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Synthesis of polylactide acrylate derivatives for the preparation of 3D structures by photo-curing

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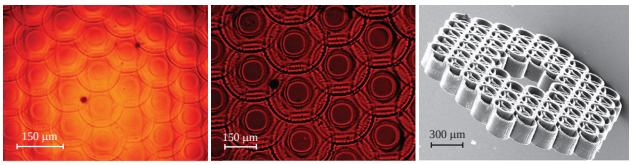
The polylactide acrylate derivatives have been synthesized *via* the esterification of terminal hydroxy and carboxy groups of polylactide with acrylic acid chloroanhydride and ethylene glycol monoacryl ester. Spatially cross-linked structures suitable for the formation of implants have been prepared by the photopolymerization of these derivatives.



Polylactides (PLA) are biodegradable polymers, which are widely used in medicine and environmental protection.[1] In particular, bone-plastic mineral-filled composites for implantology are made on a polylactide basis, primarily, for the creation of artificial joints or their parts (for example, in the maxillofacial osteoplastics). The duration of their degradation is up to five years, depending on the molecular weight, stereoisomerism (L, D or L/D form) and porosity of the polymer.[2,3] The use of PLA and their copolymers in tissue engineering is of particular interest, primarily, in bone tissue engineering, in which a 3D structure is formed from a biodegradable material, autologous stem cells are seeded on that structure, and formation of a new tissue occurs upon embedding such a construct into a bone defect due to the cell growth and differentiation.[4–6] However, the essential PLA disadvantages are their low strength and elasticity: these polymers undergo a brittle fracture already at a 10% deformation.[7] Moreover, PLA are characterized by high hydrophobicity, which reduces the cell adhesion to the polymer surface,[8] and poor processability.[9,10] One can control the set of mechanical and surface PLA properties by varying the composition of stereoisomeric monomers (*l*-, *d*-, *meso*-lactide) or by synthesizing copolymers with polyesters or glycols.[11–13] To increase the adsorption activity of polylactide, the polymer surface is treated with lasers.[14] For the creation of antibacterial properties on PLA surfaces, the grafting of polymers with bactericidal properties is used.[15] There are a number of methods for bulk PLA modification to enhance their mechanical properties, first, their strength, to increase the rate of polymer degradation and to enhance its processability. The synthesis of either a star-shape polymer[16] or linear copolymers with esters, glycols and urethanes[17] is mainly used in PLA modification for 3D photo-curing. Such 3D structures could be used for bone grafting[16] or peripheral neural tissue engineering applications.[18] It has been shown earlier[19] that the polymerizable acrylate derivatives of PLA can also be prepared by the modification of terminal hydroxy groups of polylactide *via* the reaction of urethane formation.

In this study, we synthesized the polymerizable acrylate derivatives of PLA *via* the esterification of terminal carboxy and hydroxy groups of the polymer, performed their photo-curing and obtained 3D structures by a two-photon polymerization technique.

We performed the esterification of the terminal carboxy groups of PLA with ethylene glycol monoacrylate (EGA) in toluene by an equilibrium condensation method with azeotropic water removal using *p*-toluenesulfonic acid as a catalyst.[20] Note that several reactions may simultaneously occur in the system. In particular, under the esterification conditions, *i.e.* at an elevated temperature and in the presence of *p*-toluenesulfonic acid, partial PLA destruction was possible. Moreover, reactive EGA is prone to disproportionation with the formation of ethylene glycol diacrylate and its subsequent dimerization. Indeed, the results of chromatographic analysis after partial solvent (toluene, retention time V_r = 31 min) removal confirm the above assumptions. In particular, the initial EGA, which was taken in an excess, was absolutely absent (V_r = 27.708 min). However, we observed the appearance of two new products with *MM* = 250 and 400, which correspond to EGA dimerization products.

We performed the esterification of PLA terminal hydroxy groups with the chloroanhydride of acrylic acid (CAA) using nonequilibrium condensation in the presence of tertiary amines as catalysts.[21] The reaction proceeded almost without the formation of by-products, as evidenced by a gel chromatogram of the reaction products, which was similar to the chromatogram of initial PLA. At the molar ratio PLA:CAA = 1:1.5, the yield of modified PLA was 60–65%. We controlled the formation of acrylate derivatives in the esterification of both carboxy and hydroxy groups of PLA *via* the appearance of double bond absorption bands (1629 and 1637 cm^{-1} in the first and second processes, respectively) in the IR spectra (a Varian Fourier transfer IR spectrometer) of the purified esterification products (Figure 1).

To study the application of the esterification-derived acrylate derivatives of PLA in laser stereolithography, we exposed the products to unfiltered radiation from a DRT1000 UV lamp for

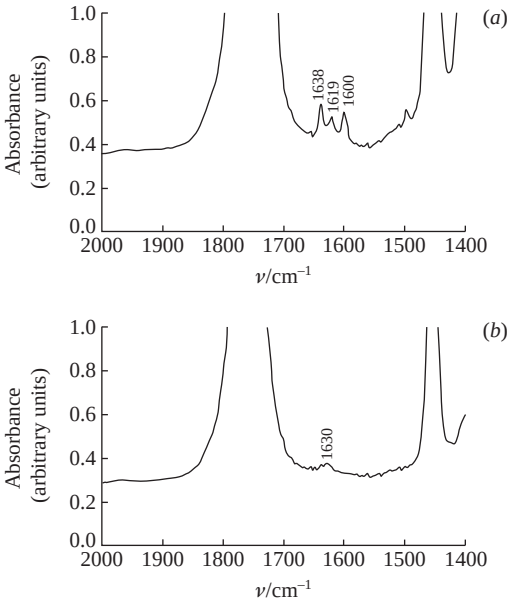


Figure 1 Fragments of the IR spectra of PLA acrylate derivatives after esterification of the polymer terminal groups: (*a*) carboxy group, esterification with ethylene glycol monoacrylate, (*b*) hydroxy group, esterification with acrylic acid chloroanhydride.

3 min in the presence of 2 wt% Darocur-4265 photoinitiator (Aldrich). We estimated the degree of cross-linking by the amount of PLA extracted from a sample in THF after irradiation. The reaction product of PLA with ethylene glycol monoacrylate appeared to form a 3D-cross-linked structure almost insoluble in THF. The degree of cross-linking was 25–35%. At the same time, the product of PLA interaction with CAA completely dissolved in THF after photopolymerization, indicating the absence of network structures in the product and the formation of linear PLA acrylate derivatives. Hence, for the preparation of 3D cross-linked structures based on acrylate PLA derivatives – products

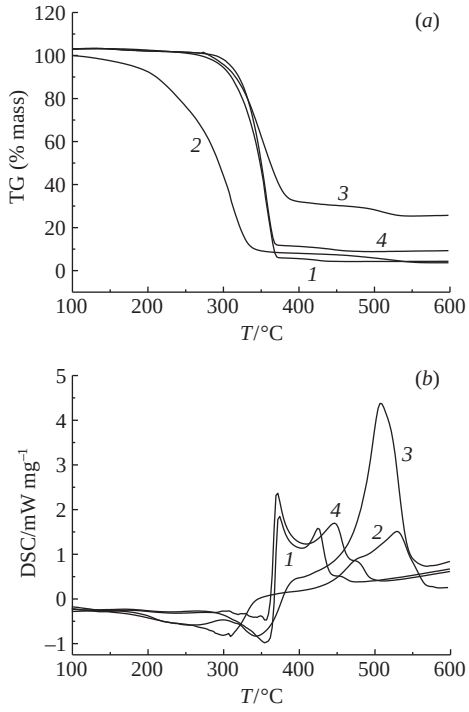


Figure 2 Thermal-oxidative destruction of the polymers: (*a*) loss of mass curves, (*b*) heat effect curves. (*1*) Initial PLA, (*2*, *3*) PLA EGA-modified *via* the carboxy group (*2*) before and (*3*) after photopolymerization, and (*4*) PLA CAA-modified *via* the hydroxy group after photopolymerization.

of interaction with CAA – one should add a cross-linker, which would play a role of by-product diacrylates formed in the reaction of PLA with ethylene glycol monoacrylate. Indeed, the addition of diacrylates to CAA-esterified polylactide led to the formation of cross-linked modified PLA, insoluble in THF, in the subsequent photopolymerization. For a comparative analysis of the supramolecular structure of the cross-linked systems based on esterification products by hydroxy and carboxy groups of polylactide, we studied the products of the PLA-EGA and PLA-CAA reactions before and after photopolymerization using thermogravimetric analysis (Figure 2).

In the PLA samples obtained by EGA esterification, the cross-linking reaction occurred after UV-irradiation [Figure 2(*a*), curves *2* and *3*]. At the same time, the temperature of a 5% mass loss increased from 180 to 270 °C as a result of cross-linking, the value of carbon residue increased from 7.3 to 30.3%, and the maximum rate of mass loss decreased. In addition, we observed a change in the heat effects accompanying the thermal oxidative destruction of samples [Figure 2(*b*)]; the heat flow (*Q*) increased from 1099 to 1700 J g^{-1}. All the above testifies the presence of 3D cross-linked fragments in the samples, whose destruction proceeds in higher temperature ranges *via* different reactions. In the samples of PLA modified by esterification with CAA, almost no changes were observed upon the thermal-oxidative destruction, as compared to the initial PLA (curves *1* and *4* in Figure 2), which indicates the absence of cross-linked fragments from the modified PLA structure. These results correlate well with the above data on the solubility of modified PLA in THF.

At the final stage, we formed 3D structures using two-photon polymerization *via* a described technique[22] (Figure 3). The patterning was performed in the presence of 1% Michler's ketone

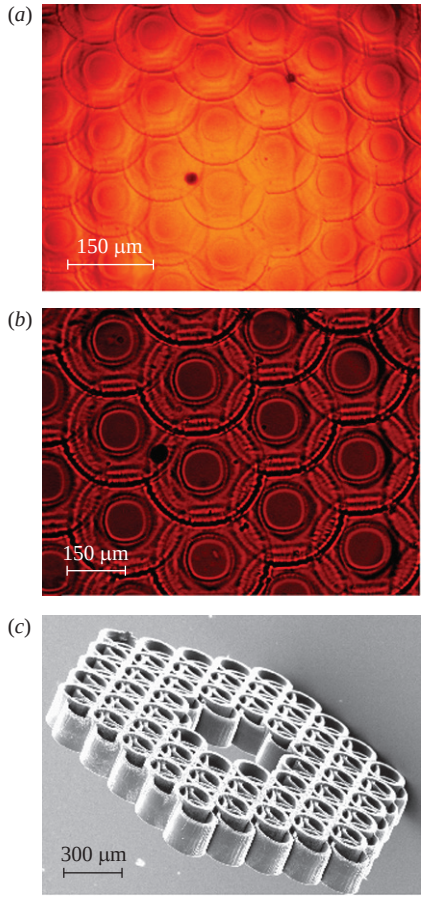


Figure 3 Micrographs of structures obtained upon two-photon polymerization using (*a*, *b*) an optical microscope and (*c*) a scanning electron microscope.

(as an initiator) in accordance with a published procedure;[16] dichloromethane (98%) was used to remove the unreacted material. The formation of 3D structures proceeded without deformations and shrinkage; thus, the developed approach can be used for the creation of precise biodegradable structures.

In conclusion, we found that lactic acid polymers can be modified at functional groups to obtain the polymerizable acrylic derivatives of PLA, which can further be applied to the formation of cross-linked films and 3D structures.

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References

1 D. Garlotta, *J. Polym. Environ*., 2001, **9**, 63.
2 K. Bessho, T. Iizuka and K.-I. Murakami, *J. Oral Maxillofac. Surg*., 1997, **55**, 941.
3 A. V. Janorkar, A. T. Metters and D. E. Hirt, *Macromolecules*, 2004, **37**, 9151.
4 R. L. Knight, H. E. Wilcox, S. A. Korossis, J. Fisher and E. Ingham, *Proc. Inst. Mech. Eng. H*, 2008, **222**, 129.
5 J. Li, J. Hong, Q. Zheng, X. Guo, S. Lan, F. Cui, H. Pan, Z. Zou and C. Chen, *J. Orthop. Res*., 2011, **29**, 1741.
6 J. Y. Tan, C. K. Chua, K. F. Leong, K. S. Chian, W. S. Leong and L. P. Tan, *Biotechnol. Bioeng.*, 2012, **109**, 1.
7 R. M. Rasal and D. E. Hirt, *J. Biomed. Mater. Res., Part A*, 2008, **88A**, 1079.
8 B. D. Ratner, *Biosens. Bioelectron*., 1995, **10**, 797.
9 R. Auras, *Macromol. Biosci*., 2004, **4**, 835.
10 K. S. Anderson, K. M. Schreck and M. A. Hillmyer, *Polym. Rev.*, 2008, **48**, 85.
11 R. E. Drumright, P. R. Gruber and D. E. Henton, *Adv. Mater.*, 2000, **12**, 1841.
12 A. Sodergard and M. Stolt, *Prog. Polym. Sci.*, 2002, **27**, 1123.
13 S.-M. Ho and A. M. Young, *Eur. Polym. J.*, 2006, **42**, 1775.
14 P. Rytlewski, W. Mróz, M. Żenkiewicz, J. Czwartos and B. Budner, *J. Mater. Process. Technol*., 2012, **212**, 1700.
15 S. El Habnouni, J.-P. Lavigne, V. Darcos, B. Porsio, X. Garric, J. Coudane and B. Nottelet, *Acta Biomater.*, 2013, **9**, 7709.
16 P. Timashev, D. Kuznetsova, A. Koroleva, N. Prodanets, A. Deiwick, Y. Piskun, K. Bardakova, N. Dzhoyashvili, S. Kostjuk, E. Zagaynova, Y. Rochev, B. Chichkov and V. Bagratashvili, *Nanomedicine*, 2016, **11**, 1041.
17 R. Gabriele, *German Patent 006988*, 2004.
18 A. Koroleva, A. A. Gill, I. Ortega, J. W. Haycock, S. Schlie, S. D. Gittard, B. N. Chichkov and F. Claeyssens, *Biofabrication*, 2012, **4**, 025005.
19 V. T. Shashkova, I. A. Matveeva, N. N. Glagolev, T. S. Zarkhina, P. S. Timashev, V. N. Bagratashvili and A. B. Solovieva, *Zh. Fiz. Khim.*, 2016, in press.
20 A. A. Berlin, G. V. Korolev, T. Ya. Kefeli and Yu. M. Sivergin, *Akrilovye oligomery i materialy na ikh osnove (Acrylic Oligomers and Materials on Their Basis*), Khimiya, Moscow, 1983, p. 39 (in Russian).
21 A. A. Berlin, G. V. Korolev, T. Ya. Kefeli and Yu. M. Sivergin, *Akrilovye oligomery i materialy na ikh osnove (Acrylic Oligomers and Materials on Their Basis)*, Khimiya, Moscow, 1983, p. 25 (in Russian).
22 T. A. Akopova, P. S. Timashev, T. S. Demina, K. N. Bardakova, N. V. Minaev, V. F. Burdukovskii, G. V. Cherkaev, L. V. Vladimirov, A. V. Istomin, E. A. Svidchenko, N. M. Surin and V. N. Bagratashvili, *Mendeleev Commun*., 2015, **25**, 280.

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