Studies on a new radiopaque polymeric biomaterial

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Studies on a new radiopaque polymeric biomaterial

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A new radiopaque polymeric biomaterial has been synthesized. The material, which actually represents an entire family of analogous radiopaque materials, is composed of 2-(p-iodobenzoyl)-ethyl methacrylate (compound 1, 21 mol%), methyl methacrylate (MMA, 60 mol%), and 2-hydroxyethyl methacrylate (HEMA, 19 mol%). The terpolymer was synthesized in a radical polymerization reaction at elevated temperature in N,N-dimethylformamide (DMF). The product was subjected to a set of physicochemical characterization techniques (gel permeation chromatography, 500 MHz 1H NMR in deuterated dimethylsulphoxide (d6DMSO) solution, differential scanning calorimetry, dynamic water contact angle measurements), as well as to an in vitro thrombogenicity assay. Furthermore, scanning electron microscopy was used to study interactions of the material with blood platelets. The most important findings are: (a) the material is a genuine polymer with excellent X-ray visibility, even in the form of thin (0.4 mm) drawn fibres. This was established under realistic conditions. (b) The material exhibits low in vitro thrombogenicity, i.e. comparable to polyvinyl chloride, which is known as a passive material. These observations lead us to the suggestion that this type of radiopaque polymer holds promise with respect to application as a construction material for a new type of endovascular stent. This could be relevant in particular to stents to be used in conjunction with percutaneous transluminal coronary angioplasty (PTCA), also known as Dottering. Currently there is a clear trend away from metallic stents towards all-polymeric stents, since the latter have superior biocompatibility. Biocompatibility of the stent material is of vital importance with respect to the long-term performance of the stent, i.e. its ability to prevent the phenomenon of restenosis. Note that both stent material–vessel wall and stent material–blood interactions are crucial. Application of a radiopaque polymer as described herein should enable us to construct a new stent type with improved biocompatibility with respect to the metallic counterparts, combined with excellent X-ray visibility.

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Research on new biomaterials has expanded rapidly over the last years. It is important to realize that successful application of a biomaterial is possible only if a number of stringent requirements are met. Among these are:

1. Biocompatibility: the material will not induce any undesirable or harmful effects such as blood clotting, allergic reaction, tissue death, inflammation, tumour formation, or foreign body reactions (rejection).
2. Physical properties: aspects such as strength, elasticity or permeability must fit the application, and should be maintained during the time that the material is in function.
3. Manufacture: it is important that the material can be fabricated, purified, and sterilized without major difficulties.

Perhaps the most important aspect of a biomaterial is its biocompatibility. For example: what is the detailed 'host response' of the body upon introduction of a polymeric implant? Usually, biocompatibility of a new material is evaluated as far as possible through a battery of in vitro test experiments in the laboratory, and a follow-up of in vivo or ex vivo evaluations using animal models.

Clearly, it would be very helpful to have a technique for non-invasive evaluation of polymeric implants. This would put the researcher into a position from which it is relatively easy to make observations as a function of time without sacrificing the animal model. In some cases, this was attempted through the use of ultrasound imaging of implants. This approach,
however, suffers from the fact that ultrasound imaging has only moderate sensitivity. A relatively new and perhaps more promising approach is the development of radiopaque biomaterials, e.g. polymers that have the physical property of absorbing X-rays. Sharp images can be obtained from materials of high electron density².³

Based on these lines of reasoning, we have prepared a new polymer in which 2(p-iodobenzoyl)ethyl methacrylate (compound 1) is incorporated. The material consists of compound 1, methyl methacrylate (MMA) and hydroxyethyl methacrylate (HEMA) in the molar ratio 21:60:19, respectively. We describe the synthesis, physical characterization and some aspects of the bio (blood) compatibility of this new material. It was found that thin fibres (0.4 mm) of the material are clearly visible in a realistic experimental set-up using X-ray absorption imaging techniques that are common in the clinic. The material proved to be relatively passive in a static haemocompatibility test which is focussed on the generation of thrombin. Furthermore, our material offers good possibilities for further improvement of the mechanical properties, for instance through fibre spinning techniques.

MATERIALS AND METHODS

Monomer synthesis

A solution of 4-iodobenzoic acid (0.010 mol, 2.48 g), N,N'-dicyclohexylcarbodiimide (0.011 mol, 2.266 g), 2-hydroxyethyl methacrylate (0.011 mol, 1.43 g) and dimethylaminopyridine (0.001 mol, 0.122 g) in 75 ml of dry dichloromethane, was stirred overnight. The reaction mixture was filtered to remove precipitated N,N'-dicyclohexyl urea and the filtrate was washed successively with H₂O (50 ml, three times), 5% acetic acid (50 ml, three times) and H₂O (50 ml, three times). The organic phase was filtered to remove the last traces of N,N-dicyclohexyl urea, and concentrated. The residue was dissolved in 10 ml of a mixture of ethyl-acetate and petroleum ether 40–60 (ratio 10:90 v/v). This solution was chromatographed on a silicagel column (ϕ = 3 cm, height 20 cm) using petroleum ether 40–65 and ethyl acetate (90:10 v/v) as the mobile phase. Fractions containing pure product (RF = 0.4 in the eluent) were pooled and concentrated. This afforded pure 1 which crystallized on standing. The yield was 85%. Purity was checked with high-performance liquid chromatography (HPLC):

\[ \text{RF} = 0.4 \]  

Elemental analysis: C₁₃H₁₁₇I: Calculated: C, 43.35; H, 3.64; I, 35.24; found: C, 43.21; H, 3.62; I, 35.11.

IR (KBr): 1740 (C=O), 1640 (C=C), 1570 and 1486 cm⁻¹ (C=C, aromatic).

Purification of MMA and HEMA

Methyl methacrylate was washed with 0.5 M NaOH (three times), and with water and then dried over MgSO₄, distilled at atmospheric pressure (101°C). The middle fraction was collected and used. HEMA was distilled under reduced pressure and the middle fraction was collected and used. N,N-Dimethyl formamide (DMF) and dichloromethane were distilled from LiAlH₄ and stored over 3 Å molecular sieves. All other reagents were used without further purification.

Polymerization

The radical polymerization of acrylic components was carried out in DMF. Compound 1 (7.56 g, 21 mmol), HEMA (2.47 g, 18.45 mmol) and MMA (6.01 g, 60.45 mmol) were dissolved in 20 ml of dry DMF in a 250 ml round-bottom flask, equipped with a mechanical stirrer. The vessel was immersed in a thermostated oil bath interfaced with a programmable time temperature control system. The time–temperature profile as given in Figure 1 was then run.

Radical initiator and chain transfer agent (CTA) were added from pre-prepared stock solution. Final concentrations are given in Table 1.

After 24 h the polymer was precipitated by adding it dropwise with a pasteur pipette in demineralized H₂O (100 ml) under continuous agitation for 2 h. The solution was washed with ether (50 ml, three times) to remove the residual monomers. The obtained polymer was lyophilized from water (10 ml) overnight to obtain a yellowish powder.

Differential scanning calorimetry (DSC)

The glass transition temperature of the polymer was recorded with Perkin-Elmer DSC 7 instrument (Perkin
Preparation of polymer coatings

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<table>
<thead>
<tr>
<th>Table 1</th>
<th>Concentration of initiator and chain transfer agent used during preparation of terpolymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymer</td>
<td>Initiator* (mol%)</td>
</tr>
<tr>
<td>MMA/HEMA/1 (60:19:21)</td>
<td>0.068</td>
</tr>
</tbody>
</table>

*Initiator: tert-butyl peroxybenzoate (Trigonox™; Akzo, Deventer, The Netherlands).
†Chain transfer agent: 2-mercaptoethanol (Janssen Chimica, Boeerek, Belgium).
‡Molar fraction.

Elmer Inc., USA) and argon as gas carrier. Indium was used for temperature and heat of fusion calibration. Each time approximately 10 mg of material was run at 10 K min⁻¹. The data were abstracted from the second heating scan run.

Gel permeation chromatography (GPC)

GPC was used to measure the number-average molar mass (Mₙ) and the weight-average molar mass (Mₘ) of the terpolymer. GPC was performed using Waters apparatus (Millipore Corp., Milford, MA, USA) composed of: pump model 510; WISP III; equipped with 10⁵, 10⁶, 10⁸ µ-Styrigel (Alltech, Deerfield, IL., USA) columns (Shodex KF 80 M 2 x, 40°C). The GPC measurements were determined independently by UV (UV 440, ambient conditions) and calibrate with monodisperse polystyrene. Tetrahydrofuran (THF) was used as a mobile phase at a flow rate of 1.0 ml min⁻¹.

Nuclear magnetic resonance (NMR)

One-dimensional ¹H and ¹³C NMR spectra were recorded at ambient temperature on Bruker AM 500, or Bruker AM 400 systems (Bruker Analytische Messtechnik, Rheinstetten, Germany). Solvents were CDCl₃ for monomer, and deuterated dimethyl sulphoxide (d₆-DMSO) for polymeric materials.

Elemental analysis

Elemental analyses (C, H, I) were performed by Galbraith Laboratories, Knoxville, TN, USA.

Scanning electron microscopy (SEM)

Polymer-coated glass coverslips were incubated with platelet-rich plasma (PRP) at 37°C for half an hour. The coverslips were rinsed with a saline buffer and treated with 2.5% glutaraldehyde in 0.1 M phosphate buffer at 4°C overnight. The samples were taken out, rinsed with 0.1 M phosphate buffer, dehydrated in ethanol and dried by the critical point. The dried samples were coated and subjected to scanning electron microscopic observations using a Philips 505 SEM system (Philips, Eindhoven, The Netherlands).

Preparation of polymer coatings

Coverslips were cleaned by immersing them in chromic acid at room temperature for 1 h, rinsed with demineralized water several times to remove residual chromic acid, and then with isopropanol for 30 min. The coverslips were dried under vacuum at 50°C overnight, and the samples were stored in a desiccator.

Solution of (10%) polymer was dissolved in dry DMF, and transferred to a clean flask after filtration of the solution. Polymer coatings were prepared by casting polymer onto glass coverslips.

Thrombin generation tests were performed on circular coverslips, one side coated (d = 22 mm). Contact-angle measurements were done on square coverslips, both sides coated (20 x 20 mm).

Blood compatibility

Polymer-coated glass coverslips were subjected to in vitro thrombin generation test procedure. Thrombin is an enzyme which plays an important role in coagulation and platelet reactions. Blood was collected from a healthy donor and mixed with 0.13 M sodium citrate solution in a 9:1 v/v ratio. Coagulation is avoided by the complexation of citrate with Ca²⁺ in blood. The solution is centrifuged at two different speeds, the first one at 900 r.p.m. (15°C, 15 min) and the second one at 10 000 r.p.m. (15°C, 15 min). The polymer surface is put in contact with the inactivated plasma for 15 min under continuous shaking. The test starts when Ca²⁺ ions are added. Samples taken at timed intervals are mixed with chromogenic substrate S2238 (H-D-Phe-Pip-Arg-pNA, Kabivitrum, Stockholm, Sweden) which initiates thrombin-catalysed cleavage of S2238 into p-nitroanilide and the constituent trimeric oligopeptide. The rate of formation of p-nitroanilide was measured photomerically at 405 nm.

RESULTS AND DISCUSSION

Synthesis

Compound 1 was prepared from 2-hydroxyethyl methacrylate (HEMA) and 4-iodobenzoic acid in a standard esterification reaction (Scheme 1). The reaction was run in the presence of dicyclohexycarbodiimide (DCC)`. Compound 1 was obtained in pure form after several washing steps, and column chromatography using silicagel as the stationary phase. The title terpolymer was prepared in a solution polymerization reaction. Mercaptoethanol, a chain transfer agent, was added in order to control the average molecular weight and the average molecular weight distribution. The reaction vessel was immersed in an oil bath, interfaced with a programmable time-temperature control system. The time-temperature profile as depicted in Figure 1 was then run. The polymeric material was obtained after precipitation in water and repeated washing with ether. Lyophilization from water finally afforded the polymer as a slightly yellowish powder.

![Scheme 1](https://example.com/mdi1.png)

**Scheme 1** 1+N,N'-dicyclohexyl usea
Table 2 Results from gel permeation chromatography of the terpolymer

<table>
<thead>
<tr>
<th>MMA/HEMA/1</th>
<th>$M_w$ (kg mol$^{-1}$)</th>
<th>$M_n$ (kg mol$^{-1}$)</th>
<th>$M_w/M_n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>43.1</td>
<td>7.92</td>
<td>5.44</td>
<td></td>
</tr>
</tbody>
</table>

Characterization

DSC measurements showed a glass-transition temperature of 79°C. The weight average molar mass ($M_w$) and number-average molar mass ($M_n$) of the title terpolymer were measured by gel permeation chromatography (GPC; Table 2). Two detection techniques, UV extinction and refractive index, were applied. A set of monodisperse PS samples was used for calibration ($M_w$ in the range of $580-6 \times 10^6$ mol$^{-1}$). During the number of polymerizations we have executed, we noticed that $M_w$ of the product is especially sensitive to the concentration of the chain transfer agent [CTA]. The terpolymer we investigated in this study was prepared with [CTA] = 0.68 mol/100 g. The resulting product completely dissolved in DMF and in THF; GPC indicated $M_w = 43.1$ kg mol$^{-1}$. In another experiment, we executed the polymerization with [CTA] = 0.2 mol%; all other parameters were unchanged. This yielded a polymer which proved to be only partially soluble in DMF or THF, even upon prolonged heating. This indicates that $M_w$ exceeds the values of 43.1 kg mol$^{-1}$.

*The concentration of CTA is expressed as the ratio with respect to the other building blocks in the polymer: [CTA] = (mmol of CTA)/(mmol of HEMA + mmol of MMA + mmol of 1) $\times$ 100%.

Evidently, it was not possible to measure $M_n$ for this material. It is of interest to note that these observations contrast with data in the literature, which focussed on copolymerization of MMA, HEMA and other acryl iodine-containing monomers (i.e. triiodophenyl methacrylate or the orthalamic ester of HEMA)4-5. According to those reports, only low-molecular-weight products are formed4-5. We observed that transparent glassy materials with high $M_n$ can be made, provided that purification of all ingredients is executed judiciously. Furthermore, a one-dimensional 500 MHz $^1$H-NMR spectrum of the polymer in $d_6$-DMSO was recorded. Expansions of this spectrum are shown in Figure 2. The subspectra clearly reveal all the constituents in the polymer. This is especially clear for the protons of the 4-iodobenzoic acid groups, which appear as broadened signals at 7.9 and 7.7 p.p.m. Integration of these signals and comparison with the integrals in the subspectra (e.g. the methoxy group at 3.55 p.p.m. and the methyl groups attached to the main chain between 1.0 and 0.7 p.p.m.) confirmed that approximately 21 mol% iodine-containing building block was chemically incorporated in the material. Interestingly, the $^1$H-NMR spectrum also shows the presence of residual monomer traces (e.g. sharp peaks 7.82 and 7.6 p.p.m.). It is clear from integration that the content of free monomer in the matrix is less than 1%.

The dynamic contact angle was measured in order to investigate the hydrophilicity/hydrophobicity of the material. In these experiments we used the Wilhelmy plate technique as described by Hogt et al.8-9. The apparatus consists of a very sensitive balance, and the sample (a square glass coverslip coated with the terpolymer on both sides) is hung in a beaker contain-

Figure 2 Subspectra of the 500 MHz $^1$H-NMR spectrum of the terpolymer, dissolved in $d_6$-DMSO. Region A (8.2-7.4 p.p.m.): patterns (i) and (ii) correspond with the aromatic protons of the p-iodophenyl rings in the polymer. Note that small sharp doublets at 7.80 and 7.81 p.p.m., which are due to unpolymerized 1. The content of free 1 is less than 1 mol%, as can be calculated from integration of the signals. Region B (5.2-3.4 p.p.m.): patterns (iii) and (vi) can be ascribed to the methylene groups in the CH$_2$-CH$_2$-OH side-chains of built-in HEMA. Patterns (iv) and (v) are due to the methylene groups in the CH$_2$-CH$_2$. O C(O) p-iodophenyl groups of built in 1. Pattern (vii) is due to the methoxy groups in the MMA building blocks. Region C (2.0-0.2 p.p.m.): pattern (viii) corresponds with the methylene groups in the polymer backbone chain. Pattern (ix) is due to the methyl groups, attached directly to the polymer backbone.
ing ultra-pure water. The samples are dipped in water at constant speed of $11 \text{ mm min}^{-1}$ and the weight of the coverslips is measured as a function of the immersion depth. The receding and advancing contact angles ($\theta$) are obtained by extrapolating the plots to zero immersion depth. The contact angles are obtained from the so-called Young's law formula:

$$\cos(\theta) = \frac{(m - m_0)g}{p \cdot \gamma}$$

where:
- $\theta$ is the contact angle,
- $m_0$ is the weight of the wet sample,
- $m$ is the weight of the dry sample,
- $p$ is the perimeter,
- $g$ is the gravitational constant, and
- $\gamma$ is the surface tension of water $(72.6 \times 10^{-3} \text{ N m}^{-1})$.

The results of these measurements are summarized in Table 3.

Comparison of these data with literature on polymethyl methacrylate (PMMA), for which an advancing (receding) contact angle of $73^\circ$ ($39^\circ$) has been reported, it can be concluded that our polymer is more hydrophilic than PMMA. This is what we expected, since our polymer contains 19 mol% of hydrophilic HEMA.

**Haemocompatibility**

The terpolymer was subjected to the in vitro thrombin generation assay as developed by Lindhout et al. This test can be used to obtain a valuable first impression of the thrombogenicity of foreign surfaces. We used a single-side film coating on circular glass coverslips in the assay (see Materials and methods for details). The principle of the test is that contact between blood plasma and the foreign surfaces leads, after a lag phase, to the generation of thrombin. The duration of the lag phase designated the clotting time, is a measure of the thrombogenicity. It should be noted that clotting times are slightly donor-dependent. Typically, polyethylene, which is quite thrombogenic, has a clotting time of approximately 300 s. The more passive polyvinyl chloride (PVC) usually has a clotting time of around 600 s.

The thrombin generation test on our terpolymer first provided the graphs of Figure 3a in which the experimental parameter $dE/dt$ is plotted against experimental time ($\lambda = 405 \text{ nm}$). These curves were analysed for the amount of free thrombin according to the method of Hemker et al. The resulting profiles of free thrombin concentration versus time are shown in Figure 3b.

**Table 3** Results from contact-angle measurements

<table>
<thead>
<tr>
<th>Material</th>
<th>Contact-angles ($^\circ$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Advancing</td>
</tr>
<tr>
<td>MMA/HEMA/1</td>
<td>86.2 ± 2.3</td>
</tr>
<tr>
<td>Glass</td>
<td>72.9 ± 0.5</td>
</tr>
</tbody>
</table>

Figure 3 a, Experimental curve, e.g. $d(E)/dt$ (arbitrary unit) against time. The residual amidolytic activity at the end of the experiment (time > 15 min) is due to the $\alpha_{2}$-thrombin complex. b, Thrombin concentration as a function of time; a correction for the amidolytic activity of the $\alpha_{2}$-thrombin complex was performed according to the procedure of Lindhout et al. Typically, polyethylene, PVC-T, terpolymer (experiment in triplicate).

In another set of experiments, the terpolymer (coated on glass) was incubated with PRP for half an hour at 37°C. After staining (see Materials and methods for details), the surface was examined by scanning electron microscopy (SEM). A detailed micrograph is shown in Figure 4.

From the overall picture, it could be concluded that approximately 10% of the surface was covered with platelets. Most of them, but not all, were spread. Figure 4 illustrates the morphology of some adhered platelets. The SEM results indicate that the surface of the terpolymer leads only to moderate activation of platelets. The few adhered platelets show marked affinity for the surface as is evidenced by their considerable spreading.

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CONCLUSIONS

The terpolymer studied in this work actually represents a whole family of analogous radiopaque polymers. Firstly, it must be realized that a variety of other iodine-containing acrylic monomers can be prepared to replace 1. Secondly it is clear that the ratio MMA:HEMA:1 can be chosen to be different from 60:19:21 as was used by us. We found, however, that at least approximately 20 mol% of 1 must be used to ensure good X-ray visibility. Evidently, this percentage could be decreased substantially by using acrylic monomers containing 2, 3 or more iodine atoms per molecule.

We believe that macromolecules as described above can be prepared rather easily according to our present method. This is in contrast to other reports in the literature which state that only low-molecular-weight products are obtained upon copolymerization of tridiphenyl methacrylate or iothalamic ester with HEMA and/or MMA.

Our present results indicate that this class of radiopaque polymers offers interesting possibilities with respect to applications as biomaterials. Implants constructed of these materials can be easily located using standard imaging techniques based on X-ray absorption. Figure 5 illustrates this point. Two drawn fibres (a and b), made of the terpolymer studied in this work, were glued on a sheet of paper. Fibres c and d are controls, composed of 80% MMA and 20% HEMA (i.e. not radiopaque). The sheet was placed on an X-ray fluorometer, at the position of the patient's chest. X-ray absorption due to the patient's body was applied via a 15 cm thick layer of Plexi glass. As can be seen from Figure 5, the two fibres made out of the radiopaque terpolymer are clearly visible with this set-up.

Our intention is to evaluate further the possible utility of this type of radiopaque polymer as a biomaterial. In particular, we feel that these materials can be of importance with respect to the construction of a new type of endovascular stent. A stent is a scaffolding device used to provide local mechanical support to a damaged blood vessel. The stent is introduced via a lead catheter, and expanded at the desired location. The use of stents is particularly important in conjunction with percutaneous transluminal coronary angioplasty (PTCA, also known as Dottering). The efficacy of PTCA is seriously hampered because of so-called restenosis, i.e. renewed closure of the blood vessel after PTCA. Restenosis occurs with an incidence of approximately 30% in the first six months after PTCA. In many cases, the occurrence of restenosis is the major indication for the use of a stent. Current practice is limited to metallic stents. Some variants are composed of stainless steel (e.g. the Palmaz-Schatz balloon expandable stent, Johnson & Johnson, New Brunswick, NJ, USA), and others are made of tantalum (e.g. the Wiktor stent, Medtronic, Minneapolis, Minn, USA). The advantage of tantalum is its excellent X-ray visibility. The major disadvantage of metallic stents is their relatively poor biocompatibility. The metal-blood contact, in particular, gives rise to coagulation with the risk of reclosure of the lumen at the site of the stent. For this reason, there is a clear trend away from metallic stents toward...
We feel that a polymeric material such as the terpolymer studied in this work offers the possibility to achieve the unique combination of: (a) improved biocompatibility in comparison with metallic stents, and (b) excellent X-ray visibility. Work aimed at constructing stent prototypes on the basis of radiopaque polymers with optimized biocompatibility features is currently going on in our laboratories.

ACKNOWLEDGEMENTS

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