 °C), they were immersed in a ditch with the water purified on 24 h at the water temperature of 20 °C. This procedure is carried out to study the solubility of the received samples in the water purified. In all samples thickness of a polymeric film is 3,5 mm with a diameter of 98 mm.
In 24 h exposure, the samples got from the water purified dried and carried out measurements of diameter and thickness of polymeric films. Results of an experiment are given in **Table 4**, **Figures 2 and 3**.
The analysis of these **Table 4**, **Figures 2 and 3** showed that indicators of thickness, weight, and diameter of samples change the values when freezing during 8 h. With 8 on 12 h, the change of the studied indicator is not observed. So, we for further researches will choose the freezing time the 8th hour.

Table 4. Change of indicators of samples depending on freezing time (n=5; P 95%)

Indexes	Freezing at - 20 °C for, h				Without freezing
	6	8	10	12	
Diameter, mm	92,01 ± 3,23	94,01 ± 3,07	94,04 ± 2, 31	94,04 ± 2,71	89,11 ± 2,31
Thickness, mm	1,71 ± 0,01	1,90 ± 0,01	1,91 ± 0,03	1,91 ± 0,01	1,42 ± 0,02
Mass, g	11,71 ± 1,37	13,65 ± 1,21	13,65 ± 1,19	13,65 ± 1,46	9,0 ± 1,09

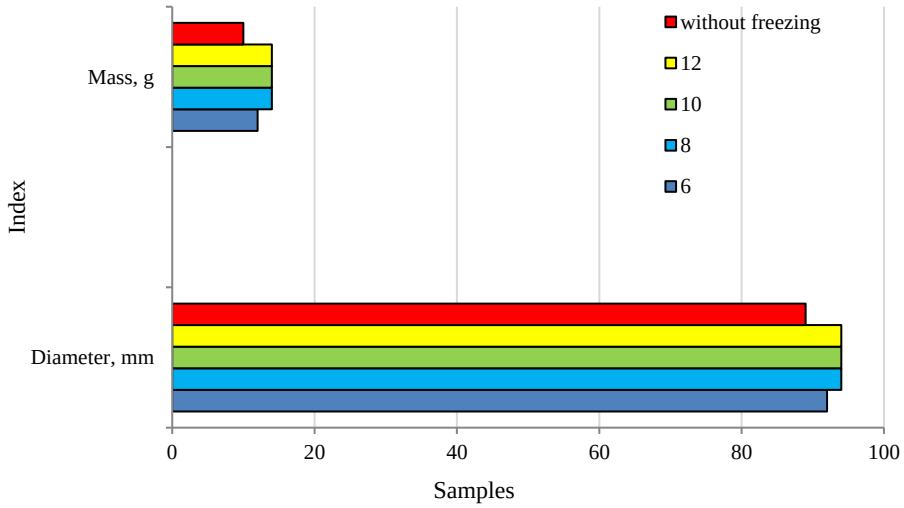

Figure 2. The histogram of changes of diameter and mass of samples depending on freezing time

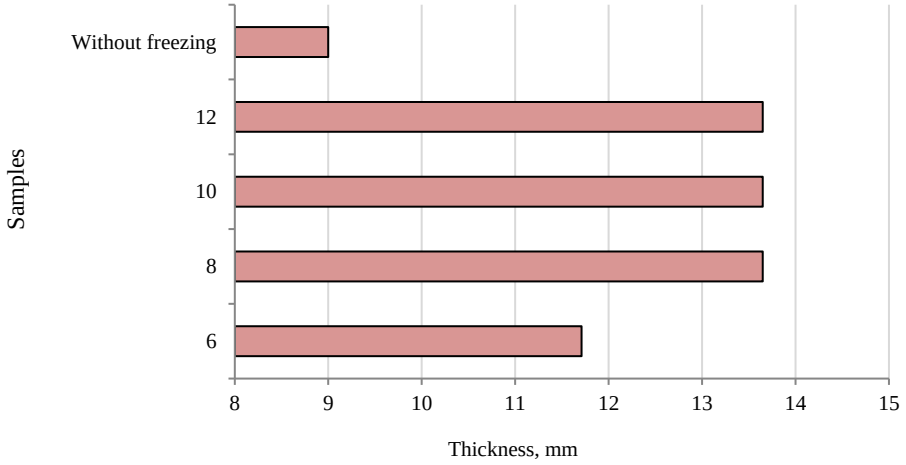

Figure 3. The histogram of change of thickness of samples depending on freezing time

Therefore, we found that obtaining a polymer film with a thickness of 3.5 mm and a diameter of 98 mm requires a polymer mass of 30 g. The duration of freezing of the samples is 8 h at -20 ° C (freezing time - 8 h), and thawing - 44 –45 minutes at room temperature (20 ° C).

Thus, we have mathematically calculated the concentration of PVA (15%), thickness (0.35 mm), weight, diameter (98 mm), percentage of shrinkage (2%), freezing time (8 h at a temperature of -20 ° C) and thawing (44-45 minutes at room temperature - 20 ° C).

Conclusion

1. The conducted pilot studies became a logical continuation of the attention of the scientific community of many countries of the world to the development of cryotropic polymeric structures. A comprehensive study of cryogels has both theoretical and practical interest as they can serve as new perspective material in pharmacy for receiving new medicines.

2. It was found that obtaining a polymer film with a thickness of 3.5 mm and a diameter of 98 mm requires a polymer mass of 30 g. The duration of freezing of samples is 8 h at a temperature of -20 ° C (freezing time - 8 h), and thawing - 44- 45 min at room temperature (20 ° C).
3. During the study, mathematical calculations substantiated the concentration of PVA (15%), thickness (0.35 mm), weight, diameter (98 mm), percentage of shrinkage (2%), freezing time (8 h at -20 ° C), and thawing (44-45 min at room temperature - 20 ° C).

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