Polyurethane-maleamides for cardiovascular applications: synthesis and properties

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Several polyurethane-maleamides (PUMAs) containing polyether or polycarbonate soft segments, and aromatic or aliphatic hard segments were synthesized by solution or bulk polymerization, using maleic acid (MA) or a mixture of MA and butanediol as chain extenders. Using this process, activated double bonds are introduced into the polymer chains and the base polyurethanes may undergo further modification via specific grafting, thus improving their tissue compatibility. PUMAs chemicophysical properties were evaluated by gel permeation chromatography (GPC), intrinsic viscosity analyses, differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FT-IR) and tensile mechanical tests. Polycarbonate diol (PCU)-based PUMAs showed higher molecular weights than polyether diol (PEU)-based ones. The use of butanediol in mixture with maleic acid led to an increase of molecular weights. FT-IR confirmed the presence of the bands related to the amide groups and to the conjugated double bond, yet more evident for the polymer obtained in solution. The higher crystallinity shown by this polymer was also indicative of a better phase separation. All the PCU-PUMAs exhibited similar tensile properties with a higher stiffness than PEU-PUMAs. Among the PEU-PUMAs, the highest tensile properties were shown by the polymer obtained in solution, and by the one derived from a mixture of maleic acid and butanediol.

1. Introduction

Materials and designs currently used for vascular repair fail to adequately support endothelial cell growth. Therefore, the development of innovative materials able to permanently support cell attachment and growth is of crucial priority.

Segmented polyurethanes (SPUs) have been extensively used for the construction of cardiovascular devices. Their biocompatibility as well as their desirable physical properties have made them primary candidates for cardiovascular implants [1]. Among the family of SPUs, polyurethane-amides (PUAm) appear to be of particular interest.

PUAms are obtained with dicarboxylic acids as chain extenders, instead of traditional diols and diamines [2, 3]. Because of the presence of amide bonds in the macromolecular chains, these materials are able to form strong intermolecular hydrogen bonds leading to well-developed hard domains. Moreover, the use of fumaric or maleic acid as chain extenders allows the insertion in the polymer chain of reactive double bonds, which can perform as grafting sites for further derivatization, thus allowing specific tailoring of the base polymers [2–4].

In this work, different polyurethane-maleamides (PUMAs) carrying polyether or polycarbonate soft segments were synthesized by solution or bulk polymerization using aromatic or aliphatic diisocyanates, and maleic acid (MA) or a mixture of MA and butanediol as chain extenders. Fig. 1 gives a schematic view of the PUMAs structure, showing that the use of maleic acid as chain extender introduces double bonds, activated by the presence of amide groups in the polyurethane. The present work deals with the chemicophysical properties of the obtained polymers, whereas cytocompatibility and surface modification via the grafting of adhesive receptors or other suitable molecules for cell attachment will be described separately.

2. Materials and methods

Pure commercial reagents were used, namely: poly-(tetramethyleneglycol) (PTMG, MW 2022, Polysciences), poly-1,6-hexylcarbonate diol (PHCD, MW 2076, Bayer), methylene bis (*p*-phenyl isocyanate) (MDI), 1,6-hexamethylendiisocyanate (HDI), 1,4-butane-diol (BD), maleic acid (MA), dibutyl-tin-dilaurate (DBTDL), stannous octanoate (SnOct), and *N,N*-dimethylacetamide (DMAC). The macrodiols were vacuum dried just before each synthesis, MDI was stored at $-30\,^{\circ}C$; and molten just before the synthesis.

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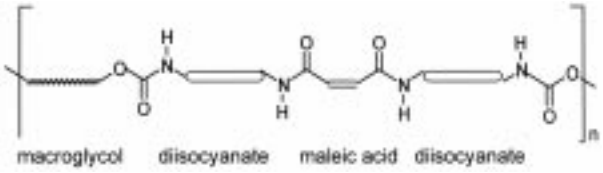

Figure 1 Schematic structure of polyurethane-maleamides (PUMAs).

All the syntheses were made using a macrodiol: diisocyanate : chain extender stoichiometric ratio respectively of 1 : 2 : 1.

2.1. Solution synthesis

To a mixture of HDI and DBTDL dissolved in freshly distilled DMAC, a solution of the required amount of PTMG in DMAC was added under N_2, and stirred at 70 °C for 90 min. Then the appropriate quantity of MA dissolved in DMAC was added and the reaction, followed by a standard dibutylamine back-titration method, was completed after 3 h. The polymer was precipitated in a 2% w/v solution of ethylenediamine-tetraacetic acid disodic salt (Na_2EDTA) in water, washed twice with distilled water and vacuum dried.

2.2. Two-step bulk synthesis

The required amount of macrodiol was mixed at 80 °C with the catalyst and diisocyanate into a polypropylene beaker. After 1 min stirring at 2000 r.p.m., maleic acid (alone, or in mixture 1 : 1 with butanediol) was added under stirring for 2 min. The reaction mixture was then poured into a polypropylene mold and placed in an oven at 80 °C for 4 h.

2.3. Chemicophysical characterization

All the polymers were further purified from the residual catalyst by dissolution in DMAC and precipitation in 0.1 N HCl. Molecular weights evaluation was performed by intrinsic viscosity [η] analyses (in DMAC + 0.1% w/v LiBr at 40 °C), and gel permeation chromatography (GPC), using a Waters system equipped with a refractive index detector and three Ultrastyragel columns, with HPLC-grade DMAC + 0.05 M LiBr as eluent (40 °C, flow rate = 0.8 ml min^{-1}).

2.3.1. Thermal properties

Thermal properties were analyzed with a Mettler TA3000 differential scanning calorimeter (DSC) in the temperature range − 150–250 °C, under N_2, and a heating rate of 20 °C min^{-1}. The per cent crystallinity of soft segments ($\%C_{ss}$) was calculated from the melting ΔH values in pure macroglycols (ΔH_m) and the ones in PUMA polymers (ΔH_c), as follows

$$\%C_{ss} = [(\Delta H_c/\Delta H_m) \times \%S_s] \times 100$$

where $\%S_s$ is the percentage of soft segment in the considered polymer.

FT-IR spectra were performed on PUMA films solvent cast over a KBr disc, with a Mattson 5000 FTIR spectrometer equipped with WinFirst™ software. Peak analysis was performed with GRAMS 362 (Galactic Industries).

2.3.2. Tensile mechanical tests

These tests were carried out on solvent-cast (tetra hydrofuran (THF) : dioxane 2 : 1) dog-bone specimens ($n = 5$; ASTM D-638 Standard Practice), using an MTS instrument equipped with an MTS EX 44 extensometer, and a crosshead speed of 200 mm min^{-1}.

3. Results and discussion

The composition of the obtained poly-urethane-maleamides is provided in Table I, whereas Table II presents data of molecular weights, thermal properties (second DSC heating run) and per cent crystallinity of soft segments ($C_{ss}\%$). Polycarbonate-diol (PCU)-based polymers showed higher molecular weights than polyether-diol (PEU)-based ones. The use of butanediol in mixture with maleic acid led to an increase of molecular weights. All the materials showed a glass transition temperature (T_g) well below 0 °C and a melting transition of soft segments, whereas the melting transition of hard segments was not detected in the temperature range of the analyses. All PCU-PUMAs exhibited higher T_g values than PEU-PUMAs.

FT-IR analyses confirmed the presence of bands characteristic of polyether-urethanes (or polycarbonate-urethanes), of bands related to the amide groups (1680 cm^{-1} and 1570 cm^{-1}) and the one of —C═C— double bond conjugated with the carbonyl group (1632 cm^{-1}). As shown in Fig. 2, these characteristic bands of PUMAs are more evident for the polymer obtained in solution (PEUMAsol). These findings are in

TABLE I Composition of polyurethane-maleamides

Name	Soft segment	Diisocyanate	Chain extender	Catalyst (% $w/w_{soft\ segment}$)	
PEUMAsol	PTMG	HDI	MA	DBTDL	(1)
PEUD2HM	PTMG	HDI	MA	DBTDL	(0.05)
PEUO2HM	PTMG	HDI	MA	SnOct	(0.05)
PEUD2HX	PTMG	HDI	MA + BD	DBTDL	(0.05)
PEUD2MM	PTMG	MDI	MA	DBTDL	(0.05)
PCUD2HM	PHCD	HDI	MA	DBTDL	(0.05)
PCUO2HM	PHCD	HDI	MA	SnOct	(0.05)
PCUD2HX	PHCD	HDI	MA + BD	DBTDL	(0.05)

TABLE II Chemicophysical characterization data of PUMAs

PUMA type	[η] (dl g^{-1})	M_w	M_n	d	$T_{g,\,soft}$ (°C)	$T_{m,\,soft}$ (°C) (ΔHJ g^{-1})	C_{ss} (%)
PEUMAsol	0.42	55 000	27 500	2.0	− 71	23 (77)	>80
PEUD2HM	0.43	40 500	20 600	2.0	− 72	18 (39)	56
PEUO2HM	0.38	27 000	10 000	2.7	− 64	17 (43)	62
PEUD2HX	0.52	56 800	27 500	2.1	− 73	19 (29)	42
PEUD2MM	0.43	13 700	7000	2.0	− 63	18 (48)	76
PCUD2HM	0.49	85 500	36 700	2.3	− 43	34 (15)	45
PCUO2HM	0.44	93 800	20 900	4.5	− 41	41 (26)	76
PCUD2HX	0.50	70 000	37 500	1.9	− 41	34 (18)	54

TABLE III Tensile properties of PUMAs

PUMA type	σ_{break} (MPa)	$\varepsilon\%_{break}$ (%)	$E_{10\%}$ (MPa)	$E_{50\%}$ (MPa)	$E_{100\%}$ (MPa)	$E_{300\%}$ (MPa)	$E_{500\%}$ (MPa)
PEUMAsol	17.9 ± 2.1	935 ± 91	9.4 ± 0.3	4.3 ± 0.4	2.7 ± 0.2	1.7 ± 0.1	1.8 ± 0.1
PEUD2HM	2.2 ± 0.2	501 ± 70	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.4 ± 0.0	0.4 ± 0.0
PEUO2HM	4.3 ± 0.2	634 ± 58	1.1 ± 0.1	1.2 ± 0.2	1.1 ± 0.1	0.7 ± 0.1	0.7 ± 0.1
PEUD2HX	16.1 ± 0.3	983 ± 30	2.4 ± 0.2	2.4 ± 0.3	2.4 ± 0.2	1.2 ± 0.0	1.2 ± 0.0
PEUD2MM	5.2 ± 0.1	793 ± 103	1.8 ± 0.1	1.8 ± 0.1	1.8 ± 0.1	0.9 ± 0.0	0.8 ± 0.0
PCUD2HM	18.9 ± 1.8	617 ± 19	3.5 ± 0.5	3.5 ± 0.5	3.5 ± 0.5	3.4 ± 0.4	3.2 ± 0.2
PCUO2HM	24.1 ± 0.3	527 ± 43	5.7 ± 1.6	6.1 ± 2.2	5.7 ± 1.6	4.8 ± 0.1	4.5 ± 0.3
PCUD2HX	20.7 ± 0.2	604 ± 34	4.0 ± 0.2	4.0 ± 0.1	4.0 ± 0.1	4.0 ± 0.1	3.6 ± 0.0

σ_{break} = stress at break; $\varepsilon\%_{break}$ = elongation at break; E = secant modules (at 50, 100 300 and 500% elongation).

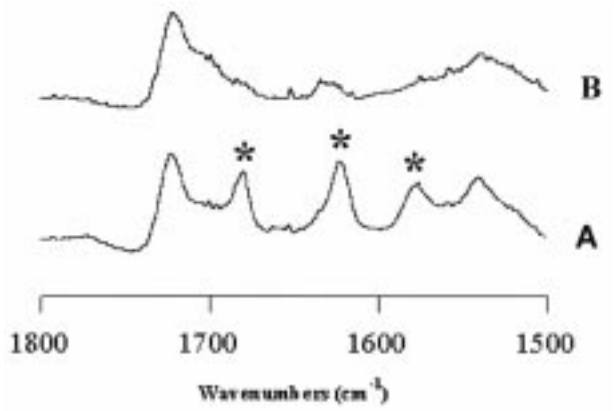

Figure 2 FT-IR spectra of polyether-urethane-maleamides: (a) obtained by solution synthesis (PEUMAsol) and (b) obtained by bulk synthesis (PEUD2HM). Asterisks indicate the characteristic bands of the amide groups (1680 cm^{-1} and 1570 cm^{-1}) and of the double bond conjugated with the amide carbonyl group (1632 cm^{-1}).

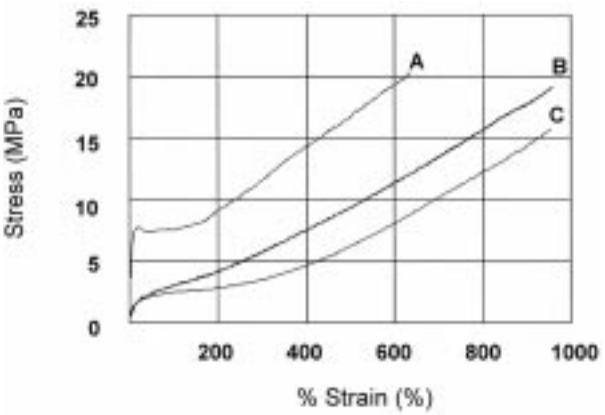

Figure 3 Stress/strain behavior of a polycarbonate-urethane-maleamide (PCUD2HM), and two polyether-urethane-maleamides (PEUMAsol and PEUD2HX).

agreement with the higher values of soft segments melting enthalpy and crystallinity shown by PEUMAsol (Table II), indicative of a better phase separation obtained by solution synthesis.

The results of the tensile tests are shown in Table III, whereas selected stress/stain curves are provided in Fig. 3. All the PCU-PUMAs exhibited a homogeneous behavior with a higher stiffness than PEU-PUMAs. Among the PEU-PUMAs, the highest tensile properties were shown by the polymer obtained in solution, comparable only with PEUD2HX, i.e. the one derived from a mixture of maleic acid and butanediol.

4. Conclusions

The main advantages of the synthesis in bulk, compared to that in solution, are the need of much lower quantities of catalyst and the possibility to get much larger batch quantities of polymers. With the solution synthesis, however, the control of the polyurethane structure and morphology (i.e. phase separation) is easier. On the other hand, the satisfactory results obtained in bulk with polycarbonate-urethane-amides suggest that the chain extension reaction with maleic acid needs to be optimized for PEU-PUMAs.

In all the obtained PUMA polymers the presence of activated double bonds, and therefore the possibility of further derivatization, was confirmed by FT-IR. Moreover, cytocompatibility of the base polymers was successfully checked with human skin fibroblasts after the assessment of the purification procedure (data presented elsewhere), whereas their ability to bind fibronectin and cell-adhesive peptides is now under investigation.

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