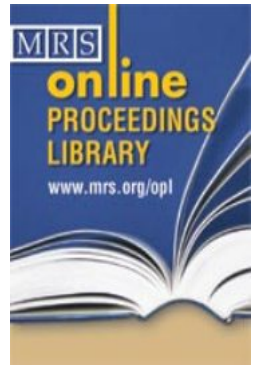

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Design of semi-interpenetrating networks based on poly(ethyl-2-cyanoacrylate) and oligo(ethylene glycol) diglycidyl ether

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ABSTRACT

The synthesis of semi-interpenetrating networks (SIPN) based on linear poly(ethyl 2-cyanoacrylate) (PECA) and oligo(ethylene glycol) diglycidyl ether (OEGDG) based polymer networks was motivated by the hypothesis that the brittleness of polycyanoacrylates may be overcome by incorporating them into a polymer network architecture. A sequential synthetic route was applied, in which first PECA was prepared by anionic polymerization. Subsequently, OEGDG was crosslinked with different anhydrides and curing catalysts to form networks with hydrolyzable ester bonds and interpenetrating PECA. These SIPNs showed a low water uptake compared to other polyether based networks. Some of the obtained materials were transparent and exhibited a great flexibility, which was maintained also after 24 h of immersion in water and subsequent drying. Such networks could be components of future stimuli-sensitive material systems.

INTRODUCTION

Poly(alkyl-2-cyanoacrylate)s (PACAs) are degradable and biocompatible linear polymers. However, their extensive use as biomaterials is limited by their hydrophobicity and poor flexibility [1]. Brittleness of PACAs is linked to their high glass transition temperature T_g, e.g., 146 °C for PECA [2] or 118 °C for poly(*n*-butyl-2-cyanoacrylate)[3]. Recently, a number of design strategies for obtaining elastic PACAs were reported in the literature, but none of them succeed. For instance, blending PECA with oligo(ethylene glycol) diglycidyl ether (OEGDG) resulted in highly flexible materials [2]. However, these blends lost their advantageous mechanical properties upon exposure to water due to extraction of the polyether component [2].

Covalently crosslinked polymer networks are attractive for biomedical applications since it is possible to tailor their elastic properties and functions by adjusting their chemical composition and architecture [4], [5]. Polymer segments incorporated in such networks cannot be extracted due to their covalent crosslinking. Degradability of the material can be established by introducing hydrolizable bonds in the polymer segment or netpoints [6]. It was hypothesized, that by incorporating PECA into a polymer network with much lower T_g, the brittleness of the PECA material may be reduced. Oligoethylene glycol (OEG) might be suitable for usage as an additional component due to its biocompatibility and low protein absorption, which makes it one of the most widely explored polymers for biomedical applications [7]. At the same time, OEG based networks are highly hydrophilic. Thus they are prone to massive swelling in an aqueous environment. Combining them with a more hydrophobic polymer such as PECA may overcome this issue.

When aiming to apply polymer networks in a living organism for a limited period of time, one of the challenges is to enable hydrolytic and/or enzymatic degradability in order to avoid the need for surgical removal. In selected cases such as for physical barriers to prevent

postsurgical adhesions, interventions for removal may even delete the benefit, which had been established by their application. In this work, PECA based interpenetrating networks are explored with the aim to improve the flexibility of PACA while ensuring their hydrolytic degradability.

EXPERIMENT

Oligo(ethylene glycol) diglycidyl ether (0.84 g = 1.6 mmol; OEGDG 526 Da; from Sigma-Aldrich, Taufkirchen, Germany) has been dispersed in 10 ml of freshly distilled anhydrous tetrahydrofuran (THF) in dry 25 ml tubes. Ethyl 2-cyanoacrylate monomer (1 g; ECA; Sicomet 40® from Henkel, Hannover, Germany) has been added resulting in a molar ratio of OEGDG/moles ECA of 0.2. The water content in the OEGDG/THF solution, as determined by Karl-Fischer titration, was 786 ppm. After vigorous stirring for 4-5 h, maleic anhydride (163 mg; MA), succinic anhydride (165 mg; SA), or phthalic anhydride (246 mg; PA) all from Sigma-Aldrich (Taufkirchen, Germany) was added to the polymers solution and stirred at r.t. until complete solution. Then the tube has been placed in an oil bath at 50 °C and a catalytic amount of triethylenetetramine (1.6 µmol; TETA), triethylamine (1.6 µmol TEA) or methanesulfonic acid (1.6 µmol MSA) all from Sigma-Aldrich (Taufkirchen, Germany) has been added under stirring. After stirring for 30 min, the samples were casted on silanized petri dishes and placed in an oven at 70 °C for 4 days and then further dried in a desiccator for one day gradually decreasing the pressure to 20 mbar within 4 hours. The obtained films have been detached from the dishes and used for the subsequent evaluations.

ATR-FT-IR analysis was performed on a 8400S (Shimadzu, Duisburg, Germany). The gel content was determined by immersing squared samples with a surface of 1 cm^2 for 24 h at r.t. in water or acetone. All samples showed a thickness of 400 ± 26 µm. After 24 h at r.t., the samples have been recovered and dried under vacuum until constant weight. Five samples have been used for each material and the gel content (G) calculated according to the following formula (1), where m_i and m_r are the initial and the recovered mass of the dry sample.

$$G = \frac{m_r}{m_i} \cdot 100 \quad (1)$$

Water uptake experiments have been performed by immersing squared samples with a surface of 1 cm^2 until constant weight, which was reached for all samples after almost 18 h at r.t. in water. Initially, all samples showed a thickness of 400 ± 26 µm. At predefined time points, the samples were recovered, paper dried, and weighted. Water uptake H has been calculated by equation (2), where m_i is the initial mass of the sample before the experiment and m_s is the mass of the swollen sample.

$$H = \frac{m_s - m_i}{m_i} \cdot 100 \quad (2)$$

RESULTS AND DISCUSSION

SIPN are defined as systems consisting of at least one polymer network and at least one type of linear or branched macromolecule, which cannot be separated by physical methods [8]. Molecular dispersion of the interpenetrating polymer in the network can be obtained by different preparation techniques, e.g., by sequential formation of linear component and polymer network.

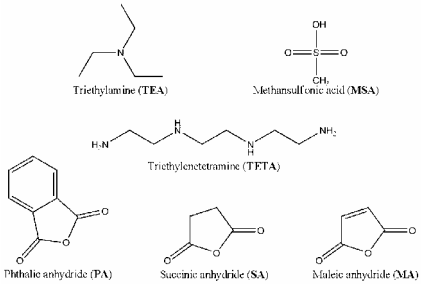

Figure 1. Chemical structures of the employed anhydrides and catalysts

Here, the authors aimed to prepare a network component with degradable ester bonds, which should be achieved by employing the epoxy/anhydride reaction. Epoxy/anhydride systems are generally considered for fast-curing applications, also allowing lower reaction temperatures than related epoxy systems without anhydrides. Common catalysts for epoxy/anhydride crosslinking are tertiary amines, alcohols, imidazoles, or acids [9].

In this study, succinic anhydride (SA), maleic anhydrides (MA), and phthalic anhydride (PA) should be evaluated (Fig. 1). They have been chosen as examples of: i) an aliphatic chain bearing anhydride (SA), ii) a double bond bearing anhydride (MA), and iii) an aromatic group bearing anhydride (PA), since these structural elements exhibit different chain flexibilities. This may impact chain alignment and thus the mechanical and thermal properties of the material [10]. As curing catalysts, triethylenetetramine (TETA), triethylamine (TEA), or methanesulfonic acid (MSA) were chosen [11-14]. A recent study indicated biocompatibility for epoxy-derived networks synthesized with TETA [15].

SIPN can in principle be obtained by simultaneous synthesis of both SIPN components. An alternative concept is a sequential synthesis of the different components [16] [17]. In order to establish a simultaneous synthesis of the SIPN components, their reactivity needs to be comparable under identical conditions. However, cyanoacrylates are rapidly polymerizing in the presence of traces of water, which are found in OEGDG even after extensive drying. Additionally, adding a basic catalyst for crosslinking of OEGDG to a network would cause the immediate anionic polymerization of the cyanoacrylate without starting the epoxy/anhydride

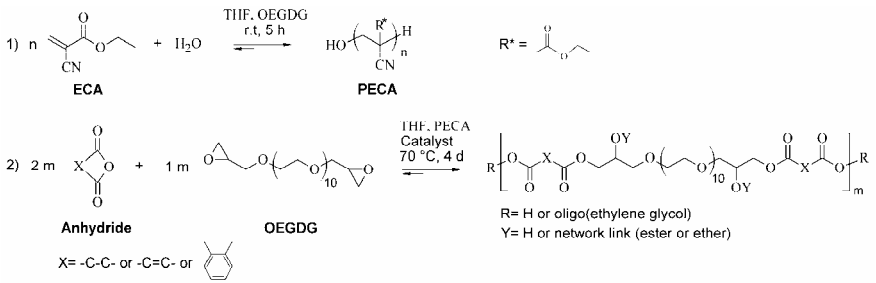

Figure 2. Sequential synthesis of SIPN from PECA and OEGDG.

crosslinking. If, on the other hand, an acidic catalyst is used, anionic polymerization of the ECA monomer may be impeded. Based on that, a sequential synthesis of the SIPN was performed as shown in Figure 2. First, the linear PECA was obtained, while OEGDG was already present in the reaction medium for good mixing of the two components. After completion of ECA polymerization, calculated amounts of different anhydrides and/or catalysts were added for crosslinking OEGDG to a network structure.

Table 1. Series of experiments to identify conditions of network formation.

Sample	PECA	OEGDG	Anhydride (MA, SA or PA)	Catalyst (TEA, TETA or MSA)
A	X			X
B	X		X	
C	X		X	X
D		X	X	
E		X		X
F		X	X	X
G	X	X		
H	X	X	X	
I	X	X		X
L	X	X	X	X

In order to establish the desired sequential synthesis of the SIPN, it had to be proven that ECA and OEGDG are not reacting at the same time as assumed. For this purpose, a series of experiments has been performed at the same temperature (Table 1). The obtained samples were subjected to a fast screening to determine on whether or not crosslinking occurred, which is why samples were incubated in different solvents. Due to the high solubility of PACA in acetone, the samples A–C (see Table 1) were incubated in this solvent and showed complete solubility as expected. No network was formed if OEGDG is not present. Since OEGDG is well soluble in water, all samples (Table 1) were also subjected to an aqueous environment. The ECA-free samples D and E with either no catalyst or no anhydride (see Table 1) were completely soluble after 24 h in water, while the samples F resulted in an OEG-derived network, which was insoluble in water. When combining ECA und OEGDG in the reaction mixture with either the catalyst, or the anhydride, or both missing (samples G, H and I) an insoluble residue was observed upon swelling in water, which could be dissolved in acetone. Only the samples L provided a material, which was insoluble in both water and acetone. These experiments confirmed that unspecific reactions can be excluded and that the presence of the catalyst is effectively promoting the OEGDG crosslinking only in the presence of the anhydrides.

In order to choose the most promising networks from this screening study, the gel content (Eq. 1) was determined and a minimum value of 70 wt.% has been used as selection criterion for successful crosslinking. The average weight amount of PECA, based on starting materials, was 45 ± 5 wt.% in this set of experiments. The nomenclature of sample codes was derived as follows: ‘P’ as in PECA, ‘O’ as in ‘OEGDG’, ‘M”/’S’/’P’ according to the selected anhydride (MA, SA, PA; compare Fig. 1), and the abbreviation of the respective catalyst (TETA, TEA, MSA; compare Fig. 1). Only the three products obtained using TETA as catalysts exhibited a gel content in the desired range.

Table 2. Selection of successfully formed SIPNs based on their gel content.

Sample			Anhydride			Catalyst			Gel content (G)
	PECA	**O**EGDG	**MA**	**SA**	**PA**	**TETA**	**TEA**	**MSA**	**wt. %**
POMTETA	X	X	X			X			**96.1 ± 2.8**
POMTEA	X	X	X				X		30.5 ± 3.7
POMMSA	X	X	X					X	42.3 ± 1.2
POSTETA	X	X		X		X			**92.3 ± 4.2**
POSTEA	X	X		X			X		8.7 ± 3.2
POSMSA	X	X		X				X	40.4 ± 4.6
POPTETA	X	X			X	X			**93.5 ± 5.2**
POPTEA	X	X			X		X		5.2 ± 1.8
POPMSA	X	X			X			X	43.9 ± 2.5

The sample POPTETA showed several non-volatile droplets on the film surface, which indicated phase separation. Additionally, these samples were opaque rather than transparent. Also the POSTETA samples appeared to exhibit phase separation and opacity in visual examination, which was less obvious than for POPTETA. In contrast, POMTETA samples were transparent and elastic (Fig 3). They showed a yellow color as common for materials derived from maleic anhydride, which was assigned to complex formation between tertiary amines and maleic acid [18].

The POMTETA and POSTETA films have been characterized by FT-IR. The disappearance of the peak at 912 cm^{-1} related to the epoxy ring confirmed the consumption of the OEGDG epoxy groups during the crosslinking reaction. Furthermore, the films were insoluble in all tested organic solvents as well as in water. They preserved their macroscopic properties such as transparency and flexibility after the extraction procedure with subsequent drying. Water uptake values for POMTETA and POSTETA films were determined to be in the range of 8-9 wt.% after Therefore, it can be expected that such a material, when employed in a physiological environment, e.g. between two tissues to avoid adhesions, will uptake some water but will not dramatically change its volume and create pressure on the surrounding tissues.

Figure 3. Picture of the film POMTETA obtained by crosslinking the OEGDG with MA using TETA as a curing catalyst.

CONCLUSIONS

In this work, the design of SIPN based on PECA and OEGDG crosslinked with maleic, succinic or phthalic anhydride has been reported, which should be prepared in a sequential one-pot synthesis and exhibit polyester bonds as easily hydrolyzable weak links. From a screening study, the SIPN obtained by crosslinking the OEGDG with maleic anhydride was identified as flexible material without macroscopic phase separation or impedance of its properties upon immersion in water for 24 h with subsequent drying. Such networks could be components of future stimuli-sensitive material systems.

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