Acta Pharm. **70** (2020) 63–75 Original research paper

https://doi.org/10.2478/acph-2020-0011

Branched PLGA derivatives with tailored drug delivery properties

EVA SNEJDROVA[1]
STEPAN PODZIMEK[2,3,4]
JURAJ MARTISKA[1,*]
ONDREJ HOLAS[1]
MILAN DITTRICH[1]

[1] *Charles University, Faculty of Pharmacy, 500 05 Hradec Kralove Czech Republic*

[2] *SYNPO, 532 07 Pardubice Czech Republic*

[3] *Wyatt Technology Europe 56307 Dernbach, Germany*

[4] *Institute of Chemistry and Technology of Macromolecular Materials, University of Pardubice, 532 10 Pardubice Czech Republic*

Accepted February 26, 2019
Published March 20, 2019

Despite several shortcomings such as extreme hydrophobicity, low drug capacity, characteristic triphasic drug release pattern with a high burst effect, poly(lactic-*co*-glycolic acid derivatives are widely used in drug delivery. Most frequent attempts to improve their properties are blending with other polymers or synthesis of block copolymers. We introduce a new class of branched poly(lactic-*co*-glycolic acid) derivatives as promising biodegradable carriers for prolonged or targeted drug release systems, employed as thin adhesive films, solid dispersions, *in situ* forming implants or nanoparticles. A series of poly(lactic-*co*-glycolic acid) derivatives with lower molar mass and star or comb architecture were synthesized by a simple, catalyst free, direct melt polycondensation method not requiring purification of the obtained sterile product by precipitation. Branching monomers used were mannitol, pentaerythritol, dipentaerythritol, tripentaerythritol and polyacrylic acid. The products were characterized by molar mass averages, average branching ratio, rheological and thermal properties.

Keywords: PLGA, branching, star polymer, polymer synthesis, light scattering

The benefit of using FDA and EMA approved poly(lactic-*co*-glycolic acid) (PLGA) based materials is their safety, biodegradability, absorbability through natural pathways and biocompatibility. Nowadays, these compounds are ubiquitous not only in surgery, orthopedics and tissue engineering (1), but their use extends to drug delivery systems with controlled and targeted release of incorporated drugs (2, 3), *e.g.*, solid dispersions, thin layers, *in situ* forming implants, microparticles, and nanoparticles (4). Modifications in molar mass distribution, molecular architecture as well as glycolic acid to lactic acid ratio make PLGA a versatile tool with tunable properties. By choosing proper material, it is possible to optimize parameters such as drug loading capacity, stability under biological conditions, target of distribution or release profile of the drug (5). Lower molar mass linear and

* Corresponding author; e-mail: martisju@faf.cuni.cz

branched polymers are particularly well suited carriers of drugs because of their shorter degradation time, within a few hours or days. Degradation leads to the accumulation of acidic monomers, lactic and glycolic acid, within the drug delivery device. A significant reduction in the pH of the microenvironment can increase the solubility of drugs better dissolved in the acidic environment, promote healing when applied topically, or help maintain the physiological pH at the application site (6). Branching inherently multiplies the number of chain ends, which can be engineered to bear active pharmaceutical ingredients. A significant parameter of the branched polyesters is their hydrophilic character due to the larger number of end groups. Increased hydrophilicity may lead to increased biomimetic parameters of drug forms, above all particulate systems (7). The presence of free hydroxyl groups available for binding water causes reduction of hydrophobicity. The triphasic drug release pattern typical of unmodified PLGA can be converted to a nearly linear kinetic profile with lower initial burst (8). The branched structure and suppressed hydrophobicity give the materials mucoadhesive properties (9). Direct polymerization was reported as a suitable method for preparation of high-molar-mass linear PLGA molecules (10), however costly because of the used catalysts, subsequent product purification, and drying (11). Nevertheless, several research groups (12–14) have employed condensation polymerizations in the synthesis of functionalized polyesters. Light scattering has become the key analytical technique of polymer analysis. Multi-angle light scattering (MALS) allows fast characterization of polymers, and their main use is that of detectors for size exclusion chromatography (SEC) or other analytical separation techniques (15, 16). In our study, we present a series of PLGA derivatives with lower molar mass, and linear, star or comb architecture. These prospective drug carriers were synthesized by a very simple, catalyst free, direct melt polycondensation method to get polyesters of lower molar mass, and linear, star or comb architecture. Hydroxyl and carboxyl branching agents were used in order to prepare OH terminated or COOH terminated molecules with varying branching ratios. The products were characterized by molar mass averages, average branching ratio, rheological and thermal properties.

EXPERIMENTAL

Materials

Glycolic acid, DL-lactic acid, pentaerythritol dipentaerythritol, tripentaerythritol, poly(acrylic acid) (average M_r ~ 2,000) solution in H_2O (w = 50 %, m/m), and mannitol were purchased from Sigma-Aldrich, Czech Republic. Solvents were purchased from Penta, Czech Republic.

Synthesis

Polyesters were synthesized by the direct melt polycondensation method. Monomers glycolic acid (GA) and DL-lactic acid (LA) in 1:1 ratio were mixed together without or with a branching agent in a round-bottomed flask equipped with a cooler to achieve gentle reflux. Branching agents used were mannitol (M), pentaerythritol (P), dipentaerythritol (D), tripentaerythritol (T), or poly(acrylic acid) (PAA) in concentrations ranging from 0.5 to 8 % (m/m). Fig. 1 shows a scheme of PLGA branched on pentaerythritol.

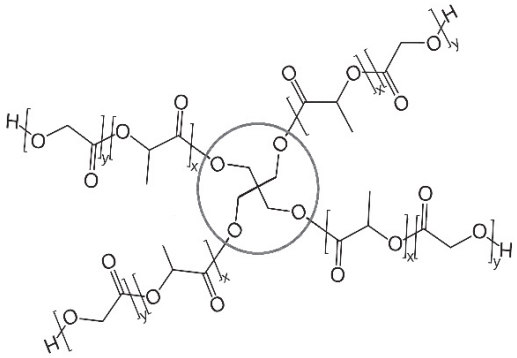

Fig. 1. Scheme of PLGA molecule branched on pentaerythritol.

The reaction mixture was gradually heated to the temperature of 160 °C under controllably increasing the vacuum provided by a rotary oil pump. At this temperature and a constant pressure of 550 Pa, the reaction continued for a total time of 20–50 h. The end of the reaction was monitored both by viscosity monitoring and based on a significant reduction of water vapour formation in a highly viscous melt.

Molar mass and branching

Molar mass distribution and branching of synthesized polyesters were characterized by a combination of size exclusion chromatography (SEC) coupled with a multi-angle light scattering (MALS) photometer and an on-line viscometer (VIS) known as triple detection.

The instrumental set-up consisted of an isocratic pump Agilent 1100, a Waters Autosampler 717, a MALS photometer HELIOS II, a refractive index (RI) detector Optilab T-rEX and a viscometer ViscoStar III. All detectors were from Wyatt Technology Corporation. Two Agilent PolyPore 300 × 7.5 mm columns were used for the separation. Tetrahydrofuran (THF) was used as a mobile phase at a flow rate of 1 mL min^{-1}. The samples were injected as solution in THF at a concentration of 30 mg min^{-1} and 100 μL injection volume.

The principle of branching characterization is based on the fact that branching decreases molecular size. Branching of polymer chains can be described by the branching ratio g', which was introduced by Zimm and Stockmayer (17) as the ratio of the mean square radius of a branched molecule divided by the mean square radius of a linear molecule at the same molar mass. The root mean square radius (RMS), radius of gyration, needed for the calculation of g', can be obtained by MALS simultaneously with molar mass. However, the RMS radius cannot be reliably determined below the radii of about 10 nm, which roughly corresponds to the molar mass of 10^5 g mol^{-1}, and thus an alternative size parameter must be used in case of smaller molecules. The branching ratio g' calculated as the ratio of intrinsic viscosity of the branched molecule and linear molecule at the same molar mass was suggested by Zimm and Kilb (18). The value of g' equals the one for linear polymers and decreases with branching. Mathematically expressed, g' is the branching ratio g to the power of the draining parameter e. There is also a simple relation between g' and g based on the RMS radius, which is in the theoretically derived relation to the

number of branch units in randomly branched polymers or the number of arms in branched polymer structures (17, 18).

$$g = \frac{6f}{(f+1)(f+2)} \tag{1}$$

where f is the number of random length arms in star polymers. However, there is no simple way to the draining parameter e, which depends on the solvent, molar mass and the degree and topology of branching. The value of e is generally supposed to fall in the range 0.5–1.5, yet the exact number for a given polymer is mostly unknown.

An alternative semi-empirical equation was proposed by Douglas *et al.* (19):

$$g' = \left(\frac{3f-2}{f^2}\right)^{0.58} \frac{0.724 - 0.015(f-1)}{0.724} \tag{2}$$

The advantage of Equation *2* is that it allows the calculation of f directly from g' whereas the limitation is given by the fact that it was derived for long Gaussian coils, which may not be fulfilled in case of smaller branched macromolecules.

Comparison of the number of arms f calculated according to Equation *1* and interrelation between g' and g with determination by Equation *2* shows that similar results are obtained for $e \approx 1.2$, *i.e.*, the value of e falling into the usual range.

Differential scanning calorimetry

The glass transition temperature (T_g) of the polyesters was determined by differential scanning calorimetry using a DSC 200 F3 Maia® (Netzsch, Germany). A constant nitrogen flow (50 mL min^{-1}) was maintained throughout the tests. A sample amount of ≈ 10 mg was placed in aluminium pans and hermetically sealed. An empty pan was used as reference. The sample was heated to 90 °C, then cooled to –50 °C before a second heating again to 90 °C. Both cooling and heating rates were 10 °C min^{-1}. The value of T_g was taken from the second heating cycle at the inflection point. The measurement was made in triplicate and averaged.

Rheological characterization

Rheological properties of polyesters were measured with a KinexusPro$^+$ Malvern rotational rheometer with the cone upper geometry of 2°/20 mm (CP 2/20) and a solvent trap system. Data were evaluated using SW r-Space version 1.72. Equilibrium flow and viscosity curves at shear rates from 0.1 to 100 s^{-1} were obtained, and evaluated by model fitting. All measurements were made in triplicate.

RESULTS AND DISCUSSION

Synthesis

The presented procedure seems suitable for the synthesis of linear and especially branched polyesters with molar mass providing degradation within several weeks. One of

the advantages is easy control of the course of the polycondensation reaction. The reaction runs satisfactorily without using a catalyst. We consider the detected increase in molecular weight by only 2 to 4 percent in the presence of the ion exchanger Dowex 50 W X8 catalyst as an insignificant difference. Products synthesized without a catalyst were clear pale yellow; polymers obtained in the presence of acid Dowex were darker, browned. Purification obviously implemented by precipitation with water from acetone solution did not have a significant effect on the molar weight parameters, and therefore we did not carry out further tests. This is very advantageous in terms of the absence of solvent residuals in final products. An important advantage is also no need of mixing the reactants by bubbling with nitrogen, as the water vapour during permanently controlled heating ensures sufficient movement of the liquid in an enclosed system. Batch mass ranged from 100 to 5000 g. A typical conversion was about 96 % and yield was 86 %. Reaction time ranging from 20 to 50 hours was influenced both by the efficiency of the pump and by the amount of reactant mixture. Based on the conditions during the polycondensation reaction (160 °C, 550 Pa, 20–50 h) and the boiling point of monomers (DL-lactic acid 122 °C, glycolic acid 112 °C), we did not expect low molecular weight molecules in the resultant product. Therefore, the products were not purified. We consider this polyester synthesis method as scalable.

Molar mass and branching ratio

Table I lists the values of the number-average molar mass (M_n), weight-average molar mass (M_w), weight-average intrinsic viscosity (h_w) and the branching ratio $g'(M_w)$ determined for various copolymers. The average branching ratio $g'(M_w)$ was calculated using Equation *1* and the experimentally determined (h_w) of the branched polymer and the hypothetical intrinsic viscosity of the corresponding linear polymer with the same M_w as the sample under analysis. Calculation of the hypothetical (h_w) of linear PLGA was performed using the Mark-Houwink relation of linear PLGA and the experimental M_w of the branched sample. The Mark-Houwink relation of linear PLGA was obtained by triple detection of the linear PLGA copolymer containing equal co-monomer weight fractions:

$$\left[\eta\right] = 9.77 \times 10^{-2} M^{0.535} \quad (\text{mL g}^{-1}, \text{THF}, 25\ ^\circ\text{C}) \qquad (3)$$

Calculation of $g'(M_w)$ can be demonstrated in the third row of Table I (polyester 3M) as follows: inserting M_w = 4,700 g mol^{-1} into Equation 3 one gets $[\eta]_w$ = 9.0 mL g^{-1}, which represents the weight-average intrinsic viscosity of linear PLGA having M_w = 4,700 g mol^{-1}. This value is related to the true $[\eta]_w$ for this polymer, which gives $g'(M_w) = 0.63$.

Data in Table I do not show any obvious effect of the amount of branching agents on molar mass, and the effect on the branching ratio is not conspicuous either. This can be explained by the effect of the multifunctional monomers used as branching agents. Branching generally leads to the formation of molecules with high molar mass, and the shift of molar mass distribution to higher values. In our case, we use branching monomers that bring additional functional groups. Excess of hydroxyl groups (or carboxyl groups) usually decreases the molar mass during polycondensation. This means we have two counteracting effects: (*i*) branching leading to higher molar masses, and (*ii*) excess of hydroxyl groups leading to lower molar masses. Given the same molar mass, branched molecules are more compact and elute at higher elution volumes. This effect is also evident from decreasing intrinsic viscosities, as displayed in Mark-Houwink plots (Fig. 1, Fig. 2).

Table I. Molar mass averages, intrinsic viscosity and branching ratio for linear and branched PLGA

Sample designation	M_n (g mol^{-1})	M_w (g mol^{-1})	$[\eta]_w$ (mL g^{-1})	$g'(M_w)$
PLGA-1	1,700	2,400	5.9	1
PLGA-2	5,400	7,500	12.2	1
3M	3,100	4,700	5.7	0.63
5M	1,800	2,700	4.8	0.72
8M	1,500	2,000	4.0	0.70
1P	3,700	7,400	8.3	0.72
3P	5,200	8,000	6.0	0.50
5P	2,000	2,700	4.5	0.67
0.5D	1,900	3,800	6.2	0.78
1D	2,200	5,000	6.3	0.63
2D	1,700	3,600	5.1	0.65
3D	3,700	6,600	6.5	0.60
5D	2,300	3,200	3.6	0.49
8D	1,600	2,500	2.9	0.45
1T	3,600	12,300	8.4	0.56
3T	5,300	17,400	7.7	0.43
5T	5,400	10,900	5.9	0.42
2PAA	8,600	14,400	8.9	0.54
4PAA	10,900	18,700	8.0	0.42

PLGA-1 and PLGA-2 are linear polyesters with different molar mass; branched polyesters are designated by number – percentage of branching agent, and capital letter – branching agent type (M – mannitol, P – pentaerythritol, D – dipentaerythritol, T – tripentaerythritol, PAA – polyacrylic acid).

It is noteworthy that the poly(acrylic acid) branched polymers show distinctly higher both M_n and M_w compared to the polymers branched with other molecules. Among the other compounds, those branched with tripentaerythritol show increased M_w. This shows that the number of branching agent functional moieties affects the resulting molar mass rather than the branching agent concentration. However, use of 3 % concentration erythritol derivatives as branching agents is most beneficial in terms of products with higher molar mass. Molecules branched with mannitol display a considerably low molar mass. Plausible explanation for this phenomenon is offered by the presence of chemically non-identical hydroxyls within the mannitol molecule. This is avoided by employing other branching agents used in this study.

At first glance, the distribution of branching in branched polymers can be evident from the comparison of Mark-Houwink plots, *i.e.*, log-log relations between the intrinsic viscosity and molar mass. Examples of Mark-Houwink plots for several prepared samples

are given in Figs. 2 and 3. A general trend of the plots is the increasing span from the plot of linear PLGA towards higher molar masses. This indicates an increasing branching ratio with increasing molar mass as typical of randomly branched polymers. The abrupt change of the slope or downward curvature in the lower molar mass region, which is evident on some of the plots, can be explained by increased polydispersity of elution volume slices at the end of the chromatogram. Increased polydispersity is caused by the specific elution behaviour of branched macromolecules that have a general tendency to elute later due to their anchoring in the pores of the SEC column packing (20). Fig. 4 shows that the major part of synthetized molecules have molar mass up to about 10^4 g mol^{-1}, and thus that the highly branched fractions are not present throughout the distribution.

Fig. 5 plots the branching ratio g' *versus* molar mass for three samples containing identical amounts of branching agent with different functionality. The plots show no evi-

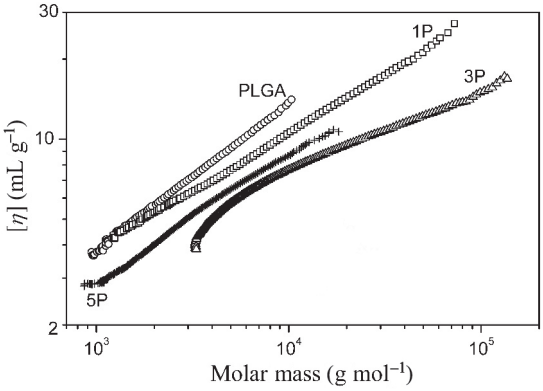

Fig. 2. Mark-Houwink plots of linear PLGA and branched PLGA containing 1, 2 and 3 % of pentaerythritol (P). Numbers correspond to the branching compound weight fraction.

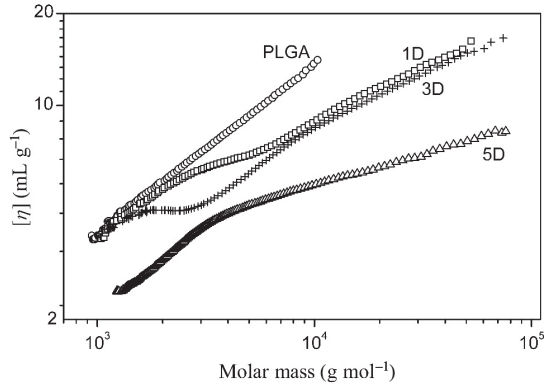

Fig. 3. Mark-Houwink plots of linear PLGA and branched PLGA containing 1, 3 and 5 % of dipentaerythritol (D). Numbers correspond to the branching compound weight fraction.

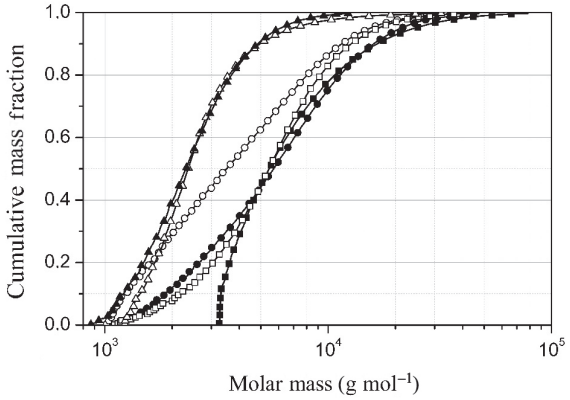

Fig. 4. Cumulative molar mass distribution plots of samples containing 1, 2 and 3 % of pentaerythritol (P): filled circle, square and triangle, respectively; and 1, 3 and 5 % of dipentaerythritol (D): empty circle, square and triangle, respectively. Numbers correspond to the branching compound mass fraction.

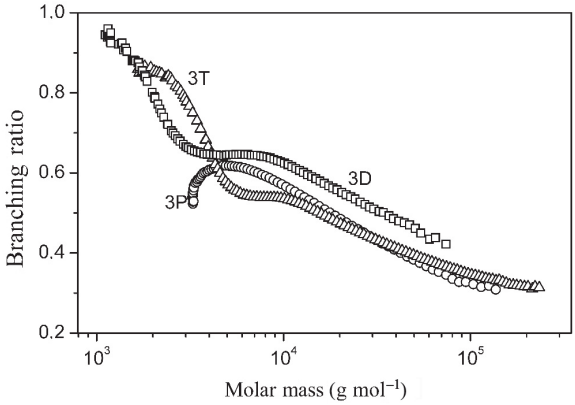

Fig. 5. Branching ratio *g´ versus* molar mass for PLGA containing 3 % of pentaerythritol (P), dipentaerythritol (D), and tripentaerythritol (T).

dent difference in the distribution of branching due to the number of functional groups of the branching compound. One of the plots is apparently affected by delayed elution, as seen from the unrealistic downward curvature at ≈ 3000 g mol^{-1}; the other two plots decrease evenly starting at $g´ \approx 1$, which shows the fractions with the lowest molar masses to be almost linear.

Thermal properties

There are two basic methods for characterization of the thermal properties of polymers, dynamic mechanical thermal analysis (DMTA) and differential scanning calorimetry

(DSC). Although DMTA has been reported as more sensitive in detecting the T_g of polymers, we have chosen DSC for the characterization of synthesized PLGA derivatives, since this method is more suited to the evaluation of miscibility of pharmaceutical blends (21). It is known that there is significant influence of the composition of chain-end groups and molar weights of branched polyesters on T_g but little effect by the polymer architecture and branching ratio (22). DSC scans exhibit a primary relaxation referred to as glass transition at a characteristic temperature (T_g) typical of amorphous polymers (Fig. 6). T_g values ranged from 12.4 °C for polyester 8D (M_n = 1,600 g mol^{-1}; g' = 0.45) to 36.1 °C for polyester 4PAA (M_n = 10,900 g mol^{-1}; g' = 0.42).

Fig. 7a depicts the dependence of glass transition temperature on the number-average molar mass. The data do not show strong dependence of T_g on M_n, though an increasing trend in the T_g *vs.* M_n plot is obvious. Apparently, there is no relation between T_g and the

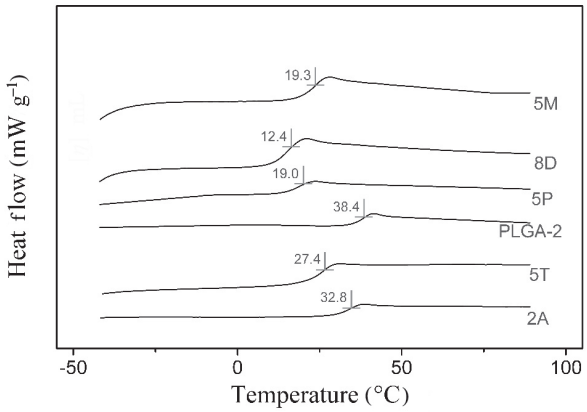

Fig. 6. DSC scans of branched polyesters with glass transition temperature (T_g) values.

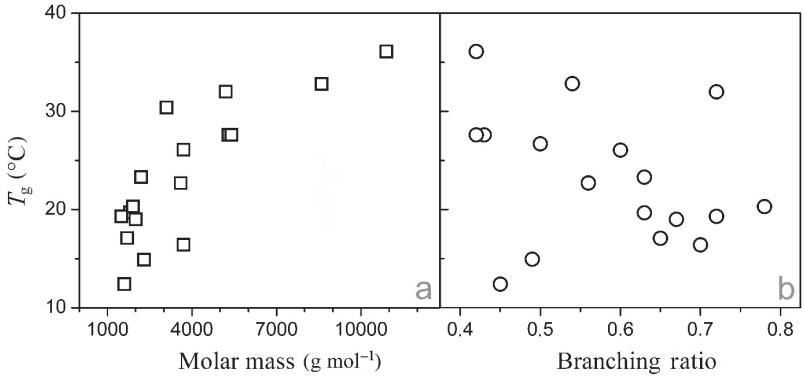

Fig. 7. a) Effect of molar mass and b) branching ratio on glass transition temperature (T_g) of branched polyesters.

branching ratio, as evident from Fig. 7b. These findings can be explained as follows: in general, T_g of oligomers increases with increasing molar mass and reaches a constant value at a molar mass of several thousands, as shown in Fig. 8. In our particular case, the effect of molar mass is superimposed by the effect of branching. Incorporation of branch units into a polymer chain has a counteracting effect on T_g, which should generally increase as the branch units decrease the chain mobility. However, the increased number of chain ends contributes to the free volume leading to a decrease of T_g.

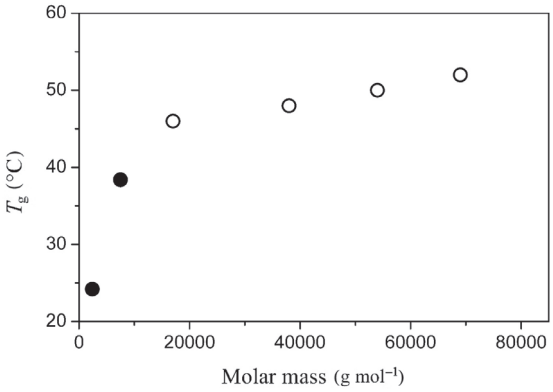

Fig. 8. Effect of molar mass on glass transition temperature (T_g) of linear polyesters (full dots are synthesized polyesters and empty dots are data for commercial Resomers® RG 502–505).

Rheological behaviour

Despite the relatively low values of T_g, PLGA polyesters are solid, very hard and brittle materials under ambient conditions. The viscosity-shear rate curve for a number of polyester melts in shear rate range from 0.1 to 100 s^{-1} was obtained, and the data were analysed using the Newtonian and Power Law models. The corresponding fitting parameters are given in Table II. Both models show high correlation. Nevertheless, the value of power law index n approaching one confirms the Newtonian flow. Melt viscosity of branched polyesters shows an increasing trend with increasing values of T_g.

Knowledge of the rheological behaviour of polyesters is important for good processing into solid dispersions, thin films, micro or nanoparticles, and the application of formulated dosage forms. Moreover, it significantly influences the course and time of degradation, adhesion to the site of application, and drug release profile. The low T_g and revelation of Newtonian behaviour of branched polyesters seem to be quite convenient particularly from the technological point of view. The required value of viscosity can be reached by only mild heating during formulation of dosage forms, gentle for incorporated active substances, for example, hot-melt extrusion as a method of formulation of solid dispersions with poorly dissolved drugs (23). The second possibility of how to set the viscosity to the needed and constant value is by plasticizing using biocompatible, degradable, and even multifunctional plasticizers (24).

Table II. Model fit of the flow curves of branched polyester melts obtained at 80 °C

PLS	Power law model fit			Newtonian model fit	
	k (Pa s)	*n*	Corr.	Viscosity (Pa s)	Corr.
3M	66.2	0.9966	0.9998	65.6	1
5M	36.5	0.9943	1	36.1	1
8M	19.2	0.9973	1	19.1	1
1P	401.1	0.9879	1	391.2	1
3P	99.6	0.9974	1	113.4	1
5P	20.6	0.9866	1	23.1	0.9999
1D	96.2	0.9974	1	95.5	1
3D	157.6	0.9972	1	179.5	1
5D	18.0	0.9926	1	17.7	1
1T	32.2	0.9957	1	31.2	0.9999
3T	295.4	0.9929	1	291.9	1
5T	56.5	0.9962	1	56.1	1
2A	1,349	0.9923	0.9999	1,321.0	1
4A	1,285	0.9915	0.9999	1,310.0	1

k – consistency, *n* – power law index ranges from 0 for very shear thinning materials to 1 for Newtonian materials, Corr. – correlation coefficient.

CONCLUSIONS

Simple direct melt polycondensation without addition of a catalyst leads to a poly(lactic-*co*-glycolide) group of star architecture when using mannitol, penta-, dipenta- or tripentaerythritol, or comb architecture using poly(acrylic acid) as a branching agent. The presented polycondensation method is readily controllable and scalable, the products obtained are sterile, and there is no need of purification by dissolution, precipitation, and drying. Basic characteristics of the obtained materials such as molar mass parameters, branching ratio, thermal and rheological behaviour are sufficiently characterized. The branched topology can be proven and semi quantified by triple detection. The Mark-Houwink plots show that for a given sample the branching ratio increases with molar mass with no obvious effect of the type of branching compound. DSC scans show fully amorphous materials. The glass transition temperature ranging from 12 to 36 °C does not depend on the branching ratio. Polymer melts at 80 °C behave as Newtonian systems; values of viscosity are in a broad range and tend to increase with increasing glass transition temperature. We assume that the PLGA derivatives with lower molar masses, branched architecture, ester or acid terminated are prospective carriers in drug delivery.

Acknowledgments. – This study was funded by The Czech Science Foundation No. 17-06841S and by MEYS No. SVV260401.

REFERENCES

1. P. Gentile, V. Chiono, I. Carmagnola and P. V. Hatton, An overview of poly(lactic-*co*-glycolic) acid (PLGA)-based biomaterials for bone tissue engineering, *Int. J. Mol. Sci.* **15** (2014) 3640–3659; https://doi.org/10.3390/ijms15033640
2. D. J. Hines and D. L. Kaplan, Poly(lactic-*co*-glycolic) acid-controlled-release systems: experimental and modeling insights, *Crit. Rev. Ther. Drug Carrier Syst.* **30** (2013) 257–276; https://doi.org/10.1615/CritRevTherDrugCarrierSyst.2013006475
3. H. K. Makadia and S. J. Siegel, Poly lactic-*co*-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier, *Polymers* **3** (2011) 1377–1397; https://doi.org/10.3390/polym3031377
4. E. Swider, O. Koshkina, J. Tel, L. J. Cruz, I. J. M. de Vries and M. Srinivas, Customizing poly(lactic-*co*-glycolic acid) particles for biomedical applications, *Acta Biomater.* **73** (2018) 38–51; https://doi.org/10.1016/j.actbio.2018.04.006
5. F. Danhier, E. Ansorena, J. M. Silva, R. Coco, A. Le Breton and V. Préat, PLGA-based nanoparticles: an overview of biomedical applications, *J. Control. Release* **161** (2012) 505–522; https://doi.org/10.1016/j.jconrel.2012.01.043
6. B. S. Nagoba, N. M. Suryawanshi, B. Wadher and S. Selkar, Acidic environment and wound healing: a review, *Wounds* **27** (2015) 5–11.
7. L. A. Dailey and T. Kissel, New poly(lactic-*co*-glycolic acid) derivatives: Modular polymers with tailored properties, *Drug Discov. Today Technol.* **2** (2005) 7–13; https://doi.org/10.1016/j.ddtec.2005.05.017
8. E. Snejdrova, M. Drastik, M. Dittrich, P. Kastner and J. Nguyenova, Mucoadhesive plasticized system of branched poly(lactic-*co*-glycolic acid) with aciclovir, *Drug Dev. Ind. Pharm.* **42** (2016) 1653–1659; https://doi.org/10.3109/03639045.2016.1160109
9. E. Snejdrova, M. Drastik and M. Dittrich, Plasticized branched aliphatic oligoesters as potential mucoadhesive drug carriers, *Int. J. Pharm.* **458** (2013) 282–286; https://doi.org/10.1016/j.ijpharm.2013.10.030
10. M. Ajioka, H. Suizu, C. Higuchi and T. Kashima, Aliphatic polyesters and their copolymers synthesized through direct condensation polymerization, *Polym. Degrad. Stab.* **59** (1998) 137–143; https://doi.org/10.1016/S0141-3910(97)00165-1
11. C. K. Williams, Synthesis of functionalized biodegradable polyesters, *Chem. Soc. Rev.* **36** (2007) 1573–1580; https://doi.org/10.1039/b614342n
12. A. Alla, K. Hakkou, F. Zamora, A. Martínez de Ilarduya, J. A. Galbis and S. Muñoz-Guerra, Poly(butylene terephthalate) Copolyesters Derived from l-Arabinitol and Xylitol, *Macromolecules* **39** (2006) 1410–1416; https://doi.org/10.1021/ma052398v
13. M. G. García-Martín, R. R. Pérez, E. B. Hernández and J. A. Galbis, Linear polyesters of the poly[alkylene (and co-arylene) dicarboxylate] type derived from carbohydrates, *Macromolecules* **39** (2006) 7941–7949; https://doi.org/10.1021/ma061325o
14. J. Hu, W. Gao, A. Kulshrestha and R. A. Gross, "Sweet polyesters": lipase-catalyzed condensation-polymerizations of alditols, *Macromolecules* **39** (2006) 6789–6792; https://doi.org/10.1021/ma0612834
15. S. Podzimek, Truths and myths about the determination of molar mass distribution of synthetic and natural polymers by size exclusion chromatography, *J. Appl. Polymer Sci.* **131** (2014); http://doi.org/10.1002/app.40111
16. S. Podzimek, Importance of multi-angle light scattering in polyolefin characterization, *Macromol. Symp.* **330** (2013) 81–91; https://doi.org/10.1002/masy.201300014
17. B. H. Zimm and W. H. Stockmayer, The dimensions of chain molecules containing branches and rings, *J. Chem. Phys.* **17** (1949) 1301–1314; https://doi.org/10.1063/1.1747157

18. H. B. Zimm and W. R. Kilb, Dynamics of branched polymer molecules in dilute solution, *J. Polymer Sci.* **37** (1959) 19–42; https://doi.org/10.1002/pol.1959.1203713102
19. J. F. Douglas, J. Roovers and K. F. Freed, Characterization of branching architecture through "universal" ratios of polymer solution properties, *Macromolecules* **23** (1990) 4168–4180; https://doi.org/10.1021/ma00220a022
20. S. Podzimek, T. Vlcek and C. Johann, Characterization of branched polymers by size exclusion chromatography coupled with multiangle light scattering detector. I. Size exclusion chromatography elution behavior of branched polymers, *J. Appl. Polymer Sci.* **81** (2001) 1588–1594; https://doi.org/10.1002/app.1589
21. D. S. Jones, Y. Tian, O. Abu-Diak and G. P. Andrews, Pharmaceutical applications of dynamic mechanical thermal analysis, *Adv. Drug Deliv. Rev.* **64** (2012) 440–448; https://doi.org/10.1016/j.addr.2011.12.002
22. Y. Shi, X. Cao, S. Luo, X. Wang, R. W. Graff, D. Hu, R. Guo and H. Gao, Investigate the glass transition temperature of hyperbranched copolymers with segmented monomer sequence, *Macromolecules* **49** (2016) 4416–4422; https://doi.org/10.1021/acs.macromol.6b01144
23. Y. Huang and W. G. Dai, Fundamental aspects of solid dispersion technology for poorly soluble drugs, *Acta Pharm. Sin. B* **4** (2014) 18–25; https://doi.org/10.1016/j.apsb.2013.11.001
24. E. Snejdrova and M. Dittrich, *Pharmaceutically Used Plasticizers*, in *Recent Advances in Plasticizers* (Ed. M. Luqman), IntechOpen, Rijeka 2012, pp. 69–90.