Biocompatible X-ray opaque polymers for medical devices

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Abstract

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During coronary catheterization X-ray imaging is used to image the coronary artery system. After the procedure X-ray imaging may be used to locate devices purposely left in the patient. The objective of this thesis was to investigate the possibility of improving X-ray opacity to medical devices made by St Jude Medical Systems AB. Two different routes were explored, inorganic-organic hybrid materials and functionalization of polymers with iodine. Sol-Gel synthesis was used to synthesize nanocomposite hybrid materials with TiO$_2$ and Ta$_2$O$_5$. Iodine was incorporated by the use of an iodine containing initiator and by end group functionalization with triiodobenzoic acid. The materials were evaluated by X-ray imaging, Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), Thermal Gravimetric Analysis (TGA) and Scanning Electron Microscopy (SEM). The optical and mechanical properties were evaluated by visual inspection and by handling of the materials. Hybrid materials with Polydimethylsiloxane (PDMS) or Poly ester copolymers and Ta$_2$O$_5$ were found to have promising mechanical properties and degree of X-ray opacity. Iodinated polyesters with ~18 wt% iodine also demonstrated sufficient properties to promote further investigation. Some of the work done and obtained results has been excluded from this report due to patent applications.
Sammanfattning

Biokompatibla röntgensynliga polymerer för medicintekniska applikationer
Karin Törne

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List of abbreviations

CL – Caprolactone
DCC – Dicyclohexylamino pyridine
DLLA – DL- Lactic acid
DMAP - Dimethylamino pyridine
DSC – Differential Scanning Calorimetry
EDX – Energy Dispersive X-ray spectrometry
EGF – End Group Functionalization
FTIR – Fourier Transform Infrared Spectroscopy
GA – Glycolic acid
ICP-SFMS – Inductively Coupled Plasma – Sector Field Mass Spectroscopy
IR – Infrared
LA – Lactic acid
PCL – Polycaprolactone
PDMS – Polydimethylenesiloxane
PGA – Polyglycolicacid
PLA – Polylacticacid
PTMC – Polytetramethylene carbonate
PU – Polyurethane
PUU – Polyurethane urea
ROP – Ring Opening Polymerization
SEM – Scanning Electron Microscope
STEM – Scanning Transmission Microscopy
TGA – Thermal Gravimetric Analysis
THF – Tetrahydrofuran
TIBA – Triiodibenzoic acid
UV – Ultra Violet
1 Background

1.1 Coronary Catheterization

Coronary catheterization is a minimally invasive procedure used to identify coronary artery disease as well as coronary lesions such as thrombosis\(^1\).

St Jude Medical Systems AB manufactures a pressure wire for coronary catheterization to measure the blood pressure in the coronary arteries before and after a stricture. The pressure after the stricture relative to the pressure before the stricture is called the Fractional Flow Reserve and gives an absolute number of the severity of the stricture. This provides better guidance, than visualization, for the physician when deciding whether it needs to be treated or not\(^2\).

During the procedure, 1-2 h, the patient lies on a radiolucent table and an imaging camera and X-ray source move separately on opposite sides of the patient chest. Typically the pressure wire is inserted into the femoral artery and guided through the main artery system to the heart. It is critical that the exact location of the pressure sensor at the tip of the wire is known when the blood pressure is measured. This is done by fluoroscopy i.e. images taken using X-ray absorption as contrast\(^3\).

After the procedure is completed and the guide wire is removed pressure is applied on the entry point of the blood vessel by hand or with a closure device to prevent blood lost\(^1\). FemoSeal is a St Jude Medical Systems product developed for this purpose. The seal consist of two disks clamped together on either side of the vessel wall. The disks are made of biodegradable polymers and are degraded after 3-6 months. However the procedure may need to be repeated within this timeframe. It is then important to avoid puncturing the seal when introducing the pressure wire again.

Introducing radiopacity to the seal would facilitate locating the seal prior to repeating the procedure.

1.2 Aim of thesis

The scope of this master degree project was to evaluate new radio opaque materials with potential use as coating for guide wires and cardiac surgery products. It is self-explanatory that all considered materials should be biocompatible and sterilization compatible.

For the closure device the material should be sufficiently radio opaque for imaging, sufficiently flexible to seal the puncture and degrade without formation of toxic byproducts. It should also have a biological degradation time of more than 3 months.

The radio opaque coating should provide sufficient X-ray visibility whilst having enough flexibility and adherence to the substrate. Today a 76 \(\mu\)m thick platinum alloy wired cable is used on the pressure wire. The radio opacity of the investigated material should ideally be as good or better.

1.3 Bio- and Hemocompatibility

Due to the complexity of the host response to a foreign material the concept of biocompatibility is under ongoing debate in the scientific community. In the classical case it is defined as “the quality of not having toxic or injurious effect on biological systems”\(^3\). This definition however does not take into
account applications where a particular response is desired. This lead to the definition proposed by Williams “Biocompatibility refers to the ability of a material to perform with an appropriate host response in a specific situation” Critique against this definition claims that it is too unspecified and not of any help to find further knowledge of biocompatibility

A number of the possible reactions of the host to a material are listed in Table 1. The extent to which these reactions occur depends largely of the properties of the material listed in Table 2. But factors such as host age, gender, general health etc as well as the quality and nature of the clinical intervention have a great influence as well.

Table 1 Possible host responses to foreign materials

| Protein adsorption and desorption characteristics |
| Complement activation |
| Platelet adhesion, activation and aggregation |
| Activation of intrinsic clotting cascade |
| Neutrophil activation |
| Fibroblast behavior and fibrosis |
| Microvascular changes |
| Macrophage activation, production of foreign body giant cells |
| Endothelial proliferation |
| Antibody production |
| Acute hypersensitivity / anaphylaxis |
| Delayed hypersensitivity |
| Genotoxicity / reproductive toxicity |
| Tumor formation |

Table 2 Material properties affecting the host response

| Bulk material composition, microstructure and morphology |
| Crystallinity and crystallography |
| Elastic constants, compliance |
| Surface chemical composition, chemical gradient, molecular mobility |
| Surface topography and porosity |
| Water content, hydrophobic-hydrophilic balance |
| Corrosion parameters, ion release profile, metal ion toxicity |
| Polymer degradation profile, degradation product toxicity |
| Leachables, catalyst, additives, contaminants |
| Wear debris release profile |
| Sterility and endotoxins |

For blood contacting applications with a short exposure time attention should be paid to the hemocompatibility of the surfaces such as thrombotic properties and platelet adhesion. Immediately upon insertion proteins adsorbs on the surface forming a provisional matrix. This matrix consists of fibrin, produced by activation of the coagulative and thrombosis system and inflammatory products released by the complement system, activated platelets, inflammatory cells and endothelial cells. Under normal conditions thrombosis is a favorable process, preventing blood loss from injuries. However, when it is caused by contact of a biomaterial blood clot formation and the subsequent risk of stroke, heart attack or pulmonary embolism is a highly adverse outcome.
1.4 Radiopacity

The process for X-ray absorption is similar to that of visible light or UV-radiation. The difference is in photon energy. Visible light (400 – 700 nm) has photon energies of 1.77 – 3.10 eV were as X-rays are commonly defined as having photon energies in the range of 100 eV - 100keV.

It is possible to calculate the ratio of the intensity transmitted through a sample to the incident intensity using the exponential attenuation law\(^1\), (equation 1). In chemical spectroscopy this law is known as Beer-Lamberts law\(^1\).

\[
\frac{I}{I_0} = \exp\left(-\frac{\mu}{\rho} x\right)
\]

(1)

Where \(I\) is the transmitted intensity, \(I_0\) the incident intensity and \(\rho\) [g/cm\(^3\)] is the density of the sample. \(X\) is the sample mass thickness, calculated as density*thickness [g/cm\(^2\)]. Finally \(\mu\) is the linear attenuation coefficient [cm\(^{-1}\)] which is dependent of the wavelength of the incident light and the cross section, \(\sigma\), of the material.

1.4.1 The cross section

The cross section is an estimate of the likelihood of interaction between the photon and the atoms in the material. It has a linear relationship with the attenuation coefficient\(^1\), (equation 2).

\[
\mu \propto \sigma
\]

(2)

\(\mu/\rho\) [cm\(^2\)/g] is called the mass attenuation coefficient. For a given X-ray energy it varies very little for different materials. Thus \(\mu\), and \(\sigma\), is highly dependent on the density of the material.

The total cross section consists of contributions from different types of interactions between the X-rays and the material, (equation 3).

\[
\sigma_{\text{tot}} = \sigma_{\text{pe}} + \sigma_{\text{coh}} + \sigma_{\text{incoh}} + \sigma_{\text{pair}}
\]

(3)

\(\sigma_{\text{pe}}\) is the cross section from the photoelectric effect. In this process the energy of the radiation is transferred to the atomic electrons which are emitted as photoelectrons, followed by relaxation of the system. (Figure 1a)

The photoelectric cross section increases with increasing atomic number, \(Z\), by the power of 4. The best X-ray absorbers are therefore found in the fifth and sixth period of the periodic table\(^1\). For photon energies lower than the rest energy of the electron, 511 keV, the photoelectric absorption is the dominant component of the total cross section\(^1\). For example at 3.98 keV \(\sigma_{\text{pe}}/\rho\) of Tantalum is 886 cm\(^2\)/g whereas \(\sigma_{\text{coh}}/\rho + \sigma_{\text{incoh}}/\rho\) is 8.61 cm\(^2\)/g.\(^12\)
$\sigma_{coh}$ and $\sigma_{incoh}$ are the coherent and incoherent scattering cross sections resulting from the interactions between the X-rays and the atomic electrons. When a charged particle, i.e. electrons, is subjected to electromagnetic radiation it starts to vibrate, and in turn emits electromagnetic radiation. If the vibrations are at the same frequency as the incident radiation the emitted radiation will have the same energy and the scattering will be coherent. This is the origin of X-ray diffraction. On the other hand, if the energy is not preserved the resultant scattering will be incoherent. All elements scatter X-rays regardless if the photoelectric effect is possible. However heavier elements, with more electrons, scatter more.

In the electron pair production $\sigma_{par}$ the photon interacts with the atomic nucleus to create an electron - positron pair. This event however only takes place at energies higher than $1.02 \text{ MeV}$ and is therefore not significant for this thesis.

### 1.4.2 The photon energy

Other than being dependent on the atomic number and density of the sample the mass attenuation coefficient is also dependent on the incident photon energy\textsuperscript{10}. The penetrating power of the X-ray beam varies approximately with the reciprocal of the photon energy to the power of 3. Due to the discrete energy distribution of atomic electrons there will be a sudden decrease of $\mu$ when the incident photon energy drops below the binding energy of an electron shell. These drops are known as absorption edges. (Figure 1b) For example the K shell electrons in Kr have a binding energy of 14.32 keV. Hence photons with higher energies have a possibility of removing a K shell electron and photons white lower energies have not. The K edge of a Kr spectrum consequently appears at 14.32 keV\textsuperscript{10}.

### 1.4.3 Quantification of X-ray absorption

The ability of a biomaterial to shield X-rays can be quantified in a number of ways according to ASTM standards\textsuperscript{13, 14}. The objective is to evaluate the likelihood of locating the object within the human body. The difference in optical density (the logarithm of the ratio of the indecent light to the transmitted light) between the sample and the background can be compared. A sufficient difference is 0.8-1.2. A second method is to compare the sample image with a standard piece simulating the
device. The contrast between the background the sample should be the same as for the simulating piece. In a third method the sample image is compared to the image of a slab of a specific thickness. As practice Aluminum is used as slab material. The comparisons in all three methods can be done either qualitatively or by quantitatively by measuring optical density or pixel intensity. A body mimic can be used in order to determine the viability of the sample inside the body. This may be an aluminum sheet, a part of a human or animal cadaver, a metal, plastic or ceramic material with appropriate dimensions.

1.5 Materials

1.5.1 Radiopaque inorganic materials

As written above, the best X-ray absorbers are found in fifth and sixth period in the periodic table. Out of these polonium and astatine are unstable. Thallium, mercury and lead are highly toxic. Mercury and cesium liquid at room temperature or just above. This excludes them as possible coating material. The properties of the remaining elements are presented in Table 3.

Table 3 Some properties of the elements in the sixth period.

<table>
<thead>
<tr>
<th>Atomic number</th>
<th>Mass attenuation coefficient* (cm⁻¹)</th>
<th>Biocompatibility</th>
<th>Mechanical properties</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ba</td>
<td>56</td>
<td>8.511</td>
<td>No**</td>
<td>reacts with air, commonly used as BaSO₄</td>
</tr>
<tr>
<td>Hf</td>
<td>72</td>
<td>3.420</td>
<td>Yes</td>
<td>ductile Chemically similar to Zr, corrosion resistant</td>
</tr>
<tr>
<td>Ta</td>
<td>73</td>
<td>3.569</td>
<td>Yes</td>
<td>ductile corrosion resistant</td>
</tr>
<tr>
<td>W</td>
<td>74</td>
<td>3.569</td>
<td>Yes</td>
<td>ductile at high purity brittle with small impurities</td>
</tr>
<tr>
<td>Re</td>
<td>75</td>
<td>3.872</td>
<td>Yes</td>
<td>ductile when annealed one of the rarest elements, expensive</td>
</tr>
<tr>
<td>Os</td>
<td>76</td>
<td>4.002</td>
<td>Yes***</td>
<td>hard and brittle the densest of all elements, difficult to machine</td>
</tr>
<tr>
<td>Ir</td>
<td>77</td>
<td>4.176</td>
<td>Yes</td>
<td>hard and brittle very rare, difficult to machine</td>
</tr>
<tr>
<td>Pt</td>
<td>78</td>
<td>4.339</td>
<td>Yes</td>
<td>ductile Noble metal, expensive</td>
</tr>
<tr>
<td>Au</td>
<td>79</td>
<td>4.529</td>
<td>Yes</td>
<td>the most ductile metal noble metal</td>
</tr>
<tr>
<td>Bi</td>
<td>83</td>
<td>5.233</td>
<td>Yes</td>
<td>brittle the lest toxic heavy metal</td>
</tr>
</tbody>
</table>

*Mass attenuation coefficient at 60 keV incident beam energy  
**Ba in its elemental form is highly toxic; BaSO₄ however is inert and commonly used as a contrast agent.  
***Os forms a toxic oxide OsO₄

Hafnium, tantalum, platinum and gold are the most suitable metals. They are all used as biomaterials; they are ductile, corrosion resistant and have a high degree of radiopacity. However simple metallic coatings on stainless steel are associated with some problems. Inability of the coating to follow substrate deformation may induce cracking and corrosion may cause metal ions to be released that may be toxic or cause allergic reactions.²⁵,²⁶
1.5.2 Radiopaque polymers

The problems with inorganic material makes an elastic X-ray opaque coating desired to prevent cracking. Biocompatible organic polymers such as polyurethanes (PU), poly caprolactone (PCL), poly glycolic acid (PGA) and poly dimethylsiloxane (PDMS) all have excellent elastic properties. Polymers however consist mostly of carbon, oxygen and hydrogen and have therefore little X-ray contrast against body tissue. Consequently the combination of the mechanical properties of organic polymers and the radiopacity of fifth and sixth period elements is of great interest.

A material consisting of two phases, one organic polymer and one inorganic, provides the possibility of combining mechanical, optical, electrical or magnetic properties otherwise impossible to achieve. A hybrid material of a heavy metal salt and a biocompatible elastic polymer can be both radiopaque and have the required mechanical properties. Depending on the type of interaction between the phases inorganic-organic hybrid materials can be categorized in two groups. Type I hybrid material have only week Van deer Waal or hydrogen bonds. Type II has stronger chemical bonds connecting the two phases\textsuperscript{17}.

Type I hybrids can easily be synthesized by simply mixing a fine powder of inorganic material with an organic polymer (Figure 2a). This can be done either with the polymer or the monomer prior to polymerization\textsuperscript{18}. The inorganic phase can be pure metal\textsuperscript{19}, a ceramic material e.g. bariumsulphate or zirconium dioxide\textsuperscript{20-23} or an organic – metal compound\textsuperscript{22, 24}. However, due to the incompatible natures of the two phases the risk of separation is high and a leakage of heavy metal salt into the body may be damaging to the patients health. The inorganic phase also weakens the mechanical properties of the polymer, so there is a limit to the inorganic content\textsuperscript{19, 22, 25}. As coating materials these hybrids also show poor adhesion to stainless steel\textsuperscript{19}.

Figure 2 a) type I hybrid made from dissolved particles in a polymer. b) A type II hybrid made from \textit{in situ} grown particles.
1.5.2.1 Sol-Gel synthesis

By using sol-gel synthesis it is possible to create highly homogeneous hybrids consisting of two nanosized interpenetrating networks; one organic and one inorganic, (Figure 2b).

Sol-gel is a commonly used synthesis method for metal oxides. At ambient temperature metal alkoxides are hydrolyzed into a sol and then condensed to a gel.

The hydrolysis step creates reactive hydroxy groups.

\[ \text{M-OR} + \text{H}_2\text{O} \rightarrow \text{M-OH} + \text{ROH} \]

The hydroxy groups can react further by two mechanisms to create an inorganic network.

a) Oxolation, the creation of an oxygen bridge
\[ \text{M-OH} + \text{M-OX} \rightarrow \text{M-O-M} + \text{HOX (X= H or R)} \]

b) Olation, the formation of a hydroxo bridge
\[ \text{M-OH} + \text{OH-M} \rightarrow \text{M-(OH)}_2\text{-M} \]

The low processing temperature allows for organic polymers to be incorporated. They can be added as polymers, or as the corresponding monomer during or after the hydrolysis-condensation reaction. The inorganic phase will be present as nanometer sized clusters, the exact size and structure of which is determined by the rate of the different chemical reactions involved.

The rate of the hydrolysis step is determined by the reactivity of the alkoxide. This in turn is determined by the electronic nature of the metal and the steric hindrance of the alkoxy groups. Si hybrids are of vast interest for the semiconductor industry and have been thoroughly investigated. Silicon alkoxides are inert to hydrolysis and a catalyst is usually added. Transition metal alkoxides are more reactive and inhibitors such as strong complexing ligands (b-diketonates, acid derivatives, etc) or inorganic acids are used to control the reactivity. Another method is to add water to the hydrolysis step, and instead cure the hybrid using the moisture in the air.

For synthesis of hybrid materials of class II the alkoxide needs to possess at least two distinct functionalities, alkoxy group (R-OM bonds available to hydrolysis leading to the formation of an oxopolymer framework) and metal to carbon links that are stable during the hydrolysis. For Si, Sn, Hg or P the C-M bond is stable. For transition metals this is not the case and the link between the inorganic and organic phases can be an M-O-C bond that is stable upon hydrolysis.

1.5.3 Inorganic-organic hybrid materials for medical applications

Hybrid materials of biocompatible organic – inorganic materials have been investigated to combine desired mechanical properties and radiopacity for a number of applications. Examples include coating of dental implants, stents and bone implants.

1.5.3.1 PDMS

Poly DimethylSiloxane (PDMS) is a suitable polymer for blood contacting applications due to its highly hydrophobic nature. Moreover it is a completely amorphous polymer and is therefore known to produce highly flexible hybrid materials. Sol-Gel synthesis with Al(OBu)₃, Ti(OEt)₄ and Ta(OEt)₅ as
inorganic precursors and silanol terminated PDMS as organic polymer have been made by Yamada et al. The storage modulus at room temperature was found to increase with increasing valence of the metal ion. The higher valence metal ion bonds with a higher number of silanol chain ends resulting in a tighter 3D network and a less ductile material. The mechanical properties of hybrid sheets from PDMS and Zr(OBu)_4 and Ta(OEt)_5 were also examined by Katayama et al. The mechanical properties of the hybrid materials were greatly influenced by reaction conditions such as acid concentration, inorganic precursor content and the molecular weight of PDMS.

Yakutat et al examined the hemocompatibility of the PDMS-TiO_2 hybrid by partial thromboplastin time, prothrombin time and the amount of fibrinogen. A platelet count was made as well. The sample values measured were close to the blank as well as the uncoated stainless steel surface. For that reason the blood coagulating properties of the hybrid was assessed to be within the allowed range.

The PDMS-TiO_2 hybrid is not very radiopaque but may serve as corrosion protection on a heavy metal coating. Cortecchia et al proposes a two step method for a radio opaque coating. In the first step Ta was sputtered on polypropylene with thicknesses varying from 1-5 μm. A protective layer of either PDMS-TiO_2 or PCL-TiO_2 hybrid was then coated on the Ta surface. The pixel intensity relative to the background increased logarithmically with the Ta layer thickness. By controlling the sputtering time the degree of radiopacity could easily be controlled. To test the mechanical strength of the hybrid layer the sheets were bent by hand and then studied in SEM. In the PCL samples substantial micro cracking was found but in the PDMS samples no evidence of cracking could be seen. PDMS only interact with the inorganic network by the chain ends. This results in a less tightly bound, more elastic network with lower TiO_2 content.

### 1.5.3.2 Polyesters

PCL, PLA, PTMC and PGA are all well known biocompatible biodegradable polyesters. Their non toxicity and controllable degradation time makes them useful materials in a number of biomedical applications such as degradable wound staples and drug delivery devices. PCL PLA and PTMC are also readily used as organic precursor for hybrid materials.

Due to the ester functionalities it is possible to synthesize hybrids with polyester with or without functionalized chain ends. The organic and the inorganic networks connect via transesterification reactions forming interactions between the carboxyl groups and the metal. Figure 5on page illustrates the metal carboxyl interactions.

Tian et al reports on the dynamic mechanical properties of hybrids with PCL and tetraethoxysilane (TEOS) precursors. It was found that the number of functional end groups per polymer chain did not affect the storage modulus; neither did the PCL molecular weight. The inorganic weight content and the curing temperature were found to be the two most important factors affecting the elasticity.

Polyesters are typically polymerized with anionic ring opening polymerization ROP. An example is given in Scheme 1 on page 10. In ROP the driving force is the release of ring strain. Ring strain is caused by bond angle distortion, conformal strain and non bonded interactions in the ring structure.
1.5.3.3 Adherence to metallic surfaces of hybrid materials

To investigate the adherence and scratch resistance of a hybrid material Han et al deposited hybrid coating with precursors TEOS, urethane acrylate and 3-(trimethoxysilyl)propyl with equal thickness to four different substrates; aluminum, brass, stainless steel and nickel. The adherence of the hybrid film was studied with SEM, STEM, and scratch testing. The adherence to Al was found to be better than to stainless steel and brass. The oxide film on Al is most likely hydrolyzed during the sol-gel synthesis and an Al-O-Si bond creates a tightly bound film. The oxides on brass and stainless steel are much less prone to hydrolysis.

1.5.4 Iodinated polymers

An alternative route to increase the radiopacity of organic polymers is the incorporation of iodine or iodine containing molecules. This is a method successfully used with acrylates and methacrylaes.

Covalent bonding of iodine to PCL copolymer backbone with substitution rates of 25 % have been achieved by a two step nucleophilic substitution reaction using Lithiumdiisopropyl amide as a catalyst. High iodine content was however found to decrease the dynamic Young’s modulus (from 60 to 13 mPa) and the biological degradation rate. Iodinated PCL demonstrated weight loss after 25 weeks whereas PCL had no weight loss after 60 weeks.

James et al have imparted radiopacity to polyurethanes. Polyurethanes are used extensively in the medical field employed in heart valves, catheters and vascular stents. Commercially available polyurethane (PU) (Tecoflex) and polyurethane urea (PUU) was rendered radiopaque by reaction with 3,4,5-triiodobenzoic acid and triiodobenzoic chloride. The iodine content of PUU was 8-10 wt% depending on reaction temperature. The iodine content of PU was found to be insufficient and instead five iodine containing molecule, N-(diidocarboxyphenyl)-3,4,5-triiodobenzenamide was used. This resulted in 8 wt% iodine content. In a third method the iodine is added as a chain extender. 4,4’-isopropylidenedi(2,6-diidophenol) was added to the chain ends of PU in a two step synthesis. This procedure yielded 23% iodine in PU.
2 Materials and methods

This section describes the practical work done for this thesis. The object was to synthesize hybrid materials using different organic and inorganic precursors and to polymerize iodinated polyesters with subsequent end group functionalization.

2.1 Materials

\(\varepsilon\)-caprolactone,(CL) were obtained from TCI, DL-lactic acid,(DL_LA) and Trimetylenecarbonate( TMC) were obtained from Boehringer-Ingelheim.

Propanediol, tin(II) ethylhexanoate and Poly(ethylene glycol) \(M_w 1000\), Histodenz (5-(N-2,3-Dihydroxypropylacetamido)-2,4,6-triiodo-N,N\(\bar{N}\)-bis(2,3 dihydroxypropyl)isophthalamide), PDMS viscosity 750 cSt, Titanium isopropoxide, Tantalum ethoxide, Dimethylaminopyridine (DMAP), Dicyclohexylaminopyridine (DCC), Triidobenzoic acid (TIBA) and \(\text{Na}_2\text{HPO}_4\) were obtained from Sigma-Aldrich Co.

\(\text{KH}_3\text{PO}_4\) was obtained from Merck KGaA.

The used suture thread was Lactoprene II, coated multifilament braid from Poly-Med Inc.

2.2 Polymerization reactions

Various polyesters were synthesized using ring-opening polymerizations, ROP. Scheme 1 demonstrates the polymerization of \(\varepsilon\)-caprolactone, CL, as an example of a ROP. The chemical structures of the monomers used are shown in Scheme 2. Tin(II)ethylhexanoate was as catalyst in al polymerization reactions.

\[
\text{HO-CH}_2\text{-CH}_2\text{-OH} + \text{O} \xrightarrow{} \text{O} \xrightarrow{}
\]

Scheme 1 Ring opening polymerization reaction of PCL

a)

b)

c)

Scheme 2 The structure of the monomers (other than CL) used to synthesize polyesters a) GA b) DL-LA c) TMC
2.2.1 General procedure for ring opening polymerization of polyesters

Both homopolymers and random copolymers were fabricated with target molecular weight (Mₘ) 20000 g/mol. A more detailed description is presented in Table 5 on page 15. All glassware was cleaned and dried at 100°C prior to use. In a typical reaction a stoichiometric amount of initiator and 0.2 mol% catalyst was added to 5 to 10 g of monomer in a 20 ml glass vial in a nitrogen atmosphere. The reaction was allowed to proceed at 140 °C over night. The polymer was then dissolved in chloroform, precipitated by dropwise addition of the solution to a medium in which the polymer is not soluble, typically hexane or methanol. The precipitated polymer was then dried in vacuum.

2.2.2 General procedure for synthesis of iodine containing polyesters

In order to incorporate iodine in the polymer back bone Histodenz, (Scheme 3), were used as initiator. Histodenz is a non-ionic, water soluble contrast agent containing six alcohol groups that can act as initiating points for the polymerization. Polyesters of various molecular weights were synthesized according to Table 4. A higher mol% catalyst was usually needed in order to reach a similar polymerization rate. Otherwise the procedure and reaction conditions were the same as above.

![Scheme 3 The Chemical structure of Histodenz, used as an iodine containing initiator.]

2.2.3 End group functionalization (EGF) of iodinated polyesters

To further increase the iodine content of polyesters initiated from Histodenz TIBA was coupled to the hydroxyl chain ends (Scheme 4). In a typical case 1-2 g of polyester and 8 mol% (per mol end group) DMAP was dissolved in dry THF in two separate containers. The DMAP was added to the polymer under nitrogen flow and cooled in an ice bath. In the same way as DMAP 166 mol% TIBA, and 210 mol% DCC was added. The reaction proceeded at ~10°C for roughly 6 hours and then at room temperature over night. The byproduct, Dicyclohexyl urea, precipitated as a white powder during the reaction. After completion it was filtered off. The THF solvent was evaporated and the polymer product was dissolved in chloroform and precipitated in methanol. Analysis of the iodine content of the resulting polymers were evaluated with ICP-SFMS performed by ALS Scandinavia AB.
Table 4 Target molecular weight and monomers ratios for polymerized iodinated polyesters

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Target molecular weight (g/mol)</th>
<th>Monomer molar ratio %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CL</td>
<td>DL-LA</td>
</tr>
<tr>
<td>Hiz1</td>
<td>3000</td>
<td>100</td>
</tr>
<tr>
<td>Hiz2</td>
<td>5000</td>
<td>100</td>
</tr>
<tr>
<td>Hiz3</td>
<td>9500</td>
<td>100</td>
</tr>
<tr>
<td>Hiz4</td>
<td>38000</td>
<td>100</td>
</tr>
<tr>
<td>Hiz5</td>
<td>75000</td>
<td>100</td>
</tr>
<tr>
<td>Hiz6</td>
<td>10000</td>
<td>100</td>
</tr>
<tr>
<td>Hiz7</td>
<td>10000</td>
<td>33</td>
</tr>
<tr>
<td>Hiz8</td>
<td>10000</td>
<td>33</td>
</tr>
<tr>
<td>Hiz9</td>
<td>10000</td>
<td>33</td>
</tr>
</tbody>
</table>

2.3 Synthesis of organic-inorganic hybrid materials

Hybrid materials with TiO₂ or Ta₂O₅ as the inorganic phase and PDMS or the polyesters previously described in section 2.2.1, were used as the organic phase. A more detailed presentation can be seen in Table 8 on page 18.

2.3.1 General procedure for hybrid synthesis

All glassware was cleaned and dried at 100 °C prior to use. In a general case 1 g of polymer was dissolved in 4 to 5 ml solvent in a round bottom flask (solution 1). Under nitrogen atmosphere the metal alkoxide was diluted by twice as much of solvent, (solution 2). When it was necessary 20 mol% of 37% HCl was added in order to control the hydrolysis of the alkoxide. Solution 1 was then added slowly and under stirring to solution 2. The final solution was poured onto a Teflon sheet in a glass Petri dish and covered with a glass lid. Over night the metal alkoxide reacted with the moisture in the air, gelled, and dried to a solid film. In order to remove any remaining solvent and to cure the film it was heat treated for 2 h in 100 °C in an ambient atmosphere.

2.4 Coating of metal wires and suture threads

Both metal wires and suture thread were dip coated with hybrid materials and polyesters.

Tantalum ribbon, 30 microns thick, was spot welded onto stainless steel wires. Both bare and tantalum covered wires were dip coated in the final hybrid solution described in section 2.3.1. The dip coating was done a few hours after the gelling process had started in order for the liquid to be sufficiently viscous.

Suture thread was coated with PCL and PCL hybrids. The braided multifilament was run through a solution of PCL and acetone or the same hybrid solution as the metal wires. A few concentrations between 0.26 and 1.5 g/ml of the PCL solutions were used to achieve different coating thicknesses. The coated suture was air-dried at room temperature to remove the solvent. The resulting coating was visually inspected using a microscope and the general properties of the suture such as flexibility
and smoothness was observed by handling the suture. The amount of coating (g PCL/cm thread) was approximated by weighing the suture before and after the coating. The solutions used were much less viscous than the ones used for coating the metal wires.

2.5 Compression molding

To compare mechanical properties as well as X-ray opacity the synthesized materials were molded into equal shapes and thicknesses.

Both pure polymers and hybrids were compression molded to films with 0.1 or 0.2 mm thickness. The pure polymers were molded at 50°C or lower and the hybrids at 150-170°C. The hybrids with copolymers containing glycolic acid did not melt until 210 °C.

The histodenz containing polyesters were also molded into shape of the inner disk used in FemoSeal.

2.6 Characterization

The materials were characterized by visual inspection and handling to evaluate optical and mechanical properties. Other than that a set of characterization techniques used are described below.

2.6.1 X-ray images

To evaluate the X-ray opacity X-ray images were taken with a Nicolet IS-10X X-ray system. The applied voltage was 70kV. Ideally the potential used during an angiography is 70-80 kV$^1$.

2.6.2 Fourier Transform Infrared spectroscopy (FTIR)

FTIR is a technique to analyze the nature of the chemical bonds present in a compound. In order to study the nature of interactions between the networks in the hybrids materials as well as the composition of the polymers FTIR measurements were made. In FTIR infrared radiation is transmitted through the sample and the intensity before and after is compared as a function of wavelength. The IR radiation is of similar energy as the vibration of chemical bonds in the sample and will be absorbed at specific wavelengths depending on the type of bonds present in the sample$^2$. FTIR-spectra were recorded using an attenuated total reflection assembly on a PerkinElmer Spectrum 100 spectrometer from 4000 to 600 cm$^{-1}$. The force gauge was set to 50 for all samples.

2.6.3 Differential Scanning Calorimetry (DSC)

DSC is used to characterize the thermodynamic properties, such as glass transition ($T_g$) and melting temperatures ($T_m$) and the corresponding enthalpies$^3$ of a material. DSC measures the heat (energy) required to increase the temperature of a sample at constant rate. This is done using a blank (air filled) sample as reference. At certain temperatures endothermic or exothermic changes will increase or decrease the required heat. DSC measurements were done with a PerkinElmer Pyris 6 DCS. Under nitrogen flow (30 ml/min) hybrid samples of 5-10 mg were heated twice to remove the thermodynamic history of the samples. First from -30 °C to 200°C at 10 °C/min followed by cooling to -50°C at 30°C/min. They were then heated to 240°C at 10°C/min and cooled to 30°C. The analysis was
done on the second heating curve. The iodinated polyesters were cooled to -100 °C heated to 100°C cooled to -100°C and heated to 100°C again.

2.6.4 Thermal Gravimetric Analysis (TGA)

The degradation of samples was studied by TGA. The samples were heated and their weight loss was recorded as a function of temperature or time against a reference. The TGA measurements were preformed with a Metler Toledo TGA/DSC Star System. Approximately 4 mg of sample were heated from 40 to 600° C at 10°C/min. A 60 ml/min nitrogen flow was applied.

2.6.5 Scanning Electron Microscopy (SEM)

The microstructure of hybrid samples was studied with an Oxford Instrument INCA X-sight SEM. The samples were scanned with high energy electrons focused by an electromagnetic lens system. Images were obtained from secondary electrons that are emitted from the sample when the electron beam interacts with the surface atoms. At the same time the elemental composition of the sample surface was investigated by Energy Dispersive X-ray Spectroscopy (EDX). This is an analysis technique commonly used together with SEM were X-ray emitted from the sample as a result of the electron beam – surface atom interaction. The energies of the emitted X-rays are equivalent to the electron edges of the atoms. In order to prevent charging effects low vacuum (0.68 torr) was used. The acceleration voltage was 20 kV and the spot size 5.

2.7 Degradation study

The degradation of Hyb 6.1 and 6.2, (see Table 8 on page 18) compared to PD 5(see Table 5 on page 15) in phosphate buffer was studied. The phosphate buffer was prepared according to ISO/DIS 15814 and ISO 13781:1997 standard using KH₂PO₄ and Na₂HPO₄. 4.58 g KH₂PO₄ was dissolved in 500 ml distilled water (solution a) and 9.51 g Na₂HPO₄ was dissolved in 1000 ml distilled water (solution b). 182 ml of solution a was then added to 818 ml of solution b. The buffer pH was 7.4, measured with a Metrohm 744 pH Meter.

Small disks, 4-10 µg were punched out of the hybrids and the precursor polymer. After being dried in vacuum over night the samples were weighed and put into 24-well plates with 2 ml of buffer per sample. They were then stored at 37 °C for 1-4 weeks. Once a week the buffer was exchanged with new buffer and 2-4 samples were collected from each hybrid and polymer. The collected samples were dried in vacuum over night prior to characterization.
3 Results and discussion

In this section the results of the synthesis and characterizations of the different materials are presented and discussed. Some results have been excluded due to patent applications.

3.1 Physical appearance and mechanic properties

3.1.1 Synthesized polyesters

The appearance and the mechanical properties of polyesters synthesized from propanediol are summarized in Table 5 below. PD 5 achieved the best mechanical properties as specified in section 1.2. The white color of some of the polymers indicated a higher degree of crystallinity than the transparent ones. The crystalline volumes of a transparent polymer are not large enough to scatter visible light (400-800 nm)

Table 5 Some properties of the synthesized polyesters

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Initiator</th>
<th>Monomer (molar ratio %)</th>
<th>Appearance</th>
<th>Mechanics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CL</td>
<td>DLA</td>
<td>TMC</td>
</tr>
<tr>
<td>PD1</td>
<td>Propane diol</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD2</td>
<td>Propane diol</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD3</td>
<td>Propane diol</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD4</td>
<td>Propane diol</td>
<td>50</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>PD5</td>
<td>Propane diol</td>
<td>33</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>PD6</td>
<td>Propane diol</td>
<td>33</td>
<td>33</td>
<td>33</td>
</tr>
</tbody>
</table>

3.1.2 Iodinated polyesters

Some properties of polyesters initiated by Histodenz are presented in Table 6. Table 7 features the same polymers after EGF. The iodine induces a yellow/brown color, the intensity of which increases with the amount of iodine. Histodenz have six potential initiation sites and thus produces multiarmed polymers. The potential sites consist of three primary alcohol and three secondary alcohol groups. Since the primary alcohol groups are more reactive than the secondary\(^{24}\) it is not certain that the polymer is six armed. The probability of a monomer reacting with a primary alcohol initiation site is higher and once an arm is started steric hindrance will reduce the probability of reaction between a monomer and a secondary alcohol site even further. The structure will most likely be distribution between 2-6 arms. The multiarmed structure entails slightly more flexible mechanical properties than the analogous linear polymer. The EGF increased this difference further. It is likely that the bulky TIBA end group molecule obstructs crystallization and therefore changes the mechanical properties. Further evidence of this is given by the DSC measurements.
Table 6 Some properties of synthesized iodinated polyesters

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Before functionalization</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Appearance</td>
<td>Mechanics</td>
<td>Iodine wt% cal*</td>
<td>Iodine wt% exp**</td>
<td>ΔH</td>
</tr>
<tr>
<td>Hiz1</td>
<td>yellow</td>
<td>Soft</td>
<td>9,97</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hiz2</td>
<td>light yellow</td>
<td>hard fragile</td>
<td>6,54</td>
<td>-</td>
<td>57</td>
</tr>
<tr>
<td>Hiz3</td>
<td>white</td>
<td>hard fragile</td>
<td>3,68</td>
<td>3.23</td>
<td>61</td>
</tr>
<tr>
<td>Hiz4</td>
<td>white</td>
<td>hard fragile</td>
<td>0,98</td>
<td>0.93</td>
<td>58</td>
</tr>
<tr>
<td>Hiz5</td>
<td>white</td>
<td>soft weak</td>
<td>0,5</td>
<td>0.53</td>
<td>55</td>
</tr>
<tr>
<td>Hiz6</td>
<td>yellow</td>
<td>very soft</td>
<td>3,5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hiz7</td>
<td>white</td>
<td>soft elastic</td>
<td>3,5</td>
<td>2.73</td>
<td>-</td>
</tr>
<tr>
<td>Hiz8</td>
<td>light yellow</td>
<td>soft glutinous</td>
<td>3,5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hiz9</td>
<td>white</td>
<td>soft tough</td>
<td>3,5</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Calculated assuming 100% polymerization  
** Iodine content analyzed with ICP-SFMS by ALS Scandinavia

Table 7 Some properties of synthesized iodinated polyesters after EGF

<table>
<thead>
<tr>
<th>Polymer</th>
<th>After functionalization</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Appearance</td>
<td>Mechanics</td>
<td>Iodine wt% cal*</td>
<td>Iodine wt% exp**</td>
<td>ΔH</td>
</tr>
<tr>
<td>Hiz 2</td>
<td>brown</td>
<td>soft weak</td>
<td>45,78</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hiz 3</td>
<td>light brown</td>
<td>hard fragile</td>
<td>25,76</td>
<td>17.5</td>
<td>43</td>
</tr>
<tr>
<td>Hiz 4</td>
<td>light brown</td>
<td>hard fragile</td>
<td>6,86</td>
<td>6.69</td>
<td>50</td>
</tr>
<tr>
<td>Hiz 5</td>
<td>white</td>
<td>soft weak</td>
<td>3,5</td>
<td>4.06</td>
<td>47</td>
</tr>
<tr>
<td>Hiz 6</td>
<td>light brown</td>
<td>soft weak</td>
<td>24,5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hiz 7</td>
<td>light brown</td>
<td>soft elastic</td>
<td>24,5</td>
<td>18.2</td>
<td>-</td>
</tr>
<tr>
<td>Hiz 8</td>
<td>light brown</td>
<td>soft elastic</td>
<td>24,5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hiz 9</td>
<td>light brown</td>
<td>soft tough</td>
<td>24,5</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Calculated assuming 100% substitution and 6-armed polymers  
** Iodine content analyzed with ICP-SFMS by ALS Scandinavia

3.1.2.1 DSC of iodinated polyesters

The heat of fusion ΔH was lower after EGF for all samples. The difference of ΔH before and after EGF increased with increasing TIBA content and Hiz2 (with the highest TIBA content) did not have a melting peak after EGF (DCS curve not shown). Hiz 3 showed an exotherm peak at -12°C after EGF most probably due to recrystallization, (Figure 3). This peak is not present in any of the other sample. In Hiz1 and 2 the recrystallization is probably hindered by the high concentration of TIBA and in Hiz 4-
9 by the higher molecular weights. The $\Delta H$ and $T_g$ of Hiz2-5 before EGF did not differ substantially from that of propane initiated PCL, (62 J/g). This suggests that the Histodenz initiated PCL crystallize at the same rate as linear PCL.

The DSC of Hiz7 as well as PD5 had no melting peaks but a $T_g$ at 0-15°C (graph not shown). This result corresponds well to Fox equation (equation 4) relating the $T_g$ of random copolymers to the weight ratio and $T_g$ of its consistuents.$^{55}$

$$\frac{1}{T_g} = \sum_{i=1}^{n} \frac{w_i}{T_{gi}}$$

(4)

Where $w_i$ is the mass fraction of component $i$ and $n$ is the number of components.

![Figure 3 DSC spectra of Hiz3 before EFG (blue) and after (red)](image)

3.1.2.2 Iodine content

The iodine content of Hiz 3-5 and 7 before EGF is proximate to the calculated value. This confirms that the polymerization has run to completion. However it does not give any information regarding the number of arms or the molecular weight distribution. After EGF the iodine weight ratio was >67 % of the calculated value, suggesting a good substitution rate. This value was calculated assuming six reaction sites on the polymer. Even for polymers with a lower number of arms the TIBA may still react with the alcohol groups on Histodenz. The iodine content of Hiz5 was slightly over the calculated amount. This indicates that the purification processes did not remove all excess TIBA from the polymer. The substitution rate of the other polymers may therefore be overestimated as well.

3.1.3 Hybrid materials

Clusters of nanometer size are too small to scatter visible light; therefore the nanocomposite hybrids were usually transparent. It was noted that low molecular weight PCL hybrids changed from transparent to white after a few weeks of storage. There seemed to be a slow change in the nanostructure of the samples. The optical and mechanical properties for all hybrids are presented in Table 8.
The effect of the inorganic phase on the mechanical properties of the polymers was detrimental. Most hybrids were hard and fragile. The only polymers that gave soft flexible hybrids were PDMS. However hybrids made from PDS5 were substantially softer than the once made from pure PCL (PD1). This suggests that further improvement could be made by tuning the monomer ratios.

Table 8 Some properties of the synthesized hybrid materials

<table>
<thead>
<tr>
<th>Hybrid</th>
<th>Ratio*</th>
<th>Inorganic precursor</th>
<th>Organic precursor</th>
<th>Solvent</th>
<th>Additives</th>
<th>Color</th>
<th>Mechanics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyb 1.1</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td>transparent</td>
<td>white</td>
<td>soft flexible</td>
</tr>
<tr>
<td>Hyb 1.2</td>
<td>50</td>
<td>TiO₂</td>
<td>PDMS</td>
<td></td>
<td>white</td>
<td></td>
<td>soft flexible</td>
</tr>
<tr>
<td>Hyb 1.3</td>
<td>75</td>
<td></td>
<td></td>
<td></td>
<td>white</td>
<td></td>
<td>soft flexible</td>
</tr>
<tr>
<td>Hyb 2.1</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td>transparent</td>
<td></td>
<td>soft flexible</td>
</tr>
<tr>
<td>Hyb 2.2</td>
<td>50</td>
<td>Ta(EtOH)₅</td>
<td>PDMS</td>
<td></td>
<td>transparent</td>
<td></td>
<td>soft flexible</td>
</tr>
<tr>
<td>Hyb 2.3</td>
<td>75</td>
<td></td>
<td></td>
<td></td>
<td>white</td>
<td></td>
<td>soft flexible</td>
</tr>
<tr>
<td>Hyb 3.1</td>
<td>25</td>
<td>TiO₂</td>
<td>PD 1</td>
<td>THF</td>
<td>transparent**</td>
<td></td>
<td>hard fragile</td>
</tr>
<tr>
<td>Hyb 3.2</td>
<td>50</td>
<td>TiO₂</td>
<td>PD 1</td>
<td>HCl</td>
<td>transparent**</td>
<td></td>
<td>hard fragile</td>
</tr>
<tr>
<td>Hyb 3.3</td>
<td>75</td>
<td></td>
<td></td>
<td></td>
<td>transparent**</td>
<td></td>
<td>hard fragile</td>
</tr>
<tr>
<td>Hyb 4.1</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td>transparent**</td>
<td></td>
<td>hard fragile</td>
</tr>
<tr>
<td>Hyb 4.2</td>
<td>50</td>
<td>Ta(EtOH)₅</td>
<td></td>
<td></td>
<td>transparent**</td>
<td></td>
<td>hard fragile</td>
</tr>
<tr>
<td>Hyb 4.3</td>
<td>75</td>
<td></td>
<td></td>
<td></td>
<td>transparent**</td>
<td></td>
<td>hard fragile</td>
</tr>
<tr>
<td>Hyb 5</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td>white</td>
<td></td>
<td>hard fragile</td>
</tr>
<tr>
<td>Hyb 6.1</td>
<td>25</td>
<td>Ta(EtOH)₅</td>
<td>PD 4</td>
<td>chloroform</td>
<td>white</td>
<td></td>
<td>soft fragile</td>
</tr>
<tr>
<td>Hyb 6.2</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td>transparent</td>
<td></td>
<td>hard fragile</td>
</tr>
</tbody>
</table>

*The molar ratio of inorganic to organic precursor
**These hybrids were transparent at first but changed to white after they had been stored at RT for a few weeks

3.1.3.1 SEM images

The SEM images of Hyb 1.2 and 2.1 (Figure 4 a and b) showed a smooth homogeneous surface with the exception of a few adsorbed foreign particles. The lack of visible organic-inorganic phase separation indicates that the desired nanostructure has been achieved.
3.2 FTIR-spectra

3.2.1 Hybrid materials

The FTIR spectra of the PDMS hybrids, Figure 6 a, showed all the peaks characteristics of the polymer as well as a broad peak at 800-600 associated with the metal oxide. The CH₃ groups of PDMS gave rise to peaks at 2960 (stretching), 1410 (asymmetric bending), 1260 (symmetric bending) and 785 (rocking) cm⁻¹. Around 1000 cm⁻¹ peaks originating from the Si-O-Si stretching were visible. In the case of PDMS-TiO₂ hybrids a peak from the Si-O-Ti bonds was expected to appear at 900-950 cm⁻¹ but is not visible (spectra not shown). This may be explained by the relatively low concentration of these bonds. In the spectra obtained from PDMS-Ta₂O₅ however a peak at 919 cm⁻¹ was clearly visible that was assigned to Si-O-Ta bonds (Figure 6a). Tantalum has a higher valence than titanium and therefore more Si-O-Ta bonds were expected. However this may not fully explain the increase in interactions between the organic and inorganic phase compared to titanium hybrids. It seemed tantalum has a stronger tendency than titanium to bond to PDMS.

The spectra of the ester polymers (Figure 6 b) were dominated by two areas of peaks. First at 2950-2850 cm⁻¹ peaks from the C-H stretch of the hydrocarbon chain were observed. At lower wave numbers the sharp bands between 1036 and 1600 cm⁻¹ were attributed to the -CH₂- deformation. The highest peak of the spectra at 1721 cm⁻¹ came from the carbonyls (C=O). It is these bonds that interact with the inorganic oxides, and due to the electron donating nature of the metals new peaks appeared just below 1721 cm⁻¹. The Hyb4.1 had one additional peak at 1532 cm⁻¹ which in the literature is ascribed to a bidentate bridging structure (Figure 5).
**Figure 5** Interactions between metal atoms and esters. Reprinted with permission from \(^{31}\). Copyright 2009 American Chemical Society.

**Figure 6** FTIR transmittance spectra of a) PDMS (red) and Hyb 2.2 (black), b) PCL (black) and Hyb 4.2 (red)

### 3.2.2 Iodinated polyesters

Compared to the polyesters initiated by propanediol the Histodenz initiated polyesters showed additional peaks due to C-N stretching\(^{49}\) at 1627 and 1545 cm\(^{-1}\) (Figure 7 a). After EGF with TIBA peaks due to aromatic C-C stretching\(^{49}\) appeared at 1545 and 1521 cm\(^{-1}\) (Figure 7 b) and at 3000-3100 cm\(^{-1}\) due to aromatic C-H stretching (spectrum not shown). The intensity of these peaks grew stronger with increasing Histodenz and TIBA content, e.g. lower molecular weight.
Figure 7 FTIR transmittance spectra of a) PCL (black), Hiz3 (purple) Hiz4 (green) and Hiz5 (red) and b) Hiz3 (purple) and end group functionalized Hiz2 (green) Hiz3 (pink) Hiz4 (orange) and Hiz5 (blue)
3.3 Coating of metal wires and suture threads

A thin and even coating of PCL (0.8mg/cm) on suture wire was achieved by dip coating in a solution with 0.26g PCL per ml solvent, (Figure 8 a). This thickness did not affect the flexibility of the suture thread. The thicker coatings made from solutions with higher concentrations made the suture thread stiff.

The hybrid coatings were smooth and glasslike but difficult to apply as a thin and even coating. In Figure 8 b the smooth surface is visible. When the metal alkoxide/ polymer solution comes in contact with air a surface film is formed which adheres to the suture or metal wire causing an irregular coating thickness.

Figure 8 a) suture wire dip coated with PCL b) Stainless steel wire dip coated with Hyb 1.2.

3.4 X-ray visibility

3.3.1 Hybrids

The degree of X-ray opacity of hybrids films corresponded to the amount and kind of inorganic content regardless of the kind of polymer used. Hybrids that had a Titanium oxide inorganic phase absorbed very little radiation. Since titanium has a low cross section this was expected. The tantalum oxide hybrids were much more visible (Figure 9 a).
3.4.2 Iodinated polyesters

These polymers had a very low X-ray absorption prior to EGF (Figure 9 b bottom). Only the polymers with very low molecular weight had some visibility. After the iodine content was increased by EGF the visibility increased as well (Figure 9 b top).

3.5 Degradation study

Already after 1 week in buffer visible and mechanical changes was apparent in the samples. Hyb 6.1 and 6.2 had visible grains in them and their mechanical properties had deteriorated. This trend continued week after week.

The average weight loss of the samples is presented as function of time in Figure 10 a. The hybrids seem to degrade faster than their organic precursor.

Figure 10 b shows the average weight loss after four weeks with 90% confidence intervals. The intervals overlap to a great extent and further investigation should be made before final conclusions can be made. The reason for this large variance in the results is the difficulty of handling the samples. The Hyb6.1 and 6.2 samples were very fragile and may have lost pieces during the drying and weighing. Samples were also lost when they separated into small pieces and could not be weighed; this lead to fewer degrees of freedom and a larger confidence interval. The changes in weight were also close to the minimum resolution of the scale used.

![Figure 10 a) average weight loss of samples over time b) Sample weight loss after 4 weeks with 90% confidence intervals.](image)

3.5.1 TGA measurements

In order to validate the weight loss result from the degradation study Hyb 6.1 was analyzed by TGA after 0 and 4 weeks in buffer. Two samples were run for each time period. The TGA curves of two samples are presented in Figure 11 as examples. The apparent weight gain at the first few degrees was explained by instability of the gas flow during the beginning of the scan. This should not have affected the results since no significant reactions takes place at such low temperatures. All samples started to degrade at roughly 230 °C in a one step process. The week 4 samples degraded over a broader temperature interval than the week 0. This indicates a larger inhomogeneity in this sample.
The average residue weight was 37 % for the week 0 sample and 50% for the sample that had been stored in buffer. It was assumed that all organic content was thermally degraded during the heating and the residue is attributed to the metal oxide. Assuming that during the sol-gel process the inorganic precursor is completely hydrolyzed a theoretical value for the oxide content was calculated. The remaining weights of the week 0 samples agree with the calculated metal oxide wt%. After four weeks of degradation in buffer the metal oxide content increased due to the degradation of the polymer. Assuming that all weight loss in the buffer was due to polymer degradation the weight loss of samples after 4 weeks was calculated from the residue weight. This theoretical value was close to the average weight loss presented in Figure 11 and supports the results of the degradation study.
4 Conclusions and future work

Two methods of improving X-ray opacity to organic polymers have been evaluated; nanocomposite hybrid materials and iodine functionalization.

The hybrid materials with Ta$_2$O$_5$ were visible on X-ray images and were soft and flexible when made with PDMS. Their X-ray absorption was however too low to fully replace the Pt wire on the pressure sensor. The possibility of replacing the Pt wire with a hybrid coated Ta wire however does deserve further exploration. The majority of the X-ray opacity would come from the Ta wire and the hybrid would serve as a protective coating. TiO$_2$ hybrids may be more suitable because of the lower cost. Ta$_2$O$_5$ hybrids may be an alternative material in the FemoSeal plug. However the polymer used today in FemoSeal is not suitable as an organic precursor due to the solvents used in hybrid synthesis. One option would be to fine tune the monomer ratios used in PD 5 to improve the mechanical properties.

The iodine functionalization also increased the X-ray opacity, but only to low molecular weight polymers. This meant a compromise in mechanical properties and depending on the intended application this may be a problem. A solution is possible by functionalization with a divalent iodine containing group so as to link polymer chains together. This would increase the molecular weight whilst maintaining the iodine content. Another possible evolution would be to use Triiodo Benzoyl Chloride instead if TIBA to increase the substitution rate. The effect of EGF on the biodegradation rate of polyesters is another subject that needs further investigation. Iodine is antiseptic as well as X-ray absorbing and an interesting possibility would be to test the antibacterial properties of these polyesters.
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6 References