

THE CATALYST-FREE POLYTRANSESTERIFICATION FOR OBTAINING LINEAR PGS OPTIMIZED WITH USE OF 2^2 FACTORIAL DESIGN

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Poly(glycerol sebacate) (PGS) is a polyester that is particularly useful for tissue engineering applications. Many researchers have focused on the application and characterization of materials made from PGS. Synthesis is often superficially described, and the prepolymer is not characterized before crosslinking. Considering the different functionality of each monomer (glycerine – 3, sebacic acid – 2), materials with a branched structure can be obtained before the crosslinking process. Branched structures are not desirable for elastomers. In this work, method to obtain linear PGS resins is presented. Moreover, synthesis was optimized with the use of the Design of Experiments method for minimizing the degree of branching and maximizing the molecular weight. The process was described *via* mathematical models, which allows to the association of process parameters with product properties. In this work ca. 1kDa and less than 10% branched PGS resin was produced. This resin could be used to make very flexible elastomers because branching is minimized.

Keywords: poly(glycerol sebacate), polycondensation, optimization

1. INTRODUCTION

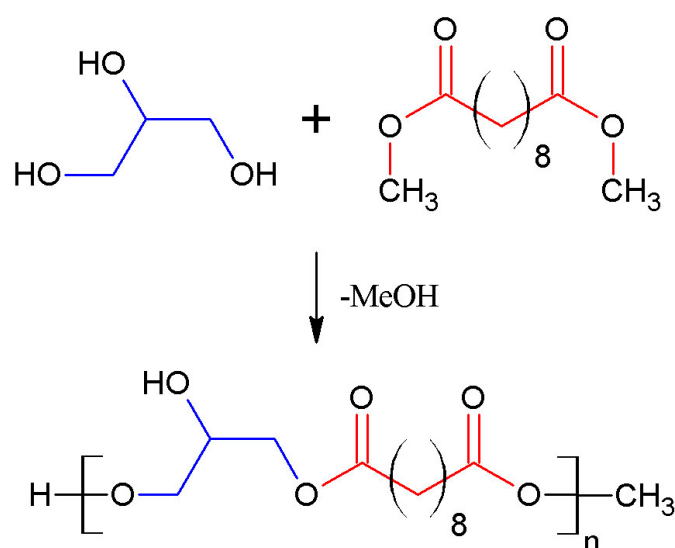
Materials containing glycerol (Fernandes et al. 2015; Landim et al. 2018), such as poly(glycerol sebacate) – PGS, are gaining on popularity due to wide range of their possible applications. PGS was firstly obtained by Wang Yadong's team in 2002 and since then it was a subject of interest in many scientific groups (Wang et al. 2002). The main aim of this work is to obtain PGS with a possible (less than 10%) degree of branching. Due to that polytransesterification process will be studied with the use of the Design of Experiments (DoE) methods.

PGS is biodegradable and non-toxic, elastomers made of PGS are mechanically stable and show high resemblance to rubber (Martina and Hutmacher, 2007). However, the most desirable feature of this polymer is its ability to interact with living cells (Kempainen and Hollister, 2010; Kharaziha et al., 2013), what makes PGS an object of interest of tissue engineering. PGS undergoes reversible deformation without disturbing tissues when influenced by dynamic mechanical forces present in the environment of the human body, therefore is material for potential use in fabrication of cell scaffolds Sant et al., 2011; Saudi et al., 2019), bone implants (Higuchi et al., 1999; Kokubo et al., 2003) or cardiac patches (Gao et al., 2006; Ravichandran et al., 2012; 2011). PGS mechanical properties such as thermal expansion, Young's modulus or degradation time can be easily modified by changing the synthesis conditions (for example temperature

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or synthesis time) or substrates molar ratio (Liu et al., 1996; Loh et al., 2015; Wang et al., 2002). Due to that, by using DoE it is possible to create a mathematical model to associate process parameters with product (Gadomska-Gajadthur et al., 2018; Wrzecionek et al., 2021). It is worth mentioning, that this material can be formed by electrospinning, easy to scale-up technique (Denis et al., 2019; Saudi et al., 2019; Xu et al., 2016). In most of the respected works, the polyester is synthesized by polycondensation of glycerine and sebacic acid (Kafouris et al., 2013; Larsson et al., 2014; Li et al., 2013; Liu et al., 2007; Liu et al., 2012; Loh et al., 2015; Rai et al., 2012; Wang et al., 2002). However, aforementioned method usually results with the branched product (Rai et al., 2012). Currently, a lot of effort is devoted to develop a synthetic path of linear PGS and other glycerol polyesters in general. Proposed approach imply use of arylboronic acids as polymerization catalysts. Due to the selective activation of the primary hydroxyl group of glycerine by the organoboronic catalyst, polymers are formed with a significant predominance of the 1,3-esterified glycerol units (Slavko and Taylor, 2017) It was also suggested to utilize a lipase enzyme as a biocatalyst (Godinho et al., 2018; Kumar et al., 2016). However, the later synthetic route leads to resin mainly consisted of low molecular weight oligomers (< 1000 g/mol) (Godinho et al., 2018). Since purifying the product from the catalyst might be of a problem, especially in a larger scale, and high purity of a material to be used in medical devices is necessary, catalyst-free processes are of high interest.

Herein, we present catalyst-free, following principles of Green Chemistry (Li and Trost, 2008) synthetic method meeting the needs of material purity and quality for use in tissue engineering and medicine. Basing on our experience on PGS synthesis (Gadomska-Gajadthur et al., 2018), we have decided to develop a new process of polytransesterification (Scheme 1) using dimethyl ester, a substrate characterized by lower activity than that of acid. Transesterification is an equilibrium process, which generates by-product, in this particular case, methanol. Reaction might be accelerated by acid or base catalyst (Otera, 1993) or, what was our, more desirable approach, by simultaneous collection of low molecular weight by-product. However, it should be mentioned, that shifting reaction equilibrium towards the product should be subtle, if linear polyester (degree of branching less than 10%) of high molecular weight (M_n greater than 1 kDa) is to be obtained. Since linearity and high molecular weight were our goals, we decided to use Dean-Stark apparatus to collect methanol and additionally use glycerine twofold excess, since it is favourable for obtaining linear PGS. What is more, results of our optimization procedures allows the presented process to be commercialized with less scale-up risk. Commercialization of biomaterials is very challenging, yet innovative applications of developed materials are worth the effort (Harris et al., 2018).



Scheme 1. Polytransesterification of glycerine and dimethyl sebacate

2. MATERIALS AND METHODS

2.1. Materials

Commercially available reagents (glycerol, 99%, Fisher BioReagents; dimethyl sebacate, 99%, Sigma-Aldrich) were used without further purification.

2.2. Synthesis procedure

All presented reactions were carried out in MultiMax Mettler Toledo system in four glass reactors (50 mL) equipped with a mechanical stirrer, temperature sensor and reflux condenser. We have performed series of 7 reactions characterized by different conditions, but in all cases the same molar ratio and masses of substrates were applied: 0.1 mol (23.02 g) dimethyl sebacate and 0.2 mol (18.42 g) anhydrous glycerol.

2.3. Analytical methods

2.3.1. Infrared spectroscopy

IR spectra were obtained using a BRUKER ALPHA II Platinum ATR spectrometer (in ATR technics).

2.3.2. Nuclear magnetic resonance spectroscopy

NMR spectra were obtained using an Agilent spectrometer (400 MHz).

2.3.3. Determination of esterification degree

Acid and ester numbers of PGS were determined as in our previous work (Gadomska-Gajadur et al., 2018). The analysis consisted in the titration of polymer end groups in the presence of indicators (titration with 1M KOH in the presence of thymol blue and titration of hydrolysed samples with 1M HCl in the presence of phenolphthalein).

2.4. Calculation and graphic software

Graphics and calculations were made in StatSoft Statistica with use of standard 2² factorial design from Design of Experiments mode.

3. RESULTS

We optimized synthesis using 2² factorial design of experiments changing temperature (x_1) in 160–170° range and reaction time (x_2) in 30–40 h range. As stated above, we aimed at receiving linear PGS with possible high molecular weight. Results and experimental data of optimization processes are gathered in Table 1. To our surprise, in all cases results were very good ($DB < 8\%$ and $M_n > 1115$ Da). It was unexpected to obtain satisfactory parameters for every condition set used.

Table 1. 2² factorial design with experimental and calculated results. Center of the plan presented below a dotted line

x_1 [°]	x_2 [h]	DB [%]	DB^{CAL} [%]	Mn [Da]	Mn^{CAL} [Da]
170	40	8.0	8.1	1776	1771
160	40	1.9	2.0	1115	1110
170	30	2.8	2.9	1554	1549
160	30	3.4	3.5	1611	1606
165	35	4.3	4.1	1359	1509
165	35	4.4	4.1	1475	1509
165	35	3.9	4.1	1673	1509

DB – degree of branching; CAL – calculated

The structure of the polyester was confirmed by FTIR spectroscopy (Fig. 1) and ¹H NMR spectroscopy (Fig. 2).

The FTIR spectrum shows characteristic bands for functional groups:

- 3414.14 cm⁻¹, a wide band characteristic of the vibrations of the O–H bond in glycerine,
- 2927.16 and 2855.70 cm⁻¹, two narrow bands characteristic for the vibration of C–H sp³ bonds occurring in the glycerine and sebacic parts of polyester,
- 1732.01 cm⁻¹, a narrow band characteristic for carbonyls together with band at 1168.50 cm⁻¹ characteristic for the acyl group and a band at 1044.51 cm⁻¹ characteristic for the alkoxy group, prove the production of polyester.

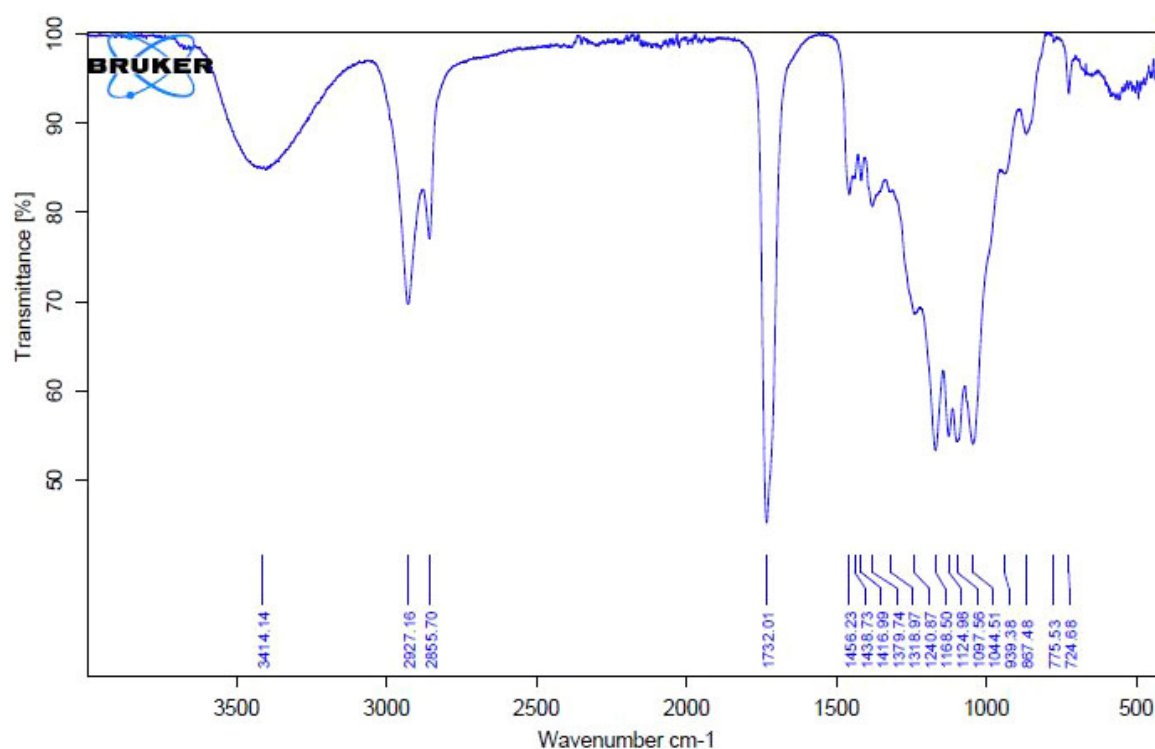


Fig. 1. FTIR spectrum of poly(glycerol sebacate)

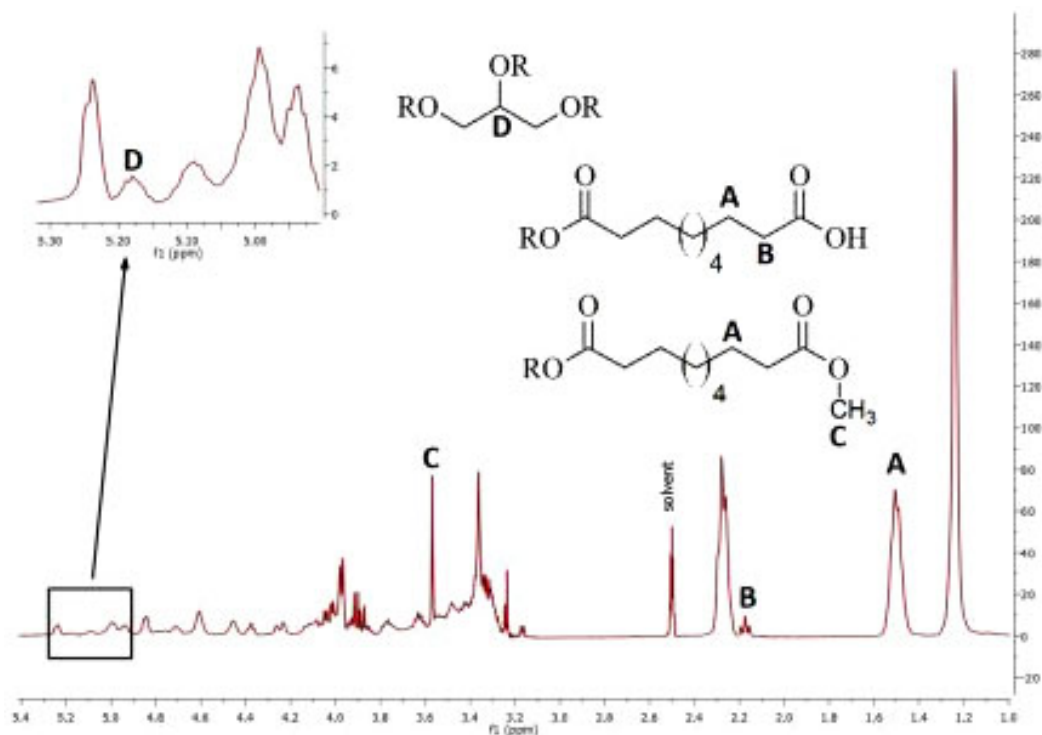


Fig. 2. ¹H NMR spectrum of poly(glycerol sebacate) with signals interpretation

Surprisingly, we have observed signal from sebacic acid on the ¹H NMR spectrum (2.15 ppm), what might suggest some share of hydroxyl groups in the polyester terminal groups. To assess the contribution made by hydrolyzed terminal groups, we have calculated acid number and ester number for all seven samples of PGS which were in range of 15–17 mgKOH/g and 291–308 mgKOH/g, respectively, what corresponds with esterification degree in the range of 94–96%. A non-zero acid number testifies to hydrolysis of the ester, what corresponds to ¹H NMR observations. Hydrolysis is unlikely to be caused by storing samples without any protection from atmospheric conditions, it is rather a part of the synthesis mechanism. This matter is not a subject of our work since lowered esterification degree of PGS does not affect the quality of the product, however it may be worth further meticulous analysis in the future.

Comparing the intensity of the signals in the ¹H NMR spectrum (Fig. 2) there is a possibility to estimate polymerization degree (*X_n*) and degree of branching (*DB*). To do that every integral was normalized relative to the number of protons before comparing, exactly as are shown in Equations (1) and (2):

$$X_n = \frac{A/2}{B/2 + C/3} \quad (1)$$

$$DB = \frac{D/1}{A/2} \times 100\% \quad (2)$$

Number average molecular weight is simply calculated by multiplication polymerization degree and molecular weight of repetitive unit (276.32).

With the use of Design of Experiments, we calculated mathematical models which describe the influence of temperature and time on *DB* and *M_n* parameters and their mutual dependencies. The first model, describing the degree of branching is presented with a fitted surface and scaled with heat map in Fig. 3. Since the proposed model contains a term that is a product of both variables (*x*₁ · *x*₂; *x*₁ – temperature and *x*₂ – reaction time), it is impossible to indicate which factor is more important. Analysis of the Pareto chart for *DB* parameter (Fig. 4) leads to a conclusion, that the most influential is the interaction of both analysed

variables, despite the low value of the coefficient equalled to 0.001. The fitted surface shows how degree of branching increases with the increase both of temperature and reaction time. The model has a good representation of reality, what is reflected in small disparities between the experimental and calculated values of *DB*. The maximum difference between the values is 0.3%, while the average difference is 0.14%. Additional evidence for good fit of the model is the value of determination coefficient for DB^{CAL} (*DB*) relation which equals to 0.991.

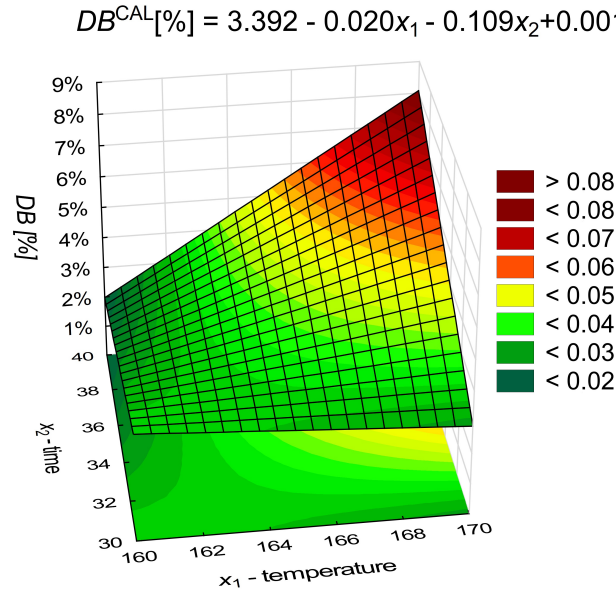


Fig. 3. The *DB* dependency shown on the fitted surface created by the mathematical model

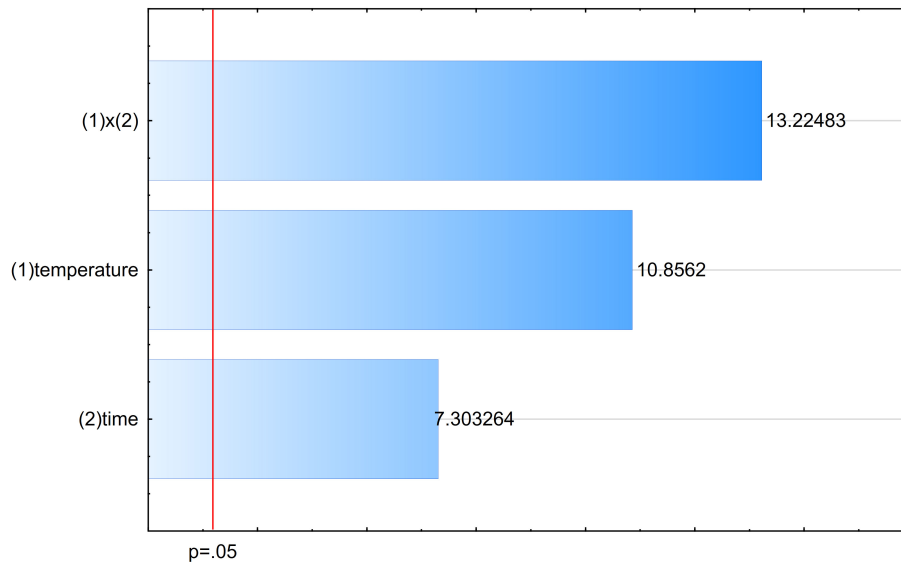


Fig. 4. Pareto chart for the model which describe *DB*

The second model, describing a dependence of *Mn* on the analysed variables x_1 and x_2 , is shown with a fitted surface in Fig. 5. Performed statistical calculations, illustrated on the Pareto chart (Fig. 6), indicate that the coefficients of every term in the equation are below the threshold of relevance, and therefore the model might be considered to be inadequate. Significant differences between experimental and calculated values of *Mn* are observed only for experiments in the centre of the plan (165°, 35 h, Table 1). Mn^{CAL} for the other experiments remain in good agreement with experimental *Mn* values. Moreover, the most

noticeable difference is 164 Da, what is less than the molecular weight of the repetitive unit (276 Da). Notwithstanding, since the model is statistically insufficient, interpretation of its practical meaning allows to consider it accurate enough for our needs.

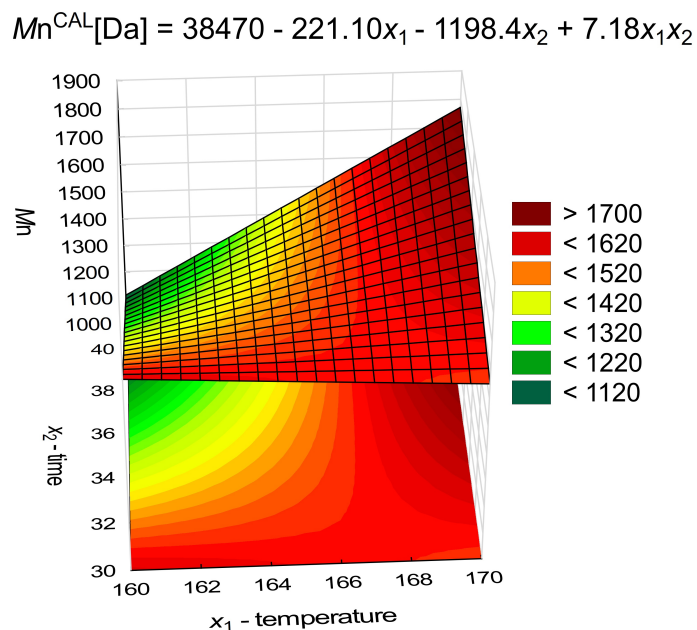


Fig. 5. *Mn* dependency shown on the fitted surface created by the mathematical model

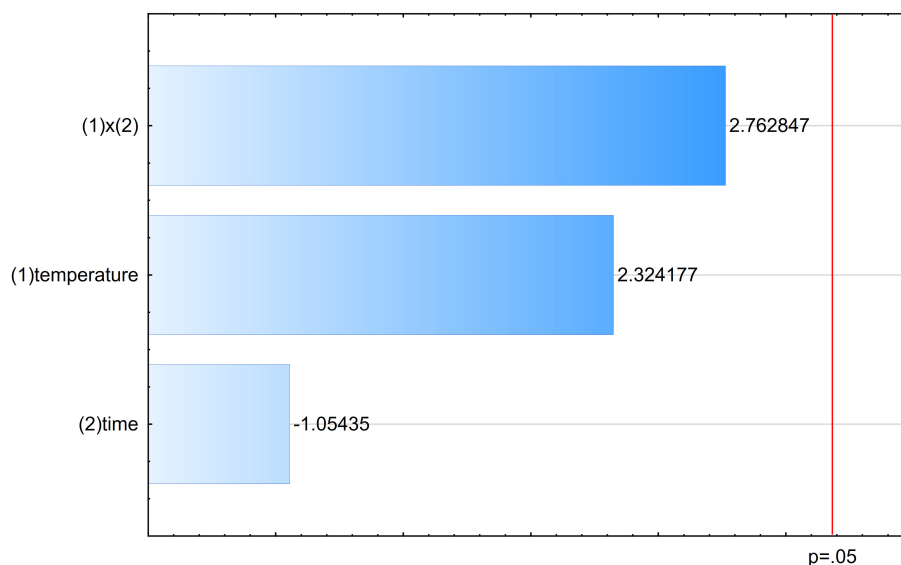


Fig. 6. Pareto chart for the model which describe *Mn*

With the help of usability profiles in Statistica software, we determined the optimal condition for polymer synthesis with the lowest value of *DB* and the highest molecular weight. According to the computational results, the most optimal conditions are 160° and 30 h. Since we have already performed an experiment at those exact conditions (Table 1), there was no need for additional synthesis. PGS resulting from the optimal reaction conditions is characterized with exceptionally rare branched structure (*DB* equal to 3.5%) and relatively high *Mn* (about 1.6 kDa), what in general is more than satisfactory outcome for the catalyst-free process.

4. DISCUSSION

In this work we have presented new method of catalyst-free transesterification of dimethyl sebacate and glycerine, resulting with PGS polyester. We have conducted seven independent experiments in changing conditions of temperature (x_1) and reaction time (x_2) according to 2^2 factorial plan. All preformed experiments resulted with the polyester characterized by smaller than 10% degree of branching and higher than 1100 Da molecular weight. Results should be considered as a great success for catalyst-free polytransesterification, especially when comparing to other known works. Additionally, we have performed series of statistical computations to determine mathematical models describing relation between DB as well as Mn parameters and reaction variables. After careful analysis of the results, we may conclude, that both models; $DB(x_1, x_2)$ and $Mn(x_1, x_2)$; represent experimental values sufficiently well. We have also computed and tested conditions optimal for synthesis of high molecular weight and linear PGS. Optimal parameters for this process are 160° and 30 h, which allows to obtain PGS with 3.5% degree of branching and 1.6 kDa molecular weight.

During our work, we have noticed an intriguing appearance of the acid terminal groups in all PGS samples. We can only assume that the phenomena is intertwined with the mechanism of the presented process. Slow hydrolysis of the substrate may be the first reaction step, followed by sebacic acid and glycerol condensation. Undoubtedly the origin of partial PGS hydrolysis is an interesting matter and it should be an object of another work. Fortunately, residual terminal hydroxyl groups do not affect parameters of the PGS and therefore obtained resins might be used to produce elastomers, what will be further investigated by the authors in their next work.

5. CONCLUSIONS

Summarizing, the work presented is a demonstration of the transesterification reaction utility for the synthesis of linear glycerol polyesters. In this work PGS with 3.5% degree of branching and 1,6 kDa molecular weight was obtained. The developed mathematical models reflect reality very well. Performing such experiments allows for easier scaling up of the process, opening the door for exploiting proposed procedures in the industrial scale.

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