Poly(ether–ester) networks prepared by polycondensation of R,S-malic acid with diols and polyether alcohols in the presence of *N,N'*-dicyclohexylcarbodiimide

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The possibility of preparing polyester and poly(ether–ester) networks from R,S-malic acid and diols or poly(ether alcohol)s by polycondensation was investigated. The reactions were carried out in tetrahydrofuran in the presence of *N,N'*-dicyclohexylcarbodiimide and *p*-toluenesulfonic acid and pyridine as catalyst. I.r., ^{1}H n.m.r. and mass spectra of the crosslinked products obtained, confirmed their ester and ether–ester structure. The dependence of swelling and some thermodynamic parameters upon the kind of alcohol used was established. The new synthesized crosslinked polymers, which can be swelled in a variety of solvents and are thermohydrolytically unstable, can be used as biodegradable carriers for drugs and microelements.

(Keywords: poly(ethylene glycol); crosslinking; polyester)

INTRODUCTION

Multicomponent polymer networks based on poly(ethylene glycol)s (PEGs) are of considerable interest as tailor-made materials. Their good biocompatibility due to the hydrophilic oxyethylene chains is a prerequisite for biomedical application, irrespective of the nature of the crosslinker. Gnanou *et al.*[1] have synthesized hydrophilic polyurethane networks by step-growth polymerization between poly(ethylene oxide) precursors and suitable aliphatic or aromatic pluriisocyanates. The materials thus obtained are suitable as biomaterials since they are perfectly transparent, highly hydrophilic and possess satisfactory mechanical properties. In some cases, PEGs can be incorporated into multicomponent systems via prior attachment of highly reactive functional groups at the ends. Weber and Stadler[2,3] have prepared 1,2,4-triazoline-3,5-dione modified PEG as reactive telechelics which, via 'ene' reactions with polybutadiene molecules, resulted in two-component networks of poly(ethylene oxide)–polybutadiene. Gustafson and Flodin[4] have prepared thermoreversible polyurethane urea hydrogels using the reaction of PEG with diisocyanates. A similar procedure was used by Graham and Zulfigar[5] for the synthesis of a wide range of materials with tailored crystallinity and swelling properties.

In our previous investigation[6] on the polycondensation of dicarboxylic acids with diols in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC), an insoluble ester product was obtained when R,S-malic acid reacted with triethylene glycol (TEG). The advantage of the biodegradable polymer matrices for drug release is well known in the literature[7] but there are scanty data on crosslinked synthetic polymers based on natural acids. Pramanick and Ray[8] have shown that polyester networks can be prepared by polycondensation of citric acid and glycerol, and they offer good possibilities for biomedical application.

The aim of the present work is to investigate the possibility of preparing crosslinked polyesters or poly(ether–ester)s from R,S-malic acid and different diols — hexanediol (HD), TEG, PEG 1000, PEG 1500, PEG 2000, PEG 3000, PEG 4000, and glycerol — by polycondensation in the presence of DCC. The synthesized networks have been characterized in accordance with their future application as biodegradable carriers, particular attention being paid to the correlation between the structure and the swelling properties.

RESULTS AND DISCUSSION

In our previous work[9] it was shown that no crosslinked product was obtained by autopolycondensation of R,S-malic acid in the presence of DCC, while the interaction of the acid with TEG under the same conditions resulted in an insoluble ester[6]. To examine the possibility of preparing crosslinked polymalates, the polycondensation of R,S-malic acid with TEG in the presence of DCC in solution was studied. Crosslinked polymers were obtained only in tetrahydrofuran (THF) as a solvent (*Table 1*), while in other solvents (dioxane or dimethylformamide (DMF)) no gelation occurred and only soluble low molecular weight products were isolated. The results given in *Table 1* show that the yield of gel fraction did not depend to a great extent on the reaction temperature and reaction time when a nearly stoichiometric ratio of the functional groups

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Table 1 Polycondensation of R,S-malic acid with TEG in the presence of DCC, pyridine and *p*-TSA in THF. Mole ratios: DCC:COOH = 1.1:1, pyridine:COOH = 0.25, *p*-TSA:COOH = 0.04

No.	COOH (mol)	OH (mol)	Time (h)	Temp. (°C)	Yield of gel fraction (%)
1	2	3	5	0	15
2	4	5	2	20	40
3	1	1	4	25	58
4	4	3	3	0	55
5	4	3	2	20	52

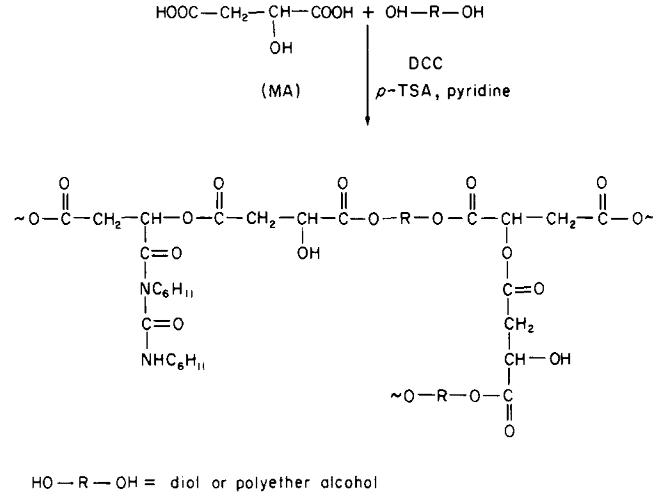
Table 2 Characterization of networks obtained by polycondensation of R,S-malic acid with diols in the presence of DCC, pyridine and *p*-TSA in THF at 65°C. Mole ratios: R,S-malic acid:diol:DCC:pyridine:*p*-TSA = 1:0.25:2.2:0.5:0.08 (COOH:OH = 4:3)

No.	Diol	Yield of gel fraction (%)	Swelling (%) in		T_g (°C)
			Water	Benzene	
1	TEG	55	190	190	21.2
2	Glycerol	70	310	220	27.6
3	PEG 1000	60	480	220	−36.2
4	PEG 1500	65	770	430	−40.7
5	PEG 2000	50	980	580	−41.0
6	PEG 3000	58	1510	690	−43.0
7	PEG 4000	61	1850	900	−45.2
8	Hexanediol	52	130	190	−7.7

(COOH:OH = 1.3–0.9) was used. Similar results were obtained with glycerol as hydroxylic component in the polycondensation reaction.

Surprisingly, when different poly(ether alcohols) (PEG 1000, PEG 1500, PEG 2000, PEG 3000 and PEG 4000) were used in polycondensation in THF at room temperature, no crosslinking occurred. This is most probably due to intramolecular condensation reactions which occur preferentially under these reaction conditions[9]. The efforts to obtain gel product via bulk polycondensation failed also because of destructive processes. Crosslinked polymers from R,S-malic acid and PEGs were successfully prepared only when the process was carried out at 65–70°C in a minimal quantity of THF as solvent, just sufficient to dissolve all reactants except PEG. Under these conditions it was possible to remove the solvent by distillation and to achieve a good homogeneity of the reaction mixture as well as a maximum concentration, known to be a precondition for polyester formation (*Table 2*).

The networks obtained by polycondensation of R,S-malic acid with TEG, HD, glycerol and PEGs are white solids insoluble but swellable in a wide range of solvents — water, alcohol, dimethyl sulfoxide (DMSO), acetone, benzene, chlorinated and nitrated hydrocarbons. In their i.r. spectra, apart from intensive ester (1750–1735 cm^{-1}) and ether (1230, 1120 cm^{-1}) peaks, an absorption at 3640–3620 cm^{-1} was registered, indicating free hydroxylic groups. Even after thoroughly washing the gels with boiling alcohol to remove traces of *N,N'*-dicyclohexylurea (DCU), typical amide peaks at 1650 cm^{-1} and 1520 cm^{-1} and no free carboxylic groups were observed. On the basis of the i.r. spectral data, the products synthesized can be classified as aliphatic polyesters or poly(ether–ester)s, containing free hydroxylic and blocked carboxylic pendent groups. The presence of these moieties can be explained with the unavoidable side *N*-acyl condensation when carbodiimides react with carboxylic acids[9]. This statement for the chemical structure of the crosslinked polymalates (*Scheme 1*) is corroborated by the ^{1}H n.m.r. spectra of the poly(ether–ester)s of different PEGs swollen in $CDCl_3$ (*Table 3*). The peak at 1.3 ppm due to the protons of the cyclohexyl ring confirms the assumption of chemically bonded DCC. Mass spectra of the products (*Table 4*) are in good agreement with the proposed structure as a whole and the peaks at 224, 225 and 226 *m/e* can be attributed to *N*-acyl carbamide moieties. The blocking process on



Scheme 1

Table 3 Peak positions in the ^{1}H n.m.r. spectra of $(MA–PEG)_n$ swollen in $CDCl_3$

No.	Product	Peak position (ppm)					
1	R,S-malic acid[a]		2.78		4.4		8.8
2	PEG[a]			3.67			
3	DCC[a]	0.89–2.213					
4	PEG 4000			3.65			
5	$(MA–PEG\ 1000)_n$	1.3	2.9	3.65	5.6	7.2	8.1
6	$(MA–PEG\ 3000)_n$	1.3	2.99	3.65	4.8	7.3	
7	$(MA–PEG\ 4000)_n$	1.2		3.65	4.7		
8	Destructive products of $(MA–PEG\ 4000)_n$	1.25	3.01	3.65			

[a] Refs 15 and 16

Table 4 Mass spectra of $(MA–PEG)_n$

No.	Product	*m/e*[a]
1	R,S-malic acid	71 $(M–CO_2–H_2O)$ 89 $(M–CO_2)$ 122 $(M–H_2O)$ 135 (M + H) 269 (2M + H)
2	PEG 1500	45 $(–CH_2CH_2O– + H)$ 73 $(–CH_2CH_2O–CH_2CH_2–)$ 89 $(–CH_2CH_2O–CH_2CH_2O–)$
3	$(MA–PEG\ 1500)_n$	56 (–CCOO) 70 $(–CH_2CCOO–)$ 99 $(–CCOOCH_2CH_2–)$ 144 $(–CCOOCH_2CH_2–OCH_2CH_2–)$ 224 (–NRCONHR + H)
4	$(MA–PEG\ 2000)_n$	45 56 61 $(–OCH_2CH_2–O)$ 67 $(–CCOOCH_2–)$ 71 100 144 225
5	$(MA–PEG\ 3000)_n$	56 61 70 99 143 224
6	$(MA–PEG\ 4000)_n$	56 61 71 99 143 225

[a] M = molecular peak

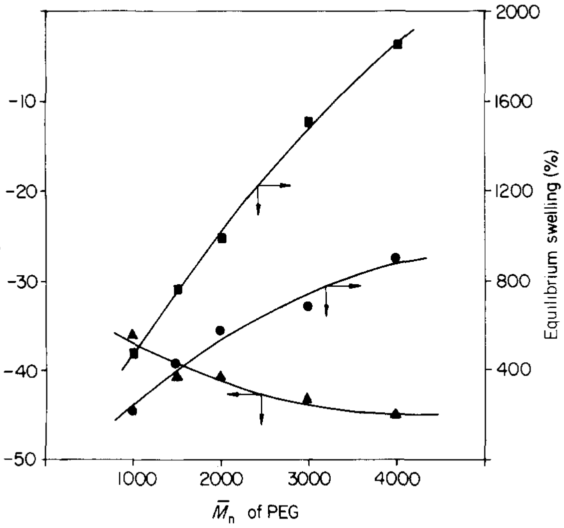


Figure 1 Dependence of equilibrium swelling in water (■) and benzene (●), and T_g (▲) of $(\text{MA–PEG})_n$ on $\bar{M}_n$ of PEG

some of the carboxylic groups is a logical explanation of the need for their excess ([COOH]:[OH] = 1.3) as a prerequisite for higher yields of gel fraction.

The equilibrium swelling data of the products in water and benzene as well as the glass transition temperatures (T_g) presented in *Table 2*, give an idea of the hydrophilic–hydrophobic nature and the crosslink density[10]. A correlation of swelling capacity and T_g on the nature of the diol and the length of the oxyethylene chain was also established. Smaller sizes of TEG, HD and glycerol molecules bring about the formation of dense networks with lower equilibrium swelling values and higher T_g values. The incorporation of PEG segments favours increased swelling in both water and benzene. The hydrophilicity of the crosslinked polymalates increases with the length of PEG molecule from PEG 1000 to PEG 4000, while the T_g values decrease (*Figure 1*). According to these two characteristics, i.e. equilibrium swelling and T_g, the crosslinked polymalates can be divided into two groups — dense networks with low swelling capacity regardless of the solvent, and hydrogels based on PEG. A similar tendency of increasing the hydrophilicity by means of including PEG chains has been established in Smid's investigations[11] on the synthesis of crosslinked polymers with definite structure based on siloxane–polyisocyanates.

The possibility for tailoring the properties by varying the nature of the hydroxylic component and the length of the oxyethylene chain is an advantage of the proposed polycondensation method.

Additional information on the structure of the crosslinked poly(ether–malate), especially on the nature and the average length of the molecular segments, was obtained by studying some destructive processes. Soxhlet extraction with water or benzene for 48 h shows that the hydrogels are hydrolytically and thermally unstable materials since they partially change to mixtures of linear oligomers. The spectral characteristics of the destructive products completely confirm their ether–ester nature and are identical with the spectra of the initial hydrogels (*Table 3*). The g.p.c. curves presented in *Figure 2* indicate that under these conditions the PEG chains remain unaffected, since molecular weights of M_{peak} correspond to the starting PEG. Obviously, the link between two molecules of malic acid (ester or anhydride bond)[9] is more unstable and that is where cleavage takes place. The presence of oligomers with higher molecular weights than the PEGs shows the preferential role of linear polycondensation, resulting in different but multiple poly(ether–ester) fragments. This is why crosslinked polymalates should be considered as heterogeneous networks.

The results of the thermohydrolytic degradation broaden our knowledge on the mechanism of multistage polyesterification in the presence of carbodiimides. Thus, the condensation of PEG and malic acid is the predominant reaction, most probably due to the different reactivities of their hydroxylic groups.

The known dependence of melting points (T_m) and degree of crystallinity on the molecular weight of the polymer[12] remains valid for the crosslinked products (*Figures 3a* and *b*). The thermodynamic parameters (T_m and ΔH_{fus}) of the crosslinked polymalates determined by d.s.c., have lower values than the corresponding diols. Hydrogels with PEG 1000 are completely amorphous while those with PEG 1500 crystallize through 'cold crystallization' under the given d.s.c. experimental conditions (*Figure 4*).

X-ray investigations show a similar tendency for crystallinity to decrease. There is an essential difference between the degrees of crystallinity determined by wide-angle X-ray scattering (WAXS) and by d.s.c. which will not be discussed now. It can be assumed that the main reason for the observed decrease in crystallinity is the lower flexibility of the oxyethylene chains. As a result,

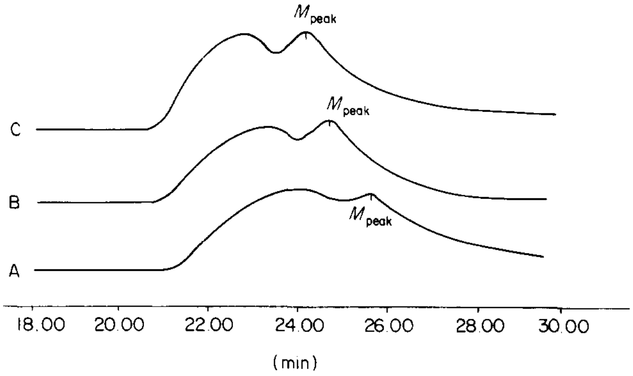


Figure 2 G.p.c. traces of destructive products, obtained after extraction of different $(\text{MA–PEG})_n$ in benzene: A, from $(\text{MA–PEG 2000})_n$, $\bar{M}_n = 2000$, $\bar{M}_w/\bar{M}_n = 2.1$, $M_{\text{peak}} = 2110$; B, from $(\text{MA–PEG 3000})_n$, $\bar{M}_n = 3100$, $\bar{M}_w/\bar{M}_n = 2.0$, $M_{\text{peak}} = 3080$; C, from $(\text{MA–PEG 4000})_n$, $\bar{M}_n = 3200$, $\bar{M}_w/\bar{M}_n = 2.2$, $M_{\text{peak}} = 4070$

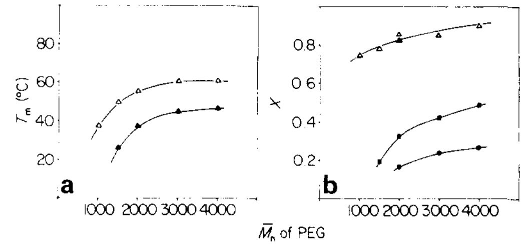


Figure 3 Dependence of T_m and degree of crystallinity (X) of PEGs and different $(\text{MA–PEG})_n$ on $\bar{M}_n$ of PEG. (a) △, T_m of PEGs; ▲, T_m of $(\text{MA–PEG})_n$; (b) △, degree of crystallinity of PEGs, determined from ΔH_{fus} data (X_h); ■, X_h of $(\text{MA–PEG})_n$; ●, degree of crystallinity of $(\text{MA–PEG})_n$, determined from WAXS (X_{WAXS}); ▲, X_{WAXS} of PEG 2000

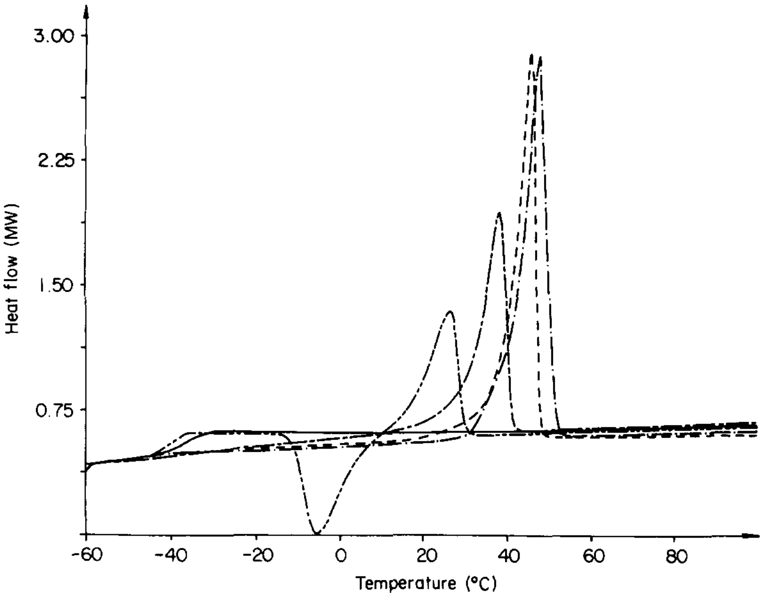


Figure 4 Thermograms of (MA–PEG)$_n$: ——, (MA–PEG 1000)$_n$; ----, (MA–PEG 1500)$_n$; ---, (MA–PEG 2000)$_n$; ---, (MA–PEG 3000)$_n$; -·-, (MA–PEG 4000)$_n$

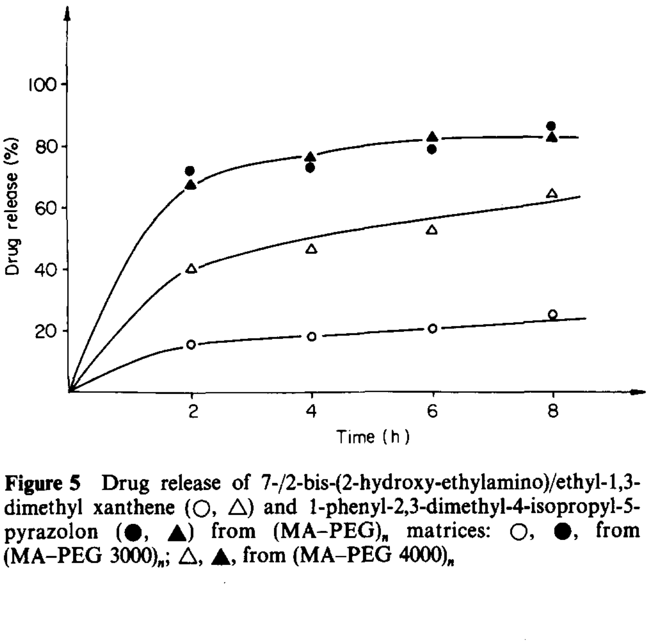


Figure 5 Drug release of 7-/2-bis-(2-hydroxy-ethylamino)/ethyl-1,3-dimethyl xanthene (○, △) and 1-phenyl-2,3-dimethyl-4-isopropyl-5-pyrazolon (●, ▲) from (MA–PEG)$_n$ matrices: ○, ●, from (MA–PEG 3000)$_n$; △, ▲, from (MA–PEG 4000)$_n$

the crystals formed are smaller and less perfect, which contributes to the lower values of ΔH_{fus} and T_m.

The crosslinked polymalates and poly(ether–malate)s can be used as carriers in drug release systems. Preliminary experiments with 7-/2-bis-(2-hydroxy-ethylamino)/ethyl-1,3-dimethyl xanthene and 1-phenyl-2,3-dimethyl-4-isopropyl-5-pyrozolone (pharmacologically active agents with low solubility in water), absorbed from an alcohol solution, reveal the advantage of the polymalate matrices for sustained drug release (*Figure 5*). Detailed investigations concerned with the crosslinked polymalates as carriers for sustained drug release will be reported later.

CONCLUSION

The method developed for polycondensation in the presence of DCC for preparing crosslinked polymalates or poly(ether–malate)s from R,S-malic acid and diols or polyether alcohols, reveals a useful possibility for synthesis of new biodegradable materials. The wide range of tailored structural and swelling characteristics of the products gives the possibility for their future applications as biodegradable carriers for drugs and microelements.

EXPERIMENTAL

All starting compounds were recrystallized or distilled under vacuum. All solvents were dried and distilled prior to use. All PEGs were dried with benzene. The i.r. spectra were registered on a Perkin-Elmer 983 spectrophotometer at a resolution of 3.0 cm^{-1}. $\bar{M}_w$, $\bar{M}_n$ and $\bar{M}_w/\bar{M}_n$ values were determined using a Waters gel-permeation chromatograph equipped with a differential refractometer R-401 and u.v.-detector M 440 and Ultrastyragel columns with porosities 500, 500 and 100 Å. THF was used as eluent, with a flow rate of 0.8 ml min^{-1} at 46°C. Calibration was made with PEG standards. The mass spectra were obtained on a double focusing Jeol 300 mass spectrometer (resolution 1000, 70 eV, at a source temperature of 170°C). The samples were heated from 50 to 400°C at a rate of 100°C min^{-1}. ^{1}H n.m.r. spectra were measured on a Bruker-250 WM n.m.r. spectrometer at 62.93 MHz in $CDCl_3$ against tetramethylsilane (TMS) as internal standard at ambient temperature. The thermal behaviour of the crosslinked products and the corresponding PEGs was analysed with a Perkin-Elmer DSC-7 differential scanning calorimeter, with temperature and energy calibrated to standard procedure, operating under argon flow. Specimens (4–6 mg) encapsulated in aluminium pans were heated beforehand in the calorimeter to 120°C and held for 5 min at this temperature, then cooled to −70°C at 10°C min^{-1} and reheated at the same scanning rate in the same temperature range. Melting points (T_m) and heats of fusion (ΔH_{fus}) were determined from the peak maxima and peak areas respectively. The degree of crystallinity (X_h) was calculated from:

$$X_h = \Delta H_{\mathrm{fus}}/\Delta H^0_{\mathrm{fus}}$$

where $\Delta H^0_{\mathrm{fus}}$, the heat of fusion of perfectly crystalline poly(ethylene oxide) (PEO), can be calculated from the equation[13]:

$$\Delta H^{0}_{\mathrm{fus}}(\mathrm{J\,g^{-1}})=178.6+0.629T_{\mathrm{m}}-2.93\times10^{-3}T_{\mathrm{m}}^{2}$$

Degree of crystallinity measured by wide-angle X-ray scattering (X_{WAXS}) was calculated from:

$$X_{\mathrm{WAXS}}=A_{\mathrm{c}}/(A_{\mathrm{c}}+A_{\mathrm{a}})$$

where A_{c} and A_{a} are the crystalline and the amorphous areas, respectively. WAXS patterns were obtained at room temperature using fine-collimated Ni-filtered CuK_{α} radiation. The diffractometer used was Siemens D 500. The range of the scattering angle 2θ was from 10 to 34°.

Percentage of equilibrium swelling [(weight of swollen sample/weight of dry sample) × 100] was determined according to Stamberg and Sevcik[14]. Drug release experiments were carried out in phosphate buffer at pH 7.2, using Erweka VASK and Bekman EU u.v. spectrophotometer, according to Paddie's method, XXI US Parmacopoeia.

Polycondensation of R,S-malic acid with TEG

R,S-malic acid (0.0075 mol), TEG (0.00375 mol), *p*-toluenesulfonic acid (*p*-TSA) (0.0006 mol) and pyridine (0.00375 mol) were dissolved in 10 ml of THF at room temperature. After complete dissolution, DCC (0.0165 mol) dissolved in a minimum amount of THF, was added. After a few seconds, a white precipitate of DCU was formed. The reaction was followed by i.r. absorption at 2115 cm^{-1} for DCC. After disappearance of this band (2 h) the reaction mixture was stirred for an additional 2 h and filtered. The precipitate, consisting of DCU and crosslinked poly(malic acid–TEG), (MA–TEG)$_n$, was boiled with a large excess of alcohol and filtered. The procedure of washing with boiling alcohol was repeated three times. (MA–TEG)$_n$ was soaked in benzene for 12 h and after filtration was dried under vacuum. All insoluble polyesters obtained via polycondensation of R,S-malic acid with TEG, HD and glycerol are white powders. Yields of gel fraction were 50–60%.

Preparation of poly(malic acid–polyethylene glycol) networks (MA–PEG)$_n$

In a 100 ml round-bottomed flask, 0.0019 mol of PEG (PEG 1000, PEG 1500, PEG 2000, PEG 3000 or PEG 4000) was placed and heated to 65–70°C using a water bath. R,S-malic acid (0.0075 mol), *p*-TSA (0.0006 mol) and pyridine (0.00375 mol) were dissolved in a minimum quantity of THF (5 ml) and poured into molten PEG under stirring. DCC (0.0165 mol) dissolved in 2 ml of THF then was added. In a few seconds a white precipitate was formed. THF was distilled until the slurry became thick and stirring was hindered. The sponge-like material was dried under vacuum to remove traces of THF, cut into small pieces and washed with a large amount of boiling alcohol. The washing procedure was repeated three times to avoid any traces of DCU. The (MA–PEG)$_n$ was then soaked in benzene for 12 h and dried under vacuum. All (MA–PEG)$_n$ were white solids. Yields of gel fraction were 50–60%.

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