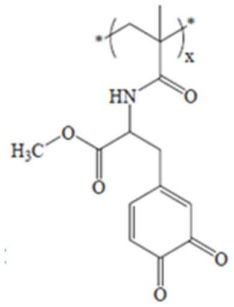
such nanogels is the loading of water-insoluble or hydrophobic bioactive molecules, therapeutic molecules or drugs resulting in an irregular release kinetic profile and a lower pharmacological efficiency.

Moreover, only low levels of hydrophobic bioactive molecules, therapeutic molecules or drugs are released from such nanogel after release initiation. Immediate pharmacological effect can therefore not be rapidly achieved, and bacterial adhesion to the medical device, biomaterial implant or bioprosthesis cannot be fully prevented.

SUMMARY

We have now found an improved nanogel comprising one or more bioactive molecules, therapeutic molecules or drugs together with an amphiphilic molecule preferably a vitamin-E derivative or most preferably an amphiphilic cyclodextrin; the nanogel exhibiting improved antibacterial efficacy and anti-antibiotic resistance.

In an aspect, there is provided a nanogel made of a poly(methacrylamide)-bearing quinone groups of formula (1)

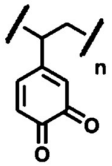


(1)

wherein x is an integer > 1, preferably x is between 1 and 100

and/or

made of a poly(vinylquinone) represented by formula (6)



(6)

wherein n is an integer > 1, preferably n is between 1 and 100;

and crosslinked with a polymer bearing primary or secondary amine groups;

wherein the nanogel comprises one or more bioactive molecule, therapeutic molecule or drug together with an amphiphilic molecule, wherein the amphiphilic molecule is not vancomycine, minocycline or ticagrelor.

The present disclosure surprisingly and advantageously provides more efficient loading of hydrophobic bioactive molecules, therapeutic molecules or drugs in nanogel and a steady, progressive and continuous release over time during weeks. The hydrophobic bioactive molecules, therapeutic molecules or drugs can be combined with a hydrophilic bioactive molecules, therapeutic molecules or drugs in such nanogels, and be released simultaneously. Moreover, the nanogel comprising the bioactive molecules, therapeutic molecules or drugs advantageously remains stable over time in liquid suspension by maintaining its structural integrity and uniform distribution in dispersed state, particularly in aqueous media.

The nanogel of the disclosure is therefore for use in treatment or prevention of bacterial infection, particularly in topical administration for host mammal.

In another aspect, there is provided the nanogel as described herein for use in topical administration.

In another aspect, there is provided use of the nanogel as described herein in the manufacture of a medicament for the treatment or prevention of bacterial infection.

In another aspect, there is provided use of a pharmaceutical composition comprising a nanogel as described herein in the manufacture of a medicament for the treatment or prevention of bacterial virulence in a host mammal by topical administration.

In another aspect, there is provided a nanogel as described herein or a pharmaceutical composition comprising a nanogel as described herein for use in therapy.

The use of such new nanogel in coating medical device, biomaterial implants or bioprosthesis, particularly catheter; also provides improved medical device, biomaterial implants or bioprosthesis.

In another aspect, there is provided a biomaterial implant, medical device or bioprosthesis wherein a surface or part thereof is coated with the nanogel as described herein.

The medical device, biomaterial implants or bioprosthesis coated with the nanogel of the disclosure, advantageously provides a more homogeneous, hydrophilic and smooth surface and content uniformity, resulting in a more reproducible kinetic release of the hydrophobic bioactive molecules, therapeutic molecules or drugs from the coated medical device, biomaterial implants or bioprosthesis, and subsequent improved pharmacological efficiency.

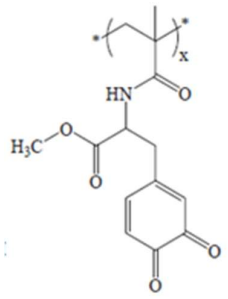
Simultaneously, medical device, biomaterial implants or bioprosthesis coated with the nanogel of the disclosure, advantageously reduces bacterial adhesion to the surface of the medical device, biomaterial implants or bioprosthesis, particularly when the nanogel comprises a combination of a bacteriostatic agent and an antivirulence or a bactericidal agent.

In another aspect, there is provided a method of making a nanogel comprising one or more bioactive molecule, therapeutic molecule or drug, together with an amphiphilic molecule, wherein the amphiphilic molecule is not vancomycine, minocycline or ticagrelor and wherein the nanogel is obtained by one of both following methods, depending whether each bioactive molecule, therapeutic molecule or drug is to be loaded separately or simultaneously with the amphiphilic molecule in the nanogel:

a) when each bioactive molecule, therapeutic molecule or drug is loaded separately with the amphiphilic molecule,

the method comprises the following in-sequence steps:

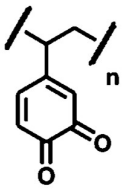
i)mixing poly(methacrylamide)-bearing quinone groups of formula (1)



(1)

wherein x is an integer > 1, preferably x is between 1 and 100

and/or a poly(vinylquinone) represented by formula (6),



(6)

wherein n is an integer > 1, preferably n is between 1 and 100;

with only one bioactive molecule, therapeutic molecule or drug together with an amphiphilic molecule;

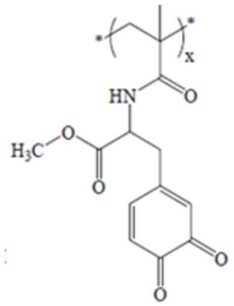
ii) adding a solution of polymer bearing primary or secondary amine groups to the resulting mixture obtained in step i) to generate a crosslinked nanogel comprising one bioactive molecule, therapeutic molecule or drug together with an amphiphilic molecule;

iii) repeating step I) and ii) for each additional bioactive molecule, therapeutic molecule or drug;

iv) mixing each crosslinked nanogel obtained at step iii) to obtain a resulting nanogel comprising two or more biological molecules, therapeutic molecules or drugs together with an amphiphilic molecule.

b) when the bioactive molecules, therapeutic molecules or drugs are loaded simultaneously with the amphiphilic molecule; the method comprises the following in-sequence steps:

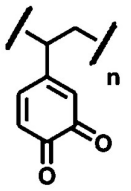
i) mixing poly(methacrylamide)-bearing quinone groups of formula (1)



(1)

wherein x is an integer > 1, preferably x is between 1 and 100

and/or a poly(vinylquinone) represented by formula (6)



(6)

wherein n is an integer > 1, preferably n is between 1 and 100 ;

with a one or more bioactive molecule, therapeutic molecule or drug together with an amphiphilic molecule;

ii) adding a solution of polymer bearing primary or secondary amine groups to the resulting mixture of step i) to generate a nanogel comprising one or more bioactive molecule, therapeutic molecule or drug together with the amphiphilic molecule.

In another aspect, there is provided a method of producing a medical device, a biomaterial implant or a bioprosthesis with a nanogel coated surface comprising one or more bioactive molecule, therapeutic molecule or drug together with an amphiphilic molecule, wherein the amphiphilic molecule is not vancomycine, minocycline or ticagrelor; comprising the following-in-sequence steps of:

ci)optionally dipping the surface to be coated in a buffer solution of dopamine;

cii)dipping the surface coated at step ci) into a solution of polymer bearing primary or secondary amine groups; then

ciii)dipping the resulting coated surface obtained at step cii) into a liquid suspension of crosslinked-nanogel comprising one or more bioactive molecule, therapeutic molecule or drug together with the amphiphilic molecule; then

civ) drying the crosslinked coated surface obtained at step (ciii) to obtain a coated crosslinked-nanogel surface comprising one or more bioactive molecule, therapeutic molecule or drug together with the amphiphilic molecule;

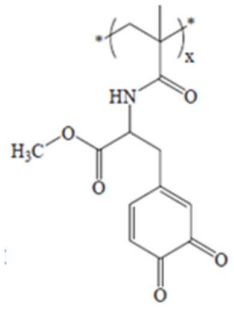
cv) optionally repeating steps cii) to civ) to obtain a surface coated with several layers of crosslinked nanogels comprising one or more bioactive molecule, therapeutic molecule or drug together with the amphiphilic molecule.

In another aspect, there is provided a method of producing a medical device, a biomaterial implant or a bioprosthesis with a coated surface, wherein the coating is obtained by the following in-sequence steps*:*

i) optionally dipping the surface to be coated in a buffer solution of dopamine;

ii) dipping the surface coated with dopamine at step i); in a solution of polymer bearing primary or secondary amine groups; then

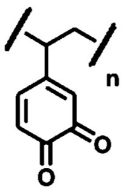
iii) dipping the resulting coated surface obtained at step ii) in a mixture of a poly(methacrylamide)-bearing quinone groups of formula (1)



(1)

wherein x is an integer > 1, preferably x is between 1 and 100

and/or of a poly(vinylquinone) of formula (6)



(6)

wherein n is an integer > 1, preferably n is between 1 and 100;

with one or more bioactive molecule, therapeutic molecule or drug together with an amphiphilic molecule, wherein the amphiphilic molecule is not vancomycine, minocycline or ticagrelor;

iv)drying the crosslinked coated surface obtained at step iii) to obtain a coated crosslinked monolayer surface comprising one or more bioactive molecule, therapeutic molecule or drug together with the amphiphilic molecule;

v)optionally repeating steps ii) to iv) to obtain a surface coated with several layers of crosslinked multilayers comprising one or more bioactive molecule, therapeutic molecule or drug together with the amphiphilic molecule, preferably the vitamin-E derivative.

In another aspect, there is provided use of a nanogel as described herein as inhibitor of bacterial adhesion on a surface of the biomaterial implant, medical device or bioprothesis.

DETAILED DESCRIPTION

The present invention relates to a new nanogel, a three-dimensional cross-linked particle with submicron particle size, which provide for a larger cargo space which may be used to incorporate bioactive molecule, therapeutic molecule or drug encapsulated by amphiphilic molecule, particularly Vitamin E derivatives or amphiphilic cyclodextrin.

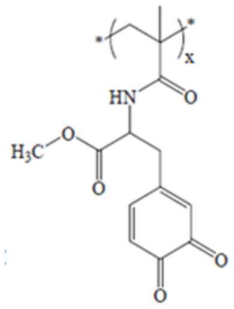
Such nanogel for use in treatment and prevention of bacterial infection, particularly bacterial virulence, is particularly useful for topical administration on host mammal in need of such treatment

Such nanogel can also be anchored or attached onto the surface of any biomaterial or medical device, be it metallic or polymeric, or on a bioprosthesis and thereby reduce or prevent infection and improve biocompatibility and hemocompatibility of transiently or permanently implanted materials to help maintain their functionality and increase their durability.

According to a first aspect, the present invention provides a nanogel made of a poly(methacrylamide)-bearing quinone groups of formula (1)

Claims

1. A nanogel made of a poly(methacrylamide)-bearing quinone groups of formula (1)

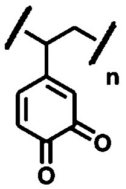


(1)

wherein x is an integer > 1, preferably x is between 1 and 100

and/or

made of a poly(vinylquinone) represented by formula (6)



(6)

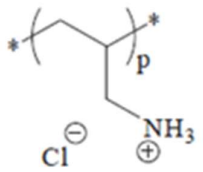
wherein n is an integer > 1, preferably n is between 1 and 100;

and crosslinked with a polymer bearing primary or secondary amine groups; wherein the nanogel comprises one or more bioactive molecule, therapeutic molecule or drug together with an amphiphilic molecule, wherein the amphiphilic molecule is not vancomycine, minocycline or ticagrelor.

2. The nanogel according to claim 1 wherein the amphiphilic molecule is a vitamin-E derivative, preferably D-α-tocophenyl polyethylene glycol succinate.

3. The nanogel according to claim 1 wherein the amphiphilic molecule is an amphiphilic cyclodextrin, preferably hydroxypropyl-beta-cyclodextrin.

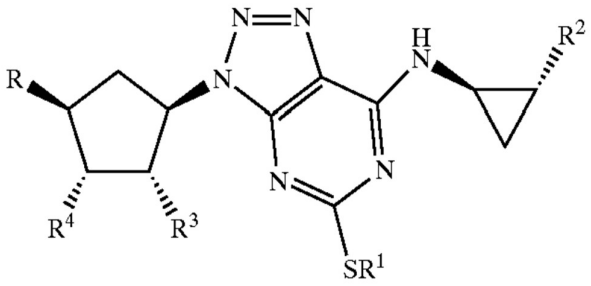
4. The nanogel according to any one of claims 1 to 3 wherein the polymer bearing primary or secondary amine groups is poly-(allylamine hydrochloride) of formula (2)



(2)

wherein p is an integer >1; preferably p is between 10 and 300.

5.The nanogel according to any one of claims 1 to 4 wherein the bioactive molecule, therapeutic molecule or drug is a triazolo(4,4-d)-pyrimidine derivative of formula (3)

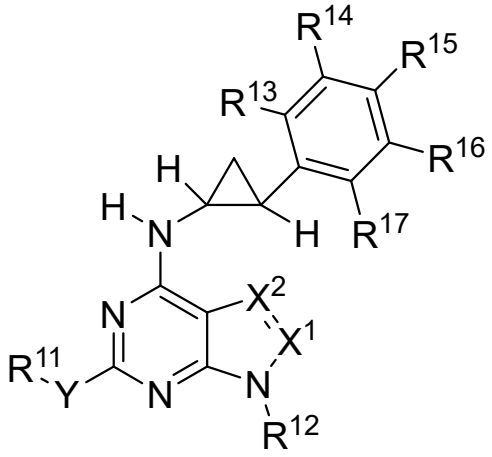


(3)

wherein R1 is C3-5 alkyl optionally substituted by one or more halogen atoms; R_2 is a phenyl group, optionally substituted by one or more halogen atoms; R_3 and R_4 are both hydroxyl; R is OH or XOH, wherein X is CH_2, OCH_2CH_2, or a bond; or a pharmaceutical acceptable salt or solvate thereof, or a solvate thereof or a solvate of such a salt provided that when X is CH_2 or a bond, R_1 is not propyl; when X is CH_2 and R_1 $CH_2CH_2CF_3$, butyl or pentyl, the phenyl group at R_2 must be substituted by fluorine; when X is OCH_2CH_2 and R_1 is propyl, the phenyl group at R_2 must be substituted by fluorine;

preferably the triazolo (4,4-d)-pyrimidine derivative is (1S,2S,3R,5S)-3-[7-[(1R,2S)-2-(3,4-difluorophenyl)cyclopropylamino]-5-(propylthio)-3H-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-1,2-cyclopentanediol) also called Triafluocyl; or is (1S,2R,3S,4R)-4-[7-[[(1R,2S)-2-(3,4-Difluorophenyl)-cyclopropyl]amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-1,2,3-cyclopentanetriol also called Fluometacyl or Fluometacyl® or is a combination thereof

6.The nanogel according to any one of claims 1 to 4 wherein the bioactive molecule, therapeutic molecule or drug is a pyrimidine derivative represented by formula (4)



(4)

or optical isomers, racemic mixtures thereof, pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, or alkylated ammonium salts or prodrug thereof;

wherein:

X^1 and X^2 are independently N, CH, CR^8 wherein R^8 is C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl ; with the exception that if one of X^1 or X^2 is equal to N, then the remaing X^1 or X^2 are selected from CH, CR^8 .

-Y- is -O- or –S-;

R^{11} and R^{12} are independently C_{1-6} -alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-6}-cycloalkyl, aryl, aryl-C_{1-6}-alkyl wherein the alkyl or cycloalkyl moiety is optionally mono or polysubstituted with OH or an halogen and the aryl moiety is optionally mono or polysubstituted with an halogen, -C_{1-6} alkyl, -C_{1-6} alkoxy, -OH, -NO_2, -CN, -NH_2, -NHR^8, -$N(R^8)_2$ -COOH, -$COOR^8$, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -SO_2NH_2, -SO_2NHR^8, or -$SO_2N(R^8)_2$;

R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are independently H, an halogen, a C_{1-6} alkyl, C_{1-6} alkoxy, -OH, -NO_2, -CN, -NH_2, -NHR^8, -$N(R^8)_2$ -COOH, -$COOR^8$, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -SO_2NH_2, -SO_2NHR^8, or –$SO_2N(R^8)_2$.

7. The nanogel according to claim 2 wherein the bioactive molecule, therapeutic molecule or drug and D-α-tocophenyl polyethylene glycol succinate are in a ratio between 1:1 w/w to 1:5 w/w.

8. The nanogel according to claim 3 wherein the bioactive molecule, therapeutic molecule or drug and hydroxypropyl-beta cyclodextrin are in a ratio between 1:1 w/w to 1:200 w/w.

9. The nanogel according to any one of claims 1 to 8 wherein the one or more bioactive molecule, therapeutic molecule or drug are an antivirulence or a bactericidal agent together with a bacteriostatic agent, preferably minocycline or chlorhexidine.

10. The nanogel according to any one of claims 1 to 9, wherein the bioactive molecule, therapeutic molecule or drug are a combination of Fluometacyl or Fluometacyl® with chlorhexidine.

11. The nanogel according to any one of claims 1 to 10, wherein the bioactive molecule, therapeutic molecule or drug are a combination of Fluometacyl or Fluometacyl® with chlorhexidine and PolymixinB.

12. The nanogel according to any one of claims 1 to 11 for use in topical administration.

13. Use of the nanogel according to any one of claims 1 to 11 in the manufacture of a medicament for the treatment or prevention of bacterial infection.

14.A biomaterial implant, medical device or bioprosthesis wherein a surface or part thereof is coated with the nanogel according to any one of claims 1 to 11.

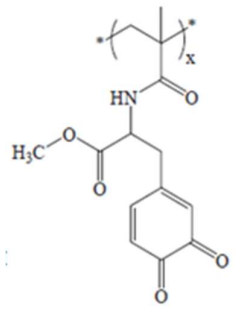
15. The biomaterial implant, medical device according to claim 14 wherein the medical device is a catheter.

16. A method of making a nanogel comprising one or more bioactive molecule, therapeutic molecule or drug, together with an amphiphilic molecule, wherein the amphiphilic molecule is not vancomycine, minocycline or ticagrelor and wherein the nanogel is obtained by one of both following methods, depending whether each bioactive molecule, therapeutic molecule or drug is to be loaded separately or simultaneously with the amphiphilic molecule in the nanogel:

a) when each bioactive molecule, therapeutic molecule or drug is loaded separately with the amphiphilic molecule,

the method comprises the following in-sequence steps:

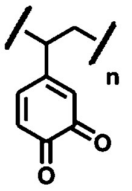
i)mixing poly(methacrylamide)-bearing quinone groups of formula (1)



(1)

wherein x is an integer > 1, preferably x is between 1 and 100

and/or a poly(vinylquinone) represented by formula (6),



(6)

wherein n is an integer > 1, preferably n is between 1 and 100;

with only one bioactive molecule, therapeutic molecule or drug together with an amphiphilic molecule;

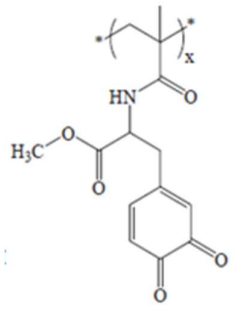
ii) adding a solution of polymer bearing primary or secondary amine groups to the resulting mixture obtained in step i) to generate a crosslinked nanogel comprising one bioactive molecule, therapeutic molecule or drug together with an amphiphilic molecule;

iii) repeating step I) and ii) for each additional bioactive molecule, therapeutic molecule or drug;

iv) mixing each crosslinked nanogel obtained at step iii) to obtain a resulting nanogel comprising two or more biological molecules, therapeutic molecules or drugs together with an amphiphilic molecule.

b) when the bioactive molecules, therapeutic molecules or drugs are loaded simultaneously with the amphiphilic molecule; the method comprises the following in-sequence steps:

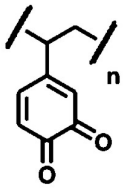
i) mixing poly(methacrylamide)-bearing quinone groups of formula (1)



(1)

wherein x is an integer > 1, preferably x is between 1 and 100

and/or a poly(vinylquinone) represented by formula (6)



(6)

wherein n is an integer > 1, preferably n is between 1 and 100 ;

with a one or more bioactive molecule, therapeutic molecule or drug together with an amphiphilic molecule;

ii) adding a solution of polymer bearing primary or secondary amine groups to the resulting mixture of step i) to generate a nanogel comprising one or more bioactive molecule, therapeutic molecule or drug together with the amphiphilic molecule.

17. The method according to claim 16, wherein the amphiphilic molecule is a vitamin-E derivative, preferably D-α-tocophenyl polyethylene glycol succinate.

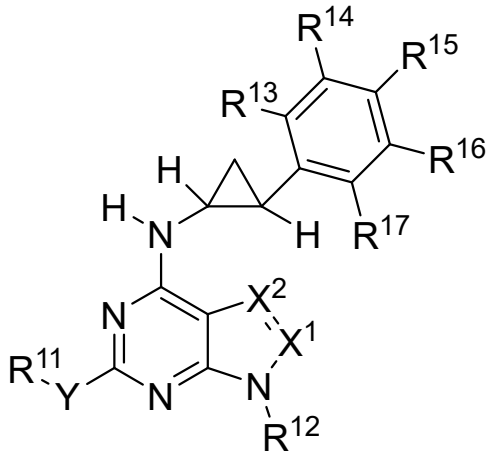
18. The method according to claim 16, wherein the amphiphilic molecule is an amphiphilic cyclodextrin, preferably hydroxypropyl-beta-cyclodextrin.

19. The method according to claim 16 wherein the ratio of bioactive molecule, therapeutic molecule or drug with D-α-tocophenyl polyethylene glycol succinate is between 1:1 w/w and 1:5 w/w.

20. The method according to claim 16 wherein the ratio of bioactive molecule, therapeutic molecule or drug with hydroxypropyl-beta-cyclodextrin is between 1:1 and 1:200.

21. The method according to any one of claims 16 to 20 wherein the one or more bioactive molecule, therapeutic molecule or drug is a triazolo(4,4-d)-pyrimidine derivative of formula (3) ; preferably the triazolo(4,4-d)-pyrimidine derivative is (1S,2S,3R,5S)-3-[7-[(1R,2S)-2-(3,4-difluorophenyl)cyclopropylamino]-5-(propylthio)-3H-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-1,2-cyclopentanediol) also called Triafluocyl; or (1S,2R,3S,4R)-4-[7-[[(1R,2S)-2-(3,4-Difluorophenyl)-cyclopropyl]amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-1,2,3-cyclopentanetriol also called Fluometacyl or Fluometacyl® or a combination thereof.

22. The method according to claim anyone of claims 16 to 20 wherein bioactive molecule, therapeutic molecule or drug is a pyrimidine derivative represented by formula (4)



(4)

or optical isomers, racemic mixtures thereof, pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, or alkylated ammonium salts or prodrug thereof;

wherein:

X^1 and X^2 are independently N, CH, CR^8 wherein R^8 is C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl ; with the exception that if one of X^1 or X^2 is equal to N, then the remaing X^1 or X^2 are selected from CH, CR^8 .

-Y- is -O- or –S-;

R^{11} and R^{12} are independently C_{1-6} -alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-6}-cycloalkyl, aryl, aryl-C_{1-6}-alkyl wherein the alkyl or cycloalkyl moiety is optionally mono or polysubstituted with OH or an halogen and the aryl moiety is optionally mono or polysubstituted with an halogen, -C_{1-6} alkyl, -C_{1-6} alkoxy, -OH, -NO_2, -CN, -NH_2, -NHR^8, -$N(R^8)_2$ -COOH, -$COOR^8$, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -SO_2NH_2, -SO_2NHR^8, or -$SO_2N(R^8)_2$;

R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are independently H, an halogen, a C_{1-6} alkyl, C_{1-6} alkoxy, -OH, -NO_2, -CN, -NH_2, -NHR^8, -$N(R^8)_2$ -COOH, -$COOR^8$, -$CONH_2$, -$CONHR^8$, -$CON(R^8)_2$, -SO_2NH_2, -SO_2NHR^8, or –$SO_2N(R^8)_2$.

23. The method according to any one of claims 16 to 20 wherein the one or more bioactive molecule, therapeutic molecule or drug are an antivirulence or a bactericidal agent together with a bacteriostatic agent, preferably minocycline or chlorhexidine.

24. A method of producing a medical device, a biomaterial implant or a bioprosthesis with a nanogel coated surface comprising one or more bioactive molecule, therapeutic molecule or drug together with an amphiphilic molecule, wherein the amphiphilic molecule is not vancomycine, minocycline or ticagrelor; comprising the following-in-sequence steps of:

ci)optionally dipping the surface to be coated in a buffer solution of dopamine;

cii)dipping the surface coated at step ci) into a solution of polymer bearing primary or secondary amine groups; then

ciii)dipping the resulting coated surface obtained at step cii) into a liquid suspension of crosslinked-nanogel comprising one or more bioactive molecule, therapeutic molecule or drug together with the amphiphilic molecule; then

civ) drying the crosslinked coated surface obtained at step (ciii) to obtain a coated crosslinked-nanogel surface comprising one or more bioactive molecule, therapeutic molecule or drug together with the amphiphilic molecule;

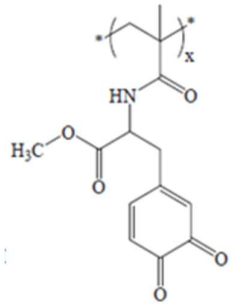
cv) optionally repeating steps cii) to civ) to obtain a surface coated with several layers of crosslinked nanogels comprising one or more bioactive molecule, therapeutic molecule or drug together with the amphiphilic molecule.

25.A method of producing a medical device, a biomaterial implant or a bioprosthesis with a coated surface, wherein the coating is obtained by the following in-sequence steps*:*

i) optionally dipping the surface to be coated in a buffer solution of dopamine;

ii) dipping the surface coated with dopamine at step i); in a solution of polymer bearing primary or secondary amine groups; then

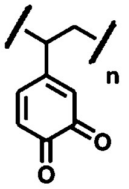
iii) dipping the resulting coated surface obtained at step ii) in a mixture of a poly(methacrylamide)-bearing quinone groups of formula (1)



(1)

wherein x is an integer > 1, preferably x is between 1 and 100

and/or of a poly(vinylquinone) of formula (6)



(6)

wherein n is an integer > 1, preferably n is between 1 and 100;

with one or more bioactive molecule, therapeutic molecule or drug together with an amphiphilic molecule, wherein the amphiphilic molecule is not vancomycine, minocycline or ticagrelor;

iv)drying the crosslinked coated surface obtained at step iii) to obtain a coated crosslinked monolayer surface comprising one or more bioactive molecule, therapeutic molecule or drug together with the amphiphilic molecule;

v)optionally repeating steps ii) to iv) to obtain a surface coated with several layers of crosslinked multilayers comprising one or more bioactive molecule, therapeutic molecule or drug together with the amphiphilic molecule, preferably the vitamin-E derivative.

26. The method according to claim 24 or 25 wherein the amphiphilic molecule is a vitamin-E derivative, preferably D-α-tocophenyl polyethylene glycol succinate.

27. The method according to claim 24 or 25 wherein the amphiphilic molecule is an amphiphilic cyclodextrine, preferably hydroxypropyl-beta-cyclodextrine.

28. The method according to any one of claims 24 to 27 wherein the one or more bioactive molecule, therapeutic molecule or drug is a triazolo(4,4-d)-pyrimidine derivative or a pyrimidine derivative together with a bacteriostatic agent, preferably minocycline or chlorhexidine.

29. The method according to anyone of claims 24 to 27 wherein the one or more bioactive molecule, therapeutic molecule or drugs is (1S,2S,3R,5S)-3-[7-[(1R,2S)-2-(3,4-difluorophenyl)cyclopropylamino]-5-(propylthio)-3H-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-1,2-cyclopentanediol) also called Triafluocyl; or (1S,2R,3S,4R)-4-[7-[[(1R,2S)-2-(3,4-Difluorophenyl)-cyclopropyl]amino]-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]-1,2,3-cyclopentanetriol also called Fluometacyl or Fluometacyl®, or a combination thereof.

30. Use of a pharmaceutical composition comprising a nanogel according to any one of claims 1 to 11 in the manufacture of a medicament for the treatment or prevention of bacterial virulence in a host mammal by topical administration.

31. Use of a nanogel according to any one of claims 1 to 11 as inhibitor of bacterial adhesion on a surface of the biomaterial implant, medical device or bioprothesis.

32. Use according to claim 31 wherein the biomaterial implant, medical device or bioprothesis is a catheter.

33. The nanogel according to any one of claims 1 to 11 or a pharmaceutical composition comprising a nanogel according to any one of claims 1 to 11 for use in therapy.