Abstract:
The invention provides a method for the preparation of a biocompatible hydrogel by prepolymerizing a one or more monomers in an aqueous reaction medium into a water-soluble, unsaturated resin, removing at least part of the aqueous reaction medium and/or treating the resin with steam, followed by photopolymerizing the resin into a hydrogel in the presence of a photoinitiator. Moreover, the invention provides the hydrogel prepared by this method, the use thereof, as well as eye implants made therefrom and/or medical implants composed of or coated with this hydrogel.
Title: Method for the preparation of a biocompatible hydrogel

Technical Field
The invention relates to a method for the preparation of a biocompatible hydrogel. More in particular, the invention relates to a method for the preparation of a biocompatible hydrogel with a high refractive index. The invention further relates to implants for eye surgery made with said hydrogels, as well as other medical applications.

Background Art
A gel is an apparently solid, jelly-like material. A hydrogel is a network of polymer chains that are water-insoluble, in which water is the dispersion medium. A hydrogel is an aqueous solution of a hydrophilic polymer which is insoluble in water but swells to some equilibrium state. Hydrogels differs in rheological properties from solutions. When a stirrer turns in a solution the stirrer forms a vortex below the surface. In a hydrogel the liquid creeps upwards the stirrer. Hydrogels possess also a degree of flexibility very similar to natural tissue, due to their significant water content.

Common uses for hydrogels are:

- currently used as scaffolds in tissue engineering. When used as scaffolds, hydrogels may contain human cells in order to repair tissue.
- environmentally sensitive hydrogels. These hydrogels have the ability to sense changes of pH, temperature, or the concentration of metabolite and release their load as result of such a change.
- as sustained-release delivery system
- provide absorption, desloughing and debriding capacities of necrotics and fibrotic tissue.
- hydrogels that are responsive to specific molecules, such as glucose or antigens can be used as biosensors as well as in DDS ("drug delivery systems").
- as dry powder in disposable diapers where they upon capturing urine form a hydrogel, or likewise in sanitary napkins
- contact lenses (silicone hydrogels, polyacrylamides)
- medical electrodes using hydrogels composed of cross linked polymers (polyethylene oxide, polyAMPS and polyvinylpyrrolidone)
- Water gel explosives
- Reverse osmosis membranes.
Other, less common uses include

- breast implants
- granules that can form a hydrogel by holding soil moisture in arid areas
- dressings for healing of burn or other hard-to-heal wounds. Wound GEL are excellent for helping to create or maintain environment.
- reservoirs in topical drug delivery; particularly ionic drugs, delivered by iontophoresis (see ion exchange resin)

Common ingredients are e.g. polyvinyl alcohol, sodium polyacrylate, acrylate polymers and copolymers with an abundance of hydrophilic groups.

For implants in eye surgery there is a demand for hydrogels with a high refraction index, high water content and good mechanical properties.

**Disclosure of Invention**

Accordingly, the invention provides for a method for the preparation of a biocompatible hydrogel by prepolymerizing one or more monomers in an aqueous reaction medium into an unsaturated, water-soluble resin, removing at least part of the aqueous reaction medium and/or treating the resin with steam, followed by photopolymerizing the resin into a hydrogel in the presence of a photoinitiator. More specifically, the invention provides for a method for the preparation of a biocompatible hydrogel by prepolymerizing a polyfunctional mercaptan, a vinylpyrrolidone and at least one water-soluble monomer or a mixture of water soluble monomers dissolved in an aqueous reaction medium into a resin, removing at least part of the aqueous reaction medium and/or treating the resin with steam, followed by photopolymerizing the resin into a hydrogel in the presence of a photoinitiator, preferably one that is cleared for medical applications. Alternatively a water-soluble mercaptan may be used, in which case a single water-soluble comonomer may suffice. Moreover, the invention provides a biocompatible hydrogel that is suitable for the uses mentioned above, in particular in medical applications, more in particular as implantation in and as application onto biomaterials.

**Mode(s) for Carrying Out the Invention**

For application were biocompatibility is necessary, the purity of the hydrogel is very important. However it has been found that by using the two-step process of the current invention, the amount of photoinitiator and impurities in the final hydrogel could remarkably be reduced, which makes the hydrogel suitable for implantation in and application onto biomaterials.

In the process of the current invention, it has been surprisingly found that polyfunctional mercaptans, although they are generally not water soluble, can form stable hydrogels when they are copolymerized with for instance a vinylpyrrolidone such as n-vinyl-2-pyrrolidone and a water soluble monomer, preferably a polyfunctional monomer, such as PEGDA. Similar
stable hydrogels may for instance be obtained using vinylformamide (VFA) instead of or in addition to the vinylpyrrolidone.

Polyfunctional mercaptans include difunctional-, trifunctional-, and multi-functional-thiols. A preferred difunctional mercapatan is ethylene glycol dimercaptopropionate. Suitable difunctional mercaptans include, but are not limited to, diethylene glycol dimercaptopropionate, 4-t-butyl-1,2-benzenedithiol, bis-(2-mercaptoethyl)sulfide, 4,4'-thiodibenzencnethiol, benzenedithiol, glycol dimercaptoacetate, glycol dimercaptopropionate ethylene bis(3-mercaptopropionate), polyethylene glycol dimercaptoacetates, polyethylene glycol di(3-mercaptopropionates), 2,2-bis(mercaptomethyl)-1,3-propanedithiol, 2,5-dimercaptoethyl-1,4-dithiane, bisphenolfluorene bis(ethoxy-3-mercaptopropionate), 4,8-bis(mercaptomethyl)-3,6,9-trithia-1,11-undecanedithiol, 2-mercaptomethyl-2-methyl-1,3-propanedithiol, 1,8-dimercapto-3,6-dioxaoctane, and thioglycerol bismercapto-acetate.

A preferred trifunctional mercapatan is trimethylol propane (tris-mercaptopropionate) (TMPTMP). Suitable tri-functional mercaptans include, but are not limited to,

trimethylolpropane tris(3-mercaptopropionate), trimethylolpropane tris(3-mercaptoacetate), tris-(3-mercaptopropyl)isocyanurate, 1,2,3-trimercaptopropane, and tris(3-mercaptopropionate)triethyl-1,3,5-triazine-2,4,6-(1H,3H,5H)-trione. Still more preferred are the ethoxylated derivatives, such as ETTMP 1300 (ethoxylated trimethylolpropane tri(3-mercaptopropionate)) with a molecular weight of 1274 g/mol.

A preferred multifunctional mercapatan is pentaerythritol tetra-3-mercapto propionate (PETMP), or better still the ethoxylated PETMP. Suitable polyfunctional mercaptans include, but are not limited to, poly (mercapto-propyl) methyl) siloxane (PMPMS); 4-mercaptopropyl-3,6-dithia-1,8-octanediolpentaerythritol tetrakis(3-mercaptoacetate), and pentaerythritol tetrakis (3-mercapto-propionate). Again, the ethoxylated versions thereof are preferred. PETMP, available from e.g., Bruno Bock in Germany, is a suitable polyfunctional mercapatan, but ETTMP 1300 available from the same supplier is the preferred mercapatan. As mentioned before, instead of or in addition to the vinylpyrrolidone, unsaturated monomers such as vinylformamide (VFA) may be used. Good results have been achieved with a vinylpyrrolidone and at least one water-soluble monomer or mixture of water soluble monomers.

Water-soluble monomers are known to the man skilled in the art. Preferred water-soluble monomers are carboxyl group-containing unsaturated monomers such as (meth)-acrylic acid and maleic acid anhydride; carboxyl acid salt group-containing monomers such as sodium (meth)acrylate, trimethylamine (meth)acrylate and triethanolamine (meth)acrylate, and quaternary ammonium salt group-containing monomers such as N,N,N-trimethyl-N-(meth)acryloxyethylammonium chloride. More preferred monomers in the present invention include, for example, acrylic acid, methacrylic acid, maleic acid, fumaric acid,
crotonic acid, sorbic acid, itaconic acid, cinnamic acid, vinyl sulfonic acid, allyl sulfonic acid, vinyl toluene sulfonic acid, styrene sulfonic acid, sulfo(meth)acrylate, sulfopropyl(meth)acrylate, 2-acrylamid-2-methylpropane sulfonic acid, 2-hydroxyethyl(meth)acryloylphosphate, phenyl-2-acryloyloxyethylphosphate, the sodium, potassium and ammonium salts thereof, maleic anhydride and combinations thereof.

Most preferred monomers in the current invention are esters, diesters and polyesters of said carboxyl-group-containing monomers on the one hand, and an alcohol, diol or a polyol on the other hand. Of particular preference are polyfunctional monomers, such as diacrylates and dimethacrylates of polyethylene glycol.

Most preferably, the water soluble monomer is polyethylene glycol diacrylate (PEGDA), with a weight average molecular weight greater than 400, preferably greater than 500, more preferably 600 or greater. SR 610, available from Sartomer in Puteaux, France, is very suitable.

Commercial available water soluble monomers, such as acrylic and methacrylic monomers, are produced according a solvation process whereby an organic solvent is used, for instance, when the monomer is a (di)ester, to remove the water which is formed during the condensation of the alcohol and the unsaturated acid. Therefore such monomers contain very often an aromatic solvent like toluene or xylene. Such monomers would therefore be not or less suitable for medical applications. However, as mentioned before, the process of the current invention overcomes this problem by forming an unsaturated resin first and having the resin solution treated by a steam distillation process (which includes removing part of the aqueous solvent by evaporation).

The preferred vinylpyrrolidone is n-vinyl-2-pyrrolidone. On the other hand, also isomers thereof may be used and/or substituted vinylpyrrolidones.

Preferably, the polyfunctional mercaptan; the vinylpyrrolidone and/or vinylformamide and the water-soluble monomer or monomers are used in a ratio resulting in a hydrogel with a refractive index corresponding to that of the refractive index of a human eye. The refractive index of the lens of a human eye is typically in the range of 1.3 to 1.5. The molar ratio of mercaptan to vinylpyrrolidone and/or vinylformamide may vary from 3:1 to 1:30, preferably from 2:1 to 1:20, more preferably from 1:1 to 1:10, most preferably around 1:6. The molar ratio of mercaptan to water-soluble monomer or monomers may vary from 3:1 to 1:20, preferably from 2:1 to 1:10, more preferably from 1:1 to 1:5. When the hydrogel is used in the treatment of eye defects, then the ratio of monomers is preferably selected such as to correspond to ±0.05 or smaller of the refractive index of the eye of the patient to be treated.

The prepolymerization may be carried out with any kind of polymerization. Preferably, however, the polymerization is carried out with a photoinitiator. Preferably, the photoinitiator is of a kind that any initiator residues are removed when the resin is treated with steam
and/or heated to the temperature that some of the water used as solvent evaporates. The initiator is therefore of a kind that the residues have a boiling point below that of water, or that forms an azeotropic vapour with steam. Suitable photoinitiators include 2-hydroxy-2-methyl-1-phenyl-propan-1-on (HMPP). HMPP is available as Darocur™ 1173 from Ciba in Basel, Switzerland. The initiator is used in amounts effective to cause the prepolymerization into a resin, e.g., in a molar ratio of mercaptan to photoinitiator of from 10,000:1 to 1:1, more preferably of from 1,000:1 to 10:1. The method of the current invention involves mixing the monomer(s) that is/are the building block of the resin in water and prepolymerizing the same. For instance, in the preferred embodiment of the current invention, the method involves mixing the vinylpyrrolidone in water, adding the water-soluble (multifunctional) monomer, the photoinitiator and the mercaptan. The order of addition is not relevant. Also the amount of water is not relevant; sufficient water should be available to dissolve all components. Then the prepolymer is made by photopolymerization. This may be done with a UV lamp. Excellent results have been achieved with the stroscopscopic UV flash lamp available from Parvus Fysica BV in Zeewolde, the Netherlands, which generates 100 flashes per second of 8 Joule each. The prepolymerization is continued until a water-soluble, unsaturated resin is obtained having an apparent weight average molecular weight (determined by GPC) in the range of from 1,000 to 300,000. Indeed, a resin should be obtained that has a sufficient degree of polymerization, thus avoiding the need for elaborate conditions to prepare the final hydrogel, without polymerizing the monomers to such a degree that the resin (due to its viscosity) can no longer be easily applied. In terms of viscosity, the prepolymerization is preferably stopped before a viscosity of 600 mPa.s. is reached.

Next, the method of the current invention involves the treatment with steam and/or the removal of some of the water, leaving a low viscous water-soluble, unsaturated resin. This resin is stable, at least for one month. Moreover, by evaporation any impurity residues (including those resulting from the photoinitiator or present as impurity in the starting monomer) are removed.

Next, the unsaturated, water-soluble resin is turned into a hydrogel by photopolymerization in the presence of a photoinitiator, preferably one that is cleared for medical applications. Again, the skilled person knows what photoinitiators may be used. Preferably, a photoinitiator is used that performs well when using an arctic source at a wavelength smaller than 400, preferably smaller than 390 nm. This has the advantage that the resin/hydrogel can be used to treat e.g., an eye condition in-vivo, without causing damage to the vitreous humour: the cornea, the iris, the ciliary body, and/or the lens of the eye. Most preferably the photoinitiator used in this step is a hydroxyaryl ketone. For instance, excellent results have been achieved with Irgacure™ 2959 from Ciba.
The monomers and/or the resin and/or the hydrogel may be mixed with other components. For instance collagen, in particular collagen Type II is often used as component in hydrogels. Moreover, the hydrogel of the current invention may include bioactive material (stem cells, hormones, enzymes, growth regulators, [slow-release] drugs) and/or cosmetic material (e.g., colorants, as well as photochromatic colorants).

The hydrogels of the current invention may be used for the common uses mentioned in the introduction of this patent application, in particular for use in the treatment of eye defects, and skin treatment.

The following example is provided to illustrate the current invention.

Example 1

333 gram (3 mole) of n-vinyl-2-pyrrolidone was dissolved in 500 gram of de-mineralized water. 146 gram (0.5 mole) of SR 610, a polyethylene glycol diacylate, was added, as well as 7 gram of HMPP. The components were mixed into a 2 litre Erlenmeyer. While the stirrer was turning, 244 gram (0.5 mole) of pentaerythrotol tetra-3-mercapto propionate (PETMP) was added. The clear liquid turned into a cloudy one, since the PETMP did not dissolve in the mixture.

The Parvus stroboscopic UV flash lamp was placed under the Erlenmeyer and switched on. Although the Erlenmeyer was made of borosilicate glass, enough UV light was transmitted into the liquid to start viscosity increase by formation of a water soluble resin. The liquid turned into a clear solution within three minutes. The irradiation was stopped when a viscosity of 300 mPa.s (room temperature) was reached.

The flash lamp was removed and replaced by a heating plate. The heating plate was turned on. When the water started boiling, the impurities including the photoinitiator residues were evaporated by steam distillation from the boiling water. Toluene and HMPP forms an azeotropie mixture with water and therefore separated from the liquid.

When 300 ml of water was removed the liquid was found to be liberated from monomer NVP and low molecular polyethylene glycol diacylate as well. The low viscous resin was stable, and did not increased in viscosity after three month storage at 7 degrees Celsius.

After addition of only 10 milligram of photoinitiator 4-(2-hydroxyethoxy)phenyl-(2-hydroxy-2-methylpropyl)ketone (Irgacure 2959) to 10 gram of the preparation, a photosensitive liquid was obtained which could be injected in a pig’s eye with a syringe. A drop of the photosensitive liquid was irradiation with an UV LED type NCCU033E from Nichia in Japan and changed within 20 seconds into a hydrogel with the stiffness of a hard boiled egg.

It has been found that the hydrogels of the current invention show biocompatibility in the eye and on grazed skin. The hydrogels prepared above has a refractive index of about 1.5. In case water is added to this, the refractive will be around 1.4, which is therefore very close to that of a human eye.
1. A method for the preparation of a biocompatible hydrogel by prepolymerizing one or more monomers in an aqueous reaction medium into a water-soluble, unsaturated resin, removing at least part of the aqueous reaction medium and/or treating the resin with steam, followed by photopolymerizing the resin into a hydrogel in the presence of a photoinitiator.

2. A method as claimed in claim 1, whereby the resin has an apparent weight average molecular weight (GPC method) of 1,000 to 300,000.

3. A method as claimed in claim 1, whereby at least a polyfunctional mercaptan and optionally one or more unsaturated monomers and optionally one or more water soluble monomers are prepolymerized into the resin.

4. A method for the preparation of a biocompatible hydrogel, as claimed in claim 3, by prepolymerizing a polyfunctional mercaptan; a vinylpyrrolidone and/or a vinylformamide, and at least one water-soluble monomer or a mixture of water soluble monomers dissolved in an aqueous reaction medium into a resin, removing at least part of the aqueous reaction medium and/or treating the resin with steam, followed by photopolymerizing the resin into a hydrogel in the presence of a photoinitiator.

5. A method as claimed in claim 4, wherein the polyfunctional mercaptan comprises a difunctional-, trifunctional-, multi-functional-thiols, or combination thereof.

6. A method as claimed in claim 5, wherein the polyfunctional mercaptan is a trifunctional or a multifunctional mercaptan, selected from pentaerythritol tetra-3-mercaptopropionate (PETMP), poly(mercaptopropyl methyl) siloxane (PMPMS); 4-mercaptopropyl-3,6-dithia-1,8-octanedithiolpentacrylic acid; and pentaerythritol tetrakis (3-mercaptopropionate), preferably an ethoxylated version thereof, more preferably ETTMP 1300 (ethoxylated trimethylpropane tri(3-mercaptopropionate)).

7. A method as claimed in any one of claims 4 to 6, wherein the water soluble monomer or monomers are carboxyl group-containing unsaturated monomers.

8. A method as claimed in claim 7, wherein the water soluble monomer is a polyfunctional monomer, preferably a diacrylate or dimethacrylate of polyethylene glycol.

9. A method as claimed in claim 8, wherein the water soluble monomer is polyethylene glycol diacrylate (PEGDA), with a weight average molecular weight greater than 400, preferably greater than 500, more preferably 600 or greater.
10. A method as claimed in any one of claims 4 to 9, wherein vinylpyrrolidone is used and the vinylpyrrolidone is n-vinyl-2-pyrrolidone.

11. A method as claimed in any one of claims 4 to 10, wherein the polyfunctional mercaptan; the vinylpyrrolidone and/or vinylformamide, and the water-soluble monomer or monomers are used in a ratio resulting in a hydrogel with a refractive index in the range of 1.3 to 1.5, corresponding to the refractive index of the lens of a human eye.

12. A method as claimed in any one of claims 4 to 10, wherein the molar ratio of mercaptan to vinylpyrrolidone and/or vinylformamide is in the range of from 3:1 to 1:30, preferably of from 2:1 to 1:20, more preferably from 1:1 to 1:10, most preferably around 1:6.

13. A method as claimed in any one of claims 4 to 10, wherein the molar ratio of mercaptan to water-soluble monomer or monomers is in the range of from 3:1 to 1:20, preferably from 2:1 to 1:10, more preferably from 1:1 to 1:5.

14. A method as claimed in any one of claims 1 to 13, wherein the prepolymerization is carried out with a photoinitiator, preferably with 2-hydroxy-2-methyl-1-phenylpropan-1-on (HMPP).

15. A method as claimed in claim 14, wherein HMPP is used in a molar ratio of monomer, preferably mercaptan, to photoinitiator of from 10,000:1 to 1:1, more preferably of from 1,000:1 to 10:1.

16. A method as claimed in any one of claims 1 to 15, wherein the resin is turned into a hydrogel by photopolymerization in the presence of a photoinitiator, preferably a hydroxyaryl ketone.

17. The hydrogel obtained by the method of any one of claims 1 to 16.

18. The hydrogel of claim 17, comprising one or more of the components: collagen, in particular collagen Type II; bioactive material (stem cells, hormones, enzymes, growth regulators, [slow-release] drugs), and/or cosmetic material (colorants and/or photochromatic colorants).

19. The hydrogel of claim 17 or 18, wherein the resin is photopolymerized using an arctic source at a wavelength smaller than 400, preferable smaller than 390 nm.

20. The hydrogel of claim 19, wherein the resin is photopolymerized into a hydrogel in vivo.

21. The hydrogel of claim 20, wherein the resin is photopolymerized in less than 5 minutes, preferably in less than 1 minute, more preferably in less than 30 seconds.

22. The hydrogel of any one of claims 17 to 21 for use as a medicament.

23. The hydrogel of any one of claims 17 to 21 for use in the treatment of eye defects, and or skin treatment.
24. The hydrogel of any one of claims 17 to 21 for use in the treatment of eye defects involving the irradiation at a wavelength smaller than 400, preferable smaller than 390 nm for a duration of less than 30 seconds, wherein the hydrogel has a refractive index in the range of 1.3 to 1.5 and corresponding within ±0.05 or less of the refractive index of the human eye to be treated.

25. Eye implants and/or dressings comprising the hydrogel of any one of claims 17 to 24.

26. Medical implants composed of or coated with the hydrogel of any one of claims 17 to 24.
### A. CLASSIFICATION OF SUBJECT MATTER

INV. C08F290/00  C08F283/00  C08F290/14  C08F290/06  C08F2/38  
C08F8/00  A61L27/16  C08L51/00  C08L51/08  C08F283/06

According to International Patent Classification (IPC) and both national classification and IPC

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C08F  C08L  A61L  B29D  G02B

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, WPI Data, PAJ

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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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
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"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

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Date of the actual completion of the international search: 24 August 2009

Date of mailing of the international search report: 01/09/2009

Name and mailing address of the ISA/Authorized officer

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Hammond, Andrew
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