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(71) Applicant (for all designated States except US): **UNIVERSITE DE LIEGE** [BE/BE]; Patent Department, avenue Pré-Aily, 4, B-4031 Angleur (BE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **JEROME, Christine** [BE/BE]; Rue de la Jacinthe 10, B-4102 Ougree (BE).
BOZUKOVA, Dimitriya [BG/BE]; Rue Hector Denis 33, B-4031 Angleur (BE).

(74) Common Representative: **UNIVERSITE DE LIEGE**; Patent Department, à l'attention de N. Anthéunis, avenue Pré-Aily, 4, B-4031 Angleur (BE).

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(54) Title: COMPOSITE COMPRISING NANOPARTICLES AND METHOD OF MAKING NANOPARTICLES

(57) Abstract: The invention relates to a method for the production of nanoparticles comprising a conjugated polymer. The method comprises (i) providing a reaction mixture with a monomer, a photosensitising agent and a solvent, and (ii) exposing the reaction mixture to photo-irradiation to form nanoparticles of a conjugated polymer wherein the photosensitising agent is immiscible with the solvent.

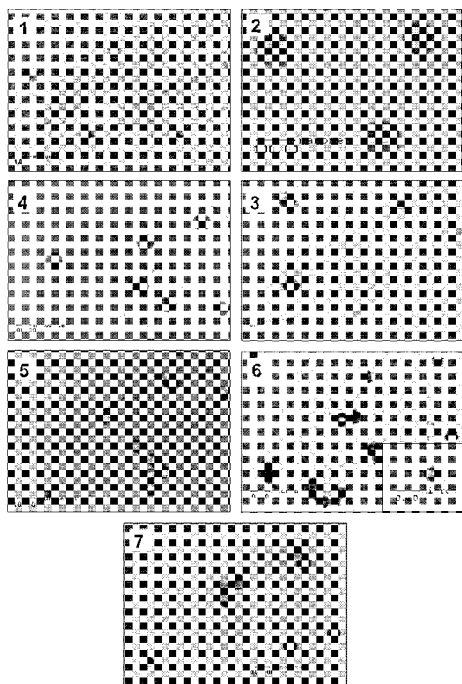


Figure 1



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5 **COMPOSITE COMPRISING NANOPARTICLES AND METHOD OF MAKING NANOPARTICLES**

The present invention relates to a method for making nanoparticles, in particular, nanoparticles for use in a composite. The composite may be a
10 hydrogel. The composite comprising nanoparticles made by the method of the invention may, for example, be for use in an intraocular lens implant.

Heterocyclic conjugated polymers are widely used in the fabrication of
15 biomaterials, such as biosensors, stimuli-responsive drug delivery systems, etc., due to their specific properties, such as electroconductivity, light absorbance, fluorescence, etc. Depending on the particular application, the polymer may be used as films, in solution or in the form of particles. Poly-thiophene (PTh), including oligo-
20 thiophene, is an example of heterocyclic conjugated polymer which is an environmentally and thermally stable material. Such polymer has been used in biomaterials, such as artificial noses and muscles.

For some biomaterial applications, such as stimuli-responsive systems,
25 drug-delivery systems, optical elements and biosensors, PTh in the shape of nanoparticles or mesoparticles has been used. Reference herein to biomaterials is intended to refer to materials, products and substances which can be used in contact with biological samples (tissues, fluids, organs, cells, cell components, etc.) under *in vitro*, *ex vivo* and *in vivo*
30 conditions.

When used in the preparation of biomaterials, it is preferable for the PTh particles to have a high purity, so that any potentially toxic effects on a biological system it may be subsequently placed in contact with are
35 reduced or eliminated. Furthermore, if PTh is used in nanoparticles, it preferably has well controlled dimensions.

5

In known methods for producing nanoparticles of conjugated polymers potential contaminants usually result from the synthesis of the conjugated molecules by polymerisation of the respective monomer, such as thiophene (Th) or its derivatives.

10

In particular, in the known methods for the production of nanoparticles of polythiophene, and/or derivatives thereof, it is difficult, if not impossible, to control the size and shape of the final particles. This is a consequence of the method of particle preparation. Some of the methods use metallic nanoparticles (i.e. gold) as templates, that are coated by the conjugated polymer (Zhai, L. et al. J. Mater. Chem. 2004, 14, 141-143); in other methods the monomer is polymerised at the surface of gold nanoparticles using electrochemistry (Si et al. J. Am. Chem. Soc. 2007, 129, 3888-3896) or chemical oxidation (Zhang, Z. et al. Mater. Lett. 2006, 60, 1039-1042); in still further methods particles are produced by precipitation of a pre-formed conjugated polymer (synthesised by chemical oxidation with an Fe^{3+} salt) on the surface of the inorganic nano-cores. Oligothiophene nanoparticles may also be precipitated from a dilute organic solution on the surface of graphite and mica (Surin et al. Synth. Met. 2004, 147, 67-72). The oligomers may then be capped by one or two short hydrophobic poly(ethylene oxide) segments. In yet another example, structurally ordered poly(3,3'-dialkylquarterthiophene) (PQT-12) nanoparticles were prepared by Fe^{3+} -catalyzed oxidation polymerisation in dichlorobenzene and used in the preparation of organic thin film transistors (OTFTs) (Ong et al. Adv. Mater. 2005, 17, 1141-1144). Similarly, Fe^{3+} -catalyzed oxidation polymerisation was used for the fabrication of nanoparticles of poly(Th) dendrimers (Advincula, Dalton Trans. 2006, 2778-2784) and core/shell poly(styrene/Th) (Lee et al. Current Appl. Phys. 2008, 659-663) and poly(3,4-ethylenedioxythiophene) (PEDOT) nanoparticles (Oh et al. Current Appl. Phys. 2002, 2, 273-277) in water. Other methods include the

5 preparation of conjugated polymers through photoinitiation in the presence of aqueous solutions containing inorganic oxidizing agents (CN 101280094, de Barros et al. Synth. Met. 2010, 160, 61-64) or aqueous solutions containing organic dyes, also referred to as metallic complexes (JP1123228 and JP2006016582).

10

In all the aforementioned known methods, the nanoparticles produced, either contain significant amounts of synthetic contaminants making them unsuitable, or less than optimal, for use in biomaterials or do not have the well-defined dimensions required for the formation of
15 composites. An aim of the present invention is therefore to provide nanoparticles of conjugated polymers which have no, or very little, toxic contaminants. It is also an aim to produce nanoparticles with controlled dimensions.

20 According to a first aspect, the invention provides a method for the production of nanoparticles comprising a conjugated polymer, said method comprises (i) providing a reaction mixture comprising a monomer, a photosensitising agent and a solvent, and (ii) exposing the reaction mixture to photo-irradiation to form nanoparticles of a
25 conjugated polymer, wherein the photosensitising agent is immiscible with the solvent and forms droplets.

Advantageously the nanoparticles are monodisperse.

30 By nanoparticle one means a particle wherein at least one dimension is equal or lower than about 1000 nm, preferably is equal or lower than about 250 nm and even more preferably is equal or lower than about 100 nm. The one dimension that is equal to or lower than about 1000 nm, preferably is equal or lower than about 250 nm and even more preferably
35 is equal or lower than about 100 nm, may be the radius, said dimension being measured by Dynamic Light Scattering

5

By conjugated polymer, one means a macromolecule containing a spatially extended π -bonding system. Preferably the conjugated polymer is an aromatic polymer, more preferably the conjugated polymer is a heterocyclic aromatic polymer.

10

The droplets formed by the photosensitising agent are in the nanometer to micrometer range and may have a large polydispersity.

Preferably the nanoparticles produced by the method of the invention are substantially spherical and are monodisperse, independently from the size and the polydispersity of the photosensitising agent.

15

The solvent may be any suitable solvent. The solvent may be water, methanol, ethanol, iso-propanol, tetrahydrofuran or a mixture thereof.

20

Preferably the solvent is water or an aqueous solution. Preferably the reaction mixture is an aqueous solution.

The photo-irradiation may be provided by a UV lamp or other light source. Preferably UV-irradiation refers to radiation in the range of 350-420 nm. This may be achieved by using a 1000 watt UV lamp.

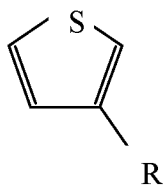
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The monomer may be any monomer capable of forming a conjugated polymer under the conditions described. The monomer may be a phenylic or a heterocyclic aromatic monomer, such as pyrrole, furan, thiophene and their substituted derivatives. The monomer may be thiophene and/or a derivative thereof. Reference herein to a polymer is intended to include what are more commonly referred to as oligomers.

30

A derivative of thiophene (Th) may be any 3-substituted thiophene molecule with the formula

35



5

wherein R is be selected from the group comprising an aliphatic group, alcohol group, amino group, alkoxy group, acryl group, meth(acryl) group, carboxyl group, ester group, (poly)ester group, ether group or (poly)ether group.

10

An aliphatic group may comprise a C1 to C12, preferably a C1 to C8, preferably a C1 to C6, more preferably a C1 to C4 alkane or alkene. The aliphatic group may be straight or branched chain, and substituted or unsubstituted.

15

An alcohol group may comprise a C1 to C12 alcohol, preferably a C1 to C8 alcohol, preferably a C1 to C6 alcohol, more preferably a C1 to C4 alcohol.

20 An amino group preferably comprises NR_1R_2 , wherein R_1 and R_2 are independently selected from hydrogen, C1 to C8 alkyl, C1 to C6 alkyl and C1 to C4 alkyl.

25 An alkoxy group may comprise a C1 to C6 alkoxy, more preferably a C1 to C4 alkoxy.

A carboxyl group may be $-\text{COOR}$, wherein R is selected from hydrogen, a C1 to C8 alkyl, C1 to C6 alkyl or C1 to C4 alkyl.

30 An ether group may be $\text{R}_\text{A}-\text{O}-\text{R}_\text{B}$, wherein R_A is a C1 to C8 alkyl, C1 to C6 alkyl or C1 to C4 alkyl; and R_B is a C1 to C8 alkyl, C1 to C6 alkyl or C1 to C4 alkyl.

- 5 Preferably R is methanol and the monomer is 3-thiophene methanol (ThM).

The monomer may comprise a mixture of monomers. The mixture may comprise two or more different monomers selected from thiophene and
10 derivatives thereof.

The nanoparticles produced by the method of the invention may comprise aromatic phenylic or heterocyclic polymers, such as polypyrrole, oligopyrrole, polyfuran, oligofuran, poly(thiophene),
15 oligothiophene and/or a copolymer thereof, and/or derivatives thereof.

Preferably the nanoparticles produced by the method of the invention comprise poly(thiophene) or a polymer of a derivative of thiophene with the above formula, such as poly(3-thiophene methanol), or a copolymer
20 thereof, such as a mixture of poly(thiophene) and poly(3-thiophene methanol).

The photosensitising agent may be selected from the group comprising the phenones, benzophenones, peroxides, or any other molecule that
25 decomposes upon UV-irradiation and is immiscible with the solvent and forms droplets. The photosensitising agent is preferably 2-hydroxy-2-methyl-propiophenone (HMPP).

Preferably the amount of photosensitising agent is from about 1 % to about 100 % in respect to the monomer, more preferably in the range
30 about 25 % to about 75 % wherein the % is vol%.

Exposure of the monomers to the photo-irradiation preferably causes polymerisation of the monomer and the production of nanoparticles. In
35 one embodiment, exposure of thiophene monomers and/or derivatives to UV-irradiation causes the polymerisation of the thiophene monomers

5 and/or derivatives thereof and the production of nanoparticles of poly(thiophene or a derivative thereof) (which includes oligo(thiophene or a derivative thereof)).

Preferably the method produces nanoparticles with a low size
10 polydispersity, inferior to 0.5, preferably inferior to 0.2, more preferably inferior to 0.1 and even more preferably equal or inferior to 0.02. The size of the particles produced will be influenced by the conditions used in the method to produce them, for example, the wavelength and length of UV-exposure, the type and amount of monomer used etc.

15 After synthesis the nanoparticles may be lyophilised and/or dried prior to use.

The method of the invention may include adding a crosslinking agent to
20 the reaction mixture. Preferably upon exposure to photo-irradiation, such as UV-irradiation, the crosslinking agent causes crosslinking to occur within the polymer chains of the nanoparticles.

The crosslinking agent may be one or more of 3-[(2-acryloyloxy)methyl]
25 thiophene (A_{Th}), 3-[(2-methacryloyloxy) methyl] thiophene, 3-[(2-acryloyloxy) ethyl] thiophene, 3-[(2-methacryloyloxy) ethyl] thiophene, 3-[(2-acryloyloxy) propyl] thiophene, 3-[(2-methacryloyloxy) propyl] thiophene, vinylmethyl thiophene, vinylethyl thiophene, vinylpropyl thiophene, epoxymethyl thiophene, epoxyethyl thiophene, epoxypropyl
30 thiophene, etc.

A crosslinker may be any molecule that disposes of one thiophene ring
able to copolymerise with the thiophene monomer and thiophene
derivatives, and a second polymerising group that will polymerise
35 separately, thus resulting in a crosslinked network.

5 Crosslinking within the nanoparticles may result in nanoparticles with improved thermal stability, and/or with improved resistance to extraction using organic solvents, and/or with improved resistance to aggregation.

10 Preferably the nanoparticles are thermally stable, preferably they are stable at temperatures up to 350°C.

Preferably the nanoparticles are stable in UV light, preferably they are stable in wavelengths up to 350 nm.

15

Preferably the nanoparticles are stable in solution, preferably they do not precipitate and remain dispersed in solution, or are easily dispersed upon shaking after long term storage (of 1 year or more).

20 Preferably the nanoparticles are substantially monodisperse, preferably the polydispersity is inferior to 0.5, more preferably the nanoparticles have a polydispersity inferior to 0.2, even more preferably inferior to 0.1 and even equal or inferior to 0.02.

25 Preferably the nanoparticles are biocompatible.

Preferably the reaction mixture used in the method of the invention is homogenised prior to exposure to photo-irradiation.

30 The reaction mixture may be exposed to photo-irradiation, such as UV-irradiation, for at least 2, 4, 6, 8, 10, 15, 20 or more hours.

Preferably nanoparticles of poly(thiophene) or a derivative thereof produced by the method of the invention are produced in a more environmentally-friendly manner than known methods used to produce
35 such nanoparticles. Preferably the method of the invention produces

5 nanoparticles with a low size polydispersity in contrast to known methods.

The method of the present invention is preferably a one step process.

10 Preferably the method of the invention does not require a metal-containing reagent, such as Fe^{3+} salts or potassium dichromate, as a catalyst. Preferably the method of the invention does not require an organic solvent, which are usually chlorinated. By avoiding a metal-containing reagent and/or an organic solvent the resulting nanoparticles
15 are less toxic, this is particularly important if the nanoparticles are to be used in a composite for use as a biomaterial.

Preferably the nanoparticles produced by the method of the invention do not contain metal or a metallic residue.

20

Preferably the nanoparticles produced by the method of the invention are biocompatible.

According to a further aspect, the invention provides a nanoparticle
25 produced by the method of the invention.

According to another aspect, the invention provides a nanoparticle obtainable by the method of the invention.

30 According to a further aspect, the invention provides a composite comprising nanoparticles of a conjugated polymer produced or obtainable by the method of the invention.

The method may comprise providing a reaction mixture comprising a
35 monomer, a photosensitising agent and a solvent, said photosensitising agent being immiscible with the solvent and forms droplets, and

5 exposing the reaction mixture to photo-irradiation to form
nanoparticles of a conjugated polymer.

In a preferred embodiment, the nanoparticles in a composite of the invention have a polydispersity inferior to 0.5, preferably inferior to 0.2, more preferably inferior to 0.1 and even more preferably equal or inferior to 0.02.

In an other preferred embodiment, the conjugated polymer is poly(thiophene) or a derivative thereof or a copolymer of thiophene and a derivative thereof. The derivative of poly(thiophene) may be poly(thiophene methanol).

Preferably the nanoparticles in a composite of the invention are particles wherein at least one dimension, such as the radius, is equal to or lower than about 1000 nm, preferably is equal or lower than about 250 nm and even more preferably is equal or lower than about 100 nm.

Preferably the nanoparticles are substantially spherical and may be referred to as nanospheres, that is, they have a radius of less than about 25 1000 nm. More preferably they have a radius equal or less than 100 nm.

Preferably the nanoparticles in a composite of the invention are stable. That is, they are preferably thermally stable and/or stable on exposure to UV-light and/or are stable in solution.

Preferably the nanoparticles in a composite of the invention do not comprise any metal or metallic residue.

Preferably the nanoparticles in a composite of the invention are
35 substantially all the same size. Preferably the nanoparticles in a
composite of the invention differ by less than about 25 %, 20 %, 15 %, 10 %, 5 % or 1 %.

- 5 10 % or less in volume. The presence of significantly larger particles would affect the absorption properties of the material. Nanoparticles significantly larger than 100 nm may increase opacification as a result of light scattering.
- 10 Preferably the composite with nanoparticles is a nanocomposite, that is, is a multiphase solid material wherein one of the phases has one, two or three dimensions of less than about 1000 nm, preferably less than about 250 nm and even more preferably less than about 100 nm.
- 15 Preferably the composite containing the nanoparticles is biocompatible. This may be determined by cytotoxicity and/or cell adhesion studies.

Preferably the nanometric size of the nanoparticles means that they can be eliminated from the body if needed and thus are biodegradable. The
20 nanometric size may also improve the optical properties of the composite; nanoparticles below 100 nm may be transparent.

Preferably the composite comprises a chemically or physically crosslinked polymer that may or may not absorb water. Most preferably
25 the composite is chemically crosslinked and stable upon dissolution. Even more preferably, the composite is a chemically crosslinked polymer capable of absorbing water, thus a hydrogel. A hydrogel may be a network of polymer chains that are substantially water-insoluble.

- 30 Preferably if the composite is a hydrogel and the nanoparticles are easily dispersed in the monomers and/or monomer mixtures used to form the hydrogel.

The hydrogel may be a hydrophilic acrylic hydrogel. Such hydrogels
35 may be used in intra-ocular lens implants.

- 5 Preferably the hydrogel comprises poly(2-hydroxyethyl methacrylate-*co*-methyl methacrylate) [poly(HEMA-*co*-MMA)] and is formed from 2-hydroxyethyl methacrylate (HEMA), methyl methacrylate (MMA) and the cross-linking agent ethylene glycol dimethacrylate (EGDMA)
- 10 Preferably a composite according to the invention prevents/reduces the transmission of UV-light (up to about 350 nm) when compared to the same material without the nanoparticles. Preferably the reduction is proportional to the amount of nanoparticles incorporated. Most preferably such a composite is capable of absorbing at least about 10 %
- 15 up to about 70 % more of the UV light at 350 nm compared to the neat host polymer (hydrogel, for instance), that is, without nanoparticles, Preferably the composite comprises 2.5 mg nanoparticles made by the method of the invention to every 1 mL of the initial monomer mixture used to prepare the polymer host material.
- 20 Preferably a composite according to the invention prevents/reduces the transmission of blue light (350 – 450 nm) when compared to the same material without the nanoparticles. Most preferably a composite according to the invention is capable of absorbing at least about 5 % up
- 25 to about 30 % more of the blue light at 450 nm compared to the neat host polymer (hydrogel, for instance) when 2.5 mg nanoparticles according to the invention are added to 1 mL of the initial monomer mixture for the preparation of the polymer host material. The composite of the invention containing the nanoparticles may be used in the production of
- 30 IOL implants which reduce the risk of damage to underlying retinal epithelial cells caused by exposure of the retinal cells to UV and/or blue light.

Preferably, in a composite of the invention with reduced UV-

35 transmission properties, the amount of nanoparticles per volume of initial monomer mixture for the preparation of the polymer host material

5 is between about 0.1 and about 10 g/L, more preferably between about 0.5 and about 2.5 g/L.

Preferably if the composite is a hydrogel the inclusion of the particles in the hydrogel has little or no significant effect on the surface properties
10 of the hydrogel. For example, causes no significant increase the attachment of cells to the hydrogel surface.

The composite of the invention may be used as an optical material, for example as a biomaterial in an IOL implant, and/or in solar cells, and/or
15 in photovoltaic cells.

The composite of the invention may be used in an implant, for example in an IOL implant or a dental implant.

20 The composite of the invention may be used as a biomaterial in a range of contexts, for example in materials, products or substances which are for use in contact with biological samples, tissues, fluids, cells, cell components, etc either *ex vivo*, *in vivo* or *in vitro*.

25 According to another aspect the invention provides a method of producing a hydrogel comprising (i) dispersing nanoparticles of a conjugated polymer in a monomer mixture, and (ii) polymerising the monomer around the particles to form a hydrogel containing the nanoparticles. Preferably the nanoparticles are produced by the method
30 of the invention.

Preferably the nanoparticles are nanoparticles of poly(thiophene), or a derivative thereof, such as poly(thiophene methanol), or a copolymer thereof.

5 Preferably the monomer is a mixture of hydroxyethyl methacrylate (HEMA) and methyl methacrylate (MMA), which polymerises to form poly(HEMA-*co*-MMA). The crosslinking agent EGDMA may be included in the monomer mix and the polymerisation may be catalysed by ATh.

10

According to another aspect the invention provides an intraocular lens implant comprising a hydrogel containing nanoparticles of a conjugated polymer.

15 Preferably the conjugated polymer particles are as described with respect to the first aspect of the invention. Preferably the conjugated polymer particles are made according to the method of the first aspect of the invention.

20 The particles and/or hydrogel may be as described above.

According to another aspect the invention provides a composite comprising nanoparticles produced by any method of the invention, wherein the composite displays reduced transmission of UV light and/or
25 blue light compared to the composite without nanoparticles.

The composite may be a hydrogel. The hydrogel may be as described herein. The nanoparticles may be as described herein.

30 It will be appreciated that, where appropriate, all optional or preferable features applicable to one aspect of the invention can be used in any combination, and in any number. Moreover, they can also be used with any of the other aspects of the invention in any combination and in any number. This includes, but is not limited to, the dependent claims from
35 any claim being used as dependent claims for any other claim in the claims of this application.

5

Embodiments and examples of the present invention will now be described, by way of example only, with reference to the following figures.

10 **Figure 1** – shows TEM images of the nanoparticles listed in Table 1. The numbering of the micrographs is the same as in Table 1.

Figure 2 – shows a schematic representation of the formation of nanoparticles of oligo(Th), oligo(ThM) or their co-oligomers in water.

15

Figure 3 – shows the IR spectra of (I) ThM and (II) parent nanoparticles (entry 6, Table 1).

20 **Figure 4** – illustrates the ultraviolet-visible (UV-Vis) spectra of: (A) aqueous solution of Th and HMPP (entry 5, Table 1) before and after UV-irradiation; (B) aqueous solution of ThM and HMPP (entry 6, Table 1) before and after UV-irradiation; (C) nanoparticles listed in Table 1 entries 2 & 4-6.

25 **Figure 5** – shows the fluorescence emission spectra of: (A) aqueous solution of Th and HMPP (entry 5, Table 1) before and after UV-irradiation; (B) aqueous solution of ThM and HMPP (entry 6, Table 1) before and after UV-irradiation; (C) nanoparticles listed in Table 1, entries 2, 5 & 6.

30

Figure 6 -- shows TEM images of the oligo(ThM) nanoparticles listed in Table 1, entry 6, and redispersed in THF and HEMA after drying.

35 **Figure 7** – shows the chemical structure of the cross-linker 3-[(2)acryloyloxy)methyl] thiophene (ATh).

5 **Figure 8** – shows TEM images of the nanoparticles prepared under the conditions reported in Table 2. The numbering of the micrographs is the same as in Table 2.

Figure 9 – shows the IR spectra of (I) uncross-linked (entry 6, Table 1)
10 and (II) ATh-cross-linked (entry 3a, Table 2) oligo(ThM) nanoparticles.

Figure 10 – shows the overlaid UV-Vis spectra of the aqueous dispersions of A) oligo(Th) nanoparticles and B) oligo(ThM) nanoparticles.

15

Figure 11 – shows the effect of the cross-linking of the oligo(ThM) nanoparticles by ATh on the fluorescence emission spectrum.

Figure 12 – shows TEM images of the ATh-stabilized oligo(ThM) nanoparticles listed in Table 2 (entry 3a) after redispersion in THF and HEMA.

20

Figure 13 – shows the TGA of the non-stabilized and ATh-stabilized oligo(ThM) nanoparticles.

25

Figure 14 – shows the Raman spectrum of ATh-stabilized poly(ThM) nanoparticles (entry 3a, Table 2) after TGA up to 950°C, at a heating rate of 10°C/min.

30 **Figure 15** – shows the TEM image of the TGA residue (up to 950°C) of the oligo(ThM) nanoparticles listed in Table 2, entry 3a.

Figure 16 – shows the microscopic observation of the cell cultures after « Extraction test » at 2.5 mg/mL concentration.

35

5 **Figure 26** – shows the TEM observation of the hydrogel nanocomposites listed in Table 5;

Figures 27A to 27C – show DSC curves for the pre-dried nanocomposites listed in Table 5;

10

Figures 28A to 28F – show the dynamic mechanical properties of the hydrogel nanocomposites listed in Table 5;

15 **Figures 29A to 29C** – show the results of thermogravimetric analysis of the pre-dried nanocomposites listed in Table 5;

Figure 30 – shows optical micrographs of LECs adhering to the surface of the hydrogel nanocomposites listed in Table 5, together with a histogram indicating the surface occupied by LECs.

20

Examples

Materials

Thiophene (Th, 99+ %), 3-thiophene methanol (ThM, 98 %), 2-hydroxy-2-methyl-propiophenone (HMPP, 97 %), 2-hydroxyethyl methacrylate (HEMA), methyl methacrylate (MMA) and ethylene glycol dimethacrylate (EGDMA) were purchased from Aldrich, stored in the dark at -20°C and used without further purification. Azo-bis-isobutyronitrile (AIBN, Fluka) was also stored in the dark at -20°C and used as received. 3-[(2-acryloyloxy)methyl] thiophene (ATh) was synthesized as described below. Milli-Q water (18.2 MΩ) was obtained by a Milli-Q system from Millipore. Acryloyl chloride (AC, Aldrich) and triethylamine (TEA, Aldrich) were dried on CaH₂ and used after distillation. All other solvents (tetrahydrofuran (THF), toluene and methanol) were of analytical grade. Conventional yellow lenses (Yellow Flex) from PhysiOL SA, Belgium, were used as reference lenses.

25

30

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5 Synthesis of 3-[(2-acryloyloxy)methyl] thiophene (ATh)

ATh was synthesised as follows : 1.68 mL (1 mol eq) of ThM, 3.23 mL (1.3 mol eq) of freshly distilled TEA and 20 mL of dry THF were added under argon atmosphere to a pre-conditioned double-necked flask equipped with a magnetic stirring-bar and a dropping funnel. The mixture was cooled down to 0°C in an ice/water bath. A 10 mL solution of 1.89 mL (1.3 mol eq) of freshly distilled AC in dry THF was then added dropwise. The mixture was allowed to warm up slowly to room temperature and to react for 20 h. The ammonium salt precipitate was filtered out. The filtrate was concentrated with a rotary evaporator, and the residue was dissolved in 200 mL diethyl ether. This solution was washed with 80 mL saturated aqueous solution of NaHCO₃, then dried over MgSO₄, followed by the elimination of the solvent. The oily residue was identified as ATh by NMR and collected with a 62.6% yield. It was used without further purification.

¹H NMR (CDCl₃) δ= 6.01 and δ = 6.57 (CH₂=CH); δ = 6.32 (CH₂=CH); δ = 5.36 (CH₂-OCO); δ = 7.46 (CH-S-CH); δ= 7.26 (CH=CH-S, overlapped with the peak for the solvent).

25 Characterisation

The average radius (R_{DLS}) and particle size distribution or polydispersity index (PDI_{DLS}) of the nanoparticles were analyzed in water by Dynamic Light Scattering (DLS). Malvern CGS-3 equipped with a He-Ne laser (633 nm) was used. The scattering cell was immersed in filtered toluene and the temperature was maintained at 25°C. Data were recorded at a scattering angle of 90°. PDI was defined as the μ_2/Γ_1^2 ratio, where μ_2 is the second cumulant and Γ_1 is the first cumulant. The DLS data were also analyzed by the CONTIN routine, a method based on constrained inverse Laplace transformation of the data and which gives access to a size distribution histogram for the particles.

5 Fluorescence emission spectra of the nanoparticles in the aqueous reaction mixture were collected on a Perkin Elmer LS50B spectrofluorimeter at 350 nm excitation wavelength. UV-Vis spectra were recorded with a HP 8453 UV-Vis spectrophotometer (Hewlett-Packard, Waldbronn, Germany) fitted with a 1024- element diode-array.

10 Infrared spectra (IR) of dried nanoparticles were collected after 8 scans on a Perkin Elmer 1600 equipment with a 4 cm^{-1} resolution. Raman spectra were recorded with a LabRam spectrometer (Jobin-Yvon) equipped with an Olympus confocal microscope (100× objective lens, 300 μm confocal pinhole) and a Peltier air-cooled, back illuminated,

15 deep depletion 1024×128 CCD detector. The exciting wavelength was 785 nm delivered by a diode laser (Torsana StarBright 785 XM; power of 4 mW). The integration time was fixed at 40 s. The particles to be analyzed were selected by viewing the sample with the CCD camera attached to the microscope. The baseline was corrected and subtracted

20 from the recorded spectra, by using a polynomial regression model. A Savitsky-Golay smoothing was also performed.

Transmission Electron Microscopy (TEM) was used to observe either nanoparticles or microtomed slices ($\sim 80\text{ nm}$ thick, RuO staining) of

25 nanocomposites. The nanoparticles were deposited on Formvar- or carbon- coated copper grids by casting a drop of a suspension in water or in an organic solvent, followed by slow solvent evaporation. A Philips CM 100 TEM equipped with a Gatan 673 CCD camera connected to a computer with the Kontron KS 10 software was used.

30

Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA) were performed on samples dried at 50°C under reduced pressure overnight. TGA was carried out with a TA Q500 apparatus at a heating rate of $10^\circ\text{C}/\text{min}$ up to 700 or 950°C . DSC was performed with a

35 TA DSC Q100 apparatus, according to the following thermal treatment: (i) cooling to -60°C , (ii) isotherm at -60°C for 5 min, (iii) heating at

- 5 15°C/min until 200°C, (iv) isotherm at 200°C for 5 min, (v) fast cooling down to -60°C, (vi) isotherm at -60°C for 5 min, (vii) heating at 15°C/min up to 200°C. The second run of heating was systematically considered.
- 10 One mm thick discs of the nanocomposites (8 mm in diameter) were analyzed by Dynamic Mechanical Analysis (DMA, Rheometric Scientific – ARES) at 20°C, with a frequency of 99.903 rad/sec and an initial strain and a final strain of 2.02 % and 10.0 % respectively. The composites were first equilibrated in a pot filled with water for at least 48 h at room
- 15 temperature. The non-absorbed water which remained on the surface of each sample was gently eliminated by filter paper, since it could impede the good contact between the surface of the sample and the surface of the analytical plate.
- 20 Water uptake (W%) was determined according to the equation:
$$W\% = [(m_{\text{hydrated}} - m_{\text{dry}}) / m_{\text{hydrated}}] * 100$$
where m_{hydrated} is the weight of the sample in the fully hydrated state (swelling for at least 48 h at room temperature in a water filled well-closed container ; non-absorbed water was removed from the surface
- 25 with a filter paper just before weighting) and m_{dry} is the weight of the same sample dried for 48 h at 50°C under reduced pressure.
- For the measurement of conductivity, poly(Th-co/or-ThM) nanoparticles (10 mg) were dispersed in 4mL 5×10^{-2} M tetrabutyl ammonium
- 30 perchlorate solution in dry acetonitrile. A home-made electrochemical conductometer was used for the measurements.
- The cell culture line L929 was used for estimating the cytotoxicity of the nanoparticles of poly(Th-co-ThM), Th/ThM of 1/2 (sample 1) and 2/1
- 35 (sample 2) ratio and the eventual compound extracted from the nanoparticles. Suspensions of 2500 cells/well were incubated in 96 well

5 Falcon box at 37°C, 5 % CO₂ in 100 µL culture medium (CM, 87 % Dulbecco's Modified Eagle's Medium (Cambrex); 10 % bovine foetal serum (Gibco) and 1 % of antibiotics (penicillin/streptomycin 10 000U/10 000µg/ml); 1 % Glutamine; 1 % HEPES). When 10 %
10 confluence was achieved after approximately 1 day, the CM was substituted by 100 µL of the respective test dispersion (containing the nanoparticles, "Direct contact test") or test solution (containing the extracts from the nanoparticles, "Extraction test"). The cells were then incubated at 37°C and 5 % CO₂ for another 72 h, which was determined to be enough for 80-90 % confluence of calibration culture. 20 µL of
15 tetrazolium salt (MTS) (Kit "The CellTiter 96® Aqueous Non-Radioactive Cell Proliferation Assay") was then added to each well, this was used as a dye for colorimetric determination of the metabolic activity of the cell culture. MTS is reduced to formazan derivative by the dehydrogenases of the living cells. The MTS was left to react with the
20 cells for 2 h at 37°C and 5 % CO₂. The absorption of the CM was then determined at 490 nm, and is proportional to the amount of formazan, which is proportional to the number of living cells.

Nanoparticle dispersions were prepared for the "Direct contact test" in
25 dimethylsulfoxide (DMSO) at concentration of 300 mg/mL. The dispersions were then diluted in CM until a concentration of 30 mg/mL was obtained. They were then used for the test. For the "Extraction test" (the cells are not in direct physical contact with the nanoparticles but with an extract of the particles), the nanoparticles were incubated in CM
30 at concentration of 2.5 mg/mL for 12 days at 37°C. The dispersions were regularly agitated. Finally, they were centrifuged for 10 min at 15 000 G and the supernatant was filtered through a 0.22 µm filter. 100 µL/ well (96 well Falcon box) of the filtered supernatant was used for the tests.

35 Lens epithelial cells (LECs) were isolated from the lens crystalline capsule of pig eyes (Pietrain-Landrace pig; from the "Abattoir communal

5 de Liège”) and cultured as reported by Dumaine, L. (Thesis: « Corrélation entre les propriétés physico-chimiques de polymères permettant de moduler la prolifération cellulaire et celles permettant de favoriser le glissement de lentilles intraoculaires ». Ecole Centrale de Lyon. 2004, 79-85). Cells in 4th to 10th passage were used for testing.

10

The LECs adhesion test (*in vitro* test) was performed as follows : The samples were pre-conditioned in a SERAG BSS® physiological solution (pH 7.3) for 2 days and cut as disks with a 6 mm diameter, thus fitting the test wells. They were washed and sterilized in physiological solution at 1.5 bar, 120°C for 21 min. They were then fixed on the bottom of a 96 well-plate and conditioned with the culture medium (CM, 87% Dulbecco’s Modified Eagle’s Medium (Cambrex); 10% bovine foetal serum (Gibco) and 1 % of antibiotics (penicillin/streptomycin 10 000 U/10 000 µg/ml); 1 % Glutamine; 1 % HEPES) in an incubator for 2 h.

15 After removal of the conditioning CM, a suspension of 7500 cells/ 200 µL was added to each well. After 3 days of contact between hydrogel samples and LECs suspension in the incubator, the culture medium was removed, followed by a careful washing with phosphate buffer saline (PBS) in order to eliminate the non-adhering and dead cells. The cells

20 were fixed with 4 % paraformaldehyde at 4°C for 2 h, washed three times with PBS and kept in PBS at 6°C until microscopic observation.

25

The sample surface was observed with an optical microscope Zeiss, Axioplan, equipped with Epiplan-NEOFLUAR objectives (5x magnification) and a CCD camera (ICD-42E model). The images were visualized with the XnView software. Each sample was analyzed in triplicate. The surface area occupied by the cells was determined by a software Dpx View Pro Image management.

30

35 **Example 1: Preparation and analysis of non-stabilized well-defined nanoparticles of oligo(Th), oligo(ThM) or their co-oligomers**

5 Predetermined quantities of Th, ThM and HMPP were mixed and then homogenised under vigorous stirring. They were then added to a reaction tube equipped with a magnetic stirring-bar and a predetermined amount of solvent, i.e. Milli-Q water. The reaction mixture was maintained under stirring for 30 min and then UV-irradiated with a UV
10 lamp (1000 watt; 350-420 nm) for 20 h, either directly or after a preliminarily de-oxygenation by argon bubbling. The nanoparticles were analyzed in the reaction mixture. Part of them were then collected by lyophilisation, followed by drying under reduced pressure overnight at 50°C before analysis. The exact quantities of all reagents are listed in
15 Tables 1 and 2.

HMPP is immiscible with water, in contrast to Th that forms an azeotropic mixture with water, whereas all of HMPP, Th and ThM are miscible with organic solvents, including toluene. We surprisingly found
20 that the immiscibility of HMPP with water and the formation of droplets led to nanoparticles. Examples are first presented in water (entries 2-7, Table 1) while a comparative example in toluene (entry 1, table 1) follow these.

25 A 2/1 (v/v) mixture of Th and ThM was polymerised in water (entry 2, Table 1). In all the experiments the one-phase mixture of HMPP and monomers was added to the solvent. The reaction medium was maintained under stirring for 30 min before being UV-irradiated for 20 h. The occurrence of a photoreaction was visible to the naked eye. The
30 colourless mixture turned light yellow as a dispersion of nanoparticles was formed.

In a second series of experiments, the volume ratio of the Th and ThM comonomers in water was changed, such that three compositions could
35 be compared (entries 2 to 4, Table 1). Moreover, each comonomer was photopolymerised separately (entries 5 and 6, Table 1). Fig. 1 (entries 2

5 to 6) demonstrates that well- defined spherical nanoparticles with narrow size distribution are formed in water, whatever the monomer and the comonomer feed composition. It was noted that nanoparticles of oligo(Th) were at least two times smaller ($R_{DLS} = 49$ nm) than the oligo(ThM) counterparts ($R_{DLS} = 109$ nm). Consistently, the average
 10 radius of the co-oligomer nanoparticles decreases whenever the Th content is increased.

In an additional experiment, the monomer/HMPP volume ratio was changed by a two-fold increase of the volume of HMPP with respect to
 15 that of ThM, the latter was kept unchanged (entry 7, Table 1). Smaller nanoparticles (micrograph 7, Fig. 1) with a broader size-distribution were found for the mixture with a higher amount of HMPP, possibly as the consequence of the faster polymerisation, promoted by the HMPP content on the nanoparticles formation. Therefore, the 2/1 (v/v)
 20 monomer/ HMPP ratio was selected in the next experiments.

Entry	Solvent 10 mL	Monomer 10 μ L	HMPP μ L	R_{DLS} nm	PDI_{DLS}	R_{TEM} nm
1	toluene	Th/ThM, 2/1 (v/v)	5	362	0.21	≈ 250
2	water	Th/ThM, 2/1 (v/v)	5	64	0.1	≈ 50
3	water	Th/ThM, 1/1 (v/v)	5	78	0.09	≈ 60
4	water	Th/ThM, 1/2 (v/v)	5	83	0.13	≈ 70
5	water	Th	5	49	0.06	≈ 35
6	water	ThM	5	109	0.02	≈ 90
7	water	ThM	10	90	0.27	≈ 55

Table 1: Experimental conditions for the preparation of nanoparticles of oligo(Th) and derivatives, together with particle size data.

5

It is not surprising that the size of the nanoparticles observed by TEM (Fig. 1) is systematically smaller, compared to DLS data (Table 1). Indeed, although the nanoparticles were analyzed by DLS in solution, they were dried prior to observation by TEM. The elimination of water and residual monomer, the monomer conversion being estimated at approximately 50 wt%, was responsible for the observed contraction of the particles.

Upon lyophilisation the nanoparticles were collected as dark brown to black powder, which is typical for the oxidized oligothiophene and derivatives. Evidence of the photo-copolymerisation of thiophene and derivatives was searched by comparative spectroscopic analyses of the monomers (Th and ThM) and the nanoparticles collected after UV-irradiation.

20

The IR spectrum of ThM shows the symmetric and antisymmetric stretching vibrations of the thienyl ring at 1335 cm^{-1} and 1416 cm^{-1} , respectively (Fig. 3 - I). These bonds are shifted upon UV-irradiation towards wavelengths characteristic of α -coupled thiophene units (Fig. 3 - II) which testifies that the polymerisation occurred. Moreover, the absorption at 1155 cm^{-1} by the C-S bond of the monomeric thienyl ring is shifted towards smaller wave-numbers after UV-irradiation, as a possible consequence of the conjugation in the polymer chains. The absorption at 2875 cm^{-1} must be assigned corresponding to the C-H stretching vibration of the methylene group of both ThM and ThM monomeric units in the chains, without distinction. The hydroxyl group of the ThM is at the origin of the absorption at 3300 cm^{-1} . The more convincing signature of polymerisation has to be found at 1688 cm^{-1} , which is typical of the aromatic C=C bending in conjugated chains.

35

5 UV-Vis spectra are shown in Fig. 4, for Th and ThM, in aqueous solution with HMPP, before and after UV-irradiation (entries 5 and 6, Table 1). An absorption maximum was observed at 250-300 nm for the non-irradiated solutions (Fig. 4, A and B). This maximum did not completely disappear upon exposure to UV, because the monomer
10 conversion was systematically limited to ~ 50 %. Nevertheless, an extra, although flat, maximum was observed at higher wavelengths as a result of UV-irradiation for 20 h and thus of partial polymerisation. This maximum is higher when ThM is compared to Th and, accordingly, it decreases with ThM content in case of the Th/ThM mixture (Fig. 4 - C).

15 The fluorescence emission spectra of the reactive aqueous dispersions were also recorded before and after UV-irradiation. An emission maximum of low intensity was observed at 425 nm with a long tail up to 600 nm for the aqueous solutions of each monomer (Th and ThM) and
20 HMPP (Fig. 5, A and B). Although this maximum grew in intensity upon UV-irradiation, only a small shift towards higher wavelengths was observed, which suggests the formation of oligomers rather than long conjugated chains. Nevertheless, this chain-length was enough for well-defined solid nanoparticles to be formed. The fluorescence emission was
25 more important for ThM than for Th (Fig. 5 - C).

Interestingly, the aqueous solutions of each monomer added with HMPP could be stored in the dark, for at least 6 months without any modification. In contrast, they turned light yellow upon exposure to
30 sunlight for 2 weeks, and a very low amount of solid nanoparticles was observed by TEM. This observation supports the suggested UV-photo-induction of the polymerisation process. No polymerisation occurred and nanoparticles were not formed whenever the aqueous solutions of monomers were UV-irradiated in the absence of HMPP, which confirms
35 the role of photo-sensitiser of this propiophenone derivative.

5 The nanoparticles collected have a strong tendency to agglomerate when the solvent is evacuated and to resist redispersion afterwards. For instance, oligo(ThM) nanoparticles (entry 6, Table 1) led to a black powder upon lyophilization, which could not be redispersed in water. However partial dispersion was observed in THF and HEMA,
10 respectively, after 1 h of stirring at original concentrations of 1 mg/ mL. The persistent aggregates were filtered out, and particles of the brown-coloured dispersions were observed by TEM on carbon-coated copper grid (Fig. 6). The average radius, R_{TEM} , of the dry particles was 20-25 nm in THF and approximately two times higher in HEMA (~ 50 nm),
15 compared to R_{TEM} of ~ 90 nm for the initial nanoparticles. These figures strongly suggest that part of the oligomers were extracted from the particles whose size decreased accordingly.

Comparative example 1:

20 In order to demonstrate the effect of the immiscibility of the photosensitising agent in the solvent, a 2/1 (v/v) mixture of Th and ThM was polymerised in toluene (entry 1, Table 1) under otherwise identical conditions. The photosensitising agent is miscible with toluene. It was observed that the co-oligomers of Th and ThM formed large particles
25 with a broad size-distribution in toluene (entry 1 in Table 1 and Fig. 1), whereas small spherical particles with low size polydispersity were collected in water (entry 2 in Table 1 and Fig. 1). The origin of this shape contrast might be found in the formation of droplets of HMPP in the aqueous reaction medium, which is not the case in toluene. The
30 monomer molecules that are originally dissolved in these droplets of photosensitising agent are the first to be polymerised under UV-irradiation, while their consumption is compensated by diffusion of molecules from the aqueous phase into the monomer-depleted nanoparticles. Fig. 2 illustrates the templating role of the HMPP droplets
35 in the formation of conjugated polymer nanoparticles.

5 Surprisingly, the HMPP droplets formed in the aqueous phase are in the nanometer to micrometer range and display an extremely high size polydispersity (higher than 0.6) in sharp contrast to the final nanoparticles collected after UV-polymerisation. The breaking/coalescence balance of the dispersed phase is thought to change
10 at the expense of the coalescence as the in situ polymerisation progresses and thus the internal viscosity increases.

The particle formation is completely different in toluene, i.e. in a homogeneous reaction medium. The oligomers that grow in solution
15 rapidly become insoluble, precipitate and aggregate, so leading to poorly defined big-particles.

Example 2: Preparation and analysis of stabilized well-defined nanoparticles of oligo(Th), oligo(ThM) and their co-oligomers by cross-linking
20

For this purpose, a dual monomer was synthesized, i.e., a compound with (i) a thiophene unit able to copolymerise with Th or ThM, and (ii) an acrylic function prone to radical polymerisation under the experimental conditions used. 3-[(2)acryloyloxy)methyl] thiophene (ATh, Fig. 7)
25 meets these requirements and was synthesized as reported above. The desired quantities of the monomer (Th and ThM), HMPP and ATh were mixed together before being added to the aqueous phase. Because of their intrinsic water-immiscibility, ATh and HMPP formed organic droplets dispersed in water (Fig. 8). Moreover, the partial solubility of
30 the monomers within these droplets is thought to be increased as a result of π - π interactions with ATh. The predicted mechanism of particles formation is basically the same as previously proposed, i.e., copolymerisation of ATh and the monomer originally in the droplets, followed by conversion of the monomer that diffuses from the aqueous
35 phase to the droplets, which are more or less rapidly depleted in ATh. Simultaneously to the incorporation of ATh in the conjugated chains the

5 acrylic substituents photopolymerise and trigger the cross-linking of the nanoparticles. So, the structure, i.e., the cross-linking density, of the particles might be heterogeneous to an extent that depends on the partition of the monomer between the aqueous phase and the organic droplets, the reactivity ratios of ATh and the monomer, and
 10 the amount of monomer that diffuses into the growing particles and polymerizes *in situ*.

The results of experiments carried out with 3.3 vol% and 33.3 vol% of ATh with respect to the monomer are listed in Table 2. A series of
 15 experiments was performed at variable conditions in order to investigate the effect of the monomer composition on the nanoparticles characteristics.

Entry	Monomer 10 μ L	ATh μ L	R_{DLS} nm	PDI_{DLS}	R_{TEM} nm
1a	Th	0.33	43	0.02	35
2a	Th/ThM, 1/2 (v/v)	0.33	45	0.01	35
3a	ThM	0.33	47	0.02	40
4a	Th	3.33	35	0.01	30
5a	Th/ThM, 1/2 (v/v)	3.33	42	0.01	33-35
6a	ThM	3.33	45	0.1	38-40

Table 2: Experimental conditions for the preparation of ATh- cross-linked nanoparticles of oligo(Th), oligo(ThM) and their co-oligomers.
 20 Reactions were conducted in 10 mL water with 5 μ L HMPP.

The addition of the lower amount of ATh to the polymerisation medium of Th (entry 1a, Table 2) had only a minor effect on the particle size, thus $R_{DLS} = 43$ nm *vs* 49 nm in the absence of ATh, while R_{TEM} did not
 25 change. A small contraction of the wet particles might be the result of

5 cross-linking. The situation was very different when ThM was substituted for Th. In this case the nanoparticles formed in absence of ATh were at least two times larger (109 nm vs 49 nm, Table 1). This effect was completely erased by the addition of ATh ($R_{DLS} = 47$ nm vs 43 nm for Th, Table 2).

10

Copolymerisation of ATh with a mixture of Th and ThM led to nanoparticles with a size intermediate to that for each of these two monomers (entry 2a, Table 2). ATh had no significant impact on the size polydispersity. The ten-fold increase in ATh in the polymerisation
15 medium (entries 4a to 6a; Table 2) decreased the size of the oligoTh nanoparticles by approximately 15 %, which might be the consequence of a higher cross-linking density. Surprisingly there was no effect on the size of the oligoThM nanoparticles.

20 The main spectra that were reported and discussed for the uncross-linked nanoparticles were also recorded for the ATh- cross-linked counterparts. The incorporation of ATh in the chains of oligo(ThM) was assessed by IR spectroscopy, even when only 3.3 vol% was used. Fig. 9 shows the absorption characteristics of the C=O stretching vibration of the acrylate
25 group of ATh at 1758 cm^{-1} . Moreover, the absorption typical of the C-H stretching, in the 2780 cm^{-1} to about 3050 cm^{-1} range dominates that one of the hydroxyl substituents of ThM where ATh is added. The contribution of the acrylic component of ATh is a reasonable explanation.

30

Fig. 10 is a comparison of the UV-Vis spectra of the aqueous dispersions of uncross-linked and ATh-cross-linked nanoparticles, prepared with the same Th (or ThM)/ HMPP composition. The major information is that the absorption by the cross-linked nanoparticles is higher above 350 nm

5 with an extension to higher wavelengths (notably for oligoThM) compared to the non-cross-linked nanoparticles.

The intensity of the emission maximum observed in the 350-600 nm range of the fluorescence emission spectrum of the oligo(ThM) nanoparticles increases dramatically upon cross-linking (Fig. 11). Therefore, the main effect of the ATh would be to increase the ThM conversion (approx. 70 %), rather than to increase the conjugated chain length.

2

15 In order to confirm that the stability of the nanoparticles towards organic solvents and monomers was improved by cross-linking, oligo(ThM) nanoparticles from entry 3a, Table 2, were dried by lyophilization and then dispersed (1 mg) in 1 mL organic phase (THF and HEMA). Stable dispersion without visible aggregates was immediately (within less than 20 5 min) obtained, but it was kept under stirring for 1 h in order to provide it the same time of contact between the particles and the organic phase, as in the case of the uncross-linked nanoparticles. The spherical particle morphology was preserved in each solvent (Fig. 12- A and B). Compared to R_{TEM} before redispersion (40 nm), the average particle size decreased 25 by ~15 % after dispersion in THF and not at all after dispersion in HEMA. An effective stabilization may be claimed, when compared to a size decrease of ~ 70 % and 45 % when the uncross-linked nanoparticles were redispersed in THF and HEMA, respectively.

30 The cross-linking of the oligo(Th) (and derivatives) nanoparticles by even a low amount of ATh (3.3 vol% with respect to the monomer) makes the particles resistant not only to organic solvents but also to aggregation when dispersed in these solvents and stored in water. Stable dispersions in monomers, such as HEMA, are ideal precursors of 35 nanocomposites.

5 **Example 3: Preparation and analysis of thermally stable nanoparticles and formation of carbon nanoparticles**

The thermal stability of nanoparticles is another important characteristic feature, this was investigated by TGA on a comparative basis for the non-stabilized, uncross-linked and the ATh-cross-link-stabilized
10 oligo(ThM) nanoparticles (entry 6 in Table 1, and entry 3a in Table 2, respectively). Non stabilized uncross-linked nanoparticles were prepared according to Example 1 and cross-link-stabilized nanoparticles were prepared according to Example 2.

15 A maximum weight loss was observed at 128°C, for the non-stabilized sample (Fig. 13), this most likely results from the elimination of the lower molar mass oligomers. This fraction amounts to approximately 35 wt%. Upon increasing the temperature, longer oligomers were progressively lost as shown by the slowly decreasing slope of the curve
20 until 700°C. A residue of 22 wt% was left at that temperature.

Cross-linking by ATh was beneficial to the thermal stability of the nanoparticles, and the maximum weight loss was shifted upwards (Fig. 13) by 30°C. In addition to the lowest molar mass ThM-oligomers,
25 polyacrylate segments could contribute to this loss peak that extended up to ~225°C and accounted for 20 wt% of the sample. A slow decomposition was again observed up to 700°C, at which a residue of 39 wt% was noted compared to 22 wt% for the un-stabilized particles. At 950°C, the residue decreased down to 29 wt%.

30

The latter residue was then analyzed by Raman spectroscopy (Fig. 14) and two peaks at 1591 cm⁻¹ and 1306 cm⁻¹ were observed. According to Qiao et al. (Carbon 2006, 44(1), 187-190), these peaks are the signatures of etches and basal planes in carbon nanoparticles, respectively. The
35 spectrum of the particles before TGA could not be recorded because of a very strong fluorescence.

5

Part of the TGA residue collected at 950°C was dispersed in ethanol, and a drop of the dispersion was deposited on a carbon-coated TEM grid. After solvent evaporation, spherical particles were observed by TEM (Fig. 15) with $R_{TEM} \sim 20$ nm, compared to 40 nm for the original ones (Fig. 8, 3a). In conclusion, carbon nanoparticles, were formed by thermolysis.

10

The herein prepared nanoparticles of oligo(Th) and derivatives are thus potential precursors of carbon nanoparticles by graphitization.

15

Example 4: Preparation and analysis of biocompatible nanoparticles

As the nanoparticles have the potential to be used in biological applications, such as in IOL implants, the cytotoxicity of the nanoparticles was determined. The cytotoxicity of crosslink-stabilized nanoparticles prepared according to Example 2 composed of Th/ThM at volume ratios of 1/2 (sample 1, entry 4 - Table 4) and 2/1 (sample 2, similar to entry 4 - Table 4, but at Th/ThM ratio 1/1 (v/v)) was tested by “Direct contact test” and “Extraction test”.

20

No significant difference was observed in the number of surviving cells from the positive control and the test wells. The slight increase of the absorbance of the test wells culture medium (CM) is probably due to the absorption of the nanoparticles themselves and not to the higher amount of formazan, and higher number of cells, respectively (Fig. 16).

25

Numerous cells with an aspect similar to that of the positive control well were observed upon microscopic inspection of the culture (Fig. 17), which is in compliance with the non-cytotoxicity of the particles determined spectroscopically. A similar result was obtained by the « Extraction test », for which a concentration of 2.5 mg/mL was used, similar to that incorporated in the poly(HEMA-co-MMA) hydrogel.

30

35

- 5 Again, the percentage of surviving cells varied by $\pm 5\%$ between the positive control and the test wells, which demonstrates the non-cytotoxicity of the extracts at that concentration (Fig. 18). Upon microscopic observation, the cells seemed to have similar morphology and aspect for the positive control and the test wells (Fig. 19).

10

Example 5: Preparation and analysis of conductive nanoparticles

- Stabilized nanoparticles were prepared according to Example 2. Conductivity measurements were performed with 10 mg ATh- stabilized nanoparticles of poly(Th-co/or-ThM) dispersed in 4mL 5×10^{-2} M tetrabutyl ammonium perchlorate solution of dry acetonitrile (Table 3).
15 The voltamperometric curves are presented in Fig. 20.

Sample	Composition
1	Same as entry 4 - Table 4
2	Similar to entry 4 – Table 4, but at Th/ThM ratio 1/1 (v/v)

Table 3: Composition of nanoparticles tested for their conductivity

- 20 It was observed that whatever the Th/ ThM ratio in the nanoparticles an anodic peak appeared at approx. -0.6 V and a cathodic one at approx. + 1.15 V (Fig. 20). These two peaks speak for the conductive nature of polymer. They are not very strong at these test conditions, probably because only a few particles are in intimate contact with the electrode
25 and may thus contribute to the electroconductivity. However, at optimised conditions, the particles may be useful for the preparation of solar and photovoltaic cells, biosensors, etc.

Example 6: Preparation and analysis of a hydrogel nanocomposite

- 30 Non-stabilized uncross-linked poly(Th-co/or-ThM) nanoparticles were prepared according to Example 1 and cross-link-stabilized nanoparticles were prepared according to Example 2. The experimental data and size characterisation features are recorded in Table 4.

5

Whatever the concentration of the reagents used the nanoparticles produced were systematically spherical with a narrow size-distribution, as shown in Fig. 21. Moreover, the average diameter of the nanoparticles systematically decreased upon both the substitution of Th for ThM and
10 the crosslinking by increasing amounts of ATh (Table 4).

The nanoparticles as described in Table 4 were then used in the production of poly(HEMA-*co*-MMA) hydrogel nanocomposites.

Entry	Monomer 10 μ L	ATh μ L	R_{DLS} nm	PDI_{DLS}	R_{TEM} nm
1	ThM	0	218	0.019	~180
2	Th/ ThM, 1/2 (v/v)	0	166	0.128	~ 140
3	Th	0.33 μ L	86	0.0183	70
4	Th/ThM, 1/2 (v/v)	0.33 μ L	90	0.0143	70
5	ThM	0.33 μ L	94	0.0209	80
6	Th	3.33 μ L	70	0.0092	60
7	Th/ThM, 1/2, (v/v)	3.33 μ L	84	0.0152	65-70
8	ThM	3.33 μ L	90	0.105	75-80

Table 4: Experimental data for the preparation of non-stabilized and
15 ATh-stabilized poly(Th-*co*/or-ThM) nanoparticles.

The addition under stirring of an aqueous dispersion of nanoparticles (1mg/mL) into the acrylic monomers precursor of the hydrogel, was unsuccessful because of unavoidable phase separation during
20 polymerisation. Therefore, the nanoparticles were recovered from the dispersion and dried (cfr Experimental Part), being then easily re-dispersed in the mixture of comonomers (95 vol% HEMA/ 4.9 vol% MMA/ 0.1 vol% EGDMA) at a content of 2.5 and 10 mg/ mL of comonomers, respectively. ATh (10 μ L/ 1 mL monomer) was
25 systematically added to the comonomers, in order to promote

5 interactions between the poly(Th- co/or-ThM) nanoparticles and
 chemically similar thiophene units incorporated in the hydrogel network.
 As schematically shown in Fig. 22, the ATh-molecules might be
 adsorbed onto the nanoparticles surface with their acrylic unsaturation
 exposed to the copolymerisation medium, which foreshadows a
 10 mechanism of stabilization of the nanoparticles within the hydrogel
 poly(HEMA-co-MMA) matrix.

Entry	Code Table 4	Nanoparticles Th/ ThM/ ATh mL	Nanoparticles content mg/ mL comonomers	Water uptake %
1a	Non-filled hydrogels with the basic composition: 95 vol% HEMA/ 4.9 vol% MMA/ 0.1 vol% EGDMA			35
2a	Entry 1	0/ 10/ 0	10	23
3a	Entry 2	3.33/ 6.67/ 0	10	19
4a	Entry 5	0/ 10/ 0.33	10	31
5a	Entry 3	10/ 0/ 0.33	2.5	36
6a	Entry 4	3.33/ 6.67/ 0.33	2.5	35
7a	Entry 5	0/ 10/ 0.33	2.5	35
8a	Entry 6	10/ 0/ 3.33	2.5	36
9a	Entry 7	3.33/ 6.67/ 3.33	2.5	35
10a	Entry 8	0/ 10/ 3.33	2.5	36

Table 5: Experimental data for the preparation of poly(HEMA-co-MMA)
 15 hydrogel nanocomposites

5 As a rule, the pre-dried poly(Th- *co/or*-ThM) nanoparticles were redispersed quasi-qualitatively within the HEMA/MMA/EGDMA/ATh mixture. It is only when the nanoparticles were not stabilized by effective crosslinking with ATh that a negligible amount of aggregates could be observed. Any aggregation was inhibited and completely
10 transparent dispersions were formed when the nanoparticles were prepared with a higher amount of ATh (entries 8a-10a, Table 5). Two contents of nanoparticles in the comonomer feed were considered (Table 5). When the content of the same nanoparticles was increased from 2.5 mg to 10 mg per mL of comonomers (e.g., entries 4a and 7a, Table 5),
15 the yellow colour turned brown, as illustrated in Fig. 23 for these samples.

The nanoparticles incorporated within the hydrogel were observed by TEM (Fig. 26). A homogeneous distribution was the rule. Due to the
20 thickness of the slices prepared by microtomy and the fact that not all the nanoparticles are observed with the same TEM focalisation distance, means the average size of the dispersed nanoparticles cannot be determined reliably from the TEM pictures. However, the apparent size is in qualitative agreement with the size reported for the nanoparticles
25 before the hydrogel loading (Table 4).

The preparation technique that consists in dispersing the preformed nanoparticles within the acrylic comonomers precursor of the hydrogel, in the presence of a 3-[(2-acryloyloxy)methyl] thiophene (ATh), leads to
30 a homogenous dispersion of the nanofiller.

Example 7: Preparation and analysis of a hydrogel nanocomposite as IOL implant

Recently, Holladay (Eurotimes, September 2007, 24) addressed the
35 question of the possible deleterious impact of the blue-light absorbing IOLs on the vision quality. He wrote that “the lens would not look

5 yellow if it didn't affect colour vision". Therefore, hydrogel nanocomposites listed in Table 5 were compared with a conventional yellow hydrogel IOL (YellowFlex, PhysIOL). Fig. 23 emphasizes a strong decrease in the yellow colour when 2.5 mg of nanoparticles were dispersed in 1 mL of acrylic comonomers (Fig. 23, 5a - 10a), compared
10 to the reference. Although weaker, the same effect holds when the hydrogel was loaded by 10 mg of nanoparticles per mL comonomers (Fig. 23, 2a - 4a).

The UV- and blue-light blocking ability of the poly(HEMA-*co*-MMA)
15 nanocomposites was established by recording the UV-Vis spectra of 1 mm thick samples. Fig. 24-A shows that the unloaded hydrogel (1a) absorbs light at and below 250 nm, whereas the transmission exceeds 89% at 430 nm (in the blue light region) which would be harmful to the eye. The addition of thiophene containing nanoparticles to the hydrogel
20 shifted the absorption towards the UV and blue light region (Fig. 24A and D). This effect is more dramatic as the content of nanoparticles in the composition is increased (Fig. 24A, 4a and 7a). Indeed, 36 % of light was transmitted at 430 nm when poly(ThM) nanoparticles were used at 10 mg of nanoparticles per ml of acrylic monomer (4a in Table 5)
25 compared to 51 % for a four times lower content of nanoparticles. Although beneficial, this effect is not dramatic with respect to the 89 % of transmittance observed with the neat hydrogel at the same wavelength (Fig. 24A, 1a).

30 The UV and blue light blocking property of the hydrogel nanocomposites was also sensitive, at least to a moderate extent, to the degree of crosslinking of the nanoparticles. For instance, a ten-fold increase in the amount of crosslinker (ATh) used for the poly(ThM) nanoparticles preparation (1a vs. 7a in Table 5) resulted in a higher transmittance at

5 430 nm from 51 % to 75 % at the same nanoparticles content (Fig. 24B and 24C – 7a and 10a).

The nanocomposite comprising poly(ThM) nanoparticles with both the lower content and the lower crosslinking degree (Fig. 24A; 7a) appears
10 to be better at reducing UV and blue light transmission mimicking the commercially available yellow IOL implant (Fig. 24A, Helio25, PhysIOL). As a rule, a change in the Th/ThM volume ratio of the nanoparticles, all the other characteristic features being the same, had only a minor influence on the light-transmitting properties, as shown in
15 Fig. 24B and 24C. Although the hydrogel nanocomposite 3a (Table 5) exhibited the higher UV and blue light blocking performance in the series studied (Fig. 24D and 24A), it should be noted that the benefits of the nanocomposite 7a which is stabilized by crosslinking (no aggregation) and used at the lower content (weaker coloration) should be
20 balanced with that of 6a. Most of the hydrogel nanocomposites under consideration in Table 5 not only transmit more than 90 % of visible light but their UV-Vis spectrum is also similar to the one of the lens crystalline of a 4 years old child (Fig. 25), which is advantageous to the visual comfort of the patient.

25

Hydrogel nanocomposites were analyzed by DSC before and after drying, with a special attention paid to the glass transition temperature (T_g). Fig. 27A shows that the dried unfilled hydrogel (1a) has a T_g of 104 °C, consistent with the same value reported by Li et al. (Polymer
30 2007, 48, 3982-3989) for poly(HEMA). The T_g of poly(HEMA-co-MMA) was increased by ~10°C upon loading with 0.25 mg nanoparticles/mL acrylic comonomers, whatever their chemical composition and degree of crosslinking (Figs. 27A (5a), 27B and 27C). The magnitude of this effect should increase with the content of the
35 nanoparticles, which might explain that T_g was no longer detected by DSC when this content was increased four times (Fig. 28A, 2a-4a).

5

Because hydrophilic acrylic IOL implants are hydrated in use, the herein described nanocomposites were tested as hydrogels and not only in the dried state as was the case for TEM observation and DSC analysis. The swelling of any crosslinked polymer by a ligand results in a loss of modulus and mechanical strength (Meakin et al. J. Mater. Sci.: Mater. Medic. 2003, 14, 783-787; Anseth et al, Biomaterials 1996, 17, 1647-1657). When IOL implants are concerned, a high impact resistance is not required. They just have to resist folding when inserted in the eye. In this work, the hydrogel nanocomposites were analyzed by DMA at 20°C with a flat-plate geometry and 1 mm thick hydrogel discs (diameter: 8 mm). The major problem faced in these experiments is the slipping of the oscillating plate on the hydrogel surface.

In the strain range investigated in this work, (0.02 % to 8 %), the unloaded hydrogel behaves as an elastic material, the storage (G') and loss (G'') moduli being strain independent, as is the damping factor ($\tan \delta = G''/G'$) (Fig. 28, 1a). This observation is consistent with the analysis of poly(HEMA) hydrogels with the same water content (35 wt%) by Meakin et al. (J. Mater. Sci. Mater. Medic. 2003, 14, 783-787). Typically, the samples with the higher content of nanoparticles (2a and 3a) have a much higher storage modulus, at least at low strains, than all the other nanocomposites that are 4 times less loaded (Fig. 28A and 28E). This filling effect reinforces the materials resistance to deformation. The sharp decrease in G' and the sharp increase in $\tan \delta$ with increasing strain, which is observed for the highly loaded samples 2a and 3a (Fig. 28A), is an experimental artefact related to the aforementioned problem of slipping of the oscillating plate on the surface of the nanocomposites with the lower content (19-23 wt% compared to 35 wt% for the other samples).

35

5 The nanocomposites with the lower content of nanoparticles can be discriminated on the basis of the crosslinking degree (and not the chemical composition) of the constitutive nanofiller. Indeed, G' and G'' are substantially higher when the nanoparticles were prepared with ten times more crosslinker (A_{Th}), as emphasized by the samples 9a and 10a compared to the less crosslinked counterparts 6a and 7a (Fig. 28D and 28E). Another reason is the reinforcing ability of the stiff filler. Once again, a discontinuity is observed in the strain dependence of G' and G'' (and an increase in $\tan \delta$) for the samples 9a and 10a, which is another signature of the “slipping” problem faced in the DMA measurements.

15

The glass transition temperature of the dried polyacrylic network increased by $\sim 10^\circ\text{C}$ at the lower content of nanoparticles, which demonstrates that the nanoparticles interact with the A_{Th} co-units of the hydrogel and accordingly have a reinforcing action. The nanofilling also has an impact on the dynamic mechanical properties of the hydrogel. The storage modulus increases with the loading. However, at a constant loading, this modulus is very sensitive to the crosslinking degree of the nanoparticles.

25 The effect of the nanoparticles on the thermal stability of the polymeric network was also investigated by thermogravimetric analysis. At the higher loading content, whatever the chemical composition of the nanoparticles (samples 2a-4a), Fig. 29A and Table 6 show that the nanofiller has a negative impact on the thermal stability of the matrix. Indeed, the first weight loss is decreased by $35\text{-}38^\circ\text{C}$ (T_d^1), and the second one by 73°C (T_d^2). The two-step decomposition is typical of the polymeric matrix. It is less affected by the nanofilling when the content of the nanoparticles is decreased (comparison of samples 5a to 10a with samples 2a to 4a Table 6).

35

- 5 According to the data reported in Table 6, the nanoparticles should not perturb significantly the stability of the hydrogel at the sterilization temperature and time used for IOL implants (120°C for 21 min, respectively).

Entry	Td ¹ (°C)	Td ² (°C)
1a	393	496
2a	358	424
3a	356	423
4a	355	423
5a	380	425
6a	394	430
8a	396	427
10a	388	430

- 10 **Table 6:** Decomposition temperatures of the pre-dried nanocomposites listed in Table 5.

As the nanocomposites/hydrogels may be used in IOL implants their biocompatibility is important, in particular their ability to inhibit cell
 15 adhesion. A common complication after cataract surgery is Posterior Capsular Opacification (PCO) which occurs due to the adhesion of lens epithelial cells (LECs) to the posterior side of both the lens and the capsular bag. Therefore the ability of LECs to adhere to nanocomposites/hydrogels according to the invention was investigated
 20 by an *in vitro* cell adhesion test.

Fig. 30 shows a slight increase in the cell adhesion to the hydrogel surface upon loading with thiophene containing nanoparticles. A possible explanation might be the partial exposure of some of the
 25 presumably hydrophobic nanoparticles to the hydrophilic surface, which would create heterogeneities known for enhancing the cell adhesion.

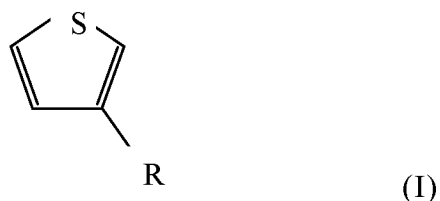
- 5 However, whatever the nanoparticles, a cell occupation of less than 8 % of the surface is estimated and testifies resistance of the nanocomposites to cell adhesion and that the nanocomposites have the potential to resist posterior capsular opacification after cataract surgery.

5 CLAIMS

1. A method for the production of nanoparticles comprising a conjugated polymer, wherein the method comprises (i) providing a reaction mixture comprising a monomer, a photosensitising agent and a solvent, and (ii) exposing the reaction mixture to photo-irradiation to form nanoparticles of a conjugated polymer characterized in that the photosensitising agent is immiscible with the solvent.

2. The method of claim 1 wherein the solvent is water or an aqueous solution.

3. The method of claim 1 or 2 wherein the monomer is thiophene or a derivative thereof, wherein the derivative is of formula (I):



wherein R is selected from the group comprising an aliphatic group, an alcohol group, an amino group, an alkoxy group, an acryl group, a meth(acryl) group, a carboxyl group, an ester group, a (poly)ester group, an ether group or a (poly)ether group.

4. The method of any preceding claim further comprising a crosslinking agent.

5. The method according to claim 4 wherein the crosslinking agent is 3-[(2)acryloyloxy)methyl] thiophene.

6. The method of any preceding claim wherein the ratio of photosensitising agent to monomer is in the range 1 % to 100 % wherein the % is vol%.

5

7. The method of any preceding claim wherein the photosensitising agent is 2-hydroxy-2-methyl-propiofenone.

10 8. A composite comprising nanoparticles produced or obtainable by any of the methods of claim 1 to 7.

9. The composite of claim 8 wherein the nanoparticles have a polydispersity inferior to 0.5, more preferably a polydispersity inferior to 0.2, even more preferably inferior to 0.1 and even equal or inferior to 0.02.

10. The composite of claim 8 or 9 wherein the nanoparticles comprise poly(thiophene or a derivative thereof, or a copolymer of thiophene and/or derivatives thereof.

11. The composite of any of claims 8 to 10 wherein the composite is a hydrogel.

25

12. The composite of any of claims 8 to 11 for use as an optical material.

13. A method of producing a hydrogel comprising (i) dispersing nanoparticles produced or obtainable by the method of any of claims 1 to 7, and (ii) polymerising the monomer around the nanoparticles to form a hydrogel containing the nanoparticles.

14. The method of claim 13 wherein the monomer is a mixture of hydroxyethyl methacrylate (HEMA) and methyl methacrylate (MMA), which polymerises to form poly(HEMA-*co*-MMA).

5

15. An intraocular lens implant comprising a hydrogel containing nanoparticles of a conjugated polymer obtained or obtainable by the method of any of claims 1 to 7.

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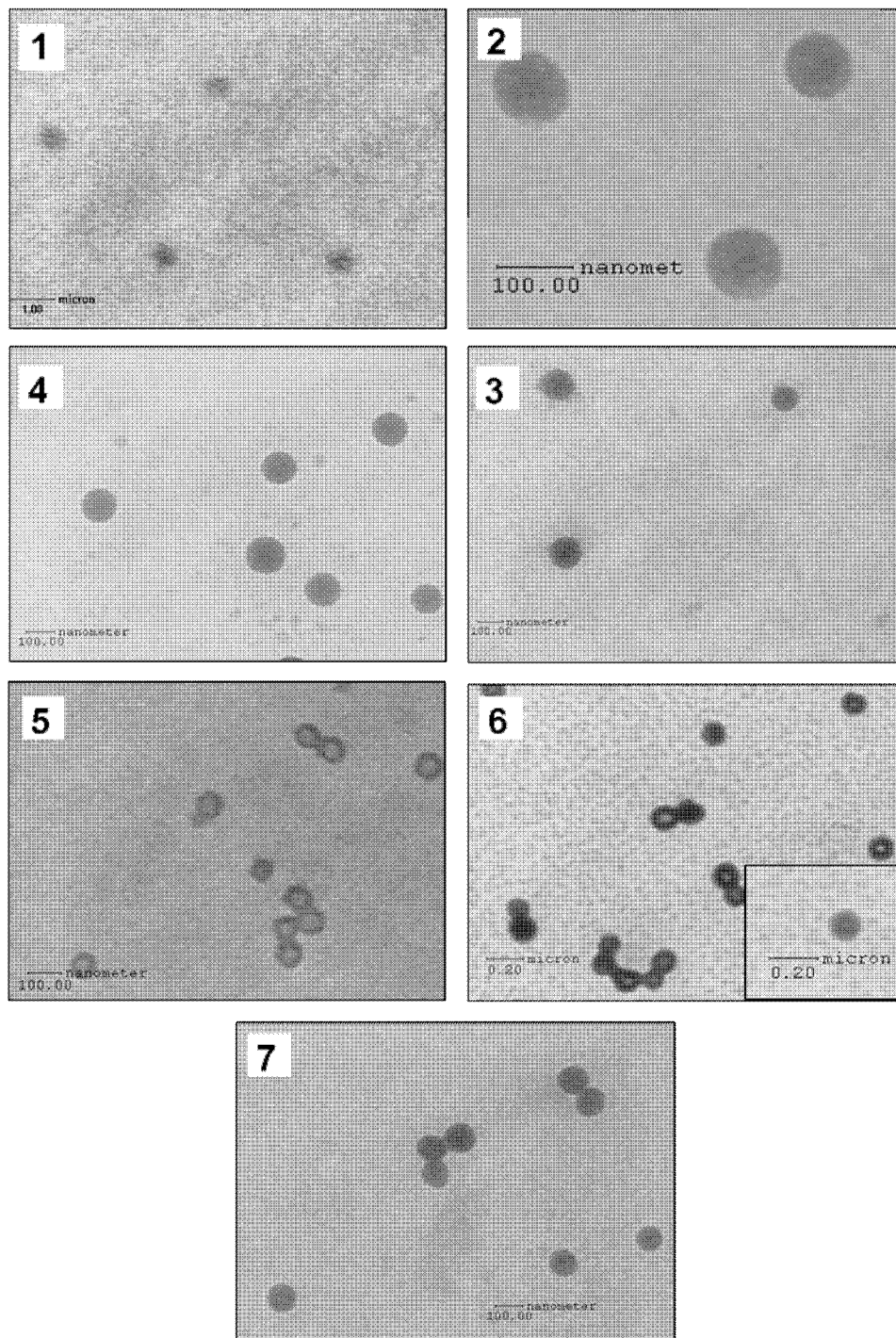
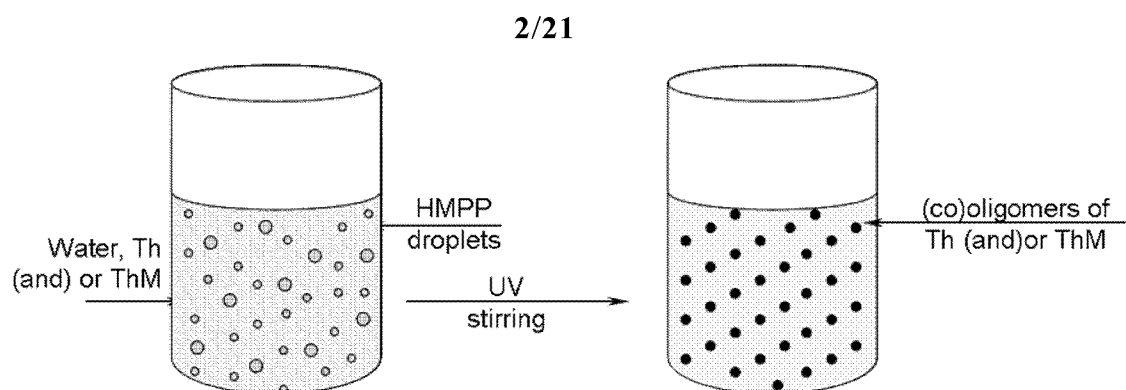
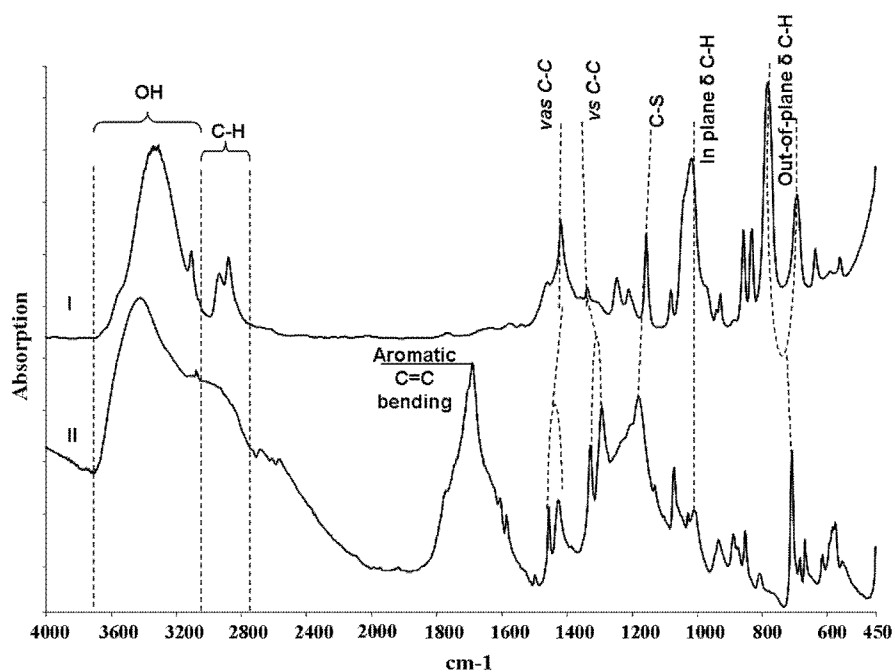


Figure 1

**Figure 2****Figure 3**

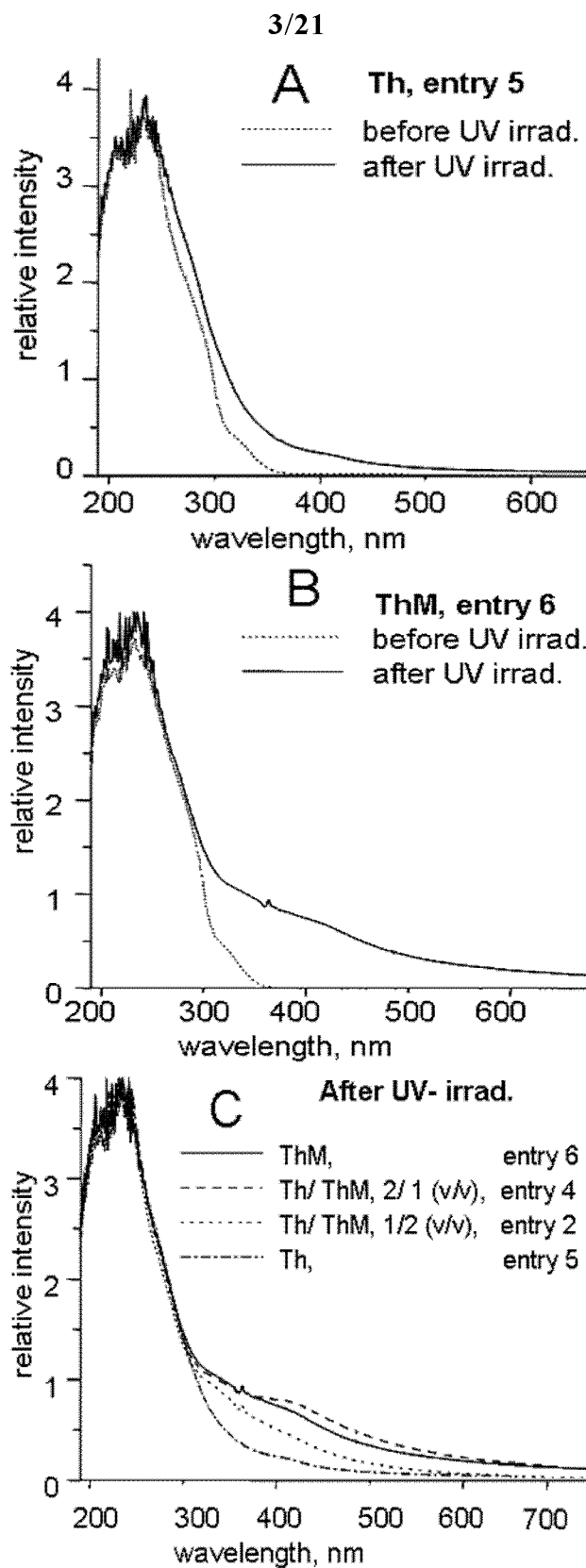


Figure 4

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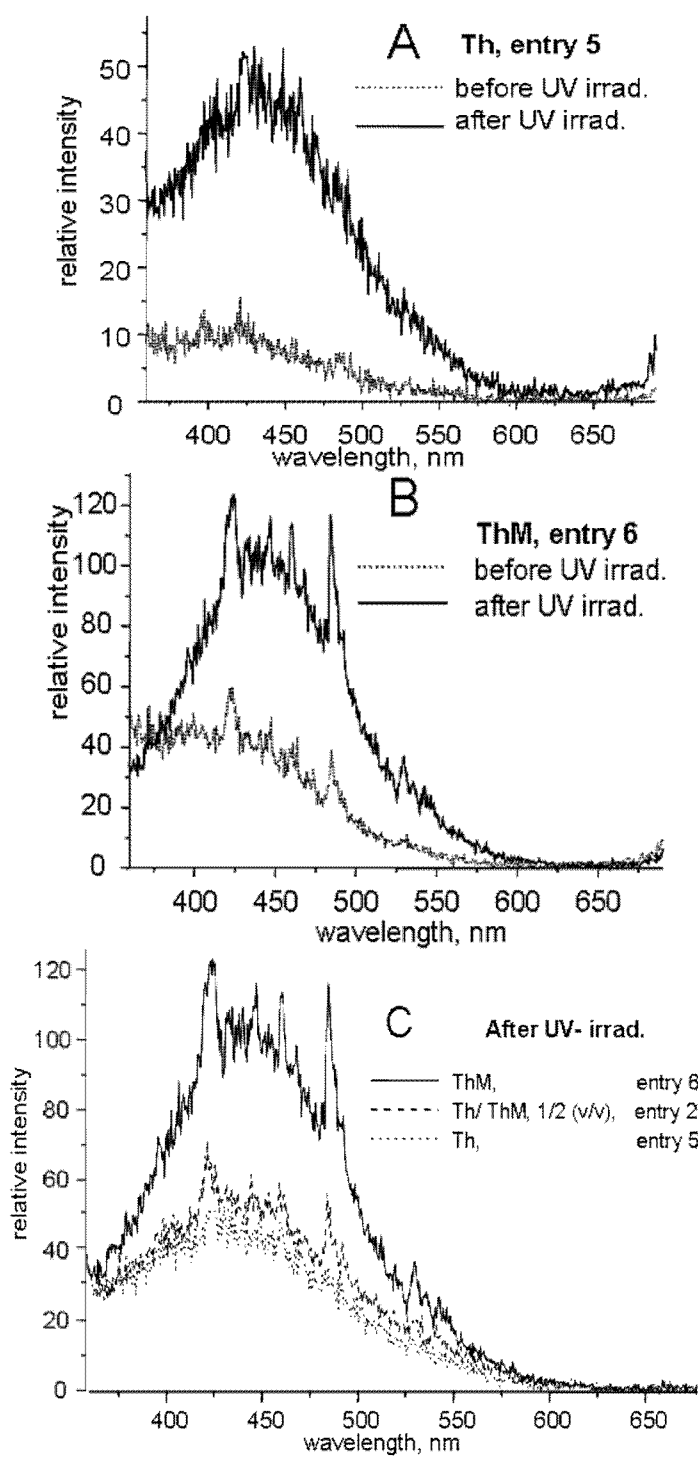
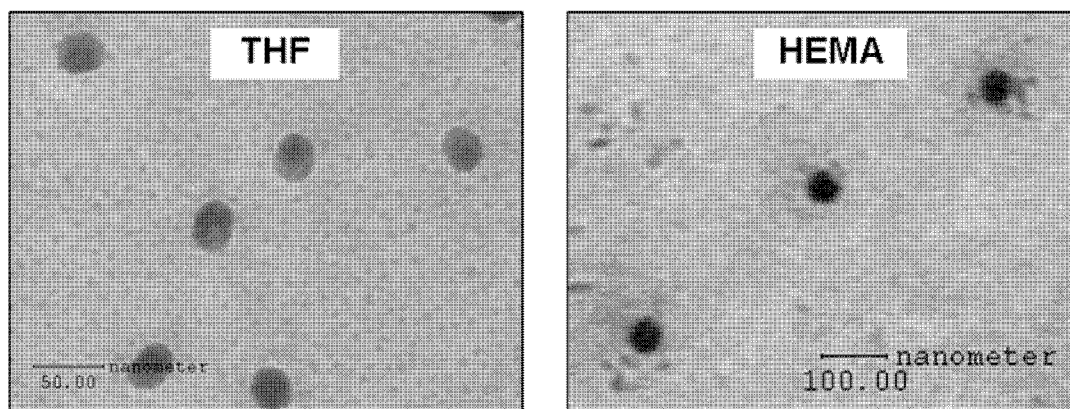
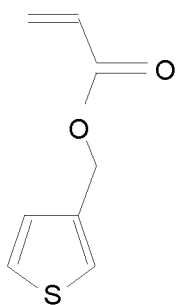
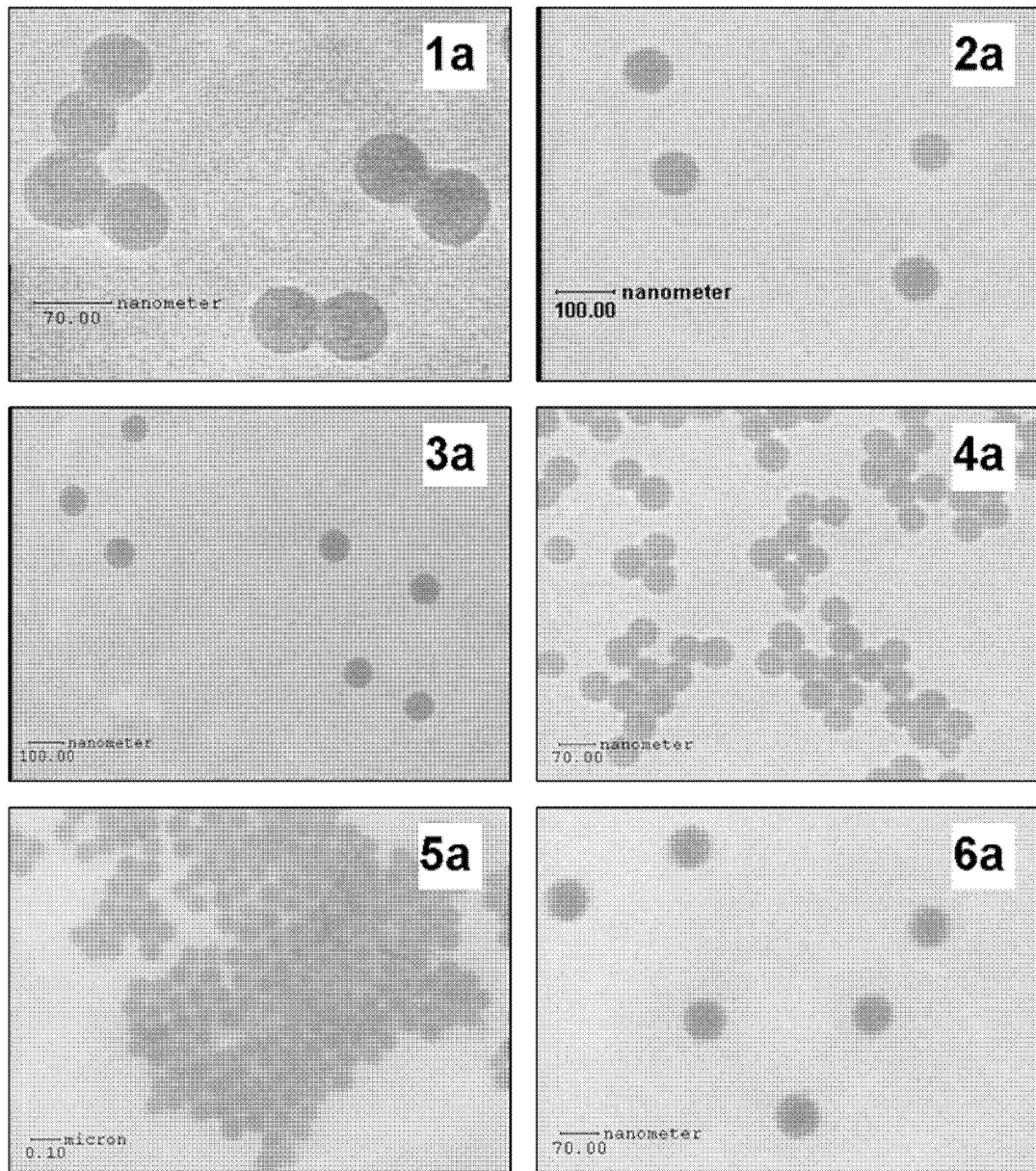


Figure 5

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**Figure 6****Figure 7**

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**Figure 8**

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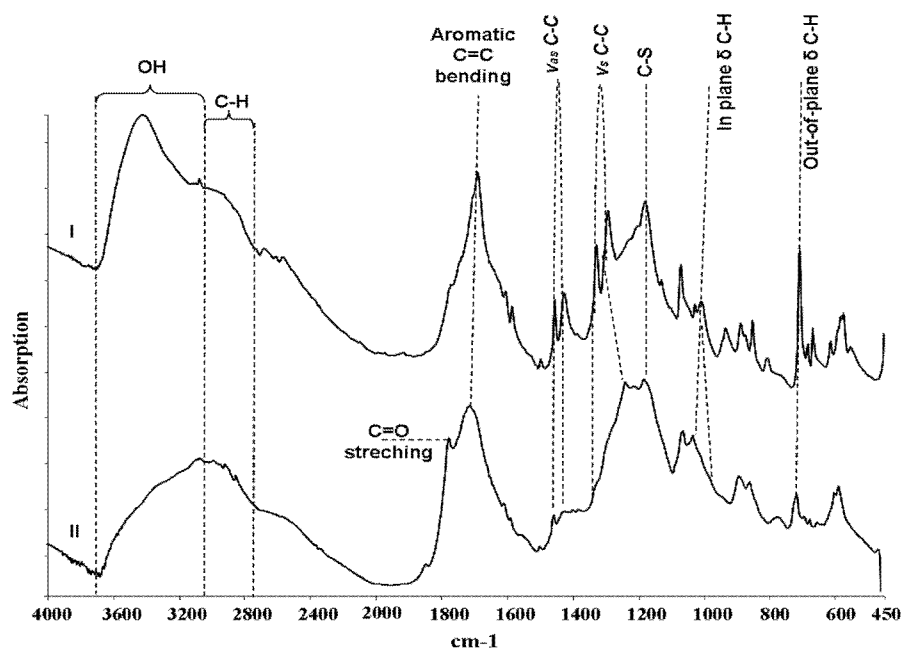


Figure 9

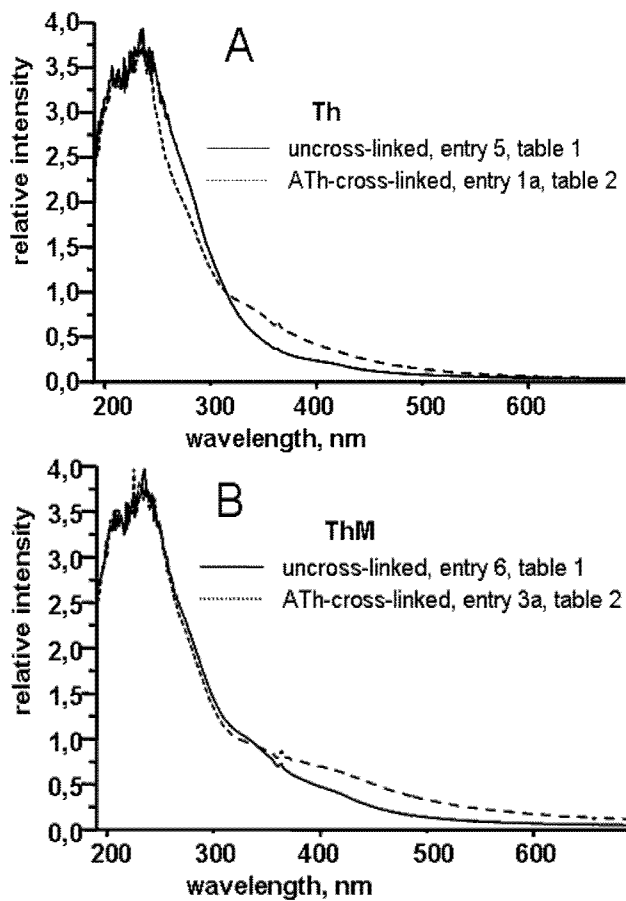


Figure 10

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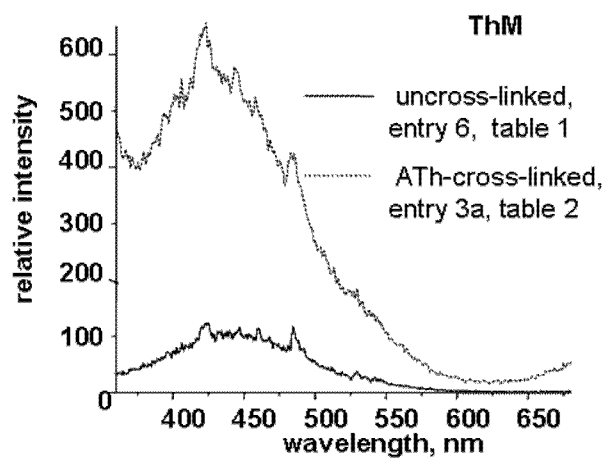


Figure 11

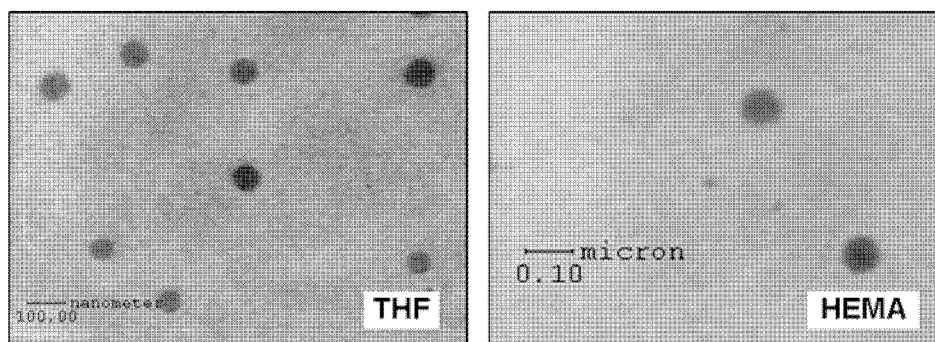


Figure 12

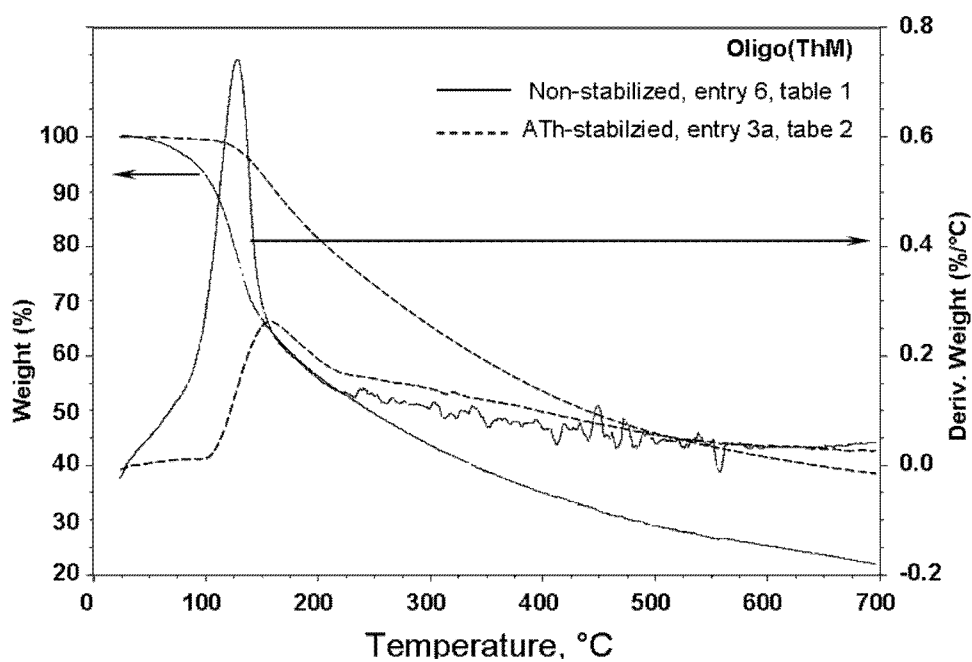
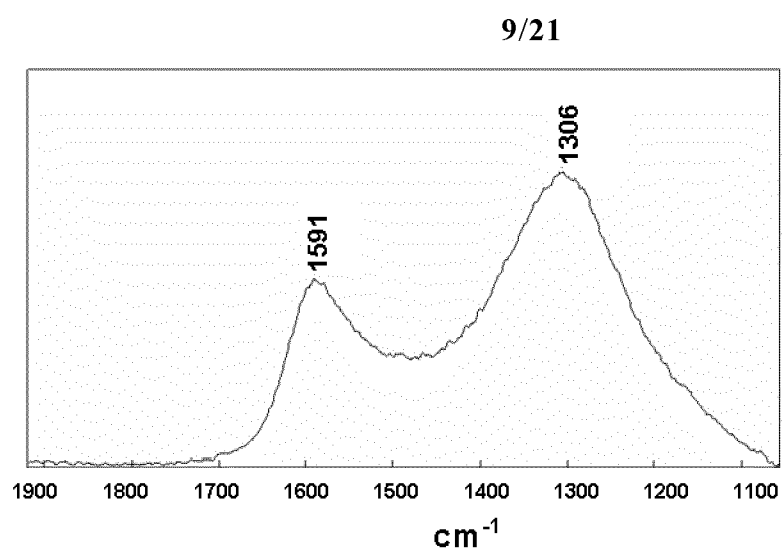
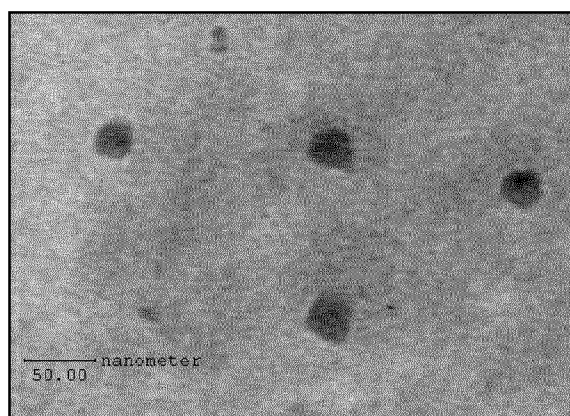
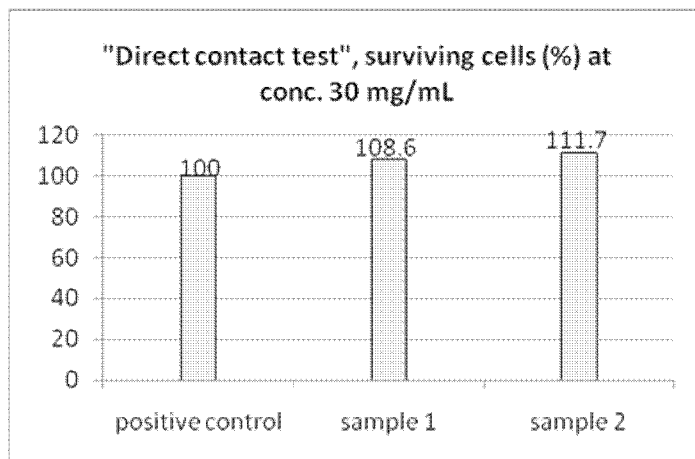
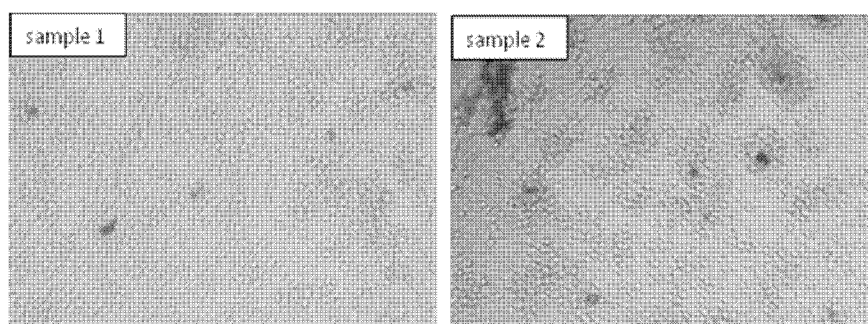
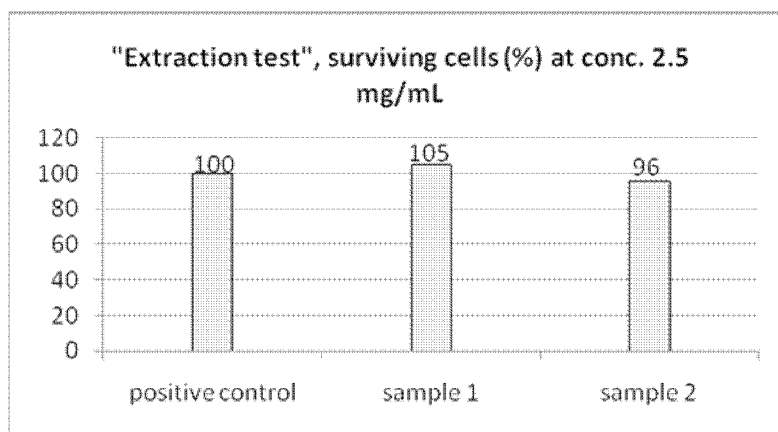


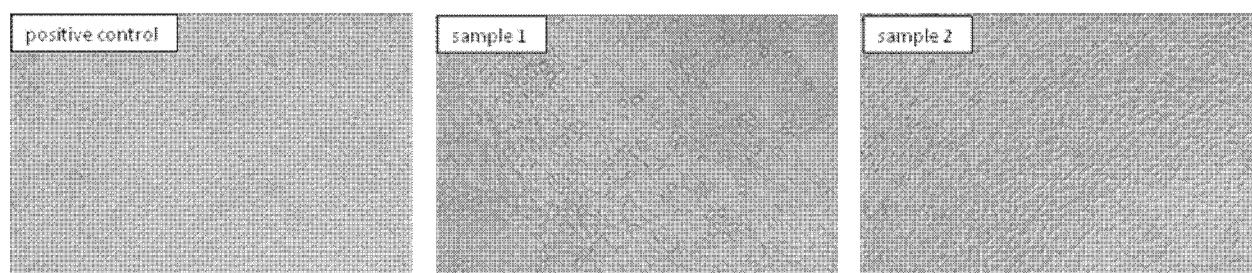
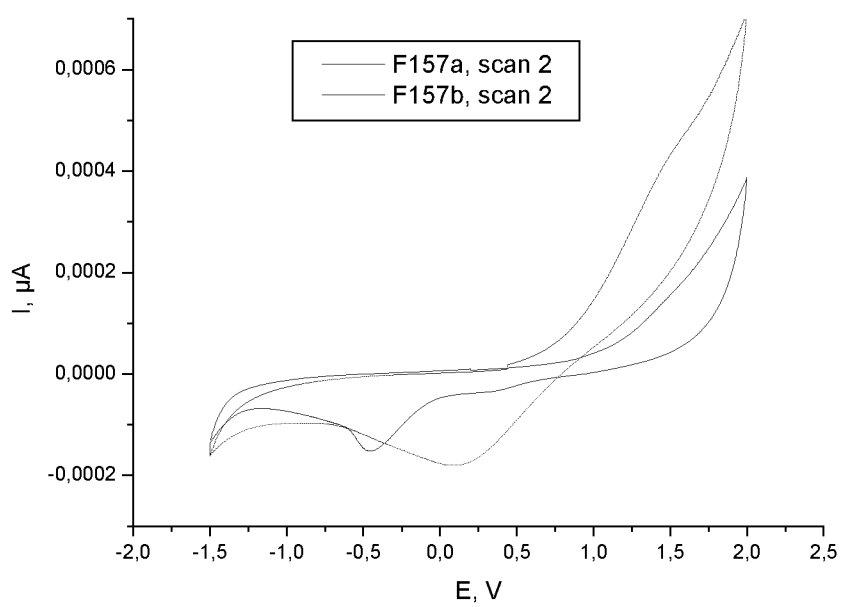
Figure 13

**Figure 14****Figure 15**

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**Figure 16****Figure 17****Figure 18**

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**Figure 19****Figure 20**

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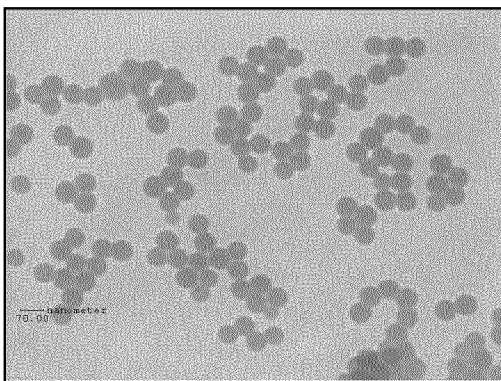


Figure 21

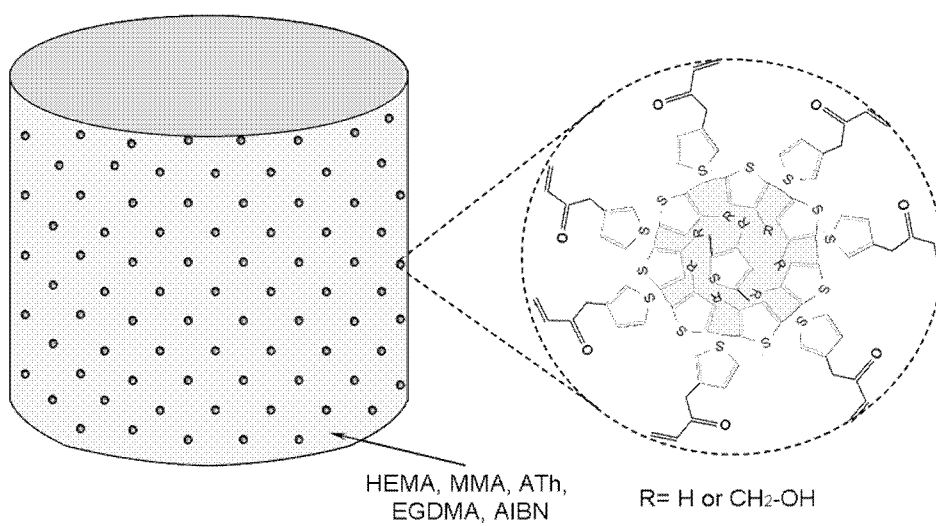


Figure 22

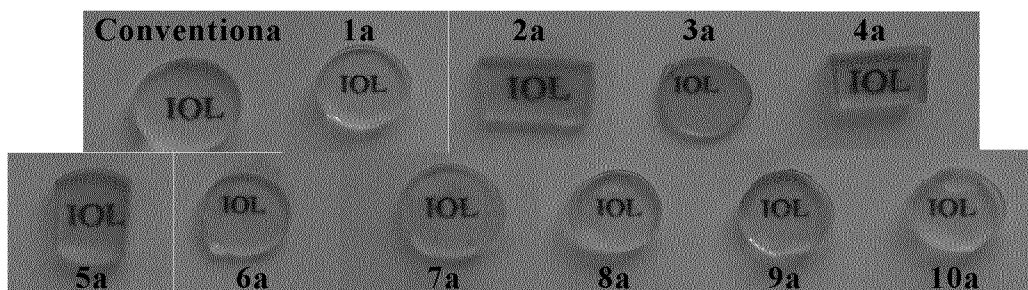


Figure 23

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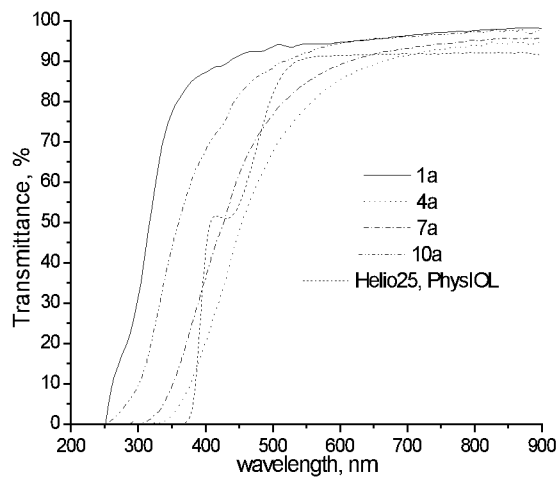


Figure 24A

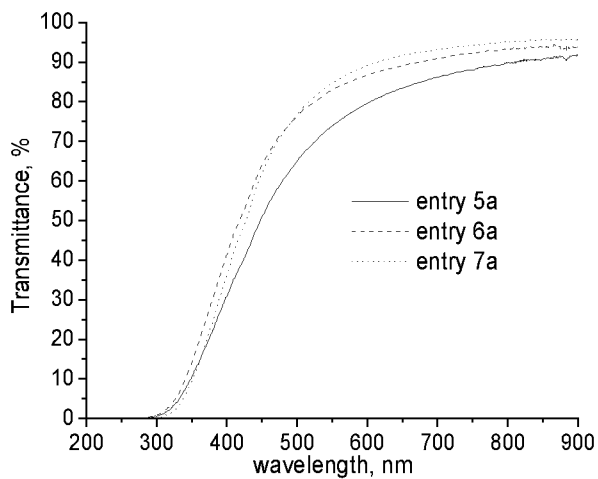


Figure 24B

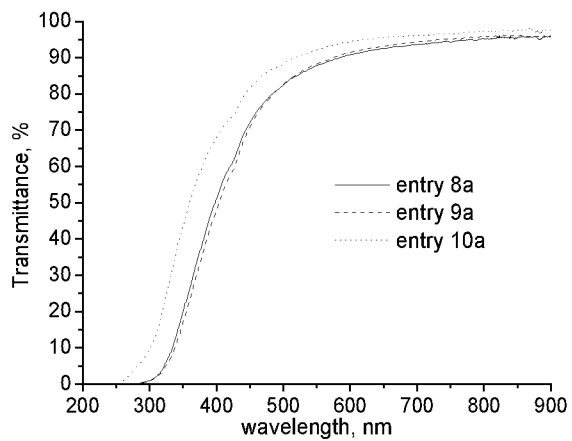


Figure 24C

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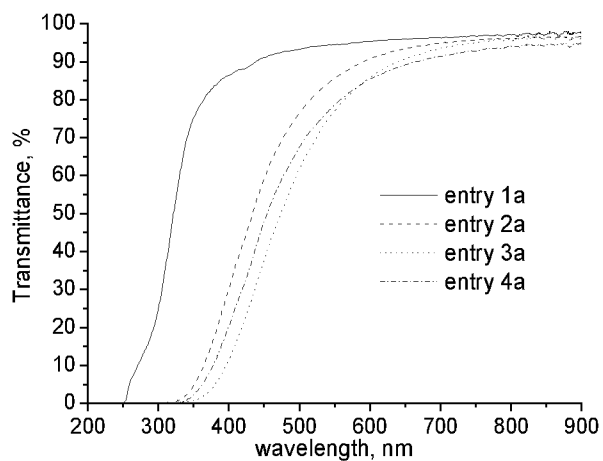


Figure 24D

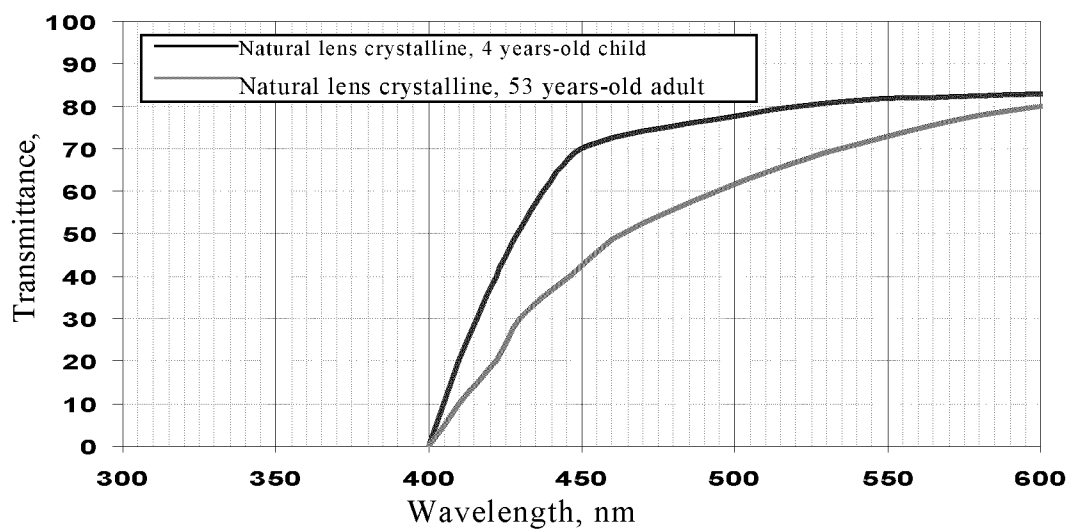


Figure 25

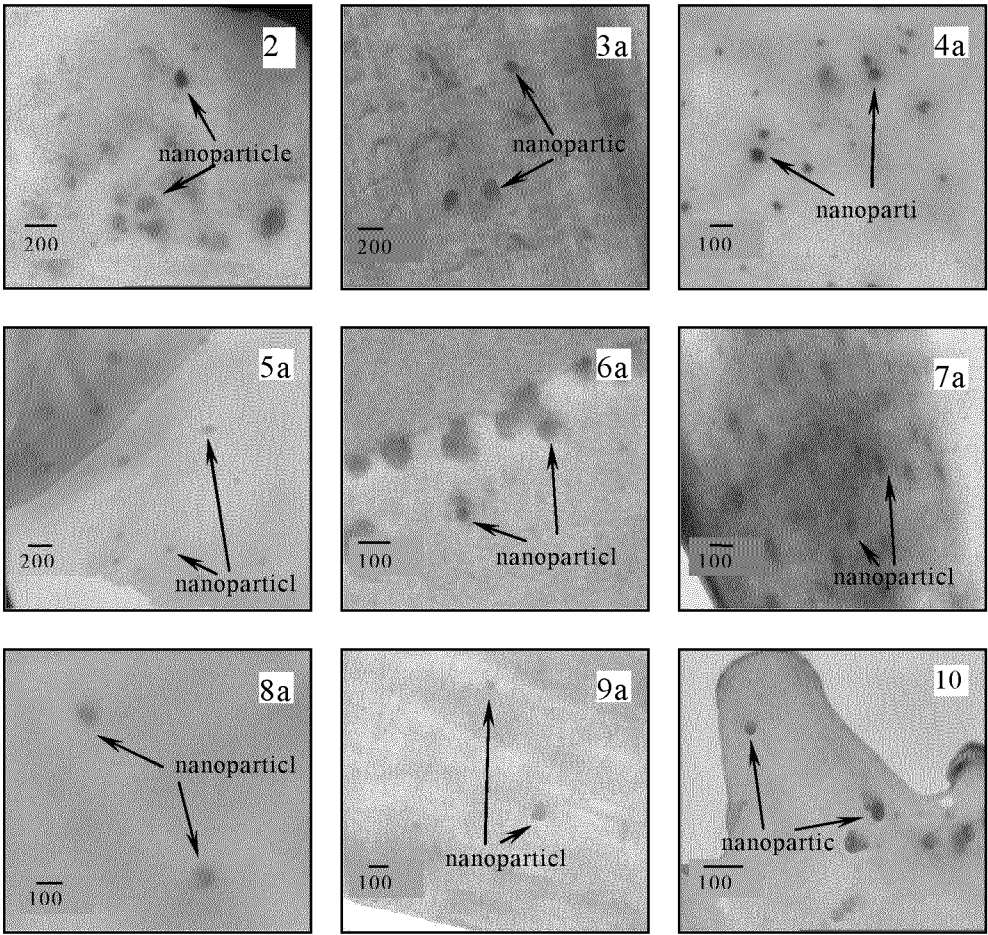


Figure 26

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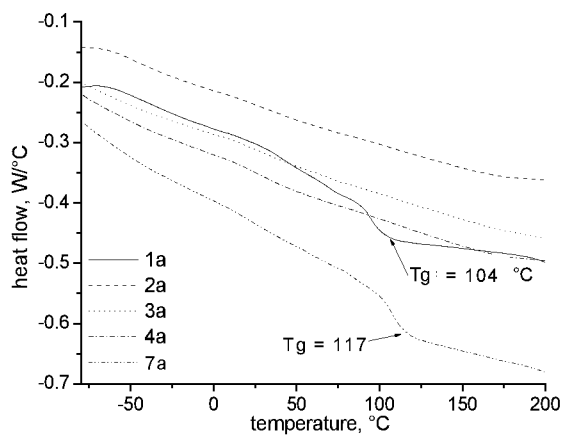


Figure 27A

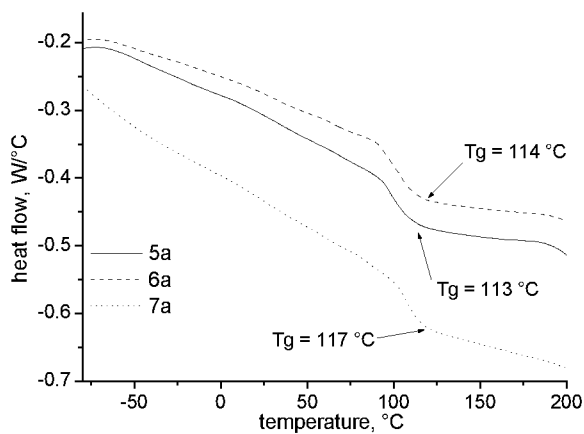


Figure 27B

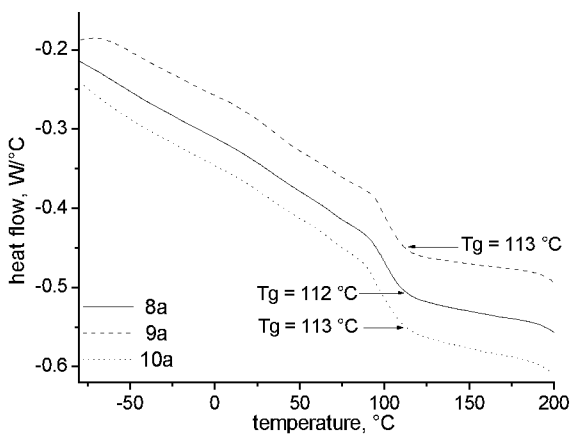


Figure 27C

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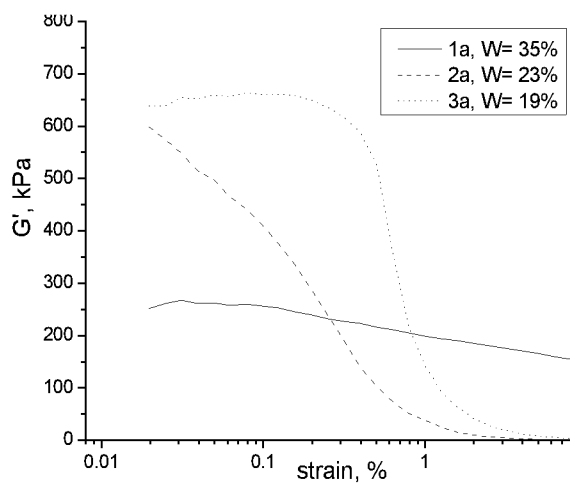


Figure 28A

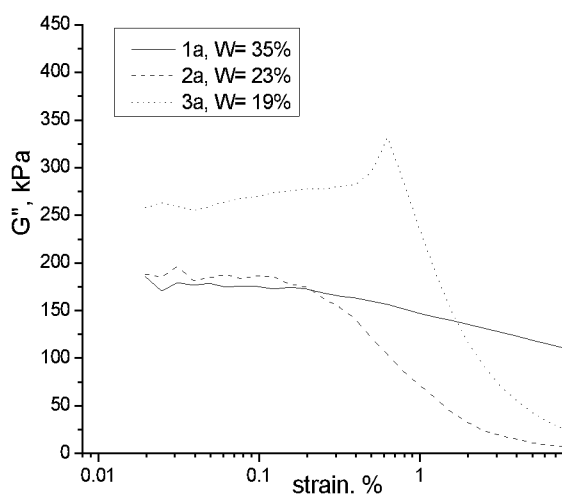


Figure 28B

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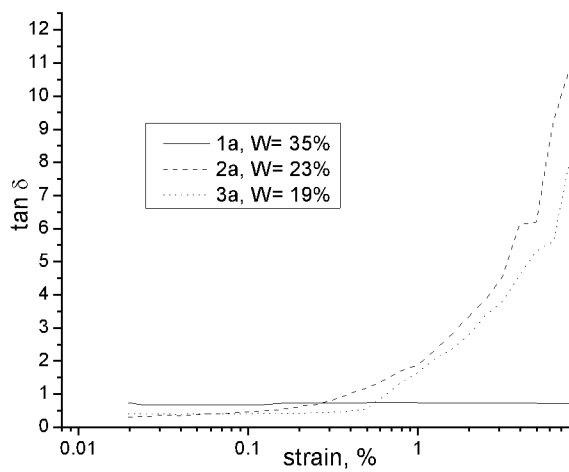


Figure 28C

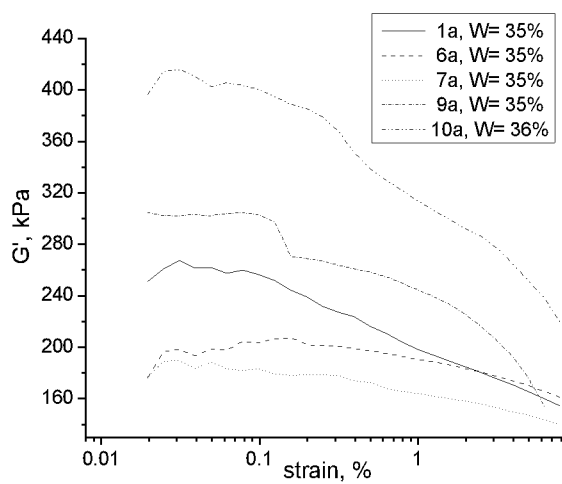


Figure 28D

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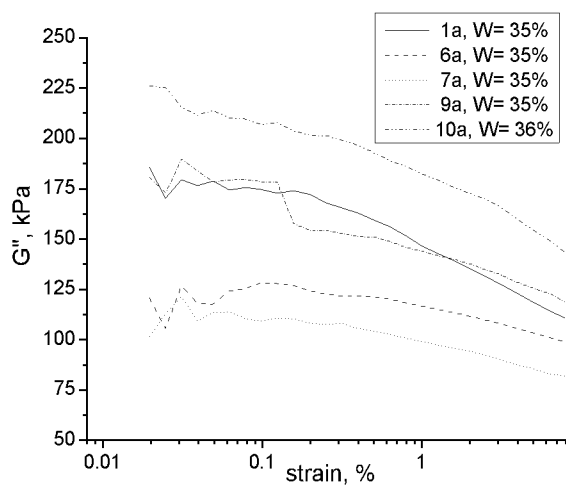


Figure 28E

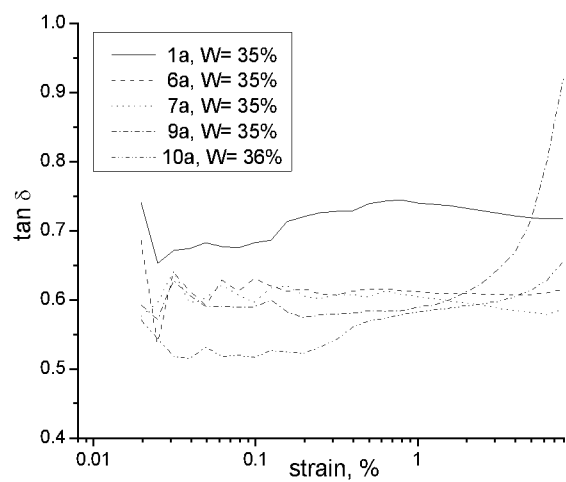


Figure 28F

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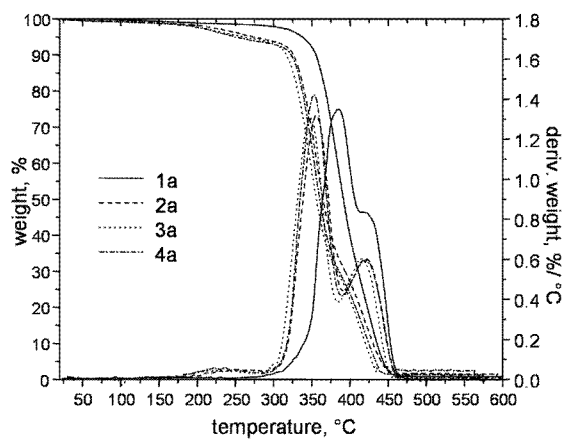


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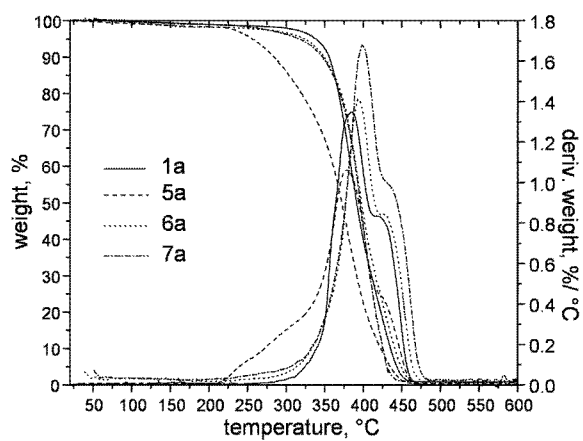


Figure 29B

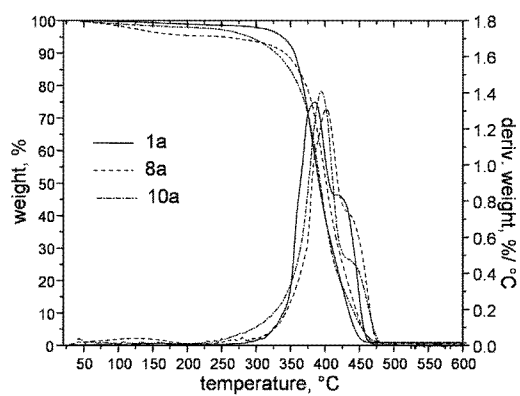
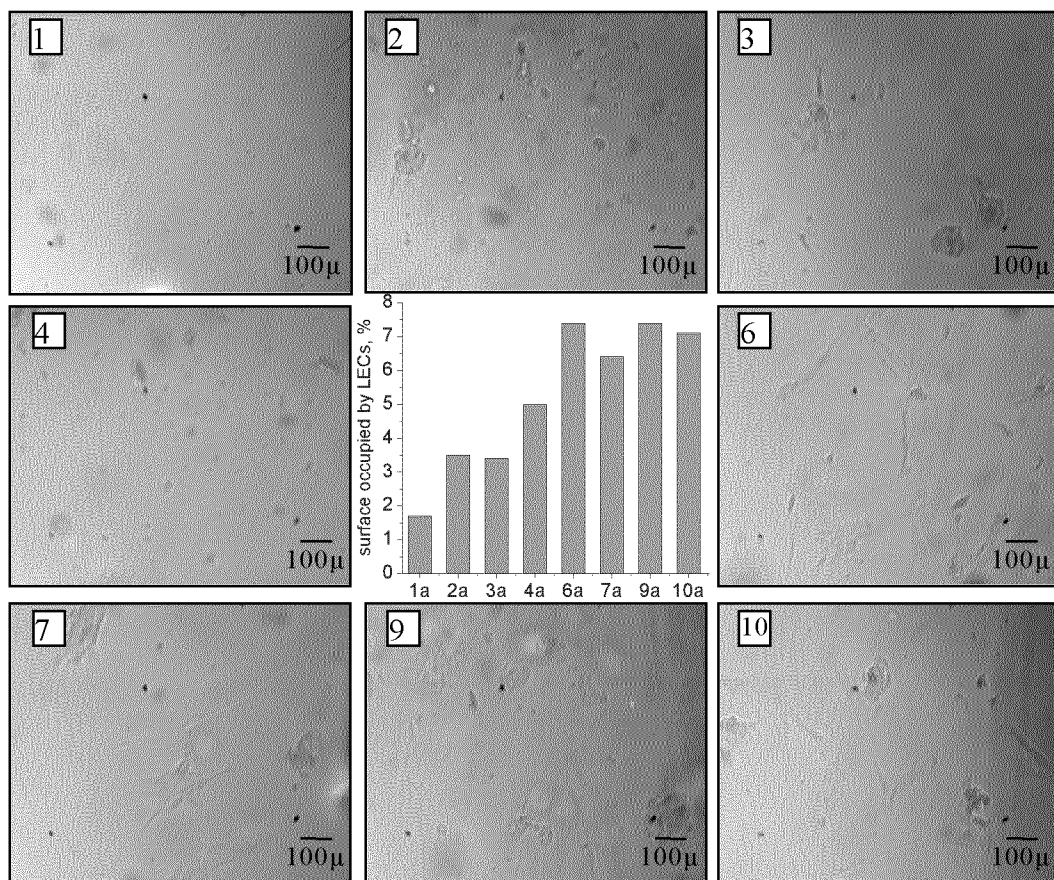


Figure 29C

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**Figure 30**

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/069990

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According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61F A61L C08G C08K C08L C09D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, CHEM ABS Data, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 9 October 2008 (2008-10-09), XU, YITING ET AL: "Method for synthesizing bioactive and biodegradable hydrogel-conductive polymer nanocomposite", XP002638028, retrieved from STN Database accession no. 2008:1216826 abstract & CN 101 280 094 A (XIAMEN UNIVERSITY, PEOP. REP. CHINA) 8 October 2008 (2008-10-08) ----- -/-	1,2,4, 6-9, 11-14
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search 15 February 2012	Date of mailing of the international search report 28/02/2012	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Meiners, Christian	

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/069990

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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