Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2021, **31**, 515–516

Mendeleev Communications

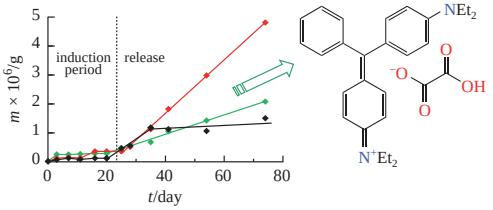
Kinetics of the release of brilliant green from nanoporous polylactide obtained by a crazing mechanism

Vladislav V. Potseleev, Elena S. Trofimchuk* and Nina I. Nikonorova

Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation. Fax: +7 495 939 0067; e-mail: elena_trofimchuk@mail.ru

DOI: 10.1016/j.mencom.2021.07.026

Structurally variable nanoporous polylactide (PLA) films containing brilliant green (BG) as a functional antiseptic additive have been obtained by a crazing mechanism. The *in vitro* release of BG from the porous PLA films into a sodium phosphate buffer solution at 37 °C has been examined by spectrophotometry.



Keywords: polylactide, crazing, porous structure, brilliant green, release.

The development of polymer-based implants and retention sutures that exhibit biological activity and contain substances having beneficial effects on tissues of a living organism is a problem of considerable current interest.[1] Such materials can be produced by the incorporation and retention of an additive *via* chemical bonding with a polymer matrix,[2] blending by a melt or solution technology,[3] or the formation of a bioactive layer on a polymer surface.[4] It is well known that the stretching of amorphous and semicrystalline polymers in a physically active liquid medium (PALM) at room temperature leads to the formation of a porous structure.[5–7] Functional additives can be introduced into a polymer by dissolving them in PALM or passive impregnation.[6,8] Usually, the release of additives from the porous structure of crazes is a slow and time-consuming process.[8] Biologically active additives and polymers should be nontoxic, biocompatible, and biodegradable, and the rates of polymer biodegradation and additive release should be comparable. A lactic acid-based polymer, polylactide (PLA), satisfies these requirements.[9] In an ideal case, the time dependence of the amount of a released drug is linear.[10] However, other additive release modes, such as instantaneous, stepwise, and delayed, can also be suitable for some purposes.[11]

The aim of this work was to perform an *in vitro* UV-VIS spectroscopic study of the kinetics of the release of brilliant green (BG), which is a component of a widely used antiseptic, from structurally different porous PLA films obtained by a crazing mechanism into a sodium phosphate buffer (PBS) solution at 37 °C. BG was used as a model substance because it is chemically stable during long-term experiments (2.5 months) and can be reliably identified by spectrophotometry at very low concentrations.

Table 1 summarizes the characteristics of the PLA† samples. The loaded porous films were prepared *via* the uniaxial stretching of the initial films in a 5% solution of BG in ethanol.

In this process, a specific fibrillar porous structure in the amorphous PLA films was formed *via* a classical crazing mechanism.[12] Sample 1 was an amorphous PLA film stretched by 80% with the structure of alternating crazes and bulk polymer regions (pore diameter, 15–25 nm). Sample 3 was an amorphous PLA film stretched in by 350%. In this case, the pores acquired a shape of slits 125 nm long and 10–15 nm wide.

The uniaxial stretching of a semicrystalline PLA film in ethanol proceeded according to a delocalized crazing mechanism.[13] Sample 2 was a crystalline PLA film stretched by 80%; the pores with a diameter of 10–20 nm were uniformly distributed throughout the sample volume.

The BG content of the samples was determined by UV-VIS spectroscopy‡ (Figure 1). The spectrum of BG has two maxima at 629 and 429 nm and a shoulder at 584 nm. The calibration plot was constructed using the optical density at 630 nm.

The calibration function $A = (0.19 \pm 0.07)C$ ($R^2 = 0.972$) was used to determine the concentrations (C) of sample solutions and to calculate the weights of BG (Table 1). The contents m_{BG} in the structurally different samples were about 1 wt%.

The ability of PLA samples to release BG into a test solution (PBS, pH 7.4) at 37 °C was studied. For this purpose, the calibration function $A = (0.1659 \pm 0.0518)C$ ($R^2 = 0.996$) was used to determine the concentration of released BG in PBS (Figure 2). During the initial several days, the samples released a small amount (no greater than 0.25 μg) of BG seemingly due to diffusion from the sample surface into the solution. Then, the BG concentration in the PBS solution remained almost unchanged for three weeks. This was most likely due to the fact that a rather dense polymer surface layer was formed upon the coagulation of fibrils in the course of sample drying as a result of the action of capillary forces and the tendency of highly dispersed systems to reduce the surface energy upon the removal of a PALM from the crazes.[6]

† Initial amorphous films 70–85 μm thick were obtained by hot pressing from PLA granules of 4032D brand (Nature Works LLC, USA) with the following parameters: concentration of D-isomer units, 2%; molecular weight, 170 kDa; dispersity, 1.67; glass-transition temperature, 60–63 °C; and melting temperature, 167 °C. To obtain crystalline samples, the initial films were heated in ethanol at 50 °C for 30 min.

‡ Weighed portions of polymer samples (12–17 mg) were dissolved in chloroform (20 ml). The spectra were measured with a Cary 1E Varian spectrophotometer at a scanning velocity of 100 nm min^{-1}. A BG-free PLA solution in chloroform with the same polymer concentration was used as a reference sample.

Table 1 Characteristics of the porous PLA samples.

Sample	Weight, m/mg	Thickness, h/μm	Surface area, S/mm^2	Tensile strain, ε(%)	Pore volume, V/mm^3 (porosity, W, vol%)	BG weight m_{BG}/mg (content, wt%)	Pore size[a] d_{pore}/nm	Localization of pores and BG distribution
1	11.0	70	210	80	5.9 (40)	0.114 (1.04)	15–25	in crazes
2	11.3	50	283	80	5.4 (38)	0.106 (0.94)	10–20	throughout the volume
3	12.2	40	300	350	2.4 (20)	0.145 (1.19)	10–15×125	throughout the volume

[a] The data on the pore sizes were obtained by small-angle X-ray scattering.[12,13]

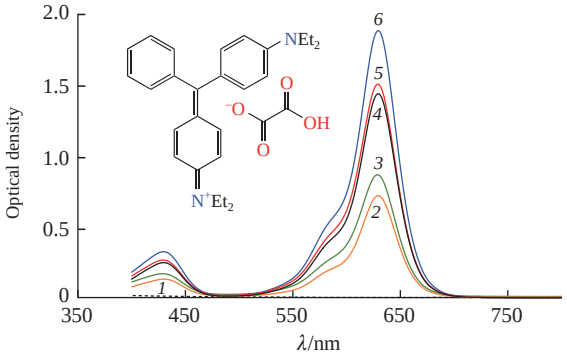


Figure 1 UV-VIS spectra of the solutions of BG in chloroform and the structural formula of BG: (*1*) blank, (*2*) reference 1 (6.3 μmol dm^{-3}), (*3*) Sample 1, (*4*) reference 2 (15.1 μmol dm^{-3}), (*5*) Sample 3 and (*6*) Sample 2.

The most intense release of BG from the PLA samples began after an exposure in the PBS solution for three weeks, which correlates with the onset of hydrolytic degradation. According to Harting *et al.*,[11] the intense degradation of PLA in PBS began after 20 days. The structure of the polymer samples was gradually loosened, and it became more accessible for the ambient solution. This delayed release of a functional additive can be of importance when an incorporated drug should begin to act after a time rather than immediately.

The rate constants of BG release from the PLA films were determined after an exposure for three weeks in the PBS solution at 37 °C. The effective rate of release k was determined as the slope of a straight line (Figure 2, Table 2). BG was most intensely released from Sample 3. The observed differences can be due to not only the structural and geometric parameters of the samples but

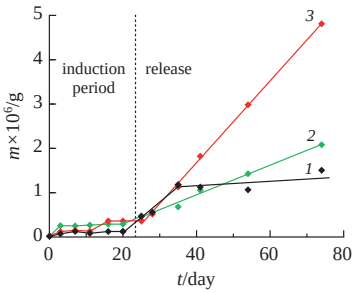


Figure 2 Time dependences of the amount of BG released from the polymer samples exposed in the PBS solution: (*1*) Sample 1, (*2*) Sample 2, and (*3*) Sample 3.

Table 2 Kinetic parameters of BG release from porous PLA samples.

Sample	Induction period/ days	Effective rate of BG release $k\times10^8$/ g day^{-1}	Effective rate constant of BG release $D\times10^5$/ m^{-1} day^{-1}	Mass of released BG/μg	Fraction of released BG on a total weight basis (%)
1	20	6.9	10.0	1.51	1.3
2	20	3.3	2.8	2.08	2.0
3	25	9.2	4.2	4.81	3.3

also different rates of their hydrolytic degradation. Effective rate constant D of this process was calculated assuming that the release of BG is described by Fick's law[14]: $k = d_m/d_t \sim -2DSd_m/d_h$. Since BG was uniformly distributed in the crazes, $d_m/d_h \sim m_{BG}/h$ and $D \sim k\,h\,/(2S\,m_{BG})$. The highest effective rate constant D was observed in Sample 1 (see Table 2), and the values of D were similar in Samples 2 and 3. This can be related to the pore sizes, which are larger in Samples 1 and 3 than those in Sample 2, and the release of bulky BG molecules is less hindered from the former. In addition, the porosity and specific surface area of fibrils decreased during the collapse. Thus, the total amount of BG released was only 1–3% because of the adsorption of BG on surface of fibrils in the polymer and a low rate of desorption. Note that the release of BG from Sample 1 ceased at the 35th day due to the hydrolytic degradation of this material. In PLA samples with alternating crazes and bulk polymer regions, the degradation was most intense in the bulk moieties, and it did not affect significantly the crazes, which decelerate the release of BG.[15]

Thus, the mechanical modification of polymer structures by a crazing mechanism with the formation of nanoporous PLA films, which have different pore geometries and morphologies and contain functional additives, seems promising for controllable drug release in medicine.

The reported study was funded by RFBR according to research project no. 18-29-17016.

References

1 P. Saini, M. Arora and M. N. V. R. Kumar, *Adv. Drug Deliv. Rev.*, 2016, **107**, 47.
2 M. Tummalapalli, S. Anjum, S. Kumari and B. Gupta, *Polym. Rev.*, 2016, **56**, 607.
3 H. Zhou, J. G. Lawrence and S. B. Bhaduri, *Acta Biomater.*, 2012, **8**, 1999.
4 Y. Li, K. N. Kumar, J. M. Dabkowski, M. Corrigan, R. W. Scott, K. Nüsslein and G. N. Tew, *Langmuir*, 2012, **28**, 12134.
5 A. S. Argon, *The Physics of Deformation and Fracture of Polymers*, Cambridge University Press, Cambridge, 2013, pp. 342–390.
6 O. V. Arzhakova, A. A. Dolgova, L. M. Yarysheva, A. L. Volynskii and N. F. Bakeev, *Polymer*, 2015, **56**, 256.
7 A. Y. Yarysheva, D. V. Bagrov, A. V. Bakirov, L. M. Yarysheva, S. N. Chvalun and A. L. Volynskii, *Eur. Polym. J.*, 2018, **100**, 233.
8 O. Weichold, P. Goel, K.-H. Lehmann and M. Möller, *J. Appl. Polym. Sci.*, 2009, **112**, 2634.
9 T. S. Lee and S. T. Bee, *Polylactic Acid: A Practical Guide for the Processing, Manufacturing, and Applications of PLA*, 2nd edn., Elsevier, 2019.
10 J. Balcerzak and M. Mucha, *Prog. Chem. Appl. Chitin Deriv.*, 2010, **15**, 117.
11 R. Harting, K. Johnston and S. Petersen, *Int. J. Biobased Plast.*, 2019, **1**, 8.
12 E. S. Trofimchuk, A. V. Efimov, M. A. Moskvina, O. A. Ivanova, N. I. Nikonorova, S. B. Zezin, A. V. Bakirov and A. L. Volynskii, *Polym. Sci., Ser. A*, 2018, **60**, 845.
13 E. S. Trofimchuk, M. A. Moskvina, O. A. Ivanova, V. V. Potseleev, V. A. Demina, N. I. Nikonorova, A. V. Bakirov, N. G. Sedush and S. N. Chvalun, *Mendeleev Commun.*, 2020, **30**, 171.
14 R. Gouda, H. Baishya and Z. Qing, *J. Dev. Drugs*, 2017, **6**, 1000171.
15 E. S. Trofimchuk, M. A. Moskvina, N. I. Nikonorova, A. V. Efimov, E. S. Garina, T. E. Grokhovskaya, O. A. Ivanova, A. V. Bakirov, N. G. Sedush and S. N. Chvalun, *Eur. Polym. J.*, 2020, **139**, 110000.

Received: 2nd March 2021; Com. 21/6473