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Synthesis and characterization of new biodegradable gels based on 2,2'-(ethylenedioxy) diethanethiol and pentaerythritol triacrylate

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ABSTRACT

The work is devoted to the synthesis and characterization of gels based on the monomers pentaerythritol triacrylate (PETriA) and 2,2'-(ethylenedioxy)diethanethiol (EDODET) by thiol-ene "click" polymerization. The properties of the obtained gels were investigated by IR, Raman spectroscopy, mechanical analysis. Sol-gel analysis of obtained networks was carried out and the degradability was investigated. The results of IR spectroscopy confirmed the presence of -C = O and -C-O-C- groups in the composition of the obtained gels. The presence of unreacted C = C bonds conjugated with C = O, as well as thiol groups, varies depending on the composition of the initial monomer mixture (IMM). Raman spectroscopy results correlate well with IR data. Raman spectra also show C-S, S-S and SH characteristic bands that are difficult to identify by IR spectroscopy. It was found that the composition of MM affects the physicochemical properties of the synthesized gels. The highest yield of the gel fraction of obtained polymers was found in samples with an equimolar composition of IMM. The analysis of mechanical properties showed that gels with an excess of PETriA exhibit more elastic properties, and an excess of EDODET leads to the formation of networks with a higher crosslinking density. The study of the ability of obtained PETriA-EDODET gels to degrade in a 3% solution of hydrogen peroxide showed that the polymer network degrades by 12% within 60 days. This property of the obtained gels can find application in the creation of targeted drug delivery systems with their prolonged release.

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Introduction

The popularity of thiol-ene "click" polymerization for the synthesis of various polymer materials is growing every year. These reactions are very versatile and can be carried out using radical conditions including photochemical initiation, or can simply be promoted with polar solvents such as N, N-dimethylformamide (DMF) [1].

Thiols and unsaturated compounds are often used in stoichiometric ratios (1:1) to achieve complete conversion and increase the mechanical properties of the target product by thiol-ene polymerization [2]. However, the resulting materials usually have inactive surfaces with such a ratio of the starting components. The work [3] reports the first use of nonstoichiometric thiol-unsaturated compound ratios leading to the production of

materials with residual unreacted functional groups both in the bulk and on the surface. The presence of unreacted thiol groups on the surface of nanoparticles as a result of nonstoichiometric thiol-ene interactions can impart mucoadhesive properties to materials - the ability to adhere and retain on the surface of the mucous membrane due to the formation of disulfide bonds with cysteine residues of mucins [4].

Recently, the use of thiol-ene polymers is mainly concentrated in the biomedical field, mostly in the form of gels [5]. A wide variety of polymer systems have been successfully synthesized using various types of multifunctional unsaturated compounds and thiols [[6], [7]]. Biodegradable thiol-ene systems are of particular interest [8]. Biodegradation in the case of biomaterials for medical use focuses on biological processes within the body that cause

gradual destruction of the material [9]. The following mechanisms of destruction are distinguished: hydrolytic and enzymatic [10]. In this work, we studied polymeric materials that contain hydrolysable bonds in the polymer chain, such as an ester group, and, accordingly, degrade by a hydrolytic mechanism.

Experimental part

Materials. Pentaerythritol triacrylate (PETriA) manufactured by Aldrich Chemical Co (USA), containing 350 ppm of hydroquinone monomethyl ester as an inhibitor, was used without further purification.

2,2'-(ethylenedioxy)diethanethiol (EDODET) manufactured by Aldrich Chemical Co (USA) was used without additional purification.

N,N-Dimethylformamide (DMF) manufactured by Aldrich Chemical Co (USA) was used without additional purification.

Gel synthesis. Synthesis of gels of various compositions (the ratio of monomers [PETriA:EDODET] = [2:1], [1:1] and [1:2] mol/mol) was carried out in closed glass penicillin vials in a DMF solvent (50 mass.% solvent and 50 mass.% monomer mixture) with constant stirring on a laboratory shaker GFL 3005 (Germany) for 24 hours at 30°C. The formation of a crosslinked gel structure was carried out within 24 hours, depending on the composition of the initial monomer mixture (IMM). Then the resulting gels were washed from unreacted monomers for 1 hour in DMF, 6 hours in acetone (3 changes of acetone) and 24 hours in water (3 changes of water). The washed polymers were dried in a lyophilic freeze-dryer to constant weight.

Physicochemical research methods. The study of the kinetics and equilibrium degree of swelling in distilled water was carried out by the gravimetric method. The equilibrium degree of swelling was calculated by the formula

$$\alpha = \frac{m_{swollen} - m_{dry}}{m_{dry}} \quad (1)$$

where $m_{swollen}$ and m_{dry} – mass of swollen and dry samples, respectively.

For sol-gel analysis the synthesized gel samples were washed from unreacted monomers for 1 hour in a DMF solution, then in an acetone solution (3 changes of solvent), and then in water. After that washed gels were dried in a freeze-dryer to constant weight.

The content of sol and gel fractions was calculated using the formulas

$$G\% = \frac{m_{dryw.}}{m_{synt}} \times 100\% \quad (2)$$

$$S\% = 100\% - G\% \quad (3)$$

where m_{synt} – mass of the synthesized gel; $m_{dryw.}$ = mass of the washed and dried gel.

An analytical balance Sartorius BP 121S (Germany) with an accuracy of 0.0001 g was used to determine the mass of synthesized and washed dried gels. Labconco FreeZone freeze-dryer (USA) was used for drying the samples.

In order to confirm the chemical composition of the synthesized samples, the methods of IR and Raman spectroscopy were used. IR spectroscopy was performed on a Carry 660 Agilent IR Fourier spectrometer (USA).

Raman spectroscopy was performed using a Solver Spectrum setup (Russia). Dried gel samples with a diameter of 0.5 mm were used for the analysis.

The physicochemical characteristics of the synthesized samples were determined on a TA.XTplus Stable Micro Systems instrument (UK) in the compression mode.

Biodegradation degree. The degradability of the resulting gels was studied in a 3% hydrogen peroxide solution. The experiments were carried out in closed glass penicillin vials at a constant temperature of 37 °C in an incubator with occasional stirring. Determination of degradable properties was carried out in several parallel experiments. The degree of degradation (DD) was investigated by the gravimetric method to a constant value of the mass of the samples and was calculated by the formula:

$$DD = \frac{m_0 - m_x}{m_0} \times 100\% \quad (4)$$

where m_x – mass of degraded gel; m_0 – initial mass of gel.

Discussion of results

In this work, the thiol-ene "click" polymerization method was used to synthesize gels based on pentaerythritol triacrylate (PETriA) and 2,2'-(ethylenedioxy)diethanethiol (EDODET) with different ratios of components in the IMM [PETriA:EDODET] = [2:1], [1:1] and [1:2] mol/mol in the presence of DMF.

The chemical composition of the synthesized PETriA-EDODET gels was studied by IR and Raman spectroscopy. IR spectra of dry samples of PETriA-EDODET gels of various compositions are shown in Figure 1. All three presented spectra have a high peak in the range of 1745-1725 cm^{-1} , which corresponds to vibrations of the -C=O group. A broader peak of lower intensity in the region of 1180-1140 cm^{-1} indicates the presence of (-C-O-C-) groups in the composition of the resulting gels [11]. It is also worth paying attention to the peaks in the region of 1640-1630 cm^{-1} for compositions 2:1 mol/mol and 1:1 mol/mol which confirm the presence of unreacted -C=C- bonds conjugated with -C=O . At the same time, for the 1:2 mol/mol composition with a predominance of the thiol component, no characteristic bands are observed in this region, which proves that all double bonds have reacted with -SH groups.

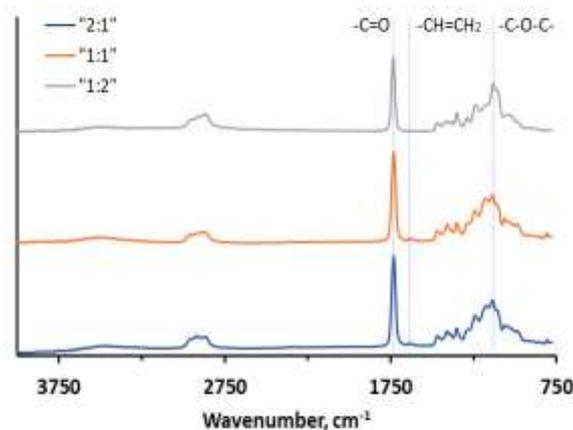


Figure 1 - IR spectra of PETriA-EDODET gels with various compositions of the IMM. [PETriA-EDODET] = [2:1], [1:1] and [1:2] mol/mol

It is known from the literature that the determination of -SH groups content requires the use of Raman spectroscopy, since thiol groups show a weak signal in the IR spectra. Figure 2 shows the results of Raman spectroscopy of PETriA-EDODET based gels. It was found that peaks at 700-650 cm^{-1} are responsible for vibrations of the C-S bond. The peak at 525 cm^{-1} indicates vibrations of the S-S bonds. The absorption band at 2590-2550 cm^{-1} confirms the presence of SH -groups, which indicates an excess of EDODET in the PETriA-EDODET gel with a monomer ratio of 1:2 mol/mol.

The absorption bands in the region of 1680 cm^{-1} are responsible for the vibrations of the -CH=CH_2 bond which confirms the presence of a large number of multiple bonds characteristic of PETriA-EDODET gels structure obtained with an excess of PETriA in

the composition of the IMM (2:1 mol/mol) and correlates with IR spectroscopy data.

Based on the results obtained by IR and Raman spectroscopy a mechanism for the formation of crosslinked gel structure was proposed. During the polymerization reaction, the interaction of monomers with the formation of covalent bonds occurs through the reaction of functional groups such as double bonds of PETriA and thiol groups of EDODET. With an excess of PETriA in the IMM, gels with unreacted multiple bonds in their composition are formed, while an excess of EDODET leads to the formation of gels with unbound thiol groups. Thus, in this work, the formation of such gel structures was confirmed by the data of IR and Raman spectroscopy.

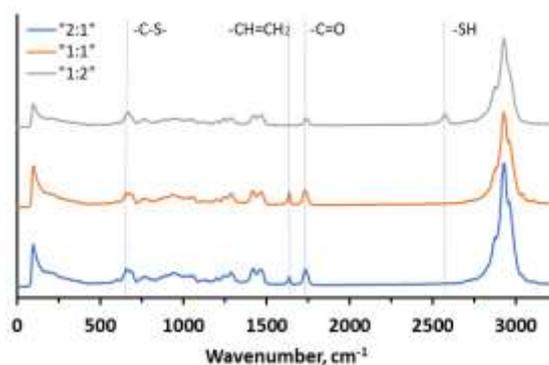


Figure 2 - Raman-spectra of PETriA-EDODET gels with various compositions of the IMM. [PETriA-EDODET] = [2:1], [1:1] and [1:2] mol/mol

Sol-gel analysis is one of the main characteristics of gels. This method allows determination of the polymer network yield. According to the results of sol-gel analysis of PETriA-EDODET gels (Figure 3), the highest yield of gel fraction is observed for the gel sample with the IMM composition of 1:1 mol/mol. This may be due to the fact that for the given IMM composition, the starting monomers PETriA and EDODET are taken in an equimolar ratio. When the ratio of monomers PETriA and EDODET in IMM is 2:1 or 1:2 mol/mol, the yield of the gel fraction decreases. It is likely that with a lack of one of the monomers in IMM, the amount of reacted monomer molecules decreases. Then, unreacted monomers are washed out of the polymer network during washing. In this case, the yield of the gel fraction at 1:2 mol/mol monomer ratio in the IMM is higher than at 2:1 mol/mol ratio. This may be due to the high activity of thiols to form disulfide bonds, which leads to the formation of PETriA-EDODET gel of a higher crosslinking density with an excess of 2,2'-(ethylenedioxy) diethanethiol in the IMM.

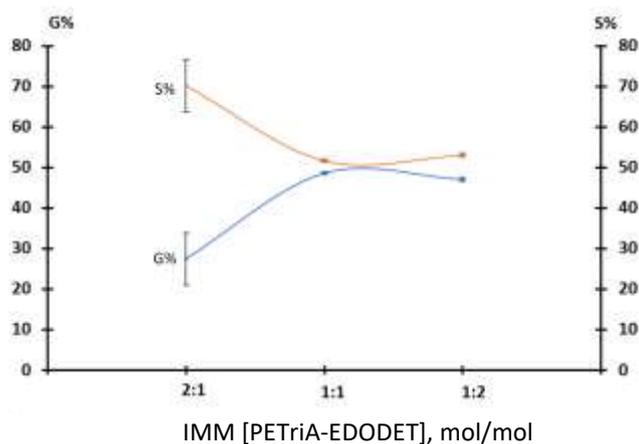


Figure 3 - Dependence of sol and gel fractions yield of PETriA-EDODET gels on IMM composition

In this work, the swelling ability of obtained PETriA-EDODET gels in distilled water was investigated. Figure 4 shows data on the change in the swelling degree of PETriA-EDODET gels over time. It can be seen from the results obtained that the ratio of the starting monomers affects swelling rate of the gels. With an increase in the content of 2,2'-(ethylenedioxy) diethanethiol, the swelling capacity of PETriA-EDODET gels decreases. This behavior may be due to the high content of -SH groups in the gel structure, which form additional disulfide bridges and increase the density of the polymer network.

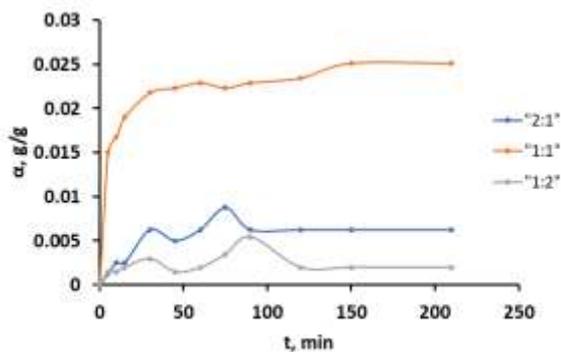


Figure 4 - Dependence of the swelling rate of PETriA-EDODET gels on IMM composition in distilled water

The study of the mechanical characteristics of the gels makes it possible to draw conclusions about the mechanical strength of the gels and indirectly judge their composition. In this work, the mechanical strength of the synthesized gels based on PETriA-EDODET in the compression mode was investigated. Figure 5 shows the deformation curves of PETriA-EDODET gels of various compositions. It was found that all gel samples are sufficiently strong and elastic and do not undergo significant

mechanical destruction. The figure also shows a noticeable effect of the ratio of monomers in the IMM on strength of the resulting gels. The presence of an excess amount of EDODET in the composition of the IMM contributes to a slight decrease in elasticity of the polymer network and an increase in its strength (hardness). This is probably due to the formation of a larger number of crosslinks in the gel, which reduce the mobility of macromolecules. Gels with an excess of PETriA in the IMM composition are more elastic, which may be due to the presence of a larger number of multiple bonds in the gel composition.

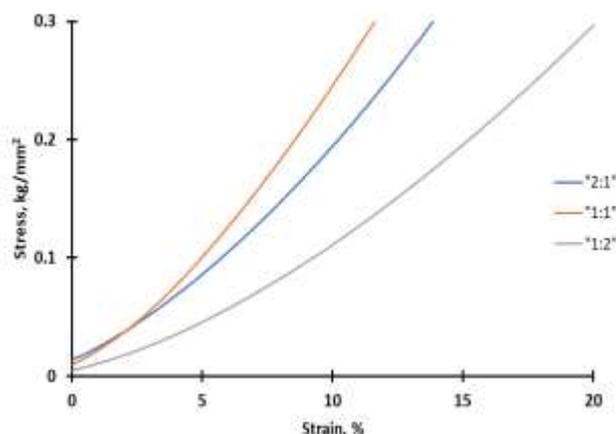


Figure 5 - Deformation curves of PETriA-EDODET gels of various IMM compositions

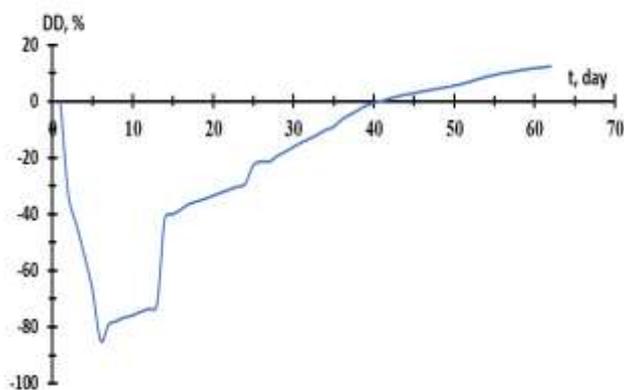
According to the mechanical analysis data, the elastic modulus was also calculated for each gel sample presented in Table 1. The elastic modulus was calculated as the slope of the initial straight section of the gel deformation curve obeying Hooke's law. It was found that an increase of EDODET concentration in IMM composition of PETriA-EDODET gel promotes an increase in the elastic modulus.

Table 1 - Values of the elastic modulus of PETriA-EDODET gels of various compositions of IMM

IMM composition [PETriA:EDODET], mol/mol	Elastic modulus, Pa
2:1	17500
1:1	21428
1:2	25745

It is known from the literature that in the human body in places of inflammation, including in places of formation of oncological tumors of various thiology,

hydrogen peroxide is released in small quantities. The release of hydrogen peroxide prevents the spread of infection and serves as a signal to attract leukocytes [12]. Various concentrations of hydrogen peroxide can be found in the literature to study oxidative degradation in vitro, mimicking in vivo conditions. While the ISO 10993-13 standard implies the use of 3 wt.% (approximately 1 M) H_2O_2 , Cosgriff-Hernandez and colleagues used 20% H_2O_2 with 0,1 M $CoCl_2$, Sun and colleagues used 5 mM H_2O_2 with 50 mM $CuSO_4$ [13]. In this work, the degradation degree of gels based on PETriA-EDODET was studied in 3% hydrogen peroxide solution. Based on the data obtained, a graph of the dependence of the degradation degree of gels on the residence time in solutions was plotted, which is shown on Figure 6. This figure shows that the degradation of the sample with a composition of 2:1 mol/mol occurs after 40 days and the stage of swelling precedes the degradation of the gel. In the first week, the gel swells rapidly, that can be noticed by a significant increase in its mass, then it decreases and the degree of degradation increases, respectively, this behavior correlates with the research data [13], where the degradability of gels based on pentaerythritol tetrakis (3-mercaptopropionate) and tri-/tetraacrylates synthesized by thiol-ene "click" reaction was studied. The degree of degradation of gels based on PETriA-EDODET by day 60 amounted $\sim 12\%$. Polymers with hydrolyzable bonds generally undergo slow degradation from several weeks to a year [14].



[PETriA:EDODET] = [2:1] mol/mol

Figure 6 - Dependence of the degree of degradation of PETriA-EDODET gels on time in a 3% solution of hydrogen peroxide

Conclusions

In this work, gels based on the monomers pentaerythritol triacrylate (PETriA) and 2,2'-(ethylenedioxy) diethanethiol (EDODET) in various ratios and in the presence of a solvent dimethylformamide (DMF) were synthesized by the thiol-ene "click" polymerization method. The properties of the obtained gels were investigated by various physicochemical methods. The results of IR spectroscopy confirmed the presence of $-C=O$ ($1745-1725\text{ cm}^{-1}$), $-C-O-C-$ ($1180-1140\text{ cm}^{-1}$) groups in the composition of the obtained gels. Bands in the region $1640-1630\text{ cm}^{-1}$ for compositions 2:1 mol/mol and 1:1 mol/mol established the presence of unreacted $C=C$ bonds, conjugated with $C=O$, whereas for 1:2 mol/mol composition with a predominance of the thiol component, there are no characteristic peaks in this region. Obtained results of Raman spectroscopy correlate well with IR spectroscopy results and confirm them. Raman spectra also show $C-S$, $S-S$ and $-SH$ characteristic bands that are difficult to identify by IR spectroscopy. It was found that IMM composition affects physicochemical properties of the synthesized gels. Analysis of mechanical properties showed that gels with an excess of PETriA exhibit more elastic properties, while an excess of EDODET leads to the formation of networks with a higher crosslinking density.

The ability of the obtained PETriA-EDODET gels to biodegradation in 3% hydrogen peroxide solution was investigated. It was found that the polymer network degrades by 12% within 60 days. This property of the obtained gels can find application in medicine as a targeted drug delivery system with their prolonged release.

Conflict of interests

On behalf of all authors, the author declares that there is no conflict of interest.

Acknowledgment

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2,2'- (этилендиокси) диэтантриол мен пентаэритритол триакрилат негізінде биологиялық деградацияға ұшырайтын жаңа гельдердің синтезі мен сипаттамасы

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<p>Мақала келді: 06 қыркүйек, 2021 Сараптамадан өтті: 15 қазан, 2021 Қабылданды: 30 қараша, 2021</p>	<p>ТҮЙІНДЕМЕ</p> <p>Жұмыс тиол-ен «клик» полимеризациясы арқылы пентаэритритол триакрилат (ПЭТриа) және 2,2'- (этилендиокси) диэтантриол (ЕДОДЭТ) мономерлері негізінде гельдерді синтездеуге және оларды сипаттауға арналған. Алынған гельдердің қасиеттері ИҚ-, Раман спектроскопиясы, механикалық талдау арқылы зерттелді. Алынған торларға золь-гельдік талдау жүргізілді және деградацияға қабілеттілігі зерттелді. ИҚ-спектроскопиясының нәтижелері алынған гельдердің құрамында -C=O және -C-O-C- топтарының болатындығын растады. C=O-мен түйскен реакцияға түспеген C=C байланыстары, сондай-ақ тиол топтары бастапқы мономер қоспасының (БМҚ) құрамына байланысты өзгереді. Раман спектроскопиясының нәтижелері ИҚ деректерімен жақсы корреляцияланады. Раман спектрлері сонымен қатар ИҚ спектроскопиясымен анықтау қиын C-S, S-S және SH-тән жолақтарды көрсетеді. БМҚ құрамы синтезделген гельдердің физикалық-химиялық қасиеттеріне әсер ететіні анықталды. Алынған полимерлердің гельдік фракциясының ең жоғары шығымы БМҚ эквимольарлық құрамы бар үлгілерде табылды. Механикалық қасиеттерді талдау көрсеткендей, ПЭТриа мөлшері артық гельдер серпімді қасиеттерге ие, ал ЕДОДЭТ-тің артық болуы өзара тығыздығы жоғары торлардың пайда болуына әкеледі. Алынған ПЭТриа-ЕДОДЭТ гельдерінің сүтегі асқын тотығының 3% ерітіндісінде ыдырау қабілетін зерттеу полимерлік желінің 60 күн ішінде 12% ыдырайтынын көрсетті. Алынған гельдердің бұл қасиеті дәрі-дәрмектердің таргетті (мақсатты) жеткізу жүйелерін құруда қолдануға болады.</p> <p>Түйін сөздер: (2,2'- (этилендиокси) диэтантриол, пентаэритритол триакрилат, гель, биодеградация, тиол-ен «клик» полимерленуі).</p>
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Синтез и характеристика новых биодеградируемых гелей на основе 2,2'- (этилендиокси) диэтантриола и пентаэритритол триакрилата

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<p>Поступила: 06 сентября 2021 Рецензирование: 15 октября 2021 Принята в печать: 30 ноября 2021</p>	<p>АННОТАЦИЯ</p> <p>Работа посвящена синтезу и характеристике гелей на основе мономеров пентаэритритол триакрилат (ПЭТриа) и 2,2'- (этилендиокси) диэтантриол (ЭДОДЭТ) методом тиол-ен «клик» полимеризации. Свойства полученных гелей были исследованы методами ИК-, Раман спектроскопии, механическим анализом. Были проведены золь-гель анализ полученных сеток и исследована способность к деградации. Результаты ИК-спектроскопии подтвердили наличие -C=O и -C-O-C- групп в составе полученных гелей. Наличие непрореагировавших C=C связей, сопряженных с C=O, а также тиольных групп варьируется в зависимости от состава исходной мономерной смеси. Результаты Раман-спектроскопии хорошо коррелируют с данными ИК-анализа. Раман-спектры также показывают C-S, S-S и SH- характеристические полосы, которые тяжело идентифицируются методом ИК-спектроскопии. Установлено, что состав исходной мономерной смеси (ИМС) влияет на физико-химические свойства синтезированных гелей. Наибольший выход гель фракции полученных полимеров обнаружен у образцов с эквимольным составом ИМС. Анализ механических свойств показал, что гели с избытком ПЭТриа проявляют более эластичные свойства, а избыток ЭДОДЭТ приводит к образованию сеток с большей плотностью сшивания. Исследование способности полученных гелей ПЭТриа-ЭДОДЭТ к деградации в 3% растворе перекиси водорода показало, что полимерная сетка деградирует на 12% в течении 60 суток. Данное свойство полученных гелей может</p>
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найти применение при создании систем таргетной доставки лекарственных средств, с их пролонгированным высвобождением.

Ключевые слова: (2,2'-(этилендиокси) диэтантол, пентаэритритол триаакрилат, гель, биодеградация, тиол-ен «клик» полимеризация).

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Reference

- [1] Lowe AB. Thiol-ene “click” reactions and recent applications in polymer and materials synthesis. *Polym. Chem.* 2010;1(1):17–36. <https://doi.org/10.1039/B9PY00216B>
- [2] Machado TO, Sayer C, Araujo PHH. Thiol-ene polymerisation: A promising technique to obtain novel biomaterials. *Eur. Polym. J.* 2017;86:200–215. <https://doi.org/10.1016/j.eurpolymj.2016.02.025>
- [3] Carlborg CF. et al. Beyond PDMS: off-stoichiometry thiol-ene (OSTE) based soft lithography for rapid prototyping of microfluidic devices. *Lab Chip.* 2011;11(18):3136. <https://doi.org/10.1039/C1LC20388F>
- [4] Bernkop-Schnürch A, Greimel A. Thiomers: The next generation of mucoadhesive polymers. *Am. J. Drug Deliv.* 2005;3:141–154. <https://doi.org/10.1016/j.addr.2005.07.002>
- [5] Kloxin AM. Thiol-ene click hydrogels for therapeutic delivery. *ACS Biomater. Sci. Eng.* 2016;2(2):165–179. <https://doi.org/10.1021/acsbomaterials.5b00420>
- [6] Hoyle CE, Bowman CN. Thiol-ene click chemistry. *Angew. Chemie - Int. Ed.* 2010;49(9):1540–1573. <https://doi.org/10.1002/anie.200903924>
- [7] Summonte S. et al. Thiolated polymeric hydrogels for biomedical application: Cross-linking mechanisms. *J. Control. Release.* 2021;330:470–482. <https://doi.org/10.1016/j.jconrel.2020.12.037>
- [8] Lüchow M, Fortuin L, Malkoch M. Modular, synthetic, thiol-ene mediated hydrogel networks as potential scaffolds for 3D cell cultures and tissue regeneration. *J. Polym. Sci.* 2020;58(22):3153–3164. <https://doi.org/10.1002/pol.20200530>
- [9] Tamariz E, Rios-ramírez A. Biodegradation of medical purpose polymeric materials and their impact on biocompatibility. *IntechOpen*; 2013. Chapter 1, Biodegradation - Life of Science, pp. 3–30. <https://doi.org/10.5772/56220>
- [10] Kamath KR, Park K. Biodegradable hydrogels in drug delivery. *Advanced Drug Delivery Reviews.* 1993;11:59–84. [https://doi.org/10.1016/0169-409X\(93\)90027-2](https://doi.org/10.1016/0169-409X(93)90027-2)
- [11] Kazitsyna LA, Kupletskaya NB. *Primenenie UF-, IR-, YaMR- i mass-spektroskopii v organicheskoy khimii (Application of UV, IR and NMR spectroscopy in organic chemistry)*. Moscow: Izdatelstvo Moskovskogo Universiteta. 1979, 237. (in Russian)
- [12] Wittman C, Chockley P, Singh SK, Pase L, Lieschke GJ, Grabher C. Hydrogen peroxide in inflammation: messenger, guide, and assassin. *Advances in Hematology.* 2012;2012:1–6. <https://doi.org/10.1155/2012/541471>
- [13] Ulbricht U, Jordan R, Luxenhofer R. On the biodegradability of polyethylene glycol, polypeptoids and poly(2-oxazoline)s. *Biomaterials.* 2014;35(17):4848–4861. <https://doi.org/10.1016/j.biomaterials.2014.02.029>
- [14] Nair LS, Laurencin CT. Biodegradable polymers as biomaterials. *Prog. Polym. Sci.* 2007;32:762–798. <https://doi.org/10.1016/j.progpolymsci.2007.05.017>