Claims

1. A method for sterilizing a biodegradable poly(ethylene glycol) based insoluble hydrogel comprising backbone moieties which are interconnected by hydrolytically degradable bonds, comprising the steps of

   (a) Providing the hydrogel;

   (b) Solvating the hydrogel in a protective solvent or in a mixture of two or more protective solvents or aqueous solutions thereof;

   (c) Subjecting the solvated hydrogel to gamma radiation.

2. The method of claim 1, wherein the protective solvent is acetic acid (aqueous solution, 0.05-1% (v/v)), acetonitrile, 4-acetylmorpholine, dimethylsulfoxide, dichloromethane, *N,N*-dimethylacetamide, dimethylcarbonate, dimethylformamide, 1-ethyl-2-pyrrolidone, *N*-ethylacetamide, *N*-ethylformamide, 4-formylmorpholine, 1-formylpyrrolidone, 1,3-dimethyl-2-imidazolidinone, 1,3-dimethyl-2-imidazolidinone, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, alkyl alcohols, formamide, hexamethylphosphoramide, *N*-methylacetamide, nicotinamide (aqueous solution, 0.1-5% (w/w)), pyridoxine (aqueous solution, 0.1-5% (w/w), N-methylformamide, NMP, 1,2-propylene carbonate, tetrahydrofuran, sulfolan, water, or mixtures thereof.

3. The method of claim 1 or 2, wherein the protective solvent is NMP, DMA, DMF or DMI.

4. The method of any of claims 1 to 3, wherein sterilization is obtained with gamma radiation with a dose of from 5 to 100 kGy.

5. The method of any of claims 1 to 4, wherein sterilization is obtained with gamma radiation with a dose of from 8 to 50 kGy.

6. The method of any of claims 1 to 5, wherein the hydrogel is loaded with small molecule biologically active moieties.

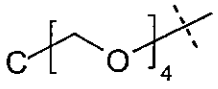
7. The method of any of claims 1 to 6, wherein the backbone moieties of the hydrogel have each a molecular weight in the range of from 1 kDa to 20 kDa.

8. The method of any of claims 1 to 7, wherein the backbone moieties of the hydrogel are interconnected by hydrolytically degradable bonds and wherein the backbone moieties are linked together through crosslinker moieties, each crosslinker moiety being terminated by at least two of the hydrolytically degradable bonds.

9. The method of any of claims 1 to 8, wherein the hydrolytically degradable bonds are carboxylic esters, carbonates, phosphoesters or sulfonic acid esters.

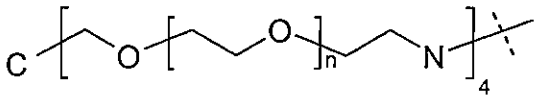
10. The method of claim 8 or 9, wherein the crosslinker moieties have a molecular weight in the range of from 60 Da to 5 kDa.

11. The method of any of claims 1 to 10, wherein the backbone moieties of the biodegradable PEG based insoluble hydrogel comprise a branching core of the following formula:



wherein the dashed line indicates attachment to the remainder of the backbone moiety.

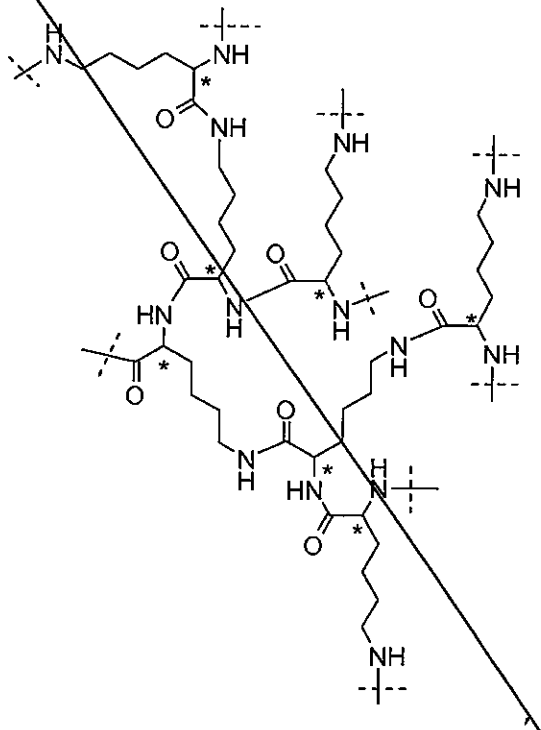
12. The method of any of claims 1 to 11, wherein the backbone moieties of the biodegradable PEG based insoluble hydrogel comprise a structure of the following formula:



wherein n is an integer of from 5 to 50 and the dashed line indicates attachment to the rest of the molecule.

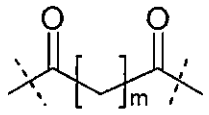
13. The method of any of claims 1 to 12, wherein the backbone moieties of the biodegradable PEG based insoluble hydrogel comprise a hyperbranched moiety Hyp.

14. The method of claim 13, wherein the backbone moieties of the biodegradable PEG based insoluble hydrogel comprise a hyperbranched moiety Hyp of the following formula:



wherein the dashed lines indicate attachment to the rest of the molecule and carbon atoms marked with asterisks indicate S-configuration.

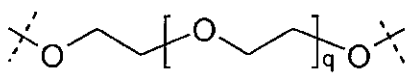
15. The method of claim 13 or 14, wherein the backbone moieties are attached to at least one spacer of the following formula:



,

wherein one of the dashed lines indicates attachment to the hyperbranched moiety Hyp and the second dashed line indicates attachment to the rest of the molecule; and wherein m is an integer of from 2 to 4.

16. The prodrug of any of claims 1 to 15, wherein the backbone moieties are linked together through crosslinker moieties comprising the following structure



,

wherein

q is an integer from 3 to 100.

17. The method of any of claims 1 to 16, wherein the protective solvent contains one or more protecting agents.

18. The method of claim 17, wherein the protecting agents are selected from propylamine, butylamine, pentylamine, sec. butylamine, ethanolamine, diethanolamine, serinol, trishydroxymethyl-aminomethane, acetic acid, formic acid, ascorbic acid, glycineamide, pivalic acid, propanoic acid, succinic acid, glutaric acid, adipic acid, thioglycerin, dithiothreitol, mercaptoethanol, reduced glutathione.

19. A sterilized biodegradable PEG-based insoluble hydrogel obtainable by any of the methods of claims 1 to 18.

1. A method for sterilizing a biodegradable poly(ethylene glycol) based insoluble hydrogel comprising backbone moieties which are interconnected by hydrolytically degradable bonds, comprising the steps of

(a) Providing the hydrogel;

(b) Solvating the hydrogel in a protective solvent or in a mixture of two or more protective solvents or aqueous solutions thereof;

(c) Subjecting the solvated hydrogel to gamma radiation; wherein

the backbone moiety has a quarternary carbon of formula $C(A\text{-}Hyp)_4$, wherein each A is independently a poly(ethylene glycol) based polymeric chain terminally attached to the quarternary carbon by a permanent covalent bond and the distal end of the PEG-based polymeric chain is covalently bound to a dendritic moiety Hyp, each dendritic moiety Hyp consists of between 5 and 21 lysines;

the backbone moieties are linked together through crosslinker moieties which consist of a PEG chain, which is symmetrically connected through ester bonds to two alpha, omega-aliphatic dicarboxylic spacers provided by backbone moieties connected to the hyperbranched dendritic moiety through permanent amide bonds;

the protective solvent is N-methyl-2-pyrrolidone, *N,N*-dimethylacetamide, dimethylformamide, or 1,3-dimethyl-2-imidazolidinone and may optionally contain one or more protecting agents.

2. The method of claim 1, wherein the protective solvent is NMP.

3. The method of claims 1 or 2, wherein sterilization is obtained with gamma radiation with a dose of from 5 to 100 kGy.

4. The method of any of claims 1 to 3, wherein sterilization is obtained with gamma radiation with a dose of from 8 to 50 kGy.

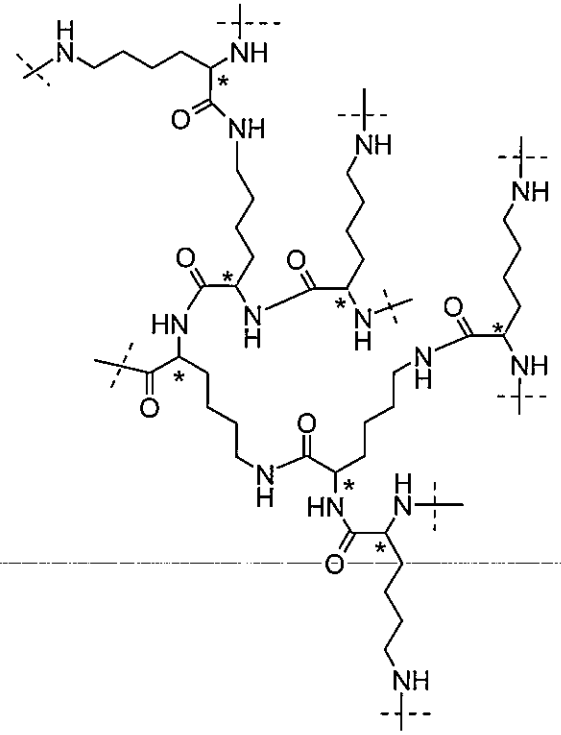
5. The method of any of claims 1 to 4, wherein the hydrogel is loaded with small molecule biologically active moieties.

6. The method of any one of claims 1 to 5, wherein the hydrogel consists of spherical microparticles with a particle diameter of 1 to 1000 microns.

7. The method of any of claims 1 to 6, wherein the backbone moieties of the hydrogel have each a molecular weight in the range of from 1 kDa to 20 kDa.

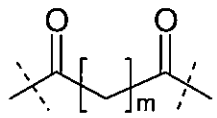
8. The method of any one of claims 1 to 7, wherein the crosslinker moieties have a molecular weight in the range of from 60 Da to 5 kDa.

9. The method of any one of claims 1 to 8, wherein the backbone moieties of the biodegradable PEG based insoluble hydrogel comprise a hyperbranched moiety Hyp of the following formula:



wherein the dashed lines indicate attachment to the rest of the molecule and carbon atoms marked with asterisks indicate S-configuration.

10. The method of any one of claims 1 to 9, wherein the backbone moieties are attached to at least one spacer of the following formula:

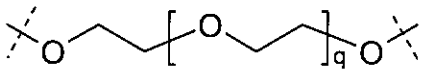


,

wherein one of the dashed lines indicates attachment to the hyperbranched moiety Hyp and the second dashed line indicates attachment to the rest of the molecule; and

wherein m is an integer of from 2 to 4.

11. The prodrug of any of claims 1 to 10, wherein the backbone moieties are linked together through crosslinker moieties comprising the following structure



,

wherein

q is an integer from 3 to 100.

12. The method of any of claims 1 to 11, wherein the protecting agents are selected from propylamine, butylamine, pentylamine, sec. butylamine, ethanolamine, diethanolamine, serinol, trishydroxymethyl-aminomethane, acetic acid, formic acid, ascorbic acid, glycineamide, pivalic acid, propanoic acid, succinic acid, glutaric acid, adipic acid, thioglycerin, dithiothreitol, mercaptoethanol, reduced glutathione.

13. The method of any one of claims 1 to 12, wherein dry biodegradable PEG-based insoluble hydrogel is solvated with 5-10 ml NMP/g dry biodegradable PEG-based insoluble hydrogel and irradiated with gamma rays with a dose of 25 kGy, using a closed container.

14. A sterilized biodegradable PEG-based insoluble hydrogel obtainable by any of the methods of claims 1 to 13.

15. Use of the hydrogel of claim 14 in tissue engineering, skin filling, intraocular devices, medical implants, surgical sealants and sponges, hemostatic agents, sustained release delivery systems, medical imaging agents and prodrug-carriers.