Synthesis of glycolide by catalytic depolymerization of glycolic acid oligomers modified by polyhydric alcohols

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Abstract. Polymers based on lactide and glycolide are widely used in medicine and pharmaceutics. Glycolide is one of initial monomer for lactide-glycolide copolymers obtainment and its purity has a great significance for production of such polymers with high molecular weight. This research is devoted to the synthesis of glycolide by depolymerization of glycolic acid oligomers modified by polyhydric alcohols in the presence of magnesium, zinc and tin (IV) oxides as the catalysts. Modification of glycolic acid oligomers by polyhydric alcohols allow controlling their molecular weight and decreasing crystallinity degree that affect the oligomers solubility in dimethyl sulfoxide and the yield and purity of target glycolide. Modification of glycolic acid oligomers by polyhydric alcohols results in increasing the yield by 5-10 % and achieving the purity of monomers by 99.0 % in comparison with synthesis from unmodified oligomers. To determine glycolide content in samples, gas chromatography using acetonitrile and hexafluoroisopropanol as solvents was carried out.

1. Introduction

Currently, polymers based on lactide and glycolide are of great interest as objects of research of chemists, biologists and physicians, because they possess a number of valuable properties, such as compatibility with human tissues, biodegradation in the body for a target time to non-toxic lactic and glycolic acids, which then metabolized to CO₂ and H₂O. The degradation time can be regulated by various factors, for example, by changing the molecular weight, the composition of the copolymer and the type of the material itself (films, scaffolds, blocks, etc.). Such polymers are widely used in medicine as suture materials, as a polymeric matrix of composite materials for implants, in pharmaceutics for shells of targeted drug delivery systems [1-6].

Glycolide along with lactide is one of initial monomers for biodegradable polymers production by ring opening polymerization [7-12]. Cyclic diesters of oxycarboxylic acids are obtained predominantly by catalytic depolymerization of oligomers of corresponding acids or its esters which occurs via intra- and intermolecular mechanisms [13-15].

One of the main requirements for glycolide is its high purity. Purification stage of monomers, in particular glycolide is labor-consuming, expensive and continuous process. Glycolide is purified by
recrystallization from different organic solvents, by sublimation and fractional distillation [16-18]. Unpurified glycolide includes hydroxyl containing impurities which are present at the monomer mainly in the form of glycolic acid and its oligomers. Oligomers of glycolic acid (GAO) do not dissolve in conventional organic solvents, therefore their physico-chemical analysis is limited and lead to inaccurate determination of glycolide’ purity that affect essentially the process of its controlled polymerization [19]. Hydroxyl containing impurities form in the glycolide, on the one hand, because of incomplete conversion of glycolic acid during oligomers synthesis. On the other hand, they can be generated directly in the course of GAO depolymerization at the high extent of its conversion and then in the form of low molecular weight oligomers and glycolic acid are distilled together with the target glycolide (figure 1).

**Figure 1.** Pathways of hydroxyl containing impurities formation during glycolic acid polycondensation (a) and GAO depolymerization (b)

In order to reduce the quantity of hydroxyl containing impurities in target glycolide we have proposed using polyhydric alcohols as modifiers of GAO. Modification of the end groups of GAO molecules by polyhydrsic alcohols leads to formation of compounds with increased thermal properties not containing hydroxyl groups (figure 2). Such approach will allow synthesizing a high pure glycolide without hydroxyl containing impurities, for instance, glycolic acid and GAO molecules with a low molecular weights.

**Figure 2.** Synthesis of modified GAO (a) and their depolymerization to glycolide (b)

Moreover, all the initial components (catalysts and modifiers) are commercially available and of moderate cost that is why modified method of glycolide synthesis, on the one hand, cheaper than
traditional one because of reduction of hydroxyl containing impurities and, thereby, reduction of purification stage prices. On the other hand, the final glycolide obtained by modified method have a higher purity in comparison with glycolide obtained by traditional method that is very important for its further controlled polymerization or copolymerization with the other monomers.

The goal of this research is synthesis of glycolide with low quantity of hydroxyl-containing impurities by depolymerization of modified GAO in the presence of oxide catalysts and investigation of the properties of obtained monomers.

2. Experimental part

2.1 Materials and methods
Glycolide synthesis included two stages: synthesis of GAO and its thermal depolymerization in vacuum in the presence of catalyst. Water solution of glycolic acid (70 %, Acros Organics), ethylene glycol, propylene glycol and glycerol (Vekton) were used for the preparation of unmodified and modified GAO. MgO, ZnO and SnO\(_2\) (catalysts of GAO depolymerization) were preliminary calcined for 5 hours at 500 °C.

Investigation of GAO structure was carried out by IR spectroscopy using Agilent Cary 630 FTIR spectrometer at the range of 4000-500 cm\(^{-1}\) and by NMR spectroscopy using spectrometer Bruker AVANCE 400 III HD (solvent – d\(_6\)-dimethyl sulfoxide). Composition of depolymerization catalysts were studied by X-Ray diffraction (XRD) method on Shimadzu XRD 6000 diffractometer, using Cu K\(\alpha\) radiation, 2\(\theta\) ranges were 20°-140°. Phases were identified using PCPDF WIN–1.3 database. Specific surface area (S\(_{BET}\)) of the catalysts was obtained from N\(_2\) adsorption–desorption isotherms at 77 K using TriStar 3020 Micrometerics apparatus.

Quantity of glycolide was measured by gas chromatography using Chromteck Crystal 5000 chromatograph on HP-5 capillary column (Agilent Technologies). Acetonitrile and hexafluoroisopropanol were used as the solvents.

2.2 Preparation of GAO
Synthesis of GAO was carried out using Heidolph rotary evaporator equipped by vacuum pump with a vacuum controller. Calculated amounts of glycolic acid solution and polyhydric alcohol, taken in a molar ratio of 17 to 1, were placed in the evaporation flask. This ratio was necessary to maintain the molecular weight of the oligomers about 1000 g/mol, which was optimal for obtaining glycolide with high yields. The synthesis was carried out at the temperature of 130-180 °C and the pressure of 500-100 mbar for 5 hours. After 5 hours, one of the selected oxide catalysts was added to the reaction flask in an amount of 1 wt.% and heating was continued at 180 °C and 100 mbar for an additional 20 minutes. The obtained oligomer was placed in prepared round bottom flasks for subsequent depolymerization (50 grams in each flask).

2.3 Depolymerization of GAO
The apparatus for GAO depolymerization consisted of a reaction flask with a modified oligomer, a branch bent tube and a receiving flask, which was cooled to -50 °C. The synthesis was carried out at a temperature of 250-270 °C and a pressure of 10-20 mbar. The crude glycolide was purified by threefold recrystallization from ethyl acetate according following method. At first stage, the crude glycolide was recrystallized from 50 wt. % of ethyl acetate regarding the total weight of unpurified sample in order to remove the main quantity of impurities. At the second and the third stages, glycolide was recrystallized from 25 wt. % of ethyl acetate regarding the total weight of glycolide obtained at the first stage. The purified glycolide was dried in the vacuum drying chamber at 50 °C and 10 mbar during 7 hours.
3. Results and discussion

3.1 Study of the properties of catalysts and the structure of modified and unmodified GAO

XRD patterns of oxide catalysts of depolymerization are shown in figure 3. According to XRD results magnesium, zinc and tin (IV) oxides are single-phase catalysts with structures of periclase, zincite and cassiterite, respectively.

![XRD patterns of depolymerization catalysts: MgO (a), ZnO (b) and SnO$_2$ (c).](image)

Depolymerization of GAO occurs in terms of heterogeneous catalysis on the surface of the catalysts which properties were studied. Summarized results of XRD and $S_{\text{BET}}$ determination of the catalysts are presented in table 1.

| Catalyst | Crystal phase | $S_{\text{BET}}, \text{m}^2 \text{g}^{-1}$ | Average crystal size (nm) |
|----------|---------------|---------------------------------|---------------------------|
| MgO      | Periclase     | 23.0                            | 30.8                      |
| ZnO      | Zincite       | 4.0                             | 42.1                      |
| SnO$_2$  | Cassiterite   | 1.8                             | 40.3                      |

Structure of unmodified GAO and GAO modified by polyhydric alcohols is investigated by IR spectroscopy. IR spectra of unmodified and modified GAO are shown in figure 4. Spectra contain following characteristic absorption bands of their functional groups: $\nu(\text{OH}) = 3600-3300 \text{ cm}^{-1}$, $\nu(\text{CH}_2) = 2950-2920 \text{ cm}^{-1}$, $\nu(\text{C}=\text{O}) = 1780-1730 \text{ cm}^{-1}$ and $\nu(\text{C}-\text{O}-\text{C}) = 3600-3300 \text{ cm}^{-1}$. Results of IR spectroscopy are in good agreement with proposed structures of modified GAO.
Figure 4. IR spectra of unmodified GAO (a) and GAO modified by ethylene glycol (b), propylene glycol (c) and glycerol (d).

Modified and unmodified GAO were also analyzed by NMR-spectroscopy. NMR $^1$H spectra were not informative because of signals superposition of related compounds. We used NMR $^{13}$C spectra for identification both the structure of GAO and their depolymerization products. For example, spectrum of GAO modified by ethylene glycol is presented in figure 5.

Figure 5. NMR $^{13}$C spectra of GAO modified by ethylene glycol.
Because of low content of polyhydric alcohol moieties in GAO molecules we did not observed the signals of ethylene glycol in the spectra. Signals of methylene and carbonyl groups in glycolic acid moieties in the GAO molecules were assigned to 60-62 ppm and 167-172 ppm, respectively.

3.2 Synthesis of glycolide
NMR $^{13}$C spectrum of raw glycolide obtained from GAO modified by ethylene glycol is presented in figure 6.

![Figure 6. NMR $^{13}$C spectra of GAO modified by ethylene glycol](image)

Table 2. Results of the glycolide synthesis from unmodified and modified GAO

| Catalyst | Modifier          | Yield of raw glycolide, % | Yield of purified glycolide, % | Purity of glycolide, wt.% * |
|----------|-------------------|---------------------------|-------------------------------|-----------------------------|
| MgO      | –                 | 50.0                      | 15.6                          | 97.5                        |
|          | C$_2$H$_4$(OH)$_2$ Ethylene glycol | 68.9                      | 26.1                          | 96.5                        |
|          | C$_3$H$_6$(OH)$_2$ Propylene glycol | 84.5                      | 28.6                          | 97.8                        |
|          | C$_3$H$_5$(OH)$_3$ Glycerol | 75.3                      | 26.7                          | 99.5                        |
|          | –                 | 78.6                      | 18.5                          | 94.3                        |
| ZnO      | C$_2$H$_4$(OH)$_2$ Ethylene glycol | 71.2                      | 25.8                          | 96.2                        |
|          | C$_3$H$_6$(OH)$_2$ Propylene glycol | 87.5                      | 36.9                          | 96.2                        |
|          | C$_3$H$_5$(OH)$_3$ Glycerol | 86.0                      | 24.7                          | 99.9                        |
|          | –                 | 73.3                      | 23.5                          | 97.0                        |
| SnO$_2$  | C$_2$H$_4$(OH)$_2$ Ethylene glycol | 86.0                      | 26.0                          | 98.9                        |
|          | C$_3$H$_6$(OH)$_2$ Propylene glycol | 77.5                      | 23.6                          | 99.7                        |
|          | C$_3$H$_5$(OH)$_3$ Glycerol | 83.0                      | 14.8                          | 99.8                        |

*after threefold recrystallization from ethyl acetate
Spectrum contains signals of carbon atoms of glycolide at 65.6 ppm (CH\textsubscript{2}) and 165.7 (C=O) as the main product and signals of carbon atoms of ethylene glycol at 63.2 ppm and residues of modified GAO at 60-62 ppm and 170-173 ppm as by-products.

Results of glycolide synthesis from both of unmodified and modified GAO are presented in Table 2. Dependences of the yields of raw and purified glycolide, obtained in the presence of the same modifier, on type of the catalyst are shown in figure 7.

The synthesis of glycolide from unmodified GAO in the presence of a catalyst is characterized by a 50-70% yield of raw glycolide. At the same time, the yield of purified glycolide was about 15-23% with a purity of not more than 97.5%. In case of glycolide synthesized from modified GAO the yields of raw glycolide and purified glycolide increase for most systems.

From table 2 and figure 7 it can be seen that all the depolymerization catalysts demonstrate similar values of the yields, but the highest yield of purified glycolide was obtained for its synthesis from GAO modified by propylene glycol in the presence of zinc oxide as a catalyst. It is worth noting that glycolide with a purity of more than 99% was obtained from GAO modified with glycerol.

![Figure 7. Type of catalyst as a function of the yield of glycolide synthesized from unmodified GAO (a) and GAO modified by ethylene glycol (b), propylene glycol (c) and glycerol (d).](image)

Taking into account the structural properties of the modified GAO and the features of their depolymerization into glycolide, it is necessary to distinguish some fundamental regularities. Polyhydric alcohols as modifiers of GAO play a dual role. First, they act as regulators of the molecular weight of oligomers in the process of polycondensation of glycolic acid, the magnitude of which substantially affects the yield and purity of cyclic diester, as shown in [20] using lactic acid oligomers as an example. Secondly, the modification of GAO with polyhydric alcohols reduces the content of free glycolic acid in oligomers that affects the activity of oxide catalysts and leads to a change in the degree of GAO crystallinity. The latter is well confirmed by the data on the solubility of GAO. Because of their high degree of crystallinity, unmodified GAO is dissolved in dimethyl sulfoxide upon heating. In contrast, modified GAO is more readily soluble in dimethyl sulfoxide. Moreover, GAO modified by glycerol dissolves already at room temperature. Increasing the solubility of the modified GAO reduces the amount of oligomeric impurities in the target glycolide, since they can be removed
during the purification by recrystallization. On the other hand, a decrease in the degree of crystallinity facilitates the interaction of GAO molecules and leads to an increase in the yields of glycolide. In case of GAO, modified by glycerol, the interaction of oligomeric molecules can be difficult due to the formation of three-dimensional structures because of the presence of three hydroxyl groups in the glycerol molecule (figure 8).

**Figure 8.** Proposed structure of GAO modified by glycerol.

Simultaneously with development of the method of glycolide synthesis, it was necessary to determine the purity of the resulting glycolide after its purification. As noted earlier, GAO and glycolic acid-based polymers are not soluble or poorly soluble in conventional organic solvents. According to the literature, hexafluoroisopropanol is the appropriate solvent for glycolide derivatives [21]. In this connection, the determination of the glycolide content in the samples was carried out by gas chromatography in acetonitrile and hexafluoroisopropanol (figures 9 and 10).

When glycolide was obtained from unmodified GAO, its content in the samples according to chromatographic determination in acetonitrile and hexafluoroisopropanol was 99.70 and 95.30 %, respectively (figure 9).

**Figure 9.** Chromatograms of glycolide synthesized from unmodified GAO in acetonitrile (a) and in hexafluoroisopropanol (b).
Figure 10. Chromatograms of glycolide synthesized from GAO modified by glycerol in acetonitrile (a) and in hexafluoroisopropanol (b).

The difference in mass fractions of glycolide is due to the presence of hydroxyl-containing oligomeric impurities that are insoluble in acetonitrile, but at the same time capable of dissolving in hexafluoroisopropanol, which allows its quantitative determination by gas chromatography. From the chromatograms of glycolide, obtained from GAO, modified by glycerol, it can be seen that the quantity of hydroxyl-containing oligomeric impurities is insignificant and is 99.80 and 99.67 % for samples dissolved in acetonitrile and hexafluoroisopropanol, respectively (figure 10). Thus, to accurately determine the purity of glycolide, it is necessary to use the method of gas chromatography and hexafluoroisopropanol as a solvent.

4. Conclusion
A method for obtainment of glycolide with a low quantity of hydroxyl-containing impurities by the depolymerization of GAO modified with polyhydric alcohols has been developed. It is noted that addition of modifiers allows obtaining GAO with a target molecular weight and to achieve a complete conversion of glycolic acid, unreacted residues of which can influence the activity of oxide catalysts of depolymerization. In addition, when GAO is modified, their degree of crystallinity decreases, which affects the solubility of oligomers, for example, in dimethyl sulfoxide. The process of obtaining glycolide from unmodified GAO is characterized by yields of about 50-70 % of the crude glycolide and by purity of target product about 97.5 %. At the same time, the modification of GAO by polyhydric alcohols makes it possible to increase the yield by 5-10 % and achieve a purity of monomers of more than 99.0 %. It can be seen from the experimental data that the highest yield of glycolide was obtained in case of its synthesis from GAO modified by propylene glycol in the presence of zinc oxide. At the same time, syntheses in the presence of magnesium and tin oxides demonstrate similar values of the yield of glycolide. Purity of glycolide synthesized from modified GAO is suitable for the production of high molecular weight polyglycolide and lactide-glycolide copolymers.

To determine the content of glycolide in the samples, the most suitable method is gas chromatography since it allows separating selectively both glycolide as the target product and glycolic acid, GAO with a low molecular weight as the by-products forming in the reaction mixture. Moreover, in case of glycolide content determination by gas chromatography the most suitable solvent is hexafluoroisopropanol since it dissolves all the hydroxyl containing impurities and thereby does not lower the exactness of the method.
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