The isocyanate based materials are toxic because they are synthetized from a toxic and hazardous phosgene. Also polyurethane based isocyanates are sensitive to moisture that can produce unstable monosubstituted carbamic acids, which decompose in a strongly exothermic reaction to produce urea and carbon dioxide.

Moreover *in vitro* and *in vivo* evaluation of polyurethane (PU) implants revealed problems associated with long-term implantation, i.e. degradation affecting the PU surface structure is observed. Accelerated calcification due to calcified host material penetration in the PU is likely to cause premature failure of the implant.

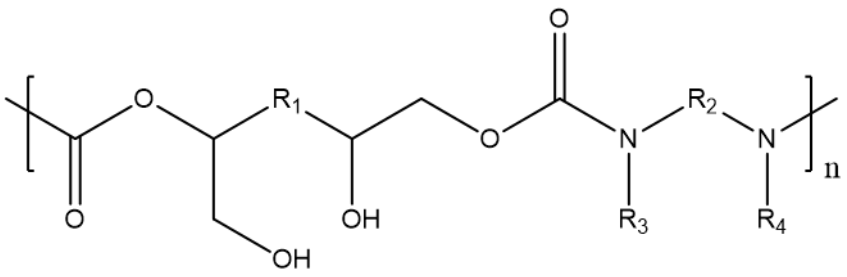
Consequently, there is a need for new affordable, safe and effective medical devices, particularly for catheter and for prosthetic valves.

SUMMARY ~~OF THE INVENTION~~

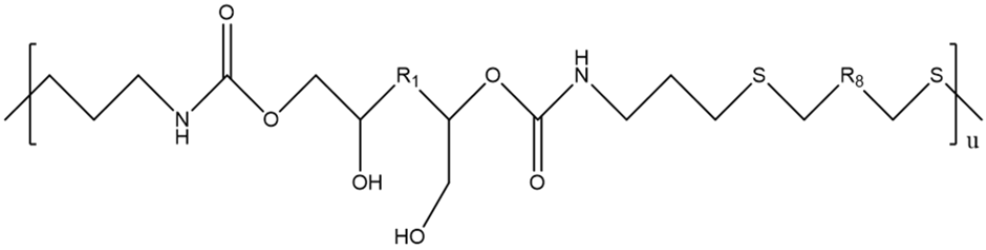
We have now found non-isocyanate polyurethanes (NIPU), also called polyhydroxyurethane (PHU) for use in the manufacture of a new medical device or for coating a medical device. The new medical device comprising one or more polyhydroxyurethane (PHU) can be loaded and release, or be grafted with bioactive molecules, particularly antibacterial, anti-thrombotic molecules or anti-calcification agents.

The use of non-isocyanate polyurethanes has many attractive features for biomedical applications, including low cost, excellent biocompatibility, low toxicity, and a variety of mechanical properties that allows their use in several manufacturing methods such as for example extrusion, co-extrusion, moulding or 3D printing methods.

In one aspect, there is provided an implantable medical device comprising one or more polyhydroxyurethane (PHU) 1 characterised in that the one or more polyhydroxyurethane (PHU) is based on formula (1) or on formula (9)



(1)



(9)

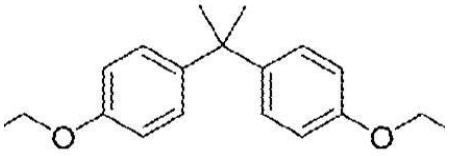
wherein R_1 is a linear or branched hydrocarbon chain, which may be unsubstituted or substituted and wherein one or more hydrocarbon group of said hydrocarbon chain may be replaced by an heteroatom, a ketone, a cycloalkyl, an heterocycle, an aryl or a heteroaryl, each of which may be substituted or unsubstituted, said hydrocarbon chain having from 2 to 60 carbon atoms;

wherein R_2 is an aryl or a heteroaryl, each of which may be unsubstituted or substituted, or a linear or branched hydrocarbon chain, which may be unsubstituted or substituted, and wherein one or several hydrocarbon groups of said hydrocarbon chain may be replaced by a heteroatom, a cycloalkyl or an heterocycle, each of which may be unsubstituted or substituted, said hydrocarbon chain having at least 2 carbon atoms, preferably from 2 to 60 carbon atoms, more preferably from 2 to 20 carbon atoms, even more preferably from 2 to 15 carbon atoms, or a mixture thereof; preferably R_2 is an alkylene;

wherein R_3 and R_4 are identical or different and represent H, a straight or branched saturated hydrocarbon chain C_{1-6}-alkyl having 1 to 6 carbon atoms; C_{1-6}-alkoxy alkyl having 1 to 6 carbon atoms

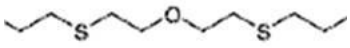
and wherein n is an integer $\geqslant 1$, preferably n is between 1 and 100, more preferably between 1 and 20;

with the exception that if R_3 and/or R_4 represents an hydrogen atom, than R_1 is not



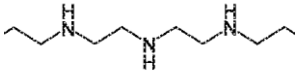
, 

, or



;

and with the exception that if R_3 and/or R_4 represents an hydrogen atom, then R_2 is not



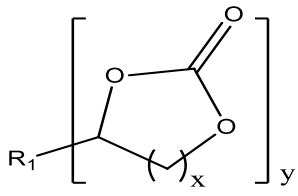
;

wherein R_8 is an aryl or a heteroaryl, each of which may be unsubstituted or substituted, or a linear or branched hydrocarbon chain, which may be unsubstituted or substituted, and wherein one or several hydrocarbon groups of said hydrocarbon chain may be replaced by a heteroatom, a cycloalkyl or an heterocycle, each of which may be unsubstituted or substituted, said hydrocarbon chain having at least 2 carbon atoms, in particular from 2 to 60 carbon atoms, more particularly from 2 to 20 carbon atoms, even more particularly from 2 to 15 carbon atoms, or a mixture thereof; preferably R_8 is an alkylene; and

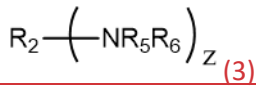
wherein u is an integer $\geqslant 1$, preferably between 1 and 10 more preferably between 1 and 5.

In another aspect, there is provided a method of manufacturing an implantable medical device comprising polyhydroxyurethane as defined herein; characterised in that the method comprises step (a) or (b) corresponding respectively to a thermal or UV polymerisation or a combination of both:

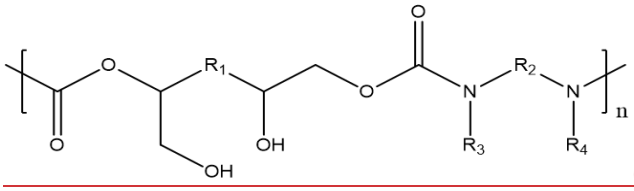
a) mixing a polycyclocarbonate of formula (2) with a polyamine of formula (3) and optionally a catalyst to obtain, by thermal polymerization, a polyhydroxyurethane based on formula (1);



(2)



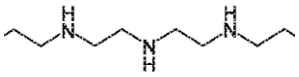
(3)



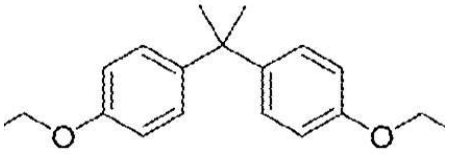
(1)

wherein R_1 is a carbon bond between a cyclic carbonate ring or is a linear or branched hydrocarbon chain, which may be unsubstituted or substituted and wherein one or more hydrocarbon groups of said hydrocarbon chain may be replaced by an heteroatom, a ketone, a cycloalkyl, an heterocycle, an aryl or a heteroaryl, each of which may be substituted or unsubstituted, said hydrocarbon chain having from 2 to 40 carbon atoms ; preferably R_1 is polypropylene oxide, polyethyleneoxide, polybutylene oxide, polytetrahydrofurane or a mixture thereof;

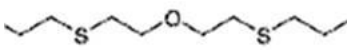
wherein R_2 is an aryl or a heteroaryl, each of which may be unsubstituted or substituted, or a linear or branched hydrocarbon chain, which may be unsubstituted or substituted, and wherein one or several hydrocarbon groups of said hydrocarbon chain may be replaced by a heteroatom, a cycloalkyl or an heterocycle, each of which may be unsubstituted or substituted, said hydrocarbon chain having at least 2 carbon atoms, preferably from 2 to 60 carbon atoms, more preferably from 2 to 20 carbon atoms, even more preferably from 2 to 15 carbon atoms;

wherein R_5 and R_6 are identical or different and represent H, a straight or branched saturated hydrocarbon chain C_{1-6}-alkyl having 1 to 6 carbon atoms; preferably R_5 and R_6 are hydrogen, with the exception that if R_5 and/or R_6 are hydrogen then R_2 is not  ;

and with the exception that if R_5 and/or R_6 are hydrogen, then R_1 is not



,  , or

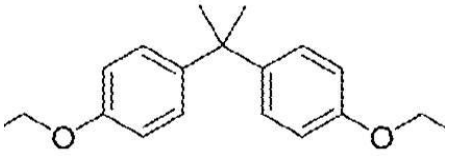


;

wherein R_3 and R_4 are identical or different and represent H, a straight or branched saturated hydrocarbon chain C_{1-6}-alkyl having 1 to 6 carbon atoms ; C_{1-6}-alkoxy alkyl having 1 to 6 carbon atoms;

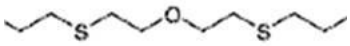
and wherein n is an integer $\geqslant 1$, preferably n is between 1 and 100, more preferably between 1 and 20;

with the exception that if R_3 and/or R_4 represents an hydrogen atom, R_1 is not



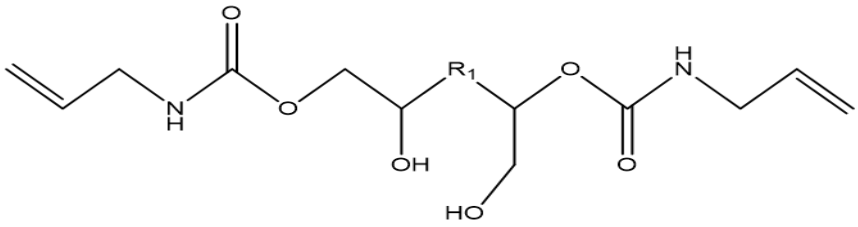


, , or



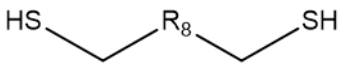
;

b) mixing a polyvinylcarbamatehydroxy derivative bearing photoresponsive groups, preferably of formula (10) with a thiol of formula (16), preferably of formula(11) and a photoiniator to obtain, by UV polymerization, a polyhydroxyurethane based on formula (9);

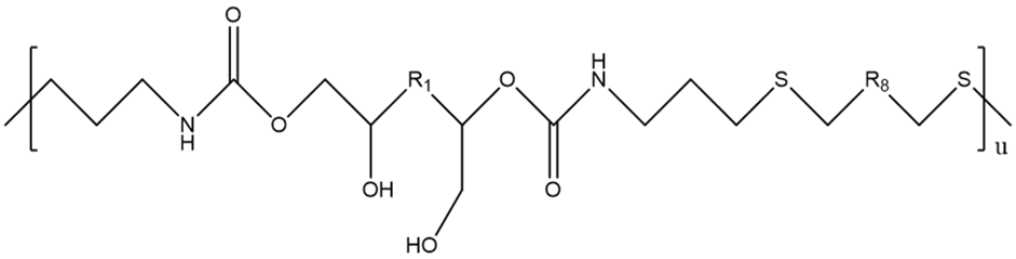


(10)

R_8-$(SH)_k$ (16);



(11)



(9)

wherein R_1 is a linear or branched hydrocarbon chain, which may be unsubstituted or substituted and wherein one or more hydrocarbon group of said hydrocarbon chain may be replaced by an heteroatom, a ketone, a cycloalkyl, an heterocycle, an aryl or a heteroaryl, each of which may be substituted or unsubstituted, said hydrocarbon chain having from 2 to 60 carbon atoms ; preferably R_1 is polypropyleneoxide, polyethylene oxide, polybutylene oxide, polytetrahydrofurane, or a mixture thereof ;

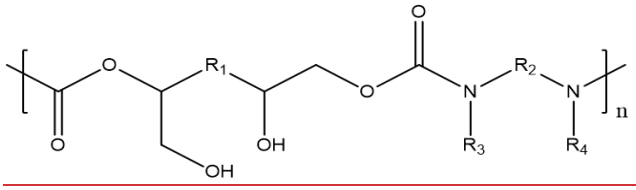
wherein R_8 is an aryl or a heteroaryl, each of which may be unsubstituted or substituted, or a linear or branched hydrocarbon chain, which may be unsubstituted or substituted, and wherein one or

several hydrocarbon groups of said hydrocarbon chain may be replaced by a heteroatom, a cycloalkyl or an heterocycle, each of which may be unsubstituted or substituted, said hydrocarbon chain having at least 2 carbon atoms, in particular from 2 to 60 carbon atoms, more particularly from 2 to 20 carbon atoms, even more particularly from 2 to 15 carbon atoms, or a mixture thereof; preferably R_8 is an alkylene; and

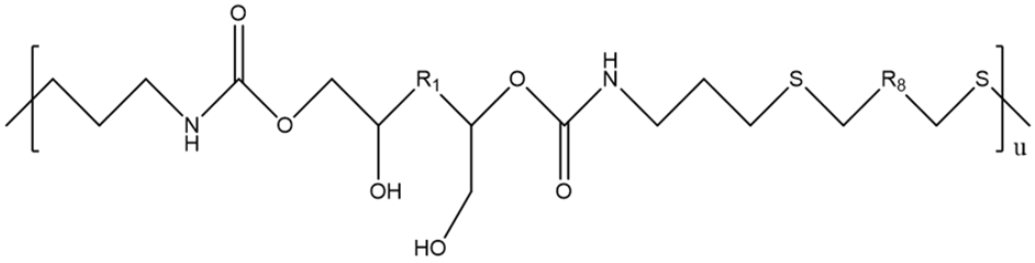
wherein k is an integer $\geqslant$ 2, preferably between 2 and 6;

wherein u is an integer $\geqslant$ 1, preferably between 1 and 10 more preferably between 1 and 5.

In another aspect, there is provided a method of coating an implantable medical device comprising a polyhydroxyurethane as defined herein; the method comprising depositing onto a surface of the medical device at least one layer of polyhydroxyurethane based on formula (1) and/or on formula (9)



(1)



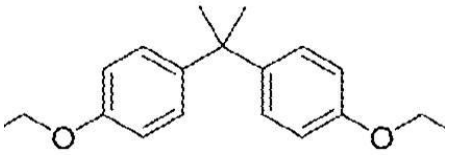
(9)

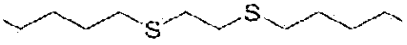
wherein R_1 is a carbon bond between a cyclic carbonate ring or is a linear or branched hydrocarbon chain, which may be unsubstituted or substituted and wherein one or more hydrocarbon groups of said hydrocarbon chain may be replaced by an heteroatom, a ketone, a cycloalkyl, an heterocycle, an aryl or a heteroaryl, each of which may be substituted or unsubstituted, said hydrocarbon chain having from 2 to 40 carbon atoms ; preferably R_1 is polypropylene oxide, polyethyleneoxide, polybutylene oxide, polytetrahydrofurane or a mixture thereof;

wherein R_2 is an aryl or a heteroaryl, each of which may be unsubstituted or substituted, or a linear or branched hydrocarbon chain, which may be unsubstituted or substituted, and wherein one or several hydrocarbon groups of said hydrocarbon chain may be replaced by a heteroatom, a cycloalkyl or an heterocycle, each of which may be unsubstituted or substituted, said hydrocarbon chain having at least 2 carbon atoms, preferably from 2 to 60 carbon atoms, more preferably from 2 to 20 carbon atoms, even more preferably from 2 to 15 carbon atoms;

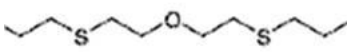
wherein R_3 and R_4 are identical or different and represent H, a straight or branched saturated hydrocarbon chain C_{1-6}-alkyl having 1 to 6 carbon atoms; C_{1-6}-alkoxy alkyl having 1 to 6 carbon atoms;

with the exception that if R_3 and/or R_4 represents an hydrogen atom, then R_1 is not



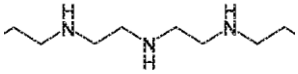


, or



,

and with the exception that if R_3 and/or R_4 represents an hydrogen atom, then R_2 is not



;

wherein R_8 is an aryl or a heteroaryl, each of which may be unsubstituted or substituted, or a linear or branched hydrocarbon chain, which may be unsubstituted or substituted, and wherein one or several hydrocarbon groups of said hydrocarbon chain may be replaced by a heteroatom, a cycloalkyl or an heterocycle, each of which may be unsubstituted or substituted, said hydrocarbon chain having at least 2 carbon atoms, in particular from 2 to 60 carbon atoms, more particularly from 2 to 20 carbon atoms, even more particularly from 2 to 15 carbon atoms, or a mixture thereof; preferably R_8 is an alkylene;

wherein u is an integer $\geqslant 1$, preferably between 1 and 10 more preferably between 1 and 5;

and wherein n is an integer $\geqslant 1$, preferably n is between 1 and 100, more preferably between 1 and 20.

DETAILED DESCRIPTION

It is an object of the present invention to provide a new medical device comprising a non-isocyanate polyurethane or polyhydroxyurethane (PHU).

The term implantable medical device as used herein refers to all implantable foreign material for clinical use in host mammal such as for prosthetic joints, pacemakers, implantable cardioverter-defibrillators, catheters, such as intravascular or urinary catheters, stent including coronary stent, prosthetic heart valves, intraocular lens, dental implants, breast implants, endotracheal tubes,