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ВИСОКОМОЛЕКУЛЯРНІ СПОЛУКИ ТА (НАНО)КОМПОЗИЦІЙНІ МАТЕРІАЛИ

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INVESTIGATION OF SORPTION / DESORPTION PROCESSES OF MEDICAL SUBSTANCES BY COMBINED HYDROGELS

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The article represents the results of studies of sorption and desorption of novocaine and lidocaine by combined polyacrylamide gelatinous hydrogels. The rates of sorption by hydrogels are different, depending on the structure and the presence of functional groups in the structure of absorbed substances. The study of the desorption of medicinal substances from the polymeric matrix of hydrogel showed that release of novocaine and lidocaine lasts for a long time, which can ensure their prolonged delivery. Developed hydrogel materials can be used in cosmetology and medicine, as transdermal drug delivery systems.

Key words: hydrogel, collagen, gelatin, sorption, novocaine, lidocaine.

Introduction

Recently, significant advances in medicine have been made due to the great attention paid to the development of controlled release dosage forms [1–4]. There are a large number of medicines intended for the release of therapeutic agents. In the treatment of wounds of different origins, transdermal therapeutic systems are increasingly used to combine the prolonged and targeted release of a wide range of therapeutic drugs [5,6]. They also provide intensive absorption of the wound exudate and create a barrier that protects the wound from infection. Synthetic and natural hydrogels are used to create transdermal therapeutic systems, however, the combination of both types is preferable in the synthesis of new hydrogel materials. Simultaneous attraction of synthetic and natural macromolecules into the hydrogel matrix endows the combined hydrogels with new valuable properties [7, 8].

Natural polymers of protein nature are widely researched and used in the creation of combined hydrogels, since they have the advantage of imitating many features of the extracellular matrix and thus have the potential to direct the cell growth and organization during tissue regeneration and wound healing [9, 10].

Collagen is one of the most common polymers of protein nature. Being the main protein component of the extracellular matrix that supports connective tissue, collagen is considered to be an ideal framework or matrix for tissue engineering [11]. However, the complexity of obtaining collagen in a form capable of hydrogel forming, as well as its high cost, makes it unpromising to create therapeutic interventions geared to the needs of the mass consumer.

At the same time it is known that a direct functional analogue of collagen is gelatin, which is obtained from it when using different processing methods. Gelatin is widely used for pharmaceutical and medical needs due to its biocompatibility and ability to biodegrade in physiological environments [12].

Gelatin forms hydrogels on the basis of physical bonds, which, however, lose their structure and break even at body temperature. In order to obtain stable hydrogels with improved physico-mechanical properties of the macromolecule, gelatin must be cross-linked through covalent bonding.

Therefore, the creation of transdermal therapeutic systems based on combined hydrogels is an urgent task.

Materials and methods of research

Reagents. Acrylamide, gelatin (GT), and formaldehyde manufactured by Aldrich were used without further purification.

Synthesis of polyacrylamide (PAA) *and synthesis of poly-N-(hydroxymethyl) acrylamide* (PNHA) were performed according to the procedure described in [13].

The hydrogels were synthezied via reaction of poly-N-(hydroxymethyl) acrylamide and polyacrylamide (during the preparation of combined hydrogels a part of the polyacrylamide was replaced by gelatin) with the given ratio. The resulting composition was homogenized, adjusted to pH of 2–3 by introducing a 10 % acid solution and heated for some time in a sealed reactor at the temperature of 313–343 K. To remove the unreacted substances, the samples were washed with water for 15 hours at 323 K.

The degree of swelling of the hydrogels (the ratio of water weight in the hydrogel sample to the polymers weight in the hydrogel sample) was determined by gravimetric method at 293 K in distilled water and was calculated according to the method [14].

The sorption of novocaine and lidocaine from their aqueous solutions by polyacrylamide and combined hydrogels was carried out as follows: 1. Hydrogel samples were washed and dried to water content of 85 %; then they were placed in eightfold (relative to hydrogel) excess of drug solution (novocaine concentration was within 0.001–0.005 g/l, lidocaine concentration was 0.02–0.5 g/l); 2. The change in the drugs concentration was controlled by sampling the solution and measuring the optical density on a UV spectrophotometer "SPECORD-M40" (Germany) (for novocaine λmax = 290 nm, for lidocaine λmax = 262 nm); 3. Quantitative evaluation of the drug content in solution was performed using the appropriate calibration dependence of the optical density of novocaine or lidocaine solution on its concentration.

Desorption of novocaine and lidocaine from polyacrylamide and combined hydrogels saturated with aqueous solutions of drugs to a given degree of swelling and their content of 2 %, was carried out as follows: 1. Samples were placed in eightfold excess of water; 2. After a certain time the samples were withdrawn and their optical density was measured; 3. Quantitative evaluation of the drug content in solution was performed using the appropriate calibration dependence and the percentage of the drug remained in the hydrogel was calculated.

Results and Discussion

To study the sorption and desorption processes polyacrylamide and combined polyacrylamide-gelatin hydrogels were used. The hydrogel materials (Fig. 1) were obtained at the reagents ratio and synthesis conditions shown in Table 1 according to the procedure described in the experimental part.

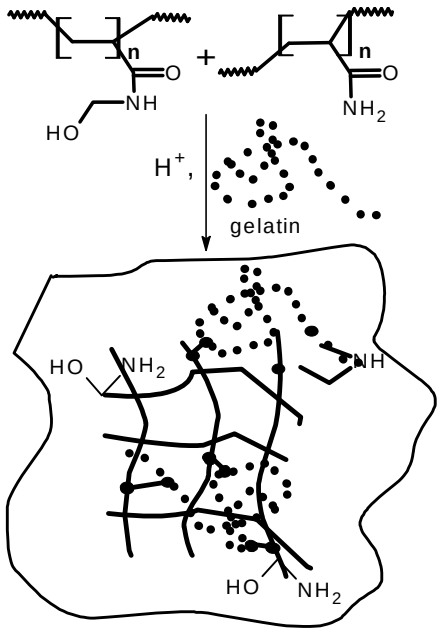


Fig. 1. Scheme of combined hydrogel formation

Table 1

Conditions for hydrogels synthesis (T=343 K, pH=2, C*=14 %, t=15 hours.)

No.	Polymers ratio			GT content in hydrogel, %	Gel-fraction, %
	PNHA	PAA	GT		
1.	1	1	0	0	90
2.	1	0.7	0.3	2.1	80
3.	1	0.6	0.4	4.2	72
4.	1	0	1	7	56
5.	1	0.8	0.2	1.4	67
6.	1	0.2	0.8	5.6	68

** Total concentration of polymers.*

The presence of methylol groups which are active in condensation reactions in the poly-N-

(hydroxymethyl) acrylamide structure makes it possible to use this compound as an effective multicenter cross-linking agent for the synthesis of three-dimensional hydrogels based on polyacrylamide.

Moreover, in this case there is ample opportunity to regulate the chemical nature of the hydrogel polymer framework through the grafting of fragments and macromolecules of another nature. The use of gelatin as a prepolymer in the synthesis of combined polyacrylamide-gelatin hydrogels alters their structure and properties compared to polyacrylamide hydrogels.

It is obvious from Fig. 2 that the introduction of gelatin increases the rate of swelling compared to polyacrylamide synthesized under the same conditions. With increasing gelatin content from 2.1 to 4.2 % in the hydrogel sample, the degree of swelling increases by 30 % (6 hours of swelling). The maximum swelling (S_{max}) of these samples determined after 7 days shows that the polyacrylamide hydrogel achieves a greater degree of swelling compared to the hydrogels with gelatin content of 2.1 % and 4.2 %, and the hydrogel with 5.6 % of gelatin was incompletely cross-linked and dissolved for 4 days. Samples of hydrogels 1, 2, and 3 (Table 1) were used to investigate the sorption and desorption of lidocaine and novocaine.

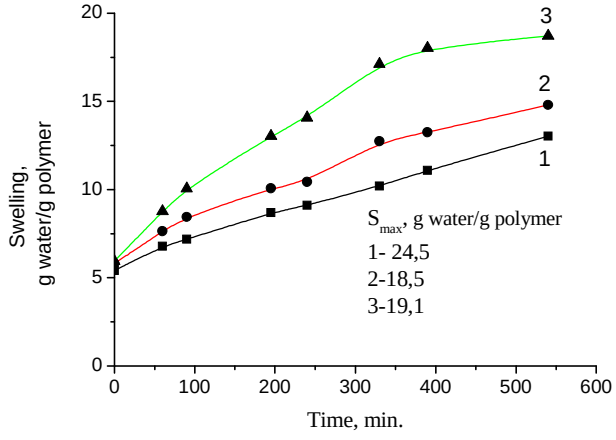


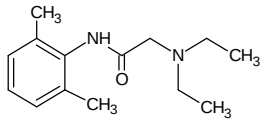
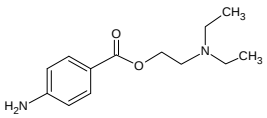
Fig. 2. Swelling curves of hydrogels of different composition: 1-hydrogel without gelatin; 2 - hydrogel with gelatin content of 2.1 %; 3- hydrogel with gelatin content of 4.2 %

To study the sorption and desorption processes the following anesthetics were selected: novocaine (procaine, 2-(diethylamino)ethyl-4-aminobenzoate) and lidocaine (xycaine, xylocaine, 2-(diethylamino)-N-(2,6-dimethylphenyl) acetamide). Table 2 shows the structural formulas and characteristics of these substances.

As it is known [6, 15], sorption of drugs by hydrogels is mainly studied by two methods. The first method is that the most swollen hydrogel is placed in the drug solution and the change in its concentration is determined. The essence of the second method is that the drug sorption and the hydrogel swelling occur simultaneously. In this work, the sorption of drugs from aqueous solutions was investigated by the second method.

Table 2

Substances used for sorption studies

Substance/ structural formula	Maximum adsorption, nм	Molar coef-ficient of extinction E, l/(mol×cm)
Lidocaine 	262	22
Novocaine 	290	12400

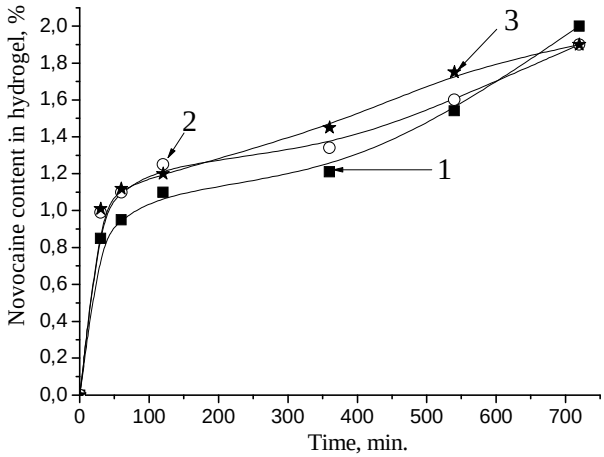


Fig. 3. Kinetic curves of novocaine sorption by combined hydrogels: 1 – hydrogel without gelatin; 2 – hydrogel with gelatin content of 2.1 %; 3 – hydrogel with gelatin content of 4.2 %

The kinetic curves of sorption by hydrogels of different composition of novocaine (Fig. 3) from their aqueous solutions, show the dependence of the sorption

rate on the structure and presence of functional groups in the structure of the adsorbed substances. Novocaine is adsorbed within 6–12 hours, and lidocaine reaches equilibrium after 2 hours. No dependence of the sorption rate on the gelatin content in hydrogels is observed during the sorption.

Figures 4 and 5 show the kinetic desorption curves of lidocaine (Fig. 4) and novocaine (Fig. 5) from hydrogels of different compositions. The hydrogels with adsorbed novocaine and lidocaine were used to study the desorption processes and the amount of drug sorbed by hydrogel was taken as 100 %.

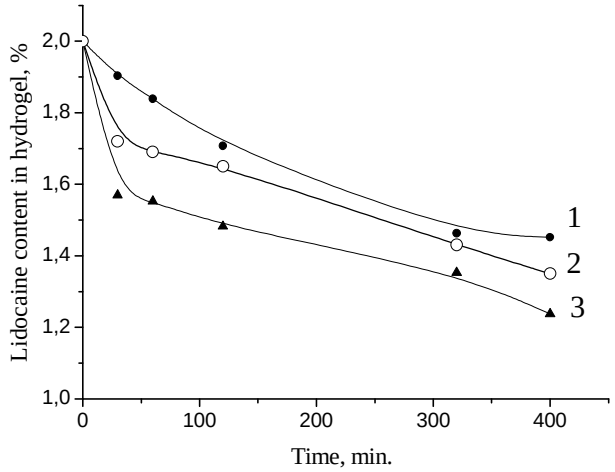


Fig. 4. Kinetic curves of lidocaine desorption from combined hydrogels: 1 – hydrogel without gelatin; 2 – hydrogel with gelatin content of 2.1 %; 3 – hydrogel with gelatin content of 4.2 %

Drug release studies have shown differences in the desorption process between lidocaine and novocaine.

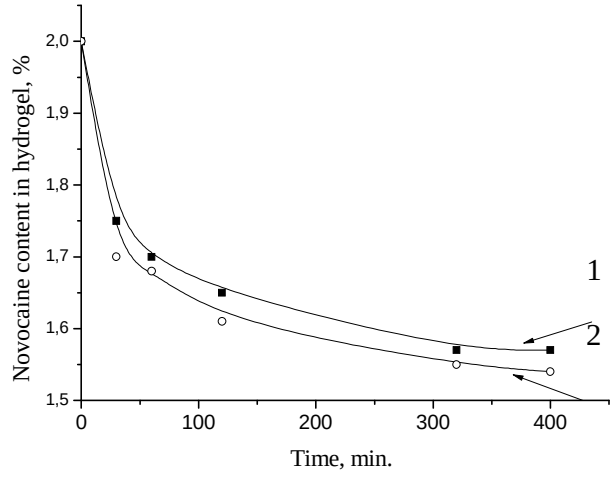


Fig. 5. Kinetic curves of novocaine desorption from combined hydrogels: 1 – hydrogel without gelatin; 2 – hydrogel with gelatin content of 2.1 %

When lidocaine is desorbed from the hydrogel, 10–20 % of the drug is released into the solution for 1 hour, and 30-40 % for 6 hours (Fig. 4). The release of lidocaine depends on gelatin content of the samples. With increasing gelatin concentration from 2.1 to 4.2 %, the difference in lidocaine release is 8–10 %, however, this effect is not observed with further increase in gelatin content in the samples. The maximum release of lidocaine (70–80 % of its initial content in the hydrogel) occurs after 24 hours.

When novocaine is desorbed, 10–15 % are released for 1 hour, 20–25 % for 6 hours (Fig. 5). The retardation of novocaine desorption is apparently due to the presence of a primary amino group in the novocaine structure capable to bind with free methylol groups of poly-N-(hydroxymethyl) acrylamide. This is also a reason that after 24 hours the novocaine release is only 30–35 % of its initial content in the hydrogel.

Conclusions

The study of drugs sorption by combined hydrogels proceeds with different rates depending on the structure and the presence of functional groups in the structure of the adsorbed substances.

The release of drugs from hydrogel polymeric matrix takes a long time, which will ensure prolonged delivery of drugs.

Thus, varying the composition and structure of the hydrogels, it is possible to create transdermal systems of prolonged delivery of therapeutic drugs of different nature.

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ДОСЛІДЖЕННЯ ПРОЦЕСІВ СОРБЦІЇ/ДЕСОРБЦІЇ ЛІКАРСЬКИХ РЕЧОВИН КОМБІНОВАНИМИ ГІДРОГЕЛЯМИ

Наведено результати досліджень щодо сорбції та десорбції комбінованими поліакриламід-желатиновими гідрогелями новокаїну та лідокаїну. Показано, що сорбція/десорбція гідрогелями проходить з різною швидкістю залежно від будови та наявності функціональних груп у структурі речовин, що сорбуються. Під час дослідження десорбції лікарських речовин з полімерної матриці гідрогелю встановлено, що вивільнення новокаїну та лідокаїну відбувається доволі тривалий час, що може забезпечити їх пролонговану доставку. Розроблені гідрогелеві матеріали можуть бути використані в косметології і медицині як трансдермальні системи доставки ліків.

Ключові слова: гідрогель, колаген, желатин, сорбція, новокаїн, лідокаїн.