Mathematical Modeling and Optimization of Technological Parameters of the Obtaining Process of Hydrogel Medical Dressings

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Abstract

By using the means of mathematical modeling and optimization, the calculation of the main technological parameters of the formation method of film hydrogel products based on silver-filled copolymers of 2-hydroxyethylmethacrylate with polyvinylpyrrolidone was performed. The technological parameters of the polymerization processes, chemical reduction of silver ions and centrifugal formation of the film cloth were substantiated. Those are the components of the technological process, which occurs in one stage in the form of a centrifugal unit. By using the obtained results, silver-filled films were obtained, which are characterized by unique properties and can be used in treatment of trophic ulcers of lower limbs.

Keywords 1

Mathematical modeling, technological parameters; hydrogel medical dressings; silver-containing hydrogels; centrifugal formation, trophic ulcers

1. Introduction

Modern methods of mathematical modeling, synthesis and optimization of technological parameters of production systems anticipate, in particular, a set of different methods of qualitative [1] and quantitative [2, 3] nature. Nowadays, the significant success has been achieved in development the new methods, optimization of synthesis conditions and properties of composite polymers [4-9]. This is prerequisite for creation materials with unique properties for different fields of application [10-13].

Especially it concerns the composite polymer hydrogels [14-17], among which the most popular in science and practice are hydrogels filled with (nano) metal particles [18-20].

The uniqueness of such materials is the combination of the properties of a polymer matrix and the metal-filler. A polymer matrix is characterized by the ability to absorb low molecular substances, including medicines, to swell in solvents, retain a significant amount of water while being in a highly elastic state. Depending on the nature of metal, composite hydrogel can acquire electro-conductive, magnetic and anti-bacterial properties, which significantly expands the fields of its usage [20-23]. Composite metal-hydrogels with antibacterial and antifungal properties are ideal materials in the medical field for the creation of dressings to treat wounds, burns, ulcers of various kinds, including venous ulcers of lower limbs [24-26].

The modern practice of the treatment of venous ulcers of lower limbs implies a combination of various methods for conservative treatment and surgical interventions. Most trophic venous ulcers are characterized by a high degree of bacterial colonization with high probability of development of

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wound infection. According to many researchers, an important condition, necessary to prevent recurrence of venous ulcers, is the application of the adequate systemic and local therapy with antibiotics and antiseptic preparations in combination with lower limb compression [27].

One of the promising methods for the treatment of venous ulcers is considered to be covering (in order to prevent the development of wound infection) with the sorption hydrogel film materials with antibacterial properties and the combination of therapy using medical preparations [28].

We established experimentally the prospects of using silver-filled film hydrogel products based on co-polymers of polyvinylpyrrolidone (PVP) with 2-hydroxyethylmethacrylat (HEMA) during the treatment of venous ulcers [25].

High elasticity, strength, sorption capacity, bactericidal and antifungal properties of the obtained materials based on co-polymers of polyvinylpyrrolidone with 2-hydroxyethylmethacrylat (pHEMA-gr-PVP) make them effective to use as hydrogel dressings for medical purposes. A unique porous structure [17], combined with the existence of hydrophilic functional groups ensures swelling of a polymer matrix in water and high permeability for dissolved low molecular substances. This, in turn, determines the suitability of the obtained hydrogel dressings for the preparation treatment by introducing medicines through the material by the transdermal method [25].

At the same time, due to the ability to absorb and retain moisture, elasticity and stability of the form in aqueous medium, such materials are compatible with a variety of biological systems.

2. The analysis of previous researchs and problem statement

A new method of obtaining metal-filled hydrogels based on copolymers HEMA with PVP was proposed, which consist in implementation of polymerization with the simultaneous reduction of metal ions by using exoeffect of polymerization [29].

The method is especially attractive both from the practical and the scientific point of view, because the particles of metal are formed at the same time with the formation of a polymer matrix. This approach makes it possible to achieve a better, uniform distribution of the filler and to obtain the material with the isotropic properties.

High reactivity and possibility to regulate within wide limits the time of HEMA/PVP compositions being in liquid state is a prerequisite of their recycling in film products by the method of centrifugal formation [25]. The technological characteristics [30], cost effectiveness of the centrifugal formation and low quality of the films, obtained by the other currently existing methods, contribute to this (casting and filling into glass or polymer form). The samples of hydrogel film materials, obtained by centrifugal formation, are characterized by various thickness, which does not exceed 1 %, high-quality surfaces and a complex of physical and mechanical properties.

Centrifugal molding is one method of plastic products production in the bodies of revolution by the filling of the material in a viscous-flow state into the form that rotates in the same plane. Centrifugally material is evenly distributed on the inner surface of the form in a continuous layer, while receiving curing required configuration [31].

The proposed technology is easy to implement into production, does not require sophisticated apparatus design. One of its advantages is the minimum amount of waste and no need of recycling or recuperation of solutions of an oxidant and a reducing agent. Such technology is a priority and needs development, taking into consideration the prospects of the obtained composites.

However, as for any technology, one of the main factors in obtaining high-quality hydrogel film products is the optimal technological parameters of the technological manufacturing process. At the same time, the establishment of some optimal technological parameters requires an implementation of a large amount of experimental studies and needs the use of mathematical modeling and forecasting methods. Developed methods of optimization provide the use of mathematical apparatus not only on the stage of analyzing research results, but also during their forecast; that gives an opportunity to decrease significantly materials and time consuming for providing the experiment occuring [32, 33]. Therefore, the aim of the research was to establish the technological parameters of obtaining hydrogel films for medical purposes by using the means of mathematical modeling. The films were obtained by the centrifugal method with the simultaneous formation of a polymer matrix and obtainment of metal-filler particles.

3. Object of investigation

Lightly crosslinked polymers obtained by radical polymerization of HEMA at the presence of PVP are selected as a matrix for filling. 2-hydroxyethylmethacrylat (Sigma Chemical Co) and high-purity polyvinylpyrrolidone (AppliChem GmbH) with MM 12000 were used for co-polymerization. The initiator of the radical type benzoyl peroxide (BP) was selected as the polymerization initiator. Such choice was determined by its wide use for the synthesis of pHEMA-gr-PVP co-polymers [20]. HEMA was distilled in vacuum (residual pressure was 130 N/m^2, T_{boil}=351 K), PVP was dried at 338 K in vacuum for 2–3 h, BP was re-crystallized from ethanol.

Polymerization was carried out with the initiator of a radical type of BP (T_0=50ºC).

Given that the silver-filled hydrogel is meant for medical purposes, silver deposition was carried out from argentum nitrate (of chemically pure brand) in the aqueous-ethanol solution. The recovery process goes on intensively at the temperature of 70 ºC [34] according to the following reaction:

$$2AgNO_3 + C_2H_5OH \rightarrow 2Ag\downarrow + 2HNO_3 + CH_3CH{=}O$$

4. The calculation results of technological parameters of the obtaining process of hydrogel films

Technological parameters are a set of conditions that ensure the obtainment of a quality product. Each parameter has a greater or lesser effect, but this influence is interrelated, so in the technology the optimal set of parameters should be established. Deviation of one of them can lead to changes in product quality (both in terms of physico-mechanical and performance characteristics, and in terms of appearance) and process productivity. For the formation of hydrogel films, a centrifugal unit was designed with the main element of centrifugal mold (Figure 1).

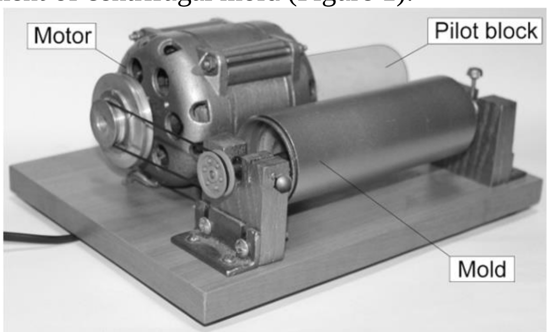


Figure 2: Installation for centrifugal molding of composite films from polymer hydrogels

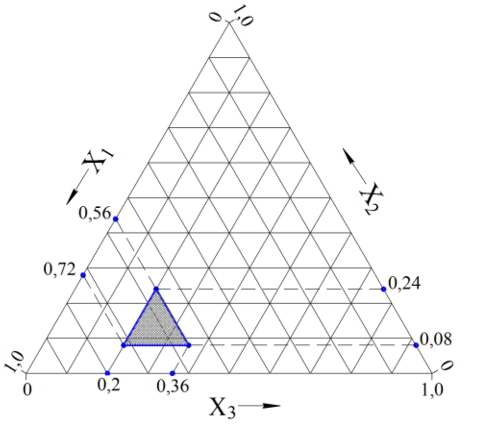
The developed obtainment method of silver-filled hydrogel films by polymerization with simultaneous reduction of Ag^+ ions anticipates the production of films in one stage on one equipment. The peculiarity of the method is that during the time of formation of the final product – the time between loading the reaction composition to removing the final product, in centrifugal form occur three processes at the same time, which differ in their nature – chemical (synthesis of polymer matrix due to copolymerization of HEMA with PVP and Ag(0) formation by reduction of Ag^+ ions) and physical (obtaining a film cloth by centrifugal molding). Each process must be carried out under certain conditions, which form a set of technological parameters of the technological obtainment process of hydrogel films.

As kinetic investigations of speed of ions reduction have shown the main parameters of the process are the duration of the induction period of reduction ($\tau_{i.r.}$), duration of reduction ($\tau_{r.t.}$), the reduction temperature (T_r) [28]. A start time of gel formation (τs.f.), a duration of gel effect area ($\tau_{d.e.}$) and the maximum exothermic temperature (T_{max}) [28, 29] were used for a characteristic of the copolymerization process HEMA with PVP [26, 27]. $\tau_{s.f.}$, $\tau_{d.e.}$, Tmax parameters have been taken on the base of thermometric polymerization research [28, 29].

In our case, it is important that the duration of the Ag^+ reduction process approaches to the duration of gel effect area of the polymerization reaction with a minimum start time of gel formation and a maximum Tmax. The duration of molding is determined by the duration of polymerization, which depends in our case mainly on the formulation of the original reaction composition and is established by the experimental method.

It needs to choose compositions, which polymerize with the maximum heat liberation, the minimum induction period and with the maximum gel effect area according to the technological features of obtaining metal-filled hydrogels by proposed method.

Experimentally, the optimal content of the initial composition components in which achieves the necessary parameters of the exothermic process could not be found. Therefore, for investigation the simultaneous influence of initial composition components on the exothermic process parameters, it was used the optimization of the experiment by means of simplex-lattice planning Scheffe in order to reduce the experimental expenses amount [35]. The result of the research is a multifactor mathematical model in the form of a polynomial of a given degree. The necessary condition in the simplex method is to provide at each experimental point a condition fulfillment $\Sigma X_i=1$, where $X_i \geq 0$ – the concentration of the i-th component in the composition. During the research of the mixtures properties, which depend only on three components, the factor space is an equilateral triangle and for the system, the ratio is executed: $X_1+X_2+X_3=1$ [35]. The vertices of the triangle correspond to the pure substances, the sides – to the double systems. In our case, not the whole concentration triangle was investigated, but only its local part, which is a simplex with vertices A_1(72% HEMA; 8% PVP; 20% H_2O); A_2 (56% HEMA; 24% PVP; 20% H_2O); A_3 (56% HEMA; 8% PVP; 36% H_2O) (Figure 2a). Let's indicate X_1 denote – HEMA, wt.%; X_2 – PVP, wt.%; X_3 – H_2O, wt.%.



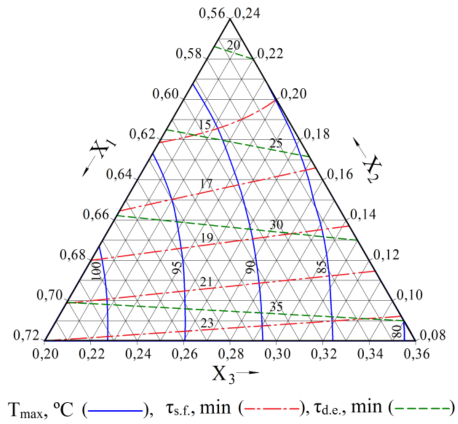


Figure 2: Triangles for the research of «composition-technological parameters» diagrams: a - local area of research; b - equal values lines of parameters of the exothermic process

The optimization was carried out for exothermic parameters – the start time of the gel formation ($\tau_{s.f.}$, min), gel-effect area ($\tau_{d.e.}$, min) and the maximum exothermic temperature (T_{max}, ºC). In Table 1, conditions and results of experiments in the form of pseudo-components and on a natural scale have been presented. The average results y_1^e (T_{max}, ºC), y_2^e ($\tau_{s.f.}$, min) and y_3^e ($\tau_{d.e.}$, min) were obtained by two parallel experiments.

Using the matrix of planning, conditions and results of the experiment (Table 1) the coefficients of the polynomial are calculated and the regression equations are derived [36]:

$$y_1 = 123.44 + 63.75X_2 - 71.25X_3 - 203.13X_2X_3 - 445.31X_2^2 - 117.19X_3^2, \quad (1)$$

$$y_2 = 33.13 - 184.38X_2 + 7.5X_3 + 109.38X_2X_3 + 312.5X_2^2 - 15.63X_3^2, \quad (2)$$

$$y_3 = 40.39 - 50.63X_2 + 28.75X_3 - 234.38X_2X_3 - 62.5X_2^2 - 23.44X_3^2, \quad (3)$$

The obtained equations give a possibility to predict the parameters change character of the exothermic copolymerization process HEMA with PVP – a start time of gel formation (y_1), a gel-effect area (y_2) and the maximum exothermic temperature (y_3) for any composition of the initial composition. According to the obtained regression equations, the isolines of the exothermic parameters change were plotted depending on each component content of the original composition (Figure 2b). The obtained lines of equal parameters values provide a quick search for a totality of values of the components concentrations in the reaction composition, which makes a possible to obtain the optimal technological conditions, that are necessary for the metal deposition during the polymerize-

Table 1
Conditions and results of experiments

№	Natural variables			y_1^e	y_2^e	y_3^e
	X_1	X_2	X_3			
1	0.72	0.08	0.20	103.5	23.00	37.00
2	0.56	0.24	0.20	84.40	13.00	18.20
3	0.56	0.08	0.36	79.00	24.20	36.50
4	0.64	0.16	0.20	96.80	16.00	28.00
5	0.64	0.08	0.28	92.00	23.70	36.90
6	0.56	0.16	0.28	84.00	17.40	26.40

tion. The main technological parameters of the centrifugal molding are rotational frequency of mold, molding pressure and centrifugal force. The frequency of mold rotation depends on the quality, physical and mechanical properties of the film. Rotational frequency affects the magnitude of the centrifugal force, and accordingly, the molding pressure and density of the film. In this work, the functional connection was established, which make it possible to determine these parameters and the relationship between them.

In order to form high-quality surface films the working rotational frequency of mold n_w must be greater than critical (n_{cr}):

$$n_w > n_{cr}. \tag{4}$$

It is established that the critical frequency of rotation of the centrifugal mold depends only on its geometric dimensions:

$$\mathrm{n_{cr}} > \sqrt{\frac{\mathrm{g}}{4\pi^2\mathrm{R}}}, \tag{5}$$

where R – radius of the inner mold surface (outer radius of the product), m.

Besides, on the basis of conducted calculations, mathematical equations were derived to calculate the pressure acting on the outer surface of the film and on the centrifugal force:

$$P = \frac{4\rho\pi^2\mathrm{n}^2(\mathrm{R}^3 - \mathrm{R}_1^3)}{3R}, \tag{6}$$

$$F_C = \frac{2\rho\pi\mathrm{l}\omega^2(\mathrm{R}^3 - \mathrm{R}_1^3)}{3}, \tag{7}$$

where: ρ – density of the composition, kg/m^3; n – rotational frequency of mold, rev/min; R – outer diameter of the film, m; R_1 – inner diameter of the film, m; l – work length of designed mold, m; ω – angular velocity, s^{-1}.

5. Implementation of the obtained results

By using the received results, experimental samples of composite hydrogel films were obtained (Figure 3). Hydrogel film material samples, obtained by centrifugal molding have attracted the attention by the isopachic not exceeding 1%, high surface quality and by complex of physico-mechanical properties.

The medical-biological studies of the resulting film products were carried out under the laboratory conditions at the Department of Microbiology of Danylo Halytskyi Lviv National Medical University. A comparative analysis of the results of medical-biological tests of the obtained materials and non-filled hydrogel films regarding the used micro-organisms revealed that non-filled films do not show any bactericidal and antifungal properties. The film products that contain silver particles block the growth of bacteria and fungi (Table 2) [25].

Based on the obtained silver-filled films, we developed hydrogel medical dressings, clinical testing of which was successfully carried out at the surgical department of the Lviv hospital at ZT PAT "Ukrainian Railway" in the treatment of venous ulcers of lower limbs. It was established that the use

Figure 3: Experimental sample of hydrogel film

Table 2
Bactericidal and antifungal activity of silver-filled hydrogel films, obtained based on copolymers of HEMA with PVP

Duration of storage of hydrogel films	Magnitude of the zone of inhibition of microorganism growth, mm				
	S. aureus	S. epidermidis	Str. viridans	E. coli	C. albicans
1 month	12, 10, 9	12, 8, 9	11, 11, 9	3, 3, 0	11, 11, 7
18 months	5, 4, 8	5, 4, 5	11, 8, 8	–	0, 4, 2

of the silver-filled hydrogel films improves the treatment results, accelerates cleaning, granulation and healing trophic ulcers and, as a result, reduces the duration of patients staying at hospital. Due to its unique properties, the developed materials can be also used for the treatment of burn and post-operative wounds.

6. Conclusions

The basic technological parameters of formation processes of a film hydrogel cloth by a centrifugal method are calculated. The technological parameters of the polymerization processes, chemical reduction of silver ions and the centrifugal method were established. They compile the technological parameters of the technological obtainment process of hydrogel dressings for medical purposes. Using the Scheffe’s simplex-lattice planning method, the optimization of the experiment was made to forecast the polymerization parameters of HEMA/PVP compositions, which define the technological regime of metals’ chemical precipitation.

The results of the clinical studies showed sufficient clinical effectiveness of using the developed hydrogel dressings for medical purposes based on hydrogels, containing silver particles. Such materials in combination with the integrated therapy help to increase the speed and intensity of treatment of trophic venous ulcers of lower limbs.

7. References

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