Linear poly(ethylene oxide)-based polyurethane hydrogels: polyurethane-ureas and polyurethane-amides

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Over the last 30 years, water-swellable and water-insoluble hydrogels have been extensively investigated and developed, leading to a large family of materials which have found uses in a wide range of biomedical applications.

While hydrogels usually present a crosslinked structure, linear polyurethane-ureas (PUUs) based on poly(ethylene oxide) have been shown to be able to absorb and swell with aqueous media without dissolving. This behavior is due to the phase separated domain morphology, where hydrogen bonded urethane/urea hard segment domains are dispersed in a PEO soft segment domain.

This work investigates the possibility of obtaining linear poly(ethylene oxide)-based polyurethane-amide (PUA) hydrogels using two amide diols as chain extenders, a mono amide diol (AD) and a diamide diol (DD), and a dicarboxylic acid (maleic acid, MA). Poly(ethylene oxide) based PUAs were obtained using a ''one-shot'' bulk polymerization technique. The chemicophysical characterization and water-solubility tests showed that these materials, while having molecular weights similar to the PUUs, do not possess sufficient phase separation, hydrogen bonding and hydrophobicity of the hard segment domains to exhibit hydrogel behavior. Crosslinked PUAs using maleic acid as chain extender show interesting hydrogel properties.
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1. Introduction

Over the last 30 years, water-swellable and water-insoluble hydrogels have been extensively investigated and developed, leading to a large family of materials which have found use in a wide range of biomedical applications such as carriers of drugs and bioactive molecules, the replacement of soft tissues, wound healing, ophthalmological applications, membranes for artificial kidneys, and materials for blood compatible and other medical devices [1–3].

While hydrogels usually present a crosslinked structure, linear polyurethane-ureas (PUUs) based on poly(ethylene oxide) have been shown to be able to absorb and swell with aqueous media without dissolving [4–6]. This behavior is due to the phase separated domain morphology, where strongly hydrogen bonded urethane/urea hard segment domains are dispersed in a PEO soft segment domain. As a result of their linear structure, the PUU hydrogels are soluble in organic solvents (e.g. methanol, ethanol and methyl ethyl ketone) and devices and coatings can be fabricated using solvent casting techniques. The PUU hydrogels may also be processed using common thermoplastic fabrication techniques such as extrusion and injection molding.

This work investigates the possibility of obtaining linear polyurethane-amide (PUA), hydrogels using two amide diols as chain extenders, a mono amide diol (AD) and a diamide diol (DD), and a dicarboxylic acid (maleic acid, MA).

Thermoplastic PUAs, using dicarboxylic acid chain-extenders, have been studied over the last 10 years [7, 8]. Due to the presence of amide bonds in the macromolecular chains, these materials are capable of forming stronger intermolecular hydrogen bonds, leading to well developed hard domains, in comparison with polyetherurethanes. Moreover, the use of maleic acid as the chain-extender allows the insertion of reactive double bonds in the copolymer chains. These double bonds can perform as grafting sites for further derivatization, thus allowing specific tailoring of the base polymers [9].

2. Experimental procedure
2.1. Materials
Pharmaceutical grade poly(ethylene glycols) (PEGs), PEG1500 and PEG3000, were obtained from B.P.

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Chemicals S.N.C., Lavéra, France. The PEGs were vacuum dried at 90–95 °C for at least 6 h on a rotary evaporator and were kept molten in an oven at 80 °C until use. The hydroxyl numbers were accurately determined as 1470 and 3130 respectively by the ASTM 1638 67T standard method. Desmodur W, biscyclohexylmethane-4,4′-diisocyanate (HMDI), manufactured by Bayer AG and supplied by Whitfield Chemicals Ltd was used without further purification. 4,4′-methylenedianiline (MDA), maleic acid (MA) and anhydrous ferric chloride (FeCl$_3$) were supplied by Aldrich Chemical Company Ltd. The chain extenders DD, an aliphatic diamide diol, and AD, an aliphatic amide diol, were synthesized by the Laboratory of Biomaterials, Department of Bioengineering, Politecnico di Milano and vacuum dried at room temperature before use.

2.2. Synthesis

Fifty-gram batches of all the polymers were prepared by a ''one-shot'' bulk polymerization technique, using 0.02% w/w FeCl$_3$ as catalyst.

A slight excess of the required amount of PEG is weighed into a round-bottom flask and dried on a rotary evaporator for 6 h at 90–95 °C. The required amount of FeCl$_3$ catalyst is then weighed directly into the molten PEG and the mixture returned to the rotary evaporator until a homogeneous solution has been obtained.

The chain extender, previously dried in a vacuum oven for 1 h, is added to the PEG/FeCl$_3$ solution at the desired concentration, and the mixture returned to the rotary evaporator to allow the complete drying and dissolution of the chain extender. The required weight of the reactant mixture is then weighed into a dry polypropylene beaker and stirred at 425 r.p.m. The diisocyanate is added to the mixture and after 2 min of vigorous stirring, the reaction mixture is poured into polypropylene test-tube molds and the molds placed in an oven at 95 °C for 20 h. On completion of the reaction, the molds are allowed to cool to room temperature and stored. The polymers are removed from the molds by freezing with solid carbon dioxide and tapping the side of the mold to release the polymer block. Films were cast onto a glass plate (or petri-dish) using 5% w/v solutions of the polymers in methanol.

2.3. Characterization of the materials

The synthesized polymers were characterized using gel permeation chromatography (GPC) and Fourier transform infrared spectroscopy (FT-IR). The water-solubility of the polymers was investigated by immersing film samples in water at room temperature.

2.3.1. FT-IR

IR spectra were performed using a Mattson 5000 FT-IR spectrometer, equipped with the Fourier infra-red software, WinFirst^{TM}, for Microsoft Windows. A thin film of the polymer sample was cast onto a KBr disc using a solution of 10 mg polymer in 500 mg of CHCl$_3$.

2.3.2. GPC

The GPC analyses were performed using a GPC Waters Millennium^{TM} Chromatography System with high-pressure liquid chromatography (HPLC) grade chloroform as eluent (1.0 ml min^{-1} flow rate, Waters Styragel^{TM} HT 6E column). The polymer samples were dissolved in the CHCl$_3$ at a concentration of 4–5 mg in 4 ml (0.1%).

As the PUU hydrogels and the PUAs were based on poly(ethylene oxide), a GPC calibration curve was obtained using poly(ethylene glycol/oxide) standards over a molecular weight range of ~ 200 to $\sim 1\,000\,000$ (Polymer Laboratories Ltd). The polymer standard solutions were prepared using HPLC grade chloroform.

2.4. Crosslinking of PUA MA 15 and PUA MA 30

Films of the PUA MA 15 and PUA MA30 (maleic acid chain-extender) compositions, cast from a 5% w/v solution in methanol in a pyrex petri dish, were cured in an oven at 95 °C for 5 h.

2.5. Swelling behavior of PUUs and PUAs in water

The swelling degree of the PUUs and PUAs in water at 37 °C ($\pm$ 0.3 °C) was measured at 24, 48 and 120 h.

Film samples of about 100 mg in weight and 1 cm^2 in size were cut from the original solvent-cast films. The samples were dried in a vacuum oven at room temperature, weighed accurately and then each sample was immersed, individually, in 40 ml of distilled water in a weighing bottle. The weighing bottles were placed in a heating block calibrated to 37 °C ($\pm$ 0.3 °C). At each time interval, the samples were removed, blotted with tissue paper and accurately weighed. The swelling measurements were carried out in duplicate. The water uptake, WU (%), versus time, was calculated as

$$WU(\%) = (W_s - W_d)/W_d \times 100$$

where W_s is the weight of the swollen sample and W_d is the weight of the sample dried under vacuum.

2.6. Water extraction of PUUs and PUAs at 37 °C

The above swollen samples (in duplicate) were dried in a vacuum oven after extracting in water at 37 °C ($\pm$ 0.3 °C) for 24, 48 and 120 h and reweighed. The percentage weight loss was plotted as a function of time.

3. Results and discussion

PUAs were obtained using a ''one-shot'' bulk polymerization technique, with 0.02% FeCl$_3$ as catalyst, from poly(ethylene oxide) (nominal molecular weights 1500 and 3000), an aliphatic diisocyanate (biscyclohexylmethane-4,4′-diisocyanate, HMDI) and different weight percentages of the DD, AD and MA chain extenders. The formulations of the synthesized materials are given in Table I.

TABLE I Composition of the PUUs and PUAs

	Soft segment (wt%)	Chain extender (wt%)	Desmodur W (wt%)
PUU MDA15	PEG 1500 (80.0)	MDA (2.0)	18.0
PUU MDA30	PEG 3000 (87.5)	MDA (2.0)	10.5
PUA AD15a	PEG 1500 (80.6)	AD (1.5)	17.9
PUA AD15b	PEG 1500 (76.9)	AD (3.0)	20.0
PUA DD30	PEG 3000 (84.0)	AD (3.0)	13.0
PUA DD15a	PEG 1500 (79.7)	DD (2.6)	17.7
PUA DD15b	PEG 1500 (75.5)	DD (5.0)	19.5
PUA DD30	PEG 3000 (87.2)	DD (2.5)	10.34
PUA MA15	PEG 1500 (70.0)	MA (5.0)	25.0
PUA MA30	PEG 3000 (76.4)	MA (5.0)	18.6

TABLE II Principal FT-IR band attribution

Frequency (cm^{-1})	Intensity	Attribution
Common bands		
3337–3322	S	ν_{N-H} urethane
2920–2913	S	ν_{CH_2} asymmetric, ether from PEO
2868–2861	M	ν_{CH_2} symmetric, ether from PEO
1717	VS	$\nu_{C=O}$ urethane carbonyl
1538–1528	VS	$\delta_{NH} + \nu_{C-N}$
1466–1452	S	δ_{CH_2} from PEO
1348	S	ω_{CH_2}
1113–1107	VS	$\nu_{CH_2-O-CH_2}$ ether
1042	S	ν_{C-O-C} CO—O—C urethane
Bands in PUU MDA		
1653	W	$\nu_{C=O}$ urea
1597	S	$\nu_{C=C}$ aromatic ring
1409	S	ν_{C-C} aromatic ring
Bands in PUA AD		
1675	W	$\nu_{C=O}$ amide carbonyl
Bands in PUA DD		
1647	S	$\nu_{C=O}$ amide carbonyl
Bands in PUA MA		
1669	M	$\nu_{C=O}$ amide carbonyl
1635	M	C=C conjugated with C=O

TABLE III GPC analyses of the PUUs and PUAs

	M_w	M_n	d
PUU MDA15	16 6 201	71 063	2.34
PUU MDA30	264 046	100 778	2.62
PUA AD15a	82 317	38 836	2.12
PUA AD15b	221 727	102 923	2.15
PUA AD30	211 993	61 199	3.46
PUA DD15a	192 273	85 387	2.25
PUA DD15b	180 619	76 527	2.36
PUA DD30	32 111	11 601	2.77
PUA MA15	17 841	7314	2.44
PUA MA30	22 071	9410	2.34

FT-IR analysis confirmed the expected structure of the polymers: the principal bands and their attributions are reported in Table II.

PUAs synthesized with AD and DD chain extenders show similar molecular weight values (Table III) to the corresponding control polyurethane-ureas (PUUs), except for the very low value obtained for the PUA DD30 composition. This is due to the incompatibility of the DD with the PEG3000.

The physicochemical characterization and the solubility tests showed that these materials, while having molecular weights similar to the PUUs, do not possess sufficient phase separation, hydrogen bonding and hydrophobicity of the hard segment domains to impart hydrogel behavior.

Although the molecular weights of the PUAs are similar to the PUUs, the water-solubility characteristics of these polymers differ: while the PUU films swell but are insoluble in water, the PUAs are soluble in water (PUA DDs > PUA ADs). The water solubility is to be

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attributed to a decrease in the inter- and inter-molecular hydrogen bonding combined with an increase in the hydrophilicity of the hard domains containing the aliphatic amide chain-extender linkages.

On the other hand, only low molecular weight polymers, probably —COOH terminated, are obtained using the maleic acid chain-extender (PUA MAs): the ''one-shot'' polymerization reaction appears not to be effective in this case. The water and solvent solubility characteristics show interesting features: while the polymer bulk is readily soluble in both water and methanol, the surface layers are not soluble but are swellable in water and methanol. It is probable that crosslinking of the polymer surfaces has taken place during the polymerization reactions possibly as a result of oxidation.

Polymer films, prepared by casting methanol solutions of the low-molecular-weight solvent-soluble fractions of the PUA MA15 and PUA MA30 compositions, were ovencured at the synthetic reaction temperature (95 °C) for 5 h. The cured thin films were found to be insoluble but swellable in water (PUA MA15C, PUA MA30C).

The FT-IR analyses of the PUA MA polymers before and after oven-curing are reported in Fig. 1. As expected, it was possible to detect a significant disappearance of the band at $1635\,cm^{-1}$, attributed to the maleic acid linkage C--C double bond, which suggests that these double bonds are involved in the crosslinking mechanism.

The water-swelling of the crosslinked polymers was measured in comparison with the PUU hydrogels (Fig. 2). The two control materials, PUU MDA15 and PUU MDA30, reach their equilibrium water uptake (EWU) in 24 h. The crosslinked PUA MA15 has a similar swelling to the corresponding control polyurethane-urea, PUU MDA15, while the water uptake of the crosslinked PUA MA30 film is lower than expected. In fact, the swelling of the crosslinked PUA MA30 film decreased over time. The weight losses exhibited by the PUA MA15C and PUA MA30C films in water can explain their swelling behavior. Significantly, the weight losses have values of around 30% for PUA MA15C and more than 40% for
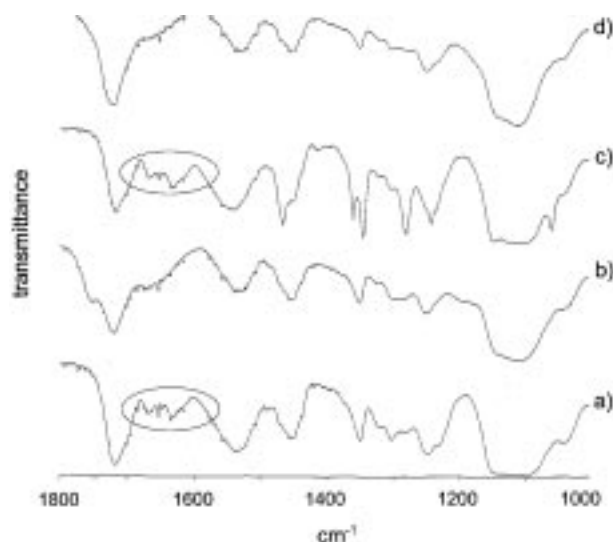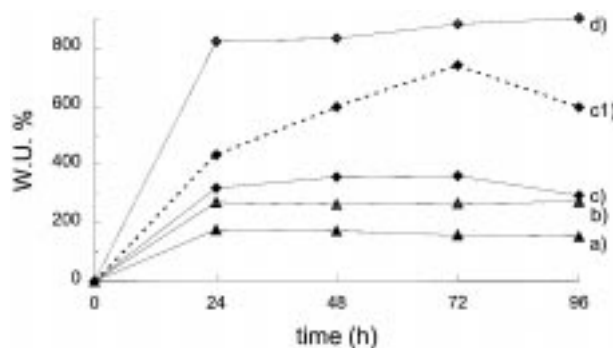

Figure 2 Water uptake percentage versus time of PU-ureas compared with PU-amides: (a) PUA MA15C; (b) PUU MDA15; (c) PUA MA30C; (c1) PUA MA30C curve recalculated using the dried weight of each samples after swelling; (d) PUU MDA30.
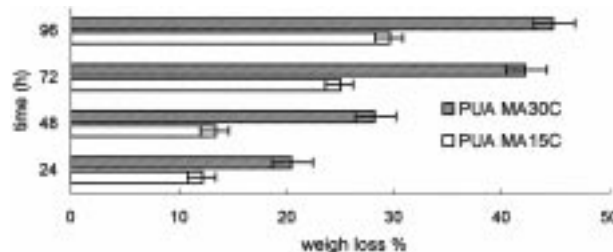

Figure 3 Weight loss percentage of PUA MA15C and PUA MA30C.

PUA MA30 (Fig. 3). By taking into account the weight loss through extraction of water-soluble material, the WU values for PUA MA30 can be recalculated using the dry weight of each sample after swelling, instead of the initial dry weight, and a new WU curve can be obtained. This new curve shows a swelling profile comparable with the control material, PUU MDA30 (Fig. 2, Curve c1).

4. Conclusions

New PEO based water-soluble polyurethane-amides (PUA AD and PUA DD) have been obtained using innovative chain extenders: the new diol chain extenders are effective for the ''one-shot'' polymerization process and produce high-molecular-weight polymers.

The reduced H-bonding capability of the PU-amides compared to the PU-ureas leads to solubility in water. It is possible that the controlled introduction of amide linkages into a PU-urea structure may produce water-insoluble but swellable hydrogels, i.e. by reducing the AD and DD content, hydrogels may be obtained. Furthermore, the amide chain extenders could allow the custom design of biocompatible PEO-based polyurethane-urea/amides with properties ranging from water-solubility to water-swellability.

The maleic acid chain-extender produces low-molecular-weight polymers using the ''one-shot'' polymerization method and the chain extension reaction needs to be studied and optimized.

PU-amides with maleic acid show potentially useful functionality. Additionally, these PU-amides were found to be crosslinkable in thin films leading to polymers with water-swelling values comparable with the corresponding PU-ureas. The high weight loss due to the extraction of water-soluble material indicates the

Figure 1 FT-IR of (a) PUA MA15, (b) PUA MA15C, (c) PUA MA30, (d) PUA MA30C.

necessity to further investigate the crosslinking and the reactivity of these polymers.

Acknowledgments

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