Copolyester of Trimellitic Acid, Glycerol, and Poly(ethylene glycol): Synthesis and Characterization

D. Pramanick, R. Pramanick,* G. Betal†

Department of Chemistry, Kalyani University, Kalyani-741235, W. B., India

Received 18 February 2003; accepted 12 March 2003

ABSTRACT: A series of copolyesters having a broad range of biodegradable crosslinks were synthesised by $FeCl_3$-catalyzed polyesterification of trimellitic acid and glycerol containing a small mol percent of poly(ethylene glycol) (PEG) of varied molecular weights. The polymer samples designated as I (1.5% PEG 2000), II (4.5% PEG 2000), III (7.5% PEG 2000), IV (1.5% PEG 4000), V (4.5% PEG 4000), VI (7.5% PEG 4000), VII (1.5% PEG 6000), VIII (4.5% PEG 6000), and IX (without PEG) are insoluble and moderately tough-to-elastic solids and were characterized by their swelling values in ethanol, glass transition temperatures (T_g), IR spectra, and X-ray diffractograms. Sample IX (0% PEG) has the lowest equilibrium swelling (12% at 25°C) and the highest T_g (155°C) and, therefore, the highest crosslink density. The swelling increases and the T_g decreases as the PEG content or PEG molecular weight in a glycerol–PEG combination increases, indicating a corresponding decrease in the crosslink density of the polymers. Further, the equilibrium swelling value increases with increasing temperature. The IR spectra of the polymers indicate the formation of ester bonds at the expense of COOH and OH groups. The X-ray diffractograms show their semicrystalline nature. The percent crystallinity values of 53, 52, 49, and 46 for II, III, V, and VII, respectively, and 54 for IX showed that the percent crystallinity decreases with an increasing PEG content and molecular weight in the same way as do the T_g values. Thus, higher T_g values are associated with a higher percent crystallinity, that is, with structures of higher order. The synthesized polymer samples with varied crosslink (biodegradable) densities are expected to be very suitable as matrices for controlled drug delivery over a varied period of time.
 J Appl Polym Sci 91: 343–346, 2004

Key words: copolyester; polyethylene; synthesis; biodegradable

INTRODUCTION

The technique of sustained and controlled drug release from a biodegradable polymer matrix has gained considerable importance in the field of drug administration.[1–5] Such polymers will have better control over the release of a drug, if they have a three-dimensional network structure involving biodegradable crosslinks as well as backbone links. This laboratory recently reported the synthesis and application of some crosslinked copolyesters of this type such as a citric acid–glycerol copolyester[6,7] and a citric acid–1,2,6-hexanetriol copolyster.[8] More recently, we developed a novel crosslinked copolyester of trimellitic acid and glycerol which is capable of releasing the entrapped drugs for a few months following a nearly zero-order release kinetics.[9,10] Here, our aim was to develop a range of graded crosslinked polymers having a broad spectrum of biodegradability for use as matrices for short-term, medium-term, and long-term drug release. The crosslink density of copolyesters from trimellitic acid can be tailored by judiciously manipulating the functionality of the hydroxy compound. To this end, we have partly replaced glycerol, a potential triol, with poly(ethylene glycol) (PEG), a potential diol, of varied molecular weights. In this communication, the synthesis of copolyesters of trimellitic acid and glycerol containing small proportions of PEG of varying molecular weights by $FeCl_3$-catalyzed polyesterification and their characterization are reported.

Correspondence to: D. Pramanick.
**Present address:* Transtech Photonics Ltd., 20th Floor, On Hing Building, 1–9 On Hing Terrace, Central, Hong Kong.
†*Present address:* Polymer Laboratory, Haldia Petrochemicals Ltd., Haldia, India.

Journal of Applied Polymer Science, Vol. 91, 343–346 (2004)

EXPERIMENTAL

Materials

Trimellitic acid was an analytical-grade reagent from E. Merck and was used as such. A.R. grade glycerol, also from E. Merck, was dried by bubbling dry nitrogen through it at 120°C. PEGs of varied molecular weights were A.R. quality BDH products and were used as received. Anhydrous $FeCl_3$ was also an A.R. grade E. Merck product and was freshly sublimed before use.

Synthesis

Trimellitic acid and a glycerol–PEG combination (1.5% PEG-99% glycerol, 4.5% PEG-97% glycerol, and 7.5%

PEG-95% glycerol, all in mol % for each molecular weight type of PEG), maintaining the stoichiometry of COOH and OH functions together with 0.4% (of the total weight of monomers) anhydrous $FeCl_3$, were taken in Jena beakers (50 mL), mixed thoroughly with a glass rod over a hot plate to a clear solution or melt, and then heated in a vacuum oven (0.1 mm) at 140°C for 1 h, at 160°C for another 1 h, then at 170°C for 2 h, and, finally, at 190°C for another 2 h, followed by 1-h postcuring under the same conditions. Nine polymer samples designated as I (1.5% PEG 2000), II (4.5% PEG 2000), III (7.5% PEG 2000), IV (1.5% PEG 4000), V (4.5% PEG 4000), VI (7.5% PEG 4000), VII (1.5% PEG 6000), VIII (4.5% PEG 6000), and IX (0% PEG) (all in mol %, 1.5 mol of PEG being equivalent to 1 mol of glycerol in respect to the OH content) were prepared and purified by leaching several times with boiling ethanol. The polymer samples were then collected carefully from the beakers in the form of thin slices and rectangular slabs using a sharp knife blade, dried in a vacuum oven, and, finally, stored in a vacuum desiccator.

Characterization

The polymer samples obtained were insoluble in water and common organic solvents and their characterization by molecular weight determination was not possible. They were characterized by their swelling property, glass transition temperature (T_g), IR spectra, and X-ray diffractograms.

The vacuum-dried polymer samples, I–IX, in the form of thin slices, were kept immersed in the swelling solvent, ethanol, at two different temperatures (25 and 37°C). At suitable time intervals, the slices were taken out, blotted dry, and weighed, and again placed in the swelling solvent until there was no more increase in weight. The final increase in weight of the slice gives the equilibrium swelling of the polymer at the selected temperature and solvent. The T_g of the polymers was measured by using a Perkin–Elmer differential scanning calorimeter (DSC2/DSC7). The samples were annealed at 500 K for 15 min and then scanned at a heating rate of 20°/min from −50 to 180°C. Again, the polymer samples were powdered cryogenically and their IR spectra were recorded on KBr pellets using a Perkin–Elmer IR spectrophotomer. For the X-ray diffraction study, the polymer samples were also powdered cryogenically and their X-ray diffraction was recorded on a Scimens D500 X-ray diffractometer using CuKα as a target at a chart speed of 10 mm per degree 2θ.

RESULTS AND DISCUSSION

In about 2 h after the start of the reaction, under a vacuum (0.1 mm) at an elevated temperature, the monomer mixture containing the catalyst became a transparent viscous liquid. Increasing the temperature in stages over the period of time mentioned in the Experimental section was found to be beneficial in respect to the conversion and the desired physical properties of the polymers obtained. Bubble formation due to the evolution of water vapor was carefully avoided by stirring with a glass rod from time to time. In about 6–8 h, the polymer samples I–IX were obtained in 75–85% yield as brownish, transparent, and moderately tough-to-elastic solids insoluble in water and common organic solvents.

TABLE I
Characterization of the Polymer Samples

Polymer samples	Equilibrium swelling (%) in ethanol at 25°C	Equilibrium swelling (%) in ethanol at 37°C	T_g (°C)	% Crystallinity
I	14	20	145	
II	21	25	111	53
III	35	46	100	52
IV	18	22	136	
V	32	41	109	49
VI	45	50	90	
VII	30	36	132	46
VIII	40	60	93	
IX	12	18	155	54

CHARACTERIZATION

Swelling behavior

Equilibrium swelling values of the polymer samples (I–IX) in ethanol at 25 and 37°C are presented in Table I. It can be seen from the table that, at a given temperature, the swelling value of the polymers increases with increase in the mol percent of PEG of a given molecular weight in a glycerol–PEG combination. Thus, the equilibrium swelling values of the polymer samples obtained using PEG 2000, PEG 4000, and PEG 6000 are in the order I < II < III, IV < V < VI, and VII < VIII, respectively. Again, with an increase in the molecular weight of the added PEG in a fixed mol percent, the equilibrium swelling value of the polymer samples also increases.

Thus, using PEG of molecular weights of 2000, 4000, and 6000, the respective equilibrium swelling values are seen to be in the order I < IV < VII for 1.5% PEG, II < V < VIII for 4.5% PEG, and III < VI for 7.5% PEG. It is further seen that the order of swelling values obtained is the same at 25 and 37°C. It is quite apparent that, with the increase in the mol percent of the added PEG (a potential diol) of a fixed molecular weight, or increase in the molecular weight of the added PEG in a fixed mol percent, the crosslink densities in the copolyster network synthesized from trimellitic acid and a glycerol–PEG combination should decrease. As expected, sample IX (0% PEG) has the lowest swelling value, 12 and 18% at 25 and 37°C, respectively, indicating the highest crosslink density.

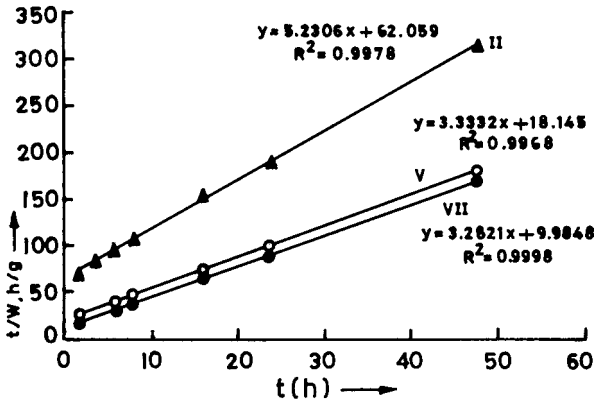


Figure 1 Swelling isotherms according to second order swelling kinetics.

The order of the swelling values obtained by us is quite in keeping with our knowledge[11] that, in a series of chemically similar crosslinked polymers, the swelling values increase with a decrease in the crosslink density in the polymer network. It is further seen from Table I that the swelling values of the polymer samples at 37°C are higher than are the corresponding values at 25°C. An increase in the temperature increases the kinetic energy of the polymer segments, generating more space among the segments in the network, which helps the polymer to imbibe more solvent, causing an increase in the swelling values. The change in the degree of swelling with the temperature is a valuable indication of the nature of the association between the polymer and the solvent and is a desirable property for a polymeric drug carrier.

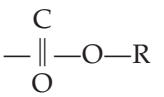
Regarding the swelling kinetics, the weight percent solvent uptake data against time give linear plots according to a second-order swelling kinetic equation[14,15] $t/w = \frac{1}{kw_\alpha^2} + t/w_\alpha$ where w_α is the maximum solvent uptake; w, the solvent uptake at time t, and k, the swelling rate constant. t/w against t plots for three typical samples II, V, and VII at 25°C are shown in Figure 1. The swelling capacity (maximum solvent uptake or equilibrium swelling, w_α) of a polymer sample can be calculated from the reciprocal of the slope and the swelling rate constant, k, from the reciprocal of the intercept and the square of the swelling capacity. The calculated swelling capacities and swelling-rate constants are 0.191 g/g and 0.44 $(gh)^{-1}$ for sample II, 0.30 g/g and 0.61 $(gh)^{-1}$ for sample V, and 0.305 g/g and 1.08 $(gh)^{-1}$ for VII, respectively. The swelling capacities calculated from graphical plots are close to the experimentally determined equilibrium swelling values at 25°C of the three polymer samples. The prevalence of second-order swelling kinetics for the three typical samples II, V, and VII indicates that all these polymers are semicrystalline in nature where progressive swelling expands the amorphous domains and increases the stress on the crystalline domains, holding the semicrystalline network together. The semicrystalline nature of these polymers was revealed also from X-ray diffraction studies to be discussed later.

Glass transition temperature (t_g)

The T_g's of the polymer samples (I–IX) are included in Table I. A typical glass transition endotherm, that of sample VII, is shown in Figure 2. Table I shows that, with an increasing mol percent of PEG of a fixed molecular weight or with increasing molecular weight of PEG in a fixed mol percent in a glycerol–PEG combination, the T_g of the polymer obtained decreases. Thus, the T_g values of the polymers from 1.5, 4.5, and 7.5 mol% of PEG are in the order I > II > III from PEG 2000 and IV > V > VI from PEG 4000 and these are in the order VII > VIII from 1.5 and 4.5 mol% of PEG 6000. Again, for polymers from PEG of molecular weights 2000, 4000, and 6000, the T_g values are in the order I > IV > VII from 1.5 mol% PEG, II > V > VIII from 4.5 mol% PEG, and III > VI from 7.5 mol% PEG. Since in a series of chemically similar crosslinked polymers the T_g values are linearly related to their crosslink densities,[14] it is clear that the order of T_g values of the polymers obtained results from the change in the crosslink densities of the copolyesters due to different proportions of PEG of a given molecular weight or due to the different molecular weight of the added PEG in a fixed proportion in a glycerol (trifunctional)–PEG (bifunctional) combination.

Infrared spectra

In the IR spectra of all the copolymers, the C═O stretching frequency shifted from 1700 cm^{-1} (in the acid monomer) to 1725 cm^{-1} and a band corresponding to —C—O— stretching in the structure



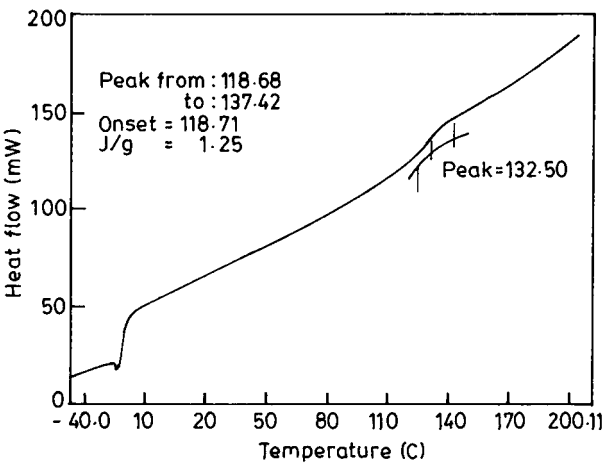


Figure 2 Glass transition endotherm of sample VII.

group appeared at about 1250 cm^{-1}. These spectral data indicate the formation of ester bonds at the expense of —COOH and —OH groups. However, the broad band found around 3450 cm^{-1} may be due to some unreacted—COOH groups or—OH groups or due to traces of moisture that crept into the polymers in the KBr pellet as the polymer is hydrophilic to some extent. A typical IR spectrum, that of copolymer V (4.5% PEG 4000), is shown in Figure 3.

X-ray diffraction

X-ray diffractogram of a typical polymer, that of sample II, is shown in Figure 4, which shows diffuse areas with no sharp band, suggesting nonuniform crystallization. In the case of such semicrystalline polymers with no well-resolved crystalline peaks, it is difficult to draw an amorphous hallow unambiguously, necessary for estimating their crystallinity. In these cases, an useful estimate of the percent crystallinity can be obtained by an approximate method,[15–17] according to which, leaving aside the background scatter from both sides of the crystalline peak, a smooth curve is drawn in the form of an arc encompassing all the base points of both sides of the rising crystalline peak to separate the amorphous scatter zone from the crystalline zone. The percent crystallinity is defined as

$$\% \text{ Crystallinity} = \frac{\text{area under the crystalline peak}}{\text{total area under crystalline and amorphous peaks}}$$

A typical graphical calculation of the percent crystallinity (of the polymer sample II) is illustrated in Figure 4. The calculated percent crystallinity values of five samples are included in Table I. The table shows that the percent crystallinity decreases when the molecular weight of PEG in a fixed mol percent or the mol percent of PEG of a fixed molecular weight increases

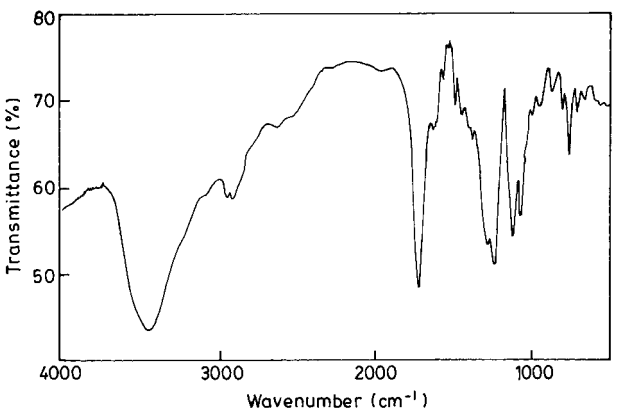


Figure 3 IR spectrum of sample V.

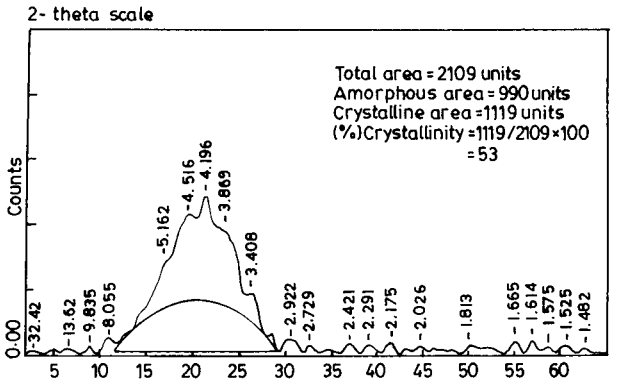


Figure 4 X-ray diffractogram of sample II and calculation of percent crystallinity.

in a glycerol–PEG combination in the synthesis of the copolyesters.

CONCLUSIONS

By using PEG of different molecular weights and in different small proportions in combination with glycerol, it was possible to synthesize a series of three-dimensional copolysters of trimellitic acid having a broad range of crosslink densities. Since the backbone links and the crosslinks are both made up of biodegradable ester bonds, these copolyesters are expected to serve as useful bioerodible matrices for drug release in a controlled manner over desired durations, that is, for short-term, medium-term, and long-term drug delivery.

References

1. Heller, J. Biomaterials 1980, 1, 51.
2. Gilding, D. K.; Reed, A. M. Polymer 1979, 20, 1459.
3. Rosenberg, H. B.; Chang, J.; Wnek, G. E.; Linhardt, R. J.; Langer, R. Biomaterials 1983, 4, 131.
4. Graham, N. B. Brit Polym J 1978, 10, 160.
5. Hopfenberg, H. B. Controlled Release Polymeric Formulations, ACS Symposium series 22, American Chemical Society: Washington, DC, 1976; p 26.
6. Pramanick, D.; Ray, T. T. Polym Bull 1988, 19, 365.
7. Pramanick, D.; Ray, T. T. J App Polym Sci 1990, 40, 1511.
8. Pramanick, D.; Abu Bakr, Md.; Ray, T. T. J Polym Mater 1996, 13, 173.
9. Pramanick, D., Betal, G., Biswas, D. J Polym Mater 2000, 17, 69.
10. Pramanick, D., Betal, G. J Polym Mater, in press.
11. Flory, P. J. Principles of Polymer Chemistry; Cornell University: New York, 1953; p 582.
12. Schott, H. J Pharm Sci 1992, 81, 467.
13. Chang, C.-M.; Bodmeier, R. J Pharm Sci 1997, 86, 747.
14. Grassie, N.; Gieks, J. J Polym Sci Polym Chem Ed 1973, 11, 1985.
15. Bloker, H. I. Natural and Synthetic Polymers: An Introduction; Marcel Dekker: New York; p 73.
16. Alexander, L. E. X ray Diffraction Method in Polymer Science; Wiley-Interscience: New York, 1969; p 137.
17. Chall, G.; Hermans, B. H.; Weidinger, A. Macromol Chem 1962, 56, 169.