

Synthesis of Porphyrin-Containing Hydrogels under Microwave Radiation Conditions

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Dedicated to the memory of Prof. G. V. Ponomarev, Prof. A. F. Mironov and T. S. Kurtikyan

The synthesis of new functional hydrogels on acrylamide and tetra-aryl-substituted porphyrins with N,N'-methylene-bis-acrylamide and the study of their physical and chemical properties are described, the hydrogels being synthesized at different ratios of initial components under microwave conditions. Electron spectroscopy and scanning electron microscopy were used to characterize the hydrogels obtained; their sorption properties being also investigated. Best sorption properties were shown by hydrogels containing mono-meso-allyloxy substituted porphyrin. The values of the gel fraction, the swelling degree and the water content in the hydrogels were established to be significantly affected by the amount of crosslinking agent used in the hydrogels synthesis.

Keywords: Porphyrin-containing hydrogels, porphyrin monomers, microwave synthesis, functional materials, sorption properties.

Синтез порфириносодержащих гидрогелей в условиях микроволнового излучения

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В работе сообщается о синтезе новых функциональных гидрогелей на основе акриламида и тетра-арилзамещенных порфиринов с N,N'-метилден-бис-акриламидом и исследовании их физико-химических свойств. Синтез гидрогелей проводили с различным соотношением исходных компонентов в условиях микроволнового излучения. Полученные гидрогели были охарактеризованы методами электронной спектроскопии, сканирующей электронной микроскопии, также были изучены их сорбционные свойства. Показано, что наилучшими сорбционными свойствами обладают гидрогели, содержащие моно-мезо-аллилокси-замещенный порфирин. Установлено, что на значения гель-фракции, степень набухания и содержание воды в гидрогелях значительное влияние оказывает количество сшивающего агента, используемого при синтезе гидрогелей.

Ключевые слова: Порфириносодержащие гидрогели, порфириновые мономеры, микроволновой синтез, функциональные материалы, сорбционные свойства.

Introduction

The involvement of new technologies in medicine requires the development of polymeric materials characterized by high biocompatibility, polymeric hydrogels of a wide range of both natural and synthetic porphyrins being a promising type of such materials. Unique physical and chemical hydrogels characteristics with their high biocompatibility made polymeric systems invaluable in a number of related to medicine industries.^[1] Smart artificial hydrogels designed due to natural stimuli-responsive materials are created to respond to environmental physical and chemical stimuli like temperature, pH, ionic strength, magnetic field, electric field, photoradiation and glucose concentration.^[2] Therefore, smart hydrogel functional materials have recently become attention-seeking in medicine.^[3–8] On the other hand, various fields of science and technology extensively exploit tetrapyrrole macroheterocyclic compounds as catalysts and photocatalysts of chemical, photochemical, and electrochemical processes,^[9–15] sensor components^[16] and dyes for solar energy conversion.^[17,18] Moreover, they appeared to be promising materials in photodynamic therapy of cancer in medicine, immunochemistry and NMR tomography.^[19–23] Combining the properties of hydrogels with those of porphyrins will allow developing new functional materials for various medical applications. Nowadays scientists are heavily developing the synthesis of porphyrin-containing hydrogels, the latter proving to be an excellent material in targeted drug delivery and release.^[2,24]

Therefore, the technique of synthesizing porphyrin-containing hydrogels with acrylamide and tetra-aryl substituted porphyrins using N,N'-methylene-bis-acrylamide as a crosslinking agent was developed, their physical and chemical properties being investigated.

Experimental

Acrylamide (AA) (Sigma-Aldrich, purity $\geq 98\%$) that was twofold purified from chloroform by recrystallization was used in the synthesis of polymeric hydrogels,^[25] the porphyrin monomers 5,10,15,20-tetrakis(5-(4'-allyloxy)phenyl)porphyrin (**p1**) and 5-(4'-allyloxyphenyl)-10,15,20-triphenylporphyrin (**p2**) being prepared according to the procedures.^[26,27] N,N'-Methylene-bis-acrylamide (MBA) (abcr GmbH, purity 97%) was used as a crosslinking agent, while 2,2'-azoisobutyronitrile (AIBN) (Vecton, Ch) as the radical polymerization initiator. AIBN was doubly purified from ethyl alcohol by recrystallization.^[25] N,N'-Methylene-bis-acrylamide was recrystallized from acetone into hexane two times. 1,4-Dioxane (Vekton, BDA) was distilled after 24-hour incubation over KOH.

The synthesis of porphyrin-containing hydrogels was performed by radical copolymerization in solution using a Discover microwave system (CEM Corporation) in dynamic power mode. Electronic reflection spectra of porphyrin-containing hydrogels were recorded on a SHIMADZU UV-2550 spectrophotometer with a diffuse reflection attachment. The hydrogels surface morphology was examined by a scanning electron microscope Tescan Vega 3 (Czech Republic). The samples were pre-coated with carbon using the film evaporator Q150TES of electrically conductive coatings (carbon, metal) (Quorum Technologies, UK).

Hydrogels Synthesis. The suspension of acrylamide, MBA and the corresponding porphyrin monomer (**p1**) was placed

in a 10 mL microwave synthesis tube to obtain hydrogels **G1.1-G1.3**, while porphyrin monomer (**p2**) was added to obtain hydrogels **G2.1-G2.9**, mass ratios of reagents being presented (Table 1). The suspension was dissolved in 4 mL of 1,4-dioxane, 1 mg of AIBN was added, then it was incubated under nitrogen for 20 min and placed in a Discover laboratory microwave system. The synthesis was performed at 70 °C and constant stirring for 50 min at a dynamic power of 30 W. The precipitate formed during the reaction was filtered off, washed with chloroform to a clear filtrate and dried at 50 °C. The hydrogels output and formulation of initial components loading are shown (Table 1).

Table 1. Loading conditions of initial components.

Hydrogel	Mass ratio p : AA	Mass ratio MBA : AA	Yield, mg
G1.1	1:20	1:10	103.6
G1.2	1:10	1:10	107.7
G1.3	3:20	1:10	106.5
G2.1	1:20	1:10	104.6
G2.2	1:10	1:10	103.1
G2.3	3:20	1:10	104.5
G2.4	1:20	3:20	113.1
G2.5	1:10	3:20	112.7
G2.6	3:20	3:20	111.7
G2.7	1:20	1:5	115.6
G2.8	1:10	1:5	117.0
G2.9	3:20	1:5	118.8

Gel fraction. The gel fraction GF, % was determined by gravimetric method. The hydrogel samples were dried in the desiccator at 50 °C for 24 hours. Then they were incubated in water for 24 hours at room temperature to remove the soluble fractions, the water being changed two times. The hydrogels were then dried again at 50 °C for 24 hours.^[28–32] The gel fraction was calculated according to the Equation (1). Each sample was measured 3 times.

$$CF = \frac{m_{\text{dry}}}{m_0} 100\% \quad (1)$$

where m_0 is the mass of dry hydrogel before extraction; m_{dry} is the mass of dried gel fraction after extraction.

Water content in the hydrogels and degree of swelling. The synthesized hydrogels were allowed to swell in 20 mL of water for 24 h. The polymers were removed from the water after 24 hours, the surface water being carefully removed with filter paper, to determine the final weight of the swollen polymer after soluble components extraction. The water content in the hydrogels WC, % and the degree of swelling SR, % were calculated from the weight of the swollen and dry sample using Equations (2) and (3), respectively.^[33–38]

$$WC = \frac{m_w}{m_s} 100\% \quad (2)$$

$$m_w = m_s - m_{\text{dry}}$$

$$SR = \frac{m_s - m_{\text{dry}}}{m_{\text{dry}}} 100\% \quad (3)$$

where m_w is the weight of water in the gel; m_s is the weight of the swollen gel; m_{dry} and m_s are the masses of dry and swollen hydrogel, respectively.

Results and Discussion

The radical copolymerization reaction between porphyrin with acrylamide and *N,N'*-methylene-*bis*-acrylamide in 1,4-dioxane was performed to obtain polymeric hydrogels (Figure 1). AIBN was used as an initiator. The reaction mixture was kept under nitrogen for 20 minutes before synthesis in order to prevent the formation of peroxides and oxidative degradation of the resulting compounds. Hydrogels with different contents of mono- or tetra-substituted porphyrin in the polymer chain were synthesized under the selected conditions. All synthesized hydrogels were light pink to dark brown in color, insoluble in water though capable of swelling in it.

The amount of crosslinking agent was varied when loading the parent components to obtain porphyrin polymers with different degrees of crosslinking (Table 1). It was impossible to obtain fully cross-linked, water-insoluble compounds with the ratio of MBA : AA < 1 : 1, crosslinked structures being yielded only with the higher ratios of MBA : AA \geq 1 : 10. The tetrapyrrole macroheterocycle seemed to incorporate into the side branch of the growing polymer chain when using mono-*meso*-substituted porphyrin (**p2**) to synthesize hydrogels, MBA appearing the crosslinking node. However, not only *N,N'*-methylene-*bis*-acrylamide but also the tetrapyrrole macroheterocycle acted as a cross-linking node when tetra-*meso*-substituted porphyrin (**p1**) was used.

All obtained compounds were studied by electron spectroscopy. Powdered hydrogels were applied to a glass substrate to record their reflection spectra. The electron reflectance spectra of hydrogels containing **p1** were shown (Figure 2). Previously, an increase in the absorption band intensity in the 650 nm region and the appearance of an additional absorption band in the 730 nm region was shown to be the result of the synthesis of water-soluble porphyrin-containing AA-based polymers in comparison to the electronic absorption spectra of the original por-

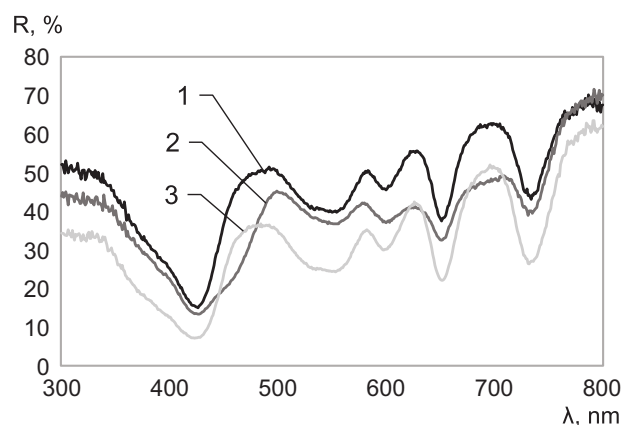


Figure 2. Electronic reflectance spectra of hydrogels based on AA, MBA, and **p1**: 1 – G1.1; 2 – G1.2; 3 – G 1.3.

phyrin monomers typical of chlorin and bacteriochlorin structures.^[39] Such changes were observed when obtaining porphyrin-containing polymers under both microwave and thermal heating conditions. Presumably, the change in the structure of tetrapyrrole macroheterocycles incorporated into the polymer chain is related to the influence of the polymer matrix as well as the initiator of radical polymerization during the preparation of porphyrin polymer systems. Similar to the experimental results given above, the synthesis of porphyrin-containing hydrogels resulted not only in the incorporation of porphyrin monomers into the side polymer chain but also in the formation of the two new chromophores.

The surface morphology of the obtained hydrogels was examined by Tescan Vega 3 scanning electron microscope. The samples were investigated at a resolution of 2–10 μm with an accelerating voltage of 5–20 kV at high vacuum, surface microphotographs of some synthesized hydrogels being presented (Figure 3).

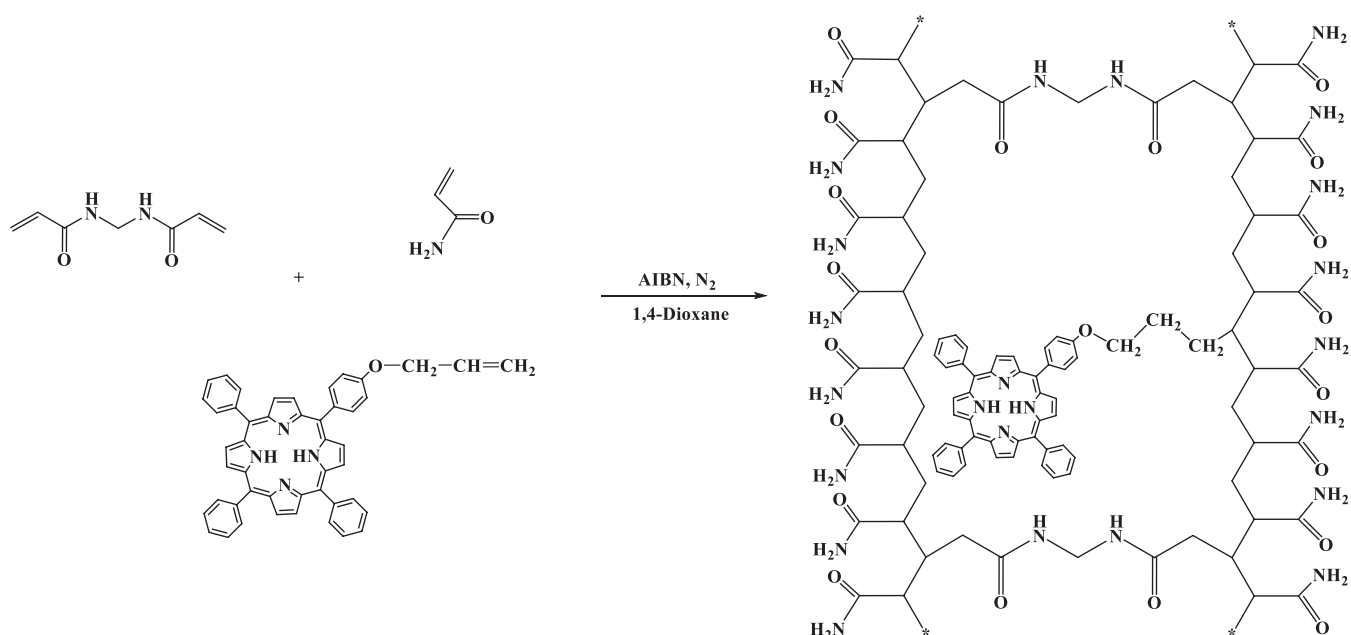


Figure 1. Reaction of hydrogel formation based on AA, MBA, and **p2**.

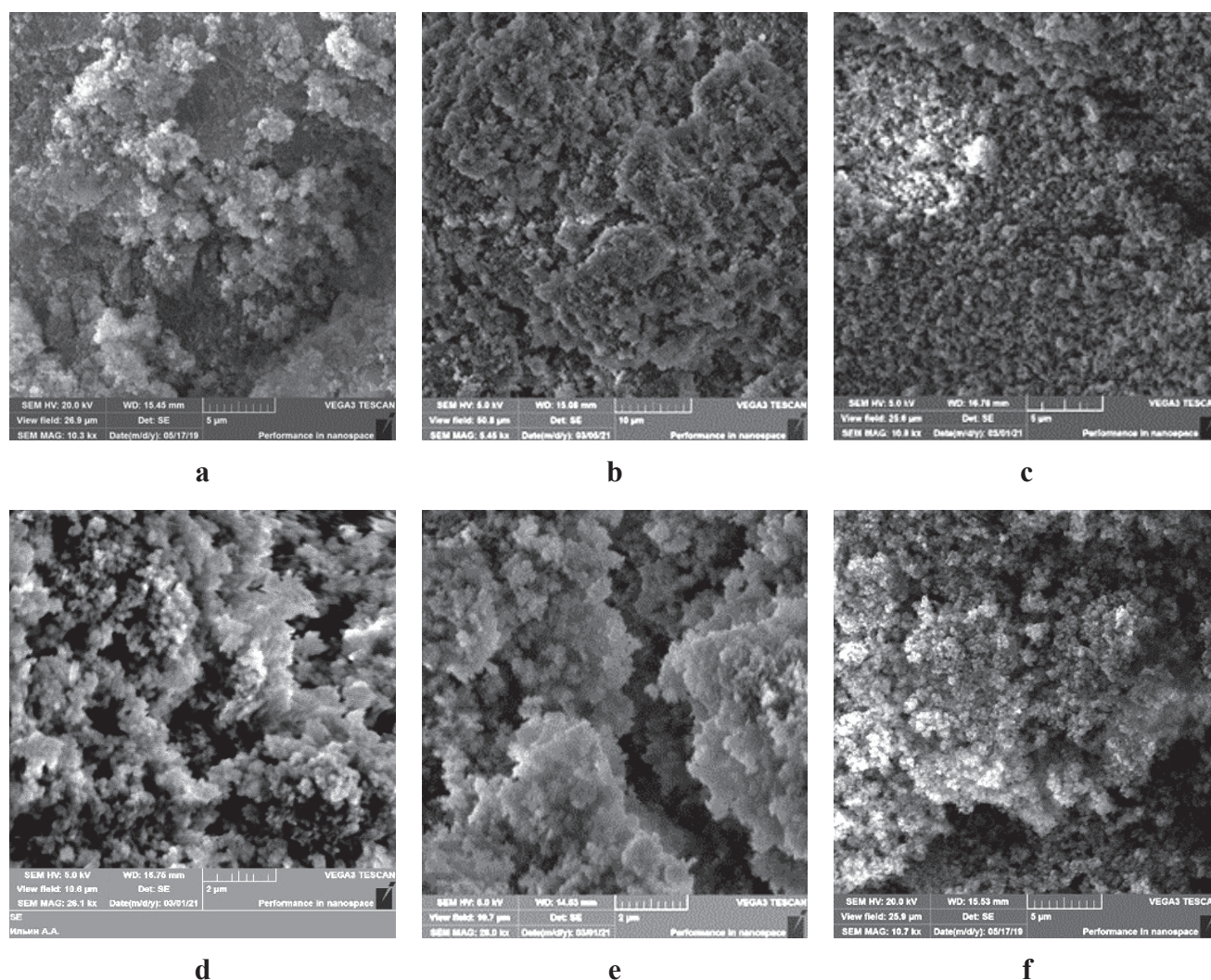


Figure 3. Surface microphotographs of the synthesized hydrogels: a – G1.2; b – G1.3; c – G2.1; d – G2.2; e – G2.3; f – cPAA.

All samples have a sufficiently loose structure. Neither the nature of the included porphyrin monomer nor its amount in the hydrogel practically affect the surface morphology of the synthesized porphyrin-containing hydrogels when compared to cross-linked unmodified polyacrylamide (cPAA).

The sorption capacity of hydrogels and the gel fraction (GF) were studied on a line of hydrogels with mono-*meso*-aryl-substituted porphyrin at the MBA : AA = 1 : 10, 3 : 20, 1 : 5 ratios as well as on a line of hydrogels with different porphyrin monomers (**p1** or **p2**) at the MBA:AA = 1:10 ratio.

The gel fraction ranging from 35 % to 85 % was calculated using equation (1) depending on the MBA : AA ratio. The results obtained were given (Table 2).

The higher the proportion of N,N'-methylene-*bis*-acrylamide in the initial mixture, the fewer the low-molecular-weight fractions in the obtained compounds. However, the higher the amount of porphyrin in the initial mixture, the higher the gel fraction in the synthesized hydrogel. The greatest loss of hydrogel mass, and hence, the content of low molecular weight fractions, was observed in the presence of tetra-*meso*-aryl-substituted porphyrin comparing GF, % of hydrogels with different porphyrin monomers and the same ratio of MBA : AA = 1 : 10 in the initial mix-

Table 2. Gel fraction content in synthesized hydrogels.

Hydrogel	Mass ratio MBA : AA	GF, %
G1.1	1:10	36.98
G1.2	1:10	42.9
G1.3	1:10	44.38
G2.1	1:10	54.85
G2.2	1:10	50.46
G2.3	1:10	55.57
G2.4	3:20	67.59
G2.5	3:20	80.40
G2.6	3:20	85.94
G2.7	1:5	74.39
G2.8	1:5	84.30
G2.9	1:5	78.85

ture. It was likely to be accounted for the large contribution of the chain breaking reaction during the copolymerization reaction of AA with tetra-*meso*-aryl-substituted porphyrin.

Table 3. Data on the sorption capacity of hydrogels based on AA and **p2** depending on the ratio of MBA : AA.

Hydrogel	Mass ratio MBA:AA	SR, %	WC, %
cPAA	1:10	2911	96.68
G2.1	1:10	1504	93.77
G2.2	1:10	1512	93.80
G2.3	1:10	1534	93.88
cPAA	3:20	2037	95.32
G2.4	3:20	1959	95.14
G2.5	3:20	1189	92.24
G2.6	3:20	1221	92.43
cPAA	1:5	1801	94.74
G2.7	1:5	1311	92.91
G2.8	1:5	812	89.04
G2.9	1:5	857	89.55

The sorption of water and other liquids being the main property of hydrogels, the sorption capacity of the obtained hydrogels with mono-*meso*-aryl-substituted porphyrin was investigated due to both the amount of crosslinking agent and the nature of the porphyrin monomer used. AA-based hydrogels unmodified by porphyrin with different crosslinking agent contents were taken as control samples.

The water content in the hydrogels WC, % and the degree of swelling SR, % were calculated by the given in the Experimental part formulas (2) and (3), respectively. The data on WC, % and SR, % of the synthesized hydrogels due to the MBA content were summarized (Table 3, Figure 4). The dependence of hydrogels WC, % and SR, % on the nature of the porphyrin monomer used was shown (Table 4).

The sorption capacity (WC, %, and SR, %) of hydrogels with **p2** was noted to be strongly influenced by the MBA : AA ratio. The higher MBA content in the initial component load, the lower the values of WC, % and SR, %. Moreover, the presence of porphyrin in the hydrogel decreased the values of SR, %, compared to unmodified cPAA. The swelling coefficient of hydrogels obtained with mono-functional porphyrin appeared to be higher than that of hydrogels obtained with tetra-functional porphyrin at the same MBA : AA ratio. However, the WC, % hydrogels values were not considerably affected by the nature of the porphyrin monomer; they were found to stay at approximately the same level.

Conclusions

The technique of synthesizing porphyrin-containing acrylamide-based hydrogels by radical copolymerization in solution under microwave radiation conditions was developed, all the compounds obtained being characterized by electron spectroscopy and scanning electron microscopy. The sorption properties of the synthesized hydrogels were examined, the content of the gel fraction being determined. The water content values and the degree of swelling of SR hydrogels were observed to be heavily influenced by the N,N'-methylene-*bis*-acrylamide/acrylamide ratio. The GF values depended on the porphyrin monomer nature as well as the N,N'-methylene-*bis*-acrylamide/acrylamide ratio. The higher the MBA content in the initial mixture, the higher GF values were observed. It is worth noting that water-soluble porphyrin-containing polymers based on acrylamide, including those containing chlorin and bacteriochlorin fragments, may be interesting in terms of their use as photosensitizers of singlet oxygen generation in biological media. The porphyrin-containing hydrogels obtained on their basis can be useful in antimicrobial

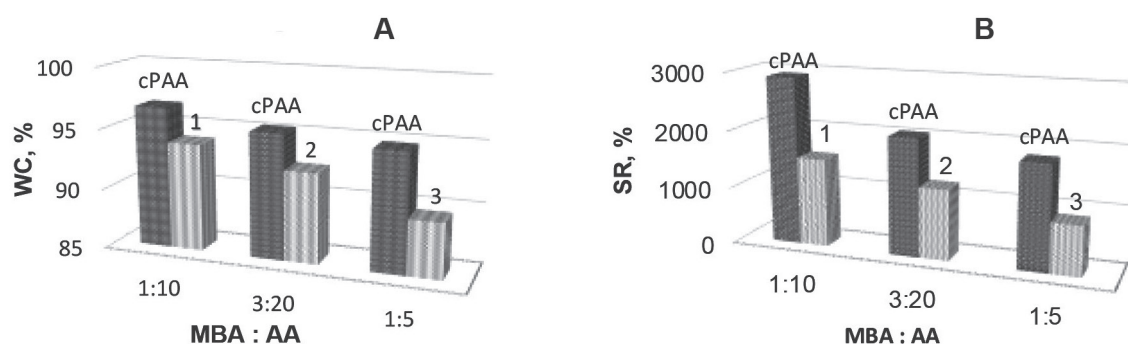

Figure 4. A – dependence of WC, % of hydrogels on the ratio of MBA : AA in the initial reaction mixture; B – dependence of SR, % on the ratio of MBA : AA in the initial mixture: 1 – **G2.3**, 2 – **G2.6**, 3 – **G2.9**.

Table 4. Sorption properties of hydrogels depending on the used porphyrin monomer nature at the ratio MBA : AA = 1 : 10.

Hydrogel	WC, %	SR, %	Hydrogel	WC, %	SR, %
G1.1	93.83	1520	G2.1	93.77	1504
G1.2	93.34	1410	G2.2	93.80	1512
G1.3	93.12	1354	G2.3	93.88	1534

photodynamic therapy in the treatment of damaged skin, which undoubtedly makes these hybrid polymeric materials attractive in medicine.

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