



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁷ : A01N 47/44, A61L 27/54</p>	<p>A1</p>	<p>(11) International Publication Number: WO 00/65915 (43) International Publication Date: 9 November 2000 (09.11.00)</p>
<p>(21) International Application Number: PCT/GB00/01644 (22) International Filing Date: 28 April 2000 (28.04.00) (30) Priority Data: 9910042.2 1 May 1999 (01.05.99) GB (71) Applicant (for all designated States except US): BIOINTER-ACTIONS LTD. [GB/GB]; University of Reading, Science & Technology Centre, Whiteknights Road, Earley Gate, Reading RG6 2EF (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): LUTHRA, Ajay, Kumar [GB/GB]; 219 Somervell Road, South Harrow, Middlesex HA2 8UA (GB). SANDHU, Shivpal, Singh [GB/GB]; 63 Lascelles Road, Slough, Berkshire SL3 7PW (GB). (74) Agent: URQUHART-DYKES & LORD; 1 Richfield Place, Richfield Avenue, Reading RG1 8EQ (GB).</p>	<p>(81) Designated States: AU, CA, JP, NO, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: INFECTION RESISTANT POLYMERS, THEIR PREPARATION AND USES</p>		
<p>(57) Abstract</p>		
<p>A family of infection resistant and biocidal polymeric materials incorporates an infection resistant biguanide such as chlorhexidine or polyhexanide pendant to the polymer chain, chemically linked to the polymer through the biguanide group secondary nitrogen atoms. The disclosure extends to the use of such polymeric materials in articles of manufacture and particularly in medical devices, and the preparation of the materials as polymer resins from which articles can be made, as solutions and emulsions which can be used for coating performed articles, and <i>in situ</i> on the surface of preformed polymeric articles.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INFECTION RESISTANT POLYMERS, THEIR PREPARATION AND USES

FIELD OF THE INVENTION

5

This invention relates to infection resistant polymers, methods for their preparation, and their uses. In particular the invention concerns a family of polymeric materials incorporating an infection resistant biguanide compound pendant to the polymer chain, the use of such polymeric materials in articles of manufacture and particularly in
10 medical devices, and the preparation of the materials as polymer resins from which articles can be made, as solutions and emulsions which can be used for coating preformed articles, and *in situ* on the surface of preformed polymeric articles.

BACKGROUND OF THE INVENTION

15

Medical apparatus, for example, medical devices such as contact lenses, catheters for vascular access (both arterial and venous), abdominal cavity tubing, drainage bags and connectors of various kinds, are required to be infection resistant. The desirable feature of such medical apparatus is control of infection that occurs during the application of the
20 apparatus when in contact with body tissue or fluid. The term medical device as used herein is intended to encompass the full range of devices for intimate contact with the human or other mammalian body, or with the corresponding body fluids, as implants, prostheses, interface devices, surgical equipment and the like.

25 Fabrication of medical apparatus is usually from polymeric materials that may comprise, but are not limited to, polyurethanes, silicones, polyvinylchloride and others, by moulding and extrusion techniques.

There are many cited efforts to eradicate the problem of infection on medical apparatus. These have largely been aimed at attaching the infection resistant material to the polymeric apparatus.

- 5 US Patent No. 3,695,921 discloses a layer of hydrophilic polymer on a catheter that is able to absorb an antibiotic. Thermoplastic polyurethane medical devices containing an anti-microbial agent on their surface are described.

- 10 US Patent No 4,581,028 discloses infection resistant vascular grafts with incorporated anti-microbial agents, such as silver sulphadiazine and piperacillin.

US Patent No 4,479,795 describes medical apparatus of permeable polymers, which incorporate releasable anti-microbial agent that is able to diffuse to the surface to form a barrier.

15

As disclosed in a Japanese Patent Application No 60/36064 chlorhexidine is adsorbed on to the surface of polyurethane or silicone catheter by dipping into an aqueous solution of chlorhexidine and then converted to a water insoluble form by dipping into a solution of an acid.

20

Japanese Patent Application No 59/228,856 discloses an elastomeric catheter possessing a water insoluble biguanide or salt as a thin coating on the surface.

- 25 PCT Application No WO 86/02561 discloses a thermoplastic polymer having up to 1% chlorhexidine contained in or upon the surface.

UK Patent Application No 2,084,466A discloses a procedure for rendering polypropylene apparatus biocidal with chlorhexidine base, and suggests that the apparatus may be prepared from other plastics.

30

Solomon et al., in US Patent No 4,713,402, discloses the bonding of a quaternary salt to the surface of a polymeric apparatus and the attachment of an antibiotic to the salt.

5 In US Patent No 4,678,660 there is disclosure of a polyurethane article having on the surface a layer of a polyurethane alloy consisting of a dispersed complex of a quaternary salt with an antibiotic.

Solomon et al. describe in US Patent No 5,451,424 a method for preparing medical apparatus by a homogenous melt of polymer and chlorhexidine and having bulk
10 distributed chlorhexidine

US Patent No 4,891,423 discloses linear polyoxyalkylene diamine biguanides and discusses other known biguanides, and their use in solid and liquid bactericidal and fungicidal compositions, including ophthalmic saline solutions.

15 US Patent No 5,142,010 discloses the vinyl copolymerisation of certain polymerisable unsymmetrical biguanide compounds.

US Patent No 5,817,325 discloses crosslinking biguanide polymers with, *inter alia*,
20 isocyanates or epoxides to form an immobile, insoluble, non-leachable surface matrix which has the ability to deliver deposited biocidal silver salts into the interior of a micro-organism. The polymers are useful for coating contact lens cases and other articles. The biocidal action is through the silver salts, not through the highly cross-linked biguanides.

25 Even though the methods for preparing infection resistant medical apparatus have addressed some of the problems, they are, however, not adequately effective. A major constraint is that the infection resistant material, when incorporated on to or into the apparatus, loses potency in inhibiting or reducing bacterial growth.

30

Another contributing factor is that the bulk distribution of the infection resistant material is not stable and in certain cases is able to permeate from the apparatus into body tissue or fluid and cause harmful effects.

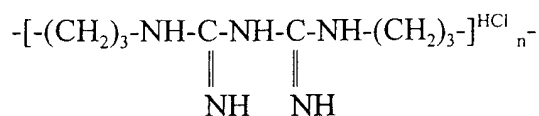
5 SUMMARY OF THE INVENTION

In accordance with the invention, novel chemically modified infection resistant materials are produced by the chemical modification of infection resistant biguanide compounds to produce polymers that can be blended into the bulk of other polymers, be used as
10 coatings, or be chemically attached to the surface of a medical device.

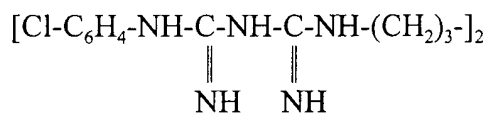
A medical device in accordance with the invention may be made of, coated with, or surface treated to form *in situ*, the novel polymers having infection resistant properties.

15 In this specification, references to infection resistant materials (IRMs) include antibiotics, anti-bacterial agents, anti-viral agents, anti-microbial agents, and the like. Infection resistant is taken to mean capable of killing, preventing the proliferation of, or inhibiting or at least substantially slowing the growth of, susceptible classes of
microorganisms. Microorganisms include but are not necessarily limited to bacteria,
20 viruses, fungi, yeasts, algae and other life forms. IRMs include, but are not limited to, antibiotics, anti-bacterial agents, anti-viral agents and anti-microbial agents.

Biguanides are strongly basic compounds containing the biguanide group
-NH-C(NH)-NH-C(NH)-NH- and have been identified as having powerful antimicrobial
25 activity. Two particularly preferred biguanides for the purposes of the present invention are polyhexanide and chlorhexidine, which are commercially available. Each includes the biguanide group adjacent a hexamethylene chain. Their respective structures can be represented as follows:



5 Polyhexanide hydrochloride salt



10

Chlorhexidine

Polyhexanide and chlorhexidine have a broad spectrum of anti-bacterial activity and at relatively low concentrations the anti-bacterial action is bacteriostatic; at higher
 15 concentration the action becomes rapidly bactericidal. The commercial water soluble salt of chlorhexidine is usually the digluconate.

In one aspect of the invention, infection resistant biguanides are chemically modified to yield novel chemically modified infection resistant materials.

20

In another aspect of the present invention the chemically modified infection resistant material is applied to medical devices to render them resistant to biological growth that induces infection.

25 In accordance with a further aspect of this invention, the application of the chemically modified infection resistant material to a medical device produces stable, non-leaching infection resistant material.

Without wishing to be bound by any particular theory, it is believed that the
 30 antimicrobial activity of biguanide compounds derives from the strongly basic character of their biguanide groups which form acid addition salts with a cationic charge delocalised over the five neighbouring secondary amine nitrogen atoms. This enables the biguanide to be rapidly attracted to a negatively charged bacterial cell. Thereafter the

biguanide interacts with the cytoplasmic membrane, upsetting the ionic balances and, ultimately, disrupting the membrane and causing irreversible damage to the cell contents.

The present invention utilises the amino nitrogen atoms of the biguanide group to anchor
5 these antimicrobial compounds to a polymeric substrate as pendant species without disabling their antimicrobial properties, although the normal acid addition salt form of these compounds interferes with their derivatisation at these amino sites. The polymeric products of the invention are thus distinguished from both linear polymeric biguanides and highly cross-linked biguanide polymers.

10

In accordance with the invention, there is provided a polymeric material incorporating an infection resistant biguanide compound pendant to the polymer chain, being chemically bound thereto through some but not all of the amine nitrogen atoms, and preferably of the secondary amine nitrogen atoms of the -NH-C(NH)-NH-C(NH)-NH- biguanide group
15 or groups, of the infection resistant biguanide compound. The pendant biguanide compounds are generally bound through the secondary amine nitrogen atoms, which may include some of the >C=NH imino nitrogen atoms, and may include some of the C-NH-C secondary amine nitrogen atoms. However, a certain amount of binding through the primary amine groups at each end of biguanides such as polyhexanide is also
20 possible.

There is also provided a medical device comprising a polymeric material incorporating a pendant infection resistant biguanide compound chemically bound to the polymer through some but not all of the amine nitrogen atoms of the biguanide, and particularly
25 the secondary amine nitrogen atoms of the -NH-C(NH)-NH-C(NH)-NH- biguanide group or groups of the infection resistant biguanide compound. Such a medical device may be formed from or coated with the polymeric material incorporating the infection resistant biguanide compound, or the medical device may first be formed from or coated with polymeric material which is thereafter chemically bound to some but not all of the
30 nitrogen atoms of the infection resistant biguanide compound, or the medical device may first be formed from or coated with polymeric material which is thereafter chemically

bound to the residuum of a non-polymeric compound that has been bound to some but not all of the nitrogen atoms of the infection resistant biguanide compound.

In other words, the biguanide can be incorporated as a pendant group into a polymer
5 which is then made into or coated on to an article, or the biguanide can be chemically
linked to polymer already on an article, or the biguanide can be bound to polymer on an
article through an intermediate non-polymeric compound. Such a compound requires
one functionality to bind with the biguanide secondary amine, and one functionality to
bind with the polymer.

10

Polymer functionality to bind with the IRM directly (either to the biguanide secondary
amine or to a functional group on a bound non-polymeric compound as described above)
may include groups such as hydroxyl (-OH), carboxyl (-COOH), anhydride
(-CO-O-CO-), isocyanate (-NCO), allyl, vinyl, acrylate, methacrylate, epoxide, sulfonic
15 (-SO₃⁻) or sulfate (-SO₄⁻) groups. Linkage to the polymer may be by covalent bonding
(including grafting) or by ionic bonding.

Chemical binding to a secondary amine nitrogen atom by means of isocyanate results in a
substituted urea linkage, or by means of isothiocyanate results in a substituted thiourea
20 linkage, or by means of epoxide results in a beta-hydroxyl-tertiary amine, or by means
of acid chloride results in a N,N- disubstituted amide, or by means of acid anhydride
results in a N,N-disubstituted amide, or by means of aldehyde or ketone results in
N,N-disubstituted hemiaminals or amins depending on the aldehyde or ketone, or by
means of unsaturated bonds results in a tertiary amine linkage.

25

Suitable medical devices to which the invention may be applied include catheters, blood
bags, dialysis or other membranes, surgical gloves, surgical instruments, vascular grafts,
stents, contact lenses and intra-ocular lenses, contact lens cases, bottles, diagnostic
apparatus, oxygenators, heart valves and pumps. A preferred medical device is formed
30 as a contact lens or intra-ocular lens.

Other articles of manufacture to which the invention may be applied include kitchen equipment such as worktops and chopping boards. Polymeric IRMs may be applied to articles by sprays, to form thin surface films.

- 5 In a further aspect, the invention provides a method of making an infection resistant polymeric material which comprises chemically binding reactive sites on a polymeric material with some but not all of the amine nitrogen atoms of an infection resistant biguanide compound, especially the secondary amine nitrogen atoms of the -NH-C(NH)-NH-C(NH)-NH- biguanide group or groups of an infection resistant biguanide
- 10 compound. The secondary amine nitrogen atoms bound to the reactive sites may include some of the $>C=NH$ imino nitrogen atoms and may include some of the C-NH-C nitrogen atoms. Primary amine end groups on suitable biguanide compounds, such as polyhexanide, may also participate in binding to polymeric materials.
- 15 In an important aspect of the method, it comprises the preliminary step of forming a free base, preferably a partial free base, of the biguanide compound before binding the reactive sites with the nitrogen atoms. By removing some but not all of the acid of the usual acid addition salt, some of the secondary amine nitrogen atoms become available for derivatisation. If the entire free base is liberated, care needs to be taken to ensure
- 20 only partial derivatisation.

The preferred reactive sites to bind with the biguanide nitrogen comprise isocyanate, isothiocyanate, epoxide, acid chloride, acid anhydride, aldehyde, ketone and unsaturated (especially acrylate, methacrylate and vinyl) sites.

- 25
- Similar considerations apply to a variation of the above method which comprises modifying a polymer precursor by chemically binding some but not all of the amine nitrogen atoms of an infection resistant biguanide compound, especially the secondary amine nitrogen atoms of the -NH-C(NH)-NH-C(NH)-NH- biguanide group or groups of
- 30 an infection resistant biguanide compound with reactive sites on the polymer precursor, and thereafter converting the so modified polymer precursor to an infection resistant

polymeric material by a method including a polymerisation step which leaves the biguanide compound residue pendant to the polymer chain.

5 The reactive sites on the polymer precursor may comprise isocyanate, isothiocyanate, epoxide, acid chloride, acid anhydride, aldehyde, ketone or unsaturated sites, or other suitable sites. Even sites comprising hydroxyl, carboxyl or amino groups can link on to the biguanide groups by using coupling agents such as carbonyl diimidazole or carbidomides.

10 The polymer precursor may also contain acrylate, methacrylate, allyl or vinyl groups, and the polymerisation step may be carried out by polymerising the modified polymer precursor through the said groups. Any other polymerisable group may also be used.

15 Similar considerations apply to a further variation of the foregoing method of making an infection resistant polymeric material which comprises modifying a non-polymeric compound by chemically binding some but not all of the amine nitrogen atoms of an infection resistant biguanide compound, especially the secondary amine nitrogen atoms of the -NH-C(NH)-NH-C(NH)-NH- biguanide group or groups of an infection resistant biguanide compound with reactive sites on the non-polymeric compound, and thereafter
20 chemically binding the so modified compound to a polymeric material. The chemical binding of the IRM to the polymeric material may be by covalent bonding (including grafting) or by ionic bonding.

25 The non-polymeric compound may also contain acrylate, methacrylate, allyl or vinyl groups, so that the modified compound may be chemically bound to a polymeric material through the said groups. Any other polymerisable group may also be used. Other functional groups carried by the non-polymeric compounds for binding with polymeric materials may include hydroxyl, carboxyl, amide, amino, epoxide, isocyanate, sulfate, sulfonate and others. In general, it is possible to provide functionality that can react with
30 available complementary chemical constituents contained in polymeric materials to form polymeric infection resistant materials or to covalently attach to surfaces.

Whichever method of preparation is used, the resulting polymer containing biguanide groups may be subsequently blended with other polymeric material to form an infection resistant polymer blend for use in forming an article of manufacture, and preferably blended with medically acceptable polymeric material to form an infection resistant
5 medical polymer blend for use in the manufacture of a medical device.

Typical materials for blending include polyurethanes, polyamides, latex, silicones, siloxanes, polyvinyl chloride, polyesters, polycarbonates, polyacrylonitrile, polymethylmethacrylate, polypropylene, polyethylene and hydrogels. Clearly the
10 biguanide polymer and the blending polymer should be suitably compatible.

The resulting polymer containing biguanide groups may be subsequently blended with ocularly acceptable lens material to form an infection resistant ocular polymer blend for use in the manufacture of a contact or intra-ocular lens.

15 Alternatively, the resulting polymer containing biguanide groups may include acrylate, methacrylate, allyl or vinyl groups, and the polymer may be subsequently copolymerised with ocularly acceptable lens material to form an infection resistant ocular polymer for use in the manufacture of a contact or intra-ocular lens.

20 Typical lens materials include, but are not limited to, hydroxyethyl methacrylate, methyl methacrylate, vinyl pyrrolidone, silicone or siloxane methacrylates, fluorocarbon methacrylates, polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene oxide, and polyethylene glycol. These polymers may contain zwitterionic functionality. Lenses can
25 be ionic or non-ionic.

Suitable zwitterionic monomers for polymerisation include 2-(methacryloyloxyethyl)-2'-(trimethylammonium) ethyl phosphate inner salt and any containing phosphorylcholine groups.

30

In a further application of the invention, the polymer containing biguanide groups may subsequently be coated on to an article of manufacture to form an infection resistant coating thereon.

- 5 Chlorhexidine and polyhexanide are the preferred biguanide compounds. Each has its own activity spectrum. To broaden the antimicrobial range of the end product, the invention includes the further step of blending the resulting polymers containing biguanide groups derived from both chlorhexidine and polyhexanide, or copolymerising precursors to form a polymer in accordance with the invention containing biguanide
10 groups derived from both chlorhexidine and polyhexanide.

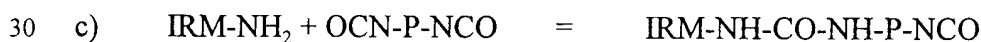
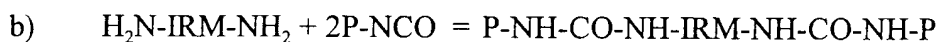
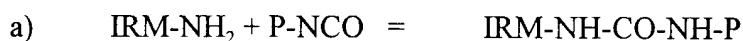
The IRM may exist in the free base or acid form or the salt thereof and as such the invention does include such forms.

15 **DETAILED DESCRIPTION OF THE INVENTION**

To illustrate the invention by a general example, an amino constituent contained in the derivatised biguanide infection resistant material (IRM-NH₂) is able to react with a polymeric isocyanate (P-NCO) constituent to form a urea linkage giving a polymeric
20 infection resistant material, as outlined in Scheme 1 a), b) and c). The converse is also true where the IRM contains isocyanate constituents and is able to react with polymeric amino.

Scheme 1.

25



Polymeric Infection Resistant Materials (PIRM) prepared as in Scheme 1 may be constituted, by way of example, into homogeneous blends of extrudable polyurethane to form medical apparatus with anti-bacterial properties that are effective and stable, in which the PIRM is unable to permeate to body tissue or fluids.

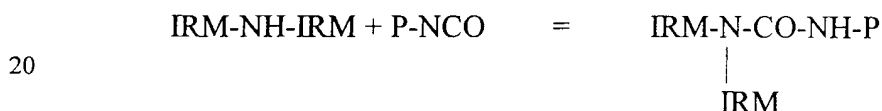
5

By way of another example the PIRM is prepared and dissolved in a suitable solvent for coating the medical article in order to give it anti-bacterial properties that are effective and stable, in which the PIRM is unable to permeate to body tissue or fluids.

10 By way of a further example the chemically modified IRM (e.g. IRM-NH₂) is attached to the surface by conventional chemical linkages. In the case of IRM-NH₂, one such method would be by way of an amide bond.

An example of chemical modification, in relation to polyhexanide, is the reaction of an
15 isocyanate to the secondary amine, as shown by Scheme 2, to give substituted ureas.

Scheme 2.



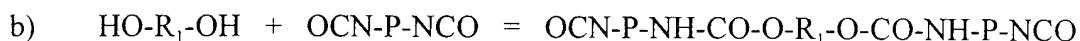
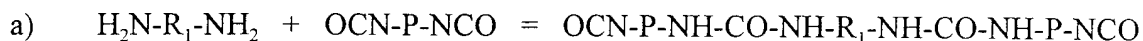
The polyisocyanates useful in the invention in producing substituted ureas with the IRM, typically polyhexanide, may be selected from a wide range of aliphatic, cycloaliphatic,
25 and aromatic polyisocyanates. The isocyanate groups may be carried on polymers having unsaturated alkyl groups, esters, ethers, siloxanes, urethanes, amides, carbonates, and mixtures thereof which can be chosen to promote compatibility with other polymers that they may subsequently be coated on or blended with.

30 Polydiisocyanates that can be utilised are those typically used in the formation of polyurethane, which when reacted with secondary amines form the substituted ureas.

Additionally, polydiisocyanates can be prepared by the reaction of a polyamine or polyol with a diisocyanate, as shown by Scheme 3.

Scheme 3

5

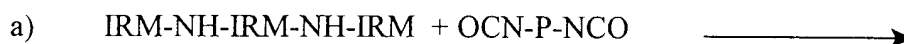


10 In Scheme 3, -R₁- and -P- can typically be aliphatic groups, cycloaliphatic groups, aromatic groups, unsaturated alkyl groups, esters, ethers, siloxanes, urethanes, amides, carbonates, and mixtures thereof. Others are of course possible.

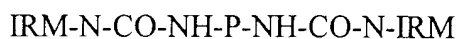
Such polydiisocyanates may then be further reacted with IRM containing appropriate
 15 reactive chemical groups, an example being the secondary amine of polyhexanide reacted with the isocyanates, as shown in Scheme 4; thus producing Polymeric Infection Resistant Materials (PIRM).

Scheme 4

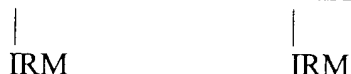
20



25



30



The PIRM can be compounded with other polymers, such as polyurethanes, polysiloxanes, polyesters, polyvinylchlorides, polybutadienes and polyamides, to produce medical apparatus, either by extrusion or moulding, that are infection resistant. The active ingredient (IRM) is stable within the medical apparatus and is non-leaching.

5

The PIRM or the IRM may contain allyl, vinyl, acrylate or methacrylate groups for polymerisation to form allyl, vinyl, acrylate, and methacrylate type polymers.

Allyl, vinyl, acrylate and methacrylate functionalities can be incorporated in the IRM by reacting the acid chloride, isocyanate, epoxide or anhydride of a molecule containing the above double bond functionality.

For instance, methacryloylchloride can be reacted with the secondary amine of a biguanide resulting in the formation of a tertiary amide with the liberation of hydrogen chloride which re-forms the hydrochloride on the biguanide group.

Isocyanatoethyl methacrylate, allyl isocyanate, glycidyl methacrylate and the anhydride or mixed anhydride of methacrylic acid can undergo reactions with the free base of the biguanide to yield methacrylate and allyl functionality on the biguanide group. The isocyanate would react to form a urethane urea bond, the epoxide would react to form a tertiary amine and the anhydride to form a tertiary amide.

Methacrolein can also react with the secondary amine of the biguanide. Here the reaction is between a secondary amine and an aldehyde which can yield a hemiaminal or aminal, depending on the aldehyde.

Allyl, vinyl, acrylate and methacrylate derivatives of IRMs can undergo homopolymerisation or copolymerisation with numerous other molecules or polymers which have a double bond under thermal or electromagnetic radiation. The allyl, vinyl, acrylate and methacrylate derivatives of IRMs can be grafted on to surfaces having

30

Either all the hydrochloride groups associated with the biguanide groups of the polyhexanide can be neutralised and then the desired chemistry carried out before re-forming their hydrochloride salts or only the desired number of hydrochlorides can be neutralised and then the chemistry carried out before re-forming their hydrochlorides.

- 5 Both are acceptable methods of derivatisation.

Similar considerations apply to chlorhexidine and other biguanide compounds.

10

Example 1

Polyhexanide starting material

400ml of a 20% w/v aqueous solution of polyhexanide (Zeneca Biocides) was placed in a Spectra/Por® membrane (MWCO: 2,000) and was dialysed against 10 litres of deionised
15 water for 16hrs. The dialysed polyhexanide was then placed in stainless steel freeze-drying trays and was freeze dried for 72hrs.

The yield of dry crystalline powder of polyhexanide was 40g.

20

Example 2

Partial free-base polyhexanide

In this example only 1 in 6 biguanide hydrochloride groups are neutralised.

25 1g (4.5662×10^{-3} moles of biguanide hydrochloride groups) of polyhexanide powder (from Example 1) was dissolved in 80ml deionised water. The number of moles of sodium hydroxide required to neutralise 1 in 6 biguanide hydrochloride groups of polyhexanide is 7.61×10^{-4} moles (0.0304g, NaOH). Sodium hydroxide (0.0304g) was dissolved in 50ml deionised water and added drop-wise to the polyhexanide solution
30 over a period of 1hr. The solution was then freeze-dried yielding a dry crystalline powder of polyhexanide partial free-base (Ph.P free-base).

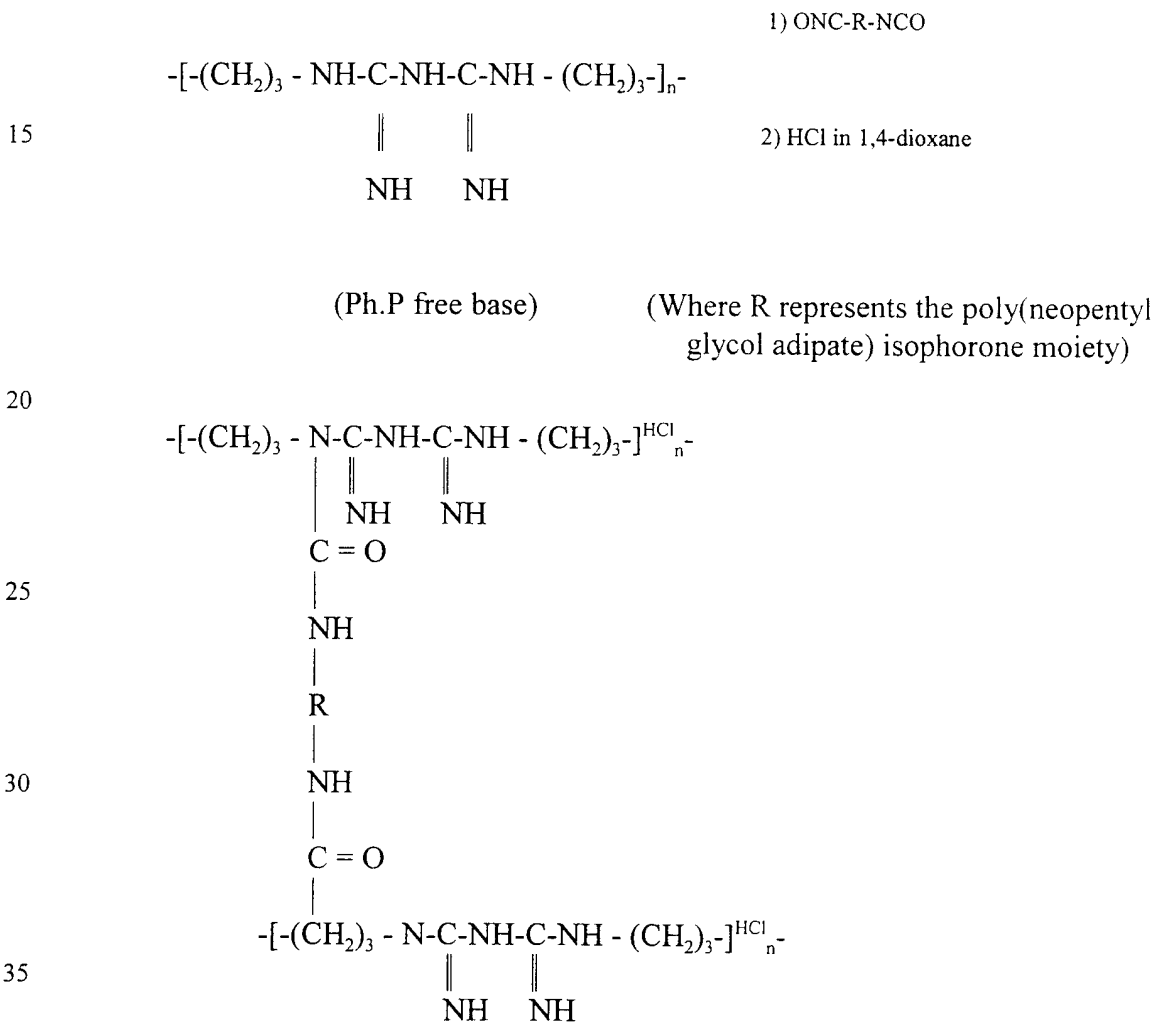
Example 3

Polyhexanide/polyisophorone urethane polymer

1.027g (7.61×10^{-4} moles) Poly (neopentyl glycol adipate) isophorone diisocyanate
 5 terminated (PNGAID, Mn 1350) (Aldrich Chemical Co.) was dissolved in 50ml
 dichloromethane. 1g of Ph.P free-base (from Example 2) was dissolved in 50ml ethanol
 and was vigorously stirred. To this polyhexanide was added the above PNGAID solution
 over a period of 1hr, to form urethane urea bonds. The solution was neutralised with
 0.019ml of 4M hydrogen chloride in 1,4 dioxane.

10

Infrared spectrum showed the disappearance of the band at 2265.9cm due to the N=C=O
 group.



Example 4*Polyhexanide/silicone copolymer*

4.158g (3.08×10^{-3} moles) PNGAID was dissolved in 50ml anhydrous dichloromethane
5 and stirred vigorously. 41.58g (1.54×10^{-3} moles) aminopropyl terminated
polydimethylsiloxane (APDS) with an average molecular weight of 27,000 (Gelect, Inc)
was dissolved in 200ml anhydrous dichloromethane, and was added drop-wise to the
dichloromethane solution of PNGAID over a period of 2hrs. The reaction formed
urethane urea bonds between the PNGAID and APDS with the resulting copolymer
10 terminating in isocyanate groups.

The infrared spectrum of the copolymer showed the existence of the band at 2265cm^{-1}
due to the N=C=O group.

15 To the above PNGAID-APDS copolymer was added allylamine (0.088g, 1.54×10^{-3}
moles) dissolved in 50ml anhydrous dichloromethane over a period of 1hr. This resulted
in the introduction of one allyl functionality to the PNGAID-APDS copolymer leaving
one reactive isocyanate.

20 1g of Ph.P free-base (from Example 2) was dissolved in a mixture containing 40ml
ethanol and 10ml dichloromethane. This solution was vigorously stirred and the above
copolymer PNGAID-APDS was added dropwise over a period of 2hrs. Infrared showed
the disappearance of the N=C=O band at 2265cm^{-1} . The secondary amine of the Ph.P
free-base reacted with the isocyanate of the PNGAID-APDS copolymer to form a
25 urethane urea bond.

The resulting solution was neutralised with 0.019ml of 4M hydrogen chloride in 1,4
dioxane.

Example 5*Extruded silicone sheets*

The copolymer resulting from Example 4 was dried initially on a rotary evaporator and
5 then dried under vacuum at 50°C for 16hrs. The yield was 47g of polyhexanide/silicone
copolymer.

The above polyhexanide/silicone copolymer (47g) was mechanically mixed in with
Silastic Q7-4736 Biomedical grade ETR (1Kg) obtained from Dow Corning. After 1hr of
10 mechanical mixing, sheets were extruded and cured at 120°C for 30 minutes.

The high consistency silicone sheets containing polyhexanide moieties had tear strengths,
elongation and tensile strength equivalent to those containing no polyhexanide/silicone
copolymer.

15

Example 6*Polyhexanide methacrylate*

2.25g (0.01027 moles of biguanide hydrochloride groups) of polyhexanide powder (from
20 Example 1) was dissolved in de-ionised water. The number of moles of sodium
hydroxide required to neutralise 1 in 12 biguanide hydrochloride groups of polyhexanide
is 8.5616×10^{-4} moles (0.03425g NaOH). Sodium hydroxide (0.03425g) was dissolved in
50ml of de-ionised water and added dropwise to the vigorously stirred solution of
polyhexanide partial free-base (Ph.P free-base).

25

The above Ph.P free-base was dissolved in 60ml anhydrous dimethyl sulphoxide and
stirred. 0.0895g (8.5616×10^{-4} moles) methacryloyl chloride was dissolved in 25ml
dimethyl sulphoxide solution containing the Ph.P free-base over a period of 1hr.

30 The above reaction involves the formation of a tertiary amide when the methacryloyl
chloride reacts with the free secondary amine of the polyhexanide and the HCl liberated

Example 7*Contact lens formation*

20mg polyhexanide methacrylate (from Example 6) was dissolved in 10ml 2-
5 hydroxyethyl-methacrylate (Fluka) containing 40mg ethylene glycol dimethacrylate and
20mg 2, 2'- azobis (2,4-dimethylvaleronitrile (Dupont)). The above clear solution was
degassed for 30min.

The above polymerisation mixture was poured into a polypropylene concave mould and
10 then a polypropylene convex mould was placed onto the concave mould allowing the
excess solution to overflow thereby uniformly filling the space between the concave and
convex moulds. The shape of the concave and convex moulds approximates a contact
lens. The sealed moulds were then heated to a temperature of 65°C for 4hrs and then at
110°C for 1 hour.

15 The moulds were then cooled and opened and a contact lens was obtained. The lens
produced was clear and transparent. The lens were hydrated in phosphate buffered saline
for 6hrs. The water content was 38% by weight.

Example 8*Polyhexanide polymer coated tubing*

20g of polyhexanide methacrylate was synthesised according to Example 6.

25 A 2 litre, 3-necked reaction vessel equipped with stirrer, thermometer, condenser and
nitrogen inlet tube was charged with 1000ml of de-ionised water and placed in a silicone
oil bath at 120°C. The solution was stirred gently, and nitrogen was bubbled through the
solution (40cm³/min).

30 140g methoxy polyethyleneglycol 2000 methacrylate (MPEG2000MA) (Inspec) was
placed in a 1 litre beaker and dissolved with stirring in 100ml de-ionised water. Then

36g methoxy polyethyleneglycol 350 methacrylate (MPEG350MA) (Inspec) was poured into the MPEG2000MA solution. Then 85g of butyl methacrylate (Aldrich) was poured into the above solution with vigorous stirring.

- 5 When the temperature in the 2 litre, 3-necked reaction vessel reached 75⁰C the above monomer mixture was poured into the reaction vessel and was stirred vigorously.

20g of polyhexanide methacrylate was dissolved in 100ml de-ionised water and was poured into the above reaction vessel containing the monomer mixture. When the
10 temperature inside the reaction vessel reached 80⁰C, 1g potassium persulphate (dissolved in 60ml of de-ionised water) was added to the reaction vessel.

After approximately 10mins a white viscous emulsion polymer had formed. The polymer was cooled down to room temperature in a water bath and then poured into a dialysis
15 membrane (MWCO 3,000-4000) and dialysed against 10 litres of water for 48hrs. After 24hrs, the 10 litres of water was replaced with fresh de-ionised water.

The polymer was removed from the dialysis membrane and poured into freeze-drying trays and was then freeze-dried for 72hrs.

20

200g of a dry white powder of the polymer resulted.

2g of the above polymer was dissolved in 30ml isopropanol and when fully dissolved to a clear solution, 70ml of tetrahydrofuran was added. Polyvinylchloride (PVC) and
25 polyurethane (PU) tubing were coated with this polymer by dipping the tubing into the above polymer solution and then allowing it to dry for 2hrs. When wetted with water, both the PVC and PU tubings were completely wetted out and were highly lubricious. 10 PVC and 10 PU (length 5cm) tubings were then incubated at 37⁰C in de-ionised water (100ml) for 72hrs. They were then removed, washed and tested for wetting. Again both
30 sets of tubings were completely wetted out and there was no diminishing in the lubricity. The de-ionised water in which the PVC and PU tubes were incubated was freeze-dried

and re-constituted in 3ml de-ionised water and the absorbance of the solution was measured at 250nm. No absorbtion was detected due to the polyhexanide. A 0.0025% w/v solution of polyhexanide, which was used as the control, had an absorpction of 0.35 o.d.

5

Example 9

Polyhexanide methacrylate contact lenses

20g Ph.P free-base (from Example 6) was dissolved in 300ml dimethyl sulphoxide. To this was added 1.623g glycidylmethacrylate (Aldrich) followed by 0.2g triethylamine. The solution was allowed to stir at 60⁰C for 3hrs. The solution was then neutralised using 0.2M HCl until pH 6.0.

The solution was diluted with water (2 litres) in a dialysis membrane (MW CO: 2,000) against 30 litres of de-ionised water for 24hrs to remove unreacted glycidylmethacrylate and triethylamine. The solution from the dialysis membrane was then freeze-dried. Yield was 21g.

Contact lenses were made from the above polyhexanide methacrylate as exactly according to Example 7. The contact lenses produced were clear and transparent. The lenses were hydrated in buffered saline and had a water content of 38%.

20g of the above polyhexanide methacrylate was polymerised exactly as in Example 8. The polymer was coated onto PVC and PU tubings and assessed for leachables. No polyhexanide leached from either set of tubings as assessed by UV absorpction.

25

Example 10

Polyhexanide methacrylate contact lenses and coatings

30 20g Ph.P free-base (from Example 6) was dissolved in 300ml ethanol and stirred vigorously. To this solution was added, drop-wise, 1.18g (7.61×10^{-3} moles) 2-

isocyanatoethyl methacrylate (IEM) (Polysciences) dissolved in 50ml ethanol over a period of 1hr. This resulted in forming a urethane urea bond between the secondary amine of the polyhexanide and the isocyanate of the IEM. Infrared showed the disappearance of the isocyanate peak due to IEM. The reaction between IEM and ethanol
5 does not occur. Even after 24 hrs the isocyanate peak still remains when only IEM and ethanol are present. Isocyanate and alcohol reactions require a catalyst and elevated temperatures for the reaction to be of any significance.

The above solution was then neutralised with 0.19ml of 4M hydrogen chloride in 1,4
10 dioxane.

As in Example 9, the above polyhexanide methacrylate was used to make contact lenses (Example 7) and also an emulsion polymer (Example 8). The results were similar to those in Example 9. Polyhexanide methacrylate formed good contact lenses and coated
15 the PVC and PU tubings without any leaching.

Example 11

Polyhexanide methacrylate contact lenses and coatings

20 30g of Ph.P free-base (from Example 6) was dissolved in 300ml ethanol and stirred vigorously. To this solution was added, drop-wise, 1.760g (0.0114 moles) methacrylic anhydride (Aldrich) dissolved in 50ml ethanol over a period of 1hr. The above reaction resulted in the formation of a tertiary amide and the reaction was followed by the infrared spectrum with the disappearance of the peaks at 1790cm^{-1} due to C=O asymmetric and
25 symmetric stretching vibrations. In the absence of Ph.P free-base no reaction could be observed between the ethanol and methacrylic anhydride for 10hrs at 22°C as observed by infrared. This reaction usually occurs in the presence of a catalyst (e.g. dimethylaminopyridine).

30 The polyhexanide methacrylate solution was neutralised with 0.285ml of 4M HCl in 1, 4 dioxane. The ethanol was rotary evaporated off and the resulting polymer was dissolved

in 100ml de-ionised water and dialysed in a dialysis membrane (MW CO: 2,000) against 10L of de-ionised water for 24hrs. The dialysed solution was then freeze-dried to yield a dry polyhexanide methacrylate (yield, 23g).

- 5 As with previous examples, (Examples 7 and 8), contact lenses and emulsion polymers were made and the results were equivalent to those in Examples 7, 8, 9 and 10.

Example 12

Chlorhexidine methacrylate

10

1g (1.9784×10^{-3} moles) chlorhexidine (Aldrich) was dissolved in 100ml anhydrous dichloromethane and stirred vigorously. 0.207g (1.9784×10^{-3} moles) methacryloylchloride was dissolved in 50ml anhydrous dichloromethane and added drop-wise to the chlorhexidine solution over a period of 1hr. Methacryloylchloride reacted
15 with the secondary amine of the chlorhexidine forming a tertiary amide. The hydrogen chloride liberated formed one hydrochloride on the chlorhexidine. The reaction was followed by infrared and observed the disappearance of the peaks of methacryloylchloride.

- 20 Chlorhexidine methacrylate monohydrochloride was formed in the above reaction. In order to obtain the dihydrochloride, 0.495ml of 4M hydrogen chloride in 1,4 dioxane was added to the reaction mixture.

The solvent was rotary evaporated off to leave a dry powder of chlorhexidine
25 methacrylate dihydrochloride (CMD).

Example 13

Chlorhexidine methacrylate

- 30 1g (1.9784×10^{-3} moles) chlorhexidine was dissolved in 100ml anhydrous dichloromethane and stirred vigorously. 0.3067g (1.9784×10^{-3} moles) 2-

isocyanatoethyl methacrylate (IEM) was dissolved in 50ml anhydrous dichloromethane and added drop-wise to the chlorhexidine solution over a period of 1hr. IEM reacted with the secondary amine of the chlorhexidine to form a urethane urea bond. Infrared showed the disappearance of the isocyanate peak due to IEM.

5

The above reaction resulted in the formation of chlorhexidine methacrylate. In order to obtain the dihydrochloride, 0.99ml of 4M hydrogen chloride in 1, 4 dioxane was added to the reaction mixture. The solvent was rotary evaporated to yield chlorhexidine methacrylate dihydrochloride.

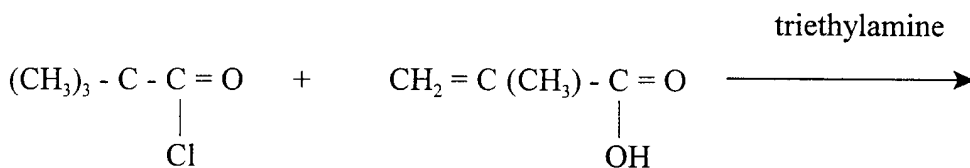
10

Example 14

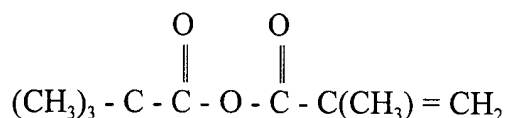
Chlorhexidine amide linkage with methacrylic acid

15 1g (8.293×10^{-3} moles) trimethylacetyl chloride was dissolved in 50ml anhydrous dichloromethane. To this was solution added 0.839g distilled triethylamine and the solution stirred. 0.714g (8.293×10^{-3} moles) methacrylic acid was dissolved in 25ml anhydrous dichloromethane and added drop-wise to the above mixture and stirred for 3hrs at 22°C. This reaction resulted in the formation of a mixed anhydride.

20



25



30 The dichloromethane was rotary evaporated leaving a liquid mixed anhydride.

1g (1.9784×10^{-3} moles) chlorhexidine was dissolved in 100ml anhydrous dichloromethane and stirred vigorously.

The above mixed anhydride was then reacted on a mole to mole basis with the chlorhexidine. The number of grams of mixed anhydride required was 0.3363g (1.978×10^{-3} moles). However, to allow for the triethylamine hydrochloride in the mixture, the number of grams required is 0.61g. Accordingly 0.61g of the mixed anhydride mixture
5 was dissolved in 50ml anhydrous dichloromethane and added dropwise to the chlorhexidine solution over a period of 1hr. The methacrylic acid formed a tertiary amide with the secondary amine of the chlorhexidine and the trimethyl acetic acid formed the counter ion to form chlorhexidine methacrylate mono trimethylacetate. 0.495ml of 4M hydrogen chloride in 1,4 dioxane was added to form the other counter ion. The solution
10 was rotary evaporated to dryness and a dry powder of the product obtained.

Chlorhexidine will preferentially react with the methacrylic acid of the mixed anhydride and not the trimethylacetic acid because the latter is sterically hindered.

15

Example 15

Chlorhexidine methacrylate homopolymer

10g (0.01978 moles) chlorhexidine was dissolved in 60ml anhydrous dimethylsulphoxide under nitrogen at 40°C (approximately 30mins) in a 3-necked round bottom flask with
20 overhead stirring. The solution was allowed to cool to room temperature and then 2.81g glycidyl methacrylate was added, followed by 0.2g triethylamine. The solution was allowed to react for 4hrs at 60°C with stirring. Then the dihydrochloride salt was formed by adding 10ml of 4M hydrogen chloride in 1,4 dioxane to give chlorhexidine methacrylate dihydrochloride.

25

Nitrogen was then bubbled through the solution and the temperature of the solution allowed to reach 75°C when 0.1g 2,2'-azobis (2,4-dimethylvaleronitrile) was added as initiator. The solution became highly viscous after 15min polymerisation at 80°C and at 30min the reaction was stopped by cooling the solution. The homopolymer of
30 chlorhexidine was precipitated by adding 500ml de-ionised water. The polymer was washed several times with water before drying in a vacuum oven at 60°C for 24hrs.

Example 16*Chlorhexidine methacrylate*

Chlorhexidine methacrylate dihydrochloride was made exactly as according to Example
5 15 except that the solvent used was anhydrous chloroform. The chloroform was rotary
evaporated to leave a dry white powder.

Example 17*Contact lens material containing chlorhexidine methacrylate polymer*

10

20mg chlorhexidine methacrylate (from Example 12) was dissolved in 10ml 2-
hydroxyethyl methacrylate with gentle warming (30°C). Then 40mg ethylene glycol
dimethacrylate and 20mg 2, 2'- azobis (2,4-dimethylvaleronitrile) was added to the
solution and stirred until a clear solution was obtained. The solution was then de-gassed
15 for 30mins.

The above polymerisation mixture was poured into a polypropylene concave mould and
then a polypropylene convex mould was placed onto the concave mould allowing the
excess solution to overflow thereby uniformly filling the space between the concave and
20 convex moulds. The shape of the concave and convex moulds approximates a contact
lens. The sealed moulds were then heated to a temperature of 65°C for 4hrs and then at
110°C for 1hr to cure the lens.

The moulds were then cooled, opened and contact lenses were obtained. The lenses
25 produced were clear and transparent. The lenses were hydrated in phosphate buffered
saline for 6hrs. The water content was measured and found to be 38%.

Contact lens material was also made in a similar manner from the chlorhexidine
methacrylate synthesised in Examples 13, 14 and 16 and they all produced good clear
30 contact lenses with water content being 38%.

Example 18*Chlorhexidine/polyisophorone urethane polymer*

3g (5.935×10^{-3} moles) chlorhexidine was dissolved in 100ml anhydrous
5 dichloromethane with stirring. 4g (2.963×10^{-3} moles) PNGAID was dissolved in 50ml
anhydrous dichloromethane and added drop-wise to the chlorhexidine solution over a
period of 1hr. When the reaction was complete, infrared showed the absence of the bond
at 2265.9cm^{-1} due to N=C=O group of PNGAID. The reaction resulted in forming a
urethane urea bond. 2 mole equivalent of chlorhexidine reacted with one mole equivalent
10 of PNGAID.

Then the dihydrochloride was formed by adding 2.97ml of 4M hydrogen chloride in 1,4
dioxane. Five 5cm long PU tubings were dip-coated with this polymer and allowed to
dry for 24hrs. The PU tubing was then placed in de-ionised water (100ml) at 37°C for
15 72hrs, after which the tubes were removed and the de-ionised water was freeze-dried.
3ml of anhydrous dichloromethane was used to wash the stainless steel tray in which the
de-ionised water was freeze-dried. A potassium bromide crystal was coated with the
washing of dichloromethane and then infrared spectroscopy was conducted. Infrared
showed no peak which related to the chlorhexidine or to the PNGAID.

Example 19*Fungistatic and bacteriostatic activity*

The silicone sheets produced in Example 5 were exposed to the following yeast, fungi and
5 bacteria: *Candida albicans*, *Aspergeillus niger*, *Staphylococcus epidermis*, *Escherichia coli*,
Staphylococcus aureus and *Bacillus subtilis*.

The sheets were incubated for 12 days at 30 ° C. The micro-organism growth is tabulated
below.

10	Organism Polyhexanide	Control Silicone Sheet	2	Silicone incorporating
		Growth per cm ² (x10 ⁶)		Growth per cm ² (x10 ⁶)
15	<i>Candida albicans</i>	60.8		2.1
	<i>Aspergeillus niger</i>	75.3		2.8
	<i>Staphylococcus epidermis</i>	53.8		0.3
20	<i>Escherichia coli</i>	83.7		0.4
	<i>Staphylococcus aureus</i>	40.6		0.2
25	<i>Bacillus subtilis</i>	68.9		0.2

Example 20*Fungistatic and bacteriostatic activity*

Coated polyurethane (PU) tubing pieces (3 cm long) from Example 8 (polyhexanide
30 coated) and from Example 18 (chlorhexidine coated) were exposed to the same micro-
organisms as in Example 19 and the results are tabulated below.

35	Organism	Uncoated (PU)	PU coated (polyhexanide)	PU coated (chlorhexidine)
		Growth per cm ² (x10 ⁶)	Growth per cm ² (x10 ⁶)	Growth per cm ² (x10 ⁶)
	<i>Candida albicans</i>	83.2	2.1	7.4
	<i>Aspergeillus niger</i>	50.6	1.1	6.5
40	<i>Staphylococcus epidermis</i>	110.0	2.8	7.3
	<i>Escherichia coli</i>	90.0	1.1	4.6
	<i>Staphylococcus aureus</i>	30.0	0.2	2.0
	<i>Bacillus subtilis</i>	45.2	0.1	4.0

CLAIMS

- 1 A polymeric material incorporating an infection resistant biguanide
compound pendant to the polymer chain, being chemically bound thereto through
5 some but not all of the amine nitrogen atoms of the infection resistant biguanide
compound.
- 2 A polymeric material according to claim 1 wherein the pendant infection
resistant biguanide compound is chemically bound to the polymer chain through
10 secondary amine nitrogen atoms of the -NC-C(NH)-NH-C(NH)-NH- biguanide
group or groups of the biguanide compound.
- 3 A polymeric material according to claim 1 or claim 2 wherein the biguanide
compound is the residue of chlorhexidine or polyhexanide.
15
- 4 A polymeric material according to claim 2 or claim 3 wherein the said
chemical binding to secondary amine nitrogen atoms is by means of a substituted
urea linkage, or a substituted thiourea linkage, or a N,N-disubstituted amide
linkage, or a N,N-disubstituted hemiaminal or aminal linkage, or a tertiary amine
20 linkage.
- 5 A medical device comprising a polymeric material incorporating a pendant
infection resistant biguanide compound chemically bound to the polymer through
some but not all of the amine nitrogen atoms of the infection resistant biguanide
25 compound.
- 6 A medical device according to claim 5 wherein the pendant infection
resistant biguanide compound is chemically bound to the polymer chain through
secondary amine nitrogen atoms of the -NC-C(NH)-NH-C(NH)-NH- biguanide
30 group or groups of the biguanide compound.

7 A medical device according to claim 5 or claim 6 wherein the medical
device is formed from or coated with the polymeric material incorporating the
infection resistant biguanide compound, or the medical device is first formed from
or coated with polymeric material which is thereafter chemically bound to some but
5 not all of the nitrogen atoms of the infection resistant biguanide compound, or the
medical device is first formed from or coated with polymeric material which is
thereafter chemically bound to the residuum of a non-polymeric compound that has
been bound to some but not all of the nitrogen atoms of the infection resistant
biguanide compound.

10

8 A medical device according to any one of claims 5 to 7 wherein the
biguanide compound is a residue of chlorhexidine or polyhexanide.

9 A medical device according to any one of claims 6 to 8 wherein the said
15 chemical binding to secondary amine nitrogen atoms is by means of a substituted
urea linkage, or a substituted thiourea linkage, or a N,N-disubstituted amide
linkage, or a N,N-disubstituted hemiaminal or aminated linkage, or a tertiary amine
linkage.

20 10 A medical device according to any one of claims 5 to 9 formed as a contact
lens or intra-ocular lens.

11 A method of making an infection resistant polymeric material which
comprises chemically binding reactive sites on a polymeric material with some but
25 not all of the amine nitrogen atoms of an infection resistant biguanide compound.

12 A method according to claim 11 wherein the amine nitrogen atoms that are
bound to the reactive sites include secondary amine nitrogen atoms of the -NH-
C(NH)-NH-C(NH)-NH- biguanide group or groups of the biguanide compound..

30

13 A method according to claim 11 or 12 which comprises the preliminary step of forming a partial free base of the biguanide compound before binding the reactive sites with the nitrogen atoms.

5 14 A method according to any one of claims 11 to 13 wherein the reactive sites comprise isocyanate, isothiocyanate, epoxide, acid chloride, acid anhydride, aldehyde, ketone or unsaturated sites.

10 15 A method according to any one of claims 11 to 13 wherein the reactive sites comprise hydroxyl, carboxyl or amino groups and the binding to the nitrogen atoms is carried out in the presence of a carbonyl diimidazole or carbidomide coupling agent.

15 16 A method of making an infection resistant polymeric material which comprises modifying a polymer precursor by chemically binding some but not all of the amine nitrogen atoms of an infection resistant biguanide compound with reactive sites on the polymer precursor, and thereafter converting the so modified polymer precursor to an infection resistant polymeric material by a method including a polymerisation step.

20

17 A method according to claim 16 wherein the amine nitrogen atoms bound to the reactive sites include secondary amine nitrogen atoms of the -NH-C(NH)-NH-C(NH)-NH- biguanide group or groups of the biguanide compound.

25 18 A method according to claim 16 or 17 which comprises the preliminary step of forming a partial free base of the biguanide compound before binding the reactive sites with the nitrogen atoms.

30 19 A method according to any one of claims 16 to 18 wherein the reactive sites comprise isocyanate, isothiocyanate, epoxide, acid chloride, acid anhydride, aldehyde, ketone or unsaturated sites.

20 A method according to any one of claims 16 to 18 wherein the reactive sites comprise hydroxyl, carboxyl or amino groups and the binding to the nitrogen atoms is carried out in the presence of a carbonyl diimidazole or carbodiimide coupling agent.

5

21 A method according to any one of claims 16 to 20 wherein the polymer precursor also contains acrylate, methacrylate, allyl or vinyl groups, and the polymerisation step is carried out by polymerising the modified polymer precursor through the said groups.

10

22 A method of making an infection resistant polymeric material which comprises modifying a non-polymeric compound by chemically binding some but not all of the amine nitrogen atoms of an infection resistant biguanide compound with reactive sites on the non-polymeric compound, and thereafter chemically
15 binding the so modified compound to a polymeric material.

23 A method according to claim 22 wherein the amine nitrogen atoms bound to the reactive sites include secondary amine nitrogen atoms of the -NH-C(NH)-NH-C(NH)-NH- biguanide group or groups of the biguanide compound.

20

24 A method according to claim 22 or 23 which comprises the preliminary step of forming a partial free base of the biguanide compound before binding the reactive sites with the nitrogen atoms.

25 25 A method according to any one of claims 22 to 24 wherein the reactive sites comprise isocyanate, isothiocyanate, epoxide, acid chloride, acid anhydride, aldehyde, ketone or unsaturated sites.

26 A method according to any one of claims 22 to 24 wherein the reactive sites
30 comprise hydroxyl, carboxyl or amino groups and the binding to the nitrogen atoms

is carried out in the presence of a carbonyl diimidazole or carbidomide coupling agent.

27 A method according to any one of claims 22 to 26 wherein the non-
5 polymeric compound also contains acrylate, methacrylate, allyl or vinyl groups, and the modified compound is chemically bound to a polymeric material through the said groups.

28 A method according to any one of claims 11 to 27 wherein the resulting
10 polymer containing biguanide groups is subsequently blended with other polymeric material to form an infection resistant polymer blend for use in forming an article of manufacture.

29 A method according to claim 28 wherein the resulting polymer containing
15 biguanide groups is subsequently blended with medically acceptable polymeric material to form an infection resistant medical polymer blend for use in the manufacture of a medical device.

30 A method according to claim 29 wherein the resulting polymer containing
20 biguanide groups is subsequently blended with ocularly acceptable lens material to form an infection resistant ocular polymer blend for use in the manufacture of a contact or intra-ocular lens.

31 A method according to claim 30 wherein the resulting polymer containing
25 biguanide groups includes acrylate, methacrylate, allyl or vinyl groups, and the polymer is subsequently copolymerised with ocularly acceptable lens material to form an infection resistant ocular polymer for use in the manufacture of a contact or intra-ocular lens.

- 32 A method according to any one of claims 11 to 27 wherein the resulting polymer containing biguanide groups is subsequently coated on to an article of manufacture to form an infection resistant coating thereon.
- 5 33 A method according to any one of claims 11 to 32 wherein the biguanide compound is chlorhexidine or polyhexanide.
- 34 A method according to claim 33 wherein the resulting polymer contains biguanide groups derived from both chlorhexidine and polyhexanide.
- 10 35 A polymeric material according to claim 1 substantially as hereinbefore described with reference to any of the specific Examples.
- 36 A method according to claim 11 substantially as hereinbefore described with
15 reference to any of the specific Examples.
- 37 A method according to claim 16 substantially as hereinbefore described with reference to any of the specific Examples.
- 20 38 A method according to claim 22 substantially as hereinbefore described with reference to any of the specific Examples.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/01644

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A01N47/44 A61L27/54

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)
IPC 7 A01N A61L

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 460 385 A (FULLER H B LICENSING FINANC) 11 December 1991 (1991-12-11) page 2, line 3 - line 8 page 2, line 50 -page 4, line 28	1,2,5-7
Y	& US 5 142 010 A 25 August 1992 (1992-08-25) cited in the application	3,4,8-38
Y	GB 2 085 454 A (KELVIN LENSES LTD) 28 April 1982 (1982-04-28) page 1, line 21 - line 31 page 1, line 42 claims 1,6,20-26	3,4,8-38
	--- -/--	

Further documents are listed in the continuation of box C.

Patent family members are listed in 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

1 September 2000

Date of mailing of the international search report

11/09/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Lamers, W

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/01644

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 103 776 A (BAYER AG) 28 March 1984 (1984-03-28) page 1, line 1 - line 3 page 3, line 1 - page 4, line 9 page 4, line 18 - line 19 page 5, line 1 - line 4 ---	3, 4, 8-38
X	PATENT ABSTRACTS OF JAPAN vol. 12, no. 103 (C-485), 5 April 1988 (1988-04-05) & JP 62 230806 A (NITTO BOSEKI), 9 October 1987 (1987-10-09) abstract ---	1, 2, 5-7
P, X	US 5 928 916 A (KEOGH JAMES R) 27 July 1999 (1999-07-27) column 3, line 11 - line 42 column 4, line 9 - line 23 column 5, line 1 - line 40 ---	1, 2, 5-7
A	US 5 707 366 A (BYRON M PARKE ET AL) 13 January 1998 (1998-01-13) column 2, line 35 - line 54 ---	1-38
A	US 5 817 325 A (SHALON TADMOR ET AL) 6 October 1998 (1998-10-06) cited in the application column 2, line 32 - line 45 column 2, line 56 - line 60 column 3, line 13 - line 44 ---	1-38
A	PATENT ABSTRACTS OF JAPAN vol. 1997, no. 01, 31 January 1997 (1997-01-31) & JP 08 226077 A (ZENEKA), 3 September 1996 (1996-09-03) abstract ---	1-38

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/01644

Patent document cited in search report	A	Publication date	Patent family member(s)	Publication date
EP 0460385	A	11-12-1991	US 5142010 A JP 4026669 A	25-08-1992 29-01-1992
GB 2085454	A	28-04-1982	DE 3174724 D EP 0050934 A US 4433111 A US 4493910 A	03-07-1986 05-05-1982 21-02-1984 15-01-1985
EP 0103776	A	28-03-1984	DE 3232917 A DE 3238358 A BR 8304792 A CA 1199925 A DK 401883 A JP 59065065 A US 4560738 A ZA 8306525 A	08-03-1984 19-04-1984 10-04-1984 28-01-1986 05-03-1984 13-04-1984 24-12-1985 30-05-1984
JP 62230806	A	09-10-1987	NONE	
US 5928916	A	27-07-1999	US 5821343 A US 5945319 A US 5728420 A US 5891506 A US 5925552 A EP 0803257 A JP 10033660 A US 6033719 A WO 9933499 A US 6017741 A AU 699145 B AU 2876897 A CA 2212602 A EP 0826382 A JP 10085321 A WO 9927968 A	13-10-1998 31-08-1999 17-03-1998 06-04-1999 20-07-1999 29-10-1997 10-02-1998 07-03-2000 08-07-1999 25-01-2000 26-11-1998 12-03-1998 09-02-1998 04-03-1998 07-04-1998 10-06-1999
US 5707366	A	13-01-1998	US 5451424 A US 5165952 A US 5013306 A AT 103497 T CA 2004366 A, C DE 69007631 D DE 69007631 T EP 0379269 A ES 2054229 T IE 64997 B JP 1993226 C JP 2234767 A JP 5023790 B US 4999210 A	19-09-1995 24-11-1992 07-05-1991 15-04-1994 18-07-1990 05-05-1994 25-08-1994 25-07-1990 01-08-1994 04-10-1995 22-11-1995 17-09-1990 05-04-1993 12-03-1991
US 5817325	A	06-10-1998	AU 5088898 A EP 0939591 A WO 9818330 A	22-05-1998 08-09-1999 07-05-1998
JP 08226077	A	03-09-1996	NONE	