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Optimizing the conditions of PGSu synthesis with simplex method

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Poly(glycerol succinate) – PGSu – is one of glycerol polyesters which has focused nowadays the interest of scientists developing new biomaterials. Probably the polyester could be used as a drug carrier or as a cell scaffold in tissue engineering. Due to its potential use in medicine, it is extremely important to develop a synthesis and then optimize it to obtain a material with desired properties. In this work one flask two-step polycondensation of glycerol and succinic anhydride to PGSu is presented. Synthesis was optimized with the simplex method and also described using a second-degree equation with two variables (temperature and time) to better find the optimum conditions. PGSu was characterized by FTIR spectroscopy, NMR spectroscopy, degree of esterification was determined, and also molecular weight was calculated for each experiment using Carothers equation. A new synthesis route was developed and optimized. Temperature and time influence on molecular weight and esterification degree of obtained polyester are presented. Based on experiments conducted in this work, it was possible to obtain poly(glycerol succinate) with molecular weight of 6.7 kDa.

Keywords: poly(glycerol succinate), polycondensation, glycerol polyesters, biomaterials, optimization

1. INTRODUCTION

Recently, an increase in glycerol production and a simultaneous decrease in its price have been observed (Ciriminna et al., 2014; Yazdani and Gonzalez, 2007). The growing prevalence of biodiesel is directly related to this, because glycerine is a by-product of its production (Valerio et al., 2018). It was estimated that every 100 L of biodiesel produced generates approximately 12.5 kg of glycerol (Yang et al., 2012). Many specialists are working on developing the possibility of using glycerine, even monographs on this topic have been written (Pagliaro and Pagliaro, 2017). One of the most interesting solutions to this problem is the synthesis of glycerol polyesters. They are often advanced products with a special application, which makes them very valuable (Valerio et al., 2018).

The best known glycerine polyester is poly(glycerol sebacate) – PGS. The first mention of its synthesis is dated 2002 and its use in medicine was immediately postulated (Wang et al. 2002). Initially, PGS was obtained in the form of an elastomer, but subsequent modifications of the synthesis parameters (temperature, time, pressure) allowed to obtain also waxes and resin (Loh et al., 2015; Wang et al., 2002a; Wang et al., 2002b). Poly(glycerol sebacate) is typically obtained by polycondensation of glycerine and sebacic acid (Chen et al., 2008; Kafouris et al., 2013; Rai et al., 2012). Sebacic acid and glycerol are usually used as substrates (Li et al., 2013; Liu et al., 2019; Maliger et al., 2013). This synthesis route has been described in many scientific articles (Gadomska-Gajadhur et al., 2018; Liu et al., 2012). Work on this material is

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at a very advanced level, recently the synthesis process has even been optimized and described using a mathematical model. Thanks to this, detailed synthesis planning is possible to obtain PGS with the desired properties (Gadomska-Gajadhur et al., 2018). Interestingly, slight differences in the synthesis, and therefore also in the properties of PGS, can significantly affect its application capabilities (Denis et al., 2019). Therefore, optimization of the production process of this material is very important. The most interesting poly(glycerol sebacate) applications, and also the most valuable, are those related to medicine. PGS can be used as a drug carrier (Loh et al., 2015; Najafabadi et al. 2018; Patel et al. 2013; Sun et al., 2009; Wang et al., 2003), surgical sealant (Chen et al., 2011; Lang et al., 2014; Rai et al., 2013), a cellular scaffold in tissue engineering (Frydrych et al., 2015; Gao et al., 2007; Hagandora et al., 2013; Jeffries et al., 2015; Motlagh et al., 2006; Rai et al., 2012) and also as a contact surface in biomedical sensors (Yan et al., 2017; 2018).

Poly(glycerol succinate) – PGSu is a less known polyester of glycerol than PGS, but due to the shorter aliphatic chain of the acid that builds it, it may have better hydrophilic properties than PGS. This is extremely important for tissue engineering applications because the human body consists of about 73% of water (Sheng and Huggins, 1979). Glycerine and succinic acid naturally occur in the body, so it is preferable to build a new biomaterial from them. Glycerine is the main component of lipids, which are the basic reserve material in the human body, and phospholipids, which build the cell wall. Glycerophospholipids are also necessary for the proper brain function (Fahy et al., 2005). Glycerol and its derivatives are also found in many metabolic pathways and are metabolized very quickly (van Hall et al., 2002). Succinic acid is one of the key products of the fast metabolic pathway i.e. the Krebs cycle (Barrett and Yousaf, 2009). Therefore, degradation products of poly(glycerol succinate) should not bioaccumulate, and what is more, they should quickly be utilized by the human body. Currently, PGSu is trying to be used as screw material to connect bones (Cai et al., 2019) and as a transdermal drug system matrix (Zabihi et al., 2019). The results of this work are promising, which confirms the above considerations.

Similar to PGS, poly(glycerol succinate) was obtained with good results in polycondensation of succinic acid and glycerol (Agach et al., 2012; Cai et al., 2019; Cheng et al., 2008; Valerio et al., 2016). This method has not been optimized yet. In order to shift the reaction balance towards products, water could be received in Dean-Stark apparatus (Cheng et al., 2008). Using succinic acid, PGS can be obtained with a molecular weight of up to about 3 kDa. PGSu was also attempted to be obtained using catalysed transesterification. The substrates for this synthesis were dimethyl succinate and glycerine, and the catalyst was immobilized lipase B *Candida Antarctica*. Unfortunately, only short oligomers were obtained (Zhao et al., 2018). The synthesis of dendrimers, i.e. spherical branched 3D structures, is interesting but also tedious. The dendrimeric structure distinguishes the material through much lower viscosity, high solubility and also miscibility (Barrett and Yousaf, 2009). Dendrimeric PGSu is obtained in a multistage reaction of succinic acid and benzylidicacetal (a protective form of glycerine). The synthesis consists in gradually building a chain through the reaction of the protected monomer, followed by deprotection, which allows the process to be repeated (Carnahan and Grinstaff, 2001). To the best of our knowledge, PGSu with the highest molecular weight was obtained with this method – about 8 kDa. The alternative is the synthesis of hyperbranched PGSu, which is characterized by a very high degree of branching, but its structure is not dendritic. For this purpose, succinic anhydride and glycerine were used as substrates, and the reaction was catalyzed with tin (II) chloride (Medeiros et al., 2014). Although hyperbranched polyester was obtained, its complete purification from the catalyst can be problematic. High purity is necessary for medical applications. In this method molecular weight of PGSu was not very high – about 1 kDa.

2. MATERIALS AND METHODS

Commercially available reagents (glycerol 99%, succinic anhydride 99,5%) were used without further purification. Reactions were carried out in MultiMax Mettler Toledo reactor systems, in glass reactors

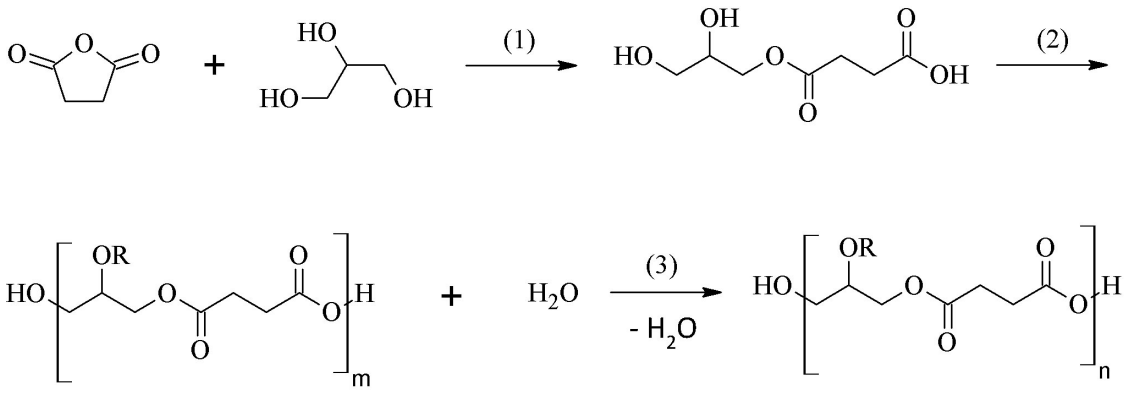
(50 mL) equipped with a mechanical stirrer, a temperature sensor and a reflux condenser or Dean-Stark apparatus. Succinic anhydride (20.00 g; 0.2 mol) and glycerol (18.40 g; 14.60 mL; 0.2 mol) were weighed into the reactor in each case. In the first stage, the reaction mixture was heated to 160 °C and kept under reflux for 24 h. In the second stage, the pressure was lowered to 500 mbar and water was collecting in a Dean-Stark apparatus. The reaction was carried out according to Table 1.

IR spectra were obtained using a BRUKER ALPHA II Platinum ATR spectrometer (in ATR technics). NMR spectra were obtained using an Agilent spectrometer (400 MHz). Esterification degree (ED) was calculated on the basis of acid and ester number as in our previous work (Gadomska-Gajadhur et al., 2018).

Graphics and calculations were made in StatSoft Statistica.

3. RESULTS AND DISCUSSION

We decided to develop a possible simple synthesis method to obtain poly (glycerine succinate) with the highest possible molecular weight. Due to its potential medical application, we have opted out the use of solvents and catalysts. This prevents a purification process, which can be troublesome. What is more, thinking about the future application of the process in industry, we decided to follow the principles of Green Chemistry (Li and Trost, 2008). Therefore, when choosing substrates, we were guided by atomic economy, ecological considerations, and minimization of potential waste. We decided to use succinic anhydride and glycerine as substrates. Our process was one-pot two-step polycondensation, with the first step for creating oligomers and the second one carried out under lower pressure was for producing polymers (Scheme 1). In the first reaction act, a monomer is formed *in situ* (1), without formation of water molecule. Then monomers react with each other to form oligomers (1), but in each reaction act one molecule of water is also generated. The last step is to create possibly the longest chain polymer. Therefore, removing water (2) is necessary for shifting polycondensation equilibrium to the product side (2). Removal of water at an earlier stage of synthesis could be associated with undesirable removal of light PGS fractions.



Scheme 1. Synthesis of poly(glycerol succinate)

In order to quickly determine the optimal conditions for conducting the synthesis (temperature and time), we decided to use a method of simplex optimization. Molecular weight was determined based on NMR spectra. Despite this, the degree of esterification that could be used to control product properties under industrial conditions was also investigated. It is a cheap and simple analysis, which does not require complicated analytical equipment. The degree of esterification is proportional to the molecular weight of the polyester.

The search for the optimum with the simplex method is based on the assumption that the response surface is an unimodal function (it has one extreme). It begins with creating the initial simplex in the factor space of independent variables, which is a convex polyhedron (the number of vertices for k variables is $n = k + 1$). After determining the experimental results for all n vertices of the simplex, the worst vertex is rejected, and instead its mirror image relative to the plane determined by the other vertices is created. The optimum search ends up when:

- the simplex returns to its previous position,
- the simplex begins to circle around one vertex,
- when the experimenter decides to do that (e.g. due to apparatus restrictions) (Jańczewski et al., 2010).

Table 1 shows experimental results. The numbering corresponds to the order in which the experiments were performed.

Table 1. All experimental results and process conditions

No.	t, h	T, °C	Mn, Da	ED, %
1	3	140	6 784	92
2	1.5	140	4 240	90
3	2.25	130	1 272	83
4	2.25	150	4 452	90
5	3.75	150	1 834	85
6	3.75	150	1 764	86
7	4.5	140	3 222	91

Analysis of FTIR spectroscopy shows that in each case a compound with a polyester structure was obtained. This is confirmed by the strong bands characteristic for ester groups – 1721 cm^{-1} and 1150 cm^{-1}. A wide band with a maximum at a wave number of 3454 cm^{-1} corresponds to the vibrations of hydroxyl groups (terminating groups). The wide band in the 3000–2800 cm^{-1} range is derived from proton-carbon bond vibration. The spectrum is presented in Fig. 1.

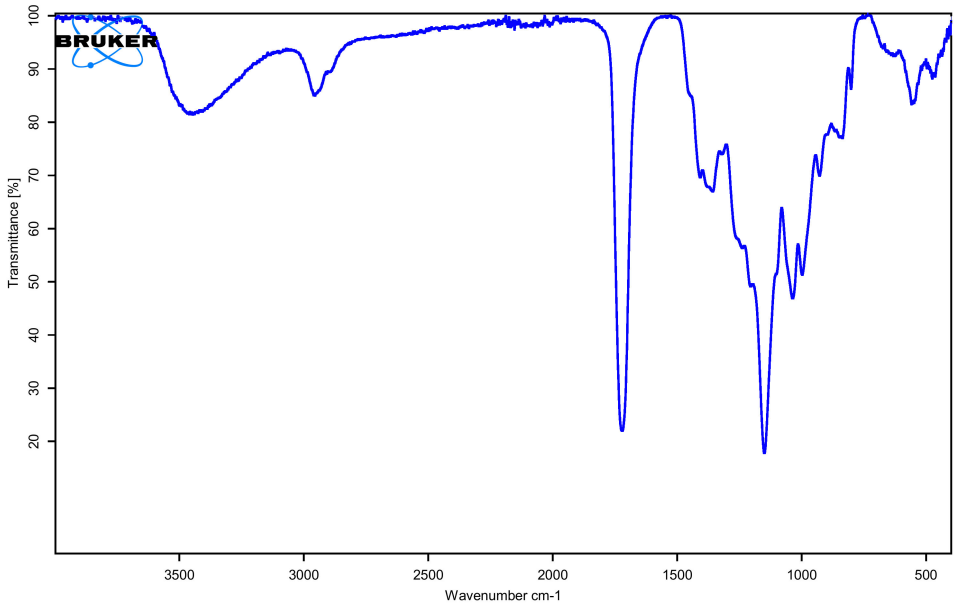


Fig. 1. FTIR spectra of poly(glycerol succinate)

Figure 2 shows ^{1}H NMR spectrum. PGSu glycerine spin systems give signals in the range of 3.2–4.2 ppm and 4.8–5.4 ppm. These multiplets are difficult to interpret and are not crucial for this work. The most important are signals coming from protons of the succinate part adjacent to the ester group (E) and adjacent to the carboxyl group (A) with a chemical shift of 2.58 ppm and 2.41 ppm, respectively.

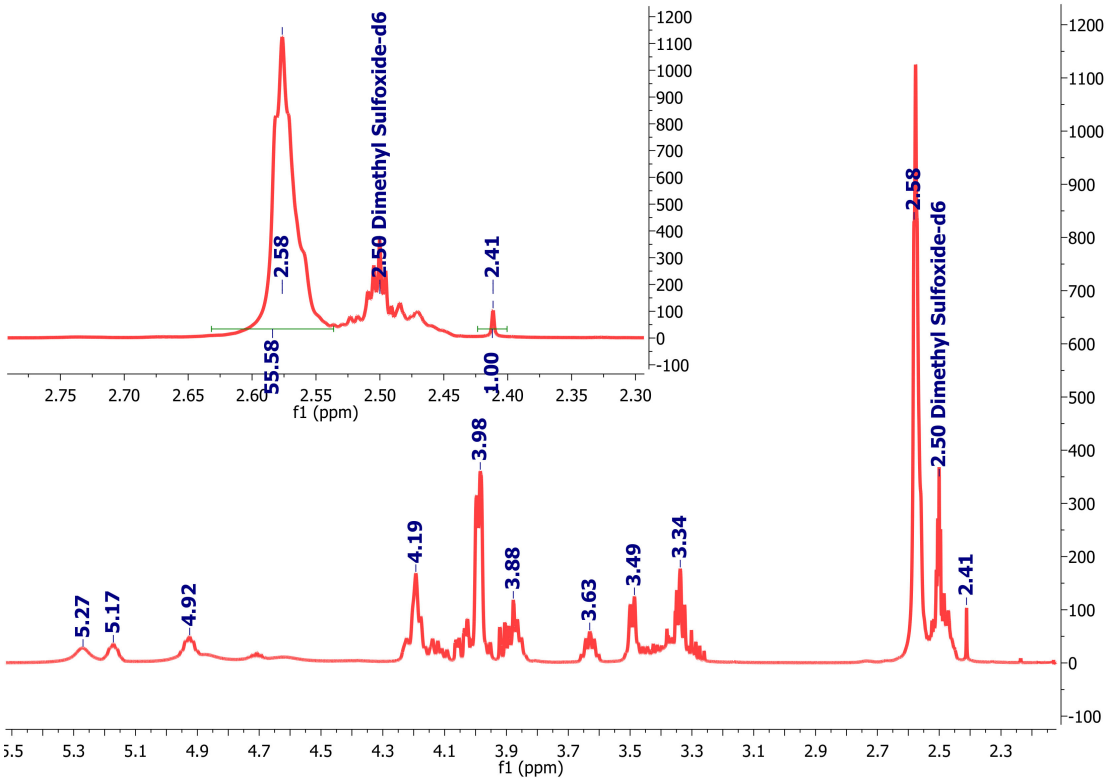


Fig. 2. 1H NMR spectrum of poly(glycerol succinate)

Based on the comparison of signal integrals, the number average molecular weight was calculated according to the formula:

$$Mn = \frac{\int E}{2 \times \int A} \times M_0 + 18 \tag{1}$$

M_0 is the molecular weight of the repeating unit, which is 192, and the number 18 corresponds to the molecular weight of water that is contained in the terminating group.

The analysis of the obtained simplexes was extremely interesting and confusing as unexpectedly the first experiment was close to optimal conditions. As can be seen in Fig. 3 after obtaining PGSu in the 5th experiment we should have gone back to 2, to finish optimization. For this reason, we repeated the experiment, but experiment no. 6 confirmed the results of the 5th. To gain confidence in the correct analysis of the results we performed experiment no.7. After that, according to the principles of the simplex methods, we should have returned to the experiment no. 4. Thanks to these operations we are sure that the experiment no. 1 was very close to the optimum.

To determine the optimal point with better accuracy, we decided to describe the synthesis process with a mathematical model. For this purpose, the algorithms of the Statistica software used for central composition plans were applied. It must be admitted, that for a full description of the process we should use one of DoE methods (e.g. factorial plan 2^2), and thus perform more experiments. In this case, we have decided to use mathematical models to confirm the correct determination of the optimal conditions with the simplex method without making additional experiments. Because the experiments were close to the optimum,

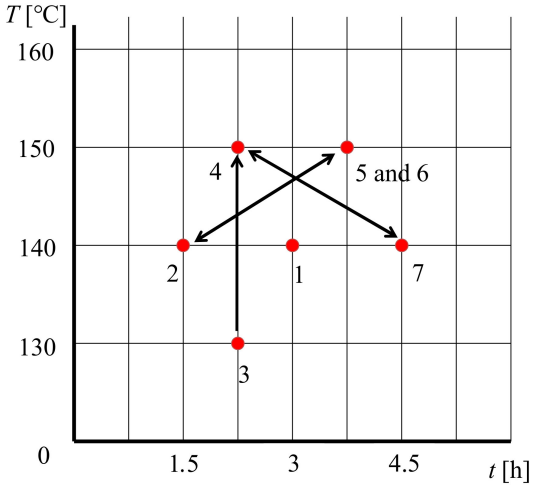


Fig. 3. Synthesis optimization by simplex method, arrows show simplexes movements

the models should allow a quite accurate determination of the optimal conditions of the process, which should allow us to state with much greater certainty than before that the optimization is satisfactory and no additional experiments are really needed. Two models were made that make *ED* and *Mn* dependent on the temperature and time of the synthesis. To correctly determine the impact of individual variables, they are presented in a coded manner in accordance with Table 2.

Table 2. Values of coded variables

Variable	Coded value		
	–1	0	1
time, t, h	1.5	3	4.5
temperature, T, °C	130	140	150

The following equations were obtained:

$$Mn = 1168.20T - 4045.92T^2 - 930.80t - 3053.00t^2 + 6784.00 \quad (2)$$

$$ED = 0.024T - 0.065T^2 - 0.006t - 0.015t^2 + 0.920 \quad (3)$$

The calculated models are graphically represented as the response surface (Fig. 4). Because the response surfaces were developed based on simplex experiments, it should be remembered that extrapolated areas may differ from real ones. The similarity of both graphs confirms the possibility of linking the degree of esterification with molecular weight. However, it should clearly be emphasized that the analysis of molecular weight based on NMR spectra is much more accurate. In both cases, determining the impact of variables is extremely difficult due to the complexity of the process. For this reason, Pareto analysis was used. In both cases, temperature has a greater impact on the process than the reaction time.

Optimal conditions determined on the basis of the models do not differ much from those determined on the basis of the simplex method (140 °C, 3 h). The synthesis parameters are 141.6 °C and 2.9 h and the resulting product should have average molecular weight of 6922 Da and an esterification degree of 92%. Because these parameters do not differ much from those in which the experiment no. 1 had been conducted, no additional experiment was carried out.

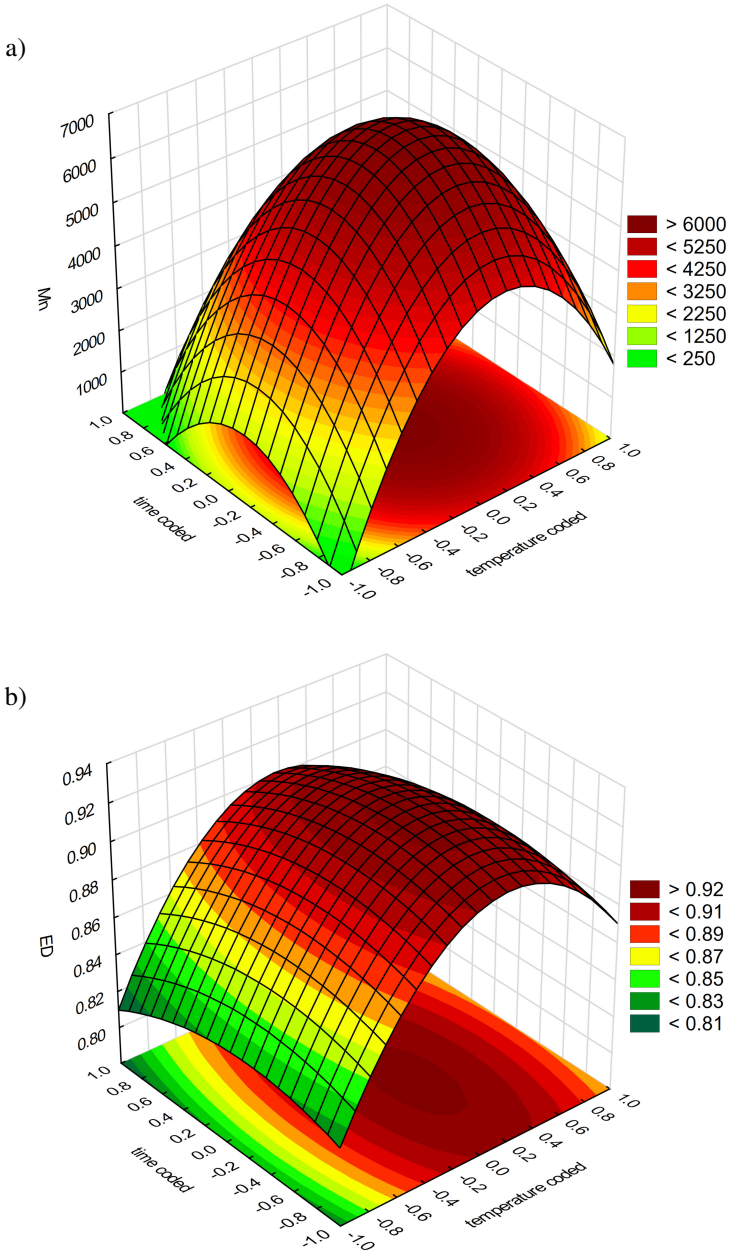


Fig. 4. Response surface for molecular weight model (a) and esterification degree (b)

4. CONCLUSIONS

In this work, a process for obtaining poly(glycerol succinate) was developed. This synthesis method does not use solvents or catalysts and complies with the principles of Green Chemistry. In order to obtain the highest molecular weight polyester, the process was optimized using the simplex method. In addition, the synthesis was described with mathematical models, which allow to predict product properties based on synthesis parameters. Good knowledge of the process and its compliance with the principles of Green Chemistry are extremely valuable for industrial society. Thanks to the developed method, PGS can be obtained with a molecular weight of up to 6 922 Da and an esterification degree up to 92%, which is a great success considering the known scientific works.

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