Досліджено особливості одержання гідрогелевих мембранних покрить на основі кополімерів 2-гідроксіетилметакрилату з полівінілпіролідоном. Досліджено структурні параметри сітки та проникність мембран для модельних речовин (електролітів) та ліків. Запропоновано модель масоперенесення із ансамблю кулястих частинок, покритих полімерною гідрогелевою оболонкою. Розроблена принципова технологічна схема формування гідрогелевих мембранних покрить для створення капсульованих форм пролонгованого вивільнення ліків

Ключові слова: гідрогелева мембрана, 2-гідроксіетилметакрилат, полівінілпіролідон, структурна сітка, капсулювання, масоперенесення, пролонговане вивільнення

Исследованы особенности получения гидрогелевых мембранных покрытий на основе сополимеров 2-оксиэтилметакрилата с поливинилпирролидоном. Исследованы структурные параметры сетки и проницаемость мембран для модельных веществ (электролитов) и лекарств. Предложена модель массопереноса с ансамбля шаровидных частиц, покрытых полимерной гидрогелевой оболочкой. Разработана принципиальная технологическая схема формирования гидрогелевых мембранных покрытий для создания капсулированных форм пролонгированного высвобождения лекарств

Ключевые слова: гидрогелевая мембрана, 2-оксиэтилметакрилат, поливинилпирролидон, структурная сетка, капсулирование, массоперенос, пролонгированное высвобождение

UDC 54-126:61.746:744
DOI: 10.15587/1729-4061.2017.92368

AN INVESTIGATION OF OBTAINING PATTERNS, STRUCTURE AND DIFFUSION PROPERTIES OF BIOMEDICAL PURPOSE HYDROGEL MEMBRANES

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1. Introduction

It is known that the dosage forms used in the biomedical and pharmaceutical fields (tablets, capsules, injections etc.), mostly are not optimal in terms of the functions they perform [1]. They do not provide long-term and continuous flow of drugs into the bloodstream and practically not contribute to their transportation to the sick organ. In the body, drugs are distributed according to their physical and chemical properties and the sick organ gets only a small share. Usually, it does not exceed 10...15 % of the introduced amount. The remaining amount of medication at best doesn't benefit, and at majority shows unwanted physiological activity and causes toxic effects in other organs. The rapid excretion of drugs from the body determines the necessity of their repeated introduction to maintain a therapeutic effect, which further increases their harmful side effects.

Drug encapsulation by polymers that dissolve in human/animal body can increase the drug efficacy and reduce their negative impact [2]. However, water-soluble polymers that are used for this purpose are ineffective yet. After dissolution, the process of substance release becomes uncontrolled causing problems with the excretion of the polymer or its metabolic products from the body.

A possible solution of these problems is to use polymer hydrogels for the systems of sustained drug release that are rarely structured polymers and have high biological compatibility. However, in Ukraine there are no materials, manufacturers and technologies of therapeutic hydrogel systems. Therefore, research in this area is important both from the scientific and practical point of view.

2. Literature review and problem statement

For the production of sustained release drug systems, especially, hydrogels based on natural polysaccharide chitosan [3] are used that have biological compatibility, bioactivity and biodegradability observed. These systems are mainly in the form of microspheres, nanoparticles, sponges etc. However, chitosan hydrogels have the major drawback that they are only suitable for immobilization in the acidic medium of drugs that have polyanionic structure [4, 5]. Other representatives of this class of polymeric carriers are pH sensitive

polyacrylamide hydrogels [6], which are not active in the stomach, but release the medicine in the large intestine. However, there are evidences of complications during the use of such materials associated with the instability of their structure. In particular, during the exploitation polyacrylamide hydrogels degrade and biodegradation products have a toxic effect on the body [7].

In this context, considerable interest is caused by hydrogels based on 2-hydroxyethylmethacrylate (HEMA) and polyvinylpyrrolidone (PVP) copolymers. Such hydrogels depending on the method of their production are used in ophthalmology for the manufacture of contact lenses and artificial lens, dental materials, (hemp)dialysis membranes and pellet controlled release systems [8]. These systems operate on the principle of drug sorption-desorption in the action medium. Properties of pellet hydrogels can be controlled by controlled change of structure and composition of copolymers and they are suitable for immobilization of drugs with different structures – cation-active, anion-active and neutral. However, their significant drawback is, in particular, relatively low sorption capacity [8].

These drawbacks can be eliminated if hydrogel is used not as a sorbent, but as a coating for solid dosage form. In a dry state, such polymer coating has a protective function. After swelling in the digestive tract, it acquires the properties of the membrane and is able to pass through the water and dissolved substances, including drugs. Diffusive transport characteristics of such hydrogels are determined by the structural parameters of their grid, which can be controlled during synthesis [9].

The transferring mechanism of components, including drugs, from encapsulated particles involves several stages (Fig. 1):

– swelling of the hydrogel membrane;

– molecular diffusion inside the capsule;

– mass transfer through the hydrogel membrane to the surrounding solution.

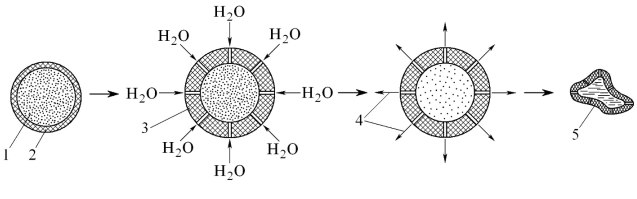


Fig. 1. The scheme of components transfer from encapsulated particles: 1 — dosage form; 2 — hard polymeric shell; 3 — swollen hydrogel; 4 — release of dosage form; 5 — used capsule

The used capsule is excreted naturally, without causing any collateral damage to the body.

3. The purpose and objectives of the research

The aim of this study was to investigate the obtaining patterns and structural-diffusion properties of hydrogel membranes based on HEMA-PVP copolymers and to develop a model of mass transfer through the hydrogel shell. This model will help to predict the duration and rate of release of the target component in an action medium.

To reach this goal, it was necessary to solve the following problems:

– to justify the temperature mode of film hydrogel synthesis, based on kinetic patterns of polymerization of HEMA-PVP compositions;

– to investigate the permeability of film hydrogels for model substances and drugs;

– to analyze the impact of key factors on the permeability of hydrogels and to develop a model of mass transfer from solid particles through the hydrogel shell;

– to develop a process flow diagram of hydrogel membrane coatings forming on solid dosage forms.

4. The materials and methods of investigating hydrogels properties

For research, the following materials have been used:

– HEMA (Bisomer®, USA), purified by vacuum distillation (residual pressure of 130 N/m^2, b.p.=351 K);

– PVP (AppliChem GmbH, Germany), highly refined with a molecular weight of $28 \cdot 10^3$ g/mol;

– Potassium persulfate (PPS), pure, purified by two-time recrystallization from aqueous solution;

– Iron (II) Sulfate, pure.

Hydrogel membranes were formed as films of different thickness by polymerization of polymer-monomer compositions in a solvent between the two surfaces of silica glass. To cover the real dosage forms, the polymerization coating at fluidized bed apparatus [8] was used. The residual monomer content in hydrogels M_{res} was defined by chemical method [10]. Resulting hydrogel membranes after synthesis were washed with water to remove unreacted products. The permeability of membranes for water and substances dissolved in it was investigated by the method described in [11]. The diffusion coefficient of the solute through the membrane (D) was calculated using the formula [12]:

$$D = \frac{l^2}{6 \cdot \tau_{del}},$$

where l – the membrane thickness, m; τ_{del} – delay time (for which the substance that diffuses appears on the other side of the membrane), s.

The molecular weight of the macrochain segment between two adjacent stitching nodes (M_n) was determined from the dependence [13]:

$$M_n = \frac{\rho \cdot \nu \cdot L^5}{0{,}5 - \mu},$$

where ρ – polymer density, kg/m^3; ν – molar volume of solvent, m^3/(kg×mol); L – linear swelling coefficient; μ – polymer-solvent interaction parameter:

$$\mu = 0{,}5 - \frac{\nu \cdot \sigma_\infty \cdot L^4}{R \cdot T \cdot (\lambda^2 - \lambda^{-1})},$$

where σ_∞ – equilibrium stress, kg/m^2;

$$\lambda = 1 + \varepsilon,\ 0 < \varepsilon < 0{,}3,$$

where ε – deformation at equilibrium stress.

Watering (W) of hydrogel membranes was calculated using the equation:

$$W = \frac{m_1 - m_0}{m_0} \cdot 100\ \%,$$

where m_0 i m_1 – weight of dry and hydrated in distilled water for 24 hours sample of hydrogel, respectively, g.

5. The research results of formation modes and properties of hydrogel membranes

5. 1. The investigation of temperature modes of film hydrogels forming

For the development of forming temperature modes and for selection of compositions (Table 1), the results of kinetic studies of such compositions polymerization and revealed practical ways of directed forming of grid structural parameters and copolymers composition [9] were used. The impact of HEMA:PVP ratio in the initial composition, water content, nature and amount of initiator (catalyst) on the rate of polymerization, which determines the duration of the synthesis were taken into account.

Table 1

The influence of composition and forming mode on the extent of reaction*

№	Initial composition, wt. %				Forming mode	M_{res}, %
	HEMA	PVP	H_2O	initiator (catalyst)		
1	90	10	100	0.3 PPS	333 K – 2 hrs., 343 K – 2 hrs.	1.5
2	80	20	100	0.3 PPS	333 K – 2 hrs., 343 K – 2 hrs.	2.0
3	80	20	50	0.05 $FeSO_4$	298 K – 1 hr.	2.5
4	80	20	100	0.05 $FeSO_4$	323 K – 0.5 hrs.	1.0
5	80	20	300	0.05 $FeSO_4$	323 K – 0.5 hrs.	1.0
6	70	30	100	0.05 $FeSO_4$	323 K – 0.5 hrs.	2.0

*Note: * – by content of residual monomer (M_{res}); PPS – potassium persulfate*

As the use of polymers and products made of them in medicine and pharmacy anticipates contact with a living organism, the important parameter to control is the content of residual monomer after polymerization (Table 1). Studies have shown that using of PVP-$FeSO_4$ (pos. 3...6) complex instead of PPS (pos. 1, 2) as an initiating system can significantly reduce the duration and temperature of copolymers synthesis. The content of residual monomer, depending on the mode of synthesis, was 0.5...2.5 wt. %. As obtained polymers are expected to be used in medical practice, to remove unreacted monomer a washing stage in the technological scheme (see p. 5.4) was provided, during which polymer is washed in the solvent that dissolves the monomer but does not dissolve the medicine.

5. 2. The investigation of hydrogel membrane permeability to model substances and drugs

Diffusive-transport characteristics of rarely-structured HEMA-PVP copolymers, that are determined by their structure, watering and structural parameters of the grid, were investigated on the model substances (potassium, sodium and calcium chlorides), and in specific dosage form – sodium diclofenac (Fig. 2, 3, Table 2).

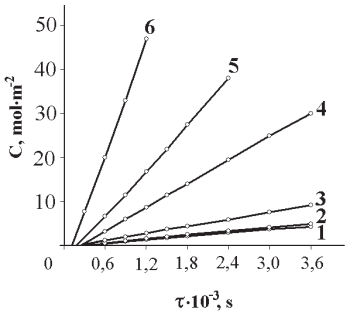


Fig. 2. Kinetic curves of NaCl release through hydrogel membranes; HEMA:PVP:H_2O, wt. %: 1, 3, 6 – 8:2:10, 2 – 10:0:10, 4 – 7:3:10, 5 – 5:5:10; δ, μm: 1 – 400, 2...5 – 200, 6 – 20

Based on the analysis of the results, it was revealed that diffusion time and transfer rates are determined by the composition of the hydrogel. The greatest delay time (about 5 minutes), which defines a diffusion of solute through the membrane, and the lowest release rate were found for the polyHEMA-based hydrogel. With the increasing of PVP amount in the original composition, delay time and transfer rate are increasing too.

When analyzing the impact of electrolyte's nature on the transfer rate, we see that it is reduced with increasing of molecular weight of salts (Fig. 3). In this case, not only the size of molecules but also dissolution rate, that is different for various salts, plays a considerable role.

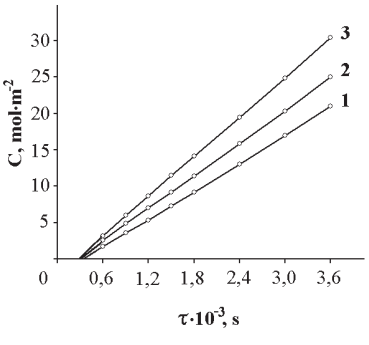


Fig. 3. Kinetic curves of salt release through hydrogel membrane; HEMA:PVP:H_2O=7:3:10 wt. %; 1 – $CaCl_2$, 2 – KCl, 3 – NaCl; δ=200 μm

The highest density of grid (the smallest molecular weight of interstitial fragment M_n) among the investigated hydrogels is present in polyHEMA (Table 2).

Table 2

Properties of hydrogel membranes

№	(Co)polymer content, wt. %		W, %	M_n, kg×mol^{-1}	D×10^{12}, m^2×s^{-1}	V×10^3, mol×m^{-2}×s^{-1}
	polyHEMA	PVP				
1	100	–	38	12	5.7/0.4*	1.26/0.11
2	91	9	45	20	18.7	2.21
3	82	18	48	24	28.0/2.2	2.99/0.21
4	77	23	53	38	37.1	3.75

*Note: W – watering; M_n – molecular weight of interstitial fragment of the hydrogel grid; V – mass transfer rate (δ=200 μm); * – nominator for sodium chloride, denominator – for sodium diclofenac*

With the introduction of PVP into composition M_n increases. This change in the structure of the copolymer, obviously, affects the diffusion characteristics of the investigated hydrogels, particularly the diffusion coefficient and the rate of substances release through the hydrogel membrane. Thus, by changing the synthesis conditions, in particular, composition, structural parameters of the copolymer grid and thus its properties can be purposefully adjusted.

On the basis of release research, the main diffusive-transport characteristics of hydrogels were calculated (Table 2).

5. 3. A mathematical model of mass transfer from solid spherical particles through hydrogel membrane

From a practical point of view, the use of encapsulated disperse materials with long-term action is essential to ensure a constant rate of their release into the environment. This problem can not always be solved using monodisperse products, so in practice often a mixture of capsulated disperse materials of different size is used. Experimental studies have shown that the diffusion properties of hydrogel membranes may vary over a wide range. Therefore, to predict these properties, a mathematical model of mass transfer of spherical particles of different size, coated with a hydrogel shell was developed. For this, the basic model of mass transfer from a spherical particle, which is described in detail in [14] was used.

When deriving a mathematical model, we assumed that there is an ensemble of spherical particles with different radii in the solution, coated with a polymer hydrogel shell of varying thickness. Let there be N spherical particles of radius R_i (i=1, 2, ..., N). On the surface of these particles, polymeric shell of thickness δ_{ni} (m) is deposited (Fig. 4, *a*). The volume of ith polymeric shell V_{ni} can be calculated using the formula:

$$V_{n_i} = \frac{4\pi \cdot \delta_{n_i} (\delta_{n_i}^{\ 2} + 3R_i\delta_{n_i} + 3R_i^{\ 2})}{3}. \quad (1)$$

During the contact of encapsulated particle with solvent, the thickness of the polymeric coating δ_i increases due to swelling. The volume change of ith polymeric shell ΔV_i due to changes in its thickness δ_i is calculated as:

$$\Delta V_i = \frac{4\pi\left[3R_i^{\ 2}\left(\delta_i - \delta_{n_i}\right) + 3R_i\left(\delta_i^{\ 2} - \delta_{n_i}^{\ 2}\right) + \left(\delta_i^{\ 3} - \delta_{n_i}^{\ 3}\right)\right]}{3}. \quad (2)$$

As

$$\Delta V_i = \alpha_i V_{n_i}, \quad (3)$$

where α_i – coefficient of swelling of ith polymeric shell, therefore regarding the equations (2) and (3), we obtain:

$$\alpha_i = \frac{4\pi\left[3R_i^{\ 2}\left(\delta_i - \delta_{n_i}\right) + 3R_i\left(\delta_i^{\ 2} - \delta_{n_i}^{\ 2}\right) + \left(\delta_i^{\ 3} - \delta_{n_i}^{\ 3}\right)\right]}{3V_{n_i}}. \quad (4)$$

As

$$\frac{d\alpha_i}{dt} = K_i\left(\alpha_i^{\ *} - \alpha_i\right),$$

therefore

$$\alpha_i = \alpha_i^{\ *}\left(1 - e^{-K_{it}}\right), \quad (5)$$

where K_i – swelling rate constant of ith polymeric shell, 1 s; $\alpha_i^{\ *}$ – maximum of swelling coefficient of ith polymeric shell.

Regarding (1), (4), (5) we have the equation for δ_i:

$$\delta_i^{\ 3} + 3R_i\delta_i^{\ 2} + 3R_i^{\ 2}\delta_i = \\ = \delta_{n_i}\left(3R_i^{\ 2} + 3R_i\delta_{n_i} + \delta_{n_i}^{\ 2}\right)\left(1 + \alpha_i^{\ *}\left(1 - e^{-K_{it}}\right)\right). \quad (6)$$

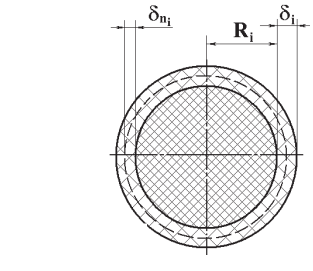
Then

$$\delta_i = \left[\left(R_i + \delta_{n_i}\right)^3 + \delta_{n_i}\alpha_i^{\ *}\left(1 - e^{-K_{it}}\right)\cdot\left(3R_i^{\ 2} + 3R_i\delta_{n_i} + \delta_{n_i}^{\ 2}\right)\right]^{1/3} - R_i. \quad (7)$$

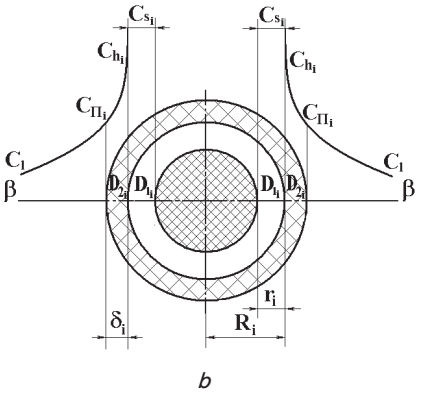
Let us establish the dependence of the substance's concentration c_i in solution. Let M_i be the mass of ith particle that didn't dissolve, and r_i – reduction of its radius R_i. Taking into account that the densities of substance flows, which pass through the shell at every time t are equal, the dependence of the diffusion rate of dissolved substrate via polymer shell can be written (Fig. 4, *b*):

$$\frac{-dM_i}{dt} = \frac{4\pi \cdot R_i^{\ 2} D_{1_i}\left(c_{s_i} - c_{h_i}\right)}{r_i} = \\ = \frac{4\pi \cdot R_i^{\ 2} D_{2_i}\left(c_{h_i} - c_{\Pi_i}\right)}{\delta_i} = 4\pi \cdot R_i^{\ 2}\beta_i\left(c_{\Pi_i} - c_1\right), \quad (8)$$

where D_{1i}, D_{2i} – diffusion coefficient of the substance in the solution inside the ith capsule and ith polymeric shell, m^2/s; c_{si}, c_{hi}, $c_{\Pi i}$, c_1 – respectively the concentration of the substance on the surface of ith solid particle, on the inner and outer surfaces of ith shell and in the solution, kg/m^3; β_i – mass transfer coefficient of ith particle, m/s.



a



b

Fig. 4. The scheme of the process:
a – hydrogel shell swelling; *b* – mass transfer

On the basis of the material balance equation, we write:

$$\rho_1 V_1^{(r)} + \rho_2 V_2^{(r)} + ... + \rho_N V_N^{(r)} = \\ = c_{s_1} V_1^{(r)} + c_{s_2} V_2^{(r)} + ... + c_{s_N} V_N^{(r)} + W c_1, \quad (9)$$

where $V_i^{(r)}$ – volume of i^{th} dissolved particle, m^3; ρ_i – density of i^{th} solid particle, kg/m^3; W – volume of solution, m^3.

Let us obtain $V_i^{(r)}$:

$$V_i^{(r)} = \frac{4\pi \cdot r_i \left(3R_i^2 - 3R_i r_i + r_i^2\right)}{3}. \quad (10)$$

By involving (10) into (9), we can obtain c_1:

$$c_1 = \frac{4\pi\left[\left(\rho_1 - c_{s_1}\right)\left(r_1^2 - 3R_1 r_1 + 3R_1^2\right) r_1 + ... + \left(\rho_N - c_{s_N}\right)\left(r_N^2 - 3R_N r_N + 3R_N^2\right) r_N\right]}{3W}. \quad (11)$$

If $r_i << R_i$, then the equation (11) could be transformed into:

$$c_1 = \frac{4\pi\left[R_1^2 r_1\left(\rho_1 - c_{s_1}\right) + R_2^2 r_2\left(\rho_2 - c_{s_2}\right) + ... + R_N^2 r_N\left(\rho_N - c_{s_N}\right)\right]}{W}. \quad (12)$$

Regarding (8) we have:

$$\frac{-dM_i}{dt} = \frac{4\pi \cdot \rho_i^2 \left(c_{s_i} - c_1\right)}{\left(r_i D_{1i}^{-1} + \delta_i D_{2i}^{-1} + \beta_i^{-1}\right)}. \quad (13)$$

As

$$M_i = \frac{4\pi \cdot \rho_i \left(R_i^3 - 3R_i^2 r_i + 3R_i r_i^2 - r_i^3\right)}{3},$$

therefore, regarding (13) we have:

$$\frac{dr_i}{dt} = \frac{R_i^2 \left(c_{s_i} - c_1\right)}{\left[\rho_i \left(R_i - r_i\right)^2 \left(r_i D_{1i}^{-1} + \delta_i D_{2i}^{-1} + \beta_i^{-1}\right)\right]}. \quad (14)$$

If $r_i << R_i$, then (14) could be transformed into:

$$\frac{dr_i}{dt} = \frac{c_{s_i} - c_1}{\left[\rho_i \left(r_i D_{1i}^{-1} + \delta_i D_{2i}^{-1} + \beta_i^{-1}\right)\right]}. \quad (15)$$

Thus, the resulting mathematical model for mass transfer of many particles was obtained, that is described by the equations (11), (14) or by simplified (12), (15). For their numerical implementation, mathematical package Maple v6.01 [15] was used.

5. 4. A process flow diagram of forming of hydrogel membrane coatings on solid dosage forms

The investigation of obtaining patterns, structure and properties of PVP hydrogels became the basis for the development of the process flow diagram for obtaining of membranous encapsulated forms of sustained drug release (Fig. 5).

HEMA from the volumetric measurer 1 and PVP from the gravimetric measurer 2 are transferred to the mixer 6; solvent and catalyst from the measurers 3 and 4 respectively – to the mixer 7. In the mixers, the compositions are mixed until dissolved. Both solutions are then mixed in the mixer 8 and transferred into the fluidized bed apparatus 9 where solid dosage form that comes from the gravimetric doser 5 is coated.

Duration of coating forming is 30...60 minutes depending on the composition. The composition is selected taking into account its combined effect on the polymerization kinetics, grid structural parameters and permeability of copolymers for dissolved substances. For PVP content above 25 wt. %, the composition becomes non-technological due to high viscosity. After coating, encapsulated particles are fed into the apparatus 10 for washing with solvent from unreacted residues of monomer. After washing, the encapsulated particles are transferred to the sieve 11 for separation from the solvent, drying in the dryer 12 and packaging.

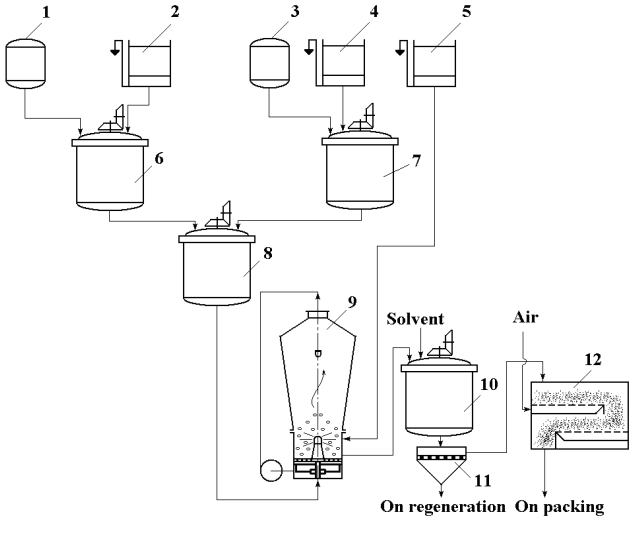


Fig. 5. Flowsheet of forming of polymeric membranous coatings, based on HEMA-PVP copolymers, on the solid dosage forms

6. Discussing the research results of obtaining patterns and properties of hydrogel membranes

The investigations (p. 5. 1) found that in the presence of water-soluble PPS it is necessary to increase gradually the temperature (to 343 K) and duration of the synthesis (to 4 h) to run the polymerization till the high conversion degrees. It is not always acceptable from economical (low performance) and technological (there is a number of drugs that can not be heated to such temperatures) points of view. Thereby it appears effective to use the PVP-$FeSO_4$ complex as the initiating system. This made it possible to significantly shorten the duration and reduce the synthesis temperature up to the room one (Table 1).

Experimental studies (p. 5. 1) showed that the diffusion properties of hydrogel membranes can be controllably changed in a wide range. For this reason, different factors of influence (copolymers composition, synthesis mode, membrane thickness etc.) can be used. Previous research has developed a mathematical model of mass transfer from a spherical particle, which is described in detail in [14]. However, from a practical point of view, there is a problem with

a constant rate of drug release into the environment. This problem can not always be solved using monodisperse products. Therefore, in practice, a mixture of capsulated disperse materials of different size is often used. To predict the diffusion-transport properties of hydrogel membrane coatings, a mathematical model of mass transfer from spherical particles of different size, coated with the hydrogel shell was developed (p. 5. 3). The model is designed for a neutral medium and enables to predict the rate and duration of drug release.

But in real circumstances, during the passage through the gastrointestinal tract, therapeutic systems are not only in neutral, but also in acidic and alkaline media. Therefore, further improvements of the mass transfer mathematical model that takes into account these factors are planned.

Implementation of developed compositions and deposition technique will help to provide the consumer market with Ukrainian controlled release drugs, increase their efficiency and reduce the effective single dose of drugs.

7. Conclusions

1. The regularities of membrane coatings forming for solid dosage forms based on HEMA-PVP hydrogels were investigated and the directions of regulation of their properties by using the targeted changes in the composition and structural parameters of the copolymers grid during their synthesis are determined.

2. Parameters of mass transfer from the solid phase of model substances and medicines through the hydrogel shell were studied. It was found that permeability for the water and dissolved low-molecular substances increases with the increasing of PVP-links content in the copolymer and with decreasing of spatial grid density.

3. The model of mass transfer from solid particles, coated with hydrogel shell, was developed. It takes into account stages of polymeric membrane swelling, dissolving of the solid component, its diffusion to the membrane's surface and through the membrane, mass transfer of dissolved component in the environment. This model makes it possible to predict the duration of release of the target component at the stage of preparation of encapsulated systems of sustained and controlled drug release on the basis of the developed hydrogels.

4. The process flow diagram of hydrogel membrane coatings forming on solid dosage forms was developed. Its distinctive feature is the possibility of combining deposition of the monomer-polymer composition on a solid dosage form and forming of hydrogel grid (polymerization deposition) simultaneously in one stage. Thanks to a possibility of simple control of the initial composition and formation modes, targeted change of grid structural parameters and, hence, the performance properties of coatings is provided.

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