Poly (glycerol-sebacate) bioelastomers: 2. Synthesis using Brabender Plasticoder® as a batch reactor

Raju B. Maliger, Peter J. Halley, Justin J. Cooper-White

Australian Institute of Bioengineering & Nanotechnology, School of Chemical Engineering, University of Queensland, St. Lucia, Brisbane, Queensland 4072, Australia
Correspondence to: R. B. Maliger (E-mail: r.maliger@gmail.com)

ABSTRACT: Poly (glycerol-sebacate) polymers are seen as useful materials for biomedical applications. In this article, poly (glycerol-sebacate) oligomers were synthesized by modifying a Brabender Plasticorder® as a batch reactor. The samples collected over a reaction period of 5 h were characterized using Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). The number-average molecular weight (M_n) and weight-average molecular weight (M_w) of the oligoesters were determined using matrix-assisted laser desorption/ionization time-of-flight spectroscopy (MALDI-TOF). The polydispersity indices of these oligoesters produced were within bounds of current commercial polymers. The gel-point of the reaction was determined from the crossover point of the storage and loss moduli, and the reaction rate constant was calculated using the torque data of the rheometer. The kinetic rate constant and the extent of the reaction in the Brabender were higher than the corresponding values obtained from the conventional laboratory reaction process. The challenges and possibilities in scaling up a batch process to a continuous process (e.g., reactive extrusion) are discussed. © 2015 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2016**, *133*, 42852.

INTRODUCTION

Poly (glycerol-sebacate) (or PGS) is a tough, biodegradable elastomer that has the potential for significant use in a variety of biotechnology and bioengineering applications.[1] However, the synthesis of such step-growth polymers via a continuous process presents a significant and challenging task, due to the inherent slow reaction rates of such reactions. The speed of polycondensation reactions is always determined by the effectiveness with which the low-molecular weight by-products are removed from the reaction mixture.[2] This is usually achieved in a twin-screw extruder by venting the by-product (e.g., water) of the reaction. However, the complexities involved during reactive processing of step-growth polymerization systems often hinders the development of a feasible, continuous process and researchers commonly use prepolymers, synthesized via batch processes, as starting materials for reactive extrusion processing.[3] Considerable research remains to be performed on reactive extrusion processing to improve the reaction efficiency and process economics so as to generate industrial interest, and thus help replace existing conventional operations with continuous processes.[4]

It is reported that the Brabender Plasticorder® can be used as a tool for the prediction of optimal processing conditions in extruders.[5] The Brabender Plasticorder is essentially an instrument that measures the viscosity-related torque caused by the resistance of the material to the shearing action of the plasticating process.[6] It has been used as an important instrument for numerous batch-process studies to, for example, characterize elastomer processability,[7] study kinetics of transesterification,[8,9] perform rheological studies,[10–12] investigate structural changes in compounds,[13] validate mathematical models,[14,15] and perform functionalization,[16–18] rubber-mastication,[19,20] rubber-crosslinking,[21,22] and compatilbilization studies.[23–25] Here, we attempted to synthesize PGS oligomers using a modified Brabender Plasticorder® as a batch reactor, that in turn may be used to generate information that will be useful in predicting reactive extrusion processing.

MATERIALS AND METHODS

Materials
Glycerol (G) (Reagent Plus grade), sebacic acid (SA) (99% pure), Glu-Fibrinopeptide B, and Angiotensin I were obtained from Sigma–Aldrich, Sydney.

Methods
Rheometry. In step-growth polymerization, the viscosity of the system changes marginally until the system begins to gel and vitrify. The aim here was to synthesize PGS prepolymer with a

degree of polymerization (DP) in the range 3–10. We could not record the torque vs. time data during the reaction due to the minimum torque limits of the Brabender rheometer not being achieved in terms of the viscosity of the mixture. To provide this important measurement, we used an ARES Rheometric Scientific Rheometer to characterize the rheology of the PGS product (pre-polymer) from the Brabender from 5 h onwards. Specifically, we examined storage modulus, loss modulus, and viscosity-related torque during the step-growth reaction. Parallel disk plates of diameter 25 mm were used. An adequate amount of PGS prepolymer, synthesized at 130°C, was placed between the two parallel plates of the rheometer and the gap size was adjusted to around 1.5 mm. The prepolymer was subjected to strain-controlled dynamic time-sweep testing at 110°C and at a frequency of 1 Hz and 100% strain. The time between the successive measurements was 10 min. At 130°C, due to their inherent low viscosity, the PGS oligomers could not be retained between the two parallel plates. Hence, all rheology experiments were conducted at 110°C.

Fourier Transform Infrared Spectroscopy. Evidence of esterification was confirmed by using FTIR spectroscopy on the samples collected at different time-points (0, 90, 180, 240, and 300 min). FTIR spectra were recorded on a Nicolet 5700 Spectrometer from 4500 to 525 cm^{-1} with an average of 32 scans at 4 cm^{-1} resolution and 1 cm^{-1} sensitivity.

Matrix-assisted Laser Desorption/Ionization Time of Flight (MALDI-Tof) Spectroscopy. Mass spectrometric studies were used to examine molecular weights of the oligimers and were performed with a Voyager-DE^{TM} STR$^{®}$ time-of-flight mass spectrometer (Applied Biosystems, Foster City, CA) equipped with a nitrogen laser ($\lambda = 337$ nm). The measurements were carried out in reflectron mode. The length of the flight path was 160 cm and laser irradiance was slightly above the threshold value. One hundred laser shots were accumulated to obtain each spectrum. Acceleration voltage was 20 kV, reflector voltage was 22.4 kV, and detector voltage was 1.6 kV.

Alpha-cyano-4-hydroxycinnamic acid (α CHCA) obtained from Sigma Aldrich (Sydney, Australia) was used as a matrix compound. α CHCA was dissolved in acetonitrile-water solution (50:50) to get a concentration of 10 mg mL^{-1}. The final concentration was adjusted to 0.1% TFA. PGS oligoester samples collected at 1.5, 3, 4, and 5 h were dissolved in THF to prepare concentrations of 9–10 mg mL^{-1}. The sample and the matrix solutions were mixed in a volume ratio of 1:1. Approximately 1 μL of the mixture was applied to the target plate and allowed to air-dry. The external calibration of the mass spectrometer was accomplished with a mixture of Glu-Fibrinopeptide B (monoisotpic mass = 1570.677) and Angiotensin I (monoisotopic mass = 1296.6853).

Differential Scanning Calorimetry. A TA instrument modulated DSC (TA 2920) was used to study the thermal transitions of the PGS oligoester after 5 h of reaction time. The sample size was ~10 mg, with a heating and cooling rate of 10°C min^{-1}.

Laboratory Reaction. Non-stoichiometric quantities (G:SA = 1.0-molar ratio) of the monomers were mixed with toluene (40% of combined monomer weight) in a round-bottomed flask, which

Figure 1. Brabender Plasti-corder$^{®}$. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

was fitted with a Dean-Stark trap (for water-removal) and a reflux condenser. Esterification was carried out at 130°C. Samples were collected in tightly sealed glass vials after every 2 h until gelation and stored in an ice-bath to avoid further reaction.

Brabender. The Brabender Plasticorder is designed for studying mixtures and reactions. A Brabender Plasticorder$^{®}$ PL-2000 was fitted with a torque rheometer and a 5 H.P. 230 volt motor with controls. The ram section of the Brabender was modified to accommodate two copper tubes (4 mm diameter) into the loading chute. One of the tubes, an inlet tube, was connected to a nitrogen cylinder and the other to a vacuum pump using silicon rubber tubes (see Figure 1).

To prevent the leakage of molten reactant mixture from the mixing chamber, the two shafts that enter the chamber were covered with tapered Teflon tapes, which sealed the gap between the shaft and the chamber entrance. Trial runs were conducted to ensure that the chamber was leak-proof.

The following procedure was adopted for reactive-mixing experiments: Equimolar quantities (G: SA = 1.0) of the monomers were premixed by charging them through the hopper into the mixing chamber set at 70°C and a rotor speed of 60 rpm. Nitrogen gas was flushed through the chamber at 10 L min^{-1} for about 5 min. The temperature was then increased to 130°C. When the monomers were turned into a molten state, the rotor speed was increased to 80 rpm and the nitrogen flow-rate was set to 5 L min° for the next 5 h. Water vapors, formed during the reaction, were removed through the other silicon tube, which was connected to the vacuum pump. The pressure was set at −4 mmHg. Care was taken to ensure that the bottom of the copper tubes were slightly above the mixing chamber during reactive-mixing. Samples were collected at the end of 90, 180, 240, and 300 min.

RESULTS AND DISCUSSION

FTIR

The FTIR spectra for the PGS oligomers collected at different reaction times from the Brabender are shown in Figure 2. The
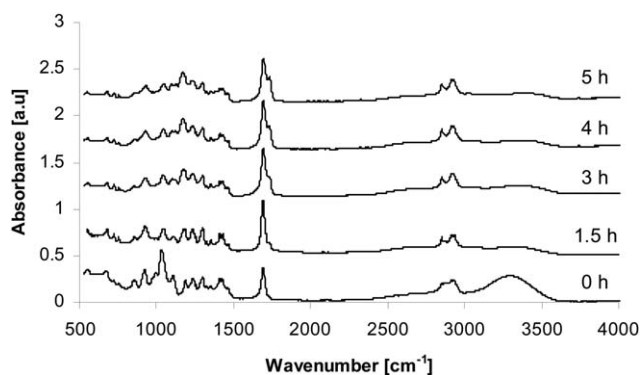
Figure 2. FTIR spectra of PGS oligomers at different reaction times.

spectra are offset by an increment of 0.5 to allow for easier discrimination of the peak positions.

Detailed peak assignments of the main absorption bands are listed in Table I.

The band assignments were made according to available spectroscopy literature.[26–28] Briefly, the peak at 1430 cm^{-1} is due to the deformation of methylene groups (CH$_2$) in the sebacic acid. The C—O—H bend in the glycerol is indicated by a band at 1405 cm^{-1}. A cluster of bands in the region 1150–1300 cm^{-1} confirms the stretching of the (O=)C—O group in the ester. The in-phase and the out-of-phase C—C—O stretching is indicated by bands at 1039 and 1186 cm^{-1}, respectively.

The important region (1600–1800 cm^{-1}) of our analysis is shown in Figure 3.

The infra-red absorption by the carbonyl groups of sebacic acid is shown by a peak at 1690 cm^{-1}. It can be observed that as time progressed, the absorbance decreased, indicating the progress of esterification. At the same time the appearance of a peak at 1740 cm^{-1}, which is due to the stretching of the ester carbonyl group, confirms the formation of the ester groups. The number-average and weight-average molecular weights of the oligoesters were quantified using matrix-assisted laser desorption/ionization time of flight spectroscopy.

Matrix-assisted Laser Desorption/Ionization Time of Flight (MALDI-Tof)
The MALDI spectra confirmed the formation of mono-protonated oligoesters as the reaction progressed. The number-average molecular weight (M_n) and the weight-average molecular weight (M_w) were calculated from the spectra using the following equations.[29]

$$M_n = \Sigma M_i N_i / \Sigma N_i \qquad (1)$$

$$M_w = \Sigma M_i^2 N_i / \Sigma M_i N_i \qquad (2)$$

where M_i is the mass of the ith oligomer and N_i is the corresponding peak intensity in the distribution.

The signals at 172, 212, 294, 379, 380.1, and 440 m/z are due to matrix ions and are represented by "M" in the spectra (Figure 4). Examination of the MALDI-TOF spectra of the oligoester samples collected at various time intervals confirmed the formation of mono-protonated oligoesters with different compositions. As

Table I. Fourier Spectral Peak Assignments of the Main Absorption Bands

Peak (cm^{-1})	Assignment
1430 (w)	CH$_2$ deformation
2940 (w) from 2780-2954	OH stretch of sebacic acid due to hydrogen bonding
1405 (w)	C—O—H bend in glycerol
1150–1300 (Band cluster)	(O=)C—O stretching vibrations
1740 (m)	C=O stretching vibrations of ester
1689 (s)	C=O symmetric stretch of sebacic acid
1130 (m)	C—O—C stretch in ester
684 (s)	C—OH deformation in glycerol
1039 (w)	In-phase C—C—O stretch
1186 (s)	Out-of-phase C—C—O stretch

the reaction progressed, the spectra showed signals separated by 91 and 168 m/z [see Figure 4(a–f)]. The signals due to oligoesters are marked on the spectra with their respective (m/z) numbers.

The relevant peaks are identified by the repeating unit number (n), which is due to either carboxyl or alcohol terminal groups of the monomers. The former series (91 m/z) suggests the addition of alcohol as an end-group with the loss of a H atom, whereas the latter series (168 m/z) suggests the addition of carboxyl groups as terminal groups, which involves the loss of two molecules of water from the two carboxyl end-groups of sebacic acid. As there are two primary hydroxyl groups in glycerol, the condensation reaction occurs through the addition of carboxyl groups at either location. Once a carboxyl group reacts with a primary hydroxyl group, further addition of a carboxyl or hydroxyl group to the growing chain depends upon the existing terminal groups on the growing chain. As the reaction progressed, signals were found to increase in the spectra from 276 m/z (at 1.5 h) to 1830 m/z (at 5 h). It is important to note that, like in previous studies, the intensities of fragments of different oligoesters were almost independent of the degree of polymerization when the laser power was adjusted slightly above
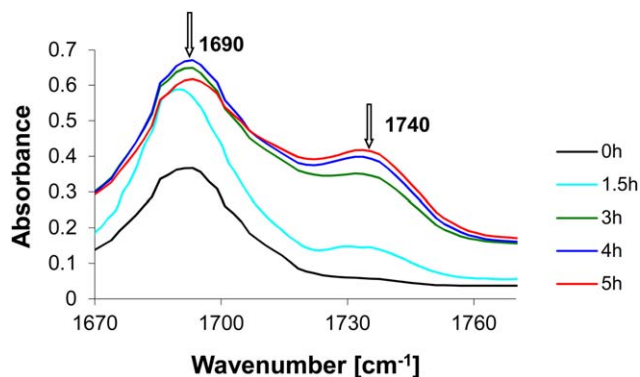

Figure 3. FTIR spectra of the region showing acid and ester peaks. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
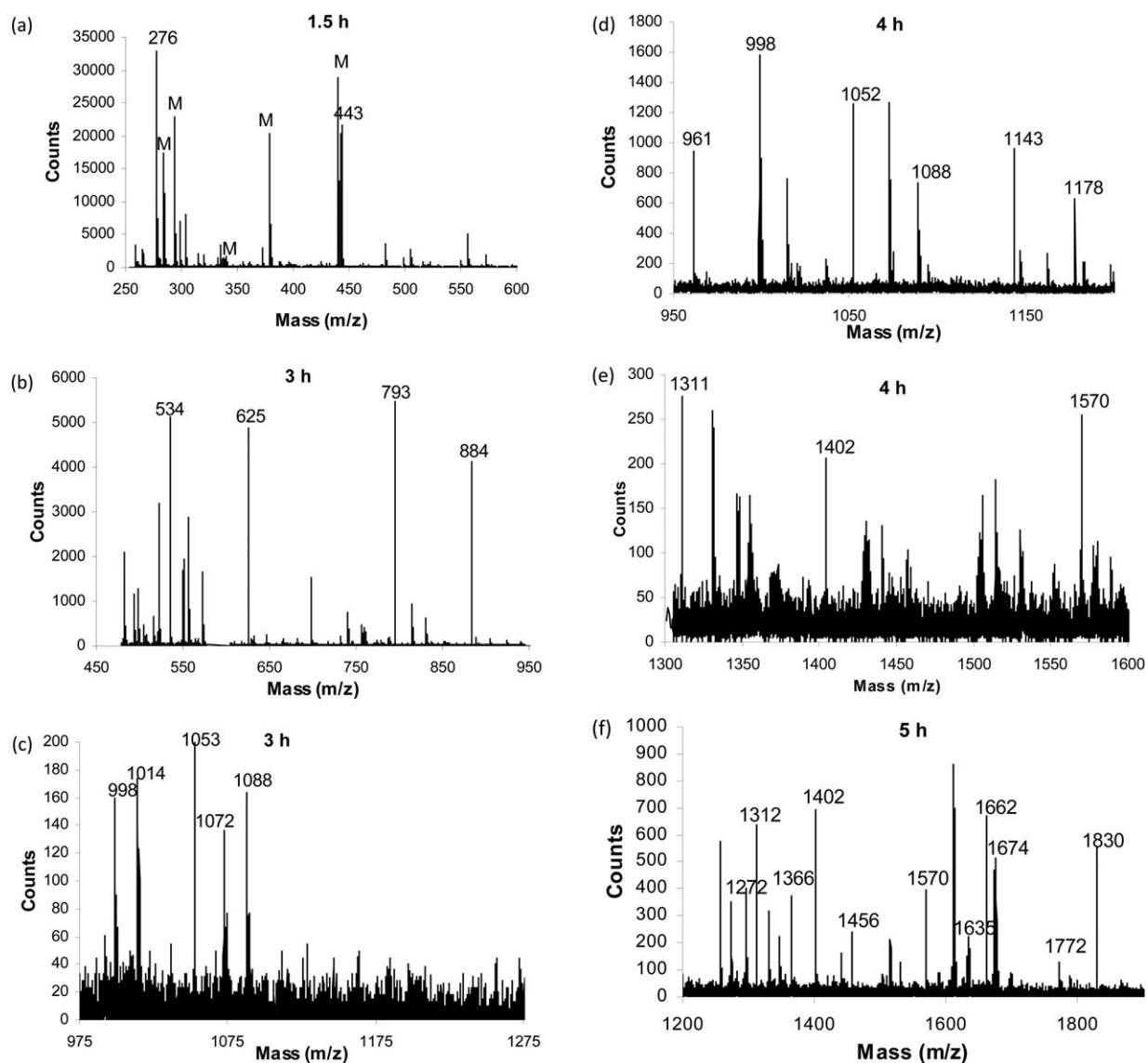
Figure 4. MALDI-TOF spectra of PGS oligoesters at different reaction times.

threshold (1990 au).[30] However, the intensity of the fragments definitely affects the polydispersity of the oligoesters.

For the spectra collected at 3 h, in addition to the 91 and 168 m/z spacings, peaks were found at 998 m/z, 1072 m/z, and at 1014 m/z and 1088 m/z, each pair being separated by 74 m/z [see Figure 4(c)]. This is likely due to the addition of hydroxyl group as the terminal group with a loss of a molecule of water. For the spectra collected at 4 h, signals were found at 298, 498, and 698 m/z (separated by 200 m/z) and 998, 1088, and 1178 m/z (separated by 90 m/z). This blend suggests a mixture of oligomers with different end-groups, having a carboxyl terminal group for the former and an alcohol terminal group for the latter [refer to Figure 4(d,e)]. The spectra collected at 5 h showed peaks from 276 to 1830 m/z with spacings of 91 and 168 m/z [refer to Figure 4(f)]. It also displayed peaks at 1178, 1272, 1366, 1456, 1633, 1674, and 1772 m/z indicating the formation of an odd mixture of oligomers with different terminal groups.

The authors believe that these oligomers may contain few inhomogeneous oligomers, the presence of which increases the molecular weight of the system. It is important to note that although the molecular weight of the oligoesters changed, the regioselectivity of the species did not change in the spectra. The calculated number-average and weight-average molecular weights of the oligomers from the MALDI spectra are given in Table II. The polydispersity indices were found to be within similar bounds to conventional polymer systems.where M_n = number-average molecular weight, M_w = Weight-average molecular weight, PDI = polydispersity index (M_w/M_n) and DP = degree of polymerization.

We also synthesized PGS oligomers (G:SA = 1.0) in a round-bottomed flask (hereafter referred to as the benchtop process) using toluene as solvent. The degree of polymerization (DP) in the Brabender Plasticorder® and the benchtop process as determined by MALDI-TOF spectra are compared and shown in Figure 5.

Table II. Molecular Weight Data from MALDI-TOF for Different Reaction Times

Time	M_n	M_w	PDI	DP
1.5 h	309	320	1.035	1.197
3 h	616	713	1.157	2.387
4 h	1296	1356	1.046	5.023
5 h	1416	1663	1.174	5.488

It can be observed that due to better shear-mixing, the degree of polymerization at any stage of the reaction is significantly higher in the Brabender.

Rheology

Figure 6 shows the experimental data for the storage modulus, G', loss modulus, G'', and torque, M, plotted against reaction time for PGS oligomers made either for batch or benchtop processes. PGS oligomers for both processes had a reaction time of 5 h.

It can be observed for the batch process that in the beginning of the reaction, G'' is greater than G', as expected for a molten prepolymer system.[31] Because of the low viscosity of the system in the early stages of the reaction, the initial values of G' were lower than the detectable range of the transducer. As the reaction progressed, with continuous removal of water, the viscosity and the elasticity of the system increased. The crossover point of the storage and loss moduli curves occurred at 23.25 Pa after 3670 min for the batch process. This crossover point is considered here as an indication of the gelation time.[32]

In a rheometer, for a step-growth system there is an observed increase in the torque, which is directly related to crosslink density, particularly when the measurements are done at relatively low frequencies.[6] If the step-growth polymerization follows first-order kinetics, then

$$\ln\ (M_\alpha - M) = -kt\ +\ \ln\ (M_\alpha - M_0) \qquad (3)$$

where $M =$ torque at time t, $M_0 =$ minimum torque, $M_\alpha =$ maximum torque, and $k =$ rate constant in the kinetics regime.

Figure 5. Comparison of DP obtained with Brabender and benchtop synthesis.

A plot of ln $[(M_\alpha - M)/(M_\alpha - M_0)]$ versus time will give a straight line and the slope of the graph is the reaction rate constant.[6] From Figure 6 it is noticeable that the torque remained linear for up to 2400 min and became nonlinear as the viscosity of the system increased. Therefore, the reaction followed first-order kinetics only in the linear region of the curve. Further, as the reaction progressed the reaction became diffusion-controlled. Considering the maximum and minimum torques in the linear region, using eq. (3) the first-order rate constant is estimated to be 9.88×10^{-4} min^{-1}.

We also studied the rheology of the PGS step-growth reaction at 110°C using the prepolymer (DP = 1.25) synthesized from benchtop studies (G:SA = 1.0) after a reaction time of 5 h. The experimental data for G', G'', and torque are shown in Figure 6. The crossover point of the storage and loss moduli curves occurred at 24.77 Pa after 5050 min. The calculated first order kinetic rate constant at 110°C was 5.15×10^{-4} min^{-1}. The corresponding value from the batch (Brabender) studies (mentioned above) was 9.88×10^{-4} min^{-1}. When compared with the benchtop process, there is an increase in the kinetic rate constant of the reaction in the Brabender by approximately a factor of 2. Thus, there is a significant increase in the rate of the reaction in the Brabender.
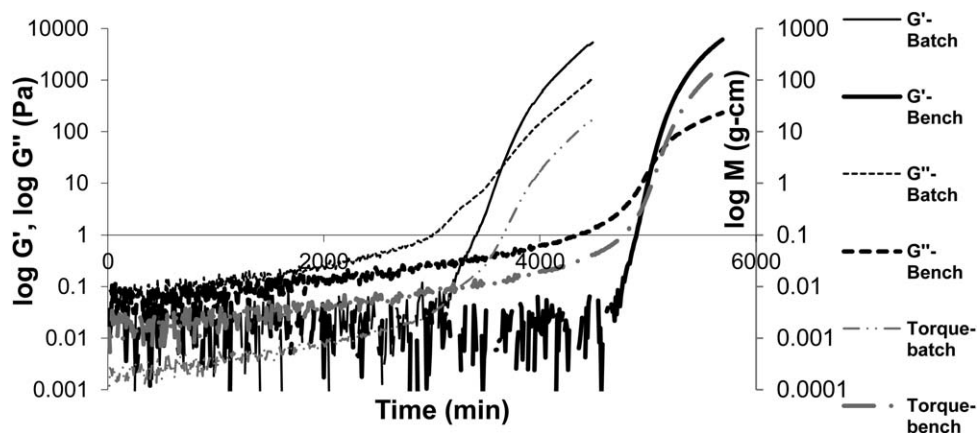

Figure 6. Rheological data (at 110°C) of storage (G') and loss moduli (G''), and torque (M) for the step-growth system starting with prepolymers obtained after a reaction time of 5 h from batch and benchtop processes.
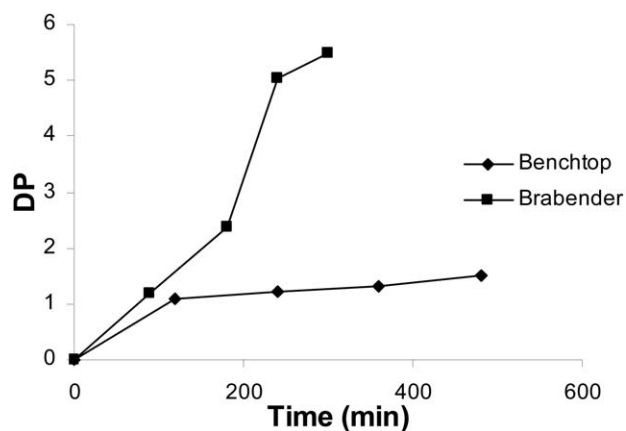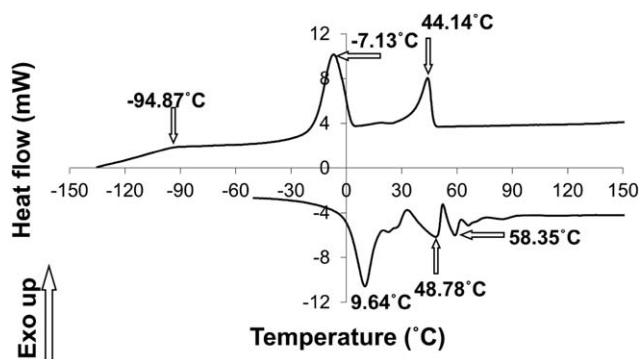
Figure 7. DSC thermogram of PGS oligomer from Brabender at 5-h reaction time.

Constant shear in the Brabender forces the macromolecules to stretch and become oriented in the direction of flow. The higher the shear rate, the more the macromolecules stretch allowing the functional groups to become more accessible to chemical interaction. The entropy stresses in the macromolecules can drive the polymer functional groups to become more active, which increases the pre-exponential factor of the Arrhenius equation.[33] This may also induce the formation of inhomogeneous structures, which increase the molecular weight of the system. It is interesting to note that MALDI-TOF analysis of the prepolymer collected from the Brabender after 5 h confirmed the formation of a set of oligomers with different terminal groups [refer to Figure 4(f)].

Differential Scanning Calorimetry (DSC)
Differential scanning calorimetry was used to determine the thermal transitions of the oligomer collected at 5 h from the Brabender. To eliminate thermal history, the sample was equilibrated at 25°C, heated to 200°C at 10°C min^{-1}, maintained under isothermal conditions for 5 min, cooled to −150°C at 10°C min^{-1}, maintained under isothermal conditions for 5 min, and heated to 200°C min^{-1} at 10°C min^{-1}. The DSC thermogram is shown in Figure 7.

It can be observed from the thermogram that the oligoester has a single, broad glass-transition temperature of −94.87°C. It is usually considered that the occurrence of single, composition-dependent T_g indicates miscibility.[34] However, previous studies have reported that the presence of a broad T_g can also be due to hydrogen-bonding and further microphase separation in such systems cannot be ruled out.[35,36] It is reported that high-shear mixing allows functional groups to become more active and accessible, resulting in an increase in the reaction rate considerably.[33] The authors believe that high-shear mixing during step-growth reactions provides a platform for synthesizing polymers with a better network-structure and stability. In a polymer network the amorphous regions impart elasticity and network-structure to the elastomer, whereas crystalline regions provide strength, stiffness, and thermoplasticity.[37] Two crystallization exotherms were found at −7.13 and 44.14°C. Crystallization at −7.13°C originates mainly from the gel parts, while the crystallization at 44.14°C comes from the sol parts.[37] When compared with previous studies on PGS characterization, where recorded crystallization temperatures were {−52.14, −18.5°C}[1] and

{−18.5, −14.3, 23.5°C},[37] our results show a positive shift in crystallization temperatures. The presence of inhomogeneous oligomers, as indicated by MALDI-TOF results, and a higher degree of polymerization due to high-shear mixing (when compared to benchtop process) could have reinforced a polymer network structure containing stable crystalline domains. As a result such networks require higher temperatures to melt those crystalline domains. This is a likely reason for observing a positive shift in the crystalline exotherms in the batch studies when compared with benchtop studies. The thermogram also displayed three melting endotherms at 9.64, 48.78, and 58.35°C. The results indicate that when compared with benchtop studies,[1,37] reactive processing causes positive shift in crystalline domains, which impart network-structure and stability to the resulting bioelastomer. Liu et al.[37] have shown that to a certain extent PGS can be thermally molded to yield thermoplastic elastomers. Here, sebacic acid may act as a plasticizer and contribute to the thermoplasticity of the elastomer. PGS is thermo-moldable and its properties are process-dependent, and it makes a good candidate for developing thermoplastic elastomers.

DISCUSSION

In step-growth reaction systems, converting a batch process to a continuous process is a task of significant industrial importance. It is particularly interesting to discuss some aspects of reactive extrusion as a continuous reactor for polycondensation reaction systems. Partial evaporation of water and removal of residual solvent, if any, can be achieved by operating zones 10–14 of a twin-screw extruder (such as ZSK-30 Werner Pfleiderer, Ramsey, NJ) under vacuum.[38] For a large-scale removal of water-vapor, special slow-operating devolatilizing extruders with several devolatilization zones in series may be required.[2] The use of reactive extrusion to prepare high-molecular weight polyesters requires longer residence times, which can be partially achieved by decreasing the screw-speed and increasing the extruder-length.[3] However, increasing the length of the extruder may not prove to be cost-effective in a continuous process. An alternative is to vent the extruder downstream to remove volatiles, especially unconverted monomers, by a vacuum pump and recycle them back in the process loop.[39] The possible vented extruder designs that can be used are bypass-vented extruder screw, rearward devolatilization, multi-vent devolatilization, cascade devolatilization, venting through the screw, and venting through a flighted barrel.[40] The use of high shear zones (by using reverse kneading elements) in the extruder allows the macromolecules to stretch, causing functional groups to become more active and accessible. An increase in the intermolecular entropy stress may mechanically break the macromolecules leading to a process called "chemical flowing." This increases the pre-exponential factor (number of collisions per unit time) and decreases the residence time in the extruder.[33] Post-extruder devices such as static mixtures help solve process constraints of reactive extrusion.[41] It is reported that the yield is considerably enhanced by the addition of post-extruder modifications and is found to be directly proportional to the reactor length, which in turn is a function of the post-extruder reactor modification.[4] More importantly, in reactive extrusion a preliminary study on

reaction kinetics is essential for designing a continuous process.[42] We have shown in our previous study [43] that the step-growth reaction between glycerol and sebacic acid is a first-order reaction with respect to sebacic acid concentration in the kinetics regime (data not shown). The main difficulty, besides the complex flow conditions in the twin-screw geometry, is the strong coupling between flow conditions (temperature and residence time), reaction kinetics, and the effect of the extent of the reaction on the rheological behaviour.[44] A consideration of the above mentioned parameters is extremely important in the design of extruders for the synthesis of step-growth polymers.

CONCLUSIONS

A Brabender Plasticorder® was used as a stirred batch reactor to synthesize oligoesters of poly (glycerol-sebacate) PGS to a high DP and compared with standard laboratory benchtop processes. Esterification within the stirred batch reactor was confirmed by the time-related growth of the ester peak at 1740 cm^{-1} in the FTIR spectra of samples taken at definite time points for up to 5 h. The degree of polymerization at each of these stages of the reaction (or time points) was calculated using MALDI-TOF. MALDI-TOF spectra gave accurate information on the molecular weights of the oligoesters with particular attention to the identification and analysis of the end-groups of the macromolecules. The degree of polymerization in the Brabender was higher than in the comparative benchtop studies. The DSC thermogram of the PGS prepolymer after 5 h of reaction in the stirred batch reactor displayed a single broad T_g at −94.87°C. Crystallization temperatures were detected at −7.13 and 44.14°C—a positive shift in the values when compared with previous studies.[1,37] The PGS prepolymer is almost completely amorphous at 58°C. Adaptability to high-shear mixing and the presence of thermo-moldable characteristics make PGS a promising candidate for developing thermoplastic bioelastomers. High-shear mixing allows the molecules to stretch, become active, and accessible during step-growth reactions.[33] However, the main difficulty in transforming a batch process into a continuous process, such as reactive extrusion, is the large-scale removal of water vapors. Although options such as using slow-operating devolatilizing extruders, increasing the length of the extruder, recycling unconverted monomers back in the loop, and using post-extruder devices such as batch-mixers to increase the yield are available, from the point of view of efficiency and feasibility with respect to PGS system, further research on this area is essential.

ACKNOWLEDGMENTS

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