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The ability to control swelling and degradation processes of hydrogels based on a mixture of PEGMA/PEGDA monomers

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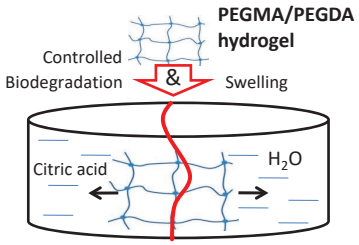
The ability of hydrogels based on acrylate derivatives of polyethylene glycol (PEG) with different ratios of monomers to swell and degrade, as well as their behavior during heating, have been explored. The possibility to control the swelling and degradation processes in the model medium by varying the ratio of PEG-methacrylate (PEGMA) and PEG-diacrylate (PEGDA) monomers was demonstrated.



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Hydrophilic crosslinked polymer matrices, such as hydrogels, have advantages that make them suitable materials for tissue engineering.[1–3] Synthetic hydrogels can have mechanical properties similar to those of soft tissues, permitting inclusion of proteins to simulate the chemical composition of extracellular matrix.[4,5] Filling hydrogels with phosphates, which are the main inorganic constituent of bones,[6–8] leads to an improvement of biological properties of such composites by release of biocompatible and bioactive components, such as calcium and phosphorus, capable of participating in the formation of new bone tissue during implant resorption, and preventing excessive swelling.[9] The hydrogels ability to swell,[10] *i.e.* to increase spontaneously their volume, the process in which the porous material spontaneously expands due to the absorption of liquid,[11] will ensure a tight fit of the material to the wall of a bone tissue. Polyethylene glycol (PEG) has high hydrophilicity (the equilibrium water content can be equal to 99%)[12] and permits the chemical modification and regulation of properties of hydrogels.[13,14] Hydrogels based on PEG-diacrylate (PEGDA) are widely used materials due to their obtainability through photocrosslinking (97% monomer conversion is achieved after 3 min of radiation),[15] which is the basis of stereolithographic 3D printing.[16–18] Exposure to UV radiation in the presence of a photoinitiator launches polymerization of double bonds in PEGDA resulting in the formation of a three-dimensional polymer network.[19,20] Mechanical strength of such a hydrogel can be varied by changing PEGDA molecular weight (as the molecular weight changes from 3.4 to 20 kDa, the modulus of elasticity increases from 11 to 64 kPa).[21–23] However, PEGDA-based hydrogels have low elastic properties (the values of elastic modulus of complex shear modulus may be equal to 100 kPa),[24] small swelling values[25] and low degradation rate in biological environment.[26,27] This problem can be solved by including a second monomer with a smaller number of functional groups and using a mixture of monomers, which will make it possible to alter the ability of hydrogel to swell and degrade. The possibility to change the hydrogel properties by using a mixture of monomers with different functional groups[28,29] or filling with an inorganic phase[30] was shown previously, but the use of PEG acrylate derivatives has been insufficiently explored, which makes it relevant to investigate the kinetics of swelling and degradation of hydrogels based on a mixture of these monomers. Citric acid solutions can be used as a model medium for the biomaterials degradation examination, since citric acid is released during bone resorption under the action of osteoclasts,[31] and the solubility of biomaterials in an acidic medium can be exploited to simulate the process of dissolution *in vitro*.

The present work was aimed at the exploration of swelling and degradation of hydrogels based on PEGMA and PEGDA monomers in a model solution in order to research their potential use as degradable bone implants.

PEGDA (Sigma–Aldrich, Germany) with a molecular weight of M_w = 575 Da and PEGMA (Sigma–Aldrich, Germany) with a molecular weight of M_w = 350 Da, being liquids at room temperature, were used as monomeric precursors in fabrication of hydrogels. The synthesis of hydrogels based on these PEG derivatives was carried out by photocrosslinking using the monomers PEGMA and PEGDA, distilled water and the photoinitiator Irgacure®819 [phenylbis(2,4,6-trimethylbenzoyl)phosphine oxide, BASF, Germany]. Mixing of all the components was performed with a magnetic stir bar for 10 min, after which photopolymerization reaction was performed under a household UV lamp (wavelength 365 nm, power 5 mW cm^{-2}).

A gravimetric method was used to estimate swelling; the mass of the samples was measured at intervals from 30 min to 7 days. The values of swelling degree (SD) and water content (WC) were used to describe the swelling process, and these

parameters were calculated according to the following equations:

$$SD = \frac{m_s - m_t}{m_t} \times 100\%, \quad (1)$$

$$WC = \frac{m_s - m_t}{m_s} \times 100\%, \quad (2)$$

where m_s is the mass of a hydrogel at the maximal swollen state, m_t is the gel mass before swelling.

Model medium (0.1 M citric acid solution) was used in the hydrogels degradation experiments; the mass of the samples after time intervals from 1 to 21 days was measured. At the same time, the swelling of hydrogels was evaluated to correct the mass changes. The description of the used equipment is given in Online Supplementary Materials.

The ability of hydrogels to swell is largely determined by the amount of space within the hydrogel network available for water placement. The amount of absorbed water depends on the porosity of hydrogel, type of monomers and crosslinking density.[32] The values of SW and WC increase with the introduction of the PEGMA monomer with a smaller number of functional groups (Figure 1). With an increase in the PEGMA content from 30 to 60%, the degree of swelling increases almost by a factor of two on the 7th day of the experiment.

Despite the difference between SD and WC when the ratio of monomers varies, the PEGMA introduction and the variation of the monomers ratio had a slight effect on the kinetics of swelling: the most intense absorption of water by hydrogels occurs during the first 2 days, afterward a slight increase in mass was observed, and after 7 days the mass did not change. The same trend was observed for WC. So, for hydrogels with the PEGMA/PEGDA ratio of 70/30 the value of WC after 2 and 7 days was 56.5 and 58.9%, respectively.

After the swelling, the mass of hydrogels was measured to determine the change of the water content after the swelling process (see Figure S1 in Online Supplementary Materials). When holding hydrogels in a dry container after the swelling process, we observed noticeable mass decrease, associated with the loss of weakly bound water from hydrogels. For hydrogels with high PEGMA content, therefore, having lower degree of crosslinking between the molecules, more absorbed water was lost, and in a completely swollen state under manual handling, the tendency to break down to fine highly swollen gel fragments was found. Such fine fragments underwent faster desorption by increasing the contact area with the surrounding dry environment.

During degradation experiments, it was shown that PEGMA-based hydrogels have a greater degree of degradation compared to PEGDA-based hydrogels after correction for their swelling (Figure 2 and Table 1). PEGMA-based hydrogels had greater swelling at the beginning of the degradation process, afterward there was a mass loss at a higher rate compared to PEGDA-based hydrogels.

Changing the monomers ratio makes it possible to control the rate and degree of degradation. A sufficiently high stability to the resorption of PEGDA-based hydrogels can be adjusted by introduction of PEGMA monomers, providing a higher rate of

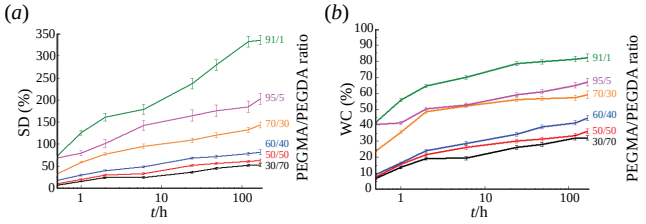

Figure 1 (*a*) Swelling degree and (*b*) water content for hydrogels based on PEGMA/PEGDA monomers mixtures.

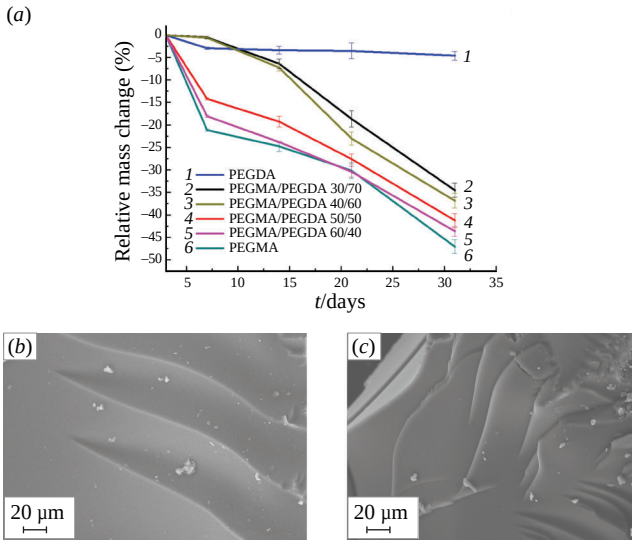

Figure 2 (*a*) The mass change of hydrogels with different PEGMA/PEGDA ratio during their degradation in citric acid solution and SEM images of hydrogels with the PEGMA/PEGDA ratio of (*b*) 30/70 and (*c*) 50/50.

biodegradation. Since slow degradation of biomaterial can prevent the formation of new tissue and even cause cell death,[33] it is necessary to control the rate of degradation of hydrogels so that it corresponds to the rate of formation of regenerated bone tissue. SEM images of hydrogels based on a mixture of PEGMA/PEGDA monomers are shown in Figure 2. For some PEGMA/PEGDA ratios crack propagation in the hydrogel was observed, and the formation of layered structure was not found, which could indicate the separation of the mixture due to different photopolymerization kinetics associated with different photopolymerization times for PEGDA and PEGMA. It should be noted that the photoinitiator remains in the polymer matrix during the destruction of hydrogels, and the presence of a photoinitiator in the composition of hydrogels during resorption, depending on its concentration, can cause a decrease in cell viability.[34] Meantime, photoinitiators can be well tolerated by many cell types,[35] as well as low content of photoinitiator, high hydrophilicity of hydrogels and the possibility of further filling of hydrogels with phosphates will reduce the negative effect of the photoinitiator remaining in the hydrogels. TG/DTA was used to study hydrogels heated to 550 °C (see Figure S2 in Online Supplementary Materials). All samples demonstrated similar weight loss behavior during temperature ramping. Mass loss occurs in the temperature range from 350 to 440 °C, being indicative of the oxidation destruction of the polymer chains, mainly due to the release of carbon dioxide.

Thus, in this work we have shown the possibility to control the swelling and degradation processes of hydrogels using a mixture of PEGMA/PEGDA monomers. It was possible to increase the degree of resorption by a factor of 8 relative to PEGDA using a 50/50 mixture of PEGMA/PEGDA monomers. When the ratio of PEGMA/PEGDA monomers changes from 60/40 to 99/1, the swelling degree increases from 50 ± 4 to

Table 1 Relative mass change of hydrogels with different composition after 31 days of degradation in citric acid solution.

PEGMA/PEGDA ratio	Relative mass change (%)
0/100	–4 ± 0.8
30/70	–34 ± 1.8
40/60	–36 ± 1.6
50/50	–41 ± 1.5
60/40	–43 ± 1.5
100/0	–47 ± 1.7

325 ± 6%. When developing hydrogels for tissue regeneration, the differences in the polymerization kinetics caused by the use of monomers with different functional groups and the differences in the resulting polymer network structure can potentially affect the behavior of cells, thereby opening the possibility for obtaining hydrogels with the required properties for a specific application.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.01.026.

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